EFFECTIVE DATE: 01|01|2024
POLICY LAST REVIEWED: 08|07|2024

OVERVIEW

Over half of patients with non-small-cell lung cancer (NSCLC) present with advanced and therefore incurable disease. Treatment in this setting has been with platinum-based chemotherapy. The identification of specific, targetable oncogenic "driver mutations" in a subset of NSCLCs has resulted in a reclassification of lung tumors to include molecular subtypes that may direct targeted therapy or immunotherapy depending on the presence of specific variants.

The following test(s) is addressed in this policy:

- InVisionFirst® (Inivata, Inc.)

MEDICAL CRITERIA

Medicare Advantage Plans and Commercial Products

InvisionFirst - Lung may be considered medically necessary for patients with advanced (Stage IIIB/IV) non-small cell lung cancer (NSCLC):

At diagnosis

- When results for EGFR (epidermal growth factor receptor) single nucleotide variants (SNVs) and insertions and deletions (indels); rearrangements in ALK and ROS1; and single nucleotide variants (SNVs) for BRAF are not available
  AND
- When tissue-based CGP is infeasible [i.e., quantity not sufficient (QNS) for tissue-based comprehensive genomic profiling (CGP) or invasive biopsy is medically contraindicated],

OR

At progression

- For patients progressing on or after chemotherapy or immunotherapy who have not been tested for EGFR (epidermal growth factor receptor) single nucleotide variants (SNVs) and insertions and deletions (indels); rearrangements in ALK and ROS1; and single nucleotide variants (SNVs) for BRAFs, and for whom tissue-based comprehensive genomic profiling (CGP) is infeasible;
  OR
- For patients progressing on EGFR tyrosine kinase inhibitors (TKIs).

PRIOR AUTHORIZATION

Prior authorization is required for Medicare Advantage Plans and recommended for Commercial Products.

Note: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any

element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

The following test may be considered medically necessary when the medical criteria above are met:

- InVisionFirst® (Inivata, Inc.)

Commercial Products

Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L. **§27-19-81** described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable laboratory benefits/coverage.

BACKGROUND

It is estimated that more than 222,500 new cases of lung cancer will be diagnosed in the United States (US) this year. This represents roughly 13% of all new cancer diagnoses and 26% of cancer deaths. At least 87% of lung cancer is NSCLC. The estimated 5-year survival rate for all NSCLC cancer patients is 17%, and only 4% for patients with advanced (stage IIIB/IV) disease.

The pathophysiological development of lung cancer is complicated, with several known genomic alterations found individually or in combination in many patients. These alterations may be due to toxic exposure or underlying genetic factors, and not all alterations have the same impact on disease development or prognosis. Some alterations appear to be integral to the transformation and ongoing growth of the tumor (driver alterations).

Among the best-studied genomic alterations are EGFR SNVs and indels and EML4-ALK rearrangements/fusions. EGFR-mutated NSCLC comprises up to 15% of all NSCLC patients in the US, with higher prevalence in certain ethnic groups (e.g., 40% in Asian Americans and 26% in Latin Americans). These mutations convey a more favorable prognosis and predict response to treatment with oral EGFR inhibitors such as erlotinib, gefitinib, osimertinib or afatinib. Rearrangements of ALK and EML4, or with other less common fusion partners, occur in approximately 4% of all NSCLC patients and predict response to treatment with oral ALK-targeted inhibitors such as crizotinib, ceritinib, or alectinib. Recently, dabrafenib in combination with trametinib has been approved for BRAF V600E positive metastatic NSCLC.

Genomic alterations in NSCLC vary by smoking history, ethnicity and age. Sequencing of tumor specimens in never-smokers demonstrates a higher mutation prevalence of EGFR than in smokers. Some non-smoking ethnic groups, such as Asian women, have a much higher mutation prevalence than their Caucasian counterparts. Prevalence of ALK rearrangements is also higher in non-smokers. In contrast, smokers have a higher prevalence of targetable alterations in the MET and BRAF genes.

Tumor Tissue Genotyping

Failure of oncologists to order genotyping, inadequate quantity or quality of tissue specimen, and the necessity for repeat invasive biopsies with their associated complications and costs are just a few issues that confound

tumor-tissue genotyping. Traditionally, tumor genotyping has been conducted by direct interrogation of tumor tissue obtained through invasive tissue sampling procedures. However, this diagnostic approach is limited by the availability of sufficient tumor tissue and the ability of patients to undergo invasive procedures.

In a recent study of more than 100 community-based oncologists, nearly one-third of NSCLC patients were not tested for EGFR or ALK mutations, and more than 75% were not tested for ROS1 fusions. Fewer than 10% of NSCLC patients were tested for all guideline-recommended alterations.11 These results are similar to a study in a single academic center where 58% of non-squamous NSCLC were tested for EGFR and 40% for ALK fusions, despite repeat invasive biopsies to obtain sufficient tissue for genomic testing in 13% of patients.12-13 Tissue availability was similarly limited in several recent series, some of which reported that more than 50% of NSCLC patients had insufficient or unobtainable material for tissue-based CGP.

Even when adequate tissue for next-generation sequencing (NGS) testing is available for testing, many specimens do not yield a complete result for a variety of reasons. Pre-analytical variables in tissue preservation are known to impact the quality and success of the NGS testing. Some of these variables include tissue fixation and processing variables, the volume of tissue (needle biopsy or resection specimen) available for testing, and the fraction of tumor cells within the specimen. Evaluating somatic mutations in formalin-fixed, paraffin-embedded (FFPE) tissue below 5% allele frequency is challenging due to these pre-analytical variables.

Within the InVision® clinical validation studies, only 33% of the prospectively recruited NSCLC patients had sufficient tissue for complete CGP. The remaining 67% either had no tissue for genomic analysis (31%) or had only enough tissue for some, but not all markers required (36%). This data underscores the marked limitation of available tissue specimens for tissue CGP testing, and emphasizes the importance of plasma-based CGP testing.

Even when successful, tissue acquisition procedures pose a significant morbidity and mortality risk to Medicare patients. In a recent report, 19% of all lung tissue acquisition procedures resulted in a serious adverse event.23 The National Lung Cancer Screening Trial reported 1-2% mortality rates in their cohorts.

Given that the majority of lung cancer diagnoses are based on needle biopsy, and that only 30%-60% of tissue specimens provide full informative results by CGP, plasma-based CGP (ctDNA testing) identifies genetic alternations for use of targeted therapies without delay in therapy, and without the risks and costs of repeat invasive biopsy. InVision® detects genomic targets linked to targeted drug therapies used at diagnosis and/or progression with response rates similar to those patients identified using tissue-based CGP and tissue-based CDx.

InVision® is a plasma-based circulating tumor DNA (ctDNA) NGS assay for detection of genomic alterations consisting of 36 commonly mutated genes. It utilizes technology first developed by the Cancer Research UK (CRUK)-funded Cambridge Institute at the University of Cambridge. The group was first to publish industry standard ctDNA methods, including hybrid capture and the highly sensitive tagged amplicon, deep sequencing or TAm-Seq™ technology. The InVision® assay utilizes an enhanced version of the TAm-Seq™ method developed by Inivata™ to detect clinically relevant cancer mutations of low allele fractions in cell free DNA (cfDNA) including substantial improvements and optimizations to maximize sensitivity and specificity of the assay.

Approximately 76% of patients with NSCLC are known to have a genomic alteration in tumor tissue for 1 of 8 genes (EGFR, ALK, ROS1, BRAF, MET, ERBB2, KRAS, STK11). These alterations constitute actionable driver alterations (EGFR, ALK, ROS1, BRAF, MET, ERBB2 - rule-ins) associated with FDA-approved therapies or are recognized as mutually exclusive for actionable changes (STK 11 and KRAS-rule-outs). These alterations have not been described as significant mutations contributing to clonal hematopoiesis of indeterminate potential.

CODING

Medicare Advantage Plans and Commercial Products

The following CPT code(s) may be medically necessary for Medicare Advantage Plans and Commercial Products when medical criteria above are met:

This code can be used for InVisionFirst:

0388U Oncology (non-small cell lung cancer), next-generation sequencing with identification of single nucleotide variants, copy number variants, insertions and deletions, and structural variants in 37 cancer-related genes, plasma, with report for alteration detection

RELATED POLICIES

Biomarker Testing Mandate
Genetic Testing Services
Proprietary Laboratory Analyses (PLA)

PUBLISHED

Provider Update, October 2024
Provider Update, July/November 2023

REFERENCES

1. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): Inivata™, InVisionFirst®, Liquid Biopsy for Patients with Lung Cancer (L37870)
2. Centers for Medicare and Medicaid Services (CMS). Local Coverage Article: Billing and Coding: Inivata™, InVisionFirst®, Liquid Biopsy for Patients with Lung Cancer (A56924)

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