# Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapy and Immunotherapy

**Policy #** 00423
Original Effective Date: 07/16/2014
Current Effective Date: 09/11/2023

*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: Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer is addressed separately in medical policy 00233.*

*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.*

*Note: Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy) is addressed separately in medical policy 00497.*

*Note: Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer is addressed separately in medical policy 00731.*

*Note: Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Prostate Cancer is addressed separately in medical policy 00809.*

*Note: Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Ovarian Cancer is addressed separately in medical policy 00810.*

Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapy and Immunotherapy

Policy # 00423
Original Effective Date: 07/16/2014
Current Effective Date: 09/11/2023

# When Services May Be Eligible for Coverage

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider comprehensive genomic profiling for selecting targeted cancer treatment to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for comprehensive genomic profiling for selecting targeted cancer treatment will be considered when **ALL** of the following criteria

- Individual has either metastatic or advanced (stages III or IV) cancer; **AND**
- Individual has not been previously tested using the same genomic profiling test, unless a new primary cancer diagnosis is made, and further cancer treatment is being considered (see Policy Guidelines); **AND**
- The test must have a U.S. Food and Drug Administration (FDA) approved or cleared indication as an in vitro companion diagnostic for use in the individual's cancer (see Policy Guidelines section); **AND**
- Treatment is considered with genomic biomarker-linked therapies approved by regulatory agencies for individual's cancer.

Based on review of available data, the Company may consider microsatellite instability and tumor mutational burden testing for selecting immunotherapy cancer treatment with pembrolizumab (Keytruda) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for microsatellite instability (MSI) and tumor mutational burden (TMB) testing for selecting treatment with pembrolizumab (Keytruda) will be considered when **ALL** of the following criteria are met:

- Individual has metastatic or unresectable solid tumor that has progressed following prior treatment and who has no satisfactory alternative treatment options (for metastatic colorectal cancer use MP 00233); **AND**

- Individual has not been previously tested using the same test, unless a new primary cancer diagnosis is made, and further cancer treatment is being considered; **AND**
- Pembrolizumab was FDA-approved for requested indication; **AND**
- The panel test is designated for TMB assessment (provides a TMB score) and has a U.S. Food and Drug Administration (FDA) approved or cleared indication as an in vitro companion diagnostic (i.e., FoundationOne CDx™‡ assay).

*Note:*
*For 5 or more gene tests being run on the same platform, such as multi-gene panel next generation sequencing (NGS), single available procedure code for the multi-gene panel test is to be utilized.*

# When 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 when criteria are not met to be **investigational.***

Based on review of available data, the Company considers the use of microsatellite instability and tumor mutational burden testing for selecting immunotherapy cancer treatment with pembrolizumab (Keytruda) when criteria are not met to be **investigational.***

Based on review of available data, the Company considers concurrent liquid based and tumor based comprehensive genomic profiling to be **investigational.***

# Policy Guidelines

For guidance on testing criteria between policy updates, refer to the FDA's List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) (https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools) for an updated list of FDA-approved tumor markers and consult the most current version of NCCN management algorithms.

Additional advanced stage cancers may be considered for TMB or MSI testing if supported by most recent NCCN guidelines with category of evidence and consensus recommendation 2A or higher.

Keytruda indications related to MSI and TMB testing using FoundationOne CDx assay include:
- Adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options
- Adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H with 10 or greater mutations/ megabase) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options
- For the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer

Per FDA label, the safety and effectiveness of Keytruda in pediatric patients with MSI-H and TMB-H central nervous system cancers have not been established.

# 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 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 3 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 review. In some cases, limited panels may be offered that are specific to 1 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% (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 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 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 |
| 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 |

| Test | Manufacturer | Tumor Type | Technology |
|---|---|---|---|
| | | | 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 |
| Omics Core(SM) | NantHealth | Solid | WES |
| PGDx elio tissue complete™‡ | Personal Genome Diagnostics | Solid | NGS |
| NYU Langone Genome PACT assay | NYU Langone Medical Center | Solid | NGS |

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

Tumor mutational burden (TMB) is an emerging biomarker associated with predicting the response to immune checkpoint inhibitors (ICIs)– therapies that have made significant progress in helping to

treat certain advanced cancers. ICIs work by releasing the brakes on the immune system's antitumor response and ICI therapy has proven most effective on tumor types with a high TMB, whereby a high TMB value indicates better treatment outcomes.

Tumor mutational burden (TMB) is the genetic characteristic of non-inherited mutations within tumor tissue, often reported as the total number of DNA mutations per one million bases (megabase). Original studies calculated TMB based on whole-exome sequencing and reported TMB as the number of mutations that exist within the exome. However, TMB testing has expanded to targeted gene sequencing panels that do not cover the entire exome. TMB may serve as a biomarker to identify patients likely to have a favorable response to immunotherapy, as high TMB levels correlate with objective response rates to immunotherapy in several different cancer types.

Microsatellites are short, repetitive segments of DNA that are highly prone to mutation. Microsatellite instability (MSI) in tumor DNA is defined as the presence of alternate sized repetitive DNA sequences that are not present in the corresponding germline DNA. Tumors with high microsatellite instability (MSI-H) are more immunogenic and may therefore respond to drugs that activate the immune system. MSI has been identified in many cancer types, with the highest prevalence in uterine endometrial carcinoma, colon adenocarcinoma, stomach adenocarcinoma, and rectal adenocarcinoma.

# 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.

FoundationOne CDx (Foundation Medicine) initially received premarket approval by the U.S. Food and Drug Administration (FDA) (P170019) in 2017. It is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 2. The approval is both tumor type and biomarker specific, and does not extend to all of the components included in the FoundationOne CDx product. The test is intended to identify patients who may benefit from treatment with targeted therapies in accordance with approved therapeutic product

labeling. "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." FDA 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." FDA product code: PZM

Subsequent marketing clearance through the FDA's 510(k) process (FDA product code PZM) include the following:

- Omics Core (NantHealth) received marketing clearance in 2019 (K190661). The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and tumor mutational burden.
- PGDx elio tissue complete (Personal Genome Diagnostics) received marketing clearance in 2020 (K192063). PGDx elio tissue complete is "intended to provide tumor mutation profiling information on somatic alterations (SNVs [single nucleotide variants], small insertions and deletions, one amplification and 4 translocations), microsatellite instability and tumor mutation burden (TMB)".
- The NYU Langone Genome PACT assay (NYU Langone Medical Center) is a 607-gene panel that received marketing clearance by the FDA in 2021 (K202304). The test assesses somatic point mutations, insertions and deletions smaller than 35 base pairs.

The intended use is by qualified health care professionals in accordance with professional guidelines for oncology, and not prescriptive for use of any specific therapeutic product.

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

Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapy and Immunotherapy

Policy # 00423
Original Effective Date: 07/16/2014
Current Effective Date: 09/11/2023

Tumor mutational burden (TMB), the number of somatic mutations per mega base of the DNA in cancer cells, is an emerging biomarker associated with predicting the response to immunotherapy treatment (NCI, 2021). A high TMB value indicates better treatment outcomes, which is observed in patients with melanoma on CTLA-4 inhibitors and patients with melanoma, non-small-cell lung carcinoma, bladder cancer, microsatellite instability cancers, and pan-tumors on PD-1/PD-L1 inhibitors. High TMB has also been associated with improved outcomes in patients on a combination of PD-1/PD-L1 and CTLA-4 inhibitors (Merino et al., 2020).

Two FDA-approved tests for calculating tumor mutational burden (TMB) include the FoundationOne CDx assay (Foundation Medicine Inc.) and MSK-IMPACT (Memorial Sloan Kettering Cancer Center).

Both of these tests, referred to as comprehensive genomic profiling (CGP), can identify all types of "molecular alterations (i.e., single nucleotide variants, small and large insertion-deletion alterations, copy number alterations, and structural variants) in cancer- related genes, as well as genomic signatures such as microsatellite instability (MSI), loss of heterozygosity, and TMB (Klempner et al., 2020)." Studies show that TMB calculation from CGP has high concordance with TMB measured from whole-exome sequencing.

On June 16, 2020, the FDA approved pembrolizumab for the treatment of adult and pediatric patients with a TMB value of greater than 10 mutations per mega base as determined by the FoundationOne®‡ CDx assay.

On February 18, 2022, the FDA expanded the indication for FoundationOne®‡CDx to include a companion diagnostic (CDx) indication for the detection of microsatellite instability- High (MSI-H) status in patients with unresectable or metastatic solid tumors that have progressed following prior treatment, have no satisfactory alternative treatment options and may benefit from treatment with KEYTRUDA®‡ (pembrolizumab). Keytruda is also approved as first-line treatment of patients with unresectable or metastatic MSI-H or dMMR CRC (FoundationOne CDx is FDA-approved companion diagnostic).

MyChoice HRD CDx, by Myriad Genetic Laboratories, was FDA-approved on October 23, 2019. Myriad MyChoice®‡ CDx is a next generation sequencing- based in vitro diagnostic test that detects

single nucleotide variants, insertions and deletions, and large rearrangement variants in protein coding regions and intron/exon boundaries of the BRCA1 and BRCA2 genes.

In 2020, the FDA approved Guardant360®‡ CDx for tumor mutation profiling in patients with any solid malignant neoplasm.

ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) by Pillar Biosciences was FDA-approved on July 30, 2021. The ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) by Pillar Biosciences, is a next generation sequencing test for detection of somatic mutations for non-small cell lung cancer (NSCLC) and colorectal cancer (CRC) tumor tissue. The test simultaneously detects clinically relevant mutations in KRAS for CRC and EGFR for NSCLC in a single assay.

**Table 2. Companion Diagnostic Indications for F1CDx**

| Tumor Type | Biomarker(s) Detected | Therapy |
|---|---|---|
| Non-small cell lung cancer (NSCLC) | *EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations | Gilotrif®‡ (afatinib), Iressa®‡ (gefitinib), Tagrisso®‡ (osimertinib), or Tarceva®‡ (erlotinib) |
| | *EGFR* exon 20 T790M alterations | Tagrisso®‡ (osimertinib) |
| | *ALK* rearrangements | Alecensa®‡ (alectinib), Xalkori®‡ (crizotinib), or Zykadia®‡ (ceritinib) |
| | *BRAF* V600E | Tafinlar®‡ (dabrafenib) in combination with Mekinist®‡ (trametinib) |
| | *MET* single nucleotide variants (SNVs) and indels that lead to *MET* exon 14 skipping | Tabrecta®‡ (capmatinib) |
| | *ROS1 fusions* | *Rozlytrek®‡ (entrectinib)* |

| | | |
|---|---|---|
| Melanoma | *BRAF* V600E | Tafinlar®‡ (dabrafenib) or Zelboraf®‡ (vemurafenib) |
| | *BRAF* V600E and V600K | Mekinist®‡ (trametinib) or Tecentriq®‡ (atezolizumab) in combination with Cotellic®‡ (cobimetinib) and Zelboraf ®‡ (vemurafenib) |
| | *BRAF* V600 mutation-positive | Mekinist®‡ (trametinib) or Tecentriq®‡ (atezolizumab) in combination with Cotellic®‡ (cobimetinib) and Zelboraf®‡ (vemurafenib) |
| Breast cancer | *ERBB2* (HER2) amplification | Herceptin®‡ (trastuzumab), Kadcyla®‡ (ado-trastuzumab-emtansine), or Perjeta®‡ (pertuzumab) |
| | PIK3CA alterations | Lynparza®‡ (olaparib) |
| | *KRAS* wild-type (absence of mutations in codons 12 and 13) | Erbitux®‡ (cetuximab) |
| Colorectal cancer | *KRAS* wild-type (absence of mutations in exons 2, 3, and 4) and NRAS wild type (absence of mutations in exons 2, 3, and 4) | Vectibix®‡ (panitumumab) |
| | *BRCA1/2* alterations | Lynparza®‡ (olaparib) or Rubraca®‡ (rucaparib) |

| | | |
|---|---|---|
| Ovarian cancer | *FGFR2* fusions and select rearrangements | Pemazyre®‡ (pemigatinib) or Truseltiq™‡ (infigratinib) |
| Cholangiocarcinoma | Homologous Recombination Repair (HRR) gene | Lynparza®‡ (olaparib) |
| Prostate cancer | Tumor mutational burden >10 mutations per megabase | Keytruda®‡ (pembrolizumab) |
| Solid Tumors | Microsatellite instability-high (MSI-H) | Keytruda®‡ (pembrolizumab) |
| | *NTRK1/2/3* fusions | IVitrakvi®‡ (larotrectinib) or Rozlytrek®‡ (entrectinib) |

F1CDx: FoundationOne Companion Diagnostic.
1 An updated list of FDA-cleared or -approved companion diagnostic devices is available at https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools

Guardant360 TissueNext™‡ (0334U) is a next-generation sequencing (NGS) based assay that identifies potential tumor-related (somatic) genomic alterations within 84 cancer-related genes through analysis of tumor DNA from a biopsy in patients with advanced-stage cancer. As of July 2023, it is noted as covered by Molecular Diagnostic Program (MolDX®‡ Program) and Centers for Medicare & Medicaid Services Local Coverage Determination (LCD). When this test is done as a reflex test, referred to as Guardant360 TissueNext (Reflex), the test is not covered by MolDX and LCD.

Decipher®‡ Bladder TURBT (0016M) is a microarray gene expression assay used to classify formalin-fixed paraffin-embedded (FFPE) bladder tumor samples into one of five molecular subtypes in patients with locally advanced bladder cancer (AJCC Stage I to IIIA). It measures RNA expression levels of 219 genes and includes an algorithmic analysis using patient data and the lab test results to report the molecular subtype of bladder cancer. As of July 2023, it is noted as covered by MolDX and LCD (see Supplemental Information under Medicare Local Coverage). Molecular subtyping of bladder tumor is currently not recommended in national society guidelines.

Policy # 00423
Original Effective Date: 07/16/2014
Current Effective Date: 09/11/2023

MI Tumor Seek Hybrid™‡ is a comprehensive genomic profiling test for patients with advanced solid tumors. The assay is tissue-based whole exome and whole transcriptome sequencing analysis and detects SNVs, INDELs, copy number alterations (CNAs), structural variants (SVs), splice-site variants, RNA-based SVs, translocations, functional splicing mutations, microsatellite instability (MSI), total mutational burden (TMB), and in select tumor types, also homologous recombination deficiency (HRD), genome-wide loss of heterozygosity (gLOH) and tissue of origin assessment for cancers of unknown primary (CUP). As of July 2023, it is noted as covered by MolDX and LCD (see Supplemental Information under Medicare Local Coverage).

# Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

**Description**

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 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.

**Summary of Evidence**

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. 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 1 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 that the technology results in an improvement in the net health outcome.

# Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

**Practice Guidelines and Position Statements**

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

**National Comprehensive Cancer Network**

The National Comprehensive Cancer Network (NCCN) guidelines 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:

Bladder cancer

- FGFR3 or FGFR2 genetic alterations for stages IVA and IVB bladder cancer are recommended (may be considered for IIIB) ideally at time of diagnosis of advanced bladder cancer to facilitate treatment decision-making, eligibility for FDA-approved therapies, and to screen for clinical trial eligibility. The therascreen FGFR RGQ RT-PCR Kit has been approved as a companion diagnostic for erdafitinib for tissue testing (urothelial cancer). Genetic alterations are known to be common in bladder cancer, with data from the Cancer Genome Atlas ranking bladder cancer as the third highest mutated cancer. The most commonly identified clinically relevant genetic alterations were CDKN2A (34%), FGFR3 (21%), PIK3CA (20%), and ERBB2 (17%). Molecular subtyping is not recommended in the 2023 NCCN guidelines.

Breast cancer

- HER2 testing for all new primary or newly metastatic breast cancers, BRCA1/2, PIK3CA, NTRK fusions, microsatellite instability and mismatch repair, and tumor mutational burden.

Colon cancer

- KRAS, NRAS, and BRAF mutation testing, HER2 amplification, NTRK fusion and microsatellite instability or mismatch repair testing for patients with metastatic colon cancer.

Non-small-cell lung cancer

- EGFR, ALK, ROS1, BRAF, MET exon 14, RET, KRAS, and NTRK fusions.

Cutaneous Melanoma

- BRAF, NRAS, KIT.
- Uncommon mutations with next-generation sequencing are ALK, ROS1, and NTRK fusions

Ovarian cancer

- BRCA 1/2, NTRK, tumor mutational burden, microsatellite instability and mismatch repair.

Pancreatic cancer

- ALK, NRG1, NTRK, ROS1, FGRF2, RET, BRAF, BRCA1/2, HER2, KRAS, PALB2, mismatch repair deficiency.

Prostate cancer

- BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51, CHEK2, CDK12, microsatellite instability, tumor mutational burden, and mismatch repair.

Updated recommendations for testing of solid tumors can be accessed at https://www.nccn.org/guidelines.

**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 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 2022, the American Society of Clinical Oncology (ASCO) published a provisional clinical opinion based on informal consensus in the absence of a formal systematic review on the appropriate use of tumor genomic testing in patients with metastatic or advanced solid tumors.28, The opinion notes the following:

**PCO 1.1.** Genomic testing should be performed for patients with metastatic or advanced solid tumors with adequate performance status in the following 2 clinical scenarios:

- When there are genomic biomarker–linked therapies approved by regulatory agencies for their cancer.
- When considering a treatment for which there are specific genomic biomarker-based contraindications or exclusions (strength of recommendation: strong).

**PCO 1.2.1.** For patients with metastatic or advanced solid tumors, genomic testing using multigene genomic sequencing is preferred whenever patients are eligible for a genomic biomarker–linked therapy that a regulatory agency has approved (strength of recommendation: moderate).

**PCO 1.2.2.** Multigene panel–based genomic testing should be used whenever more than one genomic biomarker is linked to a regulatory agency–approved therapy (strength of recommendation: strong).

**PCO 2.1.** Mismatch repair deficiency status (dMMR) should be evaluated on patients with metastatic or advanced solid tumors who are candidates for immunotherapy. There are multiple approaches, including using large multigene panel-based testing to assess microsatellite instability (MSI). Consider the prevalence of dMMR and/or MSI-H status in individual tumor types when making this decision (strength of recommendation: strong).

**PCO 2.2.** When tumor mutational burden (TMB) may influence the decision to use immunotherapy, testing should be performed with either large multigene panels with validated TMB testing or whole-exome analysis (strength of recommendation: strong).

**PCO 4.1.** Genomic testing should be considered to determine candidacy for tumor-agnostic therapies in patients with metastatic or advanced solid tumors without approved genomic biomarker–linked therapies (strength of recommendation: moderate).

**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 U.S. 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.

**Medicare Local Coverage**
According to local coverage determination (LCD L38684; 8/2023) Prognostic and Predictive Molecular Classifiers for Bladder Cancer, the Centers for Medicare and Medicaid Services will

cover molecular diagnostic tests in a beneficiary with bladder cancer when all of the following conditions are met:

(1) The beneficiary is being actively managed for bladder cancer.
(2) The beneficiary is within the population and has the indication for which the test was developed.
(3) The patient is a candidate for multiple potential treatments with varied or increasing levels of intensity based on a consensus guideline, and the physician and patient must decide among these treatments. OR The patient is a candidate for multiple therapies, and the test has shown that it predicts response to a specific therapy based on nationally recognized consensus guidelines (i.e., National Comprehensive Cancer Network [NCCN], American Society of Clinical Oncology [ASCO], Society of Urologic Oncology [SUO], or American Urological Association [AUA]).
(4) If Next-Generation Sequencing (NGS) methodology is used in testing, the conditions set by NCD 90.2 are fulfilled (patient has advanced cancer; plans on being treated for said cancer; and has not been previously testing with the same test for the same genetic content).
(5) The test demonstrates analytical validity including both analytical and clinical validations. The algorithm (if applicable) must be validated in a cohort that is not a development cohort for the algorithm.
(6) The test has demonstrated clinical validity and utility, establishing a clear and significant biological/molecular basis for stratifying patients and selecting a clinical management decision in a clearly defined population.
(7) The test successfully completes a Molecular Diagnostic Program (MolDX®‡) technical assessment that ensures the test is reasonable and necessary as described in (4) and (5) above.
(8) Only 1 test may be performed unless a second test that interrogates different genomic content meets all the criteria, is reasonable and necessary, and relevant to the therapy under consideration.

Local coverage determination (LCD L38158; 06/2023) Next-Generation Sequencing (NGS) for Solid Tumors notes that NGS for solid tumors is eligible for coverage when all criteria are met, including, as per NCD 90.2 the test is reasonable and necessary (the patient has either recurrent, relapsed, refractory, metastatic, or advanced [stages III or IV] cancer, has not been previously tested by the same test, and the patient is seeking further treatment). Additionally, the test has satisfactorily completed a technical assessment (TA) by MolDX for the stated indications of the test and the assay includes at least the minimum genes and genomic positions required for the identification of clinically relevant FDA-approved therapies with a companion diagnostic biomarker as well as other biomarkers known to be necessary for clinical decision making for its intended use. The test will be

non-covered if all the criteria in the NCD 90.2 are not met, if another comprehensive genomic profiling test was performed on the same tumor specimen, or a TA is not completed satisfactorily by MolDX.

**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 |
|---|---|---|---|
| ***Ongoing*** | | | |
| NCT03084757 | SHIVA02 - Evaluation of the Efficacy of Targeted Therapy Based on Tumor Molecular Profiling in Patients With Advanced Cancer Using Each Patient as Its Own Control | 170 | Nov 2022 |
| NCT05385081 | PREcision Medicine in Cancer in Odense, Denmark (PRECODE) Feasibility of Genomic Profiling and Frequency of Genomic Matched Treatment in Solid Tumors With no Treatment Options (PRECODE) | 900 | Dec 2023 |
| NCT04111107 | Precision Medicine for Patients With Identified Actionable Mutations at Wake Forest Baptist Comprehensive Cancer Center (WFBCCC): A Pragmatic Trial | 337 | Jun 2024 |
| 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) | 3641 | Dec 2025 |
| NCT02152254[a] | Randomized Study Evaluating Molecular Profiling and Targeted Agents in Metastatic Cancer: Initiative | 1362 | Dec 2024 |

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| | for Molecular Profiling and Advanced Cancer Therapy (IMPACT 2) | | |
| NCT05554341 | A ComboMATCH Treatment Trial ComboMATCH Treatment Trial E4: Nilotinib and Paclitaxel in Patients With Prior Taxane-Treated Solid Tumors | 40 | Jul 2025 |
| NCT05525858[a] | KOrean Precision Medicine Networking Group Study of MOlecular Profiling Guided Therapy Based on Genomic Alterations in Advanced Solid Tumors II (KOSMOSII) | 1000 | Sep 2025 |
| NCT02465060 | Molecular Analysis for Therapy Choice (MATCH) | 6452 | Dec 2025 |
| NCT05058937[a] | A Study to Examine the Clinical Value of Comprehensive Genomic Profiling Performed by Belgian NGS Laboratories: a Belgian Precision Study of the BSMO in Collaboration With the Cancer Centre - Belgian Approach for Local Laboratory Extensive Tumor Testing (BALLETT) | 936 | May 2026 |
| NCT05554367 | A ComboMATCH Treatment Trial: Palbociclib and Binimetinib in RAS-Mutant Cancers | 199 | Aug 2026 |
| NCT02645149[a] | Molecular Profiling and Matched Targeted Therapy for Patients With Metastatic Melanoma (MatchMel) | 1000 | Dec 2028 |
| 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 2026 |

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| NCT02925234[a] | 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) | 1550950 | Dec 2027 |
| NCT03784014 | Molecular Profiling of Advanced Soft-tissue Sarcomas. A Phase III Study (MULTISARC) | 960 | Oct 2024 |
| NCT04589845[a] | Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial | 770 | Sep 2032 |

NCT: national clinical trial.
a Industry-sponsored or co-sponsored.

# References

1. Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. Trends Mol Med. May 2001; 7(5): 201-4. PMID 11325631
2. 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
3. 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
4. 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

5. 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
6. 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
7. 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
8. 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
9. 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
10. 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 refractory cancer: cross-over analysis from the SHIVA trial. Ann Oncol. Mar 01 2017; 28(3): 590-596. PMID 27993804
11. 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
12. 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
13. 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
14. 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
15. 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

16. Murciano-Goroff YR, Drilon A, Stadler ZK. The NCI-MATCH: A National, Collaborative Precision Oncology Trial for Diverse Tumor Histologies. Cancer Cell. Jan 11 2021; 39(1): 22-24. PMID 33434511
17. Damodaran S, Zhao F, Deming DA, et al. Phase II Study of Copanlisib in Patients With Tumors With PIK3CA Mutations: Results From the NCI-MATCH ECOG-ACRIN Trial (EAY131) Subprotocol Z1F. J Clin Oncol. May 10 2022; 40(14): 1552-1561. PMID 35133871
18. Kalinsky K, Hong F, McCourt CK, et al. Effect of Capivasertib in Patients With an AKT1 E17K-Mutated Tumor: NCI-MATCH Subprotocol EAY131-Y Nonrandomized Trial. JAMA Oncol. Feb 01 2021; 7(2): 271-278. PMID 33377972
19. Salama AKS, Li S, Macrae ER, et al. Dabrafenib and Trametinib in Patients With Tumors With BRAF V600E Mutations: Results of the NCI-MATCH Trial Subprotocol H. J Clin Oncol. Nov 20 2020; 38(33): 3895-3904. PMID 32758030
20. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer. Version 3.2023. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf
21. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 4.2022; https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
22. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 1.2022; https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
23. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 5.2022; https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
24. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Cutaneous Melanoma. Version 3.2022; https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf.
25. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer. Version 5.2022; https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf.
26. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. Version 1.2022; https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf.

27. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Prostate Cancer. Version 1.2023; https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
28. 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
29. Chakravarty D, Johnson A, Sklar J, et al. Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion. J Clin Oncol. Apr 10 2022; 40(11): 1231-1258. PMID 35175857
30. Centers for Medicare and Medicaid Services (CMS) Local Coverage Determination (LCD). MolDX: Prognostic and Predictive Molecular Classifiers for Bladder Cancer - L38684 https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38684&ver=6&stateRegion=s23&contractorNumber=all&lcdStatus=A&sortBy=contractor&bc=8…
31. Centers for Medicare and Medicaid Services (CMS) Local Coverage Determination (LCD). MolDX: Next-Generation Sequencing for Solid Tumors - L38158 https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38158&ver=9&stateRegion=s23&contractorNumber=all&lcdStatus=A&sortBy=contractor&bc=8

# Policy History

Original Effective Date: 07/16/2014
Current Effective Date: 09/11/2023

| | |
|---|---|
| 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. |
| 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 |
| 12/20/2021 | Coding update |

Policy # 00423
Original Effective Date: 07/16/2014
Current Effective Date: 09/11/2023

| | |
|---|---|
| 03/02/2022 | Coding Update |
| 03/25/2022 | Coding update |
| 06/02/2022 | Medical Policy Committee review |
| 06/08/2022 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged.<br>Coding update |
| 10/06/2022 | Medical Policy Committee review |
| 10/11/2022 | Medical Policy Implementation Committee approval. Title changed from "Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies" to "Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapy and Immunotherapy". Extensive revisions made to the coverage section and throughout the policy. Added a Policy Guidelines section. |
| 11/03/2022 | Medical Policy Committee review |
| 11/09/2022 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 12/07/2022 | Coding update |
| 03/19/2023 | Coding update |
| 06/01/2023 | Medical Policy Committee review |
| 06/06/2023 | Coding update |
| 06/14/2023 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 08/03/2023 | Medical Policy Committee review |
| 08/09/2023 | Medical Policy Implementation Committee approval. Added Local Coverage Determination information for the Guardant360 TissueNext™‡ test, the Decipher®‡ Bladder TURBT (0016M) microarray gene expression assay, and the MI Tumor Seek Hybrid™‡ comprehensive genomic profiling test at the end of the FDA or Other Governmental Regulatory Approval section. Added bladder cancer to the Supplemental Information section under the National Comprehensive Cancer Network (NCCN) guidelines as an example for testing recommendations of common solid tumors. Added Medicare Local Coverage to the Supplemental Information section. References added from the NCCN for bladder cancer, and from CMS Local Coverage Determination (LCD) for bladder cancer and next-generation sequencing for solid tumors. Coverage eligibility unchanged. |
| 12/13/2023 | Coding update |

# 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 2022 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.*

*The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.*

CPT is a registered trademark of the American Medical Association.

Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapy and Immunotherapy

Policy # 00423
Original Effective Date: 07/16/2014
Current Effective Date: 09/11/2023

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

| Code Type | Code |
|---|---|
| CPT | 0006M, 0016M, 0036U, 0037U, 0019U, 0022U, 0048U, 0211U, 0244U, 0250U, 0329U, 0334U, 0379U, 81311, 81314, 81445, 81449, 81450, 81451, 81455, 81456, 81479, 81599<br>Delete codes effective 10/01/2022: 0013U, 0014U, 0056U<br>Delete codes effective 01/01/2023: 0050U, 81120, 81121, 81272<br>Add code effective 07/01/2023: 0391U<br>Add codes effective 01/01/2024: 81457, 81458, 81459 |
| 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 diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with 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.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment,

would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

**NOTICE:** Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

**NOTICE:** If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.