

# Protocol

## Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies

(204115)

<b>Medical Benefit</b>		<b>Effective Date:</b> 10/01/15	<b>Next Review Date:</b> 07/18
<b>Preauthorization</b>	No	<b>Review Dates:</b> 07/15, 07/16, 07/17	

***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"><li>• With cancers that have not responded to standard therapy</li></ul>	Interventions of interest are: <ul style="list-style-type: none"><li>• Testing of tumor tissue with an expanded cancer mutation panel</li></ul>	Comparators of interest are: <ul style="list-style-type: none"><li>• Next-line therapy without expanded cancer mutation panel testing</li></ul>	Relevant outcomes include: <ul style="list-style-type: none"><li>• Overall survival</li><li>• Disease-specific survival</li><li>• Test accuracy</li><li>• Test validity</li><li>• Other test performance measures</li></ul>

### Description

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. Some individual markers have established benefit in certain types of cancers; they are not addressed in this protocol. Rather, this protocol 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.

### Summary of Evidence

For individuals who have cancers that have not responded to standard therapy who receive testing of tumor tissue with an expanded cancer mutation panel, the evidence includes one randomized controlled trial (RCT), nonrandomized trials, and numerous case series. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and other test performance measures. The analytic validity of these panels is likely to be high when next-generation sequencing is used. The clinical validity of the individual mutations for particular types of cancer is not easily determined from the published literature. The large number of mutations and many types of cancer preclude determination of the clinical validity of the panels as a whole. Some evidence has reported that many of the identified mutations are false positives (i.e., not biologically active), after filtering by comparison with matched normal tissue and cancer mutation databases. 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 (the SHIVA trial) reported that

there was no difference in progression-free survival 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. In addition, there is potential for harm if ineffective therapy is given based on test results, because there may be adverse effects of therapy in absence of a benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

### Policy

The use of expanded cancer mutation panels for selecting targeted cancer treatment is considered **investigational**.

### Background

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 it arises. 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 actually 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.<sup>1</sup> They reported heterogeneity of therapeutic responses ranging from a low 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 in order to have higher rates of therapeutic responses.

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. Using genetic markers, cancers can be further classified by "pathways" defined at the molecular level. An expanding number of genetic markers have been identified. Dienstmann et al categorized these findings into three classes.<sup>2</sup> These are: (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). Utility of these markers has generally 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 protocol does not apply to the individual markers that have demonstrated efficacy. According to recent National Comprehensive Cancer Network guidelines,<sup>3</sup> the following markers have demonstrated utility for predicting treatment response to targeted therapies for the specific cancers listed:

- Breast cancer
  - *HER2 (ERBB2)*
- Colon cancer
  - *RAS mutations (KRAS, NRAS)*
  - *BRAF c1799T>A*
- Non-small-cell lung cancer (NSCLC)
  - *EGFR*
  - *ALK/ROS1*
  - *KRAS*
  - *RET*
  - *MET*
- Metastatic melanoma
  - *BRAF V600*
  - *KIT*
- Ovarian cancer
  - *BRCA (germline)*
- Chronic myeloid leukemia
  - *BRC-ABL*
- Gastrointestinal stromal tumors
  - *KIT*

Testing for these individual mutations with established utility is not covered herein. In some cases, limited panels may be offered that are specific to one type of cancer (e.g., 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 mutations. Rather, the intent is to address expanded panels that test for many potential mutations that do not have established efficacy for the specific cancer in question.

When advanced cancers are tested with expanded mutation panels, most patients are found to have at least one potentially pathogenic mutation.<sup>4-6</sup> The number of mutations varies widely by types of cancers, different mutations 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.<sup>6</sup> A total of 1813 molecular alterations were identified, and almost all patients (420/439 [96%]) had at least one molecular alteration. Median number of alterations per patient was three, and 85% of patients (372/439) had two 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 mutation among cancers that originate from different organs.<sup>2,3,7</sup> There are several examples of mutation-directed treatment that was effective in one type of cancer but ineffective in another. For example, targeted therapy for epidermal growth factor receptor (*EGFR*) mutations has been successful in NSCLC but not in trials of other cancer types. Treatment with tyrosine kinase inhibitors based on mutation 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 mutation are treated with a targeted agent, also have been performed. One such study was published in 2015 by Hyman et al.<sup>8</sup> In this study, 122 patients with *BRAF* V600 mutations 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.

#### Expanded Cancer Mutation Panels

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

Table 1. Commercially Available Solid and Hematologic Tumor Expanded Cancer Mutation Panels

Test (Manufacturer)	Tumor Type	No. of Genes Tested	Technology
FoundationOne™ test (Foundation Medicine) <sup>9</sup>	Solid	236 cancer-related genes and 47 introns from another 19 genes	NGS
FoundationOne Heme test (Foundation Medicine) <sup>9</sup>	Hematologic	405 cancer-related genes and introns from another 31 genes	RNA sequencing
OnkoMatch (GenPath Diagnostics) <sup>10</sup>	Solid	68 mutations in 14 oncogenes and tumor suppressor genes	Multiplex PCR
GeneTrails Solid Tumor Panel (Knight Diagnostic Labs) <sup>11</sup>	Solid	37 genes	
Tumor profiling service (Caris Molecular Intelligence through Caris Life Sciences) <sup>12</sup>	Solid	Up to 56 tumor-associated genes	NGS, IHC, FISH, Sanger sequencing, pyrosequencing, quantitative PCR, fragmentation analysis
SmartGenomics (PathGroup) <sup>13</sup>	Solid and hematologic	Up to 62 cancer-associated genes	NGS, cytogenomic array, other technologies
Guardant360 panel (GuardantHealth) <sup>14</sup>	Solid		Digital sequencing
Paradigm Cancer Diagnostic (PcDx) Panel (Paradigm) <sup>15</sup>	Solid	> 500 genetic targets	NGS
Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) <sup>16</sup>	Solid	341 cancer-associated genes	NGS
TruSeq® Amplicon Panel (Illumina) <sup>17</sup>	Solid	48 cancer-related genes	NGS
Illumina TruSight™ Tumor (Illumina) <sup>18</sup>	Solid	26 cancer-related genes	
Ion AmpliSeq Comprehensive Cancer Panel (Life Technologies) <sup>19</sup>	Solid	> 400 cancer-related genes and tumor suppressor genes	
Ion AmpliSeq Cancer Hotspot Panel v2 (Life Technologies) <sup>19</sup>	Solid	“Hotspot” regions of 50 cancer-related and tumor suppressor genes	

FISH: fluorescence in situ hybridization; IHC: immunohistochemistry; NGS: next-generation sequencing; PCR: chain reaction.

### Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

### Related Protocols

General Approach to Evaluating the Utility of Genetic Panels

Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing

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Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment 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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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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