Medical Coverage Policy | Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies

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OVERVIEW

There is interest in treating cancers by targeting biologic pathways characterized by specific genetic markers. Genetic panel testing offers the potential to evaluate a large number of genetic markers at a single time to identify treatments that target specific pathways. This review focuses on "expanded" panels, which are defined as 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 of cancer and stage.

MEDICAL CRITERIA

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Next Generation Sequencing 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 stages 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 of 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. 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.

PRIOR AUTHORIZATION

BlueCHiP for Medicare

Prior authorization is required for BlueCHiP for Medicare only.

Commercial Products

Not applicable

POLICY STATEMENT

BlueCHiP for Medicare

Expanded molecular panel testing of cancers using next generation sequencing to identify targeted therapies for treatment may be considered medically necessary when the criteria above has been met.

Commercial Products

The use of expanded cancer molecular panels for selecting targeting cancer treatment 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 benefits/coverage.

BACKGROUND

BlueCHiP for Medicare and Commercial Products

TRADITIONAL THERAPEUTIC APPROACHES TO CANCER

Tumor location, grade, stage, 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 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. This evidence review does not apply to the individual markers that have demonstrated efficacy. According to recent National Comprehensive Cancer Network guidelines, the following markers have demonstrated utility for predicting treatment response to targeted therapies for the specific cancers listed:

- Breast cancer
  - o HER2 (ERBB2)
- Colon cancer
  - o RAS variants (KRAS, NRAS)
  - o BRAF c1799T>A
- Non-small-cell lung cancer (NSCLC)
  - o EGFR
  - o ALK, ROS1
  - o KRAS
  - o RET
  - o MET

- Metastatic melanoma
  o BRAF V600
  o C-KIT
- Ovarian cancer
- BRCA (germline)
- Chronic myeloid leukemia
  o BRC-ABL
- Gastrointestinal stromal tumors
  o C-KIT

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, the intent is to address 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 2015 study, 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%).

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 was effective in one type of cancer but ineffective in another. For example, targeted therapy for epidermal growth factor receptor (EGFR) variants has been successful in NSCLC 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 NSCLC, Erdheim-Chester disease, and Langerhans cell histiocytosis.

More recently, sequencing technology such as NGS to read the order of nucleotide molecules on DNA has improved to more effectively provide detailed information on multiple types of genetic alterations simultaneously. The NGS oncology panel tests also provide patients and their providers a more comprehensive genetic profile of cancer and information relevant to potential cancer treatments. NGS oncology panel tests hold potential for patients and providers in optimizing (personalizing) therapies that target specific characteristics of individual patient cancers. However, it is important that these tests produce valid results that are useful in guiding therapies to improve outcomes for patients with advanced cancer.

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

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

Commercially Available Expanded Cancer Molecular Panels for Solid and Hematologic Tumor Testing	
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)	Caris Life Sciences
SmartGenomics™	PathGroup
Guardant360 panel	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
Illumina TruSight™ Tumor	Illumina
Ion AmpliSeq™ Comprehensive Cancer Panel	Thermo Fisher Scientific
Ion AmpliSeq™ Cancer Hotspot Panel v2	Thermo Fisher Scientific

RATIONALE

Commercial Products

The clinical validity of the individual variants for particular types of cancer is not easily determined from the published literature. The large number of variants and many types of cancer preclude determination of the clinical validity of the panels as a whole. There is also 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. For individuals who have cancers that have not responded to standard therapy who receive testing of tumor tissue with an expanded cancer molecular panel, the evidence is insufficient to determine the effects of the technology on health outcomes. Therefore, the service is considered not medically necessary.

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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.

CODING

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

The following codes have been assigned to some available expanded cancer molecular panels.
The following CPT codes require prior authorization for BlueCHiP for Medicare and are considered not medically necessary for Commercial products:

0036U Exome (ie, somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses (EXaCT-1 Whole Exome Testing) (New Code effective 4/1/2018)

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 (FoundationOne CDx™ (F1CDx)) (New Code effective 4/1/2018)

RELATED POLICIES

Proprietary Laboratory Analyses (PLA)

PUBLISHED

Provider Update, June 2018

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