Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer

Policy # 00233
Original Effective Date: 12/17/2008
Current Effective Date: 03/01/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Mismatch repair and microsatellite testing of colorectal cancer tissue may be indicated for Lynch Syndrome in medical policy 00190

Note: 00257 Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer

Note: For expanded panel testing, see Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies in medical policy 00423

Note: For expanded panel testing, see Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy) in medical policy 00497.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider initial tumor testing for KRAS, NRAS, BRAF V600E variants and HER2 amplification if not previously done, in individuals with metastatic colorectal cancer (mCRC) to predict treatment response to FDA-approved therapies to be **eligible for coverage.****

Based on review of available data, the Company may consider initial tumor testing for MSI/MMR status using FDA approved or cleared companion diagnostic test (i.e., FoundationOne CDx™‡), if

not previously done, in individuals with unresectable or metastatic colorectal cancer (mCRC) for selecting immunotherapy cancer treatment with pembrolizumab (Keytruda) to be **eligible for coverage.****

Based on review of available data, the Company may consider tumor testing for NTRK gene fusion in individuals with metastatic or, unresectable colorectal cancer with wild-type KRAS, NRAS, and BRAF, who progressed following standard of care or failed standard of care treatment and have no satisfactory alternative treatment options, to select patients for treatment with FDA approved therapy (e.g., larotrectinib or entrectinib) to be **eligible for coverage.****

Based on review of available data, the Company may consider circulating tumor DNA testing (ctDNA or liquid biopsy) for KRAS, NRAS and BRAF mutations, HER2 amplifications and NTRK gene fusion using FDA approved or cleared companion diagnostic test (i.e., FoundationOne Liquid CDx), if not previously tested in individuals with metastatic colorectal cancer (mCRC) when preferred tumor testing is not feasible to predict treatment response to FDA-approved therapies, to be **eligible for coverage**.**

Note: For 5 or more gene tests being run on the same platform, such as multi-gene panel next generation sequencing (NGS), single available procedure code for the multi-gene panel test is to be utilized.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers tumor mutational burden (TMB) testing to predict response to immunotherapy in patients with metastatic colorectal cancer to be **investigational.***

Based on review of available data, the Company considers circulating tumor DNA testing (ctDNA or liquid biopsy) to guide treatment in patients with metastatic colorectal cancer in all other

situations, including but not limited to concurrent liquid based and tumor based comprehensive genomic profiling, to be **investigational.***

Based on review of available data, the Company considers KRAS, NRAS, and BRAF variant testing, HER2 amplification, MSI/MMR status, and NTRK gene fusion testing of colorectal tumor tissue to guide targeted therapy or immunotherapy for all other indications to be **investigational.***

Policy Guidelines

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.

Testing for individual genes (not gene panels) associated with FDA-approved therapeutics 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.

Note that TMB is often included in panel tests and might not have separate coding.

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 NCCN management algorithms.

Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer

Policy # 00233
Original Effective Date: 12/17/2008
Current Effective Date: 03/01/2024

Background/Overview

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.

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 3% of patients with CRC, with higher prevalence in *RAS/BRAF*-wild type tumors (5% to 14%). In addition to its role as a predictive marker for HER2-targeted therapy, HER2 amplification/overexpression is being investigated as a predictor of resistance to EGFR-targeting monoclonal antibodies.

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

The percentage of stage IV colorectal tumors characterized as MSI-H (dMMR) ranged from 3.5% to 5% in clinical trials and was 6.5% in the Nurses' Health Study and Health Professionals Follow-up Study. The NCCN Guidelines recommend universal MMR or MSI testing for all patients with a personal history of colon or rectal cancer. In addition to its role as a predictive marker for immunotherapy use in the advanced CRC setting, MMR/ MSI status can also help to identify individuals with Lynch syndrome, and to inform adjuvant therapy decisions for patients with stage II disease.

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

Detecting 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, 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
Biocept	Target Selector™ ctDNA EGFR Kit	ctDNA
Foundation Medicine	FoundationOne Liquid (Previously FoundationAct)	ctDNA
Guardant Health	Guardant360®	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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Table 2 summarizes the targeted treatments approved by the U.S. Food and Drug Administration (FDA) for patients with CRC, along with the approved companion diagnostic tests. The information in Table 2 was current as of May 30, 2023; FDA maintains a list of cleared or approved companion diagnostic devices that is updated regularly.

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 mutation 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. Therefore, *BRAF* V600E variant testing to select individuals for treatment with dabrafenib in combination with trametinib is not included in this medical policy and is not listed in Table 2.

Table 2. Targeted Treatments for Metastatic Colorectal Cancer and FDA 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,	cobas KRAS Mutation Test Dako EGFR pharmDx Kit FoundationOne CDx	Van Cutsem E, Köhne CH, Hitre E, et al. (2009), Tol J, Koopman	2A or higher/ Metastatic Colorectal Cancer (v.2.2023)

	• 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	therascreen KRAS RGQ PCR Kit ONCO/Reveal Dx Lung & Colon Cancer Assay xT CDx	M, Cats A, et al. (2009)	
Braftovi (Encorafenib)	Treatment of adult patients with metastatic colorectal cancer with a BRAF V600E mutation • in combination with Erbitux (cetuximab), after prior therapy	therascreen BRAF V600E RGQ PCR Kit FoundationOne Liquid CDx	Kopetz S, Grothey A, Yaeger R, et al. (2019)	2A or higher/ Metastatic Colorectal Cancer (v.2.2023)

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 mCRC or for whom RAS mutation status is unknown.	cobas KRAS Mutation Test Dako EGFR pharmDx Kit FoundationOne CDx Praxis Extended RAS Panel therascreen KRAS RGQ PCR Kit NCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) xT CDx	Peeters M, Oliner KS, Price TJ, et al. (2015)	2A or higher/ Metastatic Colorectal Cancer (v.2.2023),
Pembrolizumab (Keytruda®‡)	Unresectable or metastatic, MSI-H or dMMR	FoundationOne CDx		

	• solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or • CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan First-line treatment of patients with unresectable or metastatic MSI-H or dMMR CRC			
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	No FDA-approved companion diagnostic	Strickler JH, Cercek A, Siena S, et al. (2023)	2A or higher/ Metastatic Colorectal Cancer (v.2.2023)

	irinotecan-based chemotherapy			

Source: FDA (2023)
CRC: colorectal cancer; EGFR: epidermal growth factor receptor; FOLFIRI: leucovorin, fluorouracil and irinotecan; FOLFOX: leucovorin, fluorouracil, and oxaliplatin; HER2: human epidermal growth factor receptor 2; mCRC: metastatic CRC;

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.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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. 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.

Summary of Evidence

For individuals with metastatic CRC who receive *KRAS, NRAS, BRAF* or *HER2* testing to guide treatment, the evidence includes FDA-approved therapeutics with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and National Comprehensive Cancer Network (NCCN) recommendations.

For individuals with cancer who are being evaluated for immune checkpoint inhibitor therapy who receive mismatch repair/microsatellite instability (MMR/MSI) testing, the evidence includes RCTs and nonrandomized trials. Relevant outcomes are OS, disease-specific survival, change in disease status, and treatment-related morbidity. Based on clinical trial data, MSI/MMR testing has received FDA approval and NCCN recommendations to select immune checkpoint inhibitor therapy in individuals with advanced or metastatic colorectal cancer and individuals with unresectable or metastatic solid tumors who have progressed following prior treatment and who have no satisfactory alternative treatment options. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with cancer who receive tumor mutational burden (TMB) testing to select treatment with immune checkpoint inhibitors, the evidence includes prospective and retrospective subgroup analyses of nonrandomized trials. Relevant outcomes include OS, disease-specific survival, test validity, quality of life, and treatment-related morbidity. In a prespecified subgroup analysis of a nonrandomized trial of pembrolizumab in individuals with various solid tumors, objective responses were observed in 24 (35%; 95% CI, 24 to 48) of 68 participants who had both tissue TMB (tTMB)-high status and PD-L1-positive tumors and in 6 (21%; 95% CI, 8 to 40) of 29 participants who had tTMB-high status and PD-L1-negative tumors. High TMB status was associated with improved response irrespective of PD-L1 status. Median OS and PFS were not significantly different between TMB groups. In exploratory analyses, retrospective observational studies have reported an association between higher TMB and longer PFS and overall survival in patients receiving immunotherapy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with metastatic CRC who receive circulating tumor DNA or circulating tumor cell testing (liquid biopsy) to guide treatment, the evidence includes observational studies. Relevant

outcomes are OS, disease-specific survival, test validity, morbid events, and medication use. Given the breadth of methodologies available to assess circulating tumor DNA and circulating tumor cells, the clinical validity of each commercially available test must be established independently. The clinical validity of the OncoBEAM™‡ RAS CRC Assay has been studied in multiple observational studies. When compared to tissue biopsy, sensitivity ranged from 70% (51% to 84%) to 96% (95% CI, 87% to 100%) and specificity ranged from 83% (95% CI, 71% to 92%) to 94% (82% to 98%). FoundationOne®‡ Liquid has been compared to tissue biopsy with the FoundationACT™‡ assay in 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2017 Input

Clinical input was sought to help determine whether the use of *BRAF* V600E variant analysis for individuals with metastatic CRC who are found to be wild-type on *KRAS* and *NRAS* variant analysis provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. In response to requests, clinical input was received from 10 respondents, including 2 specialty society-level responses, 1 physician from an academic center, and 6 physicians from 2 health systems.

For individuals who have metastatic CRC who are found to be wild-type on *KRAS* and *NRAS* variant analysis who receive *BRAF* V600E variant analysis to guide management decisions, clinical input

supports this use provides a clinically meaningful improvement in net health outcome and indicates this use is consistent with generally accepted medical practice.

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. 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 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
BRAF p.V600 (BRAF c. 1799 (p.V600) mutational analysis should be performed in colorectal cancer tissue in patients with colorectal	Recommendation	Adequate/inadequate, balance of benefits and harms	Intermediate/low

Guidelines	Type	SOE	QOE
carcinoma for prognostic stratification			
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; 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.4.2023). Guidelines are updated frequently; refer to the source document for most recent updates and for additional detail.

Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer

Policy # 00233
Original Effective Date: 12/17/2008
Current Effective Date: 03/01/2024

RAS and BRAF Testing
The guidelines recommend that 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).

Microsatellite Instability/Mismatch Repair Testing
The guidelines recommend universal mismatch repair (MMR) or microsatellite instability (MSI) testing for all patients with a personal history of colon or rectal cancer. In addition to its role as a predictive marker for immunotherapy use in the advanced colorectal cancer setting, MMR/MSI status can also help to identify individuals with Lynch syndrome and to inform adjuvant therapy decisions for patients with stage II disease (Category 2A).

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.

Tumor Mutational Burden Testing
Based on the limited data in the colorectal cancer population, the NCCN Panel does not currently recommend tumor mutational burden biomarker testing, unless measured as part of a clinical trial.

Circulating Tumor DNA
There is currently insufficient evidence to recommend use of circulating tumor DNA (ctDNA) assays outside of a clinical trial. De-escalation of care is not recommended based on ctDNA results.

The panel believes that there are insufficient data to recommend the use of multigene assays, Immunoscore, or post-surgical ctDNA to estimate risk of recurrence or determine adjuvant therapy. ESMO has released similar recommendations regarding these assays, stating that their role in predicting chemotherapy benefit is uncertain. The NCCN Panel encourages enrollment in clinical trials to help with the generation of additional data on these assays

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
A March 2018 decision memo from the Centers for Medicare & Medicaid Services addressed next-generation sequencing for Medicare beneficiaries with advanced cancer. The memo states:

> The Centers for Medicare & Medicaid Services has determined that Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally when performed in a CLIA-certified laboratory, when ordered by a treating physician and when all of the following requirements are met:
>
> 1. Patient has:
>   a. either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and
>   b. either not been previously tested using the same NGS test for the same primary diagnosis of cancer or repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physician; and
>   c. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).
>
> 2. The diagnostic laboratory test using NGS must have:
>   a. FDA [U.S. Food and Drug Administration] approval or clearance as a companion in vitro diagnostic; and
>   b. an FDA [U.S. Food and Drug Administration] approved or cleared indication for use in that patient's cancer; and
>   c. results provided to the treating physician for management of the patient using a report template to specify treatment options.

Regarding liquid biopsies, the memo states, "The NCD does not limit coverage to how to prepare a sample for performing a diagnostic laboratory test using NGS. Commenters submitted published articles on liquid biopsies (also referred to as circulating tumor DNA (ctDNA) or plasma cell-free DNA (cfDNA) tests). We reviewed and included in the evidence and analysis of 4 studies on liquid biopsies. At this time, liquid-based multi-gene sequencing panel tests are left to contractor discretion if certain patient criteria are met."

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	Jun 2023
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
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

NCT No.	Trial Name	Planned Enrollment	Completion Date
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
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	Apr 2028
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
NCT04744831	Trastuzumab Deruxtecan in Participants With HER2-overexpressing Advanced or Metastatic Colorectal Cancer (DESTINY-CRC02)	122	Aug 2023
NCT03043313	MOUNTAINEER: A Phase II, Open Label Study of Tucatinib Combined With Trastuzumab in Patients With HER2+ Metastatic Colorectal Cancer	177	Apr 2023

NCT: national clinical trial.

References

1. Amgen Inc. Vectibix (panitumumab) prescribing information. 2015; https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125147s200lbl.pdf.

2. U.S. Food & Drug Administration. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools.
3. Food & Drug Administration. 2022. FDA Grants Accelerated Approval to Dabrafenib in Combination with Trametinib for Unresectable or Metastatic Solid Tumors with BRAF V600E Mutation. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-dabrafenib-combination-trametinib-unresectable-or-metastatic-solid.
4. Van Cutsem E, Köhne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. Apr 02 2009; 360(14): 1408-17. PMID 19339720
5. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med. Feb 05 2009; 360(6): 563-72. PMID 19196673
6. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 2.2023. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
7. Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer. N Engl J Med. Oct 24 2019; 381(17): 1632-1643. PMID 31566309
8. Peeters M, Oliner KS, Price TJ, et al. Analysis of KRAS/NRAS Mutations in a Phase III Study of Panitumumab with FOLFIRI Compared with FOLFIRI Alone as Second-line Treatment for Metastatic Colorectal Cancer. Clin Cancer Res. Dec 15 2015; 21(24): 5469-79. PMID 26341920
9. Strickler JH, Cercek A, Siena S, et al. Tucatinib plus trastuzumab for chemotherapy-refractory, HER2-positive, RAS wild-type unresectable or metastatic colorectal cancer (MOUNTAINEER): a multicentre, open-label, phase 2 study. Lancet Oncol. May 2023; 24(5): 496-508. PMID 37142372
10. García-Foncillas J, Tabernero J, Élez E, et al. Prospective multicenter real-world RAS mutation comparison between OncoBEAM-based liquid biopsy and tissue analysis in metastatic colorectal cancer. Br J Cancer. Dec 2018; 119(12): 1464-1470. PMID 30467411
11. Vidal J, Muinelo L, Dalmases A, et al. Plasma ctDNA RAS mutation analysis for the diagnosis and treatment monitoring of metastatic colorectal cancer patients. Ann Oncol. Jun 01 2017; 28(6): 1325-1332. PMID 28419195
12. Schmiegel W, Scott RJ, Dooley S, et al. Blood-based detection of RAS mutations to guide anti-EGFR therapy in colorectal cancer patients: concordance of results from circulating tumor DNA and tissue-based RAS testing. Mol Oncol. Feb 2017; 11(2): 208-219. PMID 28106345

13. Grasselli J, Elez E, Caratù G, et al. Concordance of blood- and tumor-based detection of RAS mutations to guide anti-EGFR therapy in metastatic colorectal cancer. Ann Oncol. Jun 01 2017; 28(6): 1294-1301. PMID 28368441
14. Normanno N, Esposito Abate R, Lambiase M, et al. RAS testing of liquid biopsy correlates with the outcome of metastatic colorectal cancer patients treated with first-line FOLFIRI plus cetuximab in the CAPRI-GOIM trial. Ann Oncol. Jan 01 2018; 29(1): 112-118. PMID 28950295
15. Li G, Pavlick D, Chung JH, et al. Genomic profiling of cell-free circulating tumor DNA in patients with colorectal cancer and its fidelity to the genomics of the tumor biopsy. J Gastrointest Oncol 2019. http://jgo.amegroups.com/article/view/29063.
16. Sepulveda AR, Hamilton SR, Allegra CJ, et al. Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline From the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology. J Mol Diagn. Mar 2017; 19(2): 187-225. PMID 28185757
17. Centers for Medicare & Medicaid Services. Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450N). March 16, 2018. https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=290.

Policy History

Original Effective Date: 12/17/2008
Current Effective Date: 03/01/2024

12/03/2008	Medical Director review
12/17/2008	Medical Policy Committee approval. New policy.
12/04/2008	Medical Director review
12/16/2008	Medical Policy Committee approval. No change to coverage.
12/01/2010	Medical Policy Committee review
12/15/2010	Medical Policy Implementation Committee approval. No change to coverage.
12/08/2011	Medical Policy Committee review
12/21/2011	Medical Policy Implementation Committee approval. Title changed to indicate inclusion of BRAF testing to the policy. BRAF testing policy statement added as investigational to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer.

Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer

Policy # 00233
Original Effective Date: 12/17/2008
Current Effective Date: 03/01/2024

12/06/2012	Medical Policy Committee review
12/19/2012	Medical Policy Implementation Committee approval. No change to coverage.
03/04/2013	Coding revised
12/12/2013	Medical Policy Committee review
12/18/2013	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2015	Coding Update
04/02/2015	Medical Policy Committee review
04/20/2015	Medical Policy Implementation Committee approval. Title changed to indicate inclusion of NRAS testing to the policy. NRAS testing policy statement added as investigational to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
01/01/2016	Coding update
04/07/2016	Medical Policy Committee review
04/20/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/30/2016	Medical Policy Committee review
07/20/2016	Medical Policy Implementation Committee approval. Policy statement revised to indicate that NRAS testing policy statement added as medically necessary to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
09/07/2017	Medical Policy Committee review
09/20/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/01/2018	Medical Policy Committee review
02/21/2018	Medical Policy Implementation Committee approval. Title changed from “KRAS, NRAS, and BRAF Mutant Analysis in Metastatic Colorectal Cancer” to “KRAS, NRAS, and BRAF Variant Analysis in Metastatic Colorectal Cancer”. BRAF variant analysis changed from investigational to eligible for coverage. Policy revised with updated genetic nomenclature.
02/07/2019	Medical Policy Committee review

02/20/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/06/2019	Coding update
02/06/2020	Medical Policy Committee review
02/12/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Title changed from "KRAS, NRAS and BRAF Variant Analysis in Metastatic Colorectal Cancer" to "KRAS, NRAS, BRAF Variant Analysis (Including Liquid Biopsy) in Metastatic Colorectal Cancer". Investigational statement added for "using circulating tumor DNA or circulating tumor cell testing (liquid biopsy) to guide treatment for patients with metastatic colorectal cancer".
02/04/2021	Medical Policy Committee review
02/10/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/03/2022	Medical Policy Committee review
02/09/2022	Medical Policy Implementation Committee approval. Title changed from "KRAS, NRAS, BRAF Variant Analysis Biomarker Testing (Including Liquid Biopsy) in Metastatic Colorectal Cancer" to "Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer". Added eligible for coverage statement with criteria for mismatch repair/microsatellite instability testing to predict treatment response to pembrolizumab; added a related investigational statement if criteria are not met. Added investigational statements for HER2 testing to predict treatment response to immunotherapy in patients with metastatic colorectal cancer and for tumor mutational burden testing to predict response to immunotherapy in patients with metastatic colorectal cancer. Revised investigational statement for circulating tumor DNA testing in patients with colorectal cancer.
03/25/2022	Coding update
06/07/2022	Coding update
07/08/2022	Coding update
01/01/2023	Policy updated with literature review through June 2022; references added. 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 therapeutics (ie, as companion diagnostic tests) for therapies with National

	Comprehensive Cancer Network (NCCN) recommendations of 2A or higher. MN statement on BRAF variant testing expanded to include selecting individuals for treatment with FDA-approved therapies. Title changed to specify somatic testing and to list the specific biomarkers included.
09/01/2022	Medical Policy Committee review
09/14/2022	Medical Policy Implementation Committee approval. Title changed from "Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer" to "Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer". Extensive revisions made to the coverage section and throughout the policy.
02/02/2023	Medical Policy Committee review
02/08/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/19/2023	Coding update
05/31/2023	Coding update
07/06/2023	Medical Policy Committee review
07/12/2023	Medical Policy Implementation Committee approval. Added HER2 amplification to the first eligible for coverage statement for KRAS, NRAS and BRAF V600E variants. Added that circulating tumor DNA testing (ctDNA or liquid biopsy) for KRAS, NRAS and BRAF mutations, HER2 amplifications and NTRK gene fusion if not previously tested in individuals with metastatic colorectal cancer (mCRC) when preferred tumor testing is not feasible to predict treatment response to FDA-approved therapies is eligible for coverage. Removed the investigational statement for HER2 gene testing to predict treatment response to immunotherapy in patients with metastatic colon cancer. Revised the investigational statement for testing of colorectal tumor tissue to guide targeted therapy or immunotherapy.
10/30/2023	Coding update
12/13/2023	Coding update
12/07/2023	Medical Policy Committee review
12/13/2023	Medical Policy Implementation Committee approval. Added the use of FDA approved or cleared companion diagnostic test (i.e., FoundationOne Liquid CDx) to the eligible for coverage statement for circulating tumor DNA testing (ctDNA or

liquid biopsy) for KRAS, NRAS and BRAF mutations, HER2 amplifications and NTRK gene fusion. Revised the Policy Guidelines section. Added FoundationOne Liquid CDx as a companion diagnostic for Braftovi (encorafenib) to Table 2 in the FDA section. Revised the Rationale and Supplemental Information sections. Updated the References section.

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer

Policy # 00233
Original Effective Date: 12/17/2008
Current Effective Date: 03/01/2024

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0037U, 0111U, 0239U, 0242U, 0326U, 81191, 81192, 81193, 81194, 81210, 81275, 81276, 81311, 81405, 81406, 81445, 81455 Delete codes effective 1/1/2023: 81403, 81404 Add code effective 07/01/2023: 81301 Delete code effective 12/11/2023: 0368U Add codes effective 01/01/2024: 81457, 81458, 81459, 81462, 81463, 81464
HCPCS	No codes
ICD-10 Diagnosis	C18.0-C18.9, C19, C20, C21.0-C21.2, C21.8

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

Policy # 00233
Original Effective Date: 12/17/2008
Current Effective Date: 03/01/2024

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.