# Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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# Title: Somatic Biomarker Testing (including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer *(KRAS, NRAS,BRAF, MMR/MSI, HER2, and TMB)*

## Description/Background

***KRAS, NRAS, and BRAF Variants***

Cetuximab (Erbitux®, ImClone Systems) and panitumumab (Vectibix®, Amgen) are monoclonal antibodies that bind to the epidermal growth factor receptor (EGFR), preventing intrinsic ligand binding and activation of downstream signaling pathways vital for cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization. The RAS-RAF-MAP kinase pathway is activated in the EGFR cascade. RAS proteins are G-proteins that cycle between active (RAS-GTP) and inactive (RAS-GDP) forms, in response to stimulation from a cell surface receptor such as EGFR, and act as a binary switch between the cell surface EGFR and downstream signaling pathways. The *KRAS* gene can harbor oncogenic mutations that result in a constitutively activated protein, independent of EGFR ligand binding, rendering antibodies to the upstream EGFR ineffective. Approximately 40% of CRC have *KRAS* mutations in codons 12 and 13 in exon 2. Another proto-oncogene that acts downstream from *KRAS* is *NRAS (*neuroblastoma *RAS* viral (v-ras) oncogene homolog*)* which harbors oncogenic mutations in codons 12, 13, or 61 that result in constitutive activation of the EGFR- mediated pathway. These mutations are relatively rare compared with *KRAS,* detected in perhaps 2% to 7% of CRC specimens. A third proto-oncogene, *BRAF,* encodes a protein kinase, is involved in intracellular signaling and cell growth and is a principal downstream effector of *KRAS. BRAF* mutations occur in less than 10–15% of colorectal cancers and appear to be a marker of poor prognosis. *KRAS* and *BRAF* mutations 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 colorectal cancer in the refractory disease setting, FDA approval for panitumumab indicates that panitumumab is not indicated for the treatment of patients with KRAS or NRAS mutation positive disease in combination with oxaliplatin-based chemotherapy.[1]

A large body of literature has shown that metastatic CRC tumors with a variant in exon 2 (codon 12 or 13) of the *KRAS* gene do not respond to cetuximab or panitumumab therapy. More recent

evidence has shown that variants in *KRAS* outside exon 2 (i.e., in exons 3 [codons 59 and 61] and exon 4 [codons 117 and 146]) and variants in *NRAS* exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) also predict a lack of response to these monoclonal antibodies. Variant testing of these exons outside the *KRAS* exon 2 is referred to as extended *RAS* testing.

**Human Epidermal Growth Factor Receptor 2 Amplification/Overexpression**
Human epidermal growth factor receptor 2 (HER2) is a member of the HER (EGFR) family of tyrosine kinase receptors and has no specific ligand. When activated, it forms dimers with other EGFR family members. Amplification of HER2 is detected in approximately 3% of patients with CRC, with higher prevalence in *RAS/BRAF*-wild type tumors (5% to 14%). In addition to its role as a predictive marker for HER2-targeted therapy, HER2 amplification/overexpression is being investigated as a predictor of resistance to EGFR-targeting monoclonal antibodies.

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

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

**Detecting ctDNA and Circulating Tumor Cells (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 cfDNA. Therefore, more sensitive methods than the standard sequencing approaches (e.g., Sanger sequencing) are needed.

Highly sensitive and specific methods have been developed to detect ctDNA, for both single nucleotide variants (e.g. BEAMing [which combines emulsion polymerase chain reaction with magnetic beads and flow cytometry] and digital polymerase chain reaction) and copy-number variants. Digital genomic technologies allow for enumeration of rare variants in complex mixtures of DNA.

Approaches to detecting ctDNA can be considered targeted, which includes the analysis of known genetic mutations from the primary tumor in a small set of frequently occurring driver mutations, which can impact therapy decisions or untargeted without knowledge of specific variants present in the primary tumor, and include array comparative genomic hybridization, next-generation sequencing, and whole exome and genome sequencing.

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

A number of liquid biopsy tests related to targeted treatment of metastatic colorectal cancer have been developed (Table 1).

**Table 1. Examples of Liquid Biopsy Tests Related to Targeted Treatment of Metastatic Colorectal Cancer**

| Manufacturer | Test | Type of Liquid Biopsy |
|---|---|---|
| Biocept | Target Selector ctDNA EGFR Kit | ctDNA |
| CellMax Life | CellMax-CRC Colorectal Cancer Early Detection Test | CTC |
| Cynvenio | ClearID Solid Tumor Panel | ctDNA and CTC |
| Foundation Medicine | FoundationOne Liquid (Previously FoundationAct) | ctDNA |
| Guardant Health | Guardant360® | ctDNA |
| IV Diagnostics | Velox™ | CTC |
| Pathway Genomics | CancerIntercept® Detect | ctDNA |
| Personal Genome Diagnostics | PlasmaSELECT | ctDNA |
| Sysmex Inostics | OncoBEAM | ctDNA |
| Circulogene | Theranostics | ctDNA |

CTC: circulating tumor cell; ctDNA: circulating tumor DNA

## Regulatory Status:

Table 2 summarizes the targeted treatments approved by the 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.[2,]

In June 2022, the 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 colorectal cancer because of known intrinsic resistance to BRAF inhibition.[3,]

**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 |
|---|---|---|---|---|
| Cetuximab (Erbitux) | *KRAS* wild-type, EGFR-expressing, metastatic colorectal cancer as determined by an FDA-approved test<br>• in combination with FOLFIRI for first-line treatment,<br>• in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,<br>• as a single-agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan.<br>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<br>Dako EGFR pharmDx Kit<br>FoundationOne CDx<br>therascreen KRAS RGQ PCR Kit<br>ONCO/Reveal Dx Lung and Colon Cancer assay<br>xT CDx | | 2A or higher Metastatic Colorectal Cancer V.2.2023 |
| Braftovi (encorafenib) | Treatment of adult patients with metastatic colorectal cancer with a BRAF V600E mutation<br>• in combination with Erbitux (cetuximab), after prior therapy | *therascreen* BRAF V600E RGQ PCR Kit | | 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:<br>• In combination with FOLFOX for first-line treatment.<br>• As monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy. | Cobas KRAS Mutation Test<br>Dako EGFR pharmDx Kit<br>FoundationOne CDx<br>Praxis Extended RAS Panel<br>therascreen KRAS RGQ PCR Kit | | 2A or higher Metastatic Colorectal Cancer V.2.2023 |

| | | | | |
|---|---|---|---|---|
| | Limitation of Use: Vectibix is not indicated for the treatment of patients with RAS-mutant mCRC or for whom RAS mutation status is unknown. | ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) xT CDx | | |
| Pembrolizumab (Keytruda®) | Unresectable or metastatic, MSI-H or dMMR<br>• solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or<br>• CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan<br>First-line treatment of patients with unresectable or metastatic MSI-H or dMMR CRC | FoundationOne CDx | | |
| Tukysa (Tucatinib) | Treatment of adult patients with unresectable or metastatic CRC with RAS wild-type HER2-positive<br>• In combination with Trastuzumab (Herceptin)<br>• Previously treated with 5or5ropyrimidine, oxaliplatin, and irinotecan-based chemotherapy | No FDA-approved companion diagnostic | | 2A or higher/ Metastatic Colorectal Cancer (v.3.2023)[6] |

Source: FDA (2023)[2].
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

**Laboratory-Developed Tests for *KRAS, NRAS*, and *BRAF* Variant Analysis**
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. *KRAS*, *NRAS*, and *BRAF* variant analyses using polymerase chain reaction methodology are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed under the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

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## Medical Policy Statement

The safety and effectiveness of *KRAS*, *NRAS*, *BRAF, MMR/MSI, HER2, and TMB* mutation analyses on tumor tissue have been established and may be considered a useful diagnostic option for individuals with metastatic colorectal cancer to select individuals for treatment with FDA-approved therapies. It is a useful therapeutic option when indicated.

The safety and effectiveness of *KRAS*, *NRAS*, *BRAF, TMB and MSI* variant analysis using circulating tumor DNA or circulating tumor cell testing (liquid biopsy) to guide treatment for patients with metastatic colorectal cancer is considered established. It is a useful therapeutic option when indicated.

## Inclusionary and Exclusionary Guidelines

**Inclusions:**

- *KRAS*, *NRAS and BRAF (V600E)* mutation analysis is established in patients with metastatic colorectal cancer in order to determine their nonresponse to EGFR inhibitor drugs such as Vectibix® (panitumumab) and Erbitux® (cetuximab).
- Human epidermal receptor 2 (HER2) amplification testing is established 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.
- Mismatch repair/microsatellite instability testing may be considered established to select individuals for treatment with FDA-approved therapies. (Mismatch repair and microsatellite testing of colorectal cancer tissue may be indicated for Lynch Syndrome).
- TMB testing may be established for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options (example Keytruda).
- A Proprietary Laboratory Analyses (PLA) test is considered established when **all** of the following criteria are met:
    - The individual meets the FDA criteria listed in the label for the therapeutic, AND
    - The test is an FDA-approved companion diagnostic test

**Circulating Tumor DNA (liquid biopsy)**

The clinical utility of circulating tumor DNA and circulating tumor cells for management of advanced solid cancers has been established when **ALL** of the following criteria are met.

- May be considered established for guidance in the selection of appropriate targeted FDA therapeutic options for **ANY** of the following conditions:
    - Metastatic cancers
    - Inoperable locally advanced cancers
    - Refractory cancers
    - Recurrent cancers
    - Advanced cancer (stages III or IV); **AND**
- Individual has not been previously tested using the same liquid biopsy panel, unless a new primary cancer diagnosis is made, and further cancer treatment is being considered or individual is experiencing a relapse; **AND**
- There is clinical documentation that tissue-based testing cannot be performed (e.g., insufficient sample, inaccessible tumor or where there may be a delay in obtaining tumor sample) **OR** tissue-based testing is not required when there is an FDA-approved companion diagnostic device that is a circulating tumor test (liquid biopsy).

**Exclusions:**

- The use of circulating tumor DNA and circulating tumor cells is considered investigational when criteria above are not met.
- The use of circulating tumor DNA and circulating tumor cell testing is considered investigational for all other indications related to solid tumors, including measurable residual disease (MRD) testing and cancer screening (e.g., Galleri).

## CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

### *Established codes:*

| | | | | | |
|---|---|---|---|---|---|
| 81210 | 81275 | 81276 | 81301 | 81311 | 81403 |
| 81404 | 81455* | 81456* | 88363 | 0037U* | 0111U* |
| 0239U* | 0242U* | 0326U* | 0334U* | | |

*only established when above specific inclusionary criteria are met

### *Non-payable*

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## Rationale

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

### *KRAS, NRAS, and BRAF* VARIANT TESTING TO GUIDE TREATMENT FOR METASTATIC CRC

#### Clinical Context and Test Purpose

The purpose of *KRAS* variant testing in individuals with metastatic CRC is to determine *KRAS* variant status to guide treatment decisions with epidermal growth factor receptor (EGFR)–targeted therapy with the monoclonal antibodies cetuximab and panitumumab.

The purpose of *NRAS* variant testing in individuals with metastatic CRC is to determine *NRAS* variant status to guide treatment decisions with EGFR-targeted therapy with the monoclonal antibodies cetuximab and panitumumab.

The purpose of *BRAF* variant testing in individuals with metastatic CRC is to determine *BRAF* variant status to guide treatment.

The question addressed in this evidence review is: In individuals with metastatic CRC, does the use of *KRAS, NRAS and BRAF* variant testing improve the net health outcome?

The following **PICOs** elements were used to select literature to inform this review.

**Populations**
The relevant population of interest includes individuals with metastatic CRC.

**Interventions**
The test being considered is *KRAS* variant testing, *NRAS* variant testing, and *BRAF* variant testing.

**Comparators**
The following test strategy is currently being used: no *KRAS* variant testing, no *NRAS* variant testing, or no *BRAF* variant testing to guide treatment.

**Outcomes**
The beneficial outcomes of interest include progression-free survival (PFS) and overall survival (OS).

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

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

- Reported on the accuracy of the marketed version of the technology;
- Included a suitable reference standard;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

**Clinically Valid and Clinically Useful**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Randomized Controlled Trials**
*KRAS, NRAS*, and *BRAF* variant testing are associated with FDA-approved therapeutics (i.e., as companion diagnostic tests) for therapies and have NCCN recommendations of 2A or higher; thus, are not subject to extensive evidence review.

Evidence for the clinical validity of *KRAS* variants in predicting nonresponse to anti-EGFR monoclonal antibody therapy consists of multiple systematic reviews, including a TEC Assessment, and RCTs.[4,5,6,7,8,9,10,] The evidence has demonstrated that the presence of a *KRAS* variant predicts nonresponse to treatment, while *KRAS* wild-type status predicts response to anti-EGFR monoclonal antibody therapy. Direct evidence for the clinical validity of *KRAS* variant testing includes RCTs. Randomized controlled trials supporting U.S. Food and Drug Administration approvals for cetuximab and panitumumab have demonstrated that the presence of *KRAS* variants is predictive of nonresponse to anti-EGFR monoclonal antibody therapy. Documentation of *KRAS* wild-type status is required before patients are eligible for treatment with cetuximab or panitumumab.

Evidence for the clinical validity of *NRAS* variants in predicting nonresponse to anti-EGFR monoclonal antibody therapy includes prospective-retrospective analyses of RCTs and retrospective cohort studies.[11,12,13,14,] 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.[15,] In addition, there is strong support from the National Comprehensive Cancer Network and the American Society of Clinical Oncology for *NRAS* and *KRAS* testing in patients with metastatic CRC.

Evidence for the clinical validity of *BRAF* variants in predicting nonresponse to anti-EGFR monoclonal antibody therapy includes 2 meta-analyses of prospective and retrospective analyses of RCTs.[16,17,]Subgroup analyses of *KRAS* wild-type and *NRAS* wild-type patients who did not respond to anti-EGFR monoclonal antibody therapy suggested that *BRAF* variants might be predictive of nonresponse. *BRAF* variant testing has potential clinical utility in predicting nonresponse to anti-EGFR monoclonal antibody therapy in patients with documented *KRAS* wild-type and *NRAS* wild-type status. However, the direct evidence is limited for *BRAF* variant testing due to the low prevalence *BRAF* variants in CRC.

BRAF V600E variant testing in adult individuals with metastatic colorectal cancer for determining treatment with encorafenib in combination with cetuximab after previous therapy, has received FDA approval and NCCN recommendation based on the BEACON CRC Study (ARRAY-818-302; NCT02928224).[18,19,20,]This phase 3 multicenter, randomized, open-label, clinical trial showed significantly improved overall survival in the doublet-therapy group (encorafenib and cetuximab) over control group (investigators' choice of either cetuximab and irinotecan or cetuximab and FOLFIRI: folinic acid, fluorouracil, and irinotecan), as well as objective response rate and hazard ratio.

**Microsatellite Instability High/Mismatch Repair Deficient Testing to Guide Treatment for Metastatic Colorectal Cancer**

**Clinical Context and Test Purpose**
The purpose of Microsatellite-Instability/Mismatch Repair (MSI/MMR) testing in individuals with metastatic CRC is to guide decisions about treatment with immunotherapy.

The question addressed in this evidence review is: In individuals with metastatic CRC, does the use of MSI/MMR testing improve the net health outcome?

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

**Populations**
The relevant population of interest is individuals with metastatic CRC.

**Interventions**
The test being considered is MSI/MMR variant testing.

**Comparators**
The comparator of interest is standard treatment without MSI testing.

**Outcomes**
The beneficial outcomes of interest include PFS, OS, change in disease status, medication use, resource utilization, and treatment-related morbidity.

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

**Clinically Valid and Clinically Useful**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Review of Evidence**
Microsatellite-Instability/Mismatch Repair (MSI/MMR) testing in individuals with metastatic CRC is associated with an FDA-approved therapeutic (i.e., as a companion diagnostic test) and has an NCCN recommendations of 2A or higher; thus, is not subject to extensive evidence review. Evidence for the effectiveness of pembrolizumab in patients with MSI-H/dMMR metastatic CRC comes from the KEYNOTE-177 trial, reported by Andre et al (2020).[21,] The trial demonstrated a statistically significant improvement in progression free survival for patients randomized to pembrolizumab compared with chemotherapy (hazard ratio 0.60; 95% confidence interval [CI] 0.45 to 0.80; p=.0002). Final results were reported by Diaz et al (2022).[22,] Median PFS was 16.5 months (95% CI 5.4 to 38.1) with pembrolizumab versus 8.2 months (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.

**Human Epidermal Growth Factor Receptor 2 Testing to Guide Treatment for Metastatic Colorectal Cancer**

**Clinical Context and Test Purpose**
The purpose of human epidermal growth factor receptor 2 (HER2) testing in individuals with metastatic CRC is to determine HER2 status to inform decisions about targeted treatment.

The question addressed in this evidence review is: In individuals with metastatic CRC, does the use of HER2 testing improve the net health outcome in patients with metastatic CRC?

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

**Populations**
The relevant population of interest is individuals with metastatic CRC.

**Interventions**
The test being considered is HER2 testing. Use of HER2 testing is proposed to predict response to trastuzumab deruxtecan monotherapy or trastuzumab in combination with either pertuzumab or lapatinib.

Use of HER2 testing is also proposed to predict nonresponse to EGFR-targeted treatment.

**Comparators**
The following test strategy is currently being used: standard treatment with no HER2 testing.

**Outcomes**

The beneficial outcomes of interest include PFS, OS, change in disease status, medication use, resource utilization, and treatment-related morbidity.

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

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

- Reported on the accuracy of the marketed version of the technology;
- Included a suitable reference standard;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

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

**Review of Evidence**

**FDA Approved Companion Diagnostic Test**
There is no FDA approved targeted treatment or companion diagnostic test for HER2 testing in patients with metastatic CRC. Multiple tests are approved for use to select targeted treatment.

**Nonrandomized Trials**
Hainsworth et al (2018) reported results of MyPathway, an open-label, phase 2, nonrandomized basket trial of targeted treatment in 251 patients with various advanced refractory solid tumors harboring genetic alterations.[23,] The cohort included 37 patients with HER2 ampified/ 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 (range1 to 16+ months; 95% CI, 2.8 months to not estimable).

In an open-label, phase 2 trial of trastuzumab deruxtecan, objective response, the primary outcome, 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 [IQR] 19.3 to 40.1).[24,] One (2%) patient had a complete response, and 23 (43%) had a partial response. Median PFS was 6.9 months (4.1 to not evaluable). Median OS had not been reached at data cutoff (95% CI.74 months to not evaluable)

Preliminary evidence has suggested that HER2 amplification/overexpression may be predictive of nonresponse to EGFR-targeted therapy.[25,26,]

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

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

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

### Section Summary: HER2 Testing to Guide Treatment for Metastatic Colorectal Cancer
There is no FDA-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-ampified/ 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 (range1 to 16+ months; 95% CI, 2.8 months to not estimable). In an open-label, phase 2 trial of trastuzumab deruxtecan, objective response was observed in 24 of 53 patients with HER2-positive metastatic CRC (45.3%; 95% CI 31.6 to 59.6) after a median follow-up of 27.1 weeks (IQR 19.3 to 40.1). Preliminary evidence has suggested that HER2 amplification/ overexpression may be predictive of nonresponse to EGFR-targeted therapy.

## Tumor Mutational Burden Testing to Guide Treatment for Metastatic Colorectal Cancer

### Clinical Context and Test Purpose
The purpose of tumor mutational burden (TMB) testing in patients who have advanced CRC is to inform a decision on whether patients should receive immunotherapy versus another systemic therapy. The goal of immunotherapy is to preferentially kill malignant cells without significant damage to normal cells so that there is improved therapeutic efficacy along with decreased toxicity.

The question addressed in this evidence review is: In individuals with metastatic CRC, does the use of tumor mutational burden testing improve the net health outcome?

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

### Populations
The relevant population of interest is individuals with metastatic CRC.

### Interventions
Tumor mutational burden, a measure of gene mutations within cancer cells, is proposed as a biomarker for response to immunotherapy.

### Comparators
The following test strategy is currently being used: no TMB testing to guide treatment.

### Outcomes
The beneficial outcomes of interest include PFS, OS, change in disease status, medication use, resource utilization, and treatment-related morbidity.
The time frame for outcome measures varies from several months to several years.

### Study Selection Criteria
For the evaluation of clinical validity, studies that meet the following eligibility criteria were considered:
- Reported on the accuracy of the marketed version of the technology;
- Included a suitable reference standard;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

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

**Review of Evidence**

**FDA-Approved Companion Diagnostic Test**
FoundationOne CDx is FDA approved as a companion diagnostic for use with pembrolizumab in patients with TMB-high (≥ 10 mutations per megabase) solid tumors. Approval was based on results of the KEYNOTE-158 study that enrolled patients with solid tumors, but none of the patients evaluated had CRC.

**Nonrandomized Trial**
Marabelle et al (2020) reported the association of high TMB to response to pembrolizumab in patients with solid tumors enrolled in a prespecified exploratory analysis of the KEYNOTE-158 study.[27,] High TMB was defined as >10 mutations per megabase according to the FoundationOne CDx panel. The proportion of patients with an objective response in the TMB-high group was 29%. At a median follow-up of approximately 3 years, the median duration of response was not reached in the TMB-high group and was 33.1 months in the non-TMB-high group. Notably, TMB-high status was associated with improved response irrespective of programmed death-ligand 1 (PD-L1). Median PFS and OS did not differ between the high and non-high TMB groups. Objective responses were observed in 24 (35%; 95% CI 24 to 48) of 68 participants who had both TMB-high status and PD-L1-positive tumors (i.e., PD-L1 combined positive score of ≥1) and in 6 (21%; 8 to 40) of 29 participants who had TMB-high status and PD-L1-negative tumors. Study eligible cancers were limited to anal, biliary, cervical, endometrial, mesothelioma, neuroendocrine, salivary, small-cell lung, thyroid, and vulvar. tTMB-high status identifies a subgroup of patients who could have a robust tumour response to pembrolizumab monotherapy. tTMB could be a novel and useful predictive biomarker for response to pembrolizumab monotherapy in patients with previously treated recurrent or metastatic advanced solid tumours.

An increasing number of therapies are approved to treat cancers harboring specific genomic biomarkers. However, there is a lack of clarity as to when tumor genomic sequencing should be ordered, what type of assays should be performed, and how to interpret the results for treatment selection. According to the American Society of Clinical Oncology (ASCO) in a provisional clinical opinion, patients with metastatic or advanced cancer should undergo genomic sequencing in a certified laboratory if the presence of one or more specific genomic alterations has regulatory approval as biomarkers to guide the use of or exclusion from certain treatments for their disease.[28] Multigene panel–based assays should be used if more than one biomarker-linked therapy is approved for the patient's disease. Site-agnostic approvals for any cancer with a high tumor mutation burden, mismatch repair deficiency, or neurotrophic tyrosine receptor kinase (NTRK) fusions provide a rationale for genomic testing for all solid tumors. Multigene testing may also assist in treatment selection by identifying additional targets when there are few or no genotype-based therapy approvals for the patient's disease. For treatment planning, the clinician should consider the functional impact of the targeted alteration and expected efficacy of genomic biomarker–linked options relative to other approved or investigational treatments.

**Clinically Useful**

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

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

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

**Section Summary: Tumor Mutational Burden Testing to Guide Treatment for Metastatic Colorectal Cancer**
In a prespecified retrospective subgroup analysis of a nonrandomized trial of pembrolizumab in patients with various solid tumors, objective responses were observed in 35% of participants who had both TMB-high status and PD-L1-positive tumors and in 21% of participants who had TMB-high status and PD-L1-negative tumors. A TMB-high status was associated with improved response irrespective of PD-L1 status. Although median OS and PFS survival were not significantly different between TMB groups., tTMB could be a novel and useful predictive biomarker for response to pembrolizumab monotherapy in patients with previously treated recurrent or metastatic advanced solid tumors.

**Circulating Tumor DNA Testing (Liquid Biopsy) to Guide Treatment for Metastatic CRC**

**Clinical Context and Test Purpose**
One purpose of liquid biopsy testing of patients who have metastatic CRC is to inform a decision regarding treatment selection (e.g., whether to select a targeted treatment or standard treatment).

The question addressed in this evidence review is: Does use of circulating tumor DNA (ctDNA) or circulating tumor cells (CTCs) testing to select treatment in patients with metastatic CRC improve the net health outcome compared with standard tissue testing?

The following **PICOs** elements were used to select literature to inform this review.

**Populations**
The relevant population of interest includes individuals with metastatic CRC being considered for targeted therapy.

**Interventions**
The test being considered is liquid biopsy using either ctDNA or CTCs. Both targeted polymerase chain reaction-based assays and broad next-generation sequencing-based approaches are available.

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

**Outcomes**

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

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

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

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

**OncoBEAM RAS CRC Assay**
The clinical validity of the OncoBEAM *RAS* CRC assay has been evaluated in several published studies of patients with metastatic CRC. Study characteristics and results are shown in Tables 7 and 8. Study relevance, design, and conduct limitations are described in Tables 3 and 4.

**Table 3. Clinical Validity Studies of the OncoBEAM *RAS* Assay**

| Study | Study Population | Design | Reference Standard | Timing of Tissue Biopsy and Liquid Biopsy | Blinding of Assessors |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| Garcia-Foncillas et al (2018)[29] | • Patients with metastatic CRC newly diagnosed or presenting with recurrent disease after resection and/or chemotherapy at 10 centers in Spain<br>• Enrolled from November 2015 to October 2016 | Prospective | Analysis of tissue using standard-of-care procedures validated by each hospital | Plasma collected before any therapeutic intervention.<br><br>OncoBEAM used when standard of care RAS result was discordant with RAS result. The same tissue block was used for re-analysis by OncoBEAM | Not stated; central laboratory used |

| | | | | | |
|---|---|---|---|---|---|
| Vidal et al (2017)[30] | • Patients from Spain with histologically confirmed metastatic CRC<br>• Anti-EGFR treatment-I<br>• Enrolled from 2009 to 2016 | Retrospective-prospective | Analysis of tissue samples conducted using institutional standard-of-care procedures | • Tissue collected before blood<br>• Median interval, 48 d (range, 0-1783 d) | Yes |
| Schmiegel (2017)[31] | • Patients from Australia and Germany with newly diagnosed stage III/IV histologically confirmed CRC | Prospective | Analysis of tissue samples conducted using Sanger sequencing | • Blood obtained immediately prior to tissue biopsy or resection | Not stated |
| Grasselli (2017)[32] | • Patients from Spain with histologically confirmed metastatic CRC<br>• Anti-EGFR treatment-naïve but majority treated with other systemic therapies | Retrospective-prospective | Analysis of tissue samples conducted using real-time PCR | Tissue collected before blood<br>• Median interval 1.2 m (range 0 to 34) | Yes |
| Normanno (2018)[33] | • Patients with metastatic CRC who KRAS exon-2 wild-type and received first-line etuximab plus FOLFIRI within the CAPRI-GOIM trial | Retrospective-prospective | Analysis of tissue samples conducted using NGS | • Unclear when tissue was collected<br>• Blood collected at baseline | Not stated |

CRC: colorectal cancer; EGFR: epidermal growth factor receptor; NGS: next-generation sequencing; PCR: polymerase chain reaction.

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

| Study | Initial N | Final N | Excluded Samples | RAS Variant-Positive, %[a] | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Garcia-Foncillas et al (2018)[29] | 239 | 236 | 3 patients initially excluded because of total disease removal during primary surgery. *RAS* mutation status was evaluable in all 236 patients | 55.5 | 86.3 | 92.4 | NR | NR |
| Vidal et al (2017)[30] | N/A | 115 | No description of samples excluded from comparison to tissue results | 51 | 96 (87 to 100)[b] | 90 (79 to 96)[b] | 90 (79 to 96)[b] | 96 (88 to 100)[b] |
| Schmiegel (2017)[31] | 102 | 98 | N=3 (inadequate plasma DNA) N=1 (*RAS* mutation not confirmed in tissue when re-evaluated) | 53 | 90 (79 to 96) | 94 (82 to 98) | NR | NR |
| Grasselli (2017)[32] | 157 | 146 | N=11 (pre-analytical requirements or lack of tumor tissue availability) | 59 | 89 (77 to 96)[b] | 90 (82 to 95)[b] | 84 (74 to 91)[b] | 93 (87 to 97)[b] |
| Normanno (2018)[33] | 340 | 92 | Tissue and plasma unavailable (not clear if tissue samples were sampled from those available or if all available were used) | 36 | 70 (51 to 84)[b] | 83 (71 to 92)[b] | 70 (56 to 81)[b] | 83 (74 to 89)[b] |

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

## FoundationACT ctDNA Assay

The FoundationACT ctDNA assay, the predecessor of FoundationOne Liquid, was compared to tissue biopsy using the FoundationOne assay in one manufacturer-sponsored study. (Li et al 2019)[34] Study characteristics are shown in Tables 5 and 6. The researchers reported results on the subset of 51 patients with *KRAS*, *NRAS*, and *BRAF* variants. These results are shown in Table 10. Positive percent agreement was 80% for all time points for short variants and increased to 90% for cases in which tissue and liquid biopsy were measured less than 270 days apart Limitations of this study are described in Tables 7 and 8.

**Table 5. Clinical Validity Study of the FoundationACT ctDNA Assay**

| Study | Study Population | Design | Reference Standard | Timing of Reference and Index Tests | Blinding of Assessors |
|---|---|---|---|---|---|
| Li et al (2019)[34] | Patients with CRC, 74% stage IV, 19% stage III, 7% stage II | Prospective and retrospective | Previously-collected tissue biopsy with | Liquid biopsy testing was done at the discretion of the clinician at variable | Not stated |

| | | | | | |
|---|---|---|---|---|---|
| | | | FoundationOne assay | time intervals after tissue sample collection (0-709 days) | |

ctDNA: circulating tumor DNA; CRC: colorectal cancer.

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

| Study | Initial N | Final N | Excluded Samples | RAS Variant-Positive, % | Positive % Agreement (95% CI) |
|---|---|---|---|---|---|
| Li et al (2019)[34] | 96 | 73 | 22 samples did not have detectable ctDNA | 51/74 (92%) | Overall (N=73)<br>79%<br><br>Subset with KRAS, NRAS, and BRAF variants (n=51)<br><br>80% for all time points<br><br>90% for cases <270 days between tissue and liquid biopsy |

ctDNA: circulating tumor DNA.; PPV: positive predictive value.

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

| Study | Population[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Duration of Follow-Up[e] |
|---|---|---|---|---|---|
| Li et al (2019)[34] | 4.74% had metastatic disease | | 2.Reference standard was FoundationOne assay | | |
| Garcia-Foncillas et al (2018)[29] | | | | 3.PPV and NPV not reported | |
| Vidal et al (2017)[30] | | | | | |
| Schmiegel (2017) | | 2.Not clear if marketed version of test used | | | |
| Grasselli (2017)[31] | | | | | |
| Normanno (2018)[33] | | | | | |

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

**Table 8. Study Design and Conduct Limitations for Clinical Validity Studies of OncoBEAM *RAS* Assay**

| Study | Selection[a] | Blinding[b] | Delivery of Test[c] | Selective Reporting[d] | Completeness of Follow-Up[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| | | | | | | |
| Li et al (2019) | 2. Inclusion required a previously performed FoundationACT assay; previous treatments varied | 1: blinding unclear | 2. timing of liquid biopsy and tissue biopsy varied (range 0-709 days) | | 2. 20% of samples had no detectable ctDNA | |
| Garcia-Foncillas et al (2018)[29] | 1. Not clear whether samples were consecutive or convenience | 1: blinding unclear | | 1. Registration not described | | |
| Vidal et al (2017)[30] | 1. Not clear whether samples were consecutive or convenience | | 2: Blood collected approximately 1.5 m after tissue | 1. Registration not described | 1. Not clear whether there were samples that were insufficient for analysis or failed to produce results | 1. Cis not reported but calculated based on data provided |
| Schmiegel (2017)[31] | 1: Not clear how patients were selected from those that were eligible | 1: Blinding unclear | | 1. Registration not described | | |
| Grasselli (2017)[32] | 1: Not clear how patients were selected from those that were eligible | | 2: Blood collected approximately 1.5 m after tissue | | | 1. Cis not reported but calculated based on data provided |
| Normanno (2018)[33] | 1: Not clear how tumor samples were selected from those available | 1: Blinding unclear | 1.Unclear when tissue was collected | 1. Registration not described | 2.Only 27% of CAPRI-GOIM trial participants included | 1. Cis not reported but calculated based on data provided |

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

## Clinically Useful

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

## Direct Evidence

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

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

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

**Section Summary: Circulating Tumor DNA Testing to Guide Treatment for Metastatic Colorectal Cancer**
The clinical validity of the OncoBEAM RAS CRC Assay has been studied in multiple observational studies. When compared to tissue biopsy, sensitivity ranged from 70% (51% to 84%) to 96% (95% CI 87% to 100%) and specificity ranged from 83% (95% CI 71% to 92%) to 94% (82% to 98%). FoundationOne Liquid has been compared to tissue biopsy with the FoundationACT assay in one observational study; positive percent agreement was 80% overall and 90% when tissue and liquid biopsy were collected less than 270 days apart. Clinical validity studies were limited by unclear reporting of blinding, use of convenience rather than consecutive samples, and variation in the timing of sample collection. There are no published studies reporting clinical outcomes or clinical utility.

**SUMMARY OF EVIDENCE**
For individuals who have metastatic CRC who receive *KRAS* mutation testing to guide treatment, the evidence includes multiple systematic reviews including a TEC assessment. Relevant outcomes are overall survival, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Mutation testing of tumor tissue performed in prospective and retrospective analyses of randomized controlled trials (RCTs) has consistently shown that the presence of a *KRAS* mutation predicts nonresponse to cetuximab and panitumumab, either as monotherapy or in combination with other treatment regimens, and supports the use of *KRAS* mutation analysis of tumor DNA before considering a treatment regimen. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

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

For individuals who have metastatic CRC who receive *BRAF* mutation testing to guide treatment, the evidence includes two meta-analyses of prospective and retrospective analyses of RCTs. Relevant outcomes are overall survival, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. The meta-analyses showed that anti-epidermal growth factor receptor monoclonal antibody therapy did not improve survival

in patients with *RAS* wild type and *BRAF*-mutated tumors, however, the individual studies have been small and the results have not been inconsistent. Testing for the BRAF V600E variant in adult individuals with metastatic colorectal cancer 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 the effects of 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 for patients randomized to pembrolizumab compared with chemotherapy (hazard ratio 0.60; 95% confidence interval [CI] 0.45 to 0.80; p=.0002). In final results, median PFS was 16.5 months (95% CI 5.4 to 38.1) with pembrolizumab versus 8.2 months (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-ampified/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 (range1 to 16+ months; 95% CI, 2.8 months to not estimable). In an open-label, phase 2 trial of trastuzumab deruxtecan, objective response was observed in 24 of 53 patients with HER2-positive metastatic CRC (45.3%; 95% CI 31.6 to 59.6) after a median follow-up of 27.1 weeks (interquartile range 19.3 to 40.1). Preliminary evidence has suggested that patients with HER2-amplified metastatic CRC are less likely to respond to anti-EGFR therapy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with metastatic CRC who receive TMB testing to select treatment with immunotherapy, the evidence includes a prespecified retrospective subgroup analysis of a nonrandomized phase 2 trial. Relevant outcomes are OS, disease-specific survival, and test accuracy. Objective responses were observed in 35% of participants who had both TMB-high status and programmed death-ligand 1 (PD-L1)-positive tumors and in 21% of participants who had TMB-high status and PD-L1-negative tumors. High TMB status was associated with improved response irrespective of PD-L1 status. Although median OS and PFS survival were not significantly different between TMB groups., tTMB could be a novel and useful predictive biomarker for response to pembrolizumab monotherapy in patients with previously treated recurrent or metastatic advanced solid tumors. 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 ctDNA or CTC testing (liquid biopsy) to guide treatment, the evidence includes observational studies. The relevant outcomes are OS, disease-

specific survival, test validity, morbid events, and medication use. Given the breadth of methodologies available to assess ctDNA and CTC, the clinical validity of each commercially available test must be established independently. The clinical validity of the OncoBEAM *RAS* CRC Assay has been studied in multiple observational studies. When compared to tissue biopsy, sensitivity ranged from 70% (51% to 84%) to 96% (95% CI 87% to 100%) and specificity ranged from 83% (95% CI 71% to 92%) to 94% (82% to 98%). FoundationOne Liquid has been compared to tissue biopsy with the FoundationACT assay in one observational study; positive percent agreement was 80% overall and 90% when tissue and liquid biopsy were collected less than 270 days apart. Clinical validity studies were limited by unclear reporting of blinding, use of convenience rather than consecutive samples, and variation in the timing of sample collection. The evidence is sufficient to determine the effects of the technology on health outcomes.

## ONGOING AND UNPUBLISHED CLINICAL TRIALS

A currently unpublished trial that might influence this review is listed in Table 9.

**Table 9. Summary of Key Ongoing Trial**

| 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 |
| 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 Cance | 177 | Apr 2023 |

NCT: national clinical trial

# 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

### National Comprehensive Cancer Network (NCCN)[36]

The following information is based on the National Comprehensive Cancer Network (NCCN) guidelines on the treatment of colon cancer (v.3.2023). Guidelines are updated frequently; refer to the source document for most recent updates and for additional detail.

The NCCN guidelines recommend that all patients with metastatic colorectal cancer 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 panitumamab or cetuximab highly unlikely unless given with a *BRAF* inhibitor.

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

### American Society of Clinical Oncology[28]

In 2017, American Society of Clinical Oncology along with American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology published guidelines on molecular biomarkers for the evaluation of colorectal cancer. Table 10 summarizes the relevant guidelines.

**Table 10. Summary of Recommendations**

| Guidelines | Type | SOE | QOE |
|---|---|---|---|
| Colorectal carcinoma patients being considered for anti-EGFR therapy must receive RAS mutation 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 carcinoma for prognostic stratification | Recommendation | Adequate/inadequate, balance of benefits and harms | Intermediate/low |
| BRAF p. V600 mutational analysis should be performed in deficient MMR tumors with loss of MLH1 to evaluate for Lynch Syndrome risk. Presence of a BRAF mutation strongly favors a 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

## Government Regulations

### National:

There is no national coverage determination on this topic. Coverage is at the discretion of the local carrier.

A March 2018 decision memo from the Centers for Medicare & Medicaid Services addressed next-generation sequencing for Medicare beneficiaries with advanced cancer.[37] 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) Food and Drug Administration approval or clearance as a companion in vitro diagnostic; and
   b) a 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 four 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."

## Local:

**MolDX: FDA approved KRAS tests, A55162, effective 07/28/2022**

Two tests have met the FDA criteria for **KRAS** genetic testing:

1. Effective 7/6/2012
   therascreen® **KRAS** to detect seven somatic mutations in the human **KRAS** oncogene was developed to aid in the identification of colorectal cancer (CRC) patients for treatment with Erbitux® (cetuximab).
2. Effective 5/7/2015
   cobas® **KRAS** to detect mutations in codons 12 and 13 of the **KRAS** gene was developed to aid in identification of CRC patients for treatment with Erbitux® (cetuximab) or Vectibix® (panitumumab).

**MolDX: NRAS Genetic Testing, L36797, effective 07/27/2023**

This is a limited coverage policy for genetic testing of tumor tissue for somatic mutations in the NRAS gene (81311). MolDX will cover NRAS testing for metastatic colorectal cancer, per NCCN guidelines (Version 2.2016).

All other NRAS testing is non-covered.

**MolDX: FDA approved BRAF Tests, A55161, effective 07/27/2023**
Two tests have met the FDA criteria for **BRAF** genetic testing:

1. Effective 09/07/2012.
   **cobas® 4800 BRAF V600** to detect the presence of a mutation in the **BRAF** gene in melanoma cells and determine if a patient is eligible for Zelboraf ™(vemurafenib), a treatment indicated for a melanoma that cannot be surgically excised or has spread in the body.
2. Effective 5/29/13.
   **ThxID™ BRAF V600/K** to detect the **BRAF** V600E and V600K mutations in selecting melanoma patients whose tumors carry the **BRAF** V600E mutation for treatment with dabrafenib [Tafinlar®] and as an aid in selecting melanoma patients whose tumors carry the **BRAF** V600E or V600K mutation for treatment with trametinib [Mekinist™].

*(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)*

## Related Policies

- Genetic Testing-Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer
- Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer
- Circulating Tumor DNA and Circulating Tumor cells for Cancer Management (liquid biopsy)
- Genetic Testing-NGS Testing of Multiple Genes (Panel) to Identify Targeted Cancer Therapy
- Genetic Cancer Susceptibility Panels Using NGS

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*The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through August 2023 the date the research was completed.*

## Joint BCBSM/BCN Medical Policy History

| Policy Effective Date | BCBSM Signature Date | BCN Signature Date | Comments |
|---|---|---|---|
| 3/1/12 | 12/13/11 | 12/22/11 | Joint policy established. Policy split out from consolidated policy on *KRAS* mutation analysis testing. 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; *KRAS* policy statement unchanged. References updated. |
| 5/1/13 | 2/19/13 | ¾/13 | Added code 81403, deleted code S3713. References updated, policy status unchanged. |
| 1/1/15 | 10/24/14 | 11/3/14 | Routine maintenance. No change in status. Rationale and references updated. |
| 11/1/15 | 8/18/15 | 9/14/15 | Added CPT code 81404 to policy. Added *NRAS* testing as established. |
| 11/1/16 | 8/16/16 | 8/16/16 | Routine maintenance, updated references and rationale sections. |
| 11/1/17 | 8/15/17 | 8/15/17 | Routine policy maintenance. |
| 5/1/18 | 2/20/18 | 2/20/18 | Included BRAF testing as established to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer. |
| 5/1/19 | 2/19/19 | | Routine policy maintenance. No change in policy status. |
| 1/1/20 | 10/15/19 | | Title change to: KRAS, NRAS and BRAF variant analysis in metastatic colorectal cancer (including liquid biopsy).<br>Added code 0111U effective 10/1/19.<br>Added as exclusion “KRAS, NRAF, and BRAF variant analysis using circulating tumor DNA or circulating tumor cell testing (liquid biopsy) to guide treatment for patients with metastatic colorectal cancer is |

| | | | |
|---|---|---|---|
| | | | considered experimental/investigational". Added references 42-47. No change in policy status. |
| 1/1/21 | 10/20/20 | | Routine policy maintenance. No change in policy status. |
| 1/1/22 | 10/19/21 | | Added liquid biopsy to exclusion section. No change in policy status. |
| 1/1/23 | 10/18/22 | | • Title change to specify somatic testing and to list the specific biomarkers included<br>• Coverage extends to HER2, TMB, microsatellite instability testing and mismatch repair testing<br>• Add TMB language from NSCLC policy in MPS<br>• Added language for FoundationOne CDx testing to inclusion section<br>• Added codes 81210, 81301 and 0037U as covered codes<br>• Rationale section updated and reorganized. |
| 1/1/24 | 10/25/23 | | MPS simplified. Removed bullets 5 & 6 under inclusion/exclusion section, removed subbullets 1 and 4 under bullet 7. Routine policy maintenance, Liquid biopsy now covered with criteria. Added codes 81455 and 81456 as established, moved codes 0239U and 0242U to established. Added code 0326U and 0334U as established. Vendor managed: N/A (ds) |

Next Review Date: 4th Qtr. 2024

**Previous Consolidated BCBSM/BCN Medical Policy History on *KRAS* Mutations**

| Policy Effective Date | BCBSM Signature Date | BCN Signature Date | Comments |
|---|---|---|---|
| 7/1/09 | 6/3/09 | 4/21/09 | Joint policy established |

| | | | |
|---|---|---|---|
| 11/1/09 | 8/18/09 | 8/18/09 | S code added to policy effective 10/1/09; no additional literature review done. |

# BLUE CARE NETWORK BENEFIT COVERAGE
# POLICY: SOMATIC BIOMARKER TESTING (INCLUDING LIQUID BIOPSY) FOR TARGETED TREATMENT AND IMMUNOTHERAPY IN METASTATIC COLORECTAL CANCER *(KRAS, NRAS,BRAF, MMR/MSI, HER2, AND TMB)*

## I. Coverage Determination:

| | |
|---|---|
| **Commercial HMO (includes Self-Funded groups unless otherwise specified)** | *KRAS*, *NRAS*, *BRAF*, MMR/MSI, HER2 and TMB mutation analysis: Covered; criteria apply. |
| **BCNA (Medicare Advantage)** | See Government Section |
| **BCN65 (Medicare Complementary)** | Coinsurance covered if primary Medicare covers the service. |

## II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT – HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.