Prior Authorization Review Panel
MCO Policy Submission

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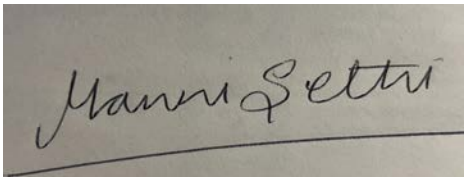
Plan: AmeriHealth Caritas Pennsylvania Community HealthChoices	**Submission Date**: 9/1/2023
Policy Number: CCP.1468	**Effective Date:** 9/2020 **Revision Date:** August 1, 2023
Policy Name: Molecular analysis for targeted therapy for colorectal cancer	
Type of Submission – Check all that apply: **New Policy** **X Revised Policy*** **Annual Review – No Revisions** **Statewide PDL**	
***All revisions to the policy must be highlighted using track changes throughout the document.** **Please provide any clarifying information for the policy below:** See tracked changes below.	
Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Molecular analysis for targeted therapy for colorectal cancer

Clinical Policy ID: CCP.1468

Recent review date: 8/2023

Next review date: 12/2024

Policy contains: Colorectal cancer, molecular analysis, targeted therapy

AmeriHealth Caritas Pennsylvania Community HealthChoices has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by AmeriHealth Caritas Pennsylvania Community HealthChoices when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania Community HealthChoices will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are not guarantees of payment.

Coverage policy

As the landscape of targeted therapies is rapidly evolving, molecular analysis for targeted therapy for colorectal cancer is clinically proven and, therefore, may be medically necessary for indications specified in National Comprehensive Cancer Network (2023a, 2023b) clinical practice guidelines and U.S. Food and Drug Administration-approved package labeling for indication and usage.

Validated molecular testing should be performed in a Clinical Laboratory Improvement Amendments-approved laboratory or by a U.S. Food and Drug Administration-approved companion diagnostic test for the following biomarkers, when all of the following criteria are met (National Comprehensive Cancer Network, 2023a, 2023b; U.S. Food and Drug Administration, 2023):

- The cancer has metastasized from the original site in the colon and/or rectum.
- Any of the following testing indications:
- *KRAS*/*NRAS* and *BRAF* V600E mutations, to predict non-response to cetuximab and panitumumab, using a U.S. Food and Drug Administration-approved companion diagnostic.
- *BRAF* mutation, to predict response to encorafenib, using a U.S. Food and Drug Administration-approved companion diagnostic.
- Microsatellite instability/deoxyribonucleic acid mismatch repair to predict response to programmed cell death protein 1 immune checkpoint inhibitors nivolumab, ipilimumab, and pembrolizumab. A U.S. Food and Drug Administration-approved companion diagnostic tests exists for pembrolizumab only.

- *HER2* amplification, if the *KRAS/NRAS* and *BRAF* mutation status is unknown, to predict response to kinase inhibitors.
- Neurotrophic tyrosine receptor kinase fusion for *RAS/BRAF*-wild type tumors to predict treatment response to larotrectinib, using a U.S. Food and Drug Administration-approved companion diagnostic.
- Neurotrophic tyrosine receptor kinase fusion for *RAS/BRAF*-wild type tumors to predict treatment response to entrectinib.
- *RET* gene fusion to predict treatment response to selpercatinib.

For medical necessity determinations of medications, refer to the applicable state approved pharmacy policy.

Limitations

Molecular testing and analysis for targeted therapy for colorectal cancer are investigational/not clinically proven for any mutation other than the ones listed in the Coverage section (above).

Alternative covered services

No alternative covered services were identified during the writing of this policy.

Background

Despite decades-long declines in incidence and mortality — primarily due to better detection of precancerous polyps after colonoscopy and other diagnostic procedures — colorectal cancer is still a common disorder. In the United States, an estimated 151,020 new cases of colorectal cancer and 52,550 new deaths from the disease will occur in 2023. Survival from colorectal cancer is highly dependent on the disease's stage. While the five-year survival in U.S. cases diagnosed from 2011 to 2017 was 91% for localized cases and 73% for regional cases, it was just 14% for distant (metastatic) cancers (American Cancer Society, undated).

Stage 1 – 2 colorectal cancer is treated with surgery or colectomy/lymphadenectomy, while stage 3 is treated with surgery and adjuvant chemotherapy. For stage 4 (metastatic) cancers, chemotherapy has been the standard treatment. In an effort to improve the low survival prospects for metastatic disease, targeted therapies have been developed in the past two decades for cancers with certain genetic variants (Bai, 2017).

Targeted therapies approved by the U.S. Food and Drug Administration for advanced colorectal cancer include the following (American Cancer Society, 2023):

- Bevacizumab (Avastin®), approved in 2004, anti-vascular endothelial growth factor therapy.
- Cetuximab, approved in 2004, anti-epidermal growth factor receptor therapy.
- Panitumumab, approved in 2006, anti-epidermal growth factor receptor therapy.
- Regorafenib (Stivarga®), approved in 2012, multikinase inhibitor, which inhibits vascular endothelial growth factor.
- Ramucirumab (Cyramza®), approved in 2015, anti-vascular endothelial growth factor therapy.
- Ziv-aflibercept (Zaltrap®), called aflibercept outside the United States, approved in 2004, anti-vascular endothelial growth factor therapy.
- Cetuximab/Encorafenib combination, approved in 2020, anti-vascular endothelial growth factor therapy. Larotrectinib, approved in 2018, a kinase inhibitor.
- Entrectinib, approved in 2019, for treating neurotrophic tyrosine receptor kinase gene fusion-positive solid tumors.
- Regorafenib, approved in 2013, a kinase inhibitor.
- For treating HER2-positive colorectal cancer:
- Trastuzumab.
- Pertuzumab.

- Tucatinib.
- Lapatinib.
- Fam-trastuzumab deruxtecan.

Immunotherapy drugs for advanced colorectal cancer have been developed for tumor with high levels of microsatellite instability or deficient mismatch repair, which are biomarkers that keep cells from repairing damaged deoxyribonucleic acid. Testing for these abnormalities must be performed before selecting patients who are candidates for treatment.

The U.S. Food and Drug Administration has approved immunotherapy drugs for patients with high levels of these biomarkers, all of which are administered intravenously, namely (American Cancer Society, 2020):

- Nivolumab, approved in 2017, for microsatellite instability – high or deficient mismatch repair tumors failing chemotherapy,
- Ipilimumab, approved in 2018, for microsatellite instability – high or deficient mismatch repair tumors failing chemotherapy.
- Pembrolizumab, approved in 2017, for microsatellite instability – high or deficient mismatch repair tumors, all origins.

Several companion diagnostic tests have been approved for predicting response to targeted therapies in metastatic colorectal cancer. Tests to determine candidacy for cetuximab and panitumumab include: Foundation One® CDx, Praxis Extended RAS Panel (only panitumumab); cobas® KRAS Mutation Test; therascreen KRAS RGQ PCR Kit; Therascreen BRAF V600E RGQ PCR Kit; EGFR pharmDx™ Kit for Dako Autostainer; and ONCO/Reveal Dx Lung & Colon Cancer Assay (U.S. Food and Drug Administration, 2023).

In addition, the *therascreen* BRAF V600E RGQ PCR Kit has been approved for determining encorafenib candidacy, and the FoundationOne CDx diagnostic test has been approved for determining larotrectinib candidacy (U.S. Food and Drug Administration, 2023).

Findings

The American Society for Clinical Oncology's updated guideline includes recommended testing for *KRAS* and *NRAS* exons 2 (codons 12 and 13), 3 (codons 59 and 61), and 4 (codons 117 and 146) (extended *RAS* testing) (Allegra, 2016).

The Society's latest guideline also includes recommended testing for the *BRAF V600E* mutation to support frontline treatment decision-making for metastatic colorectal cancer. Other biomarkers for targeted therapy include mismatch repair or multi-satellite instability and *HER2* amplification (Lieu, 2019).

The National Comprehensive Cancer Network recommendations for molecular testing for targeted therapy provision generally align with approved regulatory indications for use and continue to evolve as knowledge of molecular testing and targeted treatments evolves (National Comprehensive Cancer Network, 2023a, 2023b).

A guideline from the American Society for Clinical Pathology and three other groups also recommends testing metastatic colorectal cancer patients for *KRAS*/*NRAS* and *BRAF* V600E mutations (Sepulveda, 2017).

Accuracy of testing

A systematic review of five studies of metastatic colorectal cancer found no difference in treatment outcomes regardless of which type of molecular test was used (Westwood, 2014). A systematic review/meta-analysis of 19 studies (n = 1,810) of detecting circulating tumor deoxyribonucleic acid in metastatic colorectal cancer showed sensitivity and specificity were 0.83 and 0.91, respectively. Pooled positive and negative predictive value were both 0.87 (Galvano, 2019).

In a sample of 10 along with controls, the next-generation Praxis Extended molecular test was found to clearly distinguish single-stranded artifacts from low-frequency mutations. The assay was accurate, precise, and reproducible, achieved consistent detection of a mutation at 5% mutation frequency, exhibited minimal impact from tested interfering substances, and can simultaneously detect 56 mutations in a single run (Udar, 2020).

A study of 156 colorectal cancer samples tested by the cobas *KRAS* mutation test revealed that the incidence of *KRAS*, *NRAS*, and *BRAF* mutations were 41.0%, 9.6%, and 8.3%, respectively (Ta, 2020). Another study of cobas mutation testing of 163 colorectal cancers, compared to existing results from a hospital pathology laboratory, identified a 98.7% positive correlation and a 93.1% negative correlation (Albertini, 2017).

In a review of 461 cases of advanced colorectal cancer, the cobas test and therascreen test had invalid results for 5.2% and 10.8% of specimens, respectively. *KRAS* mutation-positive rates were similar for the two methods, i.e., 37.3% and 36.3%, respectively. Positive and negative percent agreement were 96.9% and 88.7%, respectively. Thus, accuracy of the two methods were similar (Sharma, 2016).

A systematic review/meta-analysis of 12 studies of *KRAS* mutation testing in colorectal cancer revealed pooled sensitivity and specificity of 83% and 91%, respectively. Authors commented that the number of studies as "quite small" (Ye, 2020).

Survival and other outcomes for targeted therapies are often statistically superior to those for standard chemotherapy, but typically the additional survival is measured in months. Reviews cited by the U.S. Food and Drug Administration approvals are given below.

Targeted therapy

Bevacizumab. A review of 2,526 patients given first-line combination chemotherapy were randomized into groups with and without bevacizumab. Median overall survival was significantly (P = .003) greater for the group with bevacizumab (19.0 months versus 15.9 months). The risk of stroke within six months of treatment was nearly twice as high (4.9% versus 2.5%) than for the combination group (Meyerhardt, 2012).

Cetuximab. A systematic review of 12 studies (n = 7,108) compared chemotherapy with and without cetuximab for advanced colorectal cancer. The chemotherapy alone group had significantly shorter overall survival (P < .00001), progression free survival (P = .03), and overall response rate (P = .0003) than the combination group (Li, 2020).

Panitumumab. A meta-analysis of five randomized controlled trials (n = 4,155) showed that compared with controls, panitumumab is associated with higher objective response in colorectal cancer patients with wild-type (P = .03), with no significant difference from controls for mutant *KRAS* (P = .32). Grade 3 and 4 adverse events were significantly higher in the panitumumab group than in controls (P = .0001) (Wang, 2020).

Regorafenib. A trial included 753 patients failing standard chemotherapy who were randomized to receive regorafenib or placebo. Median overall survival was higher in the regorafenib group (6.4 versus 5.0 months, P = .0052). Treatment-related adverse events occurred in 93% and 61% of those assigned to the regorafenib and placebo groups (Grothey, 2013). A systematic review/meta-analysis of seven randomized trials (n = 2,099) showed that, compared with placebo, the drug was associated with higher incidences of permanent discontinuation (9.7% versus 3.3%), dose interruptions (57.2% versus 16.7%), and dose reductions (47.0% versus 7.7%) (Rizzo, 2020).

Ramucirumab. A trial of 1,072 patients who had progressed after first-line treatment compared those given standard chemotherapy with ramucirumab versus those given standard chemotherapy. Median overall survival was greater for the ramucirumab group (13.3 months versus 11.7 months, P = .0219) (Tabernero, 2015).

Ziv-aflibercept. A study of 1,226 patients unsuccessfully treated with standard chemotherapy were randomized to receive chemotherapy of leucovorin calcium, fluorouracil, and irinotecan hydrochloride, plus aflibercept or placebo every two weeks. The median overall survival was greater for aflibercept patients in those with prior bevacizumab (12.5 months versus 11.7 months), and in those with no prior bevacizumab (13.9 months versus 12.4 months) (Tabernero, 2014).

A meta-analysis of 31 studies (n = 25,939) analyzed fatal adverse event rates for bevacizumab, cetuximab, and panitumumab in patients with colorectal cancer. No significantly increased risk ratios were observed for first line and second/further line treatments for bevacizumab (*P* = .61 and *P* = .71); for cetuximab (*P* = .93 and *P* = .27); and for panitumumab (*P* = .14 and *P* = .11) (Chen, 2020).

A systematic review/meta-analysis of 12 articles (n = 6,805), found regorafenib had a greater progression-free survival than aflibercept, ganitumab, panitumumab, and ramucirumab. Regorafenib also had greater tumor response than bevacizumab and performed better in reducing grade ≥ 3 adverse events than cetuximab and conatumumab. Authors state that combining regorafenib with chemotherapy might be a second-line treatment for the disorder (Xie, 2020).

A network meta-analysis of eight randomized trials (n = 3,832) found no differences in overall survival and progression-free survival between regorafenib, fruquintinib, panitumumab and cetuximab although they were each superior to placebo (Cao, 2020).

Immunotherapy

Pembrolizumab. A study randomized 124 patients who had at least one or two prior lines of standard chemotherapy. Each patient was given 200 milligrams of pembrolizumab every three weeks. Median response rate was 33% for both groups. Median progression-free survival was 2.3 months and 4.1 months, respectively, and median overall survival was 31.4 months for the entire group (Le, 2019).

Nivolumab. A review of 74 patients who had progressed after at least one line of treatment were given nivolumab every two weeks. At follow-up (median 12.0 months), 31% of patients had achieved an objective response, and 69% had disease control of 12 weeks or longer, with 11% over 12 months (Overman, 2017).

Ipilimumab. A study of 119 patients with at least two prior systemic therapies were given nivolumab plus ipilimumab every three weeks (total four doses), followed by nivolumab every two weeks. At 12 months, progression-free survival was 71% and overall survival was 85% (Overman, 2018).

A meta-analysis of monotherapy using anti-PD-1 inhibitors in treating metastatic colorectal cancer identified, after one year, an overall survival rate of 64.2%, a progression-free survival rate of 38.4%, a disease control rate of 56.5%, and an objective response rate of 19.7% (He, 2020).

As drugs used in immunotherapy for metastatic colorectal cancer have only been approved by the U.S. Food and Drug Administration starting in 2017, and because immunotherapy for the disease has yet to be considered clinically proven, testing and treatment remain in the early phases, with limited available results.

In 2022, we updated the coverage criteria based on guideline recommendations for molecular testing and new targeted therapy provision for advanced colon and rectal cancers. We added the following molecular testing indications to the coverage section (National Comprehensive Cancer Network, 2022a, 2022b):

- *HER2* testing is recommended for *HER2*-targeted therapies, unless the *RAS/BRAF* mutation status of the tumor is already known. Although *HER2* is rarely overexpressed in colorectal cancer, the prevalence is higher *RAS/BRAF*-wild type tumors. *HER2*-targeted therapies are recommended in patients with tumors that *RAS/BRAF*-wild type and have *HER2* overexpression.
- Micro-satellite instability/deoxyribonucleic acid mismatch repair is an established test for predicting response to programmed cell death protein 1 immune checkpoint inhibitors (e.g., pembrolizumab,

nivolumab, or ipilimumab). The FoundationOne CDx test is approved for predicting response to pembrolizumab.
- Neurotrophic tyrosine receptor kinase fusion occurs infrequently in colorectal cancer and only in *RAS/BRAF*-wild type tumors. Limited testing of neurotrophic tyrosine receptor kinase fusion may be indicated in patients with *RAS/BRAF*-wild type tumors to predict treatment response to tyrosine kinase inhibitors (e.g., larotrectinib or entrectinib). The FoundationOne CDx diagnostic test is approved for predicting response to larotrectinib.

We added a new indication for the companion diagnostic therascreen BRAF V600E RGQ PCR Kit for predicting response to encorafenib (U.S. Food and Drug Administration, 2022).

In 2023, we updated the references and added a new medically necessary indication. The National Comprehensive Cancer Network (2023a, 2023b) recommends selpercatinib for adult patients with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options. Molecular testing may be carried out by either a tissue or blood-based biopsy. No U.S Food and Drug Administration-approved companion diagnostic has been approved specifically for detecting *RET* gene fusion in colorectal tumor tissue.

References

On June 12, 2023, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “colorectal neoplasms (MeSH),” “molecular diagnostic techniques (MeSH),” “colorectal cancer,” and “targeted therapy.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

8/2020: initial review date and clinical policy effective date: 9/2020.

8/2021: Policy references updated.

8/2022: Policy references updated. Coverage modified.

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