DRAFT Medical Coverage Policy | Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies

EFFECTIVE DATE: 04|01|2023
POLICY LAST UPDATED: 12|27|2022

OVERVIEW

Comprehensive genomic profiling offers the potential to evaluate a large number of genetic markers at a single time to identify cancer treatments that target specific biologic pathways. This policy focuses on "expanded" panels, which are defined as molecular panels that test a wide variety of genetic markers in cancers without regard for whether specific targeted treatment has demonstrated benefit. This approach may result in a treatment different from that usually selected for a patient based on the type and stage of cancer.

The following tests are addressed in this policy:

- Oncomine™ Dx Target Test (Life Technologies Corp) (CPT 0022U)
- FoundationOne CDx™ (F1CDx) (Foundation Medicine) (CPT 0037U)
- MSK-IMPACT [Integrated Mutation Profiling of Actionable Cancer Targets] (Memorial Sloan Kettering Cancer Center) (CPT 0048U)
- Praxis (TM) Extended RAS Panel (Illumina) (CPT 0111U)
- myChoice® CDx (Myriad) (CPT 0172U)
- FoundationOne® Liquid CDx (Foundation Medicine) (CPT 0239U)
- Guardant360® CDx (Guardant Health) (CPT 0242U)

MEDICAL CRITERIA

Medicare Advantage Plans and Commercial Products

The following tests will be covered when performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, ordered by a treating physician and the applicable medical criteria are met:

- **Oncomine™ Dx Target Test**
- **FoundationOne CDx™ (F1CDx)**
- **Praxis (TM) Extended RAS Panel**
- **myChoice® CDx**
- **FoundationOne® Liquid CDx**
- **Guardant360® CDx**

Somatic (Acquired) Cancer:

1. Patient has:
   A. either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and
   B. not been previously tested with the same test using NGS for the same cancer genetic content, and
   C. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

AND

2. The diagnostic laboratory test using next generation sequencing (NGS) must have:
   A. Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,
   B. an FDA-approved or -cleared indication for use in that patient's cancer; and,

C. results provided to the treating physician for management of the patient using a report template to specify treatment options.

OR

Germline (Inherited) Cancer:

1. Patient has:
   A. ovarian or breast cancer; and,
   B. a clinical indication for germline (inherited) testing for hereditary breast or ovarian cancer; and,
   C. a risk factor for germline (inherited) breast or ovarian cancer; and
   D. not been previously tested with the same germline test using NGS for the same germline genetic content.

AND

2. The diagnostic laboratory test using NGS must have all of the following:
   A. FDA-approval or clearance; and,
   B. results provided to the treating physician for management of the patient using a report template to specify treatment options.

The following test will be covered when the applicable medical criteria are met:

- **MSK-IMPACT**

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).

PRIOR AUTHORIZATION

Medicare Advantage Plans and Commercial Products

Prior authorization is required for Medicare Advantage Plans and recommended for Commercial Products for the following tests:

- Oncomine™ Dx Target Test (CPT 0022U)
- FoundationOne CDx™ (F1CDx) (CPT 0037U)
- MSK-IMPACT [Integrated Mutation Profiling of Actionable Cancer Targets] (CPT 0048U)
- Praxis (TM) Extended RAS Panel CPT 0111U)
- myChoice® CDx (CPT 0172U)
- FoundationOne® Liquid CDx (CPT 0239U)
- Guardant360® CDx (CPT 0242U)

Prior authorization is required for Medicare Advantage Plans and recommended for Commercial Products and is obtained via the online tool for participating providers. See the Related Policies section.

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

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

- Oncomine™ Dx Target Test
- FoundationOne CDx™ (F1CDx)
- MSK-IMPACT
- Praxis (TM) Extended RAS Panel
- myChoice® CDx
- FoundationOne® Liquid CDx
- Guardant360® CDx

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable laboratory and not medically necessary benefits/coverage.

BACKGROUND

TRADITIONAL THERAPEUTIC APPROACHES TO CANCER

Tumor location, grade, stage, and the patient's underlying physical condition have traditionally been used in clinical oncology to determine the therapeutic approach to a specific cancer, which could include surgical resection, ionizing radiation, systemic chemotherapy, or combinations thereof. Currently, some 100 different types are broadly categorized according to the tissue, organ, or body compartment in which they arise. Most treatment approaches in clinical care were developed and evaluated in studies that recruited subjects and categorized results based on this traditional classification scheme.

This traditional approach to cancer treatment does not reflect the wide diversity of cancer at the molecular level. While treatment by organ type, stage, and grade may demonstrate statistically significant therapeutic efficacy overall, only a subgroup of patients may derive clinically significant benefit. It is unusual for a cancer treatment to be effective for all patients treated in a traditional clinical trial. Spear et al (2001) analyzed the efficacy of major drugs used to treat several important diseases. They reported heterogeneity of therapeutic responses, noting a low rate of 25% for cancer chemotherapeutics, with response rates for most drugs falling in the range of 50% to 75%. The low rate for cancer treatments is indicative of the need for better identification of characteristics associated with treatment response and better targeting of treatment to have higher rates of therapeutic responses.

TARGETED CANCER THERAPY

Much of the variability in clinical response may result from genetic variations. Within each broad type of cancer, there may be a large amount of variability in the genetic underpinnings of the cancer. Targeted cancer treatment refers to the identification of genetic abnormalities present in the cancer of a particular patient, and the use of drugs that target the specific genetic abnormality. The use of genetic markers allows cancers to be further classified as "pathways" defined at the molecular level. An expanding number of genetic markers have been identified. These may be categorized into 3 classes, (1) genetic markers that have a direct impact on care for the specific cancer of interest, (2) genetic markers that may be biologically important but are not currently actionable, and (3) genetic markers of uncertain importance.

A smaller number of individual genetic markers fall into the first category (ie, have established utility for a particular cancer type). The utility of these markers has been demonstrated by randomized controlled trials that select patients with the marker and report significant improvements in outcomes with targeted therapy compared with standard therapy. Testing for these individual variants with established utility is not covered in this evidence review. In some cases, limited panels may be offered that are specific to one type of cancer (eg,

a panel of several markers for NSCLC). This review is also not intended to address the use of cancer-specific panels that include a few variants. Rather, this review addresses expanded panels that test for many potential variants that do not have established efficacy for the specific cancer in question.

When advanced cancers are tested with expanded molecular panels, most patients are found to have at least one potentially pathogenic variant. The number of variants varies widely by types of cancers, different variants included in testing, and different testing methods among the available studies. In a study by Schwaederle et al (2015), 439 patients with diverse cancers were tested with a 236-gene panel. A total of 1813 molecular alterations were identified, and almost all patients (420/439 [96%]) had at least 1 molecular alteration. The median number of alterations per patient was 3, and 85% of patients (372/439) had 2 or more alterations. The most common alterations were in the ~~genes~~ TP53 (44%), KRAS (16%), and PIK3CA (12%) genes.

Some evidence is available on the generalizability of targeted treatment based on a specific variant among cancers that originate from different organs. There are several examples of variant-directed treatment that is effective in one type of cancer but ineffective in another. For example, targeted therapy for epidermal growth factor receptor variants have been successful in non-small-cell lung cancer but not in trials of other cancer types. Treatment with tyrosine kinase inhibitors based on variant testing has been effective for renal cell carcinoma but has not demonstrated effectiveness for other cancer types tested. "Basket" studies, in which tumors of various histologic types that share a common genetic variant are treated with a targeted agent, also have been performed. One such study was published in 2015 by Hyman et al. In this study, 122 patients with BRAF V600 variants in nonmelanoma cancers were treated with vemurafenib. The authors reported that there appeared to be antitumor activity for some but not all cancers, with the most promising results seen for non-small-cell lung cancer, Erdheim-Chester disease, and Langerhans cell histiocytosis.

<u>NGS for Somatic (Acquired) and Germline (Inherited) Cancer</u>
Clinical laboratory diagnostic tests can include tests that, for example, predict the risk associated with one or more genetic variations. In addition, *in vitro* companion diagnostic laboratory tests provide a report of test results of genetic variations and are essential for the safe and effective use of a corresponding therapeutic product. Next Generation Sequencing (NGS) is one technique that can measure one or more genetic variations as a laboratory diagnostic test, such as when used as a companion *in vitro* diagnostic test.

Patients with cancer can have recurrent, relapsed, refractory, metastatic, and/or advanced stages III or IV of cancer. Clinical studies show that genetic variations in a patient's cancer can, in concert with clinical factors, predict how each individual responds to specific treatments.

In application, a report of results of a diagnostic laboratory test using NGS (i.e., information on the cancer's genetic variations) can contribute to predicting a patient's response to a given drug: good, bad, or none at all. Applications of NGS to predict a patient's response to treatment occurs ideally prior to initiation of such treatment.

The Centers for Medicare & Medicaid Services (CMS) has determined that Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally, when performed in a CLIA-certified laboratory, when ordered by a treating physician and when the criteria above are met.

The evidence for cancers of the breast and ovary suggests that the use of NGS can identify germline mutations which will lead to better treatment and health outcomes for patients with inherited cancers of the breast and ovary. The evidence for cancer of the breast and ovary indicates that NGS as a diagnostic tool can identify the germline mutations most likely to be targeted by a treatment regimen tailored to certain germline mutation. It is likely that the identification of such tailored treatment regimens in the clinical management of inherited cancers of the breast and ovary diagnosed by NGS will improve health outcomes of Medicare beneficiaries. Use of NGS as a diagnostic test has utility for patients in the discovery of new targeted

therapies for inherited cancers and in the physician management of inherited cancers of the breast and ovary in Medicare beneficiaries.

Non-Small Cell Lung Cancer (NSCLC)
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)
The genetic factors with strong evidence for clinical decision-making (both prognostic and predictive of chemotherapy efficacy) are BRAF and RAS mutations along with 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.

CODING

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

This code can be used for Oncomine™ Dx Target Test:

0022U Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider

This code can be used for FoundationOne CDx™ (F1CDx):

0037U Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden

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 Praxis(™) Extended RAS Panel:

0111U Oncology (colon cancer), targeted KRAS (codons 12, 13, and 61) and NRAS (codons 12, 13, and 61) gene analysis utilizing formalin-fixed paraffin-embedded tissue

This code can be used for myChoice® CDx:

0172U Oncology (solid tumor as indicated by the label), somatic mutation analysis of BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) and analysis of homologous recombination deficiency pathways, DNA, formalin-fixed paraffin-embedded tissue, algorithm quantifying tumor genomic instability score

This code can be used for FoundationOne® Liquid CDx:

0239U Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations

This code can be used for Guardant360® CDx:

0242U Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements (New Code Effective 4/1/2021. For Dates of Service prior to 4/1/2021, an Unlisted CPT code must be used.)

RELATED POLICIES

Medicare Advantage Plans National and Local Coverage Determinations
Proprietary Laboratory Analyses (PLA)

PUBLISHED

Provider Update, February 2023
Provider Update, June 2021
Provider Update, February 2021
Provider Update, July 2019
Provider Update, June 2018

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