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

EFFECTIVE DATE: 07|01|2019
POLICY LAST UPDATED: 12|13|2020

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)
- FoundationOne CDx™ (F1CDx) (Foundation Medicine)
- MSK-IMPACT [Integrated Mutation Profiling of Actionable Cancer Targets] (Memorial Sloan Kettering Cancer Center)
- Praxis (TM) Extended RAS Panel (Illumina)
- myChoice® CDx (Myriad)

MEDICAL CRITERIA

BlueCHiP for Medicare

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 – 0022U**
- **FoundationOne CDx™ (F1CDx) – 0037U**
- **Praxis (TM) Extended RAS Panel – 0111U**
- **myChoice® CDx – 0172U**

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.

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 – 0048U**

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).

Commercial Products

Not applicable

PRIOR AUTHORIZATION

BlueCHiP for Medicare

Prior authorization is required for BlueCHiP for Medicare for the following tests:

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

Commercial Products

Not applicable

BlueCHiP for Medicare and Commercial Products
There is no specific CPT coding for some of the services referenced in this policy. Therefore, an Unlisted CPT code should be used (see Coding Section for details). All Unlisted genetic testing CPT codes require prior authorization to determine what service is being rendered and if the service is covered or not medically necessary. See the Related Policies section.

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

POLICY STATEMENT

BlueCHiP for Medicare
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

Commercial Products
The following tests are not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes:

- Oncomine™ Dx Target Test
- FoundationOne CDx™ (F1CDx)
- MSK-IMPACT
- Praxis (TM) Extended RAS Panel
- myChoice® 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
Commercial Products
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. Dienstmann et al (2013) categorized these findings into 3 classes, which are listed following: (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.

The following is a list of commercially available expanded cancer molecular panels.

Please note: this is NOT an all-inclusive list.

Test	**Manufacturer**
FoundationOne®CDx test (F1CDx)	Foundation Medicine
FoundationOne®CDx Heme test	Foundation Medicine

OnkoMatch™	GenPath Diagnostics
GeneTrails® Solid Tumor Panel	Knight Diagnostic Labs
Tumor profiling service	Caris Molecular Intelligence through Caris Life Sciences
SmartGenomics™	PathGroup
Paradigm Cancer Diagnostic (PcDx™) Panel	Paradigm
Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT™)	Memorial Sloan Kettering Cancer Center
TruSeq® Amplicon Panel	
TruSight™ Oncology	Illumina
Ion AmpliSeq™ Comprehensive Cancer Panel	
Ion AmpliSeq™ Cancer Hotspot Panel v2	Thermo Fisher Scientific
OmniSeq Comprehensive	OmniSeq
Oncomine DX Target Test	Thermo Fisher Scientific

In 2017, FoundationOne CDx (Foundation Medicine) received premarket approval by the U.S. Food and Drug Administration (FDA) (P170019) as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 2. "Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms."

In 2017, the Oncomine DX Target Test (Life Technologies Corp) received premarket approval by the FDA (P160045) to aid in selecting non-small cell lung cancer patients for treatment with approved targeted therapies.

MSK-IMPACT (Memorial Sloan Kettering) received de novo marketing clearance in 2017 (DEN170058). "The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and microsatellite instability for use by qualified health care professionals in accordance with professional guidelines and is not conclusive or prescriptive for labeled use of any specific therapeutic product."

For individuals who have advanced cancer that is being considered for targeted therapy who receive comprehensive genomic profiling of tumor tissue, 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 the effects of the technology on health outcomes.

BlueCHiP for Medicare

NGS for Somatic (Acquired) and Germline (Inherited) Cancer

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 require prior authorization for BlueCHiP for Medicare and are not medically necessary for Commercial Products:

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 (TM) 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

Most available expanded cancer molecular panels have not been assigned CPT codes and should be filed with an appropriate genetic testing Unlisted CPT code.

RELATED POLICIES

BlueCHiP for Medicare National and Local Coverage Determinations
Genetic Testing Services
Proprietary Laboratory Analyses (PLA)

PUBLISHED

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

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