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)

**FoundationOne**

The FoundationOne is a targeted mutation panel intended for use with solid tumors. It analyzes 236 cancer-related genes (3,769 exons) plus 47 introns from an additional 19 genes using next-generation sequencing technology. The test identifies a number of types of mutations, including base substitutions, duplications/deletions, copy number variations, and rearrangements. The test can be performed on a surgical biopsy or a needle biopsy of a solid tumor that contains at least 40 mm of tissue, 20% of which must be malignant material.

FoundationOne Heme test is a similar panel that is intended for use in hematologic malignancies. It analyzes 405 cancer-related genes and selected introns from an additional 31 genes. In addition, RNA sequencing of 265 genes is done to test for common rearrangements resulting from gene fusion.

**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
Molecular Panel Testing of Cancers to Identify Targeted Therapies

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**

GeneKey profiles a tumor genome through whole genome mRNA expression profiling and copy number variant detection. A fresh biopsy specimen is initially obtained and sent to a laboratory that runs GeneKey-specified tests. Analysis is performed by proprietary systems biology approaches. A scientific team from GeneKey is sent to present results of potential treatment options, scientific rationale and relevant literature citations to the treating physician and the individual being tested.

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**

At this time, there are no specific CPT codes for molecular pathology panel testing. 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.

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).

**Analytical 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.

Clinical Utility

To demonstrate clinical utility, controlled trials are required in which a strategy of cancer mutation testing followed by targeted treatment based on mutation analysis is compared with standard treatment without mutation testing. Randomized trials will be 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 is most important; cancer-related survival and/or progression-free survival may be acceptable surrogates. Quality-of-life measurement may also be important if study design allows for treatments with different toxicities in the experimental and control groups. There are currently no published randomized controlled trials (RCTs) with this type of design.

The published evidence consists of nonrandomized studies that are intended to be pilot trials. Three of these studies are summarized in Table 1. In a study by Von Hoff et al, 86 patients with various cancers who had progression of their disease on at least 2 different prior regimens underwent molecular profiling of their cancer. The molecular profile consisted of a panel of 51 gene expression assays and 11 proteins assessed by either immunohistochemical (IHC) or fluorescent in situ hybridization (FISH). The profiles were reviewed by 2 study physicians, who identified potential targeted treatments based on the results. The process described does not appear to be an integrative approach to profiling cancer, but as simply reviewing the profiles for consistency. It was not stated explicitly how a target was identified. If targets were identified, the first priority target was where both gene expression and protein measurements were concordant for the same target. Next priority targets indicated targets with IHC alone, and least priority targets were positive by gene expression alone.

Eighty-six patients underwent molecular profiling. The molecular profiling apparently yielded a target in 84 of 86 patients. Sixty-six patients underwent a treatment suggested by their molecular profiling result. Patients dropped out of the study for various reasons, the most common being worsening clinical condition. The treatments assigned to patients were all established cancer treatments, although they sometimes represented off-label use for that particular cancer.

The study did not include a control group. Investigators proposed that patients who responded to the targeted treatment would have a longer progression-free survival (PFS) than the treatment they had most recently failed. A PFS time greater than 1.3 times their previous treatment (PFS ratio ≥1.3) was
considered a response, and the null hypothesis was set at 15% response. In the study 18 patients (27%) had a PFS ratio 1.3 or greater.

In the study by Tsimberidou et al, 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, nor 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.

In the study by Dienstmann et al, patients with advanced refractory colorectal cancer had molecular profiling with matching to targeted treatment. Three genes (KRAS, BRAF, PIK3CA) were analyzed for specific mutations, and PTEN and pMET gene expression levels were assessed using IHC. Sixty-eight patients were enrolled in 15 different phase 1 clinical trials, in which 82 matched targeted therapies were assigned to patients. It was not explicitly stated how a therapy was considered a match.

The outcome assessed in the study was the time-to-treatment failure (TTF), which was compared with the TTF for the patients’ treatment just before enrollment in the study. Median TTF on matched treatment was 7.9 weeks versus 16.3 weeks for prior treatment, indicating worse results on matched treatment. Only 1 patient was considered to have had a confirmed partial response to matched treatment. Stable disease longer than 16 weeks was observed in 10 patients.

A major concern with clinical utility is the identification of 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. The FoundationOne website reports that in their database of over 2200 test results, the average number of variants identified per sample is 3.06 (range, 0-23). There is potential for harm with this high number of variants identified. Patients may be given treatments that have substantial toxicity and no benefit if treatment decisions are made based on variants with uncertain clinical significance.

Molecular Intelligence Service or Target Now
The published literature addressing these services is limited. Von Hoff and colleagues (2010) evaluated 86 individuals with refractory metastatic cancer. Progression-free survival (PFS) using a treatment regimen selected by Target Now molecular profiling of a malignant tumor was compared with the PFS of the most recent treatment regimen on which the individual experienced progression. A molecular target was detected in 84 of 86 (98%) participants. A total of 66 (78.6%) individuals were treated according to the molecular profile results with 18 of the 66 (27%) having a PFS ratio (defined as PFS on molecular profile–selected therapy or PFS on prior therapy) of greater than or equal to 1.3 (95% confidence interval [CI], 17% to 38%; P=0.007).

An editorial (Doroshow, 2010) accompanying the study reported that the trial had a number of significant limitations, including uncertainty surrounding the achievement of time to progression (the study's primary endpoint), and a lack of a randomized design. Additional limitations include a small number of participants and lack of duplication of study results by an independent dataset.

GeneKey has even less validation. To date, there are no studies in the published literature specifically addressing this test.

Section Summary

These 3 trials of molecular marker profiling in cancer patients are early studies in the evaluation of molecular profiling to choose treatment and do not provide strong evidence of the approach. The studies by Von Hoff et al and Dienstmann et al lacked control groups. It is uncertain whether a comparison to patients’ just previously failed treatment is a valid measure of patient response or benefit. The biologic state of patients’ cancer is probably different after treatment failure. The patients’ state of health is probably worse. In the study by Tsimberidou et al, the patients in the matched and nonmatched treatment groups were not randomly allocated, and there may be confounding in either patient characteristics or treatment responsible for the difference. In the studies of Tsimberidou et al and Dienstmann et al, the targeted treatments assigned were generally agents in phase I clinical trials, thus possibly of uncertain benefit to any kind of patient. It cannot be determined if the testing strategy apart from the treatment assigned had any influence on patient outcome. A further concern is the presence of many variants of uncertain significance, which may lead to harm due to adverse events that result from unnecessary treatment.

Table 1: Studies of Multiple Molecular Marker Profiling and Cancer Outcomes

<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</td>
</tr>
</tbody>
</table>
Summary

Genetic panels that test for a large number of cancer-associated mutations are commercially available. These expanded panels are intended for use in patients with cancer for whom a specific targeted therapy based on mutation analysis is not available. The analytic validity of these panels is likely to be high when next generation sequencing is used. The clinical validity of the individual mutations for particular types of cancer is not easily obtained from the available published literature. To demonstrate clinical utility, RCTs are needed that compare the strategy of targeted treatment based on panel results with standard care. No such trials have currently been published. The available literature on clinical utility consists of a small number of uncontrolled studies, and nonrandomized controlled trials that use imperfect comparators. This evidence is not sufficient to make any conclusions on clinical utility. 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.

Ongoing Trials

There are ongoing randomized controlled trials underway and/or in the planning stages that will address the strategy of targeted therapy based on testing for a wide range of cancer-related mutations. A few examples are provided here.

Le Tourneau et al published a description of their trial of molecular marker profiling in 2012, the SHIVA trial, which is summarized in Table 2. This is a rigorously designed trial, and it highlights important issues in the evaluation of efficacy of this approach. In this study, patients with a variety of advanced cancers will be enrolled. It is proposed that no more than 20% of patients with the same tumor type will be included. Nineteen molecular markers will be measured using genotyping, gene
expression, or IHC. Based on the pattern of abnormalities found, 9 different regimens of established cancer treatments will be assigned to the experimental treatment arm (Table 3). For example, patients with HER-2 positive cancer will be given lapatinib and trastuzumab. Patients with androgen receptor-positive cancer will be given abiraterone. The patients will be randomized to targeted treatment versus conventional therapy based on treating physicians’ choice.

Table 2. Treatment Algorithm for Experimental Arm, From Study of Le Tourneau et al

<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</td>
<td>Tamoxifen (or letrozole if contraindications) Abiraterone</td>
</tr>
<tr>
<td>Androgen receptor</td>
<td></td>
</tr>
</tbody>
</table>

The outcome of the study is progression-free survival (PFS). With 200 total patients in the study, it will have a power of 80% to detect a hazard ratio of 1.6 between the intervention and control groups, or a doubling of the 6-month PFS rate (from 15%-30%).

The National Cancer Institute is sponsoring a study called the M-PACT trial. This trial will screen patients with advanced refractory solid tumors that are resistant to standard therapy for 391 mutations in 20 genes. A total of 180 patients will be selected who have mutations for which a trial of treatment with an available targeted medication is feasible. If mutations of interest are detected, using a panel of mutations and a sequencing protocol approved by FDA, those patients will be enrolled in the trial and randomly assigned to 1 of 2 treatment arms to receive 1 of the 4 treatment regimens that are part of this study. This trial is in the early stages of implementation.

Policy Guidelines and Position Statements

NCCN guidelines do not contain recommendations for the general strategy of testing a tumor for a wide range of mutations.

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.

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