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Medical Policy

BlueCross BlueShield Kansas
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Title: Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Metastatic Colorectal Cancer (*KRAS, NRAS, BRAF, NTRK, RET* and *HER2*)

Related Policies:	▪ *Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes* ▪ *Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies* ▪ *Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer* ▪ *Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)*

Professional / Institutional
Original Effective Date: July 10, 2015
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Populations	Interventions	Comparators	Outcomes
Individuals: • With metastatic colorectal cancer who are being considered for targeted therapy	Interventions of interest are: • *KRAS, NRAS, BRAF, NTRK* or *RET* using tissue biopsy specimens testing to guide treatment	Comparators of interest are: • No *KRAS, NRAS, BRAF, NTRK* or *RET* testing to guide treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Morbid events • Medication use
Individuals: • With metastatic colorectal cancer who are being considered for targeted therapy with EGFR inhibitors	Interventions of interest are: • HER2 using tissue biopsy specimens testing to guide treatment	Comparators of interest are: • No HER2 testing to guide treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Morbid events • Medication use
Individuals: • With metastatic colorectal cancer	Interventions of interest are:	Comparators of interest are:	Relevant outcomes include: • Overall survival • Disease-specific survival

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Populations	Interventions	Comparators	Outcomes
who are being considered for targeted therapy with EGFR inhibitors	• *KRAS and NRAS* using circulating tumor DNA (ctDNA) (liquid biopsy) testing to guide treatment	• No *KRAS and NRAS* testing to guide treatment	• Test validity • Morbid events • Medication use
Individuals: • With metastatic colorectal cancer who are being considered for targeted therapy with BRAF inhibitors	Interventions of interest are: • *BRAF* using ctDNA (liquid biopsy) testing to guide treatment	Comparators of interest are: • No *BRAF* testing to guide treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Morbid events • Medication use
Individuals: • With metastatic colorectal cancer who are being considered for targeted therapy with TRK inhibitors	Interventions of interest are: • *NTRK* using ctDNA (liquid biopsy) testing to guide treatment	Comparators of interest are: • No *NTRK* testing to guide treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Morbid events • Medication use
Individuals: • With metastatic colorectal cancer who are being considered for targeted therapy with RET inhibitors	Interventions of interest are: • *RET* using ctDNA (liquid biopsy) testing to guide treatment	Comparators of interest are: • No *RET* testing to guide treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Morbid events • Medication use
Individuals: • With metastatic colorectal cancer who are being considered for targeted therapy with EGFR inhibitors	Interventions of interest are: • HER2 using ctDNA (liquid biopsy) testing to guide treatment	Comparators of interest are: • No HER2 testing to guide treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Morbid events • Medication use

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DESCRIPTION

The epidermal growth factor receptor (EGFR) is overexpressed in colorectal cancer (CRC). EGFR-targeted therapy combined with monoclonal antibodies cetuximab and panitumumab has shown a clear survival benefit in patients with metastatic CRC. However, this benefit depends on a lack of variants in certain genes in the signaling pathway downstream from the EGFR. It has been hypothesized that knowledge of tumor cell *KRAS, NRAS*, *BRAF* variant status might be used to predict nonresponse to anti-EGFR monoclonal antibody therapy. *NTRK* gene fusions, which are rare kinase fusion events, are a potential therapeutic target for CRC patients who may benefit from tropomysosin receptor kinase (TRK) inhibitor therapy. *RET* gene fusions, which are also rare, are a potential therapeutic target for CRC patients who may benefit from tyrosine kinase inhibitor therapy. More recently, human epidermal growth factor receptor 2 (HER2) testing to select patients for targeted therapy has been proposed. Typically, the evaluation of biomarker status requires tissue biopsy. Circulating tumor DNA or circulating tumor cell testing (also known as a liquid biopsy) is proposed as a non-invasive alternative.

OBJECTIVE

The objective of this review is to summarize the evidence and guidelines on using biomarker testing to select treatment with U.S. Food and Drug Administration (FDA)-approved targeted therapy for individuals with metastatic colorectal cancer (CRC).

BACKGROUND

KRAS, *NRAS*, and *BRAF* Variants

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. 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 diphosphate) forms in response to stimulation from a cell surface receptor, such as EGFR, and they 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

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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 outcomes 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 the 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.[1,]

A large body of literature has shown that metastatic CRC tumors with a variant in exon 2 (codon 12 or 13) of the *KRAS* gene do not respond to cetuximab or panitumumab therapy. More recent evidence has shown that variants in *KRAS* outside exon 2 (ie, in exons 3 [codons 59 and 61] and exon 4 [codons 117 and 146]) and variants in *NRAS* exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) also predict a lack of response to these monoclonal antibodies. Variant testing of these exons outside the *KRAS* exon 2 is referred to as extended *RAS* testing.

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 4% of patients with CRC, with higher prevalence in *RAS/BRAF*-wild type tumors (5% to 14%). [2,]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.

Neurotrophic Receptor Tyrosine Kinase (*NTRK*) Gene Fusion Testing

The presence of *NTRK* gene fusion can be detected by multiple methods including next-generation sequencing, reverse transcription-polymerase chain reaction, fluorescence in situ hybridization and immunohistochemistry. [3,] Next-generation sequencing provides the most comprehensive view of a large number of genes and may identify *NTRK* gene fusions as well as other actionable alterations, with minimal tissue needed. The fluorescence in situ hybridization using break-apart probes can detect gene rearrangements in DNA that may generate a fusion

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transcript. The immunohistochemistry techniques have generally been used in the research setting. Reverse transcription-polymerase chain reaction is designed to identify only known translocation partners and breakpoints and cannot identify novel breakpoints or novel fusion partners.

RET Gene Fusion Testing

RET (rearranged during transfection) is a proto-oncogene that encodes a receptor tyrosine kinase growth factor. Translocations that result in fusion genes with several partners have been rarely reported, with *RET* fusions occurring in roughly 0.2% colorectal cancers.[4,] Next-generation sequencing provides the most comprehensive view of a large number of genes and may identify *RET* gene fusions as well as other actionable alterations with minimal tissue needed. [5,]

Detecting Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy)

Normal and tumor cells release small fragments of DNA into the blood, which is referred to as cell-free DNA. Cell-free DNA from nonmalignant cells is released by apoptosis. Most cell-free tumor DNA is derived from apoptotic and/or necrotic tumor cells, either from the primary tumor, metastases, or circulating tumor cells. Unlike apoptosis, necrosis is considered a pathologic process and generates larger DNA fragments due to incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origin. Circulating tumor DNA can be used for genomic characterization of the tumor.

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 (eg, Sanger sequencing) are needed.

Highly sensitive and specific methods have been developed to detect ctDNA, for both single nucleotide variants (eg, 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,

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or untargeted without knowledge of specific variants present in the primary tumor, which includes array comparative genomic hybridization, next-generation sequencing, and whole exome and genome sequencing. Targeted testing may impact therapy selection.

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

A number of liquid biopsy tests related to targeted treatment of metastatic CRC 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
Foundation Medicine	FoundationOne Liquid (Previously FoundationAct)	ctDNA
Guardant Health	Guardant360®	ctDNA
	GuardantOMNI®	ctDNA
IV Diagnostics	Velox™	CTC
Personal Genome Diagnostics	PlasmaSELECT™	ctDNA
Sysmex Inostics	OncoBEAM	ctDNA
Circulogene	Theranostics	ctDNA

CTC: circulating tumor cell; ctDNA: circulating tumor DNA.

REGULATORY STATUS

Table 2 summarizes the targeted treatments approved by the FDA for patients with CRC, along with the approved companion diagnostic tests. The information in Table 2 was current as of May 24, 2025 ; FDA maintains a list of cleared or approved companion diagnostic devices that is updated regularly.[6,]

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In June 2022, FDA granted accelerated approval to dabrafenib (Tafinlar®, Novartis) in combination with trametinib (Mekinist®, Novartis) for the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with *BRAF* V600E mutations who have progressed following prior treatment and have no satisfactory alternative treatment options. However, dabrafenib in combination with trametinib is *not* indicated for patients with CRC because of known intrinsic resistance to *BRAF* inhibition.[7,] Therefore, *BRAF* V600E variant testing to select individuals for treatment with dabrafenib in combination with trametinib is not included in this evidence review and is not listed in Table 2.

Table 2. Targeted Treatments for Metastatic Colorectal Cancer and U.S. Food and Drug Administration-Approved Companion Diagnostic Tests

Treatment	Indications in Metastatic Colorectal Cancer	Companion Diagnostics	Pivotal Study	NCCN Recommendation Level/Guideline
Cetuximab (Erbitux)	*KRAS* wild-type, EGFR-expressing, metastatic colorectal cancer as determined by an FDA-approved test • in combination with FOLFIRI for first-line treatment, • in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy, • as a single-agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan. Limitations of Use: Erbitux is not indicated for treatment of RAS mutant colorectal cancer or when the results of the RAS mutation tests are unknown *BRAF* V600E Mutation-Positive Metastatic Colorectal Cancer • in combination with encorafenib, for the treatment	cobas KRAS Mutation Test Dako EGFR pharmDx Kit FoundationOne CDx therascreen KRAS RGQ PCR Kit ONCO/Reveal Dx Lung & Colon Cancer Assay xT CDx - tissue (matching with Blood/Saliva)	[8,] [9,]	2A or higher/Metastatic Colon Cancer (v. 3.2025) [10,] 2A or higher/Metastatic Rectal Cancer (v. 2.2025) [11,]

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Treatment	Indications in Metastatic Colorectal Cancer	Companion Diagnostics	Pivotal Study	NCCN Recommendation Level/Guideline
	of adult patients with metastatic colorectal cancer with a *BRAF* V600E mutation, as detected by an FDA-approved test, after prior therapy.			
Braftovi (Encorafenib)	Treatment of adult patients with metastatic colorectal cancer with a *BRAF* V600E mutation • in combination with Erbitux (cetuximab), for the treatment of adult patients with metastatic CRC with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy. • in combination with cetuximab and mFOLFOX6, for the treatment of patients with metastatic colorectal cancer (mCRC) with a BRAF V600E mutation, as detected by an FDA-approved test.	FoundationOne Liquid CDx therascreen BRAF V600E RGQ PCR Kit MI Cancer Seek (MCS)	12,	2A or higher/Metastatic Colon Cancer (v. 3.2025) [10,] 2A or higher/Metastatic Rectal Cancer (v. 2.2025) [11,]
Panitumumab (Vectibix)	Treatment of wild-type *RAS* (defined as wild-type in both *KRAS* and *NRAS* as determined by an FDA-approved test for this use) metastatic CRC: • In combination with FOLFOX for first-line treatment. • As monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy.	cobas KRAS Mutation Test CRCDx RAS Mutation Detection Assay Kit Dako EGFR pharmDx Kit FoundationOne CDx therascreen KRAS RGQ PCR Kit ONCO/Reveal Dx Lung & Colon Cancer Assay	13,	2A or higher/Metastatic Colon Cancer (v. 3.2025) [10,] 2A or higher/Metastatic Rectal Cancer (v. 2.2025) [11,]

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Treatment	Indications in Metastatic Colorectal Cancer	Companion Diagnostics	Pivotal Study	NCCN Recommendation Level/Guideline
	Treatment of *KRAS* G12C-mutated metastatic CRC: • In combination with sotorasib, for the treatment of adult patients with *KRAS* G12C-mutated mCRC, as determined by an FDA-approved test, who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. Limitation of Use: Vectibix is not indicated for the treatment of patients with *RAS*-mutant metastatic CRC or for whom *RAS* mutation status is unknown, unless used in combination with sotorasib in *KRAS* G12C-mutated mCRC.	(O/RDx-LCCA) xT CDx - tissue (Matching Blood/Saliva) MI Cancer Seek (MCS)		
Tukysa (Tucatinib)	Treatment of adult patients with unresectable or metastatic CRC with *RAS* wild-type *HER2*-positive • In combination with trastuzumab (Herceptin) for the treatment of adult patients with *RAS* wild-type *HER2*-positive unresectable or metastatic colorectal cancer that has progressed following treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.	No FDA-approved companion diagnostic	[14],	2A or higher/Metastatic Colon Cancer (v. 3.2025) [10], 2A or higher/Metastatic Rectal Cancer (v. 2.2025) [11],
Vitrakvi (larotrectinib)	Treatment of adult and pediatric patients with solid tumors that:	FoundationOne CDx TruSight Oncology Comprehensive	[15],	2A or higher/Metastatic Colon Cancer (v.

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Treatment	Indications in Metastatic Colorectal Cancer	Companion Diagnostics	Pivotal Study	NCCN Recommendation Level/Guideline
	• have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, • are metastatic or where surgical resection is likely to result in severe morbidity, and • have no satisfactory alternative treatments or that have progressed following treatment. Select patients for therapy based on an FDA-approved test.			3.2025) [10], 2A or higher/Metastatic Rectal Cancer (v. 2.2025) [11],
Rozlytrek (entrectinib)	Treatment of adult and pediatric patients older than 1 month of age with solid tumors that: • have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, as detected by an FDA-approved test without a known acquired resistance mutation, • are metastatic or where surgical resection is likely to result in severe morbidity, and • have progressed following treatment or have no satisfactory alternative therapy. Select patients for therapy based on an FDA-approved test.	FoundationOne Liquid CDx FoundationOne CDx	[16],	2A or higher/Metastatic Colon Cancer (v. 3.2025) [10], 2A or higher/Metastatic Rectal Cancer (v. 2.2025) [11],
Retevmo (selpercatinib)	Treatment of adult and pediatric patients 2 years of age and older with locally advanced or metastatic solid tumors with	FoundationOne CDx	[17],	2A or higher/Metastatic Colon Cancer (v. 3.2025) [10],

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Treatment	Indications in Metastatic Colorectal Cancer	Companion Diagnostics	Pivotal Study	NCCN Recommendation Level/Guideline
	a *RET* gene fusion, as detected by an FDA-approved test, that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.			2A or higher/Metastatic Rectal Cancer (v. 2.2025) [11]
Lumakras (sotorasib)	Treatment of adult patients with metastatic CRC with a *KRAS* G12C mutation • *KRAS* G12C-mutated Metastatic Colorectal Cancer (mCRC) In combination with panitumumab, for the treatment of adult patients with *KRAS* G12C-mutated mCRC as determined by an FDA approved-test, who have received prior fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy.	*therascreen* KRAS RGQ PCR Kit	[18], [19]	2A or higher/Metastatic Colon Cancer (v. 3.2025) [10] 2A or higher/Metastatic Rectal Cancer (v. 2.2025) [11]
Krazati (adagrasib)	Treatment of adult patients with metastatic colorectal cancer with a *KRAS G*12C mutation • In combination with cetuximab, for the treatment of adult patients with *KRAS* G12C-mutated locally advanced or metastatic CRC, as determined by an FDA-approved test, who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.	*therascreen* KRAS RGQ PCR Kit	[20], [21]	

Source: FDA (2025) [6]

CRC: colorectal cancer; EGFR: epidermal growth factor receptor; FDA: U.S. Food and Drug Administration; FOLFIRI:

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leucovorin, fluorouracil and irinotecan; FOLFOX: leucovorin, fluorouracil, and oxaliplatin; HER2: human epidermal growth factor receptor 2; mCRC: metastatic CRC; NCCN: National Comprehensive Cancer Network

Laboratory-Developed Tests

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 (CLIA). Laboratories that offer laboratory-developed tests must be licensed under CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

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POLICY

A. *KRAS, NRAS, BRAF, NTRK or RET* testing of tumor tissue biopsy specimens may be considered **medically necessary** for individuals with metastatic colorectal cancer to select individuals for treatment with U.S. Food and Drug Administration (FDA)-approved therapies.

B. All other uses of *KRAS, NRAS, BRAF, NTRK* or *RET* testing of tumor tissue to guide colorectal cancer targeted therapy are considered **experimental / investigational**.

C. Circulating tumor DNA testing (liquid biopsy) to guide treatment in individuals with metastatic colorectal cancer is considered **experimental / investigational** (see Policy Guidelines).

D. *HER2* testing of tumor tissue biopsy specimens may be considered **medically necessary** for individuals with metastatic colorectal cancer to select individuals for treatment with U.S. Food and Drug Administration (FDA)-approved therapies.

E. All other uses of *HER2* testing of tumor tissue to guide colorectal cancer targeted therapy are considered **experimental / investigational**.

F. Analysis of plasma (liquid biopsy) for somatic variants of the *KRAS* (eg, G12C) and *RAS* variants using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered **medically necessary** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to an FDA-approved therapy, in individuals with metastatic CRC, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines).

G. All other uses of analysis of *KRAS* and *NRAS* variants in plasma are considered **experimental / investigational**.

H. Analysis of plasma (liquid biopsy) for the somatic *BRAF* V600E variants using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered **medically necessary** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to an FDA-approved therapy, in individuals with metastatic CRC, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines).

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I. All other uses of analysis of *BRAF* V600E variant in plasma are considered **experimental / investigational**.

J. Analysis of plasma (liquid biopsy) for *NTRK* gene fusions using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered **medically necessary** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to an FDA-approved therapy in individuals with metastatic CRC, if the individual does not have any FDA-labeled contraindications to the requested agent and both the agent and ctDNA test are intended to be used consistently with their FDA-approved labels (see Policy Guidelines).

K. All other uses of analysis of *NTRK* fusions in plasma are considered **experimental / investigational**.

L. Analysis of plasma (liquid biopsy) for somatic *RET* variants is considered **experimental / investigational** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to an FDA-approved therapy in individuals with metastatic CRC.

M. Analysis of plasma (liquid biopsy) for somatic *HER2* variants is considered **experimental / investigational** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to an FDA-approved therapy in individuals with metastatic CRC.

N. All other uses of circulating tumor DNA testing (liquid biopsy) to guide treatment in individuals with metastatic colorectal cancer is considered **experimental / investigational** (see Policy Guidelines).

POLICY GUIDELINES

This policy does not address germline testing for inherited risk of developing cancer.

The National Comprehensive Cancer Network (NCCN) colon cancer guidelines v.3.2025 and rectal cancer guidelines v.2.2025 do not recommend testing for specific genes over a next generation sequencing panel. The guidelines additionally state that testing may be performed using either tissue or blood-based biopsy, with testing on tissue being preferred.

A. Testing for other variants may become available between policy updates.
   1. Testing for individual genes (not gene panels) associated with FDA-approved therapeutics (i.e., as companion diagnostic tests) for therapies with NCCN recommendations of 2A or higher are not subject to extensive evidence review. Note that while the FDA approval of

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companion diagnostic tests for genes might include tests that are conducted as panels, the FDA approval is for specific genes (such as driver mutations) and not for all of the genes on the test panel.

2. FDA approves tests in between policy review cycles. As such, newly approved tests might need to be considered per local Plan discretion. 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 National Comprehensive Cancer Network (NCCN) management algorithms.
3. Note: Extensive evidence review is not included for somatic tests of individual genes (not gene panels) associated with FDA-approved therapies with NCCN recommendations of 2A or higher. The pivotal evidence is included in Table 2 for informational purposes. Additionally, no evidence review is provided for somatic tests of individual genes that do not have associated FDA-approved therapies regardless of NCCN recommendations, as these off-label therapies are deemed investigational per the Blue Cross and Blue Shield Association Medical Policy Program Policies and Procedures.

B. **Concurrent Somatic Liquid-Based and Tissue-Based Genomic Testing**

1. Liquid biopsy testing uses blood samples and assesses cancer DNA and non-cancer DNA in the same blood sample. The goal is to identify options for genome-informed treatment. Some providers will order a liquid biopsy test and a tissue biopsy test at the same time to hasten time to treatment. If the intent of concurrent testing is to follow an individual over time to monitor for resistance variants, then consideration could be given to doing liquid biopsy at diagnosis with the tissue biopsy to make sure that mutations that are going to be followed longitudinally can be detected by the liquid biopsy.

C. **Recommended Testing Strategies**

1. Individuals who meet criteria for genetic testing as outlined in the policy statements above should be tested for the variants specified.

2. When tumor tissue is available, use of tissue for testing of any/all variants and biomarkers outlined in this policy is recommended, but is not required in all situations. In certain situations, circulating tumor DNA testing (liquid biopsy) may be an option.

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Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review was created using searches of the PubMed database. The most recent literature update was performed through May 23, 2025.

Testing for individual genes (not gene panels) associated with U.S. Food and Drug Administration (FDA)-approved therapeutics (ie, as companion diagnostic tests) for therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher are not subject to extensive evidence review. The pivotal evidence is included in Table 1 for informational purposes. Note that while the FDA approval of companion diagnostic tests for genes might include tests that are conducted as panels, the FDA approval is for specific genes (such as driver mutations) and not for all of the genes on the test panel.

KRAS, NRAS, BRAF, NTRK, and *RET* Variant Testing with Tissue Biopsy Specimens to Guide Treatment for Metastatic Colorectal Cancer

For individuals with metastatic colorectal cancer (mCRC) who receive *KRAS, NRAS, BRAF, NTRK,* or *RET* gene variant testing to select treatment with FDA-approved targeted therapy, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated.

HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 (HER2) OVEREXPRESSION TESTING WITH TISSUE BIOPSY TO GUIDE TREATMENT FOR METASTATIC COLORECTAL CANCER

Clinical Context and Test Purpose

Colorectal cancer (CRC) treatment selection is informed by tumor type, grade, stage, patient performance status and preference, prior treatments, and the molecular characteristics of the tumor such as the presence of driver mutations. One purpose of biomarker testing of individuals who have advanced cancer is to inform a decision regarding treatment selection (eg, whether to select a targeted treatment or standard treatment).

The following PICO was used to select literature to inform this review.

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Populations
The relevant population of interest is individuals with mCRC for whom the selection of treatment depends on the molecular characterization of the tumor.

Interventions
The test being considered is tissue biopsy using tumor tissue. Both targeted polymerase chain reaction-based assays and broad next-generation sequencing-based approaches are available.

Comparators
Decisions about treatment in CRC are based on clinical characteristics.

Outcomes
The general outcomes of interest in oncology are overall survival (OS), disease-specific survival, quality of life (QOL), treatment-related mortality and morbidity.

Beneficial outcomes resulting from a true-positive test result are prolonged survival, reduced toxicity, and improved QOL associated with receiving a more effective targeted therapy. Beneficial outcomes from a true negative result are prolonged survival associated with receiving chemotherapy in those without driver mutations.

Harmful outcomes resulting from a false-negative test result include shorter survival from receiving less effective and more cytotoxic chemotherapy in those with driver mutations; possible harmful outcomes resulting from a false-positive test result are a shorter survival from receiving potentially ineffective targeted treatment and delay in initiation of chemotherapy in those without driver mutations.

The overall response rate (ORR) may be used as a surrogate endpoint reasonably likely to predict clinical benefit in individuals with refractory solid tumors. ORR can be measured by the proportion of individuals with best overall confirmed response of complete response) or partial response by the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1),[22,] or Response Assessment in Neuro-Oncology criteria,[23,] as appropriate by a blinded and independent adjudication committee.

There are clearly defined quantitative thresholds for the follow-up of individuals in oncology trials. A general rule is a continuation of treatment until disease progression or unacceptable toxicity. Long-term follow-up outside of a study setting is conducted to determine survival status. The duration of follow-up for the outcomes of interest is 6 months and 1 year.

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The time frame for outcomes measures varies from several months to several years.

Study Selection Criteria
For the evaluation of clinical validity, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard (describe the reference standard);
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

REVIEW OF EVIDENCE

Systematic Reviews and Meta-analyses
Bekaii-Saab et al (2023) performed a systematic review and meta-analysis on the prognostic or predictive effect of HER2 amplification/overexpression on anti-epidermal growth factor receptor (EGFR) treatment outcomes.[24,] Five high-quality retrospective cohort studies were included in the meta-analysis representing 594 patients with mCRC and all patients received anti-EGFR treatment, either as monotherapy or in combination with chemotherapy. Results from the meta-analysis showed there was a 2.84 times higher risk of death or progression (95% CI, 1.44 to 5.60) in patients with HER2-positive *RAS* WT mCRC treated with anti-EGFR regimens compared with those who were HER2 negative. Based on meta-analysis of 3 studies reporting ORR (n=265) the odds of response to anti-EGFR treatment were almost 2 times higher in patients with mCRC who were HER2 negative compared with HER2-positive patients ([odds ratio [OR], 1.96; 95% CI, 1.10 to 3.48). Based on meta-analysis of 3 studies reporting OS (n=406) the results showed that there was no statistically significant difference in OS between patients with HER2-positive compared with HER2-negative *RAS* WT mCRC. While these findings do not fully account for any impact of line of therapy or confounding chemotherapy agents, they support the evidence that testing for HER2 overexpression/amplification may help inform treatment decisions and optimize outcomes for mCRC patients. Notable limitations include, but are not limited to, the retrospective study design and heterogeneity in follow-up times, treatment modalities, and doses.

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Gao et al (2022) conducted a meta-analysis to systematically evaluate the efficacy and safety of HER2-targeted inhibitors for HER2-amplified mCRC.[25,] Eight clinical trials of mCRC patients with HER2 amplification, confirmed by immunohistochemical staining and fluorescence *in situ* hybridization, treated with HER2-targeted inhibitors with at least one of the following primary outcomes available: ORR, disease control rate (DCR), progression-free survival (PFS), OS, or incidence of serious adverse events [SAEs]) were included in the meta-analysis. The pooled ORR and DCR of the 8 studies were 29% (95% CI, 20 to 40) and 71% (95% CI, 63 to 78), respectively with moderate heterogeneity in the studies using ORR and DCR as endpoints. The pooled median PFS and OS of the 8 studies were 4.89 months (95% CI, 3.82 to 5.97) and 13.04 months (95% CI, 9.45 to 16.62), respectively with high heterogeneity within the studies using PFS as the endpoint and moderate heterogeneity for studies using OS as the main outcome of interest. Furthermore, the results were considered to be unaffected by publication bias as determined by the Egger linear regression test. This meta-analysis revealed that HER2-targeted inhibitors exhibit good antitumor efficacy and safety in second line and above treatment of HER2-amplified mCRC patients. This study had some insurmountable heterogeneity issues; future large-scale, multicenter trials are required to investigate the problem in more depth. Other notable limitations include, but are not limited to, the small number of studies, insufficient sample size, lack of details regarding randomization concealment method and/or result detection method, and studies used different types and doses of therapies.

Randomized Clinical Trials

Four different regimens are recommended by the National Comprehensive Cancer Network (NCCN) panel as options for subsequent treatment of mCRC with HER2 amplifications with FDA-approved therapies: fam-trastuzumab deruxtecan-nxki (T-DXd) monotherapy or trastuzumab in combination with pertuzumab, lapatinib, or tucatinib.[26,] Pivotal clinical trials that led to the FDA approval of these therapies and NCCN recommendations include the following RCTs: the phase IIa multiple basket MyPathway trial (trastuzumab + pertuzumab),[27,] the multicenter, phase II HERACLES trial (trastuzumab and lapatinib),[28,29,] the phase 2, multicenter DESTINY-CRC01 trial (trastuzumab + tucatinib),[30,31,] and the clinical studies discussed below. Taken together these RCTs provide sufficient evidence to determine that HER2 testing using tumor tissue biopsies results in an improvement in the net health outcome.

Raghav et al (2025) conducted a randomized phase II trial (N=53) to evaluate efficacy and safety of dual-HER2 inhibition against standard-of-care anti-EGFR antibody–based therapy as second/third line treatment in HER2-positive mCRC.[32,] Patients with *RAS*/*BRAF*-WT mCRC after central confirmation of HER2 positivity (IHC 3+ or 2+ and in situ hybridization amplified [HER2/CEP17 ratio >2.0]; HCR) were assigned (1:1) to either trastuzumab plus pertuzumab (TP)

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or cetuximab plus irinotecan (CETIRI). The primary end point was PFS. Secondary end points included objective response rate (ORR), overall survival, safety, and HER2 gene copy number (GCN ≥20/<20) as a predictive factor. Efficacy of TP versus CETIRI differed significantly by *HER2* GCN (median PFS, GCN ≥20 [9.9 v 2.9 months] and GCN <20 [3.0 v 4.2 months], respectively; p=.003). On TP, ORR was 34.6% (57.1% with GCN ≥20 v 9.1% with GCN <20) with median GCN of 29.7 versus 13.2 for responders and nonresponders, respectively (p=.004). Overall, higher levels of *HER2* amplification were associated with greater degree of clinical benefit from TP compared to CETIRI. Notable limitations include, but are not limited to, small sample size due to low accrual, nonblinded investigator assessments, central HER2 testing with multiple testing methods, and insufficient power for the original design assumptions.

Raghav et al (2024) carried out a multicenter, randomized, 2-stage, 2-arm, phase 2 study (N=122) to assess antitumor activity, safety, and exploratory biomarkers of trastuzumab deruxtecan doses of 5.4 mg/kg and 6.4 mg/kg to evaluate its benefit–risk profile in patients with HER2-positive, *RAS* wild-type or variant mCRC who had previously received standard chemotherapy.[33,] In stage 1, patients were randomly assigned (1:1) to receive 5.4 mg/kg (n=40) or 6.4 mg/kg (n=40) trastuzumab deruxtecan administered intravenously every 21 days and in stage 2, patients were only assigned to the 5.4mg/kg (n=42) treatment group. The primary endpoint was confirmed objective response rate by blinded independent central review, assessed in all patients for whom treatment was assigned. The confirmed objective response rate was 37.8% (95% CI, 27.3 to 49.2) in the 5.4 mg/kg group and 27.5% (95% CI, 14.6 to 43.9) in the 6.4 mg/kg group. The confirmed disease control rate was 86.6% (95% CI, 77.3 to 93.1) in the 5.4 mg/kg group and 85.0% (95% CI, 70.2 to 94.3) in the 6.4 mg/kg group with a median PFS of 5.8 months (95% CI, 4.6 to 7.0) and 5.5 months (95% CI, 4.2 to 7.0), respectively. Notable limitations include, but are not limited to, the absence of a control group, small sample size for subgroup analysis, centralized HER2 testing with archival tissue, and PFS and OS were premature at time of the primary analysis.

Strickler et al (2023) assessed the activity of tucatinib plus trastuzumab in patients with chemotherapy-refractory, HER2-positive, *RAS* wild-type unresectable or mCRC in a global, open-label, phase 2 study. [14,] Between Aug 8, 2017, and Sept 22, 2021,117 patients enrolled into 3 cohorts (Cohort A: tucatinib plus trastuzumab [n=45], Cohort B: tucatinib plus trastuzumab [n=41], and Cohort C tucatinib monotherapy [n=31]), of whom 114 patients had locally assessed HER2-positive disease and received treatment (45 in cohort A, 39 in cohort B, and 30 in cohort C; full analysis set). As of data cutoff (March 28, 2022), in 84 patients from cohorts A and B in the full analysis set, the confirmed ORR per blinded independent central review was 38.1% (95% CI, 27.7 to 49.3; 3 patients had a complete response and 29 had a partial response). Tucatinib plus

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trastuzumab had clinically meaningful anti-tumor activity and favorable tolerability. Notable limitations include, but are not limited to, the open-label design, absence of power for a formal comparative study, heterogeneity in imaging intervals and frequency due to the study being expanded, and insufficient follow-up time for cohort C.

Gupta et al (2022) evaluated the results from the TAPUR study, a pragmatic phase II basket trial evaluating antitumor activity of commercially available targeted agents in patients with advanced cancers harboring potentially actionable genomic alterations, and reported data from 2 cohorts of patients with CRC with either *ERBB2* amplifications or *ERBB2* or *ERBB3* (*ERBB2/3*) variants treated with pertuzumab plus trastuzumab. [34,] Pertuzumab plus trastuzumab treatment was shown to have antitumor activity in patients with heavily pretreated colorectal cancer with *ERBB2* amplification (disease control [DC]: 54%, objective response [OR]: 25%, median PFS: 17.2 weeks [95% CI: 11.1 to 27.4] median OS: 60.0 weeks [95% CI: 32.1 to 102.3]) but did not demonstrate antitumor activity in patients with *ERBB2* or *ERBB3* variants (DC: 10%, OR: 0%, median PFS: 9.6 weeks [95% CI: 5.1 to 16.0], median OS: 28.8 weeks [95% CI: 7.6 to 146.3]). Notable limitations include, but are not limited to, the absence of a control group, nonblinded investigator assessments, small patient cohorts, local *ERBB2* testing with multiple testing methods, and incomplete reporting of *RAS* mutation status.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: HER2 Overexpression Testing with Tissue Biopsy to Guide Treatment for Metastatic Colorectal Cancer
For individuals with mCRC who are being considered for targeted therapy with FDA-approved therapeutics and undergo somatic testing for HER2 overexpression using tissue biopsy

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specimens, the evidence identified includes 2 systematic reviews/meta-analyses and 4 randomized clinical trials (RCTs). Relevant outcomes include OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. Results from the meta-analysis by Bekaii-Saab et al (2023) showed there was a 2.84 times higher risk of death or progression (95% CI, 1.44 to 5.60) in patients with HER2-positive *RAS* WT mCRC treated with anti-EGFR regimens compared with those who were HER2-negative. Furthermore, data from 8 clinical studies of mCRC patients with HER2 amplification, confirmed by immunohistochemical staining and fluorescence *in situ* hybridization, treated with HER2-targeted inhibitors was pooled and demonstrated an ORR of 29 percent. The 4 RCTs demonstrated that anti-HER2 therapy in mCRC patients with amplified or overexpression of HER2 had ORRs ranging from 28 to 38 percent with favorable tolerability. No tests have received FDA approval as companion diagnostics to select individuals with CRC for treatment with FDA-approved therapy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Testing for *KRAS or NRAS Variants* with Circulating Tumor DNA (Liquid Biopsy)
For individuals with mCRC who receive somatic testing for *KRAS* and *NRAS* variants using circulating tumor DNA (ctDNA) (liquid biopsy) to guide targeted treatment with FDA-approved targeted therapy, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated.

Testing *BRAF* Variants with Circulating Tumor DNA (Liquid Biopsy)
For individuals with mCRC who receive somatic testing for *BRAF* variants using ctDNA (liquid biopsy) to guide targeted treatment with FDA-approved targeted therapy, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated.

Testing for *NTRK* Gene Fusion with Circulating Tumor DNA (Liquid Biopsy)
For individuals with metastatic CRC who receive somatic testing for *NTRK* gene fusion using ctDNA (liquid biopsy) to guide targeted treatment with FDA-approved targeted therapy, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated.

Testing for *RET* Gene Fusion with Circulating Tumor DNA (Liquid Biopsy)
No plasma tests have received FDA approval as companion diagnostics to select individuals with CRC for treatment with *RET* inhibitors and no studies were identified.

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Testing for HER2 Overexpression with Circulating Tumor DNA (Liquid Biopsy)
No plasma tests have received FDA approval as companion diagnostics to select individuals with CRC for treatment with kinase inhibitors or anti-HER2 monoclonal antibodies and no studies were identified.

SUPPLEMENTAL INFORMATION
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the reference medical policy 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.

American Society of Clinical Oncology et al
In 2022, the American Society of Clinical Oncology published a provisional clinical opinion on the appropriate use of tumor genomic testing in patients with metastatic or advanced solid tumors. [35,]

Provisional Clinical Opinion
Informal consensus is based on the review of existing approved testing and therapy combinations, available marker prevalence data, and expert opinion. As no formal systematic review of the clinical trial evidence was conducted for this provisional clinical opinion (PCO), and all the recommendations are based on the informal consensus of the expert panel, no recommendation-by-recommendation
statement of evidence quality is provided.

Section 1: Framework for decision making on multigene panel–based genomic sequencing with disease-specific approved markers.

1. PCO 1.1. Genomic testing should be performed for patients with metastatic or advanced solid tumors with adequate performance status in the following two clinical scenarios:
    a. When there are genomic biomarker–linked therapies approved by regulatory agencies for their cancer.
    b. When considering a treatment for which there are specific genomic biomarker–based contraindications or exclusions (strength of recommendation: strong).

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Section 3: Testing for gene fusions and exon skipping variants

1. PCO 3.1. In patients with metastatic or advanced solid tumors, fusion testing should be performed if there are fusion-targeted therapies with regulatory approval for that specific disease (strength of recommendation: strong).
2. PCO 3.2.1. *NTRK* fusion testing should be performed in patients with metastatic or advanced solid tumors who may be candidates for TRK-inhibitor therapy, considering the prevalence of *NTRK* fusions in individual tumor types (strength of recommendation: strong).
3. PCO 3.2.2. Testing for other fusions is recommended in patients with metastatic or advanced solid tumors if no oncogenic driver alterations are identified on large panel DNA sequencing (strength of recommendation: moderate).

Section 4: Framework for decision making on panel tests with no approved disease-specific markers.

1. 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).
2. PCO 4.2. For tumors with actionable genomic alterations without approved genomic biomarker–linked targeted therapies, patient participation in clinical trials is encouraged after considering the expected efficacy of available standard-of-care options (strength of recommendation: strong).
3. PCO 4.3. Off-label and off-study use of genomic biomarker–linked therapies approved in other diseases is not recommended when a clinical trial is available or without clinical evidence of meaningful efficacy (strength of recommendation: strong).

In 2017, the American Society of Clinical Oncology along with American Society for Clinical Pathology, College of American Pathologists, and Association for Molecular Pathology published guidelines on molecular biomarkers for the evaluation of colorectal cancer.[36,] Table 3 summarizes the relevant guidelines.

Table 3. Summary of Recommendations

Guidelines	Type	SOE	QOE
Colorectal carcinoma patients being considered for anti-EGFR therapy must receive RAS mutational testing. Mutational analysis should	Recommendation	Convincing/adequate, benefits outweigh harms	High/intermediate

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Guidelines	Type	SOE	QOE
include *KRAS* and *NRAS* codons 12, 13 of exon 2; 59, 61 of exon 3; and 117 and 146 of exon 4 ("expanded" or "extended" RAS)			
BRAF p.V600 (BRAF c. 1799 [p.V600]) mutational analysis should be performed in colorectal cancer tissue in patients with colorectal carcinoma for prognostic stratification	Recommendation	Adequate/inadequate, balance of benefits and harms	Intermediate/low
BRAF p.V600 mutational analysis should be performed in deficient MMR tumors with loss of *MLH1* to evaluate for Lynch Syndrome risk. Presence of a *BRAF* mutation strongly favors sporadic pathogenesis. The absence of *BRAF* mutation does not exclude risk of Lynch syndrome	Recommendation	Adequate/inadequate, balance of benefits and harms	Intermediate/low
Clinicians should order mismatch repair status testing in patients with colorectal cancers for the identification of patients at high-risk for Lynch syndrome and/or prognostic stratification	Recommendation	Adequate/inadequate, balance of benefits and harms	Intermediate/low
There is insufficient evidence to recommend *BRAF* c.1799 (p.V600) mutational status as a predictive molecular biomarker for response to anti-EGFR inhibitors	No recommendation	Insufficient, benefits/harms balance unknown	Insufficient

EGFR: epidermal growth factor receptor; MLH1: mutL homolog 1;MMR: mismatch repair; QOE: quality of evidence; SOE: strength of evidence.

National Comprehensive Cancer Network

The following information is based on the National Comprehensive Cancer Network (NCCN) guidelines on the treatment of colon cancer (v.3.2025).[10,]Guidelines are updated frequently; refer to the source document for most recent updates and for additional detail.

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RAS and BRAF Testing

The guidelines recommend that all patients with metastatic colorectal cancer should have tumor tissue genotyped for *RAS* (KRAS and NRAS) and *BRAF* variants, individually or as part of a next-generation sequencing panel, for all patients with metastatic colon cancer. Patients with any known *KRAS* mutation (exon 2, 3, 4) or *NRAS* mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab unless given as part of a regimen targeting a *KRAS* G12C mutation (Category 2A). *BRAF* V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a *BRAF* inhibitor (Category 2A).

NTRK

The guidelines acknowledge that *NTRK* fusions are extremely rare in colorectal cancer and typically limited to tumors that are wild type for *KRAS*, *NRAS*, and *BRAF*. *NTRK* inhibitors have been shown to have activity only in those cases with *NTRK* fusions, and not with *NTRK* point mutations. Selection of the appropriate assay for *NTRK* fusion detection is stated to depend on "tumor type and genes involved, as well as consideration of other factors such as available material, accessibility of various clinical assays, and whether comprehensive genomic testing is needed concurrently."

Human Epidermal Receptor 2 Testing

The guidelines recommend testing for human epidermal receptor 2 (HER2) amplifications for patients with metastatic colorectal cancer. Anti-HER2 therapy is only indicated in HER2-ampliified tumors that are also *RAS* and *BRAF* wild type. If the tumor is already known to have a *KRAS/NRAS* or *BRAF* mutation, *HER2* testing is not indicated (Category 2A). *HER2* testing is performed via immunohistochemistry (IHC) with some results requiring reflex to fluorescence in situ hybridization (FISH); and next-generation sequencing (NGS) is another methodology endorsed for testing for HER2 amplification.

RET

The guidelines acknowledge that *RET* fusions are extremely rare in colorectal cancer and typically limited to tumors that are wild type for *KRAS*, *NRAS*, and *BRAF*. *RET* inhibitor, selpercatinib, is FDA-approved for patients with solid tumors harboring activating *RET* fusions. "The presence of *RET* fusions can be interrogated through a variety of techniques, including IHC, FISH, PCR, and either DNA- or RNA-based NGS assays. RNA-based NGS assays are fusion agnostic and as such have the advantage of identifying *RET* fusions involving any partner gene."

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Circulating Tumor DNA

The NCCN colon cancer guidelines state that determination of gene status for *KRAS/NRAS* and *BRAF* mutations may be carried out using either a tissue or blood-based (eg, liquid) biopsy, although tissue-based testing is preferred.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Currently unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Ongoing Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03365882	S1613, A Randomized Phase II Study of Trastuzumab and Pertuzumab (TP) Compared to Cetuximab and Irinotecan (CETIRI) in Advanced/Metastatic Colorectal Cancer (mCRC) With HER-2 Amplification	240	Nov 2025
NCT02465060	Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma (The MATCH Screening Trial)	6452	Dec 2025
NCT04776655	Phase III Study in mCRC Patients With RAS/BRAF Wild Type Tissue and RAS Mutated in LIquid BIopsy to Compare in First-line Therapy FOLFIRI Plus CetuxiMAb or BevacizumaB (LIBImAb Study)	280	Apr 2024 (unknown status)
NCT04264702	BESPOKE Study of ctDNA Guided Therapy in Colorectal Cancer	1788	Sep 2025
NCT05253651	An Open-label Randomized Phase 3 Study of Tucatinib in Combination With Trastuzumab and mFOLFOX6 Versus mFOLFOX6 Given With or Without Either Cetuximab or Bevacizumab as First-line Treatment for Subjects With HER2+ Metastatic Colorectal Cancer	400	Jul 2029

No update is scheduled on this Medical Policy. Blue Cross and Blue Shield of Kansas will continue to monitor published literature for any updated information. If there are questions about coverage of this service, please contact Blue Cross and Blue Shield of Kansas Customer Service, or Provider Network Solutions Representative.

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NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT04258137	Circulating DNA to Improve Outcome of Oncology PatiEnt: A Randomized Study - COPE Study	332	Apr 2025 (unknown status)
Unpublished			
NCT03457896	Study of Neratinib +Trastuzumab or Neratinib + Cetuximab in Patients With KRAS/NRAS/BRAF/PIK3CA Wild-Type Metastatic Colorectal Cancer by HER2 Status	35	Sep 2022 (unknown status)
NCT03602079	A Phase I-II, FIH Study of A166 in Locally Advanced/Metastatic Solid Tumors Expressing Human Epidermal Growth Factor Receptor 2 (HER2) or Are HER2 Amplified That Did Not Respond or Stopped Responding to Approved Therapies	49	Dec 2022 (completed)
NCT04744831	Trastuzumab Deruxtecan in Participants With HER2-overexpressing Advanced or Metastatic Colorectal Cancer (DESTINY-CRC02)	122	Oct 2024 (completed)

NCT: national clinical trial.

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CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
81191	NTRK1 (neurotrophic receptor tyrosine kinase 1) (eg, solid tumors) translocation analysis
81192	NTRK2 (neurotrophic receptor tyrosine kinase 2) (eg, solid tumors) translocation analysis
81193	NTRK3 (neurotrophic receptor tyrosine kinase 3) (eg, solid tumors) translocation analysis
81194	NTRK (neurotrophic receptor tyrosine kinase 1, 2, and 3) (eg, solid tumors) translocation analysis
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; variants in exon 2 (e.g., codons 12 and 13)
81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; additional variant(s) (e.g., codon 61, codon 146)
81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (e.g., colorectal carcinoma), gene analysis, variants in exon 2 (e.g., codons 12 and 13) and exon 3 (e.g., codon 61)
88360	Morphometric analysis, tumor immunohistochemistry (e.g., Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; manual

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CPT/HCPCS	
88363	Examination and selection of retrieved archival (i.e., previously diagnosed) tissue(s) for molecular analysis (e.g., KRAS mutational analysis)
88374	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), using computer-assisted technology, per specimen; each multiplex probe stain procedure
0111U	Oncology (colon cancer), targeted KRAS (codons 12, 13 and 61) and NRAS (codons 12, 13 and 61) gene analysis utilizing formalin-fixed paraffin-embedded tissue
0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations (FoundationOne® Liquid CDx from Foundation Medicine)
0242U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements
0338U	Oncology (solid tumor), circulating tumor cell selection, identification, morphological characterization, detection and enumeration based on differential EpCAM, cytokeratins 8, 18, and 19, and CD45 protein biomarkers, and quantification of HER2 protein biomarker–expressing cells, peripheral blood. CellSearch® HER2 Circulating Tumor Cell
0471U	Oncology (colorectal cancer), qualitative real-time PCR of 35 variants of KRAS and NRAS genes (exons 2, 3, 4), formalinfixed paraffin-embedded (FFPE), predictive, identification of detected mutations: CRCdx® RAS Mutation Detection Kit by EntroGen, Inc
0473U	Oncology (solid tumor), next generation sequencing (NGS) of DNA from formalin-fixed paraffin embedded (FFPE) tissue with comparative sequence analysis from a matched normal specimen (blood or saliva), 648 genes, interrogation for sequence variants, insertion and deletion alterations, copy number variants, rearrangements, microsatellite instability, and tumor-mutation burden

REVISIONS	
07-10-2015	Policy added to the bcbsks.com web site on 06-10-2015 with an effective date of 07-10-2015.
01-01-2016	In Coding section: ▪ Added CPT codes: 81276, 81311. ▪ Revised nomenclature of codes: 81210, 81275.
08-29-2016	Updated Description section.

No update is scheduled on this Medical Policy. Blue Cross and Blue Shield of Kansas will continue to monitor published literature for any updated information. If there are questions about coverage of this service, please contact Blue Cross and Blue Shield of Kansas Customer Service, or Provider Network Solutions Representative.

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REVISIONS	
	In Policy section: ▪ In Item B, removed "experimental / investigational", "to", "and", and "in the treatment of metastatic colorectal cancer" and added "medically necessary", "for patients with", "prior to planned therapy with", and "or" to read "*NRAS* mutation analysis is considered medically necessary for patients with metastatic colorectal cancer to predict nonresponse prior to planned therapy with anti-EGFR monoclonal antibodies cetuximab or panitumumab."
	Updated Rationale section.
	In Coding section: ▪ Removed CPT codes: 81403, 81404.
	Updated References section.
01-30-2018	Updated Policy title from "KRAS, NRAS, and BRAF Mutation Analysis in Metastatic Colorectal Cancer" to "KRAS, NRAS, and BRAF Variant Analysis in Metastatic Colorectal Cancer."
	Updated Description section.
	In Policy section: ▪ In Item A, removed "mutation" and added "variant" and "epidermal growth factor" to read, "*KRAS* variant analysis may be considered medically necessary for patients with metastatic colorectal cancer to predict nonresponse prior to planned therapy with anti-epidermal growth factor (EGFR) monoclonal antibodies cetuximab or panitumumab." ▪ In Item B, removed "mutation" and "is" and added "variant" and "may be" to read, "*NRAS* variant analysis may be considered medically necessary for patients with metastatic colorectal cancer to predict nonresponse prior to planned therapy with anti-EGFR monoclonal antibodies cetuximab or panitumumab. ▪ In Item C, removed "mutation", "is", "experimental/investigational", and "to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer" to read, "*BRAF* variant analysis may be 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." ▪ Added Policy Guidelines.
	Updated Rationale section.
	In Coding section: ▪ Removed ICD-9 codes.
	Updated References section.
	Added Appendix section.
08-29-2018	Updated Description section.
	Updated Rationale section.

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REVISIONS	
	Updated References section.
	Removed Appendix.
09-27-2019	Policy published to the bcbsks.com website on 08-28-2019 with an effective date of 09-27-2019.
	Updated Description section.
	In Policy section: ▪ Added new Item D, "*KRAS, NRAS,* and *BRAF* variant analysis using circulating tumor DNA or circulating tumor cell testing (liquid biopsy) to guide treatment for patients with metastatic colorectal cancer is considered experimental / investigational."
	Updated Rationale section.
	In Coding section: ▪ Added CPT codes: 86152, 86153, 0069U. ▪ Removed coding bullets.
	Updated References section.
10-01-2019	In Coding section: ▪ Added PLA code: 0111U
04-30-2021	Updated Description section
	Updated Rationale section
	In Coding section: • Removed CPT codes 86152 and 86153 • Added CPT code 0242U
	Updated References section
	Added Appendix 1 and 2
10-10-2021	Changed Title from "KRAS, NRAS, and BRAF Variant Analysis in Metastatic Colorectal Cancer" to "Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer"
	Updated Description section.
	In Policy section: ▪ Added Items C, D, and F. ▪ Added "as well as Mismatch repair/microsatellite instability (MMR/MSI) testing," to Item G
	Updated Rationale section.
	In Coding section: ▪ Added code CPT code: 81301 ▪ Removed CPT code: 0069U
	Updated References section.
09-22-2022	Changed Title to:

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REVISIONS	
	▪ "Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer (KRAS, NRAF, BRAF, MMR/MSI, HER2, and TMB)"
	Updated Description Section
	Updated Policy Section: ▪ Section A: Added "of tumor tissue" and "to select individuals for treatment with FDA-approved therapies. Removed: "to predict nonresponse prior to planned therapy with anti-epidermal growth factor receptor (EGFR) monoclonal antibodies cetuximab or panitumumab" ○ Reads: "*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;" ▪ Section B: Added "of tumor tissue" and "to select individuals for treatment with FDA-approved therapies. Removed: "to predict nonresponse prior to planned therapy with anti-epidermal growth factor receptor (EGFR) monoclonal antibodies cetuximab or panitumumab" ○ Reads: "*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. ▪ Section C: Added "of tumor tissue" and "to select individuals for treatment with FDA-approved therapies. ○ Reads: "*BRAF* variant analysis of tumor tissue may be considered medically necessary for individuals 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." ▪ Section D: Added "of tumor tissue" and "to select individuals for treatment with FDA-approved therapies. Removed "predict treatment response to pembrolizumab (Keytruda): 1. for first-line treatment of patients with unresectable or metastatic colorectal cancer; OR 2. in patients with colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; OR 3. in patients with colorectal cancer tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. ○ Reads: "Mismatch repair/microsatellite instability (MMR/MSI) testing of tumor tissue may be considered medically necessary to select individuals for treatment with FDA-approved therapies." ▪ Added:

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This policy is no longer effective as of February 26, 2026. For dates of service after February 26, 2026 see BCBSKS Medical Policy *Genetic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment of Advanced Cancer.*

REVISIONS	
	○ "All other uses of *KRAS* variant testing of tumor tissue to guide colorectal cancer targeted therapy or immunotherapy are considered experimental / investigational." ○ "All other uses of *NRAS* variant testing of tumor tissue to guide colorectal cancer targeted therapy or immunotherapy are considered experimental / investigational." ○ "All other uses of *BRAF* variant testing of tumor testing to guide colorectal cancer targeted therapy or immunotherapy are considered experimental / investigational. ○ "Other uses of mismatch repair/microsatellite instability variant testing of colorectal tumor tissue for guiding targeted therapy or immunotherapy are considered experimental / investigational." ○ "Circulating tumor DNA testing (liquid biopsy) to guide treatment in patients with metastatic colorectal cancer is considered experimental / investigational." ▪ Removed: ○ "*KRAS, NRAS,* and *BRAF* variant analysis, as well as Mismatch repair/microsatellite instability (MMR/MSI) testing, using circulating tumor DNA or circulating tumor cell testing (liquid biopsy) to guide treatment for patients with metastatic colorectal cancer is considered experimental / investigational." *Formatting order (A-K) has changed due to additions and removal of policy statements
	Updated Policy Guideline Section ▪ Removed: ○ "There is support from the evidence and clinical input to use BRAF V600 variant testing for prognostic stratification. " ○ "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. " ▪ Added: ○ "Testing for other variants may become available between policy updates. 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

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REVISIONS	
	markers and consult the most current version of National Comprehensive Cancer Network (NCCN) management algorithms." Updated Rationale Section Updated Coding Section ▪ Added 0239U ▪ Converted ICD-10 codes to ranges Updated References Section Removed Appendix Section
10-28-2022	Updated Coding Section ▪ Added 0338U (effective 10-01-2022)
Posted 9-12-2023 Effective 10-12-2023	Updated Title ▪ Title changed to "Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, HER2)" Updated Description Section Updated Policy Section ▪ Section A added: "*NRAS, BRAF, or HER2"* removed "variant analysis" and added "testing" ▪ Section B added: "*NRAS, BRAF, or HER2"* removed "variant" and "or immunotherapy" ▪ Removed Sections C, D, E, F, G, H, I and J C. *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. D. All other uses of *NRAS* variant testing of tumor tissue to guide colorectal cancer targeted therapy or immunotherapy are considered experimental / investigational. E. *BRAF* variant analysis of tumor tissue may be considered medically necessary for individuals 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. F. All other uses of *BRAF* variant testing of tumor testing to guide colorectal cancer targeted therapy or immunotherapy are considered experimental / investigational. G. Mismatch repair/microsatellite instability (MMR/MSI) testing of tumor tissue may be considered medically necessary to select individuals for treatment with FDA-approved therapies. H. Other uses of mismatch repair/microsatellite instability variant testing of colorectal tumor tissue for guiding targeted therapy or immunotherapy are considered experimental / investigational. I. HER2 testing is considered experimental / investigational to predict treatment response to immunotherapy in patients with metastatic colorectal cancer. J. Tumor mutational burden testing to predict response to immunotherapy in patients with metastatic colorectal cancer is considered experimental / investigational.

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REVISIONS	
	Updated Policy Guideline Section ▪ Added New Section A "The NCCN colon cancer guidelines v.2.2023 and rectal cancer guidelines v. 2.2023 do not recommend testing for specific genes over a next generation sequencing panel. The guidelines additionally state that testing may be performed using either tissue or blood-based biopsy, with testing on tissue being preferred." ▪ Added to Section B (previous section A) ○ B1 "Testing for individual genes (not gene panels) associated with FDA-approved therapeutics (i.e., as companion diagnostic tests) for therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher are not subject to extensive evidence review. Note that while the FDA approval of companion diagnostic tests for genes might include tests that are conducted as panels, the FDA approval is for specific genes (such as driver mutations) and not for all of the genes on the test panel." ○ B2 "FDA approves tests in between policy review cycles. As such, newly approved tests might need to be considered per local Plan discretion." ○ B3 "Note: Extensive evidence review is not included for somatic tests of individual genes (not gene panels) associated with U.S. Food and Drug Administration (FDA)-approved therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher. The pivotal evidence is included in Table 1 for informational purposes. Additionally, no evidence review is provided for somatic tests of individual genes that do not have associated FDA-approved therapies regardless of National Comprehensive Cancer Network (NCCN) recommendations, as these off-label therapies are deemed investigational per the Blue Cross and Blue Shield Association Medical Policy Program Policies and Procedures."
	Updated Rationale Section
	Updated Coding Section ▪ Removed ICD-10 Codes ▪ Removed 81301 ▪ Added: 88360 and 88374
	Updated References Section
07-01-2024	Updated Coding Section ▪ Added 0473U (eff. 07-01-2024)
08-27-2024	Updated Title ▪ Added "NTRK" to the title
	Updated Description Section
	Updated Policy Section

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REVISIONS	
	▪ Added "NTRK" to Section A and B
	Updated Rationale Section
	Updated Coding Section ▪ Added new code 0471U (eff. 07-01-2024) and 81191, 81192, 81193, and 81194
	Updated References Section
Posted 08-26-2025 Effective 09-25-2025	Updated Title: ▪ Added: *RET* to title "Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Metastatic Colorectal Cancer (*KRAS, NRAS, BRAF, NTRK, RET* and *HER2*)"
	Updated Description Section
	Updated Policy Section ▪ Section A: *KRAS*, *NRAS, BRAF, NTRK* or *RET* testing of tumor tissue biopsy specimens may be considered medically necessary for individuals with metastatic colorectal cancer to select individuals for treatment with U.S. Food and Drug Administration (FDA)-approved therapies. ○ Removed: *HER2* ○ Added: "*RET*" and "biopsy specimens" ▪ Section B: ○ Removed: "*HER2*" ○ Added: "*RET*" ▪ Added Section D: *HER2* testing of tumor tissue biopsy specimens may be considered medically necessary for individuals with metastatic colorectal cancer to select individuals for treatment with U.S. Food and Drug Administration (FDA)-approved therapies. ▪ Added Section E: All other uses of *HER2* testing of tumor tissue to guide colorectal cancer targeted therapy are considered experimental / investigational. ▪ Added Section F: Analysis of plasma (liquid biopsy) for somatic variants of the *KRAS* (eg, G12C) and *RAS* variants using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered medically necessary as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to an FDA-approved therapy, in individuals with metastatic CRC, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines). ▪ Added Section G: All other uses of analysis of *KRAS* and *NRAS* variants in plasma are considered experimental / investigational. ▪ Added Section H: Analysis of plasma (liquid biopsy) for the somatic *BRAF* V600E variants using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered medically necessary as an alternative to tissue biopsy

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	(see Policy Guidelines) to predict treatment response to an FDA-approved therapy, in individuals with metastatic CRC, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines). ▪ Added Section I: All other uses of analysis of *BRAF* V600E variant in plasma are considered experimental / investigational. ▪ Added Section J: Analysis of plasma (liquid biopsy) for *NTRK* gene fusions using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered medically necessary as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to an FDA-approved therapy in individuals with metastatic CRC, if the individual does not have any FDA-labeled contraindications to the requested agent and both the agent and ctDNA test are intended to be used consistently with their FDA-approved labels (see Policy Guidelines). ▪ Added Section K: All other uses of analysis of *NTRK* fusions in plasma are considered experimental / investigational. ▪ Added Section L:Analysis of plasma (liquid biopsy) for somatic *RET* variants is considered experimental / investigational as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to an FDA-approved therapy in individuals with metastatic CRC. ▪ Added Section M: Analysis of plasma (liquid biopsy) for somatic *HER2* variants is considered experimental / investigational as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to an FDA-approved therapy in individuals with metastatic CRC. ▪ Added Section N: All other uses of circulating tumor DNA testing (liquid biopsy) to guide treatment in individuals with metastatic colorectal cancer is considered experimental / investigational (see Policy Guidelines).
	Updated Policy Guidelines Section ▪ Added: This policy does not address germline testing for inherited risk of developing cancer. ▪ Added Section B: Concurrent Somatic Liquid-Based and Tissue-Based Genomic Testing 1. Liquid biopsy testing uses blood samples and assesses cancer DNA and non-cancer DNA in the same blood sample. The goal is to identify options for genome-informed treatment. Some providers will order a liquid biopsy test and a tissue biopsy test at the same time to hasten time to treatment. If the intent of concurrent testing is to follow an individual overtime to monitor for resistance variants, then consideration could be given to doing liquid biopsy at diagnosis with the tissue biopsy

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	to make sure that mutations that are going to be followed longitudinally can be detected by the liquid biopsy. ▪ Added Section C:Recommended Testing Strategies 1. Individuals who meet criteria for genetic testing as outlined in the policy statements above should be tested for the variants specified. 2. When tumor tissue is available, use of tissue for testing of any/all variants and biomarkers outlined in this policy is recommended, but is not required in all situations. In certain situations, circulating tumor DNA testing (liquid biopsy) may be an option.
	Updated Rationale Section
	Updated Reference Section
02-26-2026	Archived ▪ Policy incorporated into BCBSKS Medical Policy Genetic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment of Advanced Cancer

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