Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies

Policy # 00423
Original Effective Date: 07/16/2014
Current Effective Date: 06/19/2019

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 molecular panels for selecting targeting cancer treatment to be investigational.*

Policy Guidelines
Genetics Nomenclature Update
The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society’s nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.
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Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
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</table>

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

**Background/Overview**

**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...
Spear et al (2001) 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. Testing for 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 non-small-cell lung cancer). This review also does not address the use of cancer-specific panels that include a few variants. Rather, this review addresses 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 1 potentially pathogenic variant. 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 study by Schwaederle et al (2015), 439 patients with diverse cancers were tested with a 236-gene panel. A total of 1813 molecular alterations were identified, and almost all patients (420/439 [96%]) had at least 1 molecular alteration. The median number of alterations per patient was 3, and 85%
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(372/439) of patients had 2 or more alterations. The most common alterations were in the \textit{TP53} (44\%), \textit{KRAS} (16\%), and \textit{PIK3CA} (12\%) genes.

Some evidence is available on the generalizability of targeted treatment based on a specific variant among cancers that originate from different organs. There are several examples of variant-directed treatment that is effective in 1 type of cancer but ineffective in another. For example, targeted therapy for epidermal growth factor receptor variants have been successful in non-small-cell lung cancer 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 by Hyman et al (2015). In this study, 122 patients with \textit{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 non-small-cell lung cancer, Erdheim-Chester disease, and Langerhans cell histiocytosis.

\textbf{Expanded Cancer MOLECULAR Panels}

Table 1 provides a select list of commercially available expanded cancer molecular panels.

<table>
<thead>
<tr>
<th>Test</th>
<th>Manufacturer</th>
<th>Tumor Type</th>
<th>Technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>FoundationOne®‡ test</td>
<td>Foundation Medicine</td>
<td>Solid</td>
<td>NGS</td>
</tr>
<tr>
<td>FoundationOne®‡ Heme test</td>
<td>Foundation Medicine</td>
<td>Hematologic</td>
<td>RNA sequencing</td>
</tr>
<tr>
<td>OnkoMatch™†</td>
<td>GenPath Diagnostics</td>
<td>Solid</td>
<td>Multiplex PCR</td>
</tr>
<tr>
<td>GeneTrails®‡ Solid Tumor Panel</td>
<td>Knight Diagnostic Labs</td>
<td>Solid</td>
<td></td>
</tr>
<tr>
<td>Tumor profiling service</td>
<td>Caris Molecular Intelligence through Caris Life Sciences</td>
<td>Solid</td>
<td>Multiple technologies</td>
</tr>
<tr>
<td>SmartGenomics™†</td>
<td>PathGroup</td>
<td>Solid and hematologic</td>
<td>NGS, cytogenomic array, other technologies</td>
</tr>
</tbody>
</table>

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<th>Technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guardant360 panel (GuardantHealth, 2015 #399)</td>
<td>GuardantHealth</td>
<td>Solid</td>
<td>Digital sequencing</td>
</tr>
<tr>
<td>Paradigm Cancer Diagnostic (PcDx™) Panel</td>
<td>Paradigm</td>
<td>Solid</td>
<td>NGS</td>
</tr>
<tr>
<td>Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets</td>
<td>MSK-IMPACT™; Memorial Sloan Kettering Cancer Center</td>
<td>Solid</td>
<td>NGS</td>
</tr>
<tr>
<td>TruSeq® Amplicon Panel</td>
<td>Illumina</td>
<td>Solid</td>
<td>NGS</td>
</tr>
<tr>
<td>Illumina TruSight™ Tumor</td>
<td>Illumina</td>
<td>Solid</td>
<td>NGS</td>
</tr>
<tr>
<td>Ion AmpliSeq™ Comprehensive Cancer Panel</td>
<td>Thermo Fisher Scientific</td>
<td>Solid</td>
<td>NGS</td>
</tr>
<tr>
<td>Ion AmpliSeq™ Cancer Hotspot Panel v2</td>
<td>Thermo Fisher Scientific</td>
<td>Solid</td>
<td>NGS</td>
</tr>
<tr>
<td>OmniSeq Comprehensive</td>
<td>OmniSeq</td>
<td>Solid</td>
<td>NGS</td>
</tr>
</tbody>
</table>

NGS: next-generation sequencing; PCR: polymerase chain reaction.

## FDA or Other Governmental Regulatory Approval

**U.S. Food and Drug Administration (FDA)**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

## Rationale/Source

Genetic panel testing offers the potential to evaluate a large number of genetic markers at a single time to identify cancer treatments that target specific biologic pathways. Some individual markers have established benefit in certain types of cancers; they are not addressed in this evidence review. Rather, this review focuses on “expanded” panels, which are defined as molecular panels that test a...
Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies

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A wide variety of genetic markers in cancers without regard for whether specific targeted treatment has demonstrated benefit. This approach may result in a treatment different from that usually selected for a patient based on the type and stage of cancer.

For individuals who have a cancer that is being considered for targeted therapy who receive testing of tumor tissue with an expanded cancer molecular panel, the evidence includes a randomized controlled trial, nonrandomized trials, and numerous case series. Relevant outcomes are overall survival, disease-specific survival, test validity, and quality of life. A large number of variants and many types of cancer preclude determination of the clinical validity of the panels as a whole. To demonstrate clinical utility, direct evidence from interventional trials, ideally randomized controlled trials, are needed that compare the strategy of targeted treatment based on panel results with standard care. The first such published randomized controlled trial, molecularly targeted therapy based on tumour molecular profiling vs conventional therapy for advanced cancer, (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. Also, there is potential for harm if ineffective therapy is given based on test results, because there may be adverse events of therapy in the absence of a benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements
The National Comprehensive Cancer Network guidelines do not contain recommendations for the general strategy of testing a tumor for a wide range of variants. The guidelines do contain recommendations for specific genetic testing for individual cancers, based on situations where there is a known mutation-drug combination that has demonstrated benefits for that specific tumor type. Some examples of recommendations for testing of common solid tumors are listed below:

- Breast cancer
  - HER2 testing, when specific criteria are met.
- Colon cancer
  - KRAS, NRAS, and BRAF testing for patients with metastatic colon cancer.
Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies

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- Non-small-cell lung cancer
  - KRAS, EGFR, ALK, and ROS1 as part of broad molecular profiling to minimize wasting of tissue.
- Melanoma
  - BRAF V600 testing for patients with metastatic disease
  - KIT in the appropriate clinical setting for patients with metastatic disease
- Ovarian cancer
  - BRCA
- Chronic myelogenous leukemia
  - BCR-ABL1
- Gastric cancer
  - CDH1 for hereditary cancer predisposition syndromes.
  - Bladder cancer
  - Comprehensive molecular profiling for advanced disease.

**College of American Pathologists et al**
The College of American Pathologists and 2 other associations (2018) updated their joint guidelines on molecular testing of patients with non-small-cell lung cancer. The groups gave a strong recommendation for EGFR, ALK, and ROS1 testing. Based on expert consensus opinion KRAS was recommended as a single gene test if EGFR, ALK, and ROS1 were negative. Tests that were not recommended for single gene testing outside of a clinical trial were BRAF, RET, ERBB2 (HER2), and MET, although these genes should be tested if included in a panel.

**American Society of Clinical Oncology**
The American Society of Clinical Oncology (2018) affirmed the majority of these guidelines. The Society guidelines also recommended BRAF testing on all patients with advanced lung adenocarcinoma.

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

**Medicare National Coverage**
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.
Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td>Ongoing</td>
<td></td>
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<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>1440</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>1391</td>
<td>May 2020</td>
</tr>
<tr>
<td>NCT022999999</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 MatchedTargeted Therapy for Patients With Metastatic Melanoma</td>
<td>1000</td>
<td>Aug 2021</td>
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<tr>
<td>NCT02154490</td>
<td>A Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer (Lung-MAP)</td>
<td>10000</td>
<td>Apr 2022</td>
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<tr>
<td>NCT02465060</td>
<td>Molecular Analysis for Therapy Choice (MATCH)</td>
<td>6452</td>
<td>Jun 2022</td>
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<tr>
<td>NCT02029001</td>
<td>Adapting Treatment to the Tumor Molecular Alterations for Patients with Advanced Solid Tumors: My Own Specific Treatment</td>
<td>560</td>
<td>Oct 2022</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

References


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07/10/2014 Medical Policy Committee review
07/16/2014 Medical Policy Implementation Committee approval. New policy.
06/04/2015 Medical Policy Committee review
06/17/2015 Medical Policy Implementation Committee approval. Updated rationale and references. No change in coverage.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
06/02/2016 Medical Policy Committee review
06/20/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
06/01/2017 Medical Policy Committee review
06/21/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/01/2018 Coding update
06/07/2018 Medical Policy Committee review
06/20/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/01/2018 Coding update
01/01/2019 Coding update
06/06/2019 Medical Policy Committee review
06/19/2019 Medical Policy Implementation Committee approval. Title changed from Molecular Panel Testing of Cancers to Identify Targeted Therapies” to “Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies”. Changed “mutation” to “molecular” in the INV statement.
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Next Scheduled Review Date: 06/2020

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

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<td>Code added eff 1/1/19: 81173, 81174, 81204</td>
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<td>HCPCS</td>
<td>No codes</td>
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<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
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</table>
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*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:

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
3. Reference to federal regulations.

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