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Corporate Medical Policy

Testing for Colorectal Cancer Management AHS - M2026

File Name: testing_for_colorectal_cancer_management
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Description of Procedure or Service

Colorectal cancer (CRC) involves the accumulation of genetic and epigenetic modifications within pathways that regulate proliferation, apoptosis, and angiogenesis resulting in carcinoma of the colon and rectum (Bardhan & Liu, 2013). Tumors originate in adenomas or flat dysplasia and evolve into different morphologic patterns with invasion and expansion (Compton, 2023).

Monoclonal antibodies that bind the epidermal growth factor receptor (EGFR), such as cetuximab, and block its activation have led to significant clinical benefits for metastatic colorectal cancer (mCRC) patients (De Roock et al., 2010). Mutations in downstream effectors of the EGFR pathway have been associated with resistance to EGFR antibody chemotherapies (Allegra et al., 2009; Compton, 2022; Sepulveda et al., 2017).

Related Policies
Lynch Syndrome AHS-M2004
Genetic Testing for Polyposis Syndromes AHS-M2024
Genetic Cancer Susceptibility Using Next Generation Sequencing AHS-M2066
Microsatellite Instability and Tumor Mutational Burden Testing AHS-M2178

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for testing for colorectal cancer management when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Testing for Colorectal Cancer Management is covered

1. For all individuals with metastatic colorectal cancer, *KRAS, NRAS* and *BRAF* mutation genotyping of the primary or the metastatic tumor is considered medically necessary.

2. For individuals with metastatic colorectal cancer for whom tumor tissue testing did not identify a mutation in *KRAS, NRAS* **or** *BRAF*, HER2 amplification testing is considered medically necessary.

When Testing for Colorectal Cancer Management is not covered

For all other situations, not described above, testing for *KRAS, NRAS* and *BRAF* is considered investigational.

To determine the prognosis of stage II colon cancer following surgery, gene expression profiling is considered investigational.

Note: For 5 or more gene tests being run on the same platform, please refer to AHS-R2162 Reimbursement Policy.

Policy Guidelines

Colorectal cancer (CRC) is the third leading cause of cancer-related deaths in the United States following lung cancer. The American Cancer Society (ACS) estimates 106,180 new cases of colon cancer and 44,850 new cases of rectal cancer for 2022. Overall, there is a 4% lifetime risk of developing colorectal cancer (ACS, 2023). Metastatic colorectal cancer (mCRC), which occurs in 22% of patients with colorectal cancer, has a significantly poorer prognosis than colorectal cancer that hasn't metastasized. The five-year survival is 14% in patients with distant metastases from CRC, as compared to 71% for all CRC patients (El-Deiry et al., 2015; Wang et al., 2020).

Approximately one-quarter of the patients with colon cancer present with stage II disease (Kopetz, 2008). The current National Comprehensive Cancer Network (NCCN) guidelines include adjuvant chemotherapy as a treatment option in this setting, particularly for high-risk stage II patients, as determined by clinical and pathological parameters (NCCN, 2023b). Although some of the routinely used parameters for estimating recurrence risk, such as T-stage and mismatch repair (MMR) status, are well established, they may not be reliable predictors of recurrence risk in this population (Gray et al., 2011; Gunderson et al., 2010; Harris et al., 2008; Ribic et al., 2003; Sargent et al., 2010; Venook et al., 2013).

Certain mutations may affect treatment of CRC. For example, the activation of the epidermal growth factor receptor (*EGFR*) signaling cascade is associated with colon tumorigenesis (Therkildsen et al., 2014); therefore, medications such as cetuximab or panitumumab that target the *EGFR* pathway may be used in treatment of CRC. However, activating mutations in the *KRAS* oncogene will cause anti-*EGFR* resistance since these mutations can result in a constitutively active pathway, even with anti-*EGFR* treatment (Clark & Sanoff, 2023). Consequently, tumors with mutated *KRAS* are unresponsive to anti-*EGFR* therapy. As a result, testing for mutational status as a negative predictive factor for anti-*EGFR* therapy has become part of routine pathological evaluation for CRC. Other mutations in the RAS oncogene (primarily *NRAS*) may also lead to the same phenotype (Frucht & Lucas, 2022). Another gene that may be overexpressed within the *EGFR* pathway is *HER2* (human epidermal growth factor receptor 2). This gene plays a role in activating signal transduction pathways controlling epithelial cell growth. Although *HER2* is more traditionally known as a breast cancer-associated gene, up to five percent of colorectal cancer cases are found to overexpress *HER2* (Clark & Sanoff, 2023).

Another component of the RAS signaling pathway, *BRAF*, has also been found to affect anti-*EGFR* treatment. *BRAF* V600E mutations may also confer a lack of response to anti-*EGFR* treatment even when paired with a wild-type RAS oncogene. Mutations in this region occur in less than 10% of sporadic CRCs, and the mutation at position 600 is the primary polymorphism found in CRC. Non-V600 *BRAF* mutations are rarer (composing about 2.2% of patients with metastatic CRC) and confer a generally better prognosis than their V600 mutated counterparts; a study found non-V600 genotypes to lead to better median overall survival and fewer high-grade tumors (Jones et al., 2017).

Proprietary Testing

Gene expression assays have been commercially produced to predict prognosis of colon cancer. The 12-gene Oncotype DX Colon Cancer Assay (Genomic Health, Inc., Redwood City, CA) is a reverse transcriptase polymerase chain reaction–based assay that provides a Recurrence Score (RS) result

(O'Connell et al., 2010). This test assesses the activity level of 12 genes (7 cancer-related genes, 5 reference genes), and this gene expression is scored from 1-100. This test is intended for resected stage II, MMR-P or stage III A/B colon cancer. Low risk is a score under 30, moderate risk is 31-40, and higher risk is ≥41 (Oncotype, 2020a, 2020b).

The ColDx assay (Almac Diagnostics, Craigavon, Northern Ireland) uses microarray technology for assessing the gene expression of 634 genes to stratify patients into low and high recurrence risk groups. ColDx identified 73 high risk patients with a hazard ratio of 2.62 during cross validation. In an independent validation, the assay identified high-risk patients with a hazard ratio of 2.53 (Kennedy et al., 2011).

ColoPrint (Agendia, Amsterdam, The Netherlands) is a gene expression classifier that uses whole-genome expression data of 18 key genes to distinguish patients with low versus high risk of disease relapse. In a study using 206 fresh frozen tumor tissue samples from 188 patients with stage I through IV CRC, ColoPrint classified "60% of patients as low risk and 40% as high risk," and was "superior to American Society of Clinical Oncology criteria in assessing the risk of cancer recurrence without prescreening for microsatellite instability" (Salazar et al., 2011). In a study of 416 stage II colon cancer patients, "ColoPrint identified 63% of patients as low risk with a 5-year ROR of 10%, whereas high-risk patients (37%) had a 5-year ROR of 21%." Alternatively, the 2013 NCCN clinical risk factors could not distinguish low and high-risk patients (Kopetz et al., 2015).

Analytical Validity

Cenaj et al. (2019) evaluated the correlation between "*ERBB2* amplification by next-generation sequencing (NGS) with HER2 overexpression by immunohistochemistry". NGS was performed on specimens with 20% or more tumor, and 1300 cases of colorectal cancer were included. *ERBB2* amplification was detected in 2% of cases. HER2 amplification was examined in "15 cases with *ERBB2* amplification (six or more copies), 10 with low gain (three to five copies), and 77 copy neutral". *ERBB2* amplification was found to have perfect concordance with HER2 immunochemistry at H-scores of 105 or more. Further, *ERBB2* amplification was found to inversely correlate with RAS/RAF mutations. The authors concluded that "NGS-detected *ERBB2* amplification highly correlates with HER2 overexpression in CRC", which may support authors' original hypothesis that ERBB2 amplification/overexpression may predict response to HER2 inhibitors (Cenaj et al., 2019).

Fan et al. (2021) analyzed the relationship between mismatch repair (MMR) protein, *RAS*, *BRAF,* and *PIK3CA* expression and clinicopathological characteristics in elderly patients with CRC. From 327 patients, the researchers found that "the mutation rates of the *KRAS, NRAS, BRAF* and *PIK3CA* genes in elderly CRC patients were 44.95% (147/327), 2.45% (8/327), 3.36% (11/327) and 2.75% (9/327), respectively." They also identified that "*KRAS* was closely related to tumor morphology ($P = 0.002$) but not to other clinicopathological features ($P > 0.05$), and there were no significant differences between *NRAS* gene mutation and clinicopathological features ($P > 0.05$). The *BRAF* gene mutation showed a significant difference in pathological type, tumor location, differentiation degree and lymph node metastasis ($P < 0.05$), but was not correlated with sex, tumor size and tumor morphology ($P > 0.05$)" (Fan et al., 2021). This demonstrates the critical nature of mutation analysis for these specific genes to aid in identifying potential therapies that would better patient prognoses especially in such a vulnerable population like the elderly.

Formica et al. (2020) examined tumor tissue (T) mutational analysis in terms of discordance with circulating tumor DNA (ctDNA) obtained by liquid biopsy from plasma (PL) and assessed through real time polymerase chain reaction (PCR). Despite finding concordance for patients with *BRAF* mutations between the tissue and plasma samples, 20% of patients were *RAS* discordant. Mutations identified from ctDNA were able to refine the prognosis determined by tissue samples. "*RAS* wild type in T and mutated in PL had significantly shorter PFS than concordant *RAS* wild type in T and PL: mPFS [median progression free survival] 9.6 vs. 23.3 months, respectively, $p = 0.02$. Patients RAS mutated in T and wild type in PL had longer PFS than concordant RAS mutated in T and PL: 24.4 vs. 7.8 months,

respectively, $p = 0.008$." This raises a limitation to using tumor tissue as the mainstay for mutational analysis and considering combining with or replacing tumor tissue genotyping with plasma ctDNA as a measure of prognosis going forward (Formica et al., 2020).

Pinheiro et al. (2022) studied the analytical validity of using ctDNA as a possible strategy to analyze *KRAS* and *NRAS* mutations from patients with metastatic colorectal cancer. The BEAMing Digital PCR (OncoBEAM) and Idylla ctDNA qPCR were compared and the concordance rate was reported. Blood samples from 47 mCRC patients were tested and the overall agreement and concordance rate were noted. "The overall agreement between tumor tissue and ctDNA analyses was 83% and 78.7% using the OncoBEAM and Idylla assays, respectively, with the concordance being 96.2% and 88.5% in naive treatment patients. The overall agreement between OncoBEAM and Idylla ctDNA analyses was 91.7%" (Pinheiro et al., 2022). The authors conclude that Idylla ctDNA qPCR method is a cheaper alternative with equivalent performance in comparison to the OncoBEAM assay. Analysis of ctDNA can be used to detect "RAS mutations in plasma, either at diagnosis or after progression when considering anti-EGFR treatment rechallenge" (Pinheiro et al., 2022).

Clinical Utility and Validity

In a meta-analysis by Xu et al, (2013), a total of 2875 patients were evaluated, with 246 patients having *BRAF* mutations. The objective response rate(ORR) to *EGFR* therapy was 18.4% (40/217) in mutant *BRAF* group and 41.7% (831/1993) in the wild-type *BRAF* group. The overall risk ratio for the ORR of *BRAF* mutations compared to wild-type *BRAF* patients was 0.58. The median progression free survival (hazard ratio 2.98) and overall survival (hazard ratio: 2.85) were significantly shorter of patients with *BRAF* mutations compared to patients with wild-type *BRAF* mutations (Xu et al., 2013).

Douillard et al. (2013) evaluated the effect of panitumumab plus oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) compared to just FOLFOX4 on patients with varying RAS and *BRAF* mutations. 639 patients with metastatic CRC without mutations in *KRAS* exon 2 had at least one of the following: *KRAS* exon 3 or 4; *NRAS* exon 2, 3, or 4; or *BRAF* exon 15. 228 patients had neither RAS nor *BRAF* mutations, and this group was evaluated to have better survival metrics with panitumumab plus FOLFOX4 than the group with just FOLFOX4 (median of 10.8 months progression-free survival and 28.3 months overall survival for panitumumab group vs 9.2 and 20.9 respectively for the group without). However, 296 patients with either a *RAS* or *BRAF* mutation were treated with panitumumab plus FOLFOX4, and this group's survival metrics were lower than the group only treated with FOLFOX4. The *RAS*/*BRAF* group treated with panitumumab plus FOLFOX4 had a median of only 7.3 months progression-free survival and 15.3 months overall survival vs 8.0 and 18.0 for the 305 patients treated with only FOLFOX4). The authors concluded that additional RAS mutations predicted a lack of response to panitumumab plus FOLFOX4 (Douillard et al., 2013).

Therkildsen et al. (2014) performed a meta-analysis of the clinical impact of anti-*EGFR* treatment on patients with *KRAS*, *NRAS*, and *BRAF* mutations (as well as PIK3CA and PTEN). A total of 22 studies (2395 participants) were evaluated. Odds ratios for objective response rate (ORR) and hazard ratios (HR) for progression-free survival rate (PFS) and overall survival (OS) were calculated. Mutations in *KRAS* exons 3 and 4 and *BRAF* predicted poor ORR (0.26 and 0.29 respectively), *KRAS*, *NRAS*, and *BRAF* mutations all led to significantly lower progression-free survival (HR = 2.19, 2.30, and 2.95 respectively) and significantly lower overall survival (HR = 1.78, 1.85, and 2.52 respectively) (Therkildsen et al., 2014).

Rebersek et al investigated the impact of molecular biomarkers on survival and response to first line therapy in metastatic colorectal cancer patients. The study included 154 patients with 42% harboring *KRAS* mutations and 3% harboring *BRAF* mutations. Median overall survival (OS) was found to be 56.5 months for wild-type *KRAS* patients and 58 months for mutated *KRAS* patients. Median OS for mutated exon 12 patients was 57 months compared to 44 months for mutated exon 13 patients. Wild-type *KRAS* was found to affect the response to first-line systemic therapy, whereas no other parameters were found to affect response (Rebersek et al., 2019).

Sartore-Bianchi et al investigated the effect of *HER2* positivity on anti-*EGFR* treatment. 100 patients HER2-positive (of 1485 wild-type *KRAS* exon 2 patients) with metastatic colorectal cancer were included. The authors found that HER2-positive patients had more frequent lung metastases (odds ratio [OR] = 2.04) and higher tumor burden (OR = 1.48). The 79 *HER2*-positive patients given anti-*EGFR* treatment were also found to have poorer clinical outcomes, with lower objective response rate (31.2% compared to 46.9% for all others) and lower progression-free survival (5.7 months vs 7 months). The authors concluded that HER2 testing should be offered because "occurrence of this biomarker is unlikely to be predicted based on main clinicopathological features" (Sartore-Bianchi et al., 2019).

The prognostic benefit was corroborated by Chang et al. (2021), who found that the *BRAF* gene mutation was "associated with cancer thrombosis in blood vessels" and was "negatively correlated with the OS [overall survival] rate of CRC patients" in their patient population (n=410) from Central China. Like Fan et al. (2021), *KRAS* also had the greatest mutation rate at 47.56% in this study, showing more awareness needed for tissue genotyping for mCRC (Chang et al., 2021).

Loree et al. (2021) characterized the clinical prevalence of atypical *KRAS/NRAS* mutations in metastatic colorectal cancer. The authors evaluated tissue and DNA samples from 9,485 patients to characterize atypical *RAS* variants using an in-vitro cell-based assay, studying the signaling changes across mutations. According to the results, "*KRAS* exon 2, extended *RAS*, and atypical *RAS* mutations were noted in 37.8%, 9.5%, and 1.2% of patients, respectively. Among atypical variants, *KRAS* L19F, Q22K, and D33E occurred at prevalence ≥0.1%, whereas no *NRAS* codon 117/146 and only one *NRAS* codon 59 mutation was noted. Atypical *RAS* mutations had worse overall survival than *RAS/BRAF* wild-type mCRC." Of the 57 atypical *RAS* variants, 18 (31.6%) had signaling below wild-type, 23 (40.4%) had signaling between wild-type and activating control, and 16 (28.1%) were hyperactive beyond the activating control. The authors concluded that "*KRAS* L19F, Q22K, D33E, and T50I are more prevalent than many guideline-included RAS variants and functionally relevant" (Loree et al., 2021).

Benavides et al. (2022) studied how effective liquid biopsy-tailored assays were in identifying guideline-recommended biomarkers, including *RAS* and *BRAF*, in comparison to standard of care tissue genotyping for patients newly diagnosed with mCRC. To quantify the effectivity of liquid biopsy assays for biomarkers, the researchers utilized the Guardant360 for comprehensive ctDNA analysis, and OncoBEAM for targeted RAS and BRAF analysis. Among the 155 patients included in this prospective study, physician discretion standard of care tissue genotyping identified guideline-recommended biomarkers in 52.9% of patients, in comparison to the 56.8% from the comprehensive Guardant360 ctDNA analysis and 44.5% from targeted ctDNA analysis by OncoBEAM. An additional 19.5% more samples were included in the ctDNA assays "by rescuing those without tissue results either due to tissue insufficiency, test failure, or false negatives." The complete processing of ctDNA assays was faster (10 days versus 27 days on median) and maintained accuracy even 10 days after sample collection (52.0% vs 10.2%). This could allow inclusion of ctDNA genotyping in the care of patients with mCRC and could enable accelerated personalized treatment regimens for patients with the quick turnaround and comparable results to current practices.

Several studies have evaluated the impact of the gene expression profiling on clinical decision making in certain colon cancer subgroups. Brenner et al. (2016) assessed the clinical impact of the 12-gene Colon Cancer Recurrence Score Assay in treatment of T3 mismatch repair proficient (MMR-P) stage II colon cancer. Out of 269 patients, 102 patients had their treatment changed because of the assay's results. The authors concluded that testing significantly impacted adjuvant treatment decisions in clinical practice (Brenner et al., 2016).

Cartwright et al. (2014) performed a web-based survey evaluating the impact of the 12-gene Colon Cancer Recurrence Score Assay in stage II colon cancer patients. The authors surveyed 346 oncologists about their use of the Oncotype DX assay; the survey included questions about courses of treatment before and after using the assay and the stage of cancer their patient had. The authors found that 29% of treatment recommendations were changed for patients receiving Recurrence Score testing (Cartwright et al., 2014). Srivastava et al. (2014) conducted a prospective study assessing the impact of recurrence score results on physician recommendations regarding adjuvant chemotherapy in T3 MMR-P stage II colon

cancer patients. A total of 141 patients were eligible for analysis, and the study concluded that treatment recommendation changes were made for 63 (45%) of patients (Srivastava et al., 2014).

Chang et al. (2020) reviewed the "entire database" of the OncoType Colon Recurrence Score test to identify any age-related differences in Recurrence Score (RS) and single-gene results. 20478 Stage II and IIIA/B colon cancer patients were included. RS results were categorized into low, medium, and high risk, and single-gene results were organized by median and interquartile ranges. 72.5% of all patients and 72.6% of patients under 40 years old were found to have a low-risk RS. However, there were no significant differences in either RS or single-gene results among the four age groups (<40, 40-54, 55-64, >65). Young-onset cancer was also not found to differ by gene expression in individual RS genes. Overall, most patients in stages II or III colon cancer were found to have low-risk disease per the OncoType assay (Chang et al., 2020).

Allar et al. (2022) evaluated how the OncoType Colon Recurrence Score influences clinical practice. The study included 105 patients with stage IIa colon cancer and investigated the association between the RS and the decision to offer adjuvant chemotherapy after resection. 52 patients underwent RS testing, seven (13%) of whom received adjuvant chemotherapy. The authors found no significant effect or clear association of RS on the odds of undergoing chemotherapy. The authors conclude that "RS was not associated with the decision to start adjuvant chemotherapy" and suggest that "the RS should not be obtained in patients with stage IIa colon cancer" (Allar et al., 2022).

Chaudhari and Issa (2022) conducted a study to compare the cost-effectiveness of various genomic tests used to prognosticate stage II colorectal cancer patients. The researchers compared a 12-gene assay, 18-gene expression assay, 482-gene signature assay, and Immunoscore assay in a hypothetical cohort to investigate recurrence risk and death. Using a Markov model, the authors found that "the cost of the Immunoscore assay strategy in stage II colorectal cancer patients was estimated to be US $23,564 with a gain of 3.903 quality-adjusted life years (QALYs) as compared with the 12-gene assay strategy at US $24,545 and 3.903 QALYs; the 18-gene assay strategy at US $28,374 and 3.623 QALYs; and the 482-gene signature treatment strategy at US $33,315 with 3.704 QALYs." This, along with further analysis, led to the conclusion that the Immunoscore assay may be the "dominant strategy," in that it may reduce costs associated with treatment in long-term, but for the gene expression signature assays alone, the 12-gene assay may generate more cost savings than the 18-gene expression assay, equivalent to $3900 (Chaudhari & Issa, 2022).

Guidelines and Recommendations

American Society of Clinical Oncology (ASCO)

ASCO published a Provisional Clinical Opinion (PCO) that states "*RAS* mutational testing of colorectal carcinoma tissue should be performed in a Clinical Laboratory Improvement Amendments–certified laboratory for all patients who are being considered for anti-*EGFR* MoAb therapy". ASCO recommends that "mutational analysis should include *KRAS* and *NRAS* codons 12 and 13 of exon 2; 59 and 61 of exon 3; and 117 and 146 of exon 4. The weight of current evidence indicates that anti-*EGFR* MoAb therapy (currently cetuximab and panitumumab) should only be considered for treatment of patients with mCRC who are identified as having tumors with no mutations detected after such extended RAS mutation analysis" (Allegra et al., 2016).

This guideline was archived and replaced by Sepulveda et al. (2017) (ASCO).

In 2020, ASCO published a guideline titled "Treatment of Patients with Late-Stage Colorectal Cancer". ASCO recommends that all patients with mCRC should be tested for key molecular markers (when possible) if targeted treatments are available. *RAS* and *BRAF* are mentioned as examples of molecular markers (Chiorean et al., 2020).

American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology

These joint guidelines focus on "Molecular Biomarkers for the Evaluation of Colorectal Cancer." They list the following recommendations for *KRAS*, *NRAS*, and *BRAF* for CRC:

- "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)."
- "*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."
- "There is insufficient evidence to recommend *BRAF* c.1799 p.V600 mutational status as a predictive molecular biomarker for response to anti-*EGFR* inhibitors" (Sepulveda et al., 2017).

National Comprehensive Cancer Network (NCCN)

The guidelines version 1.2023 recommends that "all patients with metastatic colorectal cancer should have tumor genotyped for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations individually or as part of an NGS panel. Patients with any known *KRAS* mutation (exon 2, 3, and 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."

The NCCN guidelines state that testing for *KRAS*, *NRAS* and *BRAF* mutations should be performed only in laboratories that are CLIA-1988 certified as qualified to perform high complexity clinical laboratory (molecular pathology) testing. Testing can be performed on formalin fixed paraffin embedded tissue (preferred) or blood-based assay.

The NCCN further states that "testing can be performed on the primary colorectal cancers and/or the metastasis, as literature has shown that the *KRAS NRAS*, and *BRAF* mutations are similar in both specimen types."

BRAF genotyping of tumor tissue is recommended at stage IV disease. Allele-specific PCR or NGS may be used to determine *BRAF* status.

The NCCN notes that *HER2* may be overexpressed in *RAS*/*BRAF* wild-type tumors despite being rarely amplified/overexpressed in CRC (3% overall), *HER2*-targeted therapies are now recommended in patients with tumors that are *RAS/BRAF* wild-type and with HER2 overexpression. Therefore, the NCCN now recommends testing for *HER2* amplifications in patients with metastatic CRC. However, *HER2* testing is not indicated in patients with known *KRAS*/*NRAS* or *BRAF* mutations (NCCN, 2023a).

Routine *EGFR* testing is not recommended (NCCN, 2023a).

Overall, in patients with mCRC, the NCCN recommends "determination of tumor gene status for *RAS* and *BRAF* mutations and *HER2* amplifications (individually or as part of tissue- or blood-based NGS panel" and "determination of tumor [mismatch repair] or [microsatellite instability] status (if not previously done)" (NCCN, 2023a).

Regarding the OncoType DX colon cancer assay, the NCCN remarks that clinical validation in patients with stages II or III cancer from the QUASAR and NSABP clinical trials shows that "recurrence scores are prognostic for recurrence, DFS [disease free survival], and OS [overall survival] in stage II and stage III colon cancer but are not predictive of benefit to adjuvant therapy." ColoPrint, an 18-gene classifier for recurrence risk, was also found to independently predict recurrence risk and is currently being validated to predict 3-year relapse rates in patients with stage II colon cancer in a prospective trial. Similarly, ColDx, a microarray based multigene assay, was found to independently predict recurrence risk. However, despite these tests' ability to further inform risk of recurrence, the panel questions the value added. The panel also noted that "evidence of predictive value in terms of the potential benefit of chemotherapy is lacking" and that "there are insufficient data to recommend the use of multi-gene assays,

Immunoscore, or post-surgical ctDNA to estimate risk of recurrence or determine adjuvant therapy" (NCCN, 2023b).

European Society for Medical Oncology (ESMO)

In its 2023 guidelines, ESMO recommends the following for mCRC genetic testing:

- "Determining the *RAS* mutational testing on a tumor biopsy [I, A] (or through a liquid biopsy in case no tumor sample is available [II, B]) is mandatory to guide the best treatment decision.
- Testing for mismatch repair (MMR) status and *KRAS, NRAS* exon 2, 3, and 4 as well as *BRAF* mutations is recommended in all patients at the time of mCRC diagnosis [I, A]
- Identification of human epidermal growth factor receptor (HER2) amplification by immunohistochemistry (IHC) or FISH [fluorescence in-situ hybridization] is recommended in *RAS* wild-type (wt) patients to detect those who may benefit from HER2 blockade [III, B]
- *RAS* testing is mandatory before treatment with anti-EGFR mAbs and can be carried out on either the primary tumor or other metastatic sites [III, A]
- *BRAF* mutation status should be assessed simultaneously with the evaluation of *RAS*, for prognostic assessment [I, B] and for the option of treatment with cetuximab ~~e~~ncorafenib [I, A].
- dMMR [deficient mismatch repair]/MSI testing in mCRC can assist in genetic counselling for Lynch syndrome [II, B].
- dMMR/MSI status is also recommended as the initial molecular work-up in metastatic disease for its predictive value for the use of ICIs [immune checkpoint inhibition] [I, A]" (Cervantes et al., 2023).

With regards to localized colon cancer, ESMO states that "besides MSI status, other genetic markers, e.g. *RAS* and *BRAF* mutations are not recommended for the routine assessment of risk of recurrence in non-metastatic patients, based on their lack of utility in the adjuvant decision-making process" (Argilés et al., 2020).

In their newly released guidelines, ESMO does not provide recommendations for using gene expression profiling assays for prognosticating patients with stage II colon cancer (Cervantes et al., 2023).

American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology Joint Guidelines

The joint guidelines state that further research is required to study the clinical validity and utility of gene expression profiling assays in colon cancer patients (Sepulveda et al., 2017).

Research Committee and the Guidelines Committee of the European Society of Coloproctology (ESCP)

This systematic review was performed by the committee to assess the consensus levels "in guidelines from member countries of the European Society of Coloproctology, with supporting evidence." This review focuses on follow-up strategies for patients "after treatment with curative intent of nonmetastatic colorectal cancer" (Bastiaenen et al., 2019).

In this review, the committee concluded that "laboratory tests other than CEA [carcinoembryonic antigen] should not be part of follow-up," although it noted that only 8 of 21 guidelines reviewed addressed this topic (Bastiaenen et al., 2019).

State and Federal Regulations, as applicable

Food and Drug Administration (FDA)

Cetuximab and panitumumab have FDA marketing approval for treatment of metastatic colorectal cancer in the refractory disease setting, and ongoing studies are investigating the use of these *EGFR* inhibitors as monotherapy and as part of combination therapy in first, second, and subsequent lines of therapy.

On May 23, 2014 the FDA approved therascreen *KRAS* RGQ PCR Kit is a real-time qualitative PCR assay used on the Rotor-Gene Q MDx instrument for the detection of seven somatic mutations in the human *KRAS* oncogene, using DNA extracted from formalin-fixed paraffin-embedded (FFPE), colorectal cancer (CRC) tissue. The therascreen *KRAS* RGQ PCR Kit is intended to aid in the identification of CRC patients for treatment with Erbitux (cetuximab) and Vectibix (panitumumab) based on a *KRAS* no mutation detected test result (FDA, 2014).

On May 7, 2015 the FDA approved cobas *KRAS* Mutation Test, for use with the cobas® 4800 System. Cobas is a real-time PCR test for the detection of seven somatic mutations in codons 12 and 13 of the *KRAS* gene in DNA derived from formalin-fixed paraffin-embedded human colorectal cancer (CRC) tumor tissue. The test is intended to be used as an aid in the identification of CRC patients for whom treatment with Erbitux (cetuximab) or with Vectibix (panitumumab) may be indicated based on a no mutation detected result (FDA, 2015).

On June 29, 2017 the FDA approved PraxisTM Extended RAS Panel as a qualitative in vitro diagnostic test using targeted high throughput parallel sequencing for the detection of 56 specific mutations in RAS genes [*KRAS* (exons 2, 3, and 4) and *NRAS* (exons 2, 3, and 4)] in DNA extracted from formalin-fixed, paraffin-embedded (FFPE) colorectal cancer (CRC) tissue samples. The Praxis™ Extended RAS Panel is indicated to aid in the identification of patients with colorectal cancer for treatment with Vectibix (panitumumab) based on a no mutation detected test result. The test is intended to be used on the Illumina MiSeqDx instrument (FDA, 2017).

On November 30, 2017, the FDA approved FoundationOne CDx, which is a next generation sequencing oncology panel. From the FDA website: "FoundationOne CDx™ (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels) and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed Table 1 in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for cancer patients with solid malignant neoplasms. The F1CDx test is a single-site assay performed at Foundation Medicine, Inc." (FDA, 2017).

In 2021, the ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) was approved. O/RDx-LCCA is a highly accurate FDA approved IVD assay for the detection of clinically relevant KRAS variants in CRC and EGFR variants in NSCLC and determination of approved therapy. "The device is a qualitative next generation sequencing based in vitro diagnostic test that uses amplicon-based target enrichment technology for detection of single nucleotide variants (SNVs) and deletions in 2 genes from DNA isolated from formalin-fixed paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) and colorectal cancer (CRC) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients with NSCLC or CRC who may benefit from treatment with the targeted therapies" (FDA, 2021).

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81210, 81275, 81276, 81311, 81405, 81479, 81525, 81599, 0111U

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

For Policy Titled: KRAS, NRAS and BRAF Mutation Analysis in Colorectal Cancer

For Policy Re-Titled: Testing for Colorectal Cancer Management

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For Policy Titled: Tumor Tissue Mutation Analysis in Colorectal Cancer

Specialty Matched Consultant Advisory Panel 8/2019

Medical Director review 8/2019

Specialty Matched Consultant Advisory Panel 8/2020

Medical Director review 7/2020

Medical Director review 8/2020

Specialty Matched Consultant Advisory Panel 8/2021

For Policy Re-Titled: KRAS, NRAS and BRAF Mutation Analysis in Colorectal Cancer

Medical Director review 8/2022

For Policy Re-Titled: Testing for Colorectal Cancer Management

Medical Director review 7/2023

Policy Implementation/Update Information

For Policy Titled: KRAS, NRAS, and BRAF Mutation Analysis in Colorectal Cancer

1/1/2019 New policy developed. BCBSNC will provide coverage for KRAS, NRAS, and BRAF mutation analysis in colorectal cancer when it is determined to be medically necessary and criteria are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)

For Policy Titled: Tumor Tissue Mutation Analysis in Colorectal Cancer

9/10/19 Specialty Matched Consultant Advisory Panel 8/21/19. Reviewed by Avalon 2nd Quarter 2019 CAB**. Title changed from KRAS, NRAS, and BRAF Mutation Analysis in Colorectal Cancer to Tumor Tissue Mutation Analysis in Colorectal Cancer.** Under "When Covered" section: added "NOTE: For more than 5 gene tests being run on a tumor specimen (i.e. non-liquid biopsy) on the same platform, such as multi-gene panel next generation sequencing, please refer to policy AHS-2109 Molecular Panel Testing of Cancers to Identify Targeted Therapy" for clarity; and removed "E" from BRAF V600E" as other mutations may exist. Added "Related Policies" section. Coding table removed from Billing/Coding section. Medical Director review 8/2019. (lpr)

10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (hb)

9/8/20 Specialty Matched Consultant Advisory Panel review 8/19/2020. No changes to policy statement. (lpr)

10/1/20 Reviewed by Avalon 2nd Quarter 2020 CAB. Added CPT code 0111U to Billing/Coding section for effective date 10/1/2020. Medical Director review 7/2020. Added related policies. Updated references and policy guidelines. (lpr).

9/7/21 Reviewed by Avalon 2nd Quarter 2021 CAB. Updated Policy Guidelines. References added. Specialty Matched Consultant Advisory panel review 8/18/2021. No change to policy statement. (lpr)

For Policy Re-Titled: KRAS, NRAS and BRAF Mutation Analysis in Colorectal Cancer

9/13/22 Reviewed by Avalon 2nd Quarter 2022 CAB. Medical Director review 8/2022. Removed related policy AHS-M2109 Molecular Panel Testing of Cancers to Identify Targeted Therapy. Updated policy guidelines and references. Under Billing/Coding section: removed CPT 81403 and 88363. **Title changed from: Tumor Tissue Mutation Analysis in Colorectal Cancer to: KRAS, NRAS and BRAF Mutation Analysis in Colorectal Cancer.** (lpr)

For Policy Re-Titled: Testing for Colorectal Cancer Management

8/15/23 Reviewed by Avalon Q2 2023 CAB. Medical Director review 7/2023. Updated description, policy guidelines and references. Added related policy AHS-M2178.
Policy information and criteria from AHS-M2111 Multigene Expression Assay for Predicting Colon Cancer Recurrence was moved into this policy. "When covered and when not covered" sections clarified and edited due to added information from M2111. Added CPT codes 81479, 81525, 81599 to Billing/Coding section.
Title changed from: KRAS, NRAS and BRAF Mutation Analysis in Colorectal Cancer to: Testing for Colorectal Cancer Management. (lpr)