MEDICAL POLICY

POLICY TITLE	**SOMATIC BIOMARKER TESTING (INCLUDING LIQUID BIOPSY) FOR TARGETED TREATMENT AND IMMUNOTHERAPY IN METASTATIC COLORECTAL CANCER (KRAS, NRAS, BRAF, MMR/MSI, HER2, AND TMB)**
POLICY NUMBER	**MP 2.316**

Effective Date:	**5/1/2023**

I. POLICY

KRAS variant analysis of tumor tissue may be considered **medically necessary** for individuals with metastatic colorectal cancer to select individuals for treatment with FDA-approved therapies.

NRAS variant analysis of tumor tissue may be considered **medically necessary** for individuals with metastatic colorectal cancer to select individuals for treatment with FDA-approved therapies.

BRAF variant analysis of tumor tissue may be considered **medically necessary** for patients with metastatic colorectal cancer who are found to be wild-type on KRAS and NRAS variant analysis to guide management decisions, and to select individuals for treatment with FDA-approved therapies.

All other uses of KRAS, NRAS, and BRAF 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.

Mismatch repair/microsatellite instability testing may be considered **medically necessary** to select individuals for treatment with FDA-approved therapies.

All other uses of mismatch repair/microsatellite instability variant testing of colorectal tumor tissue for guiding 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.

Human epidermal growth factor receptor 2 testing is considered **investigational** to predict treatment response to immunotherapy in patients with metastatic colorectal cancer. There is insufficient evidence to support a general conclusion concerning the health outcomes or the benefits associated with this procedure.

Tumor mutational burden testing to predict response to immunotherapy in patients with metastatic colorectal cancer is 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 conclusion concerning the health outcomes or benefits associated with this procedure.

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

Mismatch repair and microsatellite testing of colorectal cancer tissue may be indicated for Lynch Syndrome (see policy MP 5.013 Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes).

For expanded panel testing, see MP 2.259 Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies.

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.

There is support from the evidence and clinical input to use BRAF V600 variant testing for prognostic stratification. Clinical input suggests that patients who are positive for this variant may be considered for clinical trials.

It is uncertain whether the presence of a BRAF V600 variant in patients with metastatic colorectal cancer who are wild type on KRAS and NRAS variant analysis is predictive of response to anti-epidermal growth factor receptor therapy. Furthermore, there is mixed opinion in clinical guidelines and clinical input on the use of BRAF variant analysis to predict response to treatment.

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 disorder

Table PG1. Nomenclature to Report on Variants Found in DNAPrevious	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 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.

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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 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 10% to 15% of CRCs and appear to be a marker 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

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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.

Mismatch Repair Deficiency/Microsatellite Instability

Mismatch repair deficiency (dMMR) and high levels of microsatellite instability (MSI-H) describe cells that have alterations in certain genes involved in correcting errors made when DNA is replicated. Tumors with dMMR are characterized by a high tumor mutational load and potential responsiveness to anti-PD-L1-immunotherapy. Deficiency in MMR is most common in CRC, other types of gastrointestinal cancer, and endometrial cancer, but it may also be found in other cancers including breast cancer. Testing of MSI is generally performed using polymerase chain reaction (PCR) for 5 biomarkers, although other biomarker panels and next generation sequencing are sometimes performed. High MSI is defined as 2 or more of the 5 biomarkers showing instability or more than 30% of the tested biomarkers showing instability depending on what panel is used. Microsatellite instability testing is generally paired with immunohistochemistry assessing lack of protein expression from 4 DNA mismatch repair genes thereby reflecting dMMR.

Tumor Mutational Burden

Tumor mutational burden (TMB), a measure of gene mutations within cancer cells, is an emerging biomarker of outcomes with immunotherapy in multiple tumor types. Initially, assessments of TMB involved whole exome sequencing. More recently, targeted next generation sequencing panels are being adapted to estimate TMB. Currently FoundationOne® CDx is the only U.S. Food and Drug Administration (FDA) approved panel for estimating TMB, but others are in development.

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

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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)[2.]

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

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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

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 MSI/MMR testing to guide treatment, the evidence includes an RCT of pembrolizumab compared to chemotherapy and nonrandomized trials. Relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Effectiveness of pembrolizumab compared to chemotherapy in patients with previously untreated, unresectable or metastatic high-frequency MSI (MSI-H) or deficient MMR (dMMR) CRC was investigated in a multicenter, randomized, open-label, active-controlled

trial of 307 patients. The trial demonstrated a statistically significant improvement in progression free survival (PFS) for patients randomized to pembrolizumab compared with chemotherapy (hazard ratio [HR] 0.60; 95% confidence interval [CI], 0.45 to 0.80; p=.0002). In final results, median PFS was 16.5 months (95% CI, 5.4 to 38.1) with pembrolizumab versus 8.2 months (95% CI, 6.1 to 10.2) with chemotherapy (HR 0.59; 95% CI, 0.45 to 0.79). Treatment-related adverse events of grade 3 or worse occurred in 33 (22%) of 153 patients in the pembrolizumab group versus 95 (66%) of 143 patients in the chemotherapy group. 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 HER2 testing to guide treatment, the evidence includes nonrandomized trials. Relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. There is no approved targeted treatment or companion diagnostic test for HER2 testing in patients with metastatic CRC. A phase 2 basket trial included 37 patients with HER2-amplified /overexpressed metastatic CRC. Treatment with trastuzumab plus pertuzumab produced partial response in 14 patients (38%; 95% CI, 23% to 55%) and the median duration of response was 11 months (range 1 to 16+ months; 95% CI, 2.8 months to not estimable). In an open-label, phase 2 trial of trastuzumab deruxtecan, objective response was observed in 24 of 53 patients with HER2-positive metastatic CRC (45.3%; 95% CI, 31.6 to 59.6) after a median follow-up of 27.1 weeks (interquartile range 19.3 to 40.1). Preliminary evidence has suggested that patients with HER2-amplified metastatic CRC are less likely to respond to anti-EGFR therapy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with metastatic CRC who receive TMB testing to select treatment with immunotherapy, the evidence includes a prespecified retrospective subgroup analysis of a nonrandomized phase 2 trial. Relevant outcomes are OS, disease-specific survival, and test accuracy. Objective responses were observed in 35% of participants who had both TMB-high status and programmed death-ligand 1 (PD-L1)-positive tumors and in 21% of participants who had TMB-high status and PD-L1-negative tumors. High TMB status was associated with improved response irrespective of PD-L1 status. Median OS and PFS were not significantly different between TMB groups. Because no patients with CRC were included in these analyses, it is not possible to draw conclusions about the clinical validity and utility of TMB in this group of patients. Well-designed prospective studies enrolling patients in the population of interest are required. Based on the limited data in the colorectal cancer population, the NCCN Panel does not currently recommend TMB biomarker testing, unless measured as part of a clinical trial. The evidence is insufficient 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's 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

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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 Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

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								
81210	81275	81276	81301	81311	88363	88374	0069U	0111U

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

VIII. REFERENCES

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IX. POLICY HISTORY

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MP 2.316	**3/26/13 CAC Adopt BCBSA.** This policy statement was extracted from MP 5.013 Genetic Testing for Lynch Syndrome and Other Inherited Intestinal Polyposis Syndromes (formerly Genetic Testing for Colon Cancer) and this new policy created to match BCBSA. Policy statements unchanged. Added Medicare variation to reference LCD L33142. Coding complete.
	1/28/14 CAC Consensus review. References updated; No changes to the policy statements. Rationale added. Codes reviewed.
	7/24/14 Administrative update. Change for the Medicare variation - For Novitas MAC jurisdictions, the LCD has been assigned a new number. Biomarkers for Oncology LCD changed from L33124 to L34796.
	1/27/15 CAC Minor review. Title changed to indicate inclusion of NRAS testing to the policy; NRAS testing policy statement added as investigational to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer. Rationale and references updated.
	11/2/15 Administrative update. LCD number changed from L34796 to L35396 due to Novitas update to ICD-10.
	1/26/16 CAC Consensus review. No change to policy statements. Rationale reviewed. References updated. 2016 coding updates added. Coding reviewed and updated.
	7/26/16 CAC Minor revision. Policy statement revised to indicate that NRAS testing is considered medically necessary to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of

POLICY TITLE	SOMATIC BIOMARKER TESTING (INCLUDING LIQUID BIOPSY) FOR TARGETED TREATMENT AND IMMUNOTHERAPY IN METASTATIC COLORECTAL CANCER (KRAS, NRAS, BRAF, MMR/MSI, HER2, AND TMB)
POLICY NUMBER	MP 2.316

	metastatic colorectal cancer. Rationale and references updated. Appendix added. Coding reviewed. Variation section reformatted.
	1/1/17Admin update: Product variation section updated with BlueJourney product name.
	9/26/17 CAC Consensus review. No change to policy statements. References and rationale reviewed. Coding Reviewed.
	1/1/18 Admin Update: Medicare variations removed from Commercial Policies.
	5/30/18 Minor review. BRAF variant analysis is considered medically necessary for patients with metastatic colorectal cancer who are found to be wild-type on KRAS and NRAS variant analysis to guide management decisions. Coding updated.
	4/4/2019 Consensus review. No updates to policy statement. References updated.
	3/31/2020: Minor Review. Title change and policy statement updated to include Liquid Biopsy analysis. References reviewed and updated. Code 0069U added.
	5/17/2021 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.

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