MEDICAL POLICY

POLICY TITLE	MOLECULAR PANEL TESTING OF CANCERS TO IDENTIFY TARGETED THERAPIES
POLICY NUMBER	MP 2.259

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	RETIRED 7/1/2026

I. POLICY

The use of comprehensive genomic profiling for selecting targeted cancer treatment is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Cross-References:

MP 2.211 Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers
MP 2.241 Molecular Analysis (Including liquid biopsy (for Targeted Therapy or Immunotherapy of Non-Small Cell Lung Cancer
MP 2.267 Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)
MP 2.275 Molecular Markers in Fine Needle Aspirates of the Thyroid
MP 2.307 Genotype-Guided Tamoxifen Treatment
MP 2.316 Somatic Biomarker Testing (including Liquid Biopsy) for Target Treatment of Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, NTRK, and HER2)
MP 2.323 General Approach to Evaluating the Utility of Genetic Panels
MP 2.325 Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
MP 2.354 Laboratory and Genetic Testing for Use of 5-Fluoruracil in Patients with Cancer
MP 2.364 Somatic Genetic Testing to Select Individuals with Melanoma or Glioma for Targeted Therapy or Immunotherapy

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II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO: Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND

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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.

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 (i.e., 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 (e.g., 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.

Test	Manufacturer	Tumor Type	Technology
FoundationOne®CDx test (F1CDx)	Foundation Medicine	Solid	NGS

FoundationOne® 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 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
ACTOnco	ACT Genomics	Solid	NGS
xT CDx	Tempus Labs, Inc.	Solid	NGS

Regulatory Status

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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.
- ACTOnco (ACT Genomics) received marketing clearance in 2022 (K210017). The next-generation sequencing test is intended to provide information on point mutations, small insertions and deletions, ERBB2 gene amplification, and tumor mutational burden in patients with solid malignant neoplasms.
- xT CDx (Tempus Labs, Inc) is a 648-gene panel that received marketing clearance by the FDA in 2023. The test assesses single nucleotide variants and multi-nucleotide variants as well as insertion and deletion alterations in the included genes as well as microsatelite instability.

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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.

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), Vizimpro® (dacomitinib)
	EGFR exon 20 T790M alterations	Tagrisso® (osimertinib)
	EGFR exon 20 insertion mutations	Rybrevant® (amivantamb), Exkivity® (mobocertinib)
	ALK rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), or Zykadia® (ceritinib)
	BRAF V600E	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)
	MET	Tabrecta™ (capmatinib)
	KRAS G12C	Krazati® (adagrasib), Lumakras® (sotorasib)
	RET fusions	Gavreto® (pralsetinib), Retevmo® (selpercatinib)
	ROS1 fusions	Rozlytrek® (entrectinib)
Melanoma	*BRAF* V600E	Tafinlar® (dabrafenib), Mekinist (trametinib)or Zelboraf® (vemurafenib)
	BRAF V600E and V600K	Braftovi® (encorafenib), Mekinist® (trametinib) or Tecentriq® (atezolizumab) in combination with Cotellic® (cobimetinib) and Zelboraf® (vemurafenib)
	*HLA-A*02:01*	Kimmtrak® (tebentafusp-tebn)
Breast cancer	*ERBB2* (HER2) amplification	Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumabemtansine), Enhertu® (fam-trastuzumab deruxtecan-nxki), or Perjeta® (pertuzumab)
	ESR1 missense mutations	Orserdu® (elacestrant)

	PIK3CA alterations	Lynparza® (olaparib), Truqap® (capivasertib) in combination with Faslodex® (fulvestrant), Piqray® (alpelisib)
Colorectal cancer	*BRAF* V600E	Braftovi® (encorafenib)
	KRAS wild-type (absence of mutations in codons 12 and 13)	Erbitux® (cetuximab)
	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)
Ovarian cancer	*BRCA1/2* alterations	Lynparza® (olaparib) or Rubraca® (rucaparib)
	FOLR1 protein expression	Elahere® (mirvetuximab soravtansine-gynx)
Cholangiocarcinoma	*FGFR2* fusion or other select rearrangements	Pemazyre® (pemigatinib) or Truseltiq fgv™ (infigratinib)
	IDH1 single nucleotide variants	Tibsovo® (ivosidenib)
Prostate cancer	*BRCA1/2* alterations	Akeega® (niraparib + abiraterone acetate), Rubraca® (rucaparib), Lynparza® (olaparib)
	Homologous Recombination Repair (HRR) gene alterations	Lynparza® (olaparib)
Solid Tumors	Tumor mutational burden ≥10 mutations per megabase	Keytruda® (pembrolizumab)
	Microsatellite instability-high (MSI-H)	Keytruda® (pembrolizumab)
	NTRK1/2/3 fusions	Vitrakvi® (larotrectinib) or Rozlytrek® (entrectinib)
	MLH1, PMS2, MSH2 and MSH6	Keytruda® (pembrolizumab), Jemperli® (dostarlimag-gxly)
	RET fusions	Retevmo® (selpercatinib)

F1CDx: FoundationOne Companion Diagnostic.

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IV. RATIONALE

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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 (RCT), nonrandomized trials, and systematic reviews of these studies. Relevant outcomes are overall survival (OS), 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 RCT (SHIVA trial) that used an expanded panel reported no difference in progression free survival (PFS) 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, PFS, and OS 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 (i.e., 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.

V. DEFINITIONS

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NA

VI. DISCLAIMER

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Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These polices are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

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VII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore, not covered when used for comprehensive genomic profiling for selecting targeted cancer treatment:

Procedure Codes								
0019U	0022U	0036U	0037U	0048U	0211U	0239U	0242U	0244U
0250U	0326U	0329U	0334U	0379U	0391U	0409U	0473U	0485U
0523U	0538U	0539U	0543U	0562U	0571U	81445	81449	81450
81451	81455	81456	81479					

VIII. REFERENCES

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27. *National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Cutaneous Melanoma. Version 2.2024*
28. *National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer. Version 3.2024*
29. *National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. Version 3.2024*
30. *National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Prostate Cancer. Version 4.2024*

X. POLICY HISTORY

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MP 2.259	**12/03/2020 Administrative Update.** New code 0239U added as covered with criteria. Effective 01/01/2021
	02/01/2021 Administrative Update. New codes 0242U and 0244U added as covered with criteria. Effective 04/01/2021.
	06/15/2021 Administrative Update. Added new codes 0249U and 0250U
	09/07/2021 Administrative Update. New ICD-10 code C56.3 added. Effective 10/01/2021
	09/17/2021 Consensus Review. No changes to policy statement. NCCN language added. FEP language updated. Added additional Cross-Referenced policies. Background, Rationale and References updated.
	06/10/2022 Administrative Update. Added new code 0326U.
	09/12/2022 Administrative Update. Added New Codes 0339U & 0334U.
	12/21/2022 Consensus Review. No change to policy statement. 0339U was not previously added to policy. Removed 0111U. References updated.
	06/13/2023 Administrative Update. Added new code 0391U Effective 07/01/2023.
	08/07/2023 Minor Review. Multiple updates to criteria around NCCN and FDA approvals. Coding, references, background and rationale update.
	09/07/2023 Administrative Update. New code 0409U effective 10/01/2023
	01/19/2024 Administrative Update. Clinical benefit added.
	03/15/2024 Administrative Update. Added code 0448U for 04/01/2024
	06/10/2024 Administrative Update. Added code 0473U. Effective 07/01/2024.
	09/19/2024 Administrative Update. Added code 0485U. Effective 10/01/2024

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	12/03/2024 Major Review. Policy statement updated to reflect that comprehensive genomic profiling for selecting targeted cancer treatment is now considered investigational. Removed box stating that this policy is only to be used if there is not a specific policy that outlines criteria. Background, Rationale and References updated. Added codes 0019U, 0022U, 0048U, 0329U, 0379U, 81445, 81449, 81450, 81451, 81455, 81456.
	12/11/2024 Administrative Update. Added 0523U, removed 0448U. Effective 01/01/2025
	03/13/2025 Administrative Update. Added 0538U, 0539U, 0543U. Effective 04/01/2025
	06/10/2025 Administrative Update. Added 0571U, 0562U. Effective 07/01/2025.
	06/12/2025 Administrative Update. Removed Benefit Variations Section and updated Disclaimer.
	08/05/2025 Consensus Review. Policy statement unchanged. Removed procedure codes 0009U & 0249U
	03/09/2026 Retirement Review. Services managed by EviCore.

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