
Medical Policy



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

Description

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

Medical Policy Statement

KRAS, *NRAS*, *BRAF*, *NTRK*, *RET* and *HER2*, mutation analyses on tumor tissue are established when criteria are met.

KRAS, *NRAS*, *BRAF*, *NTRK*, *RET* and *HER2* variant analysis using circulating tumor DNA or circulating tumor cell testing (liquid biopsy) is established when criteria are met.

Inclusionary and Exclusionary Guidelines

Inclusions (for all FDA-approved therapies, please check the FDA site):

- *KRAS*, *NRAS*, *BRAF* (V600E), and *RET* 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).
- *NTRK* mutation analysis is established in patients with tumors that are pan-wild-type (normal/no mutation) in *KRAS*, *NRAS*, and *BRAF*. The following medications are FDA approved when *NTRK* mutation is identified: for example, Repotrectinib, Larotrectinib, entrectinib.
- Human epidermal receptor 2 (HER2) amplification testing is established 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.
- 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
 - Please refer to the established codes for current coverage. A code may not be listed but could still be established if it 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 for colorectal cancer are not met.
- The use of circulating tumor DNA and circulating tumor cell testing is considered investigational for measurable residual disease (MRD) testing and cancer screening (e.g., Galleri).

Note: Blue Cross Blue Shield of Michigan and Blue Care Network follow National Comprehensive Cancer Network (NCCN) 2A and above recommendations. Due to frequent NCCN updates, please refer to the appropriate guideline for the most recent standards and intended coverage.

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:

81191	81192	81193	81194	81210	81275	81276	81311	81403	81404
81455*	81456*	88363	0037U*	0111U*	0211U	0239U*	0242U*	0326U*	0334U*
0471U*	0473U*								

*only established when above specific inclusionary criteria are met

Non-payable

86152	86153	0530U
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Background

KRAS, NRAS, and BRAF Variants

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

Human Epidermal Growth Factor Receptor 2 Amplification/Overexpression

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

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

The presence of *NTRK* gene fusion can be detected by multiple methods including next-generation sequencing, reverse transcription-polymerase chain reaction, fluorescence in situ hybridization and immunohistochemistry.² Next-generation sequencing provides the most comprehensive view of a large number of genes and may identify *NTRK* gene fusions as well as other actionable alterations, with minimal tissue needed. The fluorescence in situ hybridization using break-apart probes can detect gene rearrangements in DNA that may generate a fusion transcript. The immunohistochemistry techniques have generally been used in the research setting. Reverse transcription-polymerase chain reaction is designed to identify only known translocation partners and breakpoints and cannot identify novel breakpoints or novel fusion partners.

***RET* Gene Fusion Testing**

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

Detecting 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
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® GuardantOMNI®	ctDNA
IV Diagnostics	Velox™	CTC
Pathway Genomics	CancerIntercept® Detect	ctDNA
Personal Genome Diagnostics	PlasmaSELECT	ctDNA
Sysmex Inostics	OncoBEAM	ctDNA

Circulogene	Theranostics	ctDNA
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CTC: circulating tumor cell; ctDNA: circulating tumor DNA

SUMMARY OF EVIDENCE

For individuals with metastatic CRC who are being considered for targeted therapy with an FDA-approved drug and undergo somatic testing for who receive *KRAS*, *NRAS*, *BRAF*, *NTRK*, *RET* or HER2 variants using tissue biopsy specimens or liquid biopsy specimens to guide treatment, the evidence includes FDA-approved therapeutics with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and National Comprehensive Cancer Network (NCCN) recommendations. 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; $p=0.0002$). 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 are being considered for targeted therapy with FDA-approved drug and undergo somatic testing for HER2 overexpression using tissue biopsy specimens or liquid biopsy specimens, the evidence identified includes 2 systematic reviews/meta-analyses and 4 randomized clinical trials as well as the pivotal studies leading to FDA approved medications and NCCN recommendations. Relevant outcomes include overall survival, disease-specific survival, test validity, quality of life, and treatment-related morbidity.

Results from the meta-analysis by Bekaii-Saab et al (2023) showed there was a 2.84 times higher risk of death or progression (95% CI, 1.44 to 5.60) in patients with HER2-positive *RAS* WT mCRC treated with anti-EGFR regimens compared with those who were HER2-negative. Furthermore, data from 8 clinical studies of mCRC patients with HER2 amplification, confirmed by immunohistochemical staining and fluorescence *in situ* hybridization, treated with HER2-targeted inhibitors was pooled and demonstrated an ORR of 29 percent. Overall, the 4 randomized clinical trials demonstrated that higher levels of *HER2* amplification were associated with greater degree of clinical benefit from anti-HER2 therapy and had clinically meaningful anti-tumor activity with a favorable tolerability profile. No tests have received FDA approval as companion diagnostics to select individuals with CRC for treatment with FDA-approved targeted 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, TMB 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.

Rationale

Evidence reviews assess clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to individuals and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms. The following is a summary of the key literature to date.

***KRAS, NRAS, NTRK, BRAF, RET and HER2* VARIANT TESTING TO GUIDE TREATMENT FOR METASTATIC CRC**

For individuals with metastatic colorectal cancer (mCRC) who receive *KRAS*, *NRAS*, *NTRK*, *RET*, *BRAF* or *HER2* gene variant testing to select treatment with FDA-approved targeted therapy, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated.

Clinical Context and Test Purpose

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

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.

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.

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.

Systematic Reviews and Meta-analysis

Bekaii-Saab et al (2023) performed a systematic review and meta-analysis on the prognostic or predictive effect of HER2 amplification/overexpression on anti-EGFR treatment outcomes.³⁸ Five high-quality retrospective cohort studies were included in the meta-analyses representing 594 patients with mCRC and all patients received anti-EGFR treatment, either as monotherapy or in combination with chemotherapy. Results from the meta-analysis showed there was a 2.84 times higher risk of death or progression (95% CI, 1.44 to 5.60) in patients with HER2-positive *RAS* WT mCRC treated with anti-EGFR regimens compared with those who were HER2-negative. Based on meta-analysis of 3 studies reporting ORR (n = 265 patients) the odds of response to anti-EGFR treatment were almost 2 times higher in patients with mCRC who were HER2-negative compared with HER2-positive (OR: 1.96, 95% CI: 1.10 to 3.48). Based on meta-analysis of 3 studies reporting OS (n = 406 patients) the results showed that there was no statistically significant difference in OS between patients with HER2-positive, compared with HER2-negative, *RAS* WT mCRC. While these findings do not fully account for any impact of line of therapy or confounding chemotherapy agents, they support the evidence that testing for HER2 overexpression/amplification may help inform treatment decisions and optimize outcomes for mCRC patients. Notable limitations include, but are not limited to, the retrospective study design and heterogeneity in follow-up times, treatment modalities, and doses.

Gao et al (2022) conducted a meta-analysis to systematically evaluate the efficacy and safety of human epidermal growth factor receptor 2 (HER2)-targeted inhibitors for HER2-amplified

metastatic colorectal cancer (mCRC).³⁹ Eight clinical trials of mCRC patients with HER2 amplification, confirmed by immunohistochemical staining and fluorescence *in situ* hybridization, treated with HER2-targeted inhibitors with at least one of the primary outcomes available (objective response rate [ORR]; disease control rate [DCR]; progression-free survival [PFS]; overall survival [OS] and incidences of serious adverse events [SAEs]) were included in the meta-analysis. The pooled ORR and DCR of the 8 studies were 29% (95% CI: 20 to 40) and 71% (95% CI: 63 to 78), respectively with moderate heterogeneity in the studies using ORR and DCR as endpoints. The pooled median progression-free survival (PFS) and OS of the 8 studies was 4.89 months (95% CI: 3.82 to 5.97) and 13.04 months (95% CI: 9.45 to 16.62), respectively with high heterogeneity within the studies using PFS as the endpoint and moderate heterogeneity for studies using OS as the main outcome of interest. Furthermore, the results were considered to be unaffected by publication bias as determined by the Egger linear regression test. This meta-analysis revealed that HER2-targeted inhibitors exhibit good antitumor efficacy and safety in second line and above treatment of HER2-amplified mCRC patients. Yet, this study had some insurmountable heterogeneity issues, future large-scale, multicenter trials are required to investigate the problem in more depth. Other notable limitations include, but are not limited to, small number of studies, insufficient sample size, studies did not specify whether a randomization concealment method and/or result detection method were used, and studies used different types and doses of therapies.

Randomized Clinical Trials

Four different regimens are recommended by the National Comprehensive Cancer Network (NCCN) panel as options for subsequent treatment of mCRC with HER2 amplifications with FDA-approved therapies: fam-trastuzumab deruxtecan-nxki (T-DXd) monotherapy or trastuzumab in combination with pertuzumab, lapatinib, or tucatinib.³⁶ Pivotal clinical trials that led to the FDA approval of these therapies and NCCN recommendations include the following RCTs: the phase IIa multiple basket MyPathway trial (trastuzumab + pertuzumab),⁴⁰ the multicenter, phase II HERACLES trial (trastuzumab and lapatinib),^{41,42} the phase 2, multicenter DESTINY-CRC01 trial (trastuzumab + tucatinib),^{43,44} and the clinical studies discussed below. Taken together these RCTs provide sufficient evidence to determine that HER2 testing using tumor tissue biopsies results in an improvement in the net health outcome.

Raghav et al (2025) conducted a randomized phase II trial (N=53) to evaluate efficacy and safety of dual-HER2 inhibition against standard-of-care anti-EGFR antibody-based therapy as second/third line treatment in HER2-positive mCRC.⁴⁵ Patients with *RAS/BRAF*-WT mCRC after central confirmation of HER2 positivity (IHC 3+ or 2+ and *in situ* hybridization amplified [HER2/CEP17 ratio >2.0]; HCR) were assigned (1:1) to either trastuzumab plus pertuzumab (TP) or cetuximab plus irinotecan (CETIRI). The primary end point was PFS. Secondary end points included objective response rate (ORR), overall survival, safety, and HER2 gene copy number (GCN ≥ 20 / <20) as a predictive factor. Efficacy of TP versus CETIRI differed significantly by *HER2* GCN (median PFS, GCN ≥ 20 [9.9 v 2.9 months] and GCN <20 [3.0 v 4.2 months], respectively; $p=.003$). On TP, ORR was 34.6% (57.1% with GCN ≥ 20 v 9.1% with GCN <20) with median GCN of 29.7 versus 13.2 for responders and nonresponders, respectively ($p=.004$). Overall, higher levels of *HER2* amplification were associated with greater degree of clinical benefit from TP compared to CETIRI. Notable limitations include, but not limited to, small sample size due to low accrual, nonblinded investigator assessments, central HER2 testing with multiple testing methods, and insufficiently powered for the original design assumptions.

Raghav et al (2024) carried out a multicenter, randomized, two-stage, two-arm, phase 2 study (N=122) to assess antitumor activity, safety, and exploratory biomarkers of trastuzumab deruxtecan doses of 5.4 mg/kg and 6.4 mg/kg to evaluate its benefit–risk profile in patients with

HER2-positive, *RAS* wild-type or variant mCRC who had previously received standard chemotherapy.⁴⁶ In stage 1, patients were randomly assigned (1:1) to receive 5.4 mg/kg (n=40) or 6.4 mg/kg (n=40) trastuzumab deruxtecan administered intravenously every 21 days and in stage 2, patients were only assigned to the 5.4mg/kg (n=42) treatment group. The primary endpoint was confirmed objective response rate by blind independent central review, assessed in all patients for whom treatment was assigned. The confirmed objective response rate was 37.8% (95% CI: 27.3 to 49.2) in the 5.4 mg/kg group and 27.5% (95% CI: 14.6 to 43.9) in the 6.4 mg/kg group. The confirmed disease control rate was 86.6% (95% CI: 77.3 to 93.1) in the 5.4 mg/kg group and 85.0% (95% CI: 70.2 to 94.3) in the 6.4 mg/kg group with a median PFS of 5.8 months (95% CI: 4.6 to 7.0) and 5.5 months (95% CI: 4.2 to 7.0), respectively. Notable limitations include, but not limited to, the absence of a control group, small sample size for subgroup analysis, centralized *HER2* testing with archival tissue, and PFS and OS were premature at time of the primary analysis.

Strickler et al (2023) assessed the activity of tucatinib plus trastuzumab in patients with chemotherapy-refractory, HER2-positive, *RAS* wild-type unresectable or mCRC in a global, open-label, phase 2 study.⁴⁹ Between Aug 8, 2017, and Sept 22, 2021, 117 patients enrolled into 3 cohorts (Cohort A: tucatinib plus trastuzumab [n=45], Cohort B: tucatinib plus trastuzumab [n=41], and Cohort C tucatinib monotherapy [n=31]), of whom 114 patients had locally assessed HER2-positive disease and received treatment (45 in cohort A, 39 in cohort B, and 30 in cohort C; full analysis set). As for data cutoff (March 28, 2022), 84 patients from cohorts A and B in the full analysis set, the confirmed ORR per blinded independent central review was 38.1% (95% CI: 27.7 to 49.3; three patients had a complete response and 29 had a partial response). Tucatinib plus trastuzumab had clinically meaningful anti-tumor activity and favorable tolerability. Notable limitations include, but not limited to, the open-label design, absence of power for formal comparative study, heterogeneity in imaging intervals and frequency due to the study being expanded, and insufficient follow-up time for cohort C.

Gupta et al (2022) evaluated the results from the TAPUR study, a pragmatic phase II basket trial evaluating anti-tumor activity of commercially available targeted agents in patients with advanced cancers harboring potentially actionable genomic alterations and reported data from two cohorts of patients with CRC with either *ERBB2* amplifications or *ERBB2* or *ERBB3* (*ERBB2/3*) variants treated with pertuzumab plus trastuzumab.⁴⁷ Pertuzumab plus trastuzumab treatment was shown to have antitumor activity in patients with heavily pretreated colorectal cancer with *ERBB2* amplification (disease control [DC]: 54%, objective response [OR]: 25%, median PFS: 17.2 weeks [95% CI: 11.1 to 27.4] median OS: 60.0 weeks [95% CI: 32.1 to 102.3]) but did not demonstrate antitumor activity in patients with *ERBB2* or *ERBB3* variants (DC: 10%, OR: 0%, median PFS: 9.6 weeks [95% CI: 5.1 to 16.0], median OS: 28.8 weeks [95% CI: 7.6 to 146.3]). Notable limitations include, but not limited to, the absence of a control group, nonblinded investigator assessments, small patient cohorts, local *ERBB2* testing with multiple testing methods, and incomplete reporting of *RAS* mutation status.

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 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 1 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 reached a data cutoff (95% CI 7.4 months to not evaluable)

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

Section Summary: HER2 Testing to Guide Treatment for Metastatic Colorectal Cancer

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

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).

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 6 and 7. Study relevance, design, and conduct limitations are described in Tables 2 and 3.

Table 2. 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 - 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. 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 - Anti-EGFR treatment-I - Enrolled from 2009 to 2016	Retrospective-prospective	Analysis of tissue samples conducted using institutional standard-of-care procedures	- Tissue collected before blood - Median interval, 48 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 - Anti-EGFR treatment-naïve but majority treated with other systemic therapies	Retrospective-prospective	Analysis of tissue samples conducted using real-time PCR	Tissue collected before blood Median interval 1.2 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 - Blood collected at baseline	Not stated
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CRC: colorectal cancer; EGFR: epidermal growth factor receptor; NGS: next-generation sequencing; PCR: polymerase chain reaction.

Table 3. 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 4 and 5. 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 6 and 7.

Table 4. 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 FoundationOne assay	Liquid biopsy testing was done at the discretion of the clinician at variable time intervals after tissue sample collection (0-709 days)	Not stated

ctDNA: circulating tumor DNA; CRC: colorectal cancer.

Table 5. 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) 79% Subset with <i>KRAS</i> , <i>NRAS</i> , and <i>BRAF</i> variants (n=51) 80% for all time points 90% for cases <270 days between tissue and liquid biopsy

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

Table 6. 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 7. 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	1: Blinding unclear	1. Unclear when tissue was collected	1. Registration not described	2. Only 27% of CAPRI-GOIM trial	1. Cis not reported but calculated

	from those available				participants included	based on data provided
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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.

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.

SUPPLEMENTAL INFORMATION

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.4.2025). Guidelines are updated frequently; refer to the source document for most recent updates and for additional detail.

RAS, KRAS and BRAF Testing

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 panitumumab or cetuximab highly unlikely unless given with a *BRAF* inhibitor. (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).

***NTRK* Testing**

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

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 Oncology²⁸

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 8. summarizes the relevant guidelines.

Table 8. 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 <i>KRAS</i> and <i>NRAS</i> 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
<i>BRAF</i> p. V600 (<i>BRAF</i> 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
<i>BRAF</i> p. V600 mutational analysis should be performed in deficient MMR tumors with loss of <i>MLH1</i> to evaluate for Lynch Syndrome risk. Presence of a <i>BRAF</i> mutation strongly favors a sporadic pathogenesis. The absence of <i>BRAF</i> 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 <i>BRAF</i> 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

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	Nov 2026
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
NCT04264702	BESPOKE Study of ctDNA Guided Therapy in Colorectal Cancer	1788	Sep 2025 (active, not recruiting)
NCT05253651	An Open-label Randomized Phase 3 Study of Tucatinib in Combination with Trastuzumab and mFOLFOX6 Versus mFOLFOX6 Given with or Without Either Cetuximab or Bevacizumab as First-line Treatment for Subjects with HER2+ Metastatic Colorectal Cancer	400	Jul 2029
Unpublished			
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
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

NCT: national clinical trial

Regulatory Status:

Table 10 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 September 2024; 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 10. Targeted Treatments for Metastatic Colorectal Cancer and FDA Approved Companion Diagnostic Tests

Treatment	Indications in Metastatic Colorectal Cancer	Companion Diagnostics	NCCN recommendation Level
Cetuximab (Erbix)	<i>KRAS</i> 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 <i>KRAS</i> Mutation Test Dako EGFR pharmDx Kit FoundationOne CDx therascreen <i>KRAS</i> RGQ PCR Kit ONCO/Reveal Dx Lung and Colon Cancer assay xT CDx	2A or higher Metastatic Colorectal Cancer V.4.2025 2A or higher/Metastatic Rectal Cancer (v. 2.2025)
Braftovi (encorafenib)	Treatment of adult patients with metastatic colorectal cancer with a BRAF V600E mutation in combination with Erbitux (cetuximab), after prior therapy	FoundationOne Liquid CDx therascreen BRAF V600E RGQ PCR Kit MI Cancer Seek (MCS)	2A or higher Metastatic Colorectal Cancer V.4.2025 2A or higher/Metastatic Rectal Cancer (v. 2.2025)
Panitumumab (Vectibix)	Treatment of wild-type <i>RAS</i> (defined as wild-type in both <i>KRAS</i> and <i>NRAS</i> as determined by an FDA-approved test for this use) metastatic CRC: - In combination with FOLFOX for first-line treatment. - As monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy. Limitation of Use: Vectibix is not indicated for the treatment of patients with RAS-mutant mCRC or for whom RAS mutation status is unknown.	Cobas <i>KRAS</i> Mutation Test Dako EGFR pharmDx Kit FoundationOne CDx therascreen <i>KRAS</i> RGQ PCR Kit ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) xT CDx xT CDx - tissue (Matching Blood/Saliva) MI Cancer Seek (MCS)	2A or higher Metastatic Colorectal Cancer V.4.2025 2A or higher/Metastatic Rectal Cancer (v. 2.2025)
Pembrolizumab (Keytruda®)	Unresectable or metastatic, MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or	FoundationOne CDx	

	CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan First-line treatment of patients with unresectable or metastatic MSI-H or dMMR CRC		
Tukysa (Tucatinib)	Treatment of adult patients with unresectable or metastatic CRC with RAS wild-type HER2-positive - In combination with Trastuzumab (Herceptin) - Previously treated with 20or20rpyrimidine, oxaliplatin, and irinotecan-based chemotherapy	No FDA-approved companion diagnostic	2A or higher/ Metastatic Colorectal Cancer (v.4.2025) 2A or higher/Metastatic Rectal Cancer (v. 2.2025)
Vitrakvi (Larotrectinib)	NTRK fusion positive, metastatic CRC as determined by an FDA approved test with no satisfactory alternative treatment options In a non-first line setting	FoundationOne Liquid CDx TruSight Oncology Comprehensive	2A or higher/metstatic CRC (V.4.2025) 2A or higher/Metastatic Rectal Cancer (v. 2.2025)
Rozlytrek (entrectinib)	NTRK fusion positive, metastatic CRC as determined by an FDA approved test with no satisfactory alternative treatment options In a non-first line setting	FoundationOne Liquid CDx FoundationOne CDx	2A or higher/metstatic CRC (V.4.2025) 2A or higher/Metastatic Rectal Cancer (v. 2.2025)
Retevmo (selpercatinib)	<i>RET</i> fusion positive, metastatic CRC as determined by an FDA-approved test, that has progressed on or following prior systemic treatment or with no satisfactory alternative treatment options	FoundationOne CDx	2A or higher/Metastatic Colon Cancer (v. 4.2025) 2A or higher/Metastatic Rectal Cancer (v. 2.2025)
Lumakras (sotorasib)	Treatment of adult patients with metastatic colorectal cancer with a <i>KRAS</i> G12C mutation - in combination with Erbitux (cetuximab or panitumumab), after prior therapy - If patients are unable to tolerate EGFR inhibitor due to toxicity, single agent can be considered	<i>therascreen</i> KRAS RGQ PCR Kit	2A or higher/Metastatic Colon Cancer (v. 4.2025)
Krazati (adagrasib)	Treatment of adult patients with metastatic colorectal cancer with a <i>KRAS</i> G12C mutation - in combination with Erbitux (cetuximab or panitumumab), after prior therapy - If patient is unable to tolerate EGFR inhibitor due to toxicity, single agent can be considered	<i>therascreen</i> KRAS RGQ PCR Kit	2A or higher/Metastatic Rectal Cancer (v. 2.2025)

Source: FDA (2024)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*, *NTRK* 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.

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:

MoIDX: 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).

MoIDX: NRAS Genetic Testing, L36797, effective 07/31/2025

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

All other NRAS testing is non-covered.

MoIDX: 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
 - GT-Somatic Biomarker Testing for Immune Checkpoint Inhibitor Therapy (BRAF, MSI/MMR, PD-L1, TMB)
-

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through September 2025, 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 <i>KRAS</i> 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; <i>KRAS</i> policy statement unchanged. References updated.
5/1/13	2/19/13	3/4/13	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 <i>NRAS</i> 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: <i>KRAS</i> , <i>NRAS</i> and BRAF variant analysis in metastatic colorectal cancer (including liquid biopsy). Added code 0111U effective 10/1/19. Added as exclusion "KRAS, BRAF, 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 • Coverage extends to HER2, TMB, microsatellite instability testing and mismatch repair testing • Add TMB language from NSCLC policy in MPS • Added language for FoundationOne CDx testing to inclusion section • Added codes 81210, 81301 and 0037U as covered codes • 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)
1/1/25	10/15/24		Added NTRK to policy and title, removed MMR/MSI and TMB, removed, “and immunotherapy” from title, removed code 81301, added codes 81191-81194, 0471U & 0473U as established. Vendor managed: N/A (ds)
3/1/25	12/17/24		Added code 0530U as E/I, effective 1/1/25. Vendor managed: N/A (ds)

1/1/26	10/21/25		Added coverage for RET gene. Added code 0211U as established. Vendor managed: N/A (ds)
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Next Review Date: 4th Qtr. 2026

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 IN METASTATIC COLORECTAL CANCER (*KRAS, NRAS, BRAF, NTRK, RET AND HER2*)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	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.