BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.53 Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, and HER2)

Effective Policy Date: October 1, 2023

Original Policy Date: March 2012

Related Policies:

2.04.08 - Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
2.04.115 - Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies
2.04.141 - Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)
2.04.61 - Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer
5.21.138- Enhertu (fam-trastuzumab deruxtecan-nxkl)
5.21.50- Keytruda (pembrolizumab) 5.21.110- Braftovi (encorafenib)
5.21.84- Erbitux (cetuximab) 5.21.85-Vectibix (panitumumab)

Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, and HER2)

Description

Description

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

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

Human Epidermal Growth Factor Receptor 2 Amplification/Overexpression

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

Detecting Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy)

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

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

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

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

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

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

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

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

Manufacturer	Test	Type of Liquid Biopsy
Biocept	Target Selector™ ctDNA EGFR Kit	ctDNA
Foundation Medicine	FoundationOne Liquid (Previously FoundationAct)	ctDNA
Guardant Health	Guardant360®	ctDNA
IV Diagnostics	Velox™	CTC
Personal Genome Diagnostics	PlasmaSELECT™	ctDNA
Sysmex Inostics	OncoBEAM	ctDNA
Circulogene	Theranostics	ctDNA

CTC: circulating tumor cell; ctDNA: circulating tumor DNA.

OBJECTIVE

The objective of this review is to summarize the evidence and guidelines on using biomarker testing to select treatment with FDA approved targeted therapy for individuals with metastatic CRC. This policy does not address neurotrophic tyrosine receptor kinase (*NTRK*) testing.

POLICY STATEMENT

KRAS, NRAS, BRAF, or HER2 testing of tumor tissue may be considered **medically necessary** for individuals with metastatic colorectal cancer to select individuals for treatment with FDA-approved therapies.

All other uses of *KRAS, NRAS, BRAF,* or HER2 testing of tumor tissue to guide colorectal cancer targeted therapy are considered **investigational**.

Circulating tumor DNA testing (liquid biopsy) to guide treatment in individuals with metastatic colorectal cancer is considered **investigational**. (see Policy Guidelines)

POLICY GUIDELINES

The NCCN colon cancer guidelines v.2.2023 and rectal cancer guidelines v. 2.2023 do not recommend testing for specific genes over a next generation sequencing panel. The guidelines additionally state that testing may be performed using either tissue or blood-based biopsy, with testing on tissue being preferred.

For expanded panel testing, see evidence review 2.04.115.

Testing for other variants may become available between policy updates.

Testing for individual genes (not gene panels) associated with FDA-approved therapeutics for therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher are not subject to extensive evidence review. Note that while the FDA approval of companion diagnostic tests for genes might include tests that are conducted as panels, the FDA approval is for specific genes (such as driver mutations) and not for all of the genes on the test panel.

For somatic biomarker testing related to use of immune checkpoint inhibitor therapy (*BRAF,* microsatellite instability/mismatch repair [MSI/MMR], PD-L1, tumor mutational burden [TMB]), see evidence review 2.04.157.

.Note that TMB is often included in panel tests, and might not have separate coding; Plans with coverage for panels might consider local decision for TMB.

FDA approves tests in between policy review cycles. As such, newly approved tests might need to be considered per local Plan discretion. For guidance on testing criteria between policy updates, refer to the FDA's List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) (https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools) for an updated list of FDA-approved tumor markers and consult the most current version of NCCN management algorithms.

Note: Extensive evidence review is not included for somatic tests of individual genes (not gene panels) associated with U.S. Food and Drug Administration (FDA)-approved therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher. The pivotal evidence is included in Table 1 for informational purposes. Additionally, no evidence review is provided for somatic tests of individual genes that do not have associated FDA-approved therapies regardless of National Comprehensive Cancer Network (NCCN) recommendations, as these off-label therapies are deemed investigational per the Blue Cross and Blue Shield Association Medical Policy Program Policies and Procedures.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Some Plans may have contract or benefit exclusions for genetic testing.

FDA REGULATORY STATUS

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

In June 2022, FDA granted accelerated approval to 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	Pivotal Study	NCCN Recommendation Level/Guideline
Cetuximab (Erbitux)	*KRAS* wild-type, EGFR-expressing, metastatic colorectal cancer as determined by an FDA-approved test • in combination with FOLFIRI for first-line treatment, • 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 ONCO/Reveal Dx Lung & Colon Cancer Assay xT CDx	4, 5,	2A or higher/ Metastatic Colorectal Cancer (v.2.2023) [6,]
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	7,	2A or higher/ Metastatic Colorectal Cancer (v.2.2023) [6,]
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) xT CDx	8,	2A or higher/ Metastatic Colorectal Cancer (v.2.2023) [6,]
Tukysa(Tucatinib)	Treatment of adult patients with unresectable or metastatic CRC with *RAS* wild-type HER2-positive • In combination with Trastuzumab (Herceptin) • Previously treated with flouropyrimidine, oxaliplatin, and irinotecan-based chemotherapy	No FDA-approved companion diagnostic	9,	2A or higher/ Metastatic Colorectal Cancer (v.2.2023) [6,]

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

Laboratory-Developed Tests

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

RATIONALE

Summary of Evidence

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

For individuals with 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 overall survival (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

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.[16,] Table 3 summarizes the relevant guidelines.

Table 3. Summary of Recommendations

Guidelines	Type	SOE	QOE
Colorectal carcinoma patients being considered for anti-EGFR therapy must receive RAS mutational testing. Mutational analysis should include KRAS and NRAS codons 12, 13 of exon 2; 59, 61 of exon 3; and 117 and 146 of exon 4 ("expanded" or "extended" RAS)	Recommendation	Convincing/adequate, benefits outweigh harms	High/intermediate
BRAF p.V600 (BRAF c. 1799 (p.V600) mutational analysis should be performed in colorectal cancer tissue in patients with colorectal 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.2.2023).[6,] 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).

Human Epidermal Receptor 2 Testing

The guidelines recommend testing for human epidermal receptor 2 (HER2) amplifications for patients with metastatic colorectal cancer. Anti-HER2 therapy is only indicated in HER2-ampliified tumors that are also RAS and BRAF wild type. If the tumor is already known to have a *KRAS/NRAS* or *BRAF* mutation, HER2 testing is not indicated.(Category 2A). HER2 testing is performed via immunohistochemistry (IHC) with some results requiring reflex to fluorescence in situ hybridization (FISH); and, next-generation sequencing (NGS) is another methodology endorsed for testing for HER2 amplification.

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 (eg, liquid) biopsy, although tissue based testing is preferred.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

A March 2018 decision memo from the Centers for Medicare & Medicaid Services addressed next-generation sequencing for Medicare beneficiaries with advanced cancer.[17,] The memo states:

The Centers for Medicare & Medicaid Services has determined that Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally when performed in a CLIA-certified laboratory, when ordered by a treating physician and when all of the following requirements are met:

1. Patient has:

    a. either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and

    b. either not been previously tested using the same NGS test for the same primary diagnosis of cancer or repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physician; and

    c. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

2. The diagnostic laboratory test using NGS must have:

    a. FDA [U.S. Food and Drug Administration] approval or clearance as a companion in vitro diagnostic; and

    b. an FDA [U.S. Food and Drug Administration] approved or cleared indication for use in that patient's cancer; and

    c. results provided to the treating physician for management of the patient using a report template to specify treatment options.

Regarding liquid biopsies, the memo states, "The NCD does not limit coverage to how to prepare a sample for performing a diagnostic laboratory test using NGS. Commenters submitted published articles on liquid biopsies (also referred to as circulating tumor DNA (ctDNA) or plasma cell-free DNA (cfDNA) tests). We reviewed and included in the evidence and analysis of 4 studies on liquid biopsies. At this time, liquid-based multi-gene sequencing panel tests are left to contractor discretion if certain patient criteria are met."[17,]

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
March 2012	New policy	
March 2013	Replace policy	Policy updated with literature review, Reference 14 added, policy statements unchanged
March 2014	Replace policy	Policy updated with literature review. No references added. Policy statements unchanged except for minor wording change in statement on KRAS testing
March 2015	Replace policy	Policy updated with literature review. References 20-24, 38 added. Title change indicate inclusion of NRAS testing to the policy; NRAS testing policy statement added as investigational to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab panitumumab in the treatment of metastatic colorectal cancer
March 2018	Replace policy	Policy updated with literature review through June 2, 2017; reference 1, 2-4, 21-22, 28, and 42-43 and 46 added. Policy revised with updated genetics nomenclature. Policy statement revised to indicate that NRAS testing policy statement added as medically necessary to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer. Policy statement revised to indicate that BRAF variant analysis 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. KRAS policy statement unchanged. Title changed to "KRAS, NRAS, and BRAF Variant Analysis in Metastatic Colorectal Cancer,.
September 2018	Replace policy	Policy updated with literature review through May 10, 2018; no references added. Policy statements unchanged
September 2019	Replace policy	Policy updated with literature review through May 29, 2019; references added. Indication 4 (KRAS, NRAF, and BRAF variant analysis using circulating tumor DNA or circulating tumor cell testing [liquid biopsy] to guide treatment) removed from policy 2.01.141 and inserted here. Policy statement for Indication 4 added: "KRAS, NRAF, and BRAF variant analysis using circulating tumor DNA or circulating tumor cell testing (liquid biopsy) to guide treatment for patients with metastatic colorectal cancer is considered investigational." Title changed to include liquid biopsy.
September 2020	Replace policy	Policy updated with literature review through June 15, 2020; no references added. Policy statements unchanged.
September 2021	Replace policy	Policy updated with literature review through June 18, 2021; references added. Added new indications for MMR/MSI, HER2, and TMB testing. MMR/MSI testing may be considered medically necessary; HER2 and TMB testing is investigational. Other policy statements unchanged. Title changed to reflect additions.

Date	Action	Description
September 2022	Replace policy	Policy updated with literature review through June 13, 2022; references added. Rationale section extensively revised. Extensive evidence review is not included for somatic tests of individual genes (not gene panels) associated with U.S. Food and Drug Administration (FDA)-approved therapeutics (ie, as companion diagnostic tests) for therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher. MN statement on BRAF variant testing expanded to include selecting individuals for treatment with FDA-approved therapies. Title changed to specify somatic testing and to list the specific biomarkers included.
September 2023	Replace policy	Policy updated with literature review through May 30, 2023. Policy extensively pruned: Extensive evidence review is not included for somatic tests of individual genes (not gene panels) associated with FDA approved therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher; indications related to immunotherapy and tumor mutational burden testing removed and added to new policy 2.04.157. Policy statement revised to Medically Necessary for testing for HER2 in individuals with metastatic colorectal cancer to select individuals for targeted treatment. Information pertaining to immunotherapy was moved to policy 2.04.157.