Medical Policy

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

Related Policies:	▪ *Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes* ▪ *Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies* ▪ *Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer* ▪ *Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)*

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Populations	Interventions	Comparators	Outcomes
Individuals: • With metastatic colorectal cancer	Interventions of interest are: • *KRAS* variant testing to guide treatment	Comparators of interest are: • No *KRAS* variant testing to guide treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Medication use • Resource utilization • Treatment-related morbidity
Individuals: • With metastatic colorectal cancer	Interventions of interest are: • *NRAS* variant testing to guide treatment	Comparators of interest are: • No *NRAS* variant testing to guide treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Medication use • Resource utilization • Treatment-related morbidity
Individuals: • With metastatic colorectal cancer	Interventions of interest are: • *BRAF* variant testing to guide treatment	Comparators of interest are: • No *BRAF* variant testing to guide treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Medication use • Resource utilization • Treatment-related morbidity
Individuals: • With metastatic colorectal cancer	Interventions of interest are: • *MMR/MSI* testing to guide treatment	Comparators of interest are: • No MMR/MSI variant testing to guide treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Medication use • Resource utilization • Treatment-related morbidity
Individuals: • With metastatic colorectal cancer	Interventions of interest are: • *HER2* testing to guide treatment	Comparators of interest are: • No HER2 variant testing to guide treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Medication use • Resource utilization • Treatment-related morbidity
Individuals: • With metastatic colorectal cancer	Interventions of interest are: • Tumor mutational burden testing to guide treatment	Comparators of interest are: • No tumor mutational burden testing to guide treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Medication use • Resource utilization • Treatment-related morbidity
Individuals: • With metastatic colorectal cancer	Interventions of interest are:	Comparators of interest are:	Relevant outcomes include: • Overall survival • Disease-specific survival

Populations	Interventions	Comparators	Outcomes
	• Testing of circulating tumor DNA to select treatment	• Using tissue biopsy to guide treatment	• Test validity • Morbid events • Medication use

DESCRIPTION

The epidermal growth factor receptor (EGFR) is overexpressed in colorectal cancer (CRC). EGFR-targeted therapy combined with monoclonal antibodies cetuximab and panitumumab has shown a clear survival benefit in patients with metastatic CRC. However, this benefit depends on a lack of variants in certain genes in the signaling pathway downstream from the EGFR. It has been hypothesized that knowledge of tumor cell *KRAS, NRAS*, *BRAF* variant status might be used to predict nonresponse to anti-EGFR monoclonal antibody therapy. More recently, testing for microsatellite instability/mismatch repair (MSI/MMR) and tumor mutational burden (TMB) status to select patients for immunotherapy and human epidermal growth factor receptor 2 (HER2) testing to select patients for targeted therapy has been proposed. Typically, the evaluation of biomarker status requires tissue biopsy. Circulating tumor DNA or circulating tumor cell testing (also known as a liquid biopsy) is proposed as a non-invasive alternative.

OBJECTIVE

The objective of this evidence review is to determine whether using biomarker testing to select targeted treatment and immunotherapy improves the net health outcome in individuals with metastatic CRC. This policy does not address neurotrophic tyrosine receptor kinase (*NTRK*) testing.).

BACKGROUND

KRAS, *NRAS*, and *BRAF* Variants

Cetuximab (Erbitux®; ImClone Systems) and panitumumab (Vectibix®; Amgen) are monoclonal antibodies that bind to the epidermal growth factor receptor (EGFR), preventing intrinsic ligand binding and activation of downstream signaling pathways vital for cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization. The RAS-RAF-MAP kinase pathway is activated in the EGFR cascade. The RAS proteins are G proteins that cycle between active (RAS guanosine triphosphate) and inactive (RAS guanosine diphosphate) forms in response to stimulation from a cell surface receptor, such as EGFR, and they act as a binary switch between the cell surface EGFR and downstream signaling pathways. The *KRAS* gene can harbor oncogenic variants that result in a constitutively activated protein, independent of EGFR ligand binding, rendering antibodies to the upstream EGFR ineffective. Approximately 40% of colorectal cancers (CRCs) have *KRAS* variants in codons 12 and 13 in exon 2. Another proto-oncogene that acts downstream from *KRAS*-*NRAS* harbors oncogenic variants in codons 12, 13, or 61 that result in constitutive activation of the EGFR-mediated pathway. These variants are less common compared with *KRAS,* detected in 2% to 7% of CRC specimens. It is unclear whether *NRAS* variants predict poor response due to anti-EGFR monoclonal antibody therapy or are prognostic of poor CRC outcomes in general. A third proto-oncogene, *BRAF*, encodes a protein kinase and is involved in intracellular signaling and cell growth; *BRAF* is also a principal downstream effector

of *KRAS*. *BRAF* variants occur in fewer than 10% to 15% of CRCs and appear to be a marker of poor prognosis. *KRAS* and *BRAF* variants are considered to be mutually exclusive.

Cetuximab and panitumumab have marketing approval from the U.S. Food and Drug Administration (FDA) for the treatment of metastatic CRC in the refractory disease setting. The FDA approval for panitumumab indicates that panitumumab is not indicated for the treatment of patients with *KRAS* or *NRAS* variant-positive disease in combination with oxaliplatin-based chemotherapy.[1,]

A large body of literature has shown that metastatic CRC tumors with a variant in exon 2 (codon 12 or 13) of the *KRAS* gene do not respond to cetuximab or panitumumab therapy. More recent evidence has shown that variants in *KRAS* outside exon 2 (i.e., in exons 3 [codons 59 and 61] and exon 4 [codons 117 and 146]) and variants in *NRAS* exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) also predict a lack of response to these monoclonal antibodies. Variant testing of these exons outside the *KRAS* exon 2 is referred to as extended *RAS* testing.

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

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 Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy)

Normal and tumor cells release small fragments of DNA into the blood, which is referred to as cell-free DNA. Cell-free DNA from nonmalignant cells is released by apoptosis. Most cell-free tumor DNA is derived from apoptotic and/or necrotic tumor cells, either from the primary tumor, metastases, or circulating tumor cells. Unlike apoptosis, necrosis is considered a pathologic process and generates larger DNA fragments due to incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origin. Circulating tumor DNA can be used for genomic characterization of the tumor.

Typically, the evaluation of RAS mutation status requires tissue biopsy. Circulating tumor DNA (ctDNA) testing is proposed as a non-invasive alternative.

Detection of ctDNA is challenging because ctDNA is diluted by nonmalignant circulating DNA and usually represents a small fraction (<1%) of total ctDNA. Therefore, more sensitive methods than the standard sequencing approaches (e.g., Sanger sequencing) are needed.

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

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

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

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

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

Manufacturer	Test	Type of Liquid Biopsy
Biocept	Target Selector™ ctDNA EGFR Kit	ctDNA
Foundation Medicine	FoundationOne Liquid (Previously FoundationAct)	ctDNA
Guardant Health	Guardant360®	ctDNA
IV Diagnostics	Velox™	CTC

Manufacturer	Test	Type of Liquid Biopsy
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 June 13, 2022; FDA maintains a list of cleared or approved companion diagnostic devices that is updated regularly.[2,]

In June 2022, FDA granted accelerated approval to dabrafenib (Tafinlar®, Novartis) in combination with trametinib (Mekinist®, Novartis) for the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with *BRAF* V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. However, dabrafenib in combination with trametinib is *not* indicated for patients with CRC because of known intrinsic resistance to BRAF inhibition.[3,] Therefore, *BRAF* V600E variant testing to select individuals for treatment with dabrafenib in combination with trametinib is not included in this evidence review and is not listed in Table 2.

Table 2. Targeted Treatments for Metastatic Colorectal Cancer and FDA Approved Companion Diagnostic Tests

Treatment	Indications in Metastatic Colorectal Cancer	Companion Diagnostics
Cetuximab (Erbitux)	*KRAS* wild-type, EGFR-expressing, metastatic colorectal cancer as determined by an FDA-approved test • in combination with FOLFIRI for first-line treatment, • in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy, • as a single-agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan. Limitations of Use: Erbitux is not indicated for treatment of RAS mutant colorectal cancer or when the results of the RAS mutation tests are unknown	cobas KRAS Mutation Test Dako EGFR pharmDx Kit FoundationOne CDx therascreen KRAS RGQ PCR Kit
Braftovi (encorafenib)	Treatment of adult patients with metastatic colorectal cancer with a BRAF V600E mutation • in combination with Erbitux (cetuximab), after prior therapy	*therascreen* BRAF V600E RGQ PCR Kit

Treatment	Indications in Metastatic Colorectal Cancer	Companion Diagnostics
Panitumumab (Vectibix)	Treatment of wild-type *RAS* (defined as wild-type in both *KRAS* and *NRAS* as determined by an FDA-approved test for this use) metastatic CRC: • In combination with FOLFOX for first-line treatment. • As monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy. Limitation of Use: Vectibix is not indicated for the treatment of patients with RAS-mutant mCRC or for whom RAS mutation status is unknown.	cobas KRAS Mutation Test Dako EGFR pharmDx Kit FoundationOne CDx Praxis Extended RAS Panel therascreen KRAS RGQ PCR Kit ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA)
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 • 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	FoundationOne CDx

Source: FDA (2022)[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

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed under CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

POLICY

A. *KRAS* variant analysis of tumor tissue may be considered **medically necessary** for individuals with metastatic colorectal cancer to select individuals for treatment with FDA-approved therapies.

B. All other uses of *KRAS* variant testing of tumor tissue to guide colorectal cancer targeted therapy or immunotherapy are considered **experimental / investigational**.

C. *NRAS* variant analysis of tumor tissue may be considered **medically necessary** for individuals with metastatic colorectal cancer to select individuals for treatment with FDA-approved therapies.

D. All other uses of *NRAS* variant testing of tumor tissue to guide colorectal cancer targeted therapy or immunotherapy are considered **experimental / investigational**.

E. *BRAF* variant analysis of tumor tissue may be considered **medically necessary** for individuals with metastatic colorectal cancer who are found to be wild-type on *KRAS* and *NRAS* variant analysis to guide management decisions and to select individuals for treatment with FDA-approved therapies.

F. All other uses of *BRAF* variant testing of tumor testing to guide colorectal cancer targeted therapy or immunotherapy are considered **experimental / investigational**.

G. Mismatch repair/microsatellite instability (MMR/MSI) testing of tumor tissue may be considered **medically necessary** to select individuals for treatment with FDA-approved therapies.

H. Other uses of mismatch repair/microsatellite instability variant testing of colorectal tumor tissue for guiding targeted therapy or immunotherapy are considered **experimental / investigational**.

I. HER2 testing is considered **experimental / investigational** to predict treatment response to immunotherapy in patients with metastatic colorectal cancer.

J. Tumor mutational burden testing to predict response to immunotherapy in patients with metastatic colorectal cancer is considered **experimental / investigational.**

K. Circulating tumor DNA testing (liquid biopsy) to guide treatment in patients with metastatic colorectal cancer is considered **experimental / investigational**.

POLICY GUIDELINES

A. Testing for other variants may become available between policy updates. For guidance on testing criteria between policy updates, refer to the FDA's List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) (https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools) for an updated list of FDA-approved tumor markers and consult the most current version of National Comprehensive Cancer Network (NCCN) management algorithms.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through June 13, 2022.

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 COLORECTAL CANCER

Clinical Context and Test Purpose

The purpose of *KRAS* variant testing in individuals with metastatic colorectal cancer (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 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 *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), overall survival (OS), change in disease status, medication use, resource utilization, and treatment-related morbidity.

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.

Review of Evidence
KRAS, NRAS, and *BRAF* variant testing are associated with FDA-approved therapeutics (i.e., as companion diagnostic tests) for therapies and have National Comprehensive Cancer Network (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 (RCTs) 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 NCCN 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 OS 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 (HR).

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 PFS for patients randomized to pembrolizumab compared with chemotherapy (HR 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-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 (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 RCTs.

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-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 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. Because no patients with colorectal cancer were included in these analyses, it is not possible to draw conclusions about the clinical validity and utility of TMB in this group of patients.

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.

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. Median OS and PFS survival were not significantly different between TMB groups. Because no patients with CRC were included in these analyses, it is not possible to draw conclusions about the clinical validity and utility of TMB in this group of patients. These results need to be confirmed in well-designed prospective studies enrolling patients with CRC.

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

Clinical Context and Test Purpose
One purpose of liquid biopsy testing of 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 PICO was used to select literature to inform this review.

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

Interventions
The test being considered is liquid biopsy using either 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 PFS.

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.

Study Selection Criteria

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

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Clinically Valid

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

Review of Evidence

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

OncoBEAM *RAS* CRC Assay

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

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

Study	Study Population	Design	Reference Standard	Timing of Tissue Biopsy and Liquid Biopsy	Blinding of Assessors
Garcia-Foncillas (2018)[28,]	• Patients with metastatic CRC newly diagnosed or presenting with recurrent disease after resection and/or	Prospective	Analysis of tissue using standard-of-care procedures validated by	Plasma collected before any therapeutic intervention. OncoBEAM used when standard of care RAS result was	Not stated; central laboratory used

Study	Study Population	Design	Reference Standard	Timing of Tissue Biopsy and Liquid Biopsy	Blinding of Assessors
	chemotherapy at 10 centers in Spain • Enrolled from November 2015 to October 2016		each hospital	discordant with RAS result. The same tissue block was used for re-analysis by OncoBEAM.	
Vidal (2017)[29,]	• Patients from Spain with histologically confirmed metastatic CRC • Anti-EGFR treatment-naive • Enrolled from 2009 to 2016	Retrospective-prospective	Analysis of tissue samples conducted using institutional standard-of-care procedures	• Tissue collected before blood • Median interval, 48 days (range, 0-1783 days)	Yes
Schmiegel (2017)[30,]	• 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)[31,]	• Patients from Spain with histologically confirmed metastatic CRC • Anti-EGFR treatment-naïve but majority treated with other systemic therapies	Retrospective-prospective	Analysis of tissue samples conducted using real-time PCR	• Tissue collected before blood • Median interval 1.2 months (range 0 to 34)	Yes
Normanno (2018)[32,]	• Patients with metastatic CRC who are *KRAS* exon-2 wild-type and received first-line etuximab plus FOLFIRI within the CAPRI-GOIM trial	Retrospective-prospective	Analysis of tissue samples conducted using NGS	• Unclear when tissue was collected • Blood collected at baseline	Not stated

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

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

Study	Initial N	Final N	Excluded Samples	*RAS* Variant-Positive, %[a]	Sensitivity	Specificity	PPV	NPV
Garcia-Foncillas (2018)[28,]	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 (2017)[29,]	NA	115	No description of samples excluded from comparison to tissue results	51	96 (87 to 100) [b]	90 (79 to 96) [b]	90 (79 to 96) [b]	96 (88 to 100) [b]
Schmiegel (2017)[30,]	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)[31,]	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)[32,]	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]

CRC: 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.
[b] Confidence intervals not reported in publication; calculated from data provided.

FoundationACT ctDNA Assay

The FoundationACT ctDNA assay, the predecessor of FoundationOne Liquid, was compared to tissue biopsy using the FoundationOne assay in one manufacturer-sponsored study by Li et al in 2019.[33,] Study characteristics and results are shown in Tables 5 and 6. The researchers reported results on the subset of 51 patients with *KRAS, NRAS,* and *BRAF* variants. These results are shown in Table 10. Positive percent agreement was 80% for all time points for short variants and increased to 90% for cases in which tissue and liquid biopsy were measured less than 270 days apart. Limitations of this study are described in Tables 7 and 8..

Table 5. Clinical Validity Study of the FoundationACT ctDNA Assay

Study	Study Population	Design	Reference Standard	Timing of Reference and Index Tests	Blinding of Assessors
Li (2019)[33,]	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

CRC: colorectal cancer; ctDNA: circulating tumor DNA.

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

Study	Initial N	Final N	Excluded Samples	*RAS* Variant-Positive, %	Positive Percent Agreement (95% Confidence Interval)
Li (2019)[33,]	96	73	22 samples did not have detectable ctDNA	51/74 (92%)	Overall (N=73): 79% Subset with *KRAS*, *NRAS*, and *BRAF* variants (n=51): 80% for all timepoints 90% for cases <270 days between tissue and liquid biopsy

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

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

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Li (2019)[Li G, Pavlick D, Chung JH, et al. Genomic profilin.... /29063.	4.74% had metastatic disease		2. Reference standard was FoundationOne assay		

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Accessed July 3, 2022.]					
Garcia-Foncillas (2018)[28,]				3. PPV and NPV not reported	
Vidal (2017)[29,]					
Schmiegel (2017)[30,]		2: Not clear if marketed version of test used			
Grasselli (2017)[31,]					
Normanno (2018)[32,]					

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

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

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Completeness of Follow-Up[e]	Statistical[f]
Li (2019)[33,]	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 (2018)[28,]	1. Not clear whether samples were	1: Blinding unclear		1. Registration not described		

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Completeness of Follow-Up[e]	Statistical[f]
	consecutive or convenience					
Vidal (2017)[29,]	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)[30,]	1: Not clear how patients were selected from those that were eligible	1: Blinding unclear		1. Registration not described		
Grasselli (2017)[31,]	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)[32,]	1: Not clear how tumor samples were selected from those available	1: Blinding unclear	1: Unclear when tissue was collected	1. Registration not described	2: Only 27% of CAPRI-GOIM trial participants included	1. CIs not reported but calculated based on data provided

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

Clinically Useful

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

Direct Evidence

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

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

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

Section Summary: Circulating Tumor DNA Testing (Liquid Biopsy) to Guide Treatment for Metastatic Colorectal Cancer
The clinical validity of the OncoBEAM RAS CRC Assay has been studied in multiple observational studies. When compared to tissue biopsy, sensitivity ranged from 70% (95% CI, 51% to 84%) to 96% (95% CI, 87% to 100%) and specificity ranged from 83% (95% CI, 71% to 92%) to 94% (95% CI, 82% to 98%). FoundationOne Liquid has been compared to tissue biopsy with the FoundationACT assay in 1 observational study; positive percent agreement was 80% overall and 90% when tissue and liquid biopsy were collected less than 270 days apart. Clinical validity studies were limited by unclear reporting of blinding, use of convenience rather than consecutive samples, and variation in the timing of sample collection. There are no published studies reporting clinical outcomes or clinical utility.

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

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

For individuals with metastatic CRC who receive BRAF variant testing to guide treatment, the evidence includes 2 meta-analyses of prospective and retrospective analyses of RCTs. Relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. The meta-analyses have shown that anti-EGFR monoclonal antibody therapy did not improve survival in patients with RAS wild-type or BRAF-mutated tumors; however, the individual studies have been small, and the results have been

inconsistent. Testing for the BRAF V600E variant in adult individuals with metastatic CRC for determining treatment with encorafenib in combination with cetuximab after previous therapy, has received FDA approval and NCCN recommendation based on clinical trial results. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with metastatic CRC who receive MSI/MMR testing to guide treatment, the evidence includes an RCT of pembrolizumab compared to chemotherapy and nonrandomized trials. Relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Effectiveness of pembrolizumab compared to chemotherapy in patients with previously untreated, unresectable or metastatic high-frequency MSI (MSI-H) or deficient MMR (dMMR) CRC was investigated in a multicenter, randomized, open-label, active-controlled trial of 307 patients. The trial demonstrated a statistically significant improvement in progression free survival (PFS) for patients randomized to pembrolizumab compared with chemotherapy (hazard ratio [HR] 0.60; 95% confidence interval [CI], 0.45 to 0.80; p=.0002). In final results, median PFS was 16.5 months (95% CI, 5.4 to 38.1) with pembrolizumab versus 8.2 months (95% CI, 6.1 to 10.2) with chemotherapy (HR 0.59; 95% CI, 0.45 to 0.79). Treatment-related adverse events of grade 3 or worse occurred in 33 (22%) of 153 patients in the pembrolizumab group versus 95 (66%) of 143 patients in the chemotherapy group. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with metastatic CRC who receive HER2 testing to guide treatment, the evidence includes nonrandomized trials. Relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. There is no approved targeted treatment or companion diagnostic test for HER2 testing in patients with metastatic CRC. A phase 2 basket trial included 37 patients with HER2-amplified /overexpressed metastatic CRC. Treatment with trastuzumab plus pertuzumab produced partial response in 14 patients (38%; 95% CI, 23% to 55%) and the median duration of response was 11 months (range 1 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 insufficient 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. Median OS and PFS were not significantly different between TMB groups. Because no patients with CRC were included in these analyses, it is not possible to draw conclusions about the clinical validity and utility of TMB in this group of patients. Well-designed prospective studies enrolling patients in the population of interest are required.

The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with metastatic CRC who receive circulating tumor DNA or circulating tumor cell testing (liquid biopsy) to guide treatment, the evidence includes observational studies. Relevant outcomes are OS, disease-specific survival, test validity, morbid events, and medication use. Given the breadth of methodologies available to assess circulating tumor DNA and circulating tumor cells, the clinical validity of each commercially available test must be established independently. The clinical validity of the OncoBEAM™ RAS CRC Assay has been studied in multiple observational studies. When compared to tissue biopsy, sensitivity ranged from 70% (51% to 84%) to 96% (95% CI, 87% to 100%) and specificity ranged from 83% (95% CI, 71% to 92%) to 94% (82% to 98%). FoundationOne® Liquid has been compared to tissue biopsy with the FoundationACT™ assay in 1 observational study; positive percent agreement was 80% overall and 90% when tissue and liquid biopsy were collected less than 270 days apart. Clinical validity studies were limited by unclear reporting of blinding, use of convenience rather than consecutive samples, and variation in the timing of sample collection. There are no published studies reporting clinical outcomes or clinical utility. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

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

2017 Input

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

For individuals who have metastatic CRC who are found to be wild-type on *KRAS* and *NRAS* variant analysis who receive *BRAF* V600E variant analysis to guide management decisions, clinical input supports this use provides a clinically meaningful improvement in net health outcome and indicates this use is consistent with generally accepted medical practice.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given

to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society of Clinical Oncology et al

In 2017, the American Society of Clinical Oncology along with American Society for Clinical Pathology, College of American Pathologists, and Association for Molecular Pathology published guidelines on molecular biomarkers for the evaluation of colorectal cancer.[34,] Table 9 summarizes the relevant guidelines.

Table 9. Summary of Recommendations

Guidelines	Type	SOE	QOE
Colorectal carcinoma patients being considered for anti-EGFR therapy must receive RAS mutational testing. Mutational analysis should include KRAS and NRAS codons 12, 13 of exon 2; 59, 61 of exon 3; and 117 and 146 of exon 4 ("expanded" or "extended" RAS)	Recommendation	Convincing/ adequate, benefits outweigh harms	High/intermediate
BRAF p.V600 (BRAF c. 1799 (p.V600) mutational analysis should be performed in colorectal cancer tissue in patients with colorectal carcinoma for prognostic stratification	Recommendation	Adequate/inadequate, balance of benefits and harms	Intermediate/low
BRAF p.V600 mutational analysis should be performed in deficient MMR tumors with loss of MLH1 to evaluate for Lynch Syndrome risk. Presence of a BRAF mutation strongly favors sporadic pathogenesis. The absence of BRAF mutation does not exclude risk of Lynch syndrome	Recommendation	Adequate/inadequate, balance of benefits and harms	Intermediate/low
Clinicians should order mismatch repair status testing in patients with colorectal cancers for the identification of patients at high-risk for Lynch syndrome and/or prognostic stratification	Recommendation	Adequate/inadequate, balance of benefits and harms	Intermediate/low
There is insufficient evidence to recommend BRAF c.1799 p.V600 mutational status as a predictive molecular biomarker for response to anti-EGFR inhibitors	No recommendation	Insufficient, benefits/harms balance unknown	Insufficient

EGFR: epidermal growth factor receptor; QOE: quality of evidence; SOE: strength of evidence.

National Comprehensive Cancer Network

The following information is based on the National Comprehensive Cancer Network (NCCN) guidelines on the treatment of colon cancer (v.1.2022).[35,] Guidelines are updated frequently; refer to the source document for most recent updates and for additional detail.

RAS and BRAF Testing

The guidelines recommend that all patients with metastatic colorectal cancer should have tumor tissue genotyped for RAS (KRAS and NRAS) and BRAF variants, individually or as part of a next-generation sequencing panel, for all patients with metastatic colon cancer Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab. BRAF V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a BRAF inhibitor (Category 2A).

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

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

Ongoing and Unpublished Clinical Trials
Currently unpublished trials that might influence this review are listed in Table 10.

Table 10. Summary of Key Ongoing Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04425239	Intermittent or Continuous Panitumumab Plus FOLFIRI for First-line Treatment of Patients With RAS/B-RAF Wild-type Metastatic Colorectal Cancer: a Randomized Phase 2 Trial	151	Apr 2022
NCT04008030	A Phase 3 Randomized Clinical Trial of Nivolumab Alone, Nivolumab in Combination With Ipilimumab, or an	748	Aug 2025

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Investigator's Choice Chemotherapy in Participants With Microsatellite Instability High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer		
NCT02997228	Colorectal Cancer Metastatic dMMR/MSI-H Immuno-Therapy (COMMIT) Study: A Randomized Phase III Study of mFOLFOX6/Bevacizumab/Atezolizumab Combination Versus Single Agent Atezolizumab in the First-Line Treatment of Patients With Deficient DNA Mismatch Repair (dMMR)/Microsatellite Instability-High (MSI-H) Metastatic Colorectal Cancer	231	Nov 2024
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

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; variants in exon 2 (e.g., codons 12 and 13)
81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; additional variant(s) (e.g., codon 61, codon 146)
81301	Microsatellite instability analysis (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (e.g., BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (e.g., colorectal carcinoma), gene analysis, variants in exon 2 (e.g., codons 12 and 13) and exon 3 (e.g., codon 61)
88363	Examination and selection of retrieved archival (i.e., previously diagnosed) tissue(s) for molecular analysis (e.g., KRAS mutational analysis)
0111U	Oncology (colon cancer), targeted KRAS (codons 12, 13 and 61) and NRAS (codons 12, 13 and 61) gene analysis utilizing formalin-fixed paraffin-embedded tissue
0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations (FoundationOne® Liquid CDx from Foundation Medicine)
0242U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements
0338U	Oncology (solid tumor), circulating tumor cell selection, identification, morphological characterization, detection and enumeration based on differential EpCAM, cytokeratins 8, 18, and 19, and CD45 protein biomarkers, and quantification of HER2 protein biomarker–expressing cells, peripheral blood. CellSearch® HER2 Circulating Tumor Cell

ICD-10 DIAGNOSES	
C18.0-C18.9	Malignant neoplasm of colon code range
C19	Malignant neoplasm of rectosigmoid junction

ICD-10 DIAGNOSES	
C20	Malignant neoplasm of rectum
C78.5	Secondary malignant neoplasm of large intestine and rectum

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07-10-2015	Policy added to the bcbsks.com web site on 06-10-2015 with an effective date of 07-10-2015.
01-01-2016	In Coding section: ▪ Added CPT codes: 81276, 81311. ▪ Revised nomenclature of codes: 81210, 81275.
08-29-2016	Updated Description section.
	In Policy section: ▪ In Item B, removed "experimental / investigational", "to", "and", and "in the treatment of metastatic colorectal cancer" and added "medically necessary", "for patients with", "prior to planned therapy with", and "or" to read "*NRAS* mutation analysis is considered medically necessary for patients with metastatic colorectal cancer to predict nonresponse prior to planned therapy with anti-EGFR monoclonal antibodies cetuximab or panitumumab."
	Updated Rationale section.
	In Coding section: ▪ Removed CPT codes: 81403, 81404.
	Updated References section.
01-30-2018	Updated Policy title from "KRAS, NRAS, and BRAF Mutation Analysis in Metastatic Colorectal Cancer" to "KRAS, NRAS, and BRAF Variant Analysis in Metastatic Colorectal Cancer."
	Updated Description section.
	In Policy section: ▪ In Item A, removed "mutation" and added "variant" and "epidermal growth factor" to read, "*KRAS* variant analysis may be considered medically necessary for patients with metastatic colorectal cancer to predict nonresponse prior to planned therapy with anti-epidermal growth factor (EGFR) monoclonal antibodies cetuximab or panitumumab." ▪ In Item B, removed "mutation" and "is" and added "variant" and "may be" to read, "*NRAS* variant analysis may be considered medically necessary for patients with metastatic colorectal cancer to predict nonresponse prior to planned therapy with anti-EGFR monoclonal antibodies cetuximab or panitumumab. ▪ In Item C, removed "mutation", "is", "experimental/investigational", and "to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer" to read, "*BRAF* variant analysis may be is considered medically necessary for patients with metastatic colorectal cancer who are found to be wild-type on *KRAS* and *NRAS* variant analysis to guide management decisions." ▪ Added Policy Guidelines.
	Updated Rationale section.
	In Coding section: ▪ Removed ICD-9 codes.
	Updated References section.
	Added Appendix section.
08-29-2018	Updated Description section.
	Updated Rationale section.

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	Updated References section.
	Removed Appendix.
09-27-2019	Policy published to the bcbsks.com website on 08-28-2019 with an effective date of 09-27-2019.
	Updated Description section.
	In Policy section: ▪ Added new Item D, "*KRAS, NRAS,* and *BRAF* variant analysis using circulating tumor DNA or circulating tumor cell testing (liquid biopsy) to guide treatment for patients with metastatic colorectal cancer is considered experimental / investigational."
	Updated Rationale section.
	In Coding section: ▪ Added CPT codes: 86152, 86153, 0069U. ▪ Removed coding bullets.
	Updated References section.
10-01-2019	In Coding section: ▪ Added PLA code: 0111U
04-30-2021	Updated Description section
	Updated Rationale section
	In Coding section: • Removed CPT codes 86152 and 86153 • Added CPT code 0242U
	Updated References section
	Added Appendix 1 and 2
10-10-2021	Changed Title from "KRAS, NRAS, and BRAF Variant Analysis in Metastatic Colorectal Cancer" to "Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer"
	Updated Description section.
	In Policy section: ▪ Added Items C, D, and F. ▪ Added "as well as Mismatch repair/microsatellite instability (MMR/MSI) testing," to Item G
	Updated Rationale section.
	In Coding section: ▪ Added code CPT code: 81301 ▪ Removed CPT code: 0069U
	Updated References section.
09-22-2022	Changed Title to: ▪ "Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer (KRAS, NRAF, BRAF, MMR/MSI, HER2, and TMB)"
	Updated Description Section
	Updated Policy Section: ▪ Section A: Added "of tumor tissue" and "to select individuals for treatment with FDA-approved therapies. Removed: "to predict nonresponse prior to planned therapy with anti-epidermal growth factor receptor (EGFR) monoclonal antibodies cetuximab or panitumumab" o Reads: "*KRAS* variant analysis of tumor tissue may be considered medically necessary for individuals with metastatic colorectal cancer to select individuals for treatment with FDA-approved therapies;" ▪ Section B: Added "of tumor tissue" and "to select individuals for treatment with FDA-approved therapies. Removed: "to predict nonresponse prior to planned

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	therapy with anti-epidermal growth factor receptor (EGFR) monoclonal antibodies cetuximab or panitumumab" ○ Reads: "*NRAS* variant analysis of tumor tissue may be considered medically necessary for individuals with metastatic colorectal cancer to select individuals for treatment with FDA-approved therapies. ▪ Section C: Added "of tumor tissue" and "to select individuals for treatment with FDA-approved therapies. ○ Reads: "*BRAF* variant analysis of tumor tissue may be considered medically necessary for individuals with metastatic colorectal cancer who are found to be wild-type on *KRAS* and *NRAS* variant analysis to guide management decisions and to select individuals for treatment with FDA-approved therapies." ▪ Section D: Added "of tumor tissue" and "to select individuals for treatment with FDA-approved therapies. Removed "predict treatment response to pembrolizumab (Keytruda): 1. for first-line treatment of patients with unresectable or metastatic colorectal cancer; OR 2. in patients with colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; OR 3. in patients with colorectal cancer tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. ○ Reads: "Mismatch repair/microsatellite instability (MMR/MSI) testing of tumor tissue may be considered medically necessary to select individuals for treatment with FDA-approved therapies." ▪ Added: ○ "All other uses of *KRAS* variant testing of tumor tissue to guide colorectal cancer targeted therapy or immunotherapy are considered experimental / investigational." ○ "All other uses of *NRAS* variant testing of tumor tissue to guide colorectal cancer targeted therapy or immunotherapy are considered experimental / investigational." ○ "All other uses of *BRAF* variant testing of tumor testing to guide colorectal cancer targeted therapy or immunotherapy are considered experimental / investigational. ○ "Other uses of mismatch repair/microsatellite instability variant testing of colorectal tumor tissue for guiding targeted therapy or immunotherapy are considered experimental / investigational." ○ "Circulating tumor DNA testing (liquid biopsy) to guide treatment in patients with metastatic colorectal cancer is considered experimental / investigational." ▪ Removed: ○ "*KRAS, NRAS,* and *BRAF* variant analysis, as well as Mismatch repair/microsatellite instability (MMR/MSI) testing, using circulating tumor DNA or circulating tumor cell testing (liquid biopsy) to guide treatment for patients with metastatic colorectal cancer is considered experimental / investigational." *Formatting order (A-K) has changed due to additions and removal of policy statements
	Updated Policy Guideline Section ▪ Removed: ○ "There is support from the evidence and clinical input to use BRAF V600 variant testing for prognostic stratification. " ○ "It is uncertain whether the presence of a BRAF V600 variant in patients with metastatic colorectal cancer who are wild-type on KRAS and NRAS

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	variant analysis is predictive of response to anti-epidermal growth factor receptor therapy. Furthermore, there is mixed opinion in clinical guidelines and clinical input on the use of BRAF variant analysis to predict response to treatment. " ▪ Added: ○ "Testing for other variants may become available between policy updates. For guidance on testing criteria between policy updates, refer to the FDA's List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) (https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools) for an updated list of FDA-approved tumor markers and consult the most current version of National Comprehensive Cancer Network (NCCN) management algorithms."
	Updated Rationale Section
	Updated Coding Section ▪ Added 0239U ▪ Converted ICD-10 codes to ranges
	Updated References Section
	Removed Appendix Section
10-28-2022	Updated Coding Section ▪ Added 0338U (effective 10-01-2022)

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