Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies

Policy Number: 2.04.115  Last Review: 2/2017
Origination: 2/2015  Next Review: 2/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for Molecular Panel Testing of Cancers to Identify Targeted Therapies. This is considered investigational.

Note: This is a type of genetic testing that may be excluded in some contracts. Verify benefits prior to review for Medical Necessity.

When Policy Topic is covered
Not Applicable

When Policy Topic is not covered
The use of expanded cancer mutation panels for selecting targeting cancer treatment is considered investigational.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>With various cancers that have not</td>
<td>• Testing of tumor tissue with an expanded</td>
<td>• Standard therapy without use of an expanded</td>
<td>• Overall survival</td>
</tr>
<tr>
<td>responded to standard therapy</td>
<td>cancer mutation panel</td>
<td>cancer mutation panel</td>
<td>• Disease-specific survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Test accuracy</td>
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<td></td>
<td></td>
<td></td>
<td>• Test validity</td>
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<tr>
<td></td>
<td></td>
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<td>• Other test performance measures</td>
</tr>
</tbody>
</table>

Currently, there is interest in treating cancers by targeting biological “pathways” that are 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. There are some individual markers that have established benefit in certain types of cancers; these situations are not addressed in this policy. Rather, the focus of this review is 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 different treatment than usually selected for a patient based on the type of cancer and its stage.

The evidence for the use of expanded mutation panels to direct targeted cancer treatment includes 1 randomized controlled trial (RCT), several 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 obtained from the available published literature. The large number of mutations and many different types of cancer preclude determination of clinical validity for the panels as a whole. Some evidence reports that many of the identified mutations are false positives (ie, not biologically active), after filtering by comparison with matched normal tissue and cancer mutation databases. To demonstrate clinical utility, RCTs are needed that compare the strategy of targeted treatment based on panel results with standard care. The first such RCT published, 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.

**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.(1) They reported heterogeneity of therapeutic responses ranging from a low of 25% for cancer chemotherapeutics to a high of 80% for medications such as COX-2 inhibitors, 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 be a result of 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 that are 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 categorize these findings into 3 categories.(2) 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 unknown importance.

There are a smaller number of individual genetic markers that fall into the first category, ie, have established utility for a particular cancer type. Utility of these markers has generally been demonstrated by randomized controlled trials (RCTs) that select patients with the marker, and report significant improvements in outcomes with targeted therapy compared with standard therapy. This policy does not apply to these individual markers that have demonstrated efficacy. According to recent National Comprehensive Cancer Network (NCCN) guidelines,(3) 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**
  - 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 will not be covered in this policy. In some cases, limited panels may be offered that are specific to one particular type of cancer, for example a panel of several markers for non-small-cell lung cancer. This policy is also not intended to address the use of these 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 1 potentially pathogenic mutation. 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. A total of 1813 molecular alterations were identified, and almost all patients (420/439 [96%]) had at least 1 molecular alteration. 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 mutation among cancers that originate from different organs. There are several examples of mutation-directed treatment that was effective in one type of cancer but not effective in another. For example, targeted therapy for epidermal growth factor receptor (EGFR) mutations have been successful in non-small-cell lung cancer 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. 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>
<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)</td>
<td>Solid</td>
<td>236 cancer-related genes and 47 introns from another 19 genes</td>
<td>NGS</td>
</tr>
<tr>
<td>FoundationOne Heme test (Foundation Medicine)</td>
<td>Hematologic</td>
<td>405 cancer-related genes and introns from another 31 genes</td>
<td>RNA sequencing</td>
</tr>
<tr>
<td>Test Description</td>
<td>Test Type</td>
<td>Genes</td>
<td>Technology/Approaches</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------------</td>
<td>-----------------</td>
<td>----------------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>OnkoMatch (GenPath Diagnostics)</td>
<td>Solid</td>
<td>68 mutations in 14 oncogenes and tumor suppressor genes</td>
<td>Multiplex PCR</td>
</tr>
<tr>
<td>GeneTrails Solid Tumor Panel (Knight Diagnostic Labs)</td>
<td>Solid</td>
<td>37 genes</td>
<td></td>
</tr>
<tr>
<td>Tumor profiling service (Caris Molecular Intelligence through Caris Life Sciences)</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)</td>
<td>Solid and hematologic</td>
<td>Up to 62 cancer-associated genes</td>
<td>NGS, cytogenomic array, other technologies</td>
</tr>
<tr>
<td>Guardant360 panel (GuardantHealth)</td>
<td>Solid</td>
<td>&gt;500 genetic “targets”</td>
<td>NGS</td>
</tr>
<tr>
<td>Paradigm Cancer Diagnostic (PcDx) Panel (Paradigm)</td>
<td>Solid</td>
<td>&gt;500 genetic “targets”</td>
<td>NGS</td>
</tr>
<tr>
<td>Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT)</td>
<td>Solid</td>
<td>341 cancer-associated genes</td>
<td>NGS</td>
</tr>
<tr>
<td>TruSeq® Amplicon Panel (Illumina)</td>
<td>Solid</td>
<td>48 cancer-related genes</td>
<td>NGS</td>
</tr>
<tr>
<td>Illumina TruSight™ Tumor (Illumina)</td>
<td>Solid</td>
<td>26 cancer-related genes</td>
<td></td>
</tr>
<tr>
<td>Ion AmpliSeq Comprehensive Cancer Panel (Life Technologies)</td>
<td>Solid</td>
<td>&gt;400 cancer-related genes and tumor suppressor genes</td>
<td></td>
</tr>
<tr>
<td>Ion AmpliSeq Cancer Hotspot Panel v2 (Life Technologies)</td>
<td>Solid</td>
<td>“Hotspot” regions of 50 cancer-related and tumor suppressor genes</td>
<td></td>
</tr>
</tbody>
</table>

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 (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.

**Rationale**

This evidence review was developed in March 2014 and has been updated periodically with literature review of the MEDLINE database. The most recent update covers the period through August 29, 2016. 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 mutation that is present or in excluding a mutation 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).

**Analytic Validity**

No published studies were identified that evaluated the analytic validity of these panels. The panels are performed primarily by next-generation sequencing (NGS), which has a high analytic validity. Some panels supplement NGS with additional testing methods, such as polymerase chain reaction (PCR), for intronic regions included as components of the panel. PCR is generally 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 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 mutations and large number of potential cancers for which they can be used. Clinical validity would need to be reported for each mutation for a particular type of cancer. Because there are hundreds of mutations 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 mutations 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 mutations with matched normal tissue can provide evidence about whether mutations are truly somatic cancer mutations or whether they are incidental variants that do not have meaningful biologic activity. Jones et al performed comprehensive mutation 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 mutations present in normal tissue, there was an average of 4.34 mutations per patient on targeted analysis and 135 mutations 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 mutations identified by targeted analysis were true positives and 62% were false positives; on whole exome analysis, 10% of mutations were true positives and 90% were false positives.
**Section Summary: Clinical Validity**

The evidence on clinical validity of expanded panels is incomplete. Because of the large number of mutations contained in expanded panels, it is not possible to determine clinical validity for the panels as a whole. While some mutations have a strong association with 1 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 mutations by comparison with matched normal tissue and cancer mutation databases, most identified mutations are found to be false positives. Thus, it is likely that clinical validity will need to be determined for each mutation and for 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 mutation testing followed by targeted treatment with a standard treatment strategy without mutation testing. Randomized trials are necessary to control for selection bias in treatment decisions, because clinicians may select candidates for mutation testing based on clinical, demographic, and other factors. Outcomes of these trials would be the morbidity and mortality associated with cancer and cancer treatment. Overall survival (OS) is most important; cancer-related survival and/or progression-free survival (PFS) may be acceptable surrogates. 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.\(^\text{22}\) Their definition of personalized treatment was driven by a biomarker, which could be genetic or nongenetic. Therefore, this analysis not only included studies of matched versus unmatched treatment based on genetic markers, but also included studies that personalized treatment based on nongenetic 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 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.\(^\text{23}\) 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 to 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 nongenetic.
Randomized Controlled Trials
The SHIVA trial was a randomized controlled trial of treatment directed by cancer mutation testing versus standard care, with the first results published in 2015. In this study, 195 patients with a variety of advanced cancers refractory to standard treatment were enrolled from 8 academic centers in France. Mutation testing included comprehensive analysis for 3 molecular pathways (hormone receptor pathway, PI3K/AKT/mTOR pathway, RAF/MEK pathway) performed by targeted NGS, 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><strong>KIT, ABL, RET</strong></td>
<td>• Imatinib</td>
</tr>
<tr>
<td><strong>AKT, mTORC1/2, PTEN, PI3K</strong></td>
<td>• Everolimus</td>
</tr>
<tr>
<td><strong>BRAF V600E</strong></td>
<td>• Vemurafenib</td>
</tr>
<tr>
<td><strong>PDGFRA/B, FLT-3</strong></td>
<td>• Sorafenib</td>
</tr>
<tr>
<td><strong>EGFR</strong></td>
<td>• Erlotinib</td>
</tr>
<tr>
<td><strong>HER2</strong></td>
<td>• Lapatinib and trastuzumab</td>
</tr>
<tr>
<td><strong>SRC, EPHA2, LCK, YES</strong></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 versus 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 versus 3 (3.4%) of 89 assessable patients in the standard care group. On subgroup analysis by molecular pathway, there were no significant differences in PFS between groups.

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 (Foundation One 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 (Adapted from Wheler et al, 2016)**

<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></td>
<td>0.061</td>
<td>0.001</td>
<td>0.087</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></td>
<td>0.028</td>
<td>&lt;0.001</td>
<td>0.121</td>
</tr>
</tbody>
</table>

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 get standard care.

An individual study of this type is Tsimberidou et al. In it, patients with advanced or metastatic cancer refractory to standard therapy underwent molecular profiling. PCR-based targeted sequencing was used to assess mutations in 10 cancer genes. Loss of PTEN was determined using immunohistochemistry, and anaplastic lymphoma kinase (ALK) translocation was assessed using FISH. 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 nonmatched 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 nonmatched 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 nonmatched therapy (p<0.001). At a median 15-month follow-up, survival was
13.4 months versus 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 to exclusion of certain groups.

Section Summary: Clinical Utility
Clinical utility has not been demonstrated for the use of expanded mutation panels
to direct targeted cancer treatment. One published RCT (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: (1) differences in clinical and demographic factors, (2)
differences in the severity of disease or prognosis of disease (ie 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 in general
whether or not patients were matched. As a result, these types of nonrandomized
studies do not provide definitive evidence on treatment efficacy. Further RCTs are
needed that randomize patients to a treatment strategy of mutation testing
followed by targeted treatment versus 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 mutation panel, the
evidence includes 1 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 (ie, 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.

**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 mutations. 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**
  - HER2 testing, when specific criteria are met.

- **Colon cancer**
  - KRAS and NRAS testing for patients with metastatic colon cancer.
  - Consider BRAF V600E 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 KIT mutations for patients with metastatic disease

- **Ovarian cancer**
  - BRCA

- **Chronic myelogenous leukemia**
  - BCR-ACL

- **Gastrointestinal stromal tumors**
  - 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 (NCD). In the absence of an NCD, 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>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02299999</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>460</td>
<td>Oct 2018</td>
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<tr>
<td>NCT02152254</td>
<td>Randomized Study Evaluating Molecular Profiling and Targeted Agents in Metastatic Cancer: Initiative for Molecular Profiling and Advanced Cancer Therapy (IMPACT 2)</td>
<td>1362</td>
<td>May 2019</td>
</tr>
<tr>
<td>NCT02029001</td>
<td>Adapting Treatment to the Tumor Molecular Alterations for Patients with Advanced Solid Tumors: My Own Specific Treatment</td>
<td>560</td>
<td>Feb 2020</td>
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<tr>
<td>NCT02645149</td>
<td>Molecular Profiling and Matched Targeted Therapy for Patients With Metastatic Melanoma</td>
<td>1000</td>
<td>Jun 2021</td>
</tr>
<tr>
<td>NCT02154490</td>
<td>A Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer (Lung-MAP)</td>
<td>10000</td>
<td>Apr 2022</td>
</tr>
<tr>
<td>NCT02465060</td>
<td>Molecular Analysis for Therapy Choice (MATCH)</td>
<td>3000</td>
<td>Jun 2022</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

There are also large-scale nonrandomized studies evaluating the efficacy of targeted treatment directed by genetic testing. The TAPUR study, sponsored by the American Society for Clinical Oncology, seeks to evaluate antitumor activity of targeted treatment based on genomic analysis. The following is a description from the study website:

“The Targeted Agent and Profiling Utilization Registry (TAPUR) Study is a prospective, non-randomized clinical trial that aims to describe the performance (both safety and efficacy) of commercially available, targeted anticancer drugs prescribed for treatment of patients with advanced cancer that has a potentially actionable genomic variant. The study also aims to simplify patient access to approved targeted therapies that are contributed to the program by collaborating pharmaceutical companies, catalogue the choice of genomic profiling test by clinical oncologists and learn about the utility of registry data to develop hypotheses for additional clinical trials.”

The trial plans to enroll patients with advanced solid tumors, multiple myeloma, and B-cell non-Hodgkin lymphoma that are refractory to standard care. The primary outcome is tumor response, as measured by RECIST criteria. A response rate of less than 10% will signify lack of efficacy, while a response rate of greater than 30% will signify potential efficacy, which will need to be corroborated in confirmatory trials.
References

### Billing Coding/Physician Documentation Information

81210  BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)

81235  EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)

81275  KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)

81323  PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant

81479  Unlisted molecular pathology procedure

88368  Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), manual, per specimen; initial single probe stain procedure

88381  Microdissection (ie, sample preparation of microscopically identified target); manual

### ICD-10 Codes

C00- D49  Neoplasms code range

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 mutation which is listed in the codes 81200-81409 would be reported using those codes and the other mutations in the panel which are not listed would be reported with 1 unit of the unlisted molecular pathology code 81479.

As an example of the coding that might be used, GenPath recommends the following CPT codes in their 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).

### Additional Policy Key Words

N/A

### Policy Implementation/Update Information

2/1/2015  New policy. Molecular Panel Testing of Cancers to Identify Targeted Therapies is considered investigational or a benefit exclusion.

2/1/2016  Title changed to “Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies”. Added CPT codes. No policy statement changes.

2/1/2017  No policy statement changes.
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