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: 08/14/2023

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
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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 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.*
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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
Testing for individual genes (not gene panels) associated with FDA-approved therapeutics (ie, as companion diagnostic tests) for therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher are not subject to extensive evidence review. 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.

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.

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

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Test</th>
<th>Type of Liquid Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biocept</td>
<td>Target Selector™ ctDNA EGFR Kit</td>
<td>ctDNA</td>
</tr>
<tr>
<td>Foundation Medicine</td>
<td>FoundationOne Liquid (Previously FoundationAct)</td>
<td>ctDNA</td>
</tr>
<tr>
<td>Guardant Health</td>
<td>Guardant360®‡</td>
<td>ctDNA</td>
</tr>
<tr>
<td>IV Diagnostics</td>
<td>Velox™‡</td>
<td>CTC</td>
</tr>
<tr>
<td>Personal Genome Diagnostics</td>
<td>PlasmaSELECT™‡</td>
<td>ctDNA</td>
</tr>
<tr>
<td>Sysmex Inostics</td>
<td>OncoBEAM</td>
<td>ctDNA</td>
</tr>
<tr>
<td>Circulogene</td>
<td>Theranostics</td>
<td>ctDNA</td>
</tr>
</tbody>
</table>

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 June 13, 2022; 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
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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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indications in Metastatic Colorectal Cancer</th>
<th>Companion Diagnostics</th>
</tr>
</thead>
</table>
| Cetuximab       | **KRAS** wild-type, **EGFR**-expressing, metastatic colorectal cancer as determined by an FDA-approved test  
• in combination with FOLFIRI for first-line treatment,  
• in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,  
• as a single-agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan.  
Limitations of Use: Erbitux is not indicated for treatment of **RAS** mutant colorectal cancer or when the results of the **RAS** mutation tests are unknown | cobas KRAS Mutation Test  
Dako EGFR pharmDx Kit  
FoundationOne CDx  
ONCO/Reveal Dx Lung & Colon Cancer Assay  
therascreen KRAS RGQ PCR Kit |
| 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 |
### Panitumumab (Vectibix)

<table>
<thead>
<tr>
<th>Treatment of wild-type RAS (defined as wild-type in both <em>KRAS</em> and <em>NRAS</em> as determined by an FDA-approved test for this use) metastatic CRC:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- In combination with FOLFOX for first-line treatment.</td>
</tr>
<tr>
<td>- As monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy.</td>
</tr>
</tbody>
</table>

**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 |
| ONCO/Reveal Dx Lung & Colon Cancer Assay |
| Praxis Extended RAS Panel |
| therascreen KRAS RGQ PCR Kit |

### Pembrolizumab (Keytruda®)

<table>
<thead>
<tr>
<th>Unresectable or metastatic, MSI-H or dMMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>- solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or</td>
</tr>
<tr>
<td>- CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan</td>
</tr>
</tbody>
</table>

First-line treatment of patients with unresectable or metastatic MSI-H or dMMR CRC

| FoundationOne CDx |

### Entrectinib (Rozyltrek®; Genentech)

| 2019: treatment of adults and pediatric patients 12 years of age and older with solid tumors that have a NTRK gene fusion without a known acquired resistance mutation, that are metastatic or where surgical treatment is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory standard therapy |

| No FDA-approved companion diagnostic |
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**Larotrectinib** (Vitrakvi®‡; Loxo Oncology/Bayer) | • 2018: treatment of adult and pediatric patients with solid tumors that have a NTRK gene fusion without a known acquired resistance mutation, that are metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment | 2020: FoundationOne CDxTM‡ (Foundation Medicine)

Source: FDA (2022)

CRC: colorectal cancer; dMMR: mismatch repair deficient; 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; MSI-H: microsatellite instability-high

**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.

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, testing for microsatellite instability/mismatch repair (MSI/MMR) and tumor mutational burden (TMB) status to select patients for immunotherapy and human epidermal growth factor receptor 2 (HER2) testing to select patients for targeted therapy has been proposed. Typically, the evaluation of biomarker...
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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 variant testing to guide treatment, the evidence includes multiple systematic reviews including a TEC Assessment. Relevant outcomes are overall survival (OS), disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Variant testing of tumor tissue performed in prospective and retrospective analyses of randomized controlled trials has consistently shown that the presence of a KRAS variant predicts nonresponse to cetuximab and panitumumab, either as monotherapy or in combination with other treatment regimens. Analyses also support the use of KRAS variant analysis of tumor DNA before considering a treatment regimen. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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

For individuals with metastatic CRC who receive BRAF variant testing to guide treatment, the evidence includes 2 meta-analyses of prospective and retrospective analyses of RCTs. Relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. The meta-analyses have shown that anti-EGFR monoclonal antibody therapy did not improve survival in patients with RAS wild-type or BRAF-mutated tumors; however, the individual studies have been small, and the results have been inconsistent. Testing for the BRAF V600E variant in adult individuals with metastatic CRC for determining treatment with encorafenib in combination with cetuximab after previous therapy, has
received FDA approval and NCCN recommendation based on clinical trial results. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with metastatic CRC who receive MSI/MMR testing to guide treatment, the evidence includes an RCT of pembrolizumab compared to chemotherapy and nonrandomized trials. Relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Effectiveness of pembrolizumab compared to chemotherapy in patients with previously untreated, unresectable or metastatic high-frequency MSI (MSI-H) or deficient MMR (dMMR) CRC was investigated in a multicenter, randomized, open-label, active-controlled trial of 307 patients. The trial demonstrated a statistically significant improvement in progression free survival (PFS) for patients randomized to pembrolizumab compared with chemotherapy (hazard ratio [HR] 0.60; 95% confidence interval [CI] 0.45 to 0.80; \( p=0.0002 \)). In final results, median PFS was 16.5 months (95% CI, 5.4 to 38.1) with pembrolizumab versus 8.2 months (95% CI, 6.1 to 10.2) with chemotherapy (HR 0.59; 95% CI, 0.45 to 0.79). Treatment-related adverse events of grade 3 or worse occurred in 33 (22%) of 153 patients in the pembrolizumab group versus 95 (66%) of 143 patients in the chemotherapy group. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with metastatic CRC who receive HER2 testing to guide treatment, the evidence includes nonrandomized trials. Relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. There is no approved targeted treatment or companion diagnostic test for HER2 testing in patients with metastatic CRC. A phase 2 basket trial included 37 patients with HER2-amplified/overexpressed metastatic CRC. Treatment with trastuzumab plus pertuzumab produced partial response in 14 patients (38%; 95% CI, 23% to 55%) and the median duration of response was 11 months (range 16+ months; 95% CI, 2.8 months to not estimable). In an open-label, phase 2 trial of trastuzumab deruxtecan, objective response was observed in 24 of 53 patients with HER2-positive metastatic CRC (45.3%; 95% CI 31.6 to 59.6) after a median follow-up of 27.1 weeks (interquartile range 19.3 to 40.1). Preliminary evidence has suggested that patients with HER2-amplified metastatic CRC are less likely to respond to anti-EGFR therapy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.
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For individuals with metastatic CRC who receive TMB testing to select treatment with immunotherapy, the evidence includes a prespecified retrospective subgroup analysis of a nonrandomized phase 2 trial. Relevant outcomes are OS, disease-specific survival, and test accuracy. Objective responses were observed in 35% of participants who had both TMB-high status and programmed death-ligand 1 (PD-L1)-positive tumors and in 21% of participants who had TMB-high status and PD-L1-negative tumors. High TMB status was associated with improved response irrespective of PD-L1 status. Median OS and PFS were not significantly different between TMB groups. Because no patients with CRC were included in these analyses, it is not possible to draw conclusions about the clinical validity and utility of TMB in this group of patients. Well-designed prospective studies enrolling patients in the population of interest are required. 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

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Type</th>
<th>SOE</th>
<th>QOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>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 (&quot;expanded&quot; or &quot;extended&quot; RAS)</td>
<td>Recommendation</td>
<td>Convincing/adequate, benefits outweigh harms</td>
<td>High/intermediate</td>
</tr>
<tr>
<td>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</td>
<td>Recommendation</td>
<td>Adequate/inadequate, balance of benefits and harms</td>
<td>Intermediate/low</td>
</tr>
<tr>
<td>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</td>
<td>Recommendation</td>
<td>Adequate/inadequate, balance of benefits and harms</td>
<td>Intermediate/low</td>
</tr>
<tr>
<td>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</td>
<td>Recommendation</td>
<td>Adequate/inadequate, balance of benefits and harms</td>
<td>Intermediate/low</td>
</tr>
</tbody>
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<th>Guidelines</th>
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<th>SOE</th>
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</tr>
</thead>
<tbody>
<tr>
<td>There is insufficient evidence to recommend BRAF c.1799 p.V600 mutational status as a predictive molecular biomarker for response to anti-EGFR inhibitors</td>
<td>No recommendation</td>
<td>Insufficient, benefits/harms balance unknown</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

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.1.2022). 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 tumor tissue should be 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).

Results of previous studies may support limiting testing for NTRK fusions to those with wild-type KRAS, NRAS, and BRAF. A study of 2314 CRC specimens, of which 0.35% had NTRK fusions, found that NTRK fusions were limited to cancers that were wild-type for KRAS, NRAS, and BRAF. Furthermore, a majority of the CRCs harboring NTRK fusions were also MMR-deficient (dMMR). Per NCCN (v 1.2022), these results may support limiting testing for NTRK fusions to those with wild-type KRAS, NRAS, and BRAF. Two targeted therapies, larotrectinib and entrectinib, have been FDA-approved for the treatment of patients with metastatic, unresectable solid tumors that have an NTRK gene fusion and no satisfactory alternative treatment options. The NCCN panel added larotrectinib and entrectinib as subsequent treatment options for patients with NTRK gene fusion-positive disease, acknowledging that these therapies will not be appropriate for most patients due to the rarity of the NTRK fusion in CRC.
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-amplified 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. As HER2-targeted therapies are still under investigation, enrollment in a clinical trial is encouraged (Category 2A).

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
The NCCN Panel states there are insufficient data to recommend the use of multigene assays, Immunoscore, or post-surgical circulating tumor DNA to estimate risk recurrence or determine adjuvant therapy.

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
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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

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td>NCT04425239</td>
<td>Intermittent or Continuous Panitumumab Plus FOLFIRI for First-line Treatment of Patients With RAS/B-RAF Wild-type Metastatic Colorectal Cancer: a Randomized Phase 2 Trial</td>
<td>151</td>
<td>Apr 2022</td>
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<tr>
<td>NCT04008030</td>
<td>A Phase 3 Randomized Clinical Trial of Nivolumab Alone, Nivolumab in Combination With Ipilimumab, or an Investigator's Choice Chemotherapy in Participants With Microsatellite Instability High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer</td>
<td>748</td>
<td>Aug 2025</td>
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<tr>
<td>NCT02997228</td>
<td>Colorectal Cancer Metastatic dMMR/MSI-H Immuno-Therapy (COMMIT) Study: A Randomized Phase III Study of mFOLFOX6/Bevacizumab/Atezolizumab Combination Versus Single Agent Atezolizumab in the First-Line Treatment of Patients With Deficient DNA Mismatch Repair (dMMR)/Microsatellite Instability-High (MSI-H) Metastatic Colorectal Cancer</td>
<td>231</td>
<td>Nov 2024</td>
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<tr>
<td>NCT03365882</td>
<td>S1613, A Randomized Phase II Study of Trastuzumab and Pertuzumab (TP) Compared to Cetuximab and Irinotecan (CETIRI) in</td>
<td>240</td>
<td>Jun 2023</td>
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Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer

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<tr>
<td>NCT02465060</td>
<td>Advanced/Metastatic Colorectal Cancer (mCRC) With HER-2 Amplification</td>
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<tr>
<td>NCT03602079</td>
<td>Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma (The MATCH Screening Trial)</td>
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<tr>
<td>NCT04776655</td>
<td>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</td>
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<td>Dec 2022</td>
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<tr>
<td>NCT04776655</td>
<td>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)</td>
<td>280</td>
<td>Apr 2024</td>
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<tr>
<td>NCT05253651</td>
<td>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</td>
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<td>Apr 2028</td>
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NCT: national clinical trial.
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12/03/2008 Medical Director review
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

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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.
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,
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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

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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.

Next Scheduled Review Date: 07/2024
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*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.

**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.
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