

Protocol

Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies

(204115)

(Formerly Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies)

Medical Benefit		Effective Date: 06/01/20	Next Review Date: 03/21
Preauthorization	No	Review Dates: 07/15, 07/16, 07/17, 07/18, 03/19, 03/20	

This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none">• With advanced cancer that that is being considered for targeted therapy	Interventions of interest are: <ul style="list-style-type: none">• Comprehensive genomic profiling of tumor tissue	Comparators of interest are: <ul style="list-style-type: none">• Single gene molecular testing	Relevant outcomes include: <ul style="list-style-type: none">• Overall survival• Disease-specific survival• Test validity• Quality of life

DESCRIPTION

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. 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 a specific targeted treatment has demonstrated benefit. This approach may result in treatment different from that usually selected for a patient based on the type and stage of cancer.

SUMMARY OF EVIDENCE

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. The 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 one 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 treat-

ment 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 (i.e., 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.

POLICY

The use of comprehensive genomic profiling for selecting targeted cancer treatment is considered **investigational**.

POLICY GUIDELINES

GENETICS NOMENCLATURE UPDATE

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical protocol updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

MEDICARE ADVANTAGE

For Medicare Advantage Next Generation Sequencing (NGS) as a diagnostic laboratory test is considered **medi-**

cally necessary when performed in a Clinical Laboratory Improvement Amendments CLIA-certified laboratory, when ordered by a treating physician and when all of the following requirements are met:

1. Patient has:
 - a. any cancer diagnosis; and
 - b. a clinical indication for germline (inherited) testing for hereditary cancers; and
 - c. a risk factor for germline (inherited) cancer; and
 - d. not been previously tested with the same germline test using NGS for the same germline genetic content (Exceptions include clinical scenarios whereby repeat testing of somatically-acquired mutations (for example, pre- and post-therapy) may be required to inform appropriate therapeutic decision-making).
2. The diagnostic laboratory test using NGS must have all of the following:
 - a. Food and Drug Administration (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.

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 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 benefits. It is unusual for 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.¹ 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 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 by "pathways" defined at the molecular level. An expanding number of genetic markers have been identified. These may be categorized into three classes² (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 (i.e., 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 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 (e.g., a panel of several markers for non-small-cell lung cancer). This review also does not 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.³⁻⁵ 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.⁵ A total of 1,813 molecular alterations were identified, and almost all patients (420/439 [96%]) had at least one molecular alteration. The median number of alterations per patient was three and 85% (372/439) of patients had two or more alterations. The most common alterations were in the 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.^{2,6} 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 by Hyman et al (2015).⁷ In this study, 122 patients with BRAF V600 variants in nonmelanoma cancers were treated with vemurafenib. The authors reported that there appeared to be an 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.

EXPANDED CANCER MOLECULAR PANELS

Table 1 provides a select list of commercially available expanded cancer molecular panels.

Test	Manufacturer	Tumor Type	Technology
FoundationOne®CDx test (F1CDx)	Foundation Medicine	Solid	NGS
FoundationOne®CDx Heme test	Foundation Medicine	Hematologic	RNA sequencing
OnkoMatch™	GenPath Diagnostics	Solid	Multiplex PCR
GeneTrails® Solid Tumor Panel	Knight Diagnostic Labs	Solid	
Tumor profiling service	Caris Molecular Intelligence through Caris Life Sciences	Solid	Multiple technologies
SmartGenomics™	PathGroup	Solid and hematologic	NGS, cytogenomic array, other technologies
Guardant 360 panel	GuardantHealth	Solid	Digital sequencing
Paradigm Cancer Diagnostic (PcDx™) Panel	Paradigm	Solid	NGS
Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets	MSK-IMPACT™; Memorial Sloan Kettering Cancer Center	Solid	NGS
TruSeq® Amplicon Panel		Solid	NGS
Illumina TruSight™ Tumor	Illumina	Solid	NGS
Ion AmpliSeq™ Comprehensive Cancer Panel		Solid	NGS
Ion AmpliSeq™ Cancer Hotspot Panel v2	Thermo Fisher Scientific	Solid	NGS
OmniSeq Comprehensive®	OmniSeq	Solid	NGS

NGS: next-generation sequencing; PCR: polymerase chain reaction.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing.

In 2017, FoundationOne CDx (Foundation Medicine) received premarket approval by the U.S. Food and Drug Administration (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.” Food and Drug Administration product code: PQP

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.” Food and Drug Administration product code: PZM

OmniSeq Comprehensive® is approved by the New York State Clinical Laboratory Evaluation Program.

Table 2. Companion Diagnostic Indications for F1CDx

Tumor Type	Biomarker(s) Detected	Therapy
Non-small cell lung cancer (NSCLC)	<i>EGFR</i> exon 19 deletions and <i>EGFR</i> exon 21 L858R alterations	Gilotrif® (afatinib), Iressa® (gefitinib), Tagrisso® (osimertinib), or Tarceva® (erlotinib)
	<i>EGFR</i> exon 20 T790M alterations	Tagrisso® (osimertinib)
	<i>ALK</i> rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), or Zykadia® (ceritinib)
	<i>BRAF</i> V600E	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)
Melanoma	<i>BRAF</i> V600E	Tafinlar® (dabrafenib) or Zelboraf® (vemurafenib)
	<i>BRAF</i> V600E and V600K	Mekinist® (trametinib) or Cotellic® (cobimetinib) in combination with Zelboraf® (vemurafenib)
Breast cancer	<i>ERBB2</i> (HER2) amplification	Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumabemtansine), or Perjeta® (pertuzumab)
Colorectal cancer	<i>KRAS</i> wild-type (absence of mutations in codons 12 and 13)	Erbix® (cetuximab)
	<i>KRAS</i> wild-type (absence of mutations in exons 2, 3, and 4) and <i>NRAS</i> wild type (absence of mutations in exons 2, 3, and 4)	Vectibix® (panitumumab)
Ovarian cancer	<i>BRCA1/2</i> alterations	Lynparza® (olaparib) or Rubraca® (rucaparib)

RELATED PROTOCOLS

Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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