Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies

I. Description
Molecular profiling for malignant tumors catalogues specific biomarker information and generates potential treatment options. The personalized tumor molecular profiling services or tests are similar in that they all take an individual’s tumor tissue and, from it, produce a molecular profile of the tumor and a list of potential therapies. However, their individual testing methods vary from matching over expressed genes with drugs to more complex systems biology approaches. This policy addresses commercially available tests, including but not limited to:

- FoundationOne test (Foundation Medicine)
- FoundationOne Heme test (Foundation Medicine)
- Molecular Intelligence Service or Target Now (Caris Life Sciences)
- GeneKey (GeneKey Corp)
- GeneTrails Solid Tumor Panel (Knight Diagnostic Labs)
- Guardant 360 Panel (Guardant Health)
- OncInsights (Intervention Insights)
- OnkoMatch(GenPath Diagnostics)
- The Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT)

**FoundationOne**
Foundation One uses next generation sequencing "to interrogate the entire coding sequence of 236 cancer-related genes (3769 exons) plus 47 introns from 19 genes frequently altered or rearranged in cancer." Foundation One helps match the genomic alterations present in a tumor with specific targeted therapies or clinical trials. Recent small studies (Drilon, 2013; Lipson, 2012; Vignot, 2013) have investigated next generation sequencing in individuals with lung cancer. Others have used next generation sequencing in those with breast cancer (Ross, 2013a); colorectal cancer (Lipson, 2012), ovarian cancer (Ross, 2013b), and prostate cancer (Beltran, 2013). Limitations of these studies include small sample sizes and lack of randomization.
**Molecular Intelligence Service or Target Now**
The most widely used of the tumor molecular profiles has been the Target Now Molecular Profiling Service (Caris Life Sciences). According to the Caris Life Sciences website, their tumor profiling service is now being promoted as the Molecular Intelligence Service. Molecular Profiling Service begins with an immunohistochemistry analysis and if there is a frozen sample of tumor tissue available, a gene expression analysis by microarray may be performed. Additional tests may be added including: fluorescent in-situ hybridization to examine gene copy number variation in the tumor; polymerase chain reaction or deoxyribonucleic acid (DNA) sequencing is used to determine gene mutations in the DNA tumor. The results from each test are then applied to the published findings from cancer researchers and potential treatment options are subsequently generated. The Molecular Intelligence Service is promoted in a similar manner and is said to be available in several levels of service, "allowing the physician to customize the level of profiling they deem necessary for each patient."

Genekey (Caris Life Sciences) offers tumor profiling services that analyzes of up to 56 tumor-associated genes. According to the manufacturer’s website, panels with specific genes are not listed, but customized panels are available according to patients’ clinical information and cancer type. The panels use a variety of technologies, including NGS, immunohistochemistry, fluorescence in situ hybridization, Sanger sequencing, pyrosequencing, quantitative PCR, and fragmentation analysis.

The GeneTrails Solid Tumor Panel (Knight Diagnostic Labs, Portland OR) consists of 37 genes that are known to have mutations in solid tumors. Of the 37 mutations, 20 have known targetable treatments based on the presence or absence of mutations, and 17 have mutations that might indicate eligibility for ongoing clinical trials. According to the manufacturer, this test is intended for patients with adenocarcinomas (colon, small intestine, stomach, esophagus), squamous cell carcinomas (lung, head neck, esophagus, cervix), BRAF-negative melanomas, cholangiocarcinoma, and carcinomas of the endometrium, ovaries, salivary glands, urothelium, and adrenal cortices.

The Guardant360 panel (GuardantHealth, Redwood City, CA) analyzes 68 genes associated with solid tumors. It is intended for a wide variety of solid tumors. This panel uses novel technology to analyze cell-free DNA present in the circulating blood rather than analyzing a tumor sample. The manufacturer’s website refers to “digital sequencing” using information technology, but there is a lack of published studies that evaluate the analytic validity of this technique. The Paradigm Cancer Diagnostic (PcDx) Panel (Paradigm, Ann Arbor, MI) is a NGS-based panel that evaluates more than 500 genetic “targets.” Targets include point mutations, deletions, CNVs, fusions, mRNA expression, and protein expression. The test is intended for patients with a wide variety of cancers refractory to standard care.

OncInsights also begins with a fresh tumor sample obtained by biopsy. The lab processes the sample measuring genes and molecular data points to create a molecular pathway map of the individual's disease. The data is then processed by the company's bioinformatics platform, which analyzes information using a series of algorithms to identify key drug targets or signatures of drug response/resistance. The individual's unique profile is then compared to molecularly targeted drug databases to align disease characteristics with potential treatment options. Related scientific and clinical evidence are then located and a personalized report is generated.

OnkoMatch (GenPath Diagnostics) is a polymerase chain reaction (PCR)–based gene panel that detects 68 mutations (single nucleotide polymorphisms) in 14 oncogenes and tumor suppressor genes
that are associated with solid tumors (AKT1, APC, BRAF, CTNNB1 [beta-catenin], EGFR, IDH1, KIT, KRAS, MAP2K1, NOTCH1, NRAS, PIK3CA, PTEN, TP53). The product brochure (available on the manufacturer’s website) states that OnkoMatch is intended for use in patients with lung, breast, colon, gastrointestinal, pancreatic, head and neck, ovarian, or thyroid cancers, or melanoma. Test developers recommend its use “to support diagnostic and treatment decisions and to facilitate clinical trial enrollment.” GenPath also lists OnkoMatch Plus for Lung and OnkoMatch Plus for ALK-Negative Lung in its test catalog.

The Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) consists of 341 cancer associated genes. It is a hybridization capture-based NGS assay that detects mutations, CNVs, and structural rearrangements. This test offers paired analysis of tumor tissue with matched normal tissue to determine whether mutations are truly somatic cancer mutations.

A number of other targeted panels appear to be primarily marketed to researchers. Some of these are listed next:

- Illumina Inc. (San Diego, CA) offers several cancer panels. The TruSeq Amplicon Panel analyzes 48 cancer-related genes by NGS. The Illumina TruSight Tumor panel analyzes 26 cancer-related genes associated with solid tumors.
- Life Technologies offers several variations of its Ion AmpliSeq panels intended for use in cancer. The Ion AmpliSeq Comprehensive Cancer Panel analyzes more than 400 cancer-related genes and tumor suppressor genes. The Ion AmpliSeq Cancer Hotspot Panel v2 analyzes the “hotspot” regions of 50 cancer-related and tumor suppressor genes.

**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. They reported heterogeneity of therapeutic responses ranging from a low of 25% for cancer chemotherapeutics to as high as 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 result from genetic variations. Within each broad type of cancer, there may be a large amount of variability in the genetic underpinnings of the cancer.
Targeted cancer treatment refers to the identification of genetic abnormalities present in the cancer of a particular patient, and the use of drugs that target the specific genetic abnormality. Using genetic markers, cancers can be further classified by “pathways” defined at the molecular level. An expanding number of genetic markers have been identified. Dienstmann et al categorized these findings into 3 classes. 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.

A smaller number of individual genetic markers 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 that select patients with the marker, and report significant improvements in outcomes with targeted therapy compared with standard therapy. This evidence review does not apply to the individual markers that have demonstrated efficacy. According to recent National Comprehensive Cancer Network guidelines, the following markers have demonstrated utility for predicting treatment response to targeted therapies for the specific cancers listed:

- Breast cancer
  - HER2 (ERBB2)
- Colon cancer
  - RAS mutations (KRAS, NRAS)
  - BRAF c1799T>A
- Non-small-cell lung cancer (NSCLC)
  - EGFR
  - ALK/ROS1
  - KRAS
- Metastatic melanoma
  - BRAF v600
- Ovarian cancer
- BRCA (germline)
- Chronic myeloid leukemia
  - BRC-ABL
- Gastrointestinal stromal tumors
  - KIT

Testing for these individual mutations with established utility is not covered herein. In some cases, limited panels may be offered that are specific to 1 type of cancer (eg, a panel of several markers for NSCLC). This review 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.6 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 1 type of cancer but ineffective in another. For example, targeted therapy for epidermal growth factor receptor (EGFR) mutations has been successful in NSCLC but not in trials of other cancer types. Treatment with tyrosine kinase inhibitors based on mutation testing has been effective for renal cell carcinoma, but has not demonstrated effectiveness for other cancer types tested. “Basket” studies, in which tumors of various histologic types that share a common genetic mutation are treated with a targeted agent, also have been performed. One such study was published in 2015 by Hyman et al.8 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</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>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)13</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</td>
<td>Solid</td>
<td></td>
<td>Digital sequencing</td>
</tr>
</tbody>
</table>
Molecular Panel Testing of Cancers to Identify Targeted Therapies

<table>
<thead>
<tr>
<th>Paradigm Cancer Diagnostic (PcDx) Panel (Paradigm)</th>
<th>Solid</th>
<th>&gt;500 genetic “targets”</th>
<th>NGS</th>
</tr>
</thead>
<tbody>
<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 Panel (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>

II. Criteria/Guidelines

The use of expanded cancer mutation panels for selecting targeting cancer treatment does not meet payment determination criteria because there is a lack of evidence that this technique improves health outcomes.

III. Administrative Guidelines

Applicable Codes:

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81445</td>
<td>Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, 5-50 genes (e.g., ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed</td>
</tr>
<tr>
<td>81450</td>
<td>Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA and RNA analysis when performed, 5-50 genes (e.g., BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), INTERROGATION FOR SEQUENCE VARIANTS</td>
</tr>
<tr>
<td>81455</td>
<td>Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA and RNA analysis when performed, 51 or greater genes (e.g., 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</td>
</tr>
</tbody>
</table>
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 not specifically listed would be reported with 1 unit of the unlisted molecular pathology code 81479.

IV. Scientific Background

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

There were no published studies 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 the next-generation sequencing with additional testing methods, such as polymerase chain reaction (PCR), for intronic regions that are 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. They also report an analytic specificity of more than 99%.

CLINICAL VALIDITY

The clinical validity of the panels as a whole cannot be determined because of the many different mutations and the large number of potential cancers in which it can be used. Clinical validity would need to be reported for each specific mutation for a particular type of cancer. Because there are many hundreds of different mutations included in the panels and dozens of different 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 use of 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 that were present in normal tissue, there was
an average of 4.34 mutations/patient on targeted analysis and 135 mutations/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 specific 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 2015.22 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.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>KIT, ABL, RET</td>
<td>Imatinib</td>
</tr>
<tr>
<td>AKT, mTORC1/2, PTEN, PI3K</td>
<td>Everolimus</td>
</tr>
<tr>
<td>BRAF V600E</td>
<td>Vemurafenib</td>
</tr>
<tr>
<td>PDGFRA/B and FLT-3</td>
<td>Sorafenib</td>
</tr>
<tr>
<td>EGFR</td>
<td>Erlotinib</td>
</tr>
<tr>
<td>HER-2</td>
<td>Lapatinib and trastuzumab</td>
</tr>
<tr>
<td>SRC, EPHA2, LCK, YES</td>
<td>Dasatinib</td>
</tr>
<tr>
<td>Estrogen receptor, progesterone receptor Androgen receptor</td>
<td>Tamoxifen (or letrozole if contraindications) Abiraterone</td>
</tr>
<tr>
<td>Androgen receptor</td>
<td>Abiraterone</td>
</tr>
</tbody>
</table>

A total of 99 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 of 195 (42%) patients, alterations affecting the PI3K/AKT/mTOR pathway were found in 89 of 195 (46%) patients, and alterations affecting the RAF/MED pathway were found in 24 of 195 (12%) 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 of 98 (4.1%) assessable patients in the targeted treatment group versus 3 of 89 (3.4%) 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 this study, 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 IHC, 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 who were 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 versus 2.2 months on nonmatched therapy (p<0.001). At a median of 15 months’ follow-up, median 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 were shown to demonstrate 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, the 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 are able to get matched treatment with patients who are not able to get matched treatment, and have reported that outcomes are superior in patients receiving matched treatment. However, there are a number of 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 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 regardless of whether the patient was 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.

**Table 2: Studies of Multiple Molecular Marker Profiling and Cancer Outcomes**
## Molecular Panel Testing of Cancers to Identify Targeted Therapies

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Cancers</th>
<th>Content of Profile, Technique</th>
<th>Treatments Allocated to Subjects</th>
<th>Outcome Measure and Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Hoff et al (2010)</td>
<td>Breast (27%) Colorectal (17%) Ovarian (8%) Miscellaneous (48%)</td>
<td>11 proteins by IHC or FISH 51 genes for gene expression using microarray</td>
<td>Established cancer therapies Based on patients’ prior history, comorbidities, molecular profile, no formal algorithm</td>
<td>% of patients with PFS on targeted treatment 1.3 times longer than just prior treatment PFS (PFS ratio ≥3) 86 patients had molecular profiling (MP) 84 patients MP found target 66 patients treated with target 18/66 (27%) PFS ratio &gt;1.3</td>
</tr>
<tr>
<td>Tsimberidou et al (2012)</td>
<td>Melanoma (25%) Colorectal (21%) Thyroid (12%) Miscellaneous (43%)</td>
<td>10 genes sequenced RET, TP53, KRAS, BRAF, PIK3CA, NRAS, EGFR, GNAQ, KIT, MET genes sequenced PTEN loss with IHC ALK with FISH</td>
<td>Trial therapies (phase 1 studies) Based on known action of drugs’ action, 51 different trials. Some patients matched, some patients not matched to targeted therapies.</td>
<td>Response rate (RECIST criteria) 27% response in matched therapy 5% response in unmatched therapy Time to failure 5.2-mo failure time in matched therapy 2.2-mo failure time in unmatched therapy</td>
</tr>
<tr>
<td>Dienstmann et al (2012)</td>
<td>Colorectal cancer only</td>
<td>3 genes genotyped, sequenced KRAS, PIK3CA, BRAF by various methods PTEN, pMET with IHC</td>
<td>Trial therapies (phase 1 studies) Agents that theoretically match the tumor</td>
<td>Response rate (RECIST criteria) 1/68 patient with partial response Comparison of failure time with patients’ prior therapy 7.9-wk failure matched 16.3-wk failure unmatched</td>
</tr>
</tbody>
</table>

### Policy 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 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 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
- 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.

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.

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 Trials and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 4.

Table 3. 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>
</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>
</tbody>
</table>
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.

V. Important Reminder
The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA consider the application of this Medical Policy to the case at issue.
VI. References


