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

Policy # 00597
Original Effective Date: 03/21/2018
Current Effective Date: 04/12/2021

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 19 through 21 (eg, exon 19 deletions, L858R, T790M) within the epidermal growth factor receptor (EGFR) gene, using the cobas®‡ EGFR Mutation Test v2, Guardant360®‡ CDx test, OncoBEAM™‡ test or InVisionFirst-Lung test with plasma specimens to detect circulating tumor DNA (ctDNA) as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to an EGFR tyrosine kinase inhibitor (TKI) therapy (eg, erlotinib [Tarceva®], gefitinib [Iressa®], afatinib [Gilotrif™], or osimertinib [Tagrisso®])‡ 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 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®])‡ in patients with advanced or metastatic (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.

OTHER GENES

Based on review of available data, the Company may consider plasma tests (i.e. Guardant360 CDx, OncoBEAM or InVisionFirst- Lung test) for oncogenic driver variants deemed eligible for coverage on tissue biopsy (i.e., ALK gene, BRAF V600E, ROS1, NTRK gene fusion, RET rearrangement, MET exon 14 skipping) in patients with advanced or metastatic non-small-cell lung cancer (stage III or IV), to predict treatment response to targeted therapy to be **eligible for coverage.****

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Patient Selection Criteria
Coverage eligibility will be considered when **ALL** the following criteria are met:

- Patient does not have sufficient tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue; AND
- Follow-up tissue-based analysis is planned should no driver variant be identified via plasma testing.

Note: When criteria are met, smaller panel testing including the genes listed as eligible for coverage may be considered as an alternative to individual gene testing and is preferred to larger panel testing.

For 5 or more gene tests being run on the same platform, such as multi-gene panel NGS, an available procedure code for the smaller multi-gene panel test is to be utilized.

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 (see Policy Guidelines) 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 (see Policy Guidelines)

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 (see Policy Guidelines) to predict treatment response to ALK inhibitor therapy (crizotinib [Xalkori]) in patients NSCLC to be **investigational.***

***NTRK* TESTING**
Based on review of available data, the Company considers analysis of the *NTRK* gene fusion using plasma specimens to detect ctDNA as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to larotrectinib (Vitrakvi®)‡ or entrectinib (Rozlytrek™)‡ in patients with NSCLC to be **investigational.***

***MET* TESTING**
Based on review of available data, the Company considers analysis of the *MET* exon 14 skipping variant using plasma specimens to detect ctDNA as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to MET inhibitor therapy (capmatinib [Tabrecta]) in patients with NSCLC to be **investigational.***

***RET* TESTING**
Based on review of available data, the Company considers analysis of somatic fusion variants of the *RET* gene using plasma specimens to detect ctDNA as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to RET inhibitor therapy (eg, selpercatinib [Retevmo], pralsetinib [Gavreto]) in patients with 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.***

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

Policy Guidelines

The tests discussed herein, cobas EGFR Mutation Test v2, Guardant360 CDx test, Oncobeam test or InVisionFirst-Lung, are intended for use in patients with advanced (stage III or IV) non-small-cell lung cancer. These tests include variants beyond exons 19 through 21 of the epidermal growth factor receptor (*EGFR)* gene, and some tests additionally include variants in numerous other genes. Patients with sensitizing variants of the tyrosine kinase domain of the *EGFR* gene are considered good candidates for treatment with erlotinib, gefitinib, afatinib, dacomitinib, or osimertinib. The U.S. 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. Plasma tests for other oncogenic driver variants deemed medically necessary on tissue biopsy (see medical policy 00452) may also be appropriate for patients who do not have enough tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue; however this is only appropriate if follow-up tissue-based analysis is planned should no driver variant be identified.

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.

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 U.S. 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, dacomitinib, 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.

***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.

MET Variants

C-MET, the hepatocyte growth factor (HGF) receptor, is a tyrosine kinase receptor that is involved in cell survival and proliferation. *MET* (mesenchymal-epithelial transition) 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-naive NSCLC and *MET* and *EGFR* commutations occur in 5% to 20% of NSCLC tumors with acquired resistance to EGFR TKIs. *MET* exon 14 (*MET*ex14) skipping mutations occur in approximately 3-4% of adenocarcinomas and 1-2% of patients with other NSCLC histologies. Higher frequencies are observed in older women who are nonsmokers. *METex14* genomic alterations do not typically overlap with *EGFR*, *ROS1*, *BRAF*, and *ALK* variants. Several types of *MET*ex14 skipping mutations can occur, including mutations, base substitutions, and deletions. *MET* inhibition with capmatinib was granted accelerated approval by the FDA in 2020 for treatment of metastatic NSCLC in patients positive for *MET*ex14 skipping mutations based on results from an open-label, non-randomized, phase 2 trial in 97 subjects (NCT02414139). Among 28 treatment-naive patients, the overall response rate (ORR) was 68% with a response duration of 12.6 months. Among 69 previously treated patients, the ORR was 41% with a response duration of 9.7 months. Patients in this study were wild-type for *EGFR* variants and negative for *ALK* rearrangements,

RET Fusions

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. *RET* inhibition with pralsetinib was granted accelerated approval by the FDA in 2020 for treatment of metastatic *RET*-fusion-positive NSCLC. Approval was based on results from an open-label, non-randomized phase 1/2 trial in 114 patients (NCT03037385). Among 27 treatment-naive patients, the ORR was 70% with 58% of responses lasting 6 months or longer in duration. Among 87 patients

previously treated with chemotherapy, the ORR was 57% with 80% of responses lasting 6 months or longer in duration. RET inhibition with selpercatinib was granted accelerated approval by the FDA in 2020 for the treatment of RET fusion-positive metastatic NSCLC and advanced or metastatic medullary thyroid cancer. Approval for NSCLC was based on results from an open-label, non-randomized phase 1/2 trial in 144 patients (NCT03157128). Among 39 treatment-naive patients, the ORR was 85% with 58% of responses lasting 6 months or longer in duration. Among 105 patients previously treated with platinum chemotherapy, the ORR was 64% with 81% of responses lasting 6 months or longer in duration.

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, vandetanib). 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.

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 *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. The use of osimertinib as first-line therapy for patients who have *EGFR*-sensitizing variants was approved by the FDA in 2018 on the basis of the randomized, double-blind phase 3 FLAURA trial.

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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. 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 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 and osimertinib in 2018 (P120019/S019). Patients who test negative for the variants detected should be referred for (or "reflexed" to) routine biopsy with tissue testing for *EGFR* variants.

In August 2020, Guardant360®‡ CDx (Guardant Health), a qualitative next generation sequencing-based diagnostic of circulating cell-free DNA in plasma, was approved by the FDA through the premarket approval process (P200010). The plasma test is approved as a companion diagnostic for selecting NSCLC patients who have *EGFR* exon 19 deletions, L858R substitution variants, or T790M variants, for treatment with osimertinib. Patients who test negative for the variants detected should be referred for (or "reflexed" to) routine biopsy with tissue testing for *EGFR* variants. Testing for T790M using plasma specimens is most appropriate for consideration in patients for whom a tumor biopsy cannot be obtained, as the efficacy of osimertinib has not been established in T790M plasma-positive, tissue-negative or unknown patient populations.

In August 2020, FoundationOne®‡ Liquid CDx (Foundation Medicine), a qualitative next generation sequencing-based diagnostic for circulating cell-free DNA in plasma, was approved by the FDA through the premarket approval process (P190032). The plasma test is approved as a companion diagnostic for selecting NSCLC patients who have *EGFR* exon 19 deletions and *EGFR* exon 21 L858R substitution variants, for treatment with gefitinib, osimertinib, or erlotinib. Patients who test

negative for the variants detected should be referred for (or "reflexed" to) routine biopsy with tissue testing for *EGFR* variants. Prior versions of FoundationOne Liquid CDx were previously marketed as FoundationACT and FoundationOne laboratory developed test (LDT).

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

Rationale/Source

Description

Genetic testing of circulating tumor DNA 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, the detection of "driver mutations" or resistance variants is important for selecting patients for targeted therapy.

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 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 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 U.S. 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 CDx, OncoBEAM or InVision tests, the evidence includes several studies assessing the diagnostic characteristics of liquid biopsy compared with tissue. 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 CDx, 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) 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 CDx, 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 CDx, OncoBEAM or InVision tests, the evidence includes studies assessing the diagnostic characteristics of liquid biopsy compared with tissue reference standard. 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 CDx, 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. 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 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 studies assessing the diagnostic characteristics of liquid biopsy. 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.4.2021) discuss the role of liquid biopsy in the management of non-small-cell lung cancer (NSCLC). The guidelines state that cell-free/circulating tumor DNA testing should not be used in lieu of histologic 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. It is noted that standards for analytical performance characteristics of cell-free tumor DNA have not been established, and in contrast to tissue-based testing, no guidelines exist regarding the recommended performance characteristics of this type of testing. Cell-free tumor DNA testing can identify alterations that are unrelated to a lesion of interest, for example, clonal hematopoiesis of indeterminate potential (CHIP). They also state that cfDNA testing can be used if the patient is not medically fit for tissue sampling or there is insufficient tissue for molecular analysis. If plasma-based analysis is used, follow-up with tissue-based analysis should be planned if plasma-based analysis is negative. The guidelines also state that at progression on erlotinib, afatinib, gefitinib or dacomitinib when testing for T790M, plasma-based testing should be considered and when plasma-based testing is negative, tissue-based testing is strongly recommended.

The guidelines additionally state that if there is insufficient tissue to allow testing for *EGFR*, *ALK*, *ROS1*, *BRAF*, *NTRK*, *MET*, and *RET*, repeat biopsy and/or plasma testing should be done. If not feasible, treatment should be guided by available results, and if mutation status is unknown, patients are treated as though they do not have driver oncogenes. Diagnosis of NSCLC should be guided by tissue. The guidelines do not endorse any specific commercially available test.

International Association for the Study of Lung Cancer

In 2018, the International Association for the Study of Lung Cancer 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 et al

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

In 2018, the National Institute for Health and Care Excellence issued an innovation briefing on plasma *EGFR* mutation tests for adults with locally advanced or metastatic NSCLC. The briefing reviewed 7 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 summarised 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."
- "Key uncertainties around the evidence or technology are that tests for identifying *EGFR*-TKI 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.

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

Policy # 00597
Original Effective Date: 03/21/2018
Current Effective Date: 04/12/2021

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
Ongoing			
NCT01930474	Analysis of Mechanism of Resistance to Chemotherapy by Sequencing of Plasma DNA	200	Dec 2018 (unknown)
NCT02894853[a]	Lung Cancer Early Molecular Assessment Trial	1297	Dec 2019 (unknown)
NCT02284633[a]	Use of a New Blood Test to Identify Response to Targeted Treatment in Patients With EGFR Mutated Lung Cancer	250	Jun 2020 (ongoing)
NCT02160366	Profile Related Evidence to Determine Individualized Cancer Therapy (PREDICT) Program in Advanced Cancer Patients	2000	Sep 2020 (recruiting)
NCT03791034[a]	Prospective Feasibility Study of Cell Free Circulating Tumor DNA for the Diagnosis and Treatment Monitoring in Early-stage Non-small Cell Lung Cancer	700	Dec 2020 (recruiting)
NCT03465241	Prospective, Open Clinical Study of Postoperative ctDNA Dynamic Monitoring and Its Role of Prognosis in Patients With Stage II to IIIA Non-	200	Dec 2021 (recruiting)

NCT No.	Trial Name	Planned Enrollment	Completion Date
	small Cell Lung Cancer (NSCLC) Using Secondary Gene Sequencing (NGS)		
NCT04238130	Evaluation Perioperative Dynamic Changes in ctDNA From Patients of Non-Small-Cell Lung Cancer Following Resection for Relapse Prediction (EVOLUTION)	200	Jun 2023 (recruiting)
NCT03553550	Role of Circulating Tumor DNA (ctDNA) From LIquid Biopsy in Early Stage NSCLC Resected Lung Tumor Investigation (LIBERTI)	500	Jun 2024 (recruiting)
NCT04178889	Second Primary Lung Cancer Cohort Study (SPORT)	850	Dec 2024 (recruiting)
Unpublished			
NCT02418234	Frequency and Abundance of T790M Mutation on Circulating Tumor DNA in Patients With Non-small Cell Lung Cancer After Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors Treatment Failure: a Perspective Observational Study	314	Nov 2017 (completed)
NCT03116633[a]	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	34	May 2018 (completed)
NCT02284633[a]	Blood sample monitoring of patients with EGFR mutated lung cancer	250	Dec 2018
NCT02906852[a]	Prospective Observational Study to Evaluate the Performance of Inivata Liquid Biopsy Analysis	264	Dec 2018 (completed)

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Compared With Standard Tissue Biopsy Analysis for Detection of Genomic Alterations in Patients With Advanced Non-small Cell Lung Cancer		

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Policy History

Original Effective Date: 03/21/2018
Current Effective Date: 04/12/2021

03/01/2018	Medical Policy Committee review
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.

Policy # 00597
Original Effective Date: 03/21/2018
Current Effective Date: 04/12/2021

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
03/04/2021	Medical Policy Committee review
03/10/2021	Medical Policy Implementation Committee approval. The *EGFR* TESTING **at diagnosis** eligible for coverage section was revised to track BCBSA, except it includes Patient Selection Criteria. The *EGFR* TESTING **at progression** eligible for coverage section has some differences from BCBSA, including having Patient Selection Criteria. Removed the *"Note"* after the *EGFR* TESTING coverage statements regarding the cobas test, since it is now stated in the FDA section. Added an OTHER GENES section that is eligible for coverage with Patient Selection Criteria. Added a *"Note"* regarding smaller panel testing and tests with 5 or more genes. Added a reference to see Policy Guidelines to the investigational statements for *ALK* TESTING, *BRAF* V600E TESTING, and *ROS1* TESTING to track BCBSA. Investigational statements added for *NTRK* TESTING, *MET* TESTING, *RET* TESTING, and *HER2* TESTING to track BCBSA. Removed the OTHER GENES investigational statement that included *MET* TESTING, *RET* TESTING, and *HER2* TESTING.
03/25/2021	Coding update

Next Scheduled Review Date: 03/2022

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2020 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0179U, 81235, 81445, 81455, 81479, 86152, 86153 Added code eff 1/1/2021: 0239U Added code eff 4/1/2021: 0242U
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or

diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.