**Preauthorization is not required.**

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
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<td>Individuals:  • With newly diagnosed non-small-cell lung cancer who are able to have tissue biopsy</td>
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<td>Interventions of interest are:  • Testing for biomarkers of EGFR tyrosine kinase inhibitor resistance using circulating tumor DNA</td>
<td>Comparators of interest are:  • Testing for biomarkers of EGFR tyrosine kinase inhibitor resistance using tissue biopsy</td>
<td>Relevant outcomes include:  • Overall survival  • Disease-specific survival  • Test accuracy  • Test validity</td>
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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.

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 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.

Policy

**EGFR Testing**

Except as noted below, analysis of two 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 investigational.

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

Analysis of two 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 investigational for patients with advanced NSCLC of squamous cell type.

**Policy Guidelines**

These tests are intended for use in patients with advanced NSCLC. 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 erlotinib, gefitinib or afatinib. The Food and Drug Administration (FDA) approval for the cobas® EGFR Mutation Test v2 states that patients who are negative for EGFR exon 19 deletions or L858R variant based on the plasma test should be reflexed to routine biopsy and testing using formalin-fixed paraffin-embedded tissue. However, the plasma test may also be appropriate for patients who do not have enough tissue for standard molecular testing using formalin-fixed paraffin-embedded
tissue, do not have a biopsy-amenable lesion, cannot undergo biopsy or have indeterminate histology (in whom an adenocarcinoma component cannot be excluded).

**Genetics Nomenclature Update**

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

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

Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Disease-associated change in the DNA sequence</td>
<td>Change in the DNA sequence</td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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

**Background**

**Predicative Biomarkers in Non-Small-Cell Lung Cancer**

Several predictive genetic biomarkers have been identified for NSCLC. Predictive biomarkers are particularly important because they can define response to specific treatments. Depending on which biomarkers are identified, patients may be eligible to receive the most effective treatment or to receive a treatment that is equally effective but with fewer adverse effects.

**Tyrosine Kinase Inhibitor-Sensitizing Variants**

**EGFR VARIANTS**

Specific EGFR variants confer sensitivity to treatment with TKIs, such as erlotinib, gefitinib, and afatinib; the most common variants are deletions in exons 19 and an exon 21 substitution variant. 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 around 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 effects than patients receiving cytotoxic chemotherapy.

**ALK, ROS1, AND KRAS VARIANTS**

Anaplastic lymphoma kinase (ALK) rearrangements also confer resistance to TKIs. Between 2% and 7% 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%. Finally, the most common predictive variant in North American populations is KRAS. Patients with KRAS variants have shorter survival than those without KRAS variants, and thus KRAS is a prognostic marker. It also predicts 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.

**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.

**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 circulating tumor DNA (ctDNA). Most ctDNA is derived from apoptotic and necrotic cells, either from the primary tumor, metastases, or circulating tumor cells. Unlike apoptosis, necrosis is considered a pathologic process, generating larger DNA fragments due to an incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origins. Circulating tumor DNA 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 that are up to 500 to 1000 times more sensitive than standard sequencing approaches (e.g., 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 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 (e.g., EGFR and ALK in NSCLC); such testing can also be untargeted and may include array comparative genomic hybridization, next-generation sequencing (NGS), 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.

Regulatory Status

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 (CLIA). 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 CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test. Clinical laboratories accredited through 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.

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.

CancerIntercept® (Pathway Genomics, San Diego, CA) is a 96-gene panel designed to detect variants in nine 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 FDA through the premarket approval process (P150047). 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 two 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 two of the plasma test did not include detection of T790M variants.

Related Protocols

Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)

Miscellaneous Genetic and Molecular Diagnostic Tests

Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


