BlueCross BlueShield of Louisiana

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Molecular Panel Testing of Cancers to Identify Targeted Therapies

Policy # 00423
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of expanded cancer mutation panels for selecting targeting cancer treatment to be **investigational.***

Background/Overview

Currently, there is interest in treating cancers by targeting biological "pathways" that are characterized by specific genetic markers. Genetic panel testing offers the potential to evaluate a large number of genetic markers at a single time to identify treatments that target specific pathways. There are some individual markers that have established benefit in certain types of cancers; these situations are not addressed in this policy. Rather, the focus of this review is on "expanded" panels, which are defined as panels that test a wide variety of genetic markers in cancers without regard for whether specific targeted treatment has demonstrated benefit. This approach may result in a different treatment than usually selected for a patient based on the type of cancer and its stage.

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 a high of 80% for medications such as COX-2 inhibitors, with response rates for most drugs falling in the range of 50% to 75%. The low rate for cancer treatments is indicative of the need for better identification of characteristics associated with treatment response and better targeting of treatment in order to have higher rates of therapeutic responses.

Much of the variability in clinical response may be a result of genetic variations. Within each broad type of cancer there may be a large amount of variability in the genetic underpinnings of the cancer. Targeted cancer treatment refers to the identification of genetic abnormalities that are present in the cancer of a

particular patient, and the use of drugs that target the specific genetic abnormality. Using genetic markers, cancers can be further classified by "pathways" defined at the molecular level. An expanding number of genetic markers have been identified. Dienstmann et al categorize these findings into 3 categories. These are: (1) Genetic markers that have a direct impact on care for the specific cancer of interest, (2) Genetic markers that may be biologically important but are not currently actionable, and (3) Genetic markers of unknown importance.

There are a smaller number of individual genetic markers that fall into the first category, ie, have established utility for a particular cancer type. Utility of these markers has generally been demonstrated by randomized controlled trials (RCTs) that select patients with the marker, and report significant improvements in outcomes with targeted therapy compared with standard therapy. This policy does not apply to these individual markers that have demonstrated efficacy. According to recent National Comprehensive Cancer Network (NCCN) guidelines, the following markers have demonstrated utility for predicting treatment response to targeted therapies for the specific cancers listed:

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

Testing for these individual mutations with established utility will not be covered in this policy. In some cases, limited panels may be offered that are specific to 1 particular type of cancer, for example a panel of several markers for non-small-cell lung cancer. This policy is also not intended to address the use of these cancer-specific panels that include a few mutations. Rather, the intent is to address expanded panels that test for many potential mutations that do not have established efficacy for the specific cancer in question.
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 not effective in another. For example, targeted therapy for epidermal growth factor receptor (EGFR) mutations has been successful in non-small-cell lung cancer but not in trials of other cancer types. Treatment with tyrosine kinase inhibitors based on mutation testing has been effective for renal cell carcinoma, but has not demonstrated effectiveness for other cancer types tested.

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Expanded cancer mutation panels
The FoundationOne™ test (Foundation Medicine Inc., Cambridge, MA) is a targeted mutation panel intended for use with solid tumors. It analyzes 236 cancer-related genes and 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 µm of tissue, 20% of which must be malignant material.

FoundationOne Heme test (Foundation Medicine Inc., Cambridge, MA) 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.

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 next-generation sequencing. The Illumina TruSight™‡ Tumor panel analyzes 26 cancer-related genes associated with solid tumors.
- Life technologies Inc. offers several variations of their 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
There are no FDA-approved genetic panels for targeted cancer treatment. Commercially available panels are laboratory-developed tests that are not subject to FDA approval. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

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).

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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. Polymerase chain reaction 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 (PFS) 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 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 immunohisochemical (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.

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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 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.

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

Author	Types of Cancers	Content of Profile, Technique	Treatments Allotted to Subjects	Outcome Measure and Results
Von Hoff et al (2010)	Breast (27%) Colorectal (17%) Ovarian (8%) Miscellaneous (48%)	• 11 proteins by IHC or FISH • 51 genes for gene expression using microarray	• Established cancer therapies • Based on patients' prior history, comorbidities, molecular profile, no formal algorithm	• % 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 >1.3

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Tsimberidou et al (2012)	Melanoma (25%) Colorectal (21%) Thyroid (12%) Miscellaneous (43%)	• 10 genes sequenced • RET, TP53, KRAS, BRAF, PIK3CA, NRAS, EGFR, GNAQ, KIT, MET genes sequenced • PTEN loss with IHC • ALK with FISH	• 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.	• 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
Dienstmann et al (2012)	Colorectal cancer only	• 3 genes genotyped, sequenced • KRAS, PIK3CA, BRAF by various methods • PTEN, pMET with IHC	• Trial therapies (phase 1 studies) • Agents that theoretically match the tumor	• 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

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 non-RCTs 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. As a result, the use of expanded mutation panel testing for targeted treatment in cancer is considered investigational.

Ongoing Trials
There are ongoing RCTs 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

Molecular Abnormalities	Molecularly Targeted Agent
KIT, ABL, RET	Imatinib
AKT, mTORC1/2, PTEN, PI3K	Everolimus
BRAF V600E	Vemurafenib
PDGFRA/B and FLT-3	Sorafenib
EGFR	Erlotinib
HER-2	Lapatinib and trastuzumab
SRC, EPHA2, LCK, YES	Dasatinib
Estrogen receptor, progesterone receptor	Tamoxifen (or letrozole if contraindications)
Androgen receptor	Abiraterone

The outcome of the study is 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.

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Practice Guidelines and Position Statements
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.
  - EGFR and ALK testing for patients with metastatic adenocarcinoma
  - Consider EGFR and ALK testing especially in never smokers, mixed histology, or small biopsy specimen
- Melanoma. V600 BRAF testing for patients with metastatic disease

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81479
HCPCS	No codes
ICD-9 Diagnosis	All relative diagnoses
ICD-9 Procedure	No codes

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07/16/2014 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 7/2015

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

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1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
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