DRAFT Medical Coverage Policy | Genomic Sequence Analysis Panels in the Treatment of Solid Organ Neoplasms

EFFECTIVE DATE: 01|01|2024
POLICY LAST UPDATED: 10|02|2023

OVERVIEW

The American Cancer Society estimates that over 220,000 new cases of lung cancer will be diagnosed in 2015, with over 85% of those cancers being classified as non-small cell lung cancer.

Despite improvements in mortality secondary to advances in screening and treatment over the last several decades, CRC is the second leading cause of cancer deaths in the US, with about 50,000 deaths per year, 8% of all cancer deaths.

The pace of discovery in the fields of immunology and cancer biology is rapidly accelerating as understanding the role of the immune system in tumor initiation, progression, and metastasis evolves. Momentum is shifting away from sequential analyte testing toward adoption of ever larger NGS panels, capable of evaluating for all classes of potentially actionable genomic alterations across hundreds of genes simultaneously. Factors include decreasing cost, proliferation of actionable biomarkers, need to detect smaller amounts of DNA variants, FDA approval of tumor-type agnostic predictive biomarkers, and most recently, so-called "pan-mutational signature" biomarkers that, almost by definition, require panels that include hundreds of genes, if not whole exome sequencing (WES). Pan-tumor biomarkers make CGP testing not just a more time, specimen, and cost-effective approach, but necessary from an analytic validity standpoint.

The following test(s), among other, non-brand specific CPT codes, are addressed in this policy:

- MSK-IMPACT [Integrated Mutation Profiling of Actionable Cancer Targets] (Memorial Sloan Kettering Cancer Center) (CPT 0048U)
- PGDx elio tissue complete, Personal Genome Diagnostics, Inc. (CPT 0250U)

MEDICAL CRITERIA

Medicare Advantage Plans and Commercial Products

The services addressed in this policy may be considered medically when the following criteria are met:

Non-Small Cell Lung Cancer (NSCLC)

For the evaluation of tumor tissue in the following clinical circumstances:

- Newly diagnosed patients with advanced (stage IIIB or IV) NSCLC, who are not treatable by resection or radiation with curative intent, and who are suitable candidates for therapy at the time of testing.
- Previously diagnosed patients with advanced (stage IIIB or IV) NSCLC, who have not responded to at least one systemic therapy, or who have progressed following resection. The patient must be a candidate for treatment at the time of the testing.
- Previously diagnosed patients with advanced (stage IIIB or IV) NSCLC, who have been resistant to at least one targeted therapy, are able to undergo tumor tissue biopsy for testing, and who are suitable candidates for additional treatment at the time of testing.

Metastatic Colorectal Cancer (mCRC)

When the test is performed in a CLIA-certified laboratory qualified to perform high complexity testing, ordered by a treating physician, and the patient has:

- metastatic CRC; and
- is a candidate for intensive chemotherapy with an anti-EGFR biologic agent; and
- has not had prior RAS/BRAF testing (except after initiation of anti-EGFR therapy with evidence of acquired resistance).

Next-Generation Sequence (NGS) Comprehensive Genomic Profile (CGP) Testing

CGP NGS testing for patients with advanced cancer is reasonable and necessary only when performed in a CLIA-certified laboratory, when ordered by a treating physician, and when the patient has:

- either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and
- not been previously tested with a CGP for the same cancer genetic content; and
- decided to seek further cancer treatment (e.g., therapeutic chemotherapy); *and*
- the test performed must be able to detect at least the minimum genes and genomic positions required for the identification of clinically supported, FDA-approved therapies.
- The genes and genomic positions required are listed in Category 1 or 2A of the most current version of the National Comprehensive Cancer Network (NCCN) Biomarkers Compendium (2)
- Testing assays must be FDA approved/cleared, or if a laboratory developed test (LDT), have a published, peer-reviewed study supporting analytic validity, or certification by a third-party consistent with the New York State Department of Health's Clinical Laboratory Evaluation Program (CLEP) review standards.

PRIOR AUTHORIZATION

Medicare Advantage Plans and Commercial Products

Prior authorization is required for Medicare Advantage Plans and recommended for Commercial Products and is obtained via the online portal for participating providers.

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

Genomic sequence analysis panels in the treatment of solid organ neoplasms may be considered medically necessary when the medical criteria above are met.

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

Non-Small Cell Lung Cancer (NSCLC)

Lung cancer represents approximately 13% of all new cancer diagnoses, and approximately 27% of cancer deaths. The estimated 5yr survival rate for all lung cancer patients is 17% and is only 4% for patients with metastatic disease. Most lung cancers are epithelial in origin, with squamous cell carcinomas, adenocarcinomas, and small cell carcinomas being the predominant histologic types. The first two, squamous and adenocarcinomas, have been traditionally grouped as non-small cell lung cancer (NSCLC). Surgery remains the cornerstone of treatment for early stage NSCLC of either type, however treatment of advanced stage disease is based primarily on drugs. Distinctive response patterns to specific therapeutic drugs have

been demonstrated over the past 12years, necessitating the distinction between squamous cell and adenocarcinoma morphology. Consequently, the most recent WHO guidelines advocate sub-classification of all NSCLC in to a more specific subtype whenever possible. This is typically accomplished by histologic evaluation with support from specific immunohistochemical studies, which are particularly useful in the evaluation of small biopsies.

Adenocarcinomas account for approximately 40% of all lung cancers, and are the most common lung cancer in never- or light smokers. Adenocarcinomas are characterized by glandular differentiation, mucin production, or pneumocyte marker expression. Certain genomic alterations are more commonly found in lung adenocarcinomas (when compared to squamous or small cell carcinomas) and clinical laboratory testing to identify these alterations is important in two respects: First, some mutations are now recognized as "driver mutations," which are essential for tumor cell survival. Inhibition of these mutated proteins results in tumor cell death, making them attractive therapeutic targets. While not all driver mutations have specific therapies at this time, an important corollary of this concept is that with rare exception, such driver mutations are mutually exclusive, i.e. the identification of one driver mutation in a tumor effectively makes the likelihood that another driver mutation is present extremely unlikely.

The second reason clinical laboratory testing for specific driver mutations in lung adenocarcinomas is important is the association of specific genomic alterations with response to specific drugs. Different driver mutations respond to different targeted therapies, and only genetic testing can clearly identify which mutation is present and, therefore, which treatment should be administered. While some of the genetic alterations that affect response to targeted inhibitors are found in a higher proportion of adenocarcinomas from patients with certain clinical risk factors (i.e., low to no history of tobacco exposure, female gender, young age, Asian ethnicity) , these clinical associations are not sufficiently predictive of mutation status to appropriately determine therapy without genetic testing. Accordingly, professional practice guidelines from CAP-IASLC-AMP, WHO, and NCCN all advise against using smoking history, or other clinical risk factors, to exclude testing patients for specific genomic alterations.

NCCN Guidelines (v 7.2015) for Non-Small Cell Lung Cancer recommend testing all non-squamous NSCLCs (i.e. adenocarcinomas, large cell carcinomas, and NSCLC not otherwise specified) for specific alterations in EGFR and ALK and recommend consideration of such testing in tumors with mixed squamous and adeno histology, and in the rare squamous cell carcinomas in never smokers. The NCCN NSCLC Panel "strongly endorses broader molecular profiling to identify rare driver mutations using multiplex/NGS to ensure that patients receive the most appropriate treatment".

In total, there are over 40 single nucleotide or small insertion/deletion variants occurring at numerous specific loci in ten genes. These variants represent potential therapeutic targets and, as therapeutic agents aimed at these targets are proven safe and effective and meet Medicare coverage guidelines, additional genes may be added to National Comprehensive Cancer Network (NCCN) Category 1 or 2A Recommended Therapeutic Options. In addition, gene fusions can involve five different genes, and amplification is the significant recognized alteration in at least one gene.

Metastatic Colorectal Cancer (mCRC)

Approximately 50-60% of patients with CRC develop metastases (usually metachronous, but synchronous in 20-34%), with 80-90% unresectable metastatic liver disease. Twenty percent present with metastatic disease. Today, the median overall survival (OS) for patients with mCRC is approximately 30 months, more than double that of 20 years ago.

The level of understanding of the molecular events underlying CRC is far greater than for other common solid tumors. Sporadic disease, in which there is no family history, accounts for approximately 70% of all CRCs. Specific germline mutations are responsible for the inherited CRC syndromes, while a stepwise accumulation of somatic mutations is thought to underlie most sporadic cases.

The genetic factors with strong evidence for clinical decision-making (both prognostic and predictive of chemotherapy efficacy) are BRAF and RAS mutations along with mismatch repair deficiency (MMR) status. Guidelines from NCCN, the European Society for Medical Oncology (ESMO), as well as a combined guideline from the American Society for Clinical Pathology (ASCP), College of American Pathologists (CAP), Association for Molecular Pathology (AMP), and ASCO consider certain molecular genetic biomarkers necessary for diagnosis and management of mCRC. Testing is not necessary for mCRC patients being considered for palliative or hospice care only. Re-testing may be indicated after initiation of anti-EGFR treatment if resistance develops.

Next-Generation Sequence (NGS) Comprehensive Genomic Profile (CGP) Testing

The advent of immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1) proteins has recently emerged as a pillar of cancer care. ICI immunotherapy, however, can induce unique immune-related side effects and, in a subset of patients, trigger accelerated disease progression, termed hyper progression. Given this variability, determining a proper biomarker to select patients for ICI therapy has become increasingly important. In 2017, the FDA approved the ICI pembrolizumab(anti-PD-1) for treatment of unresectable or metastatic tumors from any tumor histology that exhibits microsatellite instability (MSI)/mismatch repair deficiency (dMMR), resulting in a hypermutator phenotype, marking the first tumor-type agnostic predictive biomarker approval. While traditionally measured using conventional, non-NGS methods (IHI, PCR), NGS CGP may detect a larger number of microsatellites with improved detection of MSI-H across different tumor types, as data have demonstrated that the variation in length of microsatellites is tissue specific.

Total mutational burden (TMB) has become of increasing interest as another potential ICI immunotherapy biomarker. TMB refers to the total number of nonsynonymous mutations per megabase in the exon coding region of the gene being evaluated in the tumor cell genome. The basis for this approach is the idea that high TMB (TMB-H) leads to more antigenic peptides and enhanced immunogenicity. TMB is theoretically a more direct measure of tumor rejection potential than MSI assays, which detect the presence of microsatellite alterations and do not quantify the mutations themselves. In fact, MSI-H may be associated with immunotherapy response largely because it results in high TMB. The most compelling data on the predictive capacity of TMB in the response to ICI immunotherapy come from the multicenter open-label phase II KEYNOTE-158 study, which established a link between TMB-H status (as determined by the FoundationOne CDx assay) and overall response rate with pembrolizumab. In June 2020, largely based on these results, the FDA granted accelerated approval to pembrolizumab for the treatment of patients with any unresectable or metastatic TMB-H [≥ 10 mutations/megabase (mut/Mb)] solid tumor by an FDA approved assay, who have progressed on prior therapy and have no alternative treatment options.

Gene fusion is another emerging area exerting pressure for NGS CGP testing, beginning with neutrotrophic tyrosine receptor kinase (NTRK)fusion-positive cancers for TRK inhibitor therapy. Two of these agents (larotrectinib, entrectinib) are approved for treatment of TRK fusion-positive refractory solid tumors, regardless of the site of disease origin, "without a known acquired resistance mutation, that are either metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment". The presence of a TRK fusion defines a new tissue-agnostic diagnostic category for solid tumors. Given the rarity of NTRK gene fusions in most cancers, assays that evaluate exclusively for the presence of NTRK gene fusions are impractical in most cases. NGS CGP testing allows the assessment of NTRK1/2/3 gene fusions in conjunction with other tumor-agnostic biomarkers as well as any relevant tumor-specific biomarkers. Although NGS sequencing of either DNA or RNA can detect NTRK gene fusions, multiple technical considerations make RNA-based methods superior.

The Association for Molecular Pathology (AMP) and the College of American Pathologists (CAP) published guidelines for validating NGS-based oncology panels and bioinformatics pipelines, and with the American

Society of Clinical Oncology (ASCO), guidelines for interpreting somatic variants. Other societal guidelines suggest the use of NGS over other methods for lung cancer, colorectal cancer, and melanoma, thyroid, and ovarian cancers, among others.

Nevertheless, the analytic and clinical validation of pan-tumor markers, the only absolute NGS CGP raison d'etre, remain problematic. Current evidence fails to support the use of TMB-H as a biomarker for ICI treatment in all tumor types, particularly with a universal one-size fits all cut-off of 10 mut/Mb. "Future studies should focus both on improving cancer type-specific assessment of TMB from targeted sequencing and cancer type-specific activity of ICIs in TMB-H tumors before broad clinical implementation". In fact, limitations to precision medicine's impact, involving the widespread assumption of clinical utility for wholesale genetic testing, is coming under new scrutiny. Others claim limitations are related to insufficient implementation.

Pan-tumor biomarker considerations aside, NGS CGP testing in advanced cancer is arguably increasingly medically necessary from both a time-effectiveness and specimen-sparing perspective. NGS CGP testing may especially benefit the 25% of patients with rare cancer types, those with no effective alternative treatment options, and underserved minority populations with less access to tumor molecular profiling or off-label therapies.

CODING

The following CPT codes may be considered medically necessary for Medicare Advantage Plans and Commercial Products when the medical criteria above are met:

81445 Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis

81449 Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis

81455 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis

81456 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis

This code can be used for MSK-IMPACT™ (Integrated Mutation Profiling of Actionable Cancer Targets):

0048U Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s)

This code can be used for PGDx elio tissue complete:

0250U Oncology (solid organ neoplasm), targeted genomic sequence DNA analysis of 505 genes, interrogation for somatic alterations (SNVs [single nucleotide variant], small insertions and deletions, one amplification, and four translocations), microsatellite instability and tumor-mutation burden

RELATED POLICIES

Biomarker Testing Mandate
Genetic Testing Services
Proprietary Laboratory Analysis (PLA) and Multianalyte Assays with Algorithmic Analyses (MAAA)

PUBLISHED

Provider Update, November 2023
Provider Update, June 2023

REFERENCES

1. Centers for Medicare and Medicaid Services. Local Covered Determination (LCD): Genomic Sequence Analysis in the Treatment of Solid Organ Neoplasms (L37810)
2. Centers for Medicare and Medicaid Services. Local Coverage Article: Billing and Coding: Genomic Sequence Analysis in the Treatment of Solid Organ Neoplasms (A56867)