Medical Policy

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Title: Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Metastatic Colorectal Cancer (*KRAS, NRAS, BRAF, NTRK* 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)*

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Populations	Interventions	Comparators	Outcomes
Individuals: • With metastatic colorectal cancer	Interventions of interest are: • *KRAS, NRAS, BRAF, NTRK* or HER2 testing to guide treatment	Comparators of interest are: • No *KRAS, NRAS, BRAF*, *NTRK* or 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: • Testing of circulating tumor DNA to select treatment	Comparators of interest are: • Using tissue biopsy to guide treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Morbid events • Medication use

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. 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 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 (i.e., 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 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.

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.[2,] 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 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.

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 (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, 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

Manufacturer	Test	Type of Liquid Biopsy
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, 2024; FDA maintains a list of cleared or approved companion diagnostic devices that is updated regularly.[3,]

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.[4,] 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	cobas KRAS Mutation Test Dako EGFR pharmDx Kit FoundationOne CDx therascreen KRAS RGQ PCR Kit ONCO/Reveal Dx Lung & Colon Cancer Assay xT CDx	[5,] [6,]	2A or higher/Metastatic Colorectal Cancer (v. 3.2024) [7,]

Treatment	Indications in Metastatic Colorectal Cancer	Companion Diagnostics	Pivotal Study	NCCN Recommendation Level/Guideline
	cancer or when the results of the RAS mutation tests are unknown			
Braftovi (Encorafenib)	Treatment of adult patients with metastatic colorectal cancer with a *BRAF*V600E mutation • in combination with Erbitux (cetuximab), after prior therapy	FoundationOne Liquid CDx therascreen BRAF V600E RGQ PCR Kit	[8,]	2A or higher/Metastatic Colorectal Cancer (v. 3.2024) [7,]
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. 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.	cobas KRAS Mutation Test CRCDx RAS Mutation Detection Assay Kit Dako EGFR pharmDx Kit FoundationOne CDx Praxis Extended RAS Panel therascreen KRAS RGQ PCR Kit ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) xT CDx	[9,]	2A or higher/Metastatic Colorectal Cancer (v. 3.2024) [7,]
Tukysa (Tucatinib)	Treatment of adult patients with unresectable or metastatic CRC with RAS wild-type HER2-positive • In combination with trastuzumab (Herceptin) • Previously treated with flouropyrimidine, oxaliplatin, and irinotecan-based chemotherapy	No FDA-approved companion diagnostic	[10,]	2A or higher/Metastatic Colorectal Cancer (v. 3.2024) [7,]
Vitrakvi (larotrectinib)	*NTRK* fusion positive, metastatic CRC as determined by an FDA-approved test with no satisfactory alternative treatment options • In a non-first line setting	FoundationOne Liquid CDx	[11,]	2A or higher/Metastatic Colorectal Cancer (v. 3.2024) [7,]
Rozlytrek (entrectinib)	*NTRK* fusion positive, metastatic CRC as determined by an FDA-approved test with	FoundationOne Liquid CDx	[12,]	2A or higher/Metastatic

Treatment	Indications in Metastatic Colorectal Cancer	Companion Diagnostics	Pivotal Study	NCCN Recommendation Level/Guideline
	no satisfactory alternative treatment options • In a non-first line setting			Colorectal Cancer (v. 3.2024) [7,]

Source: FDA (2024)[3,]
CRC: colorectal cancer; EGFR: epidermal growth factor receptor; FDA: U.S. Food and Drug Administration; FOLFIRI: 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.

POLICY

A. *KRAS, NRAS, BRAF, NTRK or HER2* testing of tumor tissue 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 *HER2* 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).

POLICY GUIDELINES

A. The National Comprehensive Cancer Network (NCCN) colon cancer guidelines v.3.2024 and rectal cancer guidelines v.3.2024 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.

B. 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 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.

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RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through May 24, 2024.

Testing for individual genes (not gene panels) associated with U.S. Food and Drug Administration (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. 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 HER2 Variant Testing to Guide Treatment for Metastatic Colorectal Cancer

For individuals with metastatic colorectal cancer (CRC) who receive *KRAS, NRAS, BRAF, NTRK,* or *HER2* 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.

CIRCULATING TUMOR DNA TESTING (LIQUID BIOPSY) TO GUIDE TREATMENT FOR METASTATIC COLORECTAL CANCER

Clinical Context and Test Purpose

One purpose of liquid biopsy testing of individuals who have metastatic CRC is to inform a decision regarding treatment selection (e.g., whether to select a targeted treatment or standard treatment).

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

Populations

The relevant population of interest is individuals with metastatic CRC being considered for targeted therapy.

Interventions

The test being considered is liquid biopsy using either circulating tumor DNA (ctDNA) or circulating tumor cells (CTCs). Both targeted polymerase chain reaction-based assays and broad next-generation sequencing-based approaches are available.

Comparators

In patients who are able to undergo a biopsy, molecular characterization of the tumor is performed using standard tissue biopsy samples. Patients unable to undergo a biopsy generally receive standard therapy.

Outcomes
True-positive liquid biopsy test results lead to the initiation of appropriate treatment (e.g., targeted therapy) without a tissue biopsy. False-positive liquid biopsy test results lead to the initiation of inappropriate therapy, which could shorten progression-free survival (PFS).

In individuals able to undergo a tissue biopsy, negative liquid biopsies reflex to tissue testing. In individuals unable to undergo a tissue biopsy, a negative liquid biopsy result would not change empirical treatment. Therefore, health outcomes related to negative test results do not differ between liquid biopsy and tissue biopsy.

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
Given the breadth of molecular diagnostic methodologies available to assess ctDNA and CTC, the clinical validity of each commercially available test must be established independently. Multiple high-quality studies are needed to establish the clinical validity of a test.

OncoBEAM RAS CRC Assay
The clinical validity of the OncoBEAM RAS CRC assay has been evaluated in several published studies of patients with metastatic CRC. Study characteristics and results are shown in Tables 3 and 4. Study relevance, design, and conduct limitations are described in Tables and 8.

Table 3. Clinical Validity Studies of the OncoBEAM RAS Assay

Study	Study Population	Design	Reference Standard	Timing of Tissue Biopsy and Liquid Biopsy	Blinding of Assessors
Garcia-Foncillas et al (2018)[13,]	• Patients with metastatic CRC newly diagnosed or presenting with recurrent disease after resection and/or	Prospective	Analysis of tissue using standard-of-care procedures validated by	Plasma collected before any therapeutic intervention. OncoBEAM used when standard of care RAS result was	Not stated; central laboratory used

Study	Study Population	Design	Reference Standard	Timing of Tissue Biopsy and Liquid Biopsy	Blinding of Assessors
	chemotherapy at 10 centers in Spain • Enrolled from November 2015 to October 2016		each hospital	discordant with RAS result. The same tissue block was used for re-analysis by OncoBEAM.	
Vidal et al (2017)[14],	• Patients from Spain with histologically confirmed metastatic CRC • Anti-EGFR treatment-naive • Enrolled from 2009 to 2016	Retrospective-prospective	Analysis of tissue samples conducted using institutional standard-of-care procedures	• Tissue collected before blood • Median interval, 48 days (range, 0 to 1783 days)	Yes
Schmiegel et al (2017)[15],	• Patients from Australia and Germany with newly diagnosed stage III/IV histologically confirmed CRC	Prospective	Analysis of tissue samples conducted using Sanger sequencing	• Blood obtained immediately prior to tissue biopsy or resection	Not stated
Grasselli et al (2017)[16],	• Patients from Spain with histologically confirmed metastatic CRC • Anti-EGFR treatment-naïve but majority treated with other systemic therapies	Retrospective-prospective	Analysis of tissue samples conducted using real-time PCR	• Tissue collected before blood • Median interval 1.2 months (range, 0 to 34)	Yes
Normanno et al (2018)[17],	• Patients with metastatic CRC who are *KRAS* exon-2 wild-type and received first-line etuximab plus FOLFIRI within the CAPRI-GOIM trial	Retrospective-prospective	Analysis of tissue samples conducted using NGS	• Unclear when tissue was collected • Blood collected at baseline	Not stated

CRC: colorectal cancer; EGFR: epidermal growth factor receptor; FOLFIRI: folinic acid, fluorouracil, irinotecan; NGS: next-generation sequencing; PCR: polymerase chain reaction.

Table 4. Clinical Validity Studies of the OncoBEAM RAS Assay-Results

Study	Initial N	Final N	Excluded Samples	RAS Variant-Positive, %[a]	Sensitivity	Specificity	PPV	NPV
Garcia-Foncillas et al (2018)[13,]	239	236	3 patients initially excluded because of total disease removal during primary surgery. RAS mutation status was evaluable in all 236 patients	55.5	86.3	92.4	NR	NR
Vidal et al (2017)[14,]	NA	115	No description of samples excluded from comparison to tissue results	51	96 (87 to 100)[b]	90 (79 to 96)[b]	90 (79 to 96)[b]	96 (88 to 100)[b]
Schmiegel et al (2017)[15,]	102	98	n=3 (inadequate plasma DNA); n=1 (RAS mutation not confirmed in tissue when re-evaluated)	53	90 (79 to 96)	94 (82 to 98)	NR	NR
Grasselli et al (2017)[16,]	157	146	N=11 (pre-analytical requirements or lack of tumor tissue availability)	59	89 (77 to 96)[b]	90 (82 to 95)[b]	84 (74 to 91)[b]	93 (87 to 97)[b]
Normanno et al (2018)[17,]	340	92	Tissue and plasma unavailable (not clear if tissue samples were sampled from those available or if all available were used)	36	70 (51 to 84)[b]	83 (71 to 92)[b]	70 (56 to 81)[b]	83 (74 to 89)[b]

NA: not available; NPV: negative predictive value; NR: not reported; PPV: positive predictive value.
[a] With tissue biopsy reference standard.
[b] Values are percent with 95% confidence interval.
[b] Confidence intervals not reported in publication; calculated from data provided.

FoundationACT ctDNA Assay

The FoundationACT ctDNA assay, the predecessor of FoundationOne Liquid, was compared to tissue biopsy using the FoundationOne assay in one manufacturer-sponsored study by Li et al in 2019.[18,] Study characteristics and results are shown in Tables 5 and 6. The researchers reported results on the subset of 51 patients with *KRAS, NRAS,* and *BRAF* variants. These results are shown in Table 10. Positive percent agreement was 80% for all time points for short variants and increased to 90% for cases in which tissue and liquid biopsy were measured less than 270 days apart. Limitations of this study are described in Tables 7 and 8.

Table 5. Clinical Validity Study of the FoundationACT ctDNA Assay

Study	Study Population	Design	Reference Standard	Timing of Reference and Index Tests	Blinding of Assessors
Li et al (2019)[18,]	Patients with CRC, 74% stage IV, 19% stage III, 7% stage II	Prospective and retrospective	Previously-collected tissue biopsy with FoundationOne assay	Liquid biopsy testing was done at the discretion of the clinician at variable time intervals after tissue sample collection (0 to 709 days).	Not stated

CRC: colorectal cancer; ctDNA: circulating tumor DNA.

Table 6. Clinical Validity Study of the FoundationACT ctDNA Assay - Results

Study	Initial N	Final N	Excluded Samples	RAS Variant-Positive, %	Positive Percent Agreement (95% Confidence Interval)
Li et al (2019)[18,]	96	73	22 samples did not have detectable ctDNA	51/74 (92%)	Overall (N=73): 79% Subset with *KRAS*, *NRAS*, and *BRAF* variants (n=51): 80% for all timepoints 90% for cases <270 days between tissue and liquid biopsy

ctDNA: circulating tumor DNA ;.

Table 7. Study Relevance Limitations for Clinical Validity Studies of Liquid Biopsy in Metastatic Colorectal Cancer

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Li et al (2019)[18,]	4.74% had metastatic disease		2. Reference standard was FoundationOne assay		

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Garcia-Foncillas et al (2018)[13],				3. PPV and NPV not reported	
Vidal et al (2017)[14],					
Schmiegel et al (2017)[15],		2: Not clear if marketed version of test used			
Grasselli et al (2017)[16],					
Normanno et al (2018)[17],					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
NPV: negative predictive value; PPV: positive predictive value.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 8. Study Design and Conduct Limitations for Liquid Biopsy in Metastatic Colorectal Cancer

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Completeness of Follow-Up[e]	Statistical[f]
Li et al (2019)[18],	2. Inclusion required a previously performed FoundationACT assay; previous treatments varied	1: Blinding unclear	2. Timing of liquid biopsy and tissue biopsy varied (range 0 to 709 days)		2. 20% of samples had no detectable ctDNA	
Garcia-Foncillas et al (2018)[13],	1. Not clear whether samples were consecutive or convenience	1: Blinding unclear		1. Registration not described		

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Completeness of Follow-Up[e]	Statistical[f]
Vidal et al (2017)[14,]	1. Not clear whether samples were consecutive or convenience		2: Blood collected approximately 1.5 m after tissue	1. Registration not described	1. Not clear whether there were samples that were insufficient for analysis or failed to produce results	1. CIs not reported but calculated based on data provided
Schmiegel et al (2017)[15,]	1: Not clear how patients were selected from those that were eligible	1: Blinding unclear		1. Registration not described		
Grasselli et al (2017)[16,]	1: Not clear how patients were selected from those that were eligible		2: Blood collected approximately 1.5 m after tissue			1. CIs not reported but calculated based on data provided
Normanno et al (2018)[17,]	1: Not clear how tumor samples were selected from those available	1: Blinding unclear	1: Unclear when tissue was collected	1. Registration not described	2: Only 27% of CAPRI-GOIM trial participants included	1. CIs not reported but calculated based on data provided

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CI: confidence interval; ctDNA: circulating tumor DNA.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Follow-Up key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples/patients excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

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.

No RCTs were identified on the clinical utility of liquid biopsy to guide treatment for patients with metastatic CRC.

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: Circulating Tumor DNA Testing (Liquid Biopsy) to Guide Treatment for Metastatic Colorectal Cancer
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% (95% confidence interval [CI], 51% to 84%) to 96% (95% CI, 87% to 100%) and specificity ranged from 83% (95% CI, 71% to 92%) to 94% (95% CI, 82% to 98%). FoundationOne Liquid has been compared to tissue biopsy with the FoundationACT assay in 1 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.

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 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.[19,] Table 9 summarizes the relevant guidelines.

Table 9. Summary of Recommendations

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

Guidelines	Type	SOE	QOE
*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. 3.2024).[7,] Guidelines are updated frequently; refer to the source document for most recent updates and for additional detail.

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. *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.

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 (e.g., 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 10.

Table 10. 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 2024
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
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	400	Apr 2028

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Bevacizumab as First-line Treatment for Subjects With HER2+ Metastatic Colorectal Cancer		
NCT04744831	Trastuzumab Deruxtecan in Participants With HER2-overexpressing Advanced or Metastatic Colorectal Cancer (DESTINY-CRC02)	122	Jul 2024
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)

NCT: national clinical trial.

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
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)

CPT/HCPCS	
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.
	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."

REVISIONS	
	▪ 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.
	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

REVISIONS	
	Updated Rationale section.
	In Coding section: ▪ Added code CPT code: 81301 ▪ Removed CPT code: 0069U
	Updated References section.
09-22-2022	Changed Title to: ▪ "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" o 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" o 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. o 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. o 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: o "All other uses of *KRAS* variant testing of tumor tissue to guide colorectal cancer targeted therapy or immunotherapy are considered experimental / investigational."

REVISIONS	
	○ "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 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	Updated Title ▪ Title changed to "Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, HER2)"

REVISIONS	
10-12-2023	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.
	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) o 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." o B2 "FDA approves tests in between policy review cycles. As such, newly approved tests might need to be considered per local Plan discretion." o 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

REVISIONS	
	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 ▪ 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

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