

EFFECTIVE DATE: 07|01|2019

POLICY LAST UPDATED: 05|07|2019

OVERVIEW

Genetic panel testing offers the potential to evaluate a large number of genetic markers at a single time to identify cancer treatments that target specific biologic pathways. Some individual markers have established benefit in certain types of cancers; they are not addressed in this evidence review. Rather, this review 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.

MEDICAL CRITERIA

BlueCHiP for Medicare

Next Generation Sequencing, using FoundationOne CDx™ (F1CDx), may be considered medically necessary as a diagnostic laboratory test when performed in a CLIA-certified laboratory, ordered by a treating physician, and all of the following requirements are met:

1. Patient has:
 - a. Either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and
 - b. Either not been previously tested using the same NGS test for the same primary diagnosis of cancer, or repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physician; and
 - c. Decided to seek further cancer treatment (e.g. therapeutic chemotherapy).
2. The diagnostic laboratory test using 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.

Genomic Sequential Analysis Panel, using MSK-IMPACT™ will be considered reasonable and necessary in the following circumstances:

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.

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

Expanded molecular panel testing of cancers using next generation sequencing, specifically FoundationOne CDx™ (F1CDx), to identify targeted therapies for treatment may be considered medically necessary when the criteria above has been met.

Genomic Sequential Analysis Panel using MSK-IMPACT™ may be considered reasonable and necessary when the criteria above has been met.

Commercial Products

The use of expanded cancer molecular panels for selecting targeted cancer treatment, including FoundationOne CDx™ (F1CDx) and MSK-IMPACT™ is considered not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes.

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. 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 available expanded cancer molecular panels.

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

Test	Manufacturer
FoundationOne® test	Foundation Medicine
FoundationOne® 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
Guardant360 panel {GuardantHealth, 2015 #399}	GuardantHealth
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	
Illumina TruSight™ Tumor	Illumina
Ion AmpliSeq™ Comprehensive Cancer Panel	
Ion AmpliSeq™ Cancer Hotspot Panel v2	Thermo Fisher Scientific
OmniSeq Comprehensive	OmniSeq

For individuals who have a cancer that is being considered for targeted therapy who receive testing of tumor tissue with an expanded cancer molecular panel, the evidence includes an RCT, nonrandomized trials, and numerous case series. 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. To demonstrate clinical utility, direct evidence from interventional trials, ideally RCTs, are needed that compare the strategy of targeted treatment based on panel results with standard care. The first such published RCT, molecularly targeted therapy based on tumour molecular profiling vs conventional therapy for advanced cancer, (the SHIVA trial) reported that there was no difference in PFS when panels were used in this way. Some nonrandomized comparative studies, comparing matched treatment with nonmatched treatment, have reported that outcomes are superior for patients receiving matched treatment. However, these studies are inadequate to determine treatment efficacy, because the populations with matched and unmatched cancers may differ on several important clinical and prognostic variables. Also, there is potential for harm if ineffective therapy is given based on test results, because there may be adverse

events of therapy in the absence of a benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

BlueCHiP for Medicare

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 advanced cancer can have recurrent, metastatic, and/or stage IV disease. From results of clinical studies it has been shown 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 the drug.

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 is met.

Non-Small Cell Lung Cancer (NSCLC) and Metastatic Colorectal Cancer (mCRC)

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.

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 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)

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, July 2019
Provider Update, June 2018

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