MEDICAL POLICY

POLICY TITLE	**SOMATIC BIOMARKER TESTING (INCLUDING LIQUID BIOPSY) FOR TARGETED TREATMENT OF METASTATIC COLORECTAL CANCER (KRAS, NRAS, BRAF, AND HER2)**
POLICY NUMBER	**MP 2.316**

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:	**7/1/2024**

I. POLICY

KRAS, NRAS, BRAF, or HER2 testing of tumor tissue may be considered **medically necessary** for individuals with metastatic colorectal cancer to select individuals for treatment with FDA-approved therapies.

All other uses of KRAS, NRAS, BRAF, or HER2 variant testing of tumor tissue to guide colorectal cancer targeted therapy or immunotherapy are considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or the benefits associated with this procedure.

Circulating tumor cell testing (liquid biopsy) to guide treatment for patients with metastatic colorectal cancer is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

If coverage of a test is requested, but is not listed above, please refer to **MP 2.259** - Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies for additional guidance.

The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat, and manage patients with cancer. Guidelines evolve continuously as new treatments and diagnostics emerge and may be used by Capital Blue Cross when determining medical necessity according to this policy.

POLICY GUIDELINES

All patients with metastatic colorectal cancer should have tumor genotyped for RAS (KRAS and NRAS) and BRAF mutations individually or as part of an NGS panel. NCCN guidelines state that testing may be performed using either tissue or blood-based biopsy, with testing on tissue being preferred.

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Identification of human epidermal growth factor receptor 2 (HER2) amplification by immunohistochemistry (IHC) or FISH is recommended in RAS wild-type (wt) patients to detect those who may benefit from HER2 blockade. For practical reasons, this could be done with the initial molecular tests, but anti-HER2 inhibition is only recommended in second and further lines. Therefore, the HER2 amplification will only influence a treatment plan after at least first-line progression.

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.

GENETICS NOMENCLATURE UPDATE

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

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

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.

Cross references:

MP 2.315 Multigene Expression Assay for Predicting Recurrence in Colon Cancer
MP 2.388 Somatic Biomarker Testing for Immune Checkpoint Inhibitor Therapy (MSI/MMR, PD-L1, TMB)
MP 5.013 Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
MP 2.259 Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies.

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross please see additional information below, and subject to benefit variations as discussed in Section VI 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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KRAS, NRAS, and BRAF Variants
The RAS-RAF-MAP kinase pathway is activated in the EGFR cascade. The RAS proteins are G-proteins that cycle between active (RAS- guanosine triphosphate) and inactive (RAS-guanosine triphosphate) forms, in response to stimulation from a cell surface receptor such as EGFR, and act as a binary switch between the cell surface EGFR and downstream signaling pathways. The KRAS gene can harbor oncogenic variants that result in a constitutively activated protein, independent of EGFR ligand binding, rendering antibodies to the upstream EGFR ineffective.

Approximately 40% of colorectal cancers (CRCs) have *KRAS* variants in codons 12 and 13 in exon 2. Another proto-oncogene that acts downstream from *KRAS-NRAS* harbors oncogenic variants in codons 12, 13, or 61 that result in constitutive activation of the EGFR-mediated pathway. These variants are less common compared with *KRAS,* detected in 2% to 7% of CRC

specimens. It is unclear whether *NRAS* variants predict poor response due to anti-EGFR monoclonal antibody therapy or are prognostic of poor CRC outcome in general.

A third proto-oncogene, *BRAF*, encodes a protein kinase and is involved in intracellular signaling and cell growth; *BRAF* is also a principal downstream effector of *KRAS*. BRAF variants occur in fewer than *BRAF* variants occur in fewer than 10% to 15% of colorectal cancers and appear to be a maker of poor prognosis. KRAS and BRAF variants are considered to be mutually exclusive.

Cetuximab and panitumumab have marketing approval from the U.S. Food and Drug Administration (FDA) for treatment of metastatic CRC in the refractory disease setting. The FDA approval for panitumumab indicates that panitumumab is not indicated for the treatment of patients with KRAS or NRAS variant positive disease in combination with oxaliplatin-based chemotherapy.

Cetuximab (Erbitux®, ImClone Systems) and panitumumab (Vectibix®, Amgen) are monoclonal antibodies that bind to the epidermal growth factor receptor (EGFR), preventing intrinsic ligand binding and activation of downstream signaling pathways vital for cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization.

Human Epidermal Growth Factor Receptor 2 Amplification/Overexpression

Human epidermal growth factor receptor 2 (HER2) is a member of the HER (EGFR) family of tyrosine kinase receptors and has no specific ligand. When activated, it forms dimers with other EGFR family members. Amplification of HER2 is detected in approximately 3% of patients with CRC, with higher prevalence in *RAS/BRAF*-wild type tumors (5% to 14%). In addition to its role as a predictive marker for HER2-targeted therapy, HER2 amplification/overexpression is being investigated as a predictor of resistance to EGFR-targeting monoclonal antibodies.

Detecting ctDNA and Circulating Tumor Cells

Typically, the evaluation of RAS mutation status requires tissue biopsy. Circulating tumor DNA (ctDNA) testing is proposed as a non-invasive alternative.

Detection of ctDNA is challenging because ctDNA is diluted by nonmalignant circulating DNA and usually represents a small fraction (<1%) of total ctDNA. Therefore, more sensitive methods than the standard sequencing approaches (e.g., Sanger sequencing) are needed.

Highly sensitive and specific methods have been developed to detect ctDNA, for both single nucleotide variants (e.g., BEAMing [which combines emulsion polymerase chain reaction with magnetic beads and flow cytometry] and digital polymerase chain reaction) and copy-number variants. Digital genomic technologies allow for enumeration of rare variants in complex mixtures of DNA.

Approaches to detecting ctDNA can be considered targeted, which includes the analysis of known genetic mutations from the primary tumor in a small set of frequently occurring driver mutations, which can impact therapy decisions or untargeted without knowledge of specific

variants present in the primary tumor, and include array comparative genomic hybridization, next-generation sequencing, and whole exome and genome sequencing.

CTC assays usually start with an enrichment step that increases the concentration of CTCs, either by biologic properties (expression of protein markers) or physical properties (size, density, electric charge). CTCs can then be detected using immunologic, molecular, or functional assays.

Despite the many clinical studies on liquid biopsy conducted in CRC and the promising preliminary results, the use of this approach in clinical practice is still extremely limited. A number of liquid biopsy tests related to targeted treatment of metastatic colorectal cancer have been developed (Table 1).

Table 1. Examples of Liquid Biopsy Tests Related to Targeted Treatment of Metastatic Colorectal Cancer

Manufacturer	Test	Type of Liquid Biopsy
Biocept	Target SElector ctDNA EGFR Kit	ctDNA
CellMax Life	CellMax-CRC Colorectal Cancer Early Detection Test	CTC
Cynvenio	Clear ID Solid Tumor Panel	ctDNA and CTC
Foundation Medicine	FoundationOne Liquid (Previously Foundation Act)	ctDNA
Guardant Health	Guardant360®	ctD
IV Diagnostics	Velox™	CTC
Pathway Genomics	CancerIntercept® Detect	ctD
Personal Genome Diagnostics	PlasmaSELECT	ctD
Sysmex Inostics	OncoBEAM	ctD
Circulogene	Theranostics	ctD

Regulatory Status

Approved Companion Diagnostic Tests for KRAS Variant Analysis to Select Cetuximab and Panitumumab in Metastatic Colorectal Cancer

Companion diagnostic tests for the selection of cetuximab and panitumumab have been approved by the FDA through the premarket approval process (Table 2):

Table 2. Companion Diagnostic Tests for the Selection of Cetuximab and Panitumumab for Metastatic Colorectal Cancer

Diagnostic Name	PMA/510(k)/HDE	Description	Approval Date	Diagnostic Manufacturer
FoundationOne CDx	P170019	Next Generation Sequencing Oncology Panel, Somatic or Germline Variant Detection System	11/30/2017	Foundation Medicine, Inc.
Praxis Extended RAS Panel	P160038	Next Generation Sequencing Oncology Panel, Somatic or Germline Variant Detection System	06/29/2017	Illumina, Inc.
cobas KRAS Mutation Test	P140023	Somatic Gene Mutation Detection System		Roche Molecular Systems, Inc.
therascreen KRAS RGQ PCR Kit	P110030 P110027	Somatic Gene Mutation Detection System	5/23/2014	Qiagen Manchester, Ltd.
Dake EGFR pharmDx Kit	P030044/S002	Immunohistochemistry Assay, Antibody, Epidermal Growth Factor Receptor	9/27/2006	Dako North America, Inc.

Source: U.S. Food and Drug Administration (2019)

Laboratory-Developed Tests for KRAS, NRAS, and BRAF Variant Analysis

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. KRAS, NRAS, and BRAF variant analyses using polymerase chain reaction methodology are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed under the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, FDA has chosen not to require any regulatory review of this test.

Liquid Biopsy

No liquid biopsy test is currently FDA approved to select treatment for patients with metastatic colorectal cancer.

IV. RATIONAL

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Summary of Evidence

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For individuals with metastatic CRC who receive KRAS variant testing to guide treatment, the evidence includes multiple systematic reviews including a TEC Assessment. The relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Variant testing of tumor tissue performed in prospective and retrospective analyses of RCTs has consistently shown that the presence of a KRAS variant predicts nonresponse to cetuximab and panitumumab, either as monotherapy or in combination with other treatment regimens and supports the use of KRAS variant analysis of tumor DNA before considering a treatment regimen. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with metastatic CRC who receive NRAS variant testing to guide treatment, the evidence includes prospective-retrospective analyses of RCTs and retrospective cohort studies. Relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Pooled analyses have shown that NRAS variants (beyond the common KRAS exon 2 variants) predict nonresponse to cetuximab and panitumumab and support the use of NRAS variant analysis of tumor DNA before considering a treatment regimen. In addition, there is strong support from the National Comprehensive Cancer Network and American Society of Clinical Oncology for NRAS and KRAS testing in patients with metastatic CRC. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with metastatic CRC who receive BRAF variant testing to guide management decisions, the evidence includes two meta-analyses of prospective and retrospective analyses of RCTs. The relevant outcomes are overall survival, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. The meta-analyses have shown that anti-EGFR monoclonal antibody therapy did not improve survival in patients with *RAS* wild-type or *BRAF*-mutated tumors; however, the individual studies have been small, and the results have been inconsistent. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with metastatic CRC who receive HER2 testing to guide treatment, the evidence includes the evidence includes FDA-approved therapeutics with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and National Comprehensive Cancer Network (NCCN) recommendations. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with metastatic CRC who receive ctDNA or CTC testing (liquid biopsy) to guide treatment, the evidence includes observational studies. The relevant outcomes are OS, disease-specific survival, test validity, morbid events, and medication use. Given the breadth of methodologies available to assess ctDNA and CTC, the clinical validity of each commercially available test must be established independently. The clinical validity of the OncoBEAM RAS CRC Assay has been studied in multiple observational studies. When compared to tissue biopsy, sensitivity ranged from 70% (51% to 84%) to 96% (95% CI 87% to 100%) and specificity

ranged from 83% (95% CI 71% to 92%) to 94% (82% to 98%). FoundationOne Liquid has been compared to tissue biopsy with the FoundationACT assay in one observational study; positive percent agreement was 80% overall and 90% when tissue and liquid biopsy were collected less than 270 days apart. Clinical validity studies were limited by unclear reporting of blinding, use of convenience rather than consecutive samples, and variation in the timing of sample collection. There are no published studies reporting clinical outcomes or clinical utility. The evidence is insufficient to determine the effects of the technology on health outcomes.

V. DEFINITIONS

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FAMILIAL ADENOMATOUS POLYPOSIS is an inherited disorder characterized by the development of myriad polyps in the colon beginning in late adolescence or early adulthood. Untreated, the condition leads to colon cancer.

LYNCH SYNDROME is a hereditary predisposition to nonpolyposis colorectal cancer and other solid tumors.

MUTATION refers to an unusual change in genetic material occurring spontaneously or by induction.

SCREENING refers to evaluating a patient for diseases such as cancer, heart disease, or substance abuse before they become clinically obvious**.**

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross' medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member

VIII. 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.

Covered when medically necessary:

Procedure Codes								
0069U	0111U	0471U	81210	81275	81276	81311	88363	88365
88374								

Codes are considered investigational:

Procedure Codes								
0421U	0464U							

ICD-10-CM Diagnosis Codes	Description
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C78.5	Secondary malignant neoplasm of large intestine and rectum
Z85.038	Personal history of other malignant neoplasm of large intestine
Z85.048	Personal history of other malignant neoplasm of rectum, rectosigmoid junction, and anus

IX. REFERENCES

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MP 2.316	**03/31/2020 Minor Review**. Title change and policy statement updated to include Liquid Biopsy analysis. References reviewed and updated. Code 0069U added.
	05/17/2021 Consensus Review. References updated. Code 0091U removed.
	11/30/2022 Minor Review. Policy stance updates reflect BCBSA changes. Clarifying language for KRAS, NRAS and BRAF tissue testing. Added MSI/MMR as MN. HER2 and tumor mutation burden listed as INV. Title change. Updates to policy guidelines, background, rationale, and references. Codes 81301 and 88374 added.
	11/20/2023 Minor Review. Policy stance consolidated for KRAS, NRAS and BRAF. HER2 now MN. Removed statement for MMR/MSI and TMB, now addressed in MP 2.388. Title change. CPT 81301 removed and 88365 added. Updated policy guidelines, background, and references.
	12/12/2023 Administrative Update. New code 0421U added as INV, effective 1/1/2024.
	06/11/2024 Administrative Update. New code 0471U and 0464U, effective 7/1/24.

POLICY TITLE	SOMATIC BIOMARKER TESTING (INCLUDING LIQUID BIOPSY) FOR TARGETED TREATMENT OF METASTATIC COLORECTAL CANCER (KRAS, NRAS, BRAF, AND HER2)
POLICY NUMBER	MP 2.316

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