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

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

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:

- HeproDX (GoPath Laboratories) (CPT 0006M)
- OncoTarget/OncoTreat (Darwin Health) (CPT 0019U)
- Oncomine™ Dx Target Test (Life Technologies Corp) (CPT 0022U)
- EXaCT-1 Whole Exome Testing (Weill Cornell Medicine Clinical Genomics Lab) (CPT 0036U)
- FoundationOne CDx™ (F1CDx) (Foundation Medicine) (CPT 0037U)
- Praxis (TM) Extended RAS Panel (Illumina) (CPT 0111U)
- myChoice® CDx (Myriad) (CPT 0172U)
- LC-MS/MS Targeted Proteomic Assay (OncoOmicDx Laboratory) (CPT 0174U)
- MI Cancer Seek™ NGS Analysis (Caris MPI d/b/a Caris Life Sciences) (CPT 0211U)
- FoundationOne® Liquid CDx (Foundation Medicine) (CPT 0239U)
- Guardant360® CDx (Guardant Health) (CPT 0242U)

MEDICAL CRITERIA

Medicare Advantage Plans and Commercial Products

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

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

<u>Somatic (Acquired) Cancer:</u>

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.

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
- FoundationOne CDx™ (F1CDx)
- Praxis (TM) Extended RAS Panel
- myChoice® CDx
- FoundationOne® Liquid CDx
- Guardant360® CDx

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)
- Praxis (TM) Extended RAS Panel
- myChoice® CDx
- FoundationOne® Liquid CDx
- Guardant360® CDx

Medicare Advantage Plans

The following tests are not covered as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome:

- HeproDx
- OncoTarget/OncoTreat
- EXaCT-1 Whole Exome Testing
- LC-MS/MS Targeted Proteomic Assay
- MI Cancer Seek™ NGS Analysis

Commercial Products
The following tests are not medically necessary as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome:

- HeproDx
- OncoTarget/OncoTreat
- EXaCT-1 Whole Exome Testing
- LC-MS/MS Targeted Proteomic Assay
- MI Cancer Seek™ NGS Analysis

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 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.

For individuals who have advanced cancer that is being considered for targeted therapy who receive comprehensive genomic profiling of tumor tissue, using some of the tests referenced in this policy, the evidence includes a randomized controlled trial, nonrandomized trials, and systematic reviews of these studies. Relevant outcomes are overall survival, disease-specific survival, test validity, and quality of life. A large number of variants and many types of cancer preclude determination of the clinical validity of the panels as a whole, and clinical utility has not been demonstrated for the use of expanded molecular panels to direct targeted cancer treatment. The 1 published randomized controlled trial (SHIVA trial) that used an expanded panel reported no difference in progression-free survival compared with standard treatment. Additional randomized and nonrandomized trials for drug development, along with systematic reviews of these trials, have compared outcomes in patients who received molecularly targeted treatment with patients who did not. Generally, trials in which therapy was targeted to a gene variant resulted in improved response rates, progression-free survival, and overall survival compared to patients in trials who did not receive targeted therapy. A major limitation in the relevance of these studies for comprehensive genomic profiling is that treatment in these trials was guided both by the tissue source and the molecular target for drug development, rather than being matched solely by the molecular marker (ie, basket trials). As a result, these types of studies do not provide evidence of the benefit of broad molecular profiling compared to more limited genetic assessments based on known tumor-specific variants. Basket trials that randomize patients with various tumor types to a strategy of comprehensive genomic profiling followed by targeted treatment are needed, and several are ongoing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 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.)

The following CPT codes are not covered for Medicare Advantage Plans and not medically necessary for Commercial Products:

This code can be used for Hepro Dx:

0006M Oncology (hepatic), mRNA expression levels of 161 genes, utilizing fresh hepatocellular carcinoma tumor tissue, with alpha-fetoprotein level, algorithm reported as a risk classifier

This code can be used for OncoTarget/OncoTreat:

0019U Oncology, RNA, gene expression by whole transcriptome sequencing, formalin-fixed paraffin embedded tissue or fresh frozen tissue, predictive algorithm reported as potential targets for therapeutic agents

This code can be used for EXaCT-1 Whole Exome Testing:

0036U Exome (ie, somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses

This code can be used for LC-MS/MS Targeted Proteomic Assay:

0174U Oncology (solid tumor), mass spectrometric 30 protein targets, formalin-fixed paraffin-embedded tissue, prognostic and predictive algorithm reported as likely, unlikely, or uncertain benefit of 39 chemotherapy and targeted therapeutic oncology agents

This code can be used for MI Cancer Seek™ NGS Analysis:

0211U Oncology (pan-tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded tissue, interpretative report for single nucleotide variants, copy number alterations, tumor mutational burden, and microsatellite instability, with therapy association

RELATED POLICIES

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

PUBLISHED

Provider Update, November 2023
Provider Update, June 2023
Provider Update, February 2023
Provider Update, June 2021
Provider Update, February 2021
~~Provider Update, July 2019~~

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