



Louisiana

Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies

Policy # 00423

Original Effective Date: 07/16/2014

Current Effective Date: 07/12/2021

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.

Note: BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy is addressed separately in medical policy 00320.

Note: Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing is addressed separately in medical policy 00382.

Note: Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer is addressed separately in medical policy 00452.

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 comprehensive genomic profiling for selecting targeted 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

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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.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

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

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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 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

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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 benefits. It is unusual for cancer treatment to be effective for all patients treated in a traditional clinical trial. 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 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. These may be categorized into three classes (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.

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Louisiana

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When advanced cancers are tested with expanded molecular panels, most patients are found to have at least one 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% (372/439) of patients had 2 or more alterations. The most common alterations were in the *TP53* (44%), *KRAS* (16%), and *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 one 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 *BRAF* V600 variants in nonmelanoma cancers were treated with vemurafenib. The authors reported that there appeared to be an 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.

Expanded Cancer Molecular Panels

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

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

Test	Manufacturer	Tumor Type	Technology
FoundationOne [®] †CDx test (F1CDx)	Foundation Medicine	Solid	NGS
FoundationOne [®] †CDx Heme test	Foundation Medicine	Hematologic	RNA sequencing

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Louisiana

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Policy # 00423

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Test	Manufacturer	Tumor Type	Technology
OnkoMatch™‡	GenPath Diagnostics	Solid	Multiplex PCR
GeneTrails®‡ Solid Tumor Panel	Knight Diagnostic Labs	Solid	
Tumor profiling service	Caris Molecular Intelligence through Caris Life Sciences	Solid	Multiple technologies
SmartGenomics™‡	PathGroup	Solid and hematologic	NGS, cytogenomic array, other technologies
Paradigm Cancer Diagnostic (PcDx™‡) Panel	Paradigm	Solid	NGS
MSK-IMPACT™‡;	Memorial Sloan Kettering Cancer Center	Solid	NGS
TruSeq®‡ Amplicon Panel		Solid	NGS
TruSight™‡ Oncology	Illumina	Solid	NGS
Ion AmpliSeq™‡ Comprehensive Cancer Panel		Solid	NGS
Ion AmpliSeq™‡ Cancer Hotspot Panel v2	Thermo Fisher Scientific	Solid	NGS
OmniSeq Comprehensive®‡	OmniSeq	Solid	NGS
Oncomine DX Target Test	Thermo Fisher Scientific	Solid	NGS

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

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Louisiana

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Policy # 00423

Original Effective Date: 07/16/2014

Current Effective Date: 07/12/2021

Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing.

In 2017, FoundationOne CDx (Foundation Medicine) received premarket approval by the U.S. Food and Drug Administration (FDA) (P170019) as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 2. "Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms." Food and Drug Administration product code: PQP

In 2017, the Oncomine DX Target Test (Life Technologies Corp) received premarket approval by the FDA (P160045) to aid in selecting non-small cell lung cancer patients for treatment with approved targeted therapies. FDA product code: PQP

MSK-IMPACT (Memorial Sloan Kettering) received de novo marketing clearance in 2017 (DEN170058). "The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and microsatellite instability for use by qualified health care professionals in accordance with professional guidelines, and is not conclusive or prescriptive for labeled use of any specific therapeutic product." Food and Drug Administration product code: PZM

OmniSeq Comprehensive is approved by the New York State Clinical Laboratory Evaluation Program.

Table 2. Companion Diagnostic Indications for F1CDx

Tumor Type	Biomarker(s) Detected	Therapy
Non-small cell lung cancer (NSCLC)	<i>EGFR</i> exon 19 deletions and <i>EGFR</i> exon 21 L858R alterations	Gilotrif ^{®†} (afatinib), Iressa ^{®†} (gefitinib), Tagrisso ^{®†} (osimertinib), or Tarceva ^{®†} (erlotinib)
	<i>EGFR</i> exon 20 T790M alterations	Tagrisso ^{®†} (osimertinib)

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	<i>ALK</i> rearrangements	Alecensa ^{®†} (alectinib), Xalkori ^{®†} (crizotinib), or Zykadia ^{®†} (ceritinib)
	<i>BRAF</i> V600E	Tafinlar ^{®†} (dabrafenib) in combination with Mekinist ^{®†} (trametinib)
	<i>MET</i>	Tabrecta(TM) (capmatinib)
Melanoma	<i>BRAF</i> V600E	Tafinlar ^{®†} (dabrafenib) or Zelboraf ^{®†} (vemurafenib)
	<i>BRAF</i> V600E and V600K	Mekinist ^{®†} (trametinib) or Cotellic ^{®†} (cobimetinib) in combination with Zelboraf ^{®†} (vemurafenib)
Breast cancer	<i>ERBB2</i> (HER2) amplification	Herceptin ^{®†} (trastuzumab), Kadcyla ^{®†} (ado-trastuzumabemtansine), or Perjeta ^{®†} (pertuzumab)
	<i>PIK3CA</i> alterations	Piqray [®] (alpelisib)
Colorectal cancer	<i>KRAS</i> wild-type (absence of mutations in codons 12 and 13)	Erbix ^{®†} (cetuximab)
	<i>KRAS</i> wild-type (absence of mutations in exons 2, 3, and 4) and <i>NRAS</i> wild type (absence of mutations in exons 2, 3, and 4)	Vectibix ^{®†} (panitumumab)
Ovarian cancer	<i>BRCA1/2</i> alterations	Lynparza ^{®†} (olaparib) or Rubraca ^{®†} (rucaparib)
Cholangiocarcinoma	<i>FGFR2</i> fusion or other select rearrangements	Pemazyre(TM) (pemigatinib)
Prostate cancer	Homologous Recombination Repair (HRR) gene alterations	Lynparza ^{®†} (olaparib)

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Rationale/Source

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

For individuals who have advanced cancer that is being considered for targeted therapy who receive comprehensive genomic profiling of tumor tissue, the evidence includes a randomized controlled trial, nonrandomized trials, and systematic reviews of these studies. The 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, and clinical utility has not been demonstrated for the use of expanded molecular panels to direct targeted cancer treatment. The one published randomized controlled trial (SHIVA trial) that used an expanded panel reported no difference in progression-free survival compared with standard treatment. Additional randomized and nonrandomized trials for drug development, along with systematic reviews of these trials, have compared outcomes in patients who received molecularly targeted treatment with patients who did not. Generally, trials in which therapy was targeted to a gene variant resulted in improved response rates, progression-free survival, and overall survival compared to patients in trials who did not receive targeted therapy. A major limitation in the relevance of these studies for comprehensive genomic profiling is that treatment in these trials was guided both by the tissue source and the molecular target for drug development, rather than being matched solely by the molecular marker (ie, basket trials). As a result, these types of studies do not provide evidence of the benefit of broad molecular profiling compared to more limited genetic assessments based on known tumor-specific variants. Basket trials that randomize patients with various tumor types to a strategy of comprehensive genomic profiling followed by targeted treatment are needed, and several are ongoing. The evidence is insufficient to determine the effects of the technology on health outcomes.

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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 for all new primary or newly metastatic breast cancers, *BRCA1/2*, *PIK3CA*, *NTRK* fusions, microsatellite instability and mismatch repair.

Colon cancer

- *KRAS*, *NRAS*, and *BRAF* mutation testing and microsatellite instability or mismatch repair testing for patients with metastatic colon cancer.

Non-small-cell lung cancer

- *EGFR*, *ALK*, *ROS1*, *BRAF*, *KRAS*, and *NTRK* fusions.

Cutaneous Melanoma

- *BRAF*, *NRAS*, *KIT*
- Uncommon mutations with next-generation sequencing are *ALK*, *ROS*, and *NTRK* fusions

Ovarian cancer

- *BRCA 1/2*, *NTRK*, microsatellite instability and mismatch repair

Chronic myeloid leukemia

- *BCR-ABL1*

Gastric cancer

- *HER2*, microsatellite instability

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- *CDH1* for hereditary cancer predisposition syndromes.

Esophageal and esophogastric junction cancer

- HER2, microsatellite instability, NTRK gene fusions

Bladder cancer

- *FGFR*

Soft Tissue Sarcomas

- *NTRK* fusions

Pancreatic cancer

- ALK, NRG1, NTRK, ROS1, BRAF, BRCA1/2, HER2, KRAS, PALB2, mismatch repair deficiency

Prostate cancer

- BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, CDK12, microsatellite instability and mismatch repair

Hepatobiliary cancer

- NTRK, FGFR2, IDH1, microsatellite instability and mismatch repair

Uterine cancer

- NTRK, microsatellite instability and tumor mutational burden

Central nervous system cancers

- NTRK, HER2, BRAF, ALK, ROS1

College of American Pathologists et al

In 2018, the College of American Pathologists, International Association for the Study of Lung Cancer, and the Association for Molecular Pathology 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

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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

In 2018, The American Society of Clinical Oncology 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

The Centers for Medicare and Medicaid Services will cover diagnostic testing with next-generation sequencing for beneficiaries with recurrent, relapsed, refractory, metastatic cancer, or advanced stages III or IV cancer if the beneficiary has not been previously tested using the same next-generation sequencing test, unless a new primary cancer diagnosis is made by the treating physician, and if the patient has decided to seek further cancer treatment (CAG-00450N). The test must have a Food and Drug Administration approved or cleared indication as an in vitro diagnostic, with results and treatment options provided to the treating physician for patient management.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT02272595	A Study to Select Rational Therapeutics Based on the Analysis of Matched Tumor and Normal Biopsies in Subjects With Advanced Malignancies	200	Nov 2020

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NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02693535 ^a	TAPUR: Testing the Use of U.S. Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer (TAPUR)	3279	Dec 2023
NCT02152254	Randomized Study Evaluating Molecular Profiling and Targeted Agents in Metastatic Cancer: Initiative for Molecular Profiling and Advanced Cancer Therapy (IMPACT 2)	1362	Dec 2024
NCT02299999 ^a	Evaluation of the Efficacy of High Throughput Genome Analysis as a Therapeutic Decision Tool for Patients with Metastatic Breast Cancer (SAFIR02_Breast)	1460	Dec 2022
NCT02465060	Molecular Analysis for Therapy Choice (MATCH)	6452	Jun 2022
NCT02645149 ^a	Molecular Profiling and Matched Targeted Therapy for Patients With Metastatic Melanoma	1000	Sep 2022
NCT02029001	A 2 period, Multicenter, Randomized, Open-label, Phase II Study Evaluating the Clinical Benefit of a Maintenance Treatment Targeting Tumor Molecular Alterations in Patients With Progressive Locally-advanced or Metastatic Solid Tumors (MOST plus)	560	Oct 2022
NCT02925234	A Dutch National Study on Behalf of the CPCT to Facilitate Patient Access to Commercially Available, Targeted Anti-cancer Drugs to Determine the Potential Efficacy in Treatment of Advanced Cancers With a Known Molecular Profile (DRUP Trial)	950	Dec 2022
NCT03784014	Molecular Profiling of Advanced Soft-tissue Sarcomas. A Phase III Study	960	Oct 2024

NCT: national clinical trial.

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^a Industry-sponsored or co-sponsored.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, “Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies”, 2.04.115, November 2020.
2. Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. *Trends Mol Med.* May 2001; 7(5): 201-4. PMID 11325631
3. Dienstmann R, Rodon J, Barretina J, et al. Genomic medicine frontier in human solid tumors: prospects and challenges. *J Clin Oncol.* May 20 2013; 31(15): 1874-84. PMID 23589551
4. Drilon A, Wang L, Arcila ME, et al. Broad, Hybrid Capture-Based Next-Generation Sequencing Identifies Actionable Genomic Alterations in Lung Adenocarcinomas Otherwise Negative for Such Alterations by Other Genomic Testing Approaches. *Clin Cancer Res.* Aug 15 2015; 21(16): 3631-9. PMID 25567908
5. Johnson DB, Dahlman KH, Knol J, et al. Enabling a genetically informed approach to cancer medicine: a retrospective evaluation of the impact of comprehensive tumor profiling using a targeted next-generation sequencing panel. *Oncologist.* Jun 2014; 19(6): 616-22. PMID 24797823
6. Schwaederle M, Daniels GA, Piccioni DE, et al. On the Road to Precision Cancer Medicine: Analysis of Genomic Biomarker Actionability in 439 Patients. *Mol Cancer Ther.* Jun 2015; 14(6): 1488-94. PMID 25852059
7. O'Brien CP, Taylor SE, O'Leary JJ, et al. Molecular testing in oncology: problems, pitfalls and progress. *Lung Cancer.* Mar 2014; 83(3): 309-15. PMID 24472389
8. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. *N Engl J Med.* Aug 20 2015; 373(8): 726-36. PMID 26287849
9. Le Tourneau C, Kamal M, Tredan O, et al. Designs and challenges for personalized medicine studies in oncology: focus on the SHIVA trial. *Target Oncol.* Dec 2012; 7(4): 253-65. PMID 23161020
10. Le Tourneau C, Delord JP, Goncalves A, et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. *Lancet Oncol.* Oct 2015; 16(13): 1324-34. PMID 26342236
11. Belin L, Kamal M, Mauborgne C, et al. Randomized phase II trial comparing molecularly targeted therapy based on tumor molecular profiling versus conventional therapy in patients with

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Current Effective Date: 07/12/2021

- refractory cancer: cross-over analysis from the SHIVA trial. *Ann Oncol.* Mar 01 2017; 28(3): 590-596. PMID 27993804
12. Schwaederle M, Zhao M, Lee JJ, et al. Impact of Precision Medicine in Diverse Cancers: A Meta-Analysis of Phase II Clinical Trials. *J Clin Oncol.* Nov 10 2015; 33(32): 3817-25. PMID 26304871
 13. Jardim DL, Fontes Jardim DL, Schwaederle M, et al. Impact of a Biomarker-Based Strategy on Oncology Drug Development: A Meta-analysis of Clinical Trials Leading to FDA Approval. *J Natl Cancer Inst.* Nov 2015; 107(11). PMID 26378224
 14. Zimmer K, Kocher F, Spizzo G, et al. Treatment According to Molecular Profiling in Relapsed/Refractory Cancer Patients: A Review Focusing on Latest Profiling Studies. *Comput Struct Biotechnol J.* 2019; 17: 447-453. PMID 31007870
 15. Wheler JJ, Janku F, Naing A, et al. Cancer Therapy Directed by Comprehensive Genomic Profiling: A Single Center Study. *Cancer Res.* Jul 01 2016; 76(13): 3690-701. PMID 27197177
 16. Tsimberidou AM, Hong DS, Ye Y, et al. Initiative for Molecular Profiling and Advanced Cancer Therapy (IMPACT): An MD Anderson Precision Medicine Study. *JCO Precis Oncol.* 2017; 2017. PMID 29082359
 17. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 6.2020
https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
 18. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 4.2020.
https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
 19. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 8.2020.
https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
 20. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Cutaneous Melanoma. Version 4.2020.
https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. September 7, 2020.
 21. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer. Version 1.2020.
https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf.
 22. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Chronic Myeloid Leukemia. Version 2.2021.

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Louisiana

Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies

Policy # 00423

Original Effective Date: 07/16/2014

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- https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf.
23. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer. Version 3.2020.
https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf.
24. National Comprehensive Cancer Network (NCCN) NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers. Version 4.2020.
https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf.
25. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer. Version 6.2020.
https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf.
26. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Soft-Tissue Sarcoma. Version 2.2020.
https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf.
27. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. Version 1:2020.
https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf.
28. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Prostate Cancer. Version 2.2020.
https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
29. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancers. Version 5.2020.
https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf.
30. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms. Volume 2.2020.
https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf.
31. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers. Version 3.2020.
https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf.
32. Lindeman NI, Cagle PT, Aisner DL, et al. Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. *J Thorac Oncol*. Mar 2018; 13(3): 323-358. PMID 29396253

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33. Kalemkerian GP, Narula N, Kennedy EB, et al. Molecular Testing Guideline for the Selection of Patients With Lung Cancer for Treatment With Targeted Tyrosine Kinase Inhibitors: American Society of Clinical Oncology Endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology Clinical Practice Guideline Update. *J Clin Oncol*. Mar 20 2018; 36(9): 911-919. PMID 29401004

Policy History

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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

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	Molecular Panel Testing of Cancers to Identify Targeted Therapies”. Changed “mutation” to “molecular” in the INV statement.
04/21/2020	Coding update
05/11/2020	Coding update
06/04/2020	Medical Policy Committee review
06/10/2020	Medical Policy Implementation Committee approval. Title changed from “Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies” to “Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies”. Language in policy statement changed from "expanded cancer molecular panels" to "comprehensive genomic profiling". The intent of coverage eligibility is unchanged.
09/22/2020	Coding update
03/25/2021	Coding update
06/03/2021	Medical Policy Committee review
06/09/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/21/2021	Coding update
09/30/2021	Coding update
Next Scheduled Review Date: 06/2022	

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2020 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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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	0006M, 0013U, 0014U, 0016M, 0019U, 0036U, 0037U, 0048U, 0056U, 0174U, 0211U, 81120, 81121, 81272, 81311, 81314, 81445, 81450, 81455, 81479, 81599 Add code eff 4/1/2021: 0244U Add code eff 7/1/2021: 0250U Add code eff 10/1/2021: 0262U
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*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

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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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