Medical Policy

MP 2.04.115
Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies

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Section: Medicine

Related Policies
2.04.93 Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing

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POLICY
The use of expanded cancer molecular panels for selecting targeting 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 evidence review 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

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>
Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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

If a panel meets the requirements for one of the specific CPT codes for targeted genomic sequence analysis panel (81445-81455), the code may be reported for the test.

If the panel does not meet the requirements for a CPT panel code, any specific variant listed in codes 81200-81409 would be reported using those codes, and the other variants in the panel not specifically listed would be reported with 1 unit of the unlisted molecular pathology code 81479.

As an example of coding that might be used, GenPath recommends the following CPT codes in its test catalog for OnkoMatch™ Tumor Genotyping (with the number of units indicated in parentheses): 81210 (1), 81235 (1), 81275 (1), 81323 (1). For OnkoMatch Tumor Genotyping + for Lung, GenPath recommends the following CPT codes: 81210 (1), 81235 (1), 81275 (1), 81323 (1), 88368 (2), 88381 (1).

BENEFIT APPLICATION

BLUE CARD/NATIONAL ACCOUNT ISSUES
Some Plans may have contract or benefit exclusions for genetic testing.

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 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 by “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 (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. 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
  - HER2 (ERBB2)
- Colon cancer
  - RAS variants (KRAS, NRAS)
  - BRAF c1799T>A
- Non-small-cell lung cancer (NSCLC)
  - EGFR
  - ALK, ROS1
  - KRAS
  - RET
  - MET
- Metastatic melanoma
  - BRAF V600
  - C-KIT
- Ovarian cancer
  - BRCA (germline)
- Chronic myeloid leukemia
  - BRC-ABL
- Gastrointestinal stromal tumors
  - 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 (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 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, have also been performed. One such study was published in 2015 by Hyman et al. In this study, 122 patients with BRAF V600 variants in non-melanoma 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 MOLECULAR PANELS
Table 1 provides a select list of commercially available expanded cancer molecular panels.

<table>
<thead>
<tr>
<th>Test (Manufacturer)</th>
<th>Tumor Type</th>
<th>No. of Genes Tested</th>
<th>Technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>FoundationOne® test (Foundation Medicine, Cambridge, MA)</td>
<td>Solid</td>
<td>315 cancer-related genes and introns from 28 genes</td>
<td>NGS</td>
</tr>
<tr>
<td>FoundationOne® Heme test (Foundation Medicine, Cambridge, MA)</td>
<td>Hematologic</td>
<td>406 cancer-related genes and selected introns from 31 genes involved in rearrangements</td>
<td>RNA sequencing</td>
</tr>
<tr>
<td>OnkoMatch™ (GenPath Diagnostics, Elmwood Park, NJ)</td>
<td>Solid</td>
<td>68 variants in 14 oncogenes and tumor suppressor genes</td>
<td>Multiplex PCR</td>
</tr>
<tr>
<td>GeneTrails® Solid Tumor Panel (Knight Diagnostic Labs, Portland, OR)</td>
<td>Solid</td>
<td>123 genes</td>
<td></td>
</tr>
<tr>
<td>Tumor profiling service (Caris Molecular Intelligence through Caris Life Sciences, Irving, TX)</td>
<td>Solid</td>
<td>Up to 56 tumor-associated genes</td>
<td>NGS, IHC, FISH, Sanger sequencing, pyrosequencing, quantitative PCR, fragmentation analysis</td>
</tr>
<tr>
<td>SmartGenomics™ (PathGroup, Nashville, TN)</td>
<td>Solid and hematologic</td>
<td>160 genes and 126 gene fusions</td>
<td>NGS, cytogenomic array, other technologies</td>
</tr>
<tr>
<td>Guardant360 panel (GuardantHealth, Redwood City, CA)</td>
<td>Solid</td>
<td></td>
<td>Digital sequencing</td>
</tr>
<tr>
<td>Paradigm Cancer Diagnostic</td>
<td>Solid</td>
<td>186 alterations</td>
<td>NGS</td>
</tr>
</tbody>
</table>
## Test (Manufacturer) | Tumor Type | No. of Genes Tested | Technology
--- | --- | --- | ---
(PcDx™) Panel (Paradigm, Phoenix, AZ)¹⁵ | Solid | 341 cancer-associated genes | NGS
Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT™; Memorial Sloan Kettering Cancer Center, New York, NY)¹⁶ | Solid | 15 | NGS
TruSeq® Amplicon Panel (Illumina, San Diego, CA)¹⁷ | Solid | 48 cancer-related genes | NGS
Illumina TruSight™ Tumor (Illumina, San Diego, CA)¹⁸ | Solid | 26 cancer-related genes | NGS
Ion AmpliSeq™ Comprehensive Cancer Panel (Thermo Fisher Scientific, Waltham, MA)¹⁹ | Solid | >400 cancer-related genes and tumor suppressor genes | NGS
Ion AmpliSeq™ Cancer Hotspot Panel v2 (Thermo Fisher Scientific, Waltham, MA)²⁰ | Solid | “Hotspot” regions of 50 cancer-related and tumor suppressor genes | NGS

FISH: fluorescence in situ hybridization; IHC: immunohistochemistry; 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. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

### RATIONALE
This evidence review was developed in March 2014 and has been updated regularly with a literature review of the MEDLINE database. The most recent literature update was performed through August 23, 2017. This review addresses BCBSA genetic category 2c (testing cancer cells from an affected individual to benefit the individual for therapeutic purposes; see Appendix Table 1).

The evaluation of a genetic test focuses on 3 main principles: (1) analytic validity (technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent); (2) clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and (3) clinical utility (how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

### EXPANDED MOLECULAR PANEL TESTING FOR CANCER

### Clinical Context and Test Purpose
The purpose of expanded molecular panel testing in individuals with cancer that has not responded to standard therapy is to identify somatic variants in tumor tissue to guide treatment decisions with targeted therapies for specific somatic variants.
The question addressed in this evidence review is: In individuals with cancer that has not responded to standard therapy, does the use of expanded molecular panel testing improve health outcomes?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest includes individuals with cancer that has not responded to standard therapy.

**Interventions**
The relevant intervention of interest is expanded molecular panel testing.

**Comparators**
The relevant comparator of interest is next-line therapy without expanded molecular panel testing.

**Outcomes**
The beneficial outcomes of interest include progression-free survival (PFS) and overall survival (OS).

**Timing**
The time frame for outcomes measures varies from several months to several years.

**Setting**
Patients with cancer are actively managed by oncologists.

**Analytic Validity**
No published studies were identified that evaluated the analytic validity of these panels. The panels are performed primarily by next-generation sequencing, which has a high analytic validity. Some panels supplement next-generation sequencing with additional testing methods, such as polymerase chain reaction, for intronic regions included as components of the panel. Polymerase chain reaction is considered to have an analytic validity of more than 95%.

Information on analytic validity of the FoundationOne test was reported on the Foundation website. This site states that the test’s analytic sensitivity is greater than 99% for base substitutions at a mutant allele frequency of 5% or more, 98% for indels at a mutant allele frequency of 10% or more, less than 95% for copy number alterations. It also reports an analytic specificity of more than 99%.

**Clinical Validity**
The clinical validity of the panels as a whole cannot be determined because of the different variants and large number of potential cancers for which they can be used. Clinical validity would need to be reported for each variant for a particular type of cancer. Because there are hundreds of variants included in the panels and dozens of cancer types, evaluation of the individual clinical validity for each pairing is beyond the scope of this review.

A major concern with clinical validity is differentiating variants that drive cancer growth from genetic variants that are not clinically important. It is expected that variants of uncertain significance will be very frequent with panels that include several hundred markers.

Comparison of cancer variants with matched normal tissue can provide evidence about whether variants are truly somatic cancer variants or whether they are incidental variants that do not have meaningful biologic activity. Jones et al (2015) performed comprehensive variant testing on 815 pairs of tumor tissue and matched normal tissue from patients with 15 different tumor types. Each sample was analyzed by both targeted sequencing and whole exome sequencing. A total of 105,672 somatic...
alterations were identified. After filtering for variants present in normal tissue, there was an average of 4.34 variants per patient on targeted analysis and 135-variants per patient on whole exome sequencing. After additional filtering using the COSMIC (Catalog of Somatic Mutations in Cancer) database, the authors estimated that 38% of the variants identified by targeted analysis were true positives, and 62% were false positives; on whole exome analysis, 10% of variants were true positives, and 90% were false positives.

Section Summary: Clinical Validity
The evidence on the clinical validity of expanded panels is incomplete. Because of the large number of variants contained in expanded panels, it is not possible to determine clinical validity for the panels as a whole. While some variants have a strong association with one or a small number of specific malignancies, none has demonstrated high clinical validity across a wide variety of cancers. Some have reported that, after filtering variants by comparison with matched normal tissue and cancer variants databases, most identified variants are found to be false positives. Thus, it is likely that clinical validity will need to be determined for each variant and each type of cancer individually.

Clinical Utility
The most direct way to demonstrate clinical utility is through controlled trials that compare a strategy of cancer variant testing followed by targeted treatment with a standard treatment strategy without variant testing. Randomized trials are necessary to control for selection bias in treatment decisions, because clinicians may select candidates for variant testing based on clinical, demographic, and other factors. Outcomes of these trials would be the morbidity and mortality associated with cancer and cancer treatment. OS is most important; cancer-related survival and/or PFS may be acceptable surrogates. A quality-of-life measurement may also be important if study designs allow for treatments with different toxicities in the experimental and control groups.

Systematic Reviews
Schwaederle et al published a meta-analysis of studies comparing personalized treatment with nonpersonalized treatment in 2015.22 Their definition of personalized treatment was driven by a biomarker, which could be genetic or non-genetic. Therefore, this analysis not only included studies of matched vs unmatched treatment based on genetic markers, but also included studies that personalized treatment based on non-genetic markers. A total of 111 arms of identified trials received personalized treatment, and they were compared with 529 arms that received nonpersonalized treatment. On random-effects meta-analysis, the personalized treatment group had a higher response rate (31% vs 10.5%, p<0.001), and a longer PFS (5.9 months vs 2.7 months, p<0.001) compared with the nonpersonalized treatment group. Another meta-analysis (2015) by this group compared outcomes from 44 Food and Drug Administration–regulated drug trials that used a personalized treatment approach to 68 trials that used a nonpersonalized approach to cancer treatment.23 Response rates were significantly higher in the personalized treatment trials (48%) than in the nonpersonalized approach (23%; p<0.001). PFS was 8.3 months in the personalized treatment trials compared with 5.5 months in the nonpersonalized approach (p<0.001). For trials that used a personalized treatment strategy, OS was significantly longer (19.3 months) than in trials that did not (13.5 months, p=0.01). Personalized treatment in these studies was based on various biomarkers, both genetic and non-genetic.

Randomized Controlled Trials
SHIVA was a randomized controlled trial of treatment directed by cancer variant testing vs standard care, with the first results published in 2015.24,25 In this study, 195 patients with a variety of advanced cancers refractory to standard treatment were enrolled from 8 academic centers in France. Variant
testing included comprehensive analysis of 3 molecular pathways (hormone receptor pathway, PI3K/AKT/mTOR pathway, RAF/MEK pathway) performed by targeted next-generation sequencing, analysis of copy number variations, and hormone expression by immunohistochemistry. Based on the pattern of abnormalities found, 9 different regimens of established cancer treatments were assigned to the experimental treatment arm (see Table 2). The primary outcome was PFS analyzed by intention to treat.

### Table 2. Treatment Algorithm for Experimental Arm, From the SHIVA Trial

<table>
<thead>
<tr>
<th>Molecular Abnormalities</th>
<th>Molecularly Targeted Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT, ABL, RET</td>
<td>Imatinib</td>
</tr>
<tr>
<td>AKT, mTORC1/2, PTEN, PI3K</td>
<td>Everolimus</td>
</tr>
<tr>
<td>BRAF V600E</td>
<td>Vemurafenib</td>
</tr>
<tr>
<td>PDGFRA, PDGFRB, FLT-3</td>
<td>Sorafenib</td>
</tr>
<tr>
<td>EGFR</td>
<td>Erlotinib</td>
</tr>
<tr>
<td>HER2</td>
<td>Lapatinib and trastuzumab</td>
</tr>
<tr>
<td>SRC, EPHA2, LCK, YES</td>
<td>Dasatinib</td>
</tr>
<tr>
<td>Estrogen receptor, progesterone receptor</td>
<td>Tamoxifen (or letrozole if contraindications)</td>
</tr>
<tr>
<td>Androgen receptor</td>
<td>Abiraterone</td>
</tr>
</tbody>
</table>

Ninety-nine patients were randomized to the targeted treatment group, and 96 to standard care. Baseline clinical characteristics and tumor types were similar between groups. Molecular alterations affecting the hormonal pathway were found in 82 (42%) of 195 patients; alterations affecting the PI3K/AKT/mTOR pathway were found in 89 (46%) of 195 patients; and alterations affecting the RAF/MED pathway were found in 24 (12%) of 195 patients. After a median follow-up of 11.3 months, the median PFS was 2.3 months (95% confidence interval [CI], 1.7 of 3.8 months) in the targeted treatment group vs 2.0 months (95% CI, 1.7 of 2.7 months) in the standard care group (hazard ratio, 0.88; 95% CI, 0.65 of 1.19, p=0.41). Objective responses were reported for 4 (4.1%) of 98 assessable patients in the targeted treatment group vs 3 (3.4%) of 89 assessable patients in the standard care group. In subgroup analysis by molecular pathway, there were no significant differences in PFS between groups.

A 2017 crossover analysis of the SHIVA trial evaluated the PFS ratio from patients who failed standard of care therapy and crossed over from molecularly targeted agents (MTA) therapy to treatment at physician’s choice (TPC) or vice versa. The PFS ratio was defined as the PFS on MTA (PFSMTA) to PFS on TPC (PFSTPC) in patients who crossed over. Of the 95 patients who crossed over, 70 patients crossed over from the TPC to MTA arm while 25 patients crossed over from MTA to TPC arm. In the TPC to MTA crossover arm, 26 (37%) of patients and 15 (61%) of patients in the MTA to TPC arm had a PFSMTA/PFSTPC ratio greater than 1.3. The post hoc analysis of the SHIVA trial has limitations because it only evaluated a subset of patients from the original clinical trial but used each patient as his/her control by using the PFS ratio. The analysis would suggest that patients may have benefited from the treatment algorithm evaluated in the SHIVA trial.

**Nonrandomized Controlled Trials**

Numerous nonrandomized studies have been published that use some type of control. Some of these studies had a prospective, interventional design. In 2016, Wheler et al reported a prospective comparative trial of patients who had failed standard treatment and had been referred to their tertiary center for admission into phase 1 trials. Comprehensive molecular profiling (FoundationOne tumor panel) was performed on 339 patients, of whom 122 went onto a phase 1 therapy that was matched to
their genetic profile; based on physician evaluation of additional information, 66 patients went onto a phase 1 trial not matched to their genetic profile. Table 3 summarizes study results; there was a significant benefit on time to treatment failure and a trend for an increased percentage of patients with stable disease and median OS in patients matched to their genetic profile. When exploratory analysis divided patients into groups that had high matching results or low matching results (number of molecular matches per patient divided by the number of molecular alterations per patient), the percentage of patients with stable disease and the median time to failure were significantly better in the high-match group. Median OS did not differ significantly between groups. Notably, those patients had failed multiple prior therapies (median, 4) and had a number (median, 5; range, 1-14) of gene alterations in the tumors. For comparison, response rates in phase 1 trials with treatment-resistant tumors are typically 5% to 10%.

Table 3. Survival Outcomes After Genetic Profile-Based Therapy

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>% SD (95% CI)</th>
<th>Median TTF (95% CI), mo</th>
<th>Median OS (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matched</td>
<td>122</td>
<td>19</td>
<td>2.8 (2.1 to 3.5)</td>
<td>9.3 (7.3 to 11.3)</td>
</tr>
<tr>
<td>Unmatched</td>
<td>66</td>
<td>8</td>
<td>1.9 (1.5 to 2.3)</td>
<td>7.2 (4.9 to 9.5)</td>
</tr>
<tr>
<td>p</td>
<td>0.061</td>
<td>0.001</td>
<td>0.087</td>
<td></td>
</tr>
<tr>
<td>High match</td>
<td>92</td>
<td>22</td>
<td>3.4 (2.6 to 4.2)</td>
<td>9.3 (7.3 to 11.3)</td>
</tr>
<tr>
<td>Low match</td>
<td>90</td>
<td>9</td>
<td>1.9 (1.6 to 2.2)</td>
<td>7.5 (5.0 to 10.0)</td>
</tr>
<tr>
<td>p</td>
<td>0.028</td>
<td>&lt;0.001</td>
<td>0.121</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Wheler et al (2016). CI: confidence interval; OS: overall survival; SD: stable disease ≥6 mo; TTF: time to failure.

Another type of study compares patients matched to targeted treatment with patients not matched. In this type of study, all patients undergo comprehensive genetic testing, but only a subset is matched to targeted therapy. Patients who are not matched continue to receive standard care.

An individual study of this type is Tsimberidou et al (2012). In it, patients with advanced or metastatic cancer refractory to standard therapy underwent molecular profiling. Polymerase chain reaction–based targeted sequencing was used to assess variants in 10 cancer genes. Loss of PTEN was determined using immunohistochemistry, and anaplastic lymphoma kinase (ALK) translocation was assessed using fluorescence in situ hybridization. Of 1144 patients, 460 had a molecular aberration based on this panel of tests. From this group of 460 patients, 211 were given “matched” treatment and 141 were given unmatched treatment. The principal analysis presented was of a subgroup of the 460 patients who had only 1 molecular aberration (n=379). Patients were enrolled in 1 of 51 phase 1 clinical trials of experimental agents. It was not stated how patients were assigned to matched or unmatched therapy, or how a particular therapy was considered a match or not. In the list of trials in which patients were enrolled, it appears that many of the investigational agents were inhibitors of specific kinases, and thus a patient with a particular aberration of that kinase would probably be considered a match for that agent.

Among the 175 patients treated with matched therapy, the overall response rate was 27%. Among the 116 patients treated with non-matched therapy, the response rate was 5% (p<0.001 for the difference in response rates). The median time to failure was 5.2 months for patients on matched therapy and 2.2 months for those on non-matched therapy (p<0.001). At a median 15-month follow-up, survival was 13.4 months vs 9.0 months (p=0.017) in favor of matched therapy. Due to small numbers, individual molecular aberrations could not be analyzed, but some sensitivity analyses, excluding certain aberrations, demonstrated that the results were robust, with the exclusion of certain groups.
**MP 2.04.115**

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**Section Summary: Clinical Utility**

Clinical utility has not been demonstrated for the use of expanded molecular panels to direct targeted cancer treatment. One published randomized controlled trial (SHIVA trial) used an expanded panel in this way and reported no difference in PFS compared with standard treatment. Nonrandomized studies have compared patients who received matched treatment with patients who did not, and have reported that outcomes are superior in patients receiving matched treatment. However, there are potential issues with this design that could compromise the validity of comparing these 2 populations. They include the following: (1) differences in clinical and demographic factors, (2) differences in the severity of disease or prognosis of disease (i.e., patients with more undifferentiated anaplastic cancers might be less likely to express genetic markers), and (3) differences in the treatments received. It is possible that one of the “targeted” drugs could be more effective than standard treatment whether or not patients were matched. As a result, these types of nonrandomized studies do not provide definitive evidence of treatment efficacy. Further controlled trials are needed that randomize patients to a treatment strategy of variant testing followed by targeted treatment vs standard care.

**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 molecular panel, the evidence includes a randomized controlled trial, 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 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. Some evidence has reported that many of the identified variants are false positives (i.e., not biologically active), after filtering by comparison with matched normal tissue and cancer variant databases. To demonstrate clinical utility, direct evidence from interventional trials, ideally randomized controlled trials are needed that compare the strategy of targeted treatment based on panel results with standard care. The first such published randomized controlled trial (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 non-matched 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.

**SUPPLEMENTAL INFORMATION**

**PRACTICE GUIDELINES AND POSITION STATEMENTS**

The National Comprehensive Cancer Network guidelines do not contain recommendations for the general strategy of testing a tumor for a wide range of variants. The guidelines do contain recommendations for specific genetic testing for individual cancers, based on situations where there is a known mutation-drug combination that has demonstrated benefits for that specific tumor type. Some examples of recommendations for testing of common solid tumors are listed below:

- Breast cancer\(^{29}\)
  - *HER2* testing, when specific criteria are met.
- Colon cancer\(^{30}\)
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- **KRAS, NRAS, and BRAF** testing for patients with metastatic colon cancer.
- **Non-small-cell lung cancer**
  - **KRAS, EGFR** [epidermal growth factor receptor], and **ALK** [anaplastic lymphoma kinase] testing for patients with metastatic adenocarcinoma
  - Consider **EGFR** and **ALK** testing especially in never smokers, mixed histology, or small biopsy specimen
  - Strongly endorses broader molecular profiling to identify rare driver mutations (**HER2, BRAF** V600E, **ROS1**, and **RET** gene rearrangements, and **MET** amplification or **MET** exon skipping)
- **Melanoma**
  - **BRAF** V600 testing for patients with metastatic disease
  - Activating **C-KIT** variants for patients with metastatic disease
- **Ovarian cancer**
  - **BRCA**
- **Chronic myelogenous leukemia**
  - **BCR-ACL**
- **Gastrointestinal stromal tumors**
  - **C-KIT**
  - **Bladder cancer**
  - Comprehensive molecular profiling for advanced disease.

**U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS**

Not applicable.

**MEDICARE NATIONAL COVERAGE**

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**ONGOING AND UNPUBLISHED CLINICAL TRIALS**

Some currently unpublished trials that might influence this review are listed in Table 4.

**Table 4. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT01891344³⁴⁰⁰</td>
<td>A Study of Rucaparib in Patients With Platinum-Sensitive, Relapsed, High-Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (ARIEL2)</td>
<td>480</td>
<td>Apr 2017</td>
</tr>
<tr>
<td>NCT01987726</td>
<td>Comprehensive Gene Sequencing in Guiding Treatment Recommendations Patients With Metastatic or Recurrent Solid Tumors</td>
<td>150</td>
<td>Dec 2017</td>
</tr>
<tr>
<td>NCT01939847</td>
<td>IMAGE Study: Personalized Molecular Profiling in Cancer Treatment at Johns Hopkins</td>
<td>96</td>
<td>Jun 2018</td>
</tr>
<tr>
<td>NCT02693535</td>
<td>TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer (TAPUR)</td>
<td>1060</td>
<td>Mar 2019</td>
</tr>
<tr>
<td>NCT02152254</td>
<td>Randomized Study Evaluating Molecular Profiling and Targeted Agents in Metastatic Cancer: Initiative for</td>
<td>1362</td>
<td>May 2019</td>
</tr>
</tbody>
</table>
MP 2.04.115
Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies

- **Molecular Profiling and Advanced Cancer Therapy (IMPACT 2)**

<table>
<thead>
<tr>
<th>NCT</th>
<th>Study Title</th>
<th>Enrollment</th>
<th>Start Date</th>
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</thead>
<tbody>
<tr>
<td>NCT02437617</td>
<td>Genomic Profiling Assay in Phase Analysis as a Therapeutic Decision Tool for Patients with Advanced Solid Tumors: My Own Specific Treatment</td>
<td>300</td>
<td>Jul 2019</td>
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<tr>
<td>NCT02029001</td>
<td>Evaluation of the Efficacy of High Throughput Genome Analysis as a Therapeutic Decision Tool for Patients with Metastatic Breast Cancer (SAFIR02_Breast)</td>
<td>560</td>
<td>Nov 2019</td>
</tr>
<tr>
<td>NCT02299999</td>
<td>Molecular Profiling and Advanced Cancer Therapy for Patients with Advanced Solid Tumors: My Own Specific Treatment</td>
<td>1460</td>
<td>Jun 2021</td>
</tr>
<tr>
<td>NCT02645149</td>
<td>Molecular Profiling and Advanced Cancer Therapy for Patients with Advanced Solid Tumors: My Own Specific Treatment</td>
<td>1000</td>
<td>Jun 2021</td>
</tr>
<tr>
<td>NCT02465060</td>
<td>Molecular Analysis for Therapy Choice (MATCH)</td>
<td>6452</td>
<td>Jun 2022</td>
</tr>
<tr>
<td>NCT02154490</td>
<td>A Biomarker-Driven Master Protocol for Previously Treated Solid Tumors</td>
<td>10000</td>
<td>Apr 2025</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

\( ^{a} \) Denotes industry-sponsored or cosponsored trial.

**REFERENCES**


**CODES**

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>No specific code. See Policy Guidelines.</td>
<td></td>
</tr>
<tr>
<td>ICD-10-CM</td>
<td>Investigational for all diagnoses</td>
<td></td>
</tr>
<tr>
<td>ICD-10-CM</td>
<td>C00-D49 Neoplasms code range</td>
<td></td>
</tr>
<tr>
<td>ICD-10-PCS</td>
<td>Not applicable. ICD-10-PCS codes are only used for inpatient services. There are no ICD procedure codes for laboratory tests.</td>
<td></td>
</tr>
</tbody>
</table>

**POLICY HISTORY**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/13/14</td>
<td>New Policy – Add to Medicine-Pathology/Laboratory section</td>
<td>New policy created with literature review through February 15, 2014. The use of expanded mutation panels to direct targeted treatment is considered investigational.</td>
</tr>
<tr>
<td>04/23/15</td>
<td>Replace policy</td>
<td>Policy updated with literature review through April 4, 2015. References 6-11 added, and references 20-23 updated. No change to</td>
</tr>
</tbody>
</table>
MP 2.04.115
Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies

Policy statements.

10/15/15 Replace policy
Policy updated with literature review through September 30, 2015; references 4, 6, 8, 16-17, 21, 23, and 26 added. Policy statement unchanged. Title changed to “Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies”.

10/13/16 Replace policy
Policy updated with literature review through August 29, 2016; references 24, 26, and 35-36 added, references 3, and 28-33 updated. Policy statement unchanged.

10/30/17 Replace policy
Blue Cross of Idaho adopted changes to policy as noted. Policy updated with literature review through August 23, 2017; reference 26 added, references 3, 9-13, 15, 17-20, 29-34, 36 and 38 updated. Minor edits to the Policy section; statement otherwise unchanged.

APPENDIX

Appendix Table 1. Categories of Genetic Testing Addressed in 2.04.115

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Testing of an affected individual’s germline to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>1a. Diagnostic</td>
<td></td>
</tr>
<tr>
<td>1b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>1c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>2a. Diagnostic</td>
<td></td>
</tr>
<tr>
<td>2b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>2c. Therapeutic</td>
<td>X</td>
</tr>
<tr>
<td>3. Testing an asymptomatic individual to determine future risk of disease</td>
<td></td>
</tr>
<tr>
<td>4. Testing of an affected individual’s germline to benefit family members</td>
<td></td>
</tr>
<tr>
<td>5. Reproductive testing</td>
<td></td>
</tr>
<tr>
<td>5a. Carrier testing: preconception</td>
<td></td>
</tr>
<tr>
<td>5b. Carrier testing: prenatal</td>
<td></td>
</tr>
<tr>
<td>5c. In utero testing: aneuploidy</td>
<td></td>
</tr>
<tr>
<td>5d. In utero testing: familial variants</td>
<td></td>
</tr>
<tr>
<td>5e. In utero testing: other</td>
<td></td>
</tr>
<tr>
<td>5f. Preimplantation testing with in vitro fertilization</td>
<td></td>
</tr>
</tbody>
</table>