Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies

Title: Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member’s benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

**DESCRIPTION**
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.

**OBJECTIVE**
The objective of this policy is to evaluate the analytic validity, clinical validity, and clinical
utility of expanded molecular panel testing of cancers to identify targeted therapies.

**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 (ie, have established utility for a particular cancer type). The utility of these markers has been demonstrated by randomized controlled trials that select patients with the marker and report significant improvements in outcomes with targeted therapy compared with standard therapy. This evidence review does not apply to the individual markers that have demonstrated efficacy. According to recent National Comprehensive Cancer Network guidelines,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 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 (eg, a panel of several markers for NSCLC). This review is also not intended to address the use of cancer-specific panels that include a few variants. Rather, the intent is to address expanded panels that test for many potential variants that do not have established efficacy for the specific cancer in question.

When advanced cancers are tested with expanded molecular panels, most patients are found to have at least one potentially pathogenic variant.4-6 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.6 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.2,3,7 There are several examples of variant-directed treatment that was effective in one type of cancer but ineffective in another. For example, targeted therapy for epidermal growth factor receptor (EGFR) variants has been successful in NSCLC but not in trials of other cancer types. Treatment with tyrosine kinase inhibitors based on variant testing has been effective for renal cell carcinoma but has not demonstrated effectiveness for other cancer types tested. “Basket” studies, in which tumors of various histologic types that share a common genetic variant are treated with a targeted agent, also have been performed. One such study was published in 2015 by Hyman et al.8 In this study, 122 patients with BRAF V600 variants in nonmelanoma cancers were treated with vemurafenib. The authors reported that there appeared to be antitumor activity for some but not all cancers, with the most promising results seen for NSCLC, Erdheim-Chester disease, and Langerhans cell histiocytosis.

Expanded Cancer Molecular Panels
Table 1 provides a select list of commercially available expanded cancer molecular panels.

Table 1. Commercially Available Molecular Panels for Solid and Hematologic Tumor Testing

<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)9</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)9</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)10</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)11</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)12</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)13</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)14</td>
<td>Solid</td>
<td></td>
<td>Digital sequencing</td>
</tr>
</tbody>
</table>
Test (Manufacturer) | Tumor Type | No. of Genes Tested | Technology
--- | --- | --- | ---
Paradigm Cancer Diagnostic (PcDx™) Panel (Paradigm, Phoenix, AZ) | Solid | 186 alterations | NGS
Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT™; Memorial Sloan Kettering Cancer Center, New York, NY) | Solid | 341 cancer-associated genes | NGS
TruSeq® Amplicon Panel (Illumina, San Diego, CA) | Solid | 48 cancer-related genes | NGS
Illumina TruSight™ Tumor (Illumina, San Diego, CA) | Solid | 26 cancer-related genes | NGS
Ion AmpliSeq™ Comprehensive Cancer Panel (Thermo Fisher Scientific, Waltham, MA) | Solid | >400 cancer-related genes and tumor suppressor genes | NGS
Ion AmpliSeq™ Cancer Hotspot Panel v2 (Thermo Fisher Scientific, Waltham, MA) | 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 (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.

**POLICY**
The use of expanded cancer molecular panels for selecting targeted cancer treatment is considered **experimental / investigational**.

**RATIONALE**
The most recent literature review covers the period through August 23, 2017. 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).

**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.20 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. 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 vs 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 (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.\textsuperscript{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 nongenetic.

**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.\textsuperscript{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\textsuperscript{24}

<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>PDGFR(\alpha), PDGFR(\beta), 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.\textsuperscript{26} The PFS ratio was defined as the PFS on MTA (PFS\textsubscript{MTA}) to PFS on TPC (PFS\textsubscript{TPC}) 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 PFS\textsubscript{MTA}/PFS\textsubscript{TPC} 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.\(^{27}\) 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></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>

Adapted from Wheler et al (2016).\(^{27}\)

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 Tsimeridou et al (2012).\(^{28}\) 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 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.28

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 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.

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 (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 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 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.

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 their recommendations for common solid tumors are listed next:

- **Breast cancer.**
  - HER2 testing, when specific criteria are met.

- **Colon cancer.**
  - KRAS/NRAS testing for patients with metastatic colon cancer.
  - Consider V600E 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 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.

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>NCT01891344a</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 (ongoing)</td>
</tr>
<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>-----------------</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 Molecular Profiling and Advanced Cancer Therapy (IMPACT 2)</td>
<td>1362</td>
<td>May 2019</td>
</tr>
<tr>
<td>NCT02437617</td>
<td>Genomic Profiling Assay in Phase</td>
<td>300</td>
<td>Jul 2019</td>
</tr>
<tr>
<td>NCT02092001</td>
<td>Adapting Treatment to the Tumor Molecular Alterations for Patients with Advanced Solid Tumors: My Own Specific Treatment</td>
<td>560</td>
<td>Nov 2019</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>1460</td>
<td>Jun 2021</td>
</tr>
<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>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 Squamous Cell Lung Cancer (Lung-MAP)</td>
<td>10000</td>
<td>Apr 2025</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.

**CODING**

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

**CPT/HCPCS**

- 81161 DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
- 81162 BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis
- 81200 ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)
- 81201 APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
- 81202 APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
- 81203 APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
- 81205 BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)
- 81206 BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
81207  BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor 
breakpoint, qualitative or quantitative
81208  BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other 
breakpoint, qualitative or quantitative
81209  BLM (Bloom syndrome, RecQ helicase-like) (eg, Bloom syndrome) gene analysis, 
2281del6ins7 variant
81210  BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), 
gene analysis, V600 variant(s)
81211  BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) 
gene analysis; full sequence analysis and common duplication/deletion variants in 
BRCA1 (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 
510bp, exon
81212  BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) 
gene analysis; 185delAG, 5385insC, 6174delT variants
81213  BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) 
gene analysis; uncommon duplication/deletion variants
81214  BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; full 
sequence analysis and common duplication/deletion variants (ie, exon 13 del 3.835kb, 
exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)
81215  BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; 
known familial variant
81216  BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; full 
sequence analysis
81217  BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; 
known familial variant
81218  CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid 
leukemia), gene analysis, full gene sequence
81219  CALR (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants 
in exon 9
81220  CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene 
analysis; common variants (eg, ACMG/ACOG guidelines)
81221  CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene 
analysis; known familial variants
81222  CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene 
analysis; duplication/deletion variants
81223  CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene 
analysis; full gene sequence
81224  CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene 
analysis; intron 8 poly-T analysis (eg, male infertility)
81225  CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug 
81226  CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug 
81227  CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug 
Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, Bacterial Artificial Chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)

Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities

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)

F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant

F5 (coagulation Factor V) (eg, hereditary hype...
81262 IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); direct probe methodology (eg, Southern blot)

81263 IGH@ (Immunoglobulin heavy chain locus) (eg, leukemia and lymphoma, B-cell), variable region somatic mutation analysis

81264 IGK@ (Immunoglobulin kappa light chain locus) (eg, leukemia and lymphoma, B-cell), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)

81265 Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (eg, pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [eg, buccal swab or other germline tissue sample]

81266 Comparative analysis using Short Tandem Repeat (STR) markers; each additional specimen (eg, additional cord blood donor, additional fetal samples from different cultures, or additional zygosity in multiple birth pregnancies) (List separately in addition to code for primary procedures)

81267 Chimerism (engraftment) analysis, post transplantation specimen (eg, hematopoietic stem cell), includes comparison to previously performed baseline analyses; without cell selection

81268 Chimerism (engraftment) analysis, post transplantation specimen (eg, hematopoietic stem cell), includes comparison to previously performed baseline analyses; with cell selection (eg, CD3, CD33), each cell type

81270 JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant

81272 KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (eg, exons 8, 11, 13, 17, 18)

81273 KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), gene analysis, D816 variant(s)

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

81276 KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)

81287 MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), methylation analysis

81288 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis

81290 MCOLN1 (mucolipin 1) (eg, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)

81291 MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)

81292 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

81293 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants

81294 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81295</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81296</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81297</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81298</td>
<td>MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81299</td>
<td>MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81300</td>
<td>MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81301</td>
<td>Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed</td>
</tr>
<tr>
<td>81302</td>
<td>MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81303</td>
<td>MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; known familial variant</td>
</tr>
<tr>
<td>81304</td>
<td>MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81310</td>
<td>NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants</td>
</tr>
<tr>
<td>81311</td>
<td>NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)</td>
</tr>
<tr>
<td>81313</td>
<td>PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)</td>
</tr>
<tr>
<td>81314</td>
<td>PDGFRα (platelet-derived growth factor receptor, alpha polypeptide) (eg, gastrointestinal stromal tumor [GIST]), gene analysis, targeted sequence analysis (eg, exons 12, 18)</td>
</tr>
<tr>
<td>81315</td>
<td>PML/RARα, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative</td>
</tr>
<tr>
<td>81316</td>
<td>PML/RARα, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative</td>
</tr>
<tr>
<td>81317</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81318</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81319</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81321</td>
<td>PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81322</td>
<td>PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant</td>
</tr>
</tbody>
</table>
81323  PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant
81324  PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
81325  PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis
81326  PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant
81330  SMPD1 (sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)
81331  SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
81332  SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z)
81340  TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using amplification methodology (eg, polymerase chain reaction)
81341  TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using direct probe methodology (eg, Southern blot)
81342  TRG@ (T cell antigen receptor, gamma) (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
81355  VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G>A, c.173+1000C>T)
81370  HLA Class I and II typing, low resolution (eg, antigen equivalents); HLA-A, -B, -C, -DRB1/3/4/5, and -DQB1
81371  HLA Class I and II typing, low resolution (eg, antigen equivalents); HLA-A, -B, and -DRB1 (eg, verification typing)
81372  HLA Class I typing, low resolution (eg, antigen equivalents); complete (ie, HLA-A, -B, and -C)
81373  HLA Class I typing, low resolution (eg, antigen equivalents); one locus (eg, HLA-A, -B, or -C), each
81374  HLA Class I typing, low resolution (eg, antigen equivalents); one antigen equivalent (eg, B*27), each
81375  HLA Class II typing, low resolution (eg, antigen equivalents); HLA-DRB1/3/4/5 and -DQB1
81376  HLA Class II typing, low resolution (eg, antigen equivalents); one locus (eg, HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each
81377  HLA Class II typing, low resolution (eg, antigen equivalents); one antigen equivalent, each
81378  HLA Class I and II typing, high resolution (ie, alleles or allele groups), HLA-A, -B, -C, and -DRB1
81379  HLA Class I typing, high resolution (ie, alleles or allele groups); complete (ie, HLA-A, -B, and -C)
81380  HLA Class I typing, high resolution (ie, alleles or allele groups); one locus (eg, HLA-A, -B, or -C), each
81381  HLA Class I typing, high resolution (ie, alleles or allele groups); one allele or allele group (eg, B*57:01P), each
81382  HLA Class II typing, high resolution (ie, alleles or allele groups); one locus (eg, HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each
81383  HLA Class II typing, high resolution (ie, alleles or allele groups); 1 allele or allele group (eg, HLA-DQB1*06:02P), each
81400  Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
81401  Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81402  Molecular pathology procedure, Level 3 (eg, >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])
81403  Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81404  Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405  Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenic array analysis)
81406  Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenic array analysis for neoplasia)
81407  Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
81408  Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
81445  Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
81450  Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, KL, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed
Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed

Unlisted molecular pathology procedure

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

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

Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden (Effective April 1, 2018)

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 a 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 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, they recommend the following CPT codes: 81210 (1), 81235 (1), 81275 (1), 81323 (1), 88368 (2), 88381 (1).

Diagnoses
Experimental / Investigational for all diagnoses related to this medical policy.

REVISIONS

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>09-05-2014</td>
<td>Policy added to the bcbksks.com web site on August 6, 2014.</td>
</tr>
<tr>
<td>06-23-2015</td>
<td>Updated Description section.</td>
</tr>
<tr>
<td></td>
<td>Updated Rationale section.</td>
</tr>
<tr>
<td></td>
<td>In Coding section:</td>
</tr>
<tr>
<td></td>
<td>▪ Added CPT codes 81246, 81287, 81288, 81313, 81370, 81371, 81372, 81373, 81374, 81375, 81376, 81377, 81378, 81379, 81380, 81381, 81382, 81383, 81445, 81450, 81455, 88368, 88381.</td>
</tr>
<tr>
<td></td>
<td>Updated References section.</td>
</tr>
<tr>
<td>01-01-2016</td>
<td>In Coding section:</td>
</tr>
<tr>
<td></td>
<td>▪ Added CPT code: 81162</td>
</tr>
<tr>
<td></td>
<td>▪ Updated nomenclature to CPT codes: 81210, 81275, 81355, 81405, 81445, 81450, 81455.</td>
</tr>
<tr>
<td>02-19-2016</td>
<td>Revised title from, &quot;Molecular Panel Testing of Cancers to Identify Targeted Therapies.&quot;</td>
</tr>
<tr>
<td></td>
<td>Updated Description section.</td>
</tr>
<tr>
<td></td>
<td>In Policy section:</td>
</tr>
</tbody>
</table>
In Policy language, revised "targeting" to "targeted" to read, "The use of expanded cancer mutation panels for selecting targeted cancer treatment is considered experimental / investigational."
- Added Policy Guidelines.

Updated Rationale section.

Updated References section.

01-20-2017
Updated Description section.

In Policy section:
- Removed Policy Guidelines.

Updated Rationale section.

In Coding section:
- Added CPT codes: 81161, 81218, 81219, 81272, 81273, 81276, 81311, 81314, 81400, 81401, 81402, 81403, 81404.
- Removed CPT codes: 81280, 81281, 81282 (Termed codes, effective December 31, 2016).

Updated References section.

11-08-2017
Updated Description section.

In Policy section:
- Removed "mutation" and added "molecular" to read, "The use of expanded cancer molecular panels for selecting targeting cancer treatment is considered experimental / investigational."

Updated Rationale section.

Updated References section.

01-01-2018
In Coding section:
- Revised nomenclature to CPT code: 81257.

03-28-2018
In Coding section:
- Added CPT code: 0037U.

REFERENCES


Other References
1. Blue Cross and Blue Shield of Kansas Pathology Liaison Committee, July 2016.

APPENDIX
Appendix Table 1. Categories of Genetic Testing Addressed in This Policy

<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: mutations</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>