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Corporate Medical Policy

Tumor Tissue Mutation Analysis in Colorectal Cancer AHS - M2026

File Name:	tumor_tissue_mutation_analysis_in_colorectal_cancer
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Description of Procedure or Service

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, 2020; Sepulveda et al., 2017).

Related Policies
Molecular Panel Testing of Cancers to Identify Targeted Therapy AHS – M2109
Lynch Syndrome AHS-M2004
Genetic Testing for Polyposis Syndromes AHS-M2024
Genetic Cancer Susceptibility Using Next Generation Sequencing AHS-M2066

******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 Tumor Tissue Mutation Analysis in Colorectal Cancer 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 Tumor Tissue Mutation Analysis in Colorectal Cancer is covered

Tumor tissue genotyping for tumor tissue mutations is considered medically necessary for all patients with metastatic colorectal cancer.

Testing for KRAS mutation (exon 2, 3, 4), NRAS (exon 2, 3, 4) and BRAF V600 mutation is considered medically necessary *prior* to deciding treatment with cetuximab or panitumumab.

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.

When Tumor Tissue Mutation Analysis in Colorectal Cancer is not covered

Testing for Tumor Tissue Mutation V600 in all other situations not described above is considered investigational.

Policy Guidelines

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths in the United States following lung cancer. 20% of patients with colorectal cancer will present with metastatic colorectal cancer (mCRC) at diagnosis and a significantly poorer prognosis. The 5-year survival is 13.1% in patients with distant metastases from CRC, as compared to 64.9% for all CRC patients (El-Deiry et al., 2015).

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, Bergmann, Henrichsen-Schnack, Ladelund, & Nilbert, 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 & Grothey, 2021). 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, 2021). 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 5% of colorectal cancer cases are found to overexpress *HER2* (Clark & Grothey, 2021).

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).

Clinical validity and utility:

In a meta-analysis by Xu et al, 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 evaluatedthe 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 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). 22 studies including 2395 patients 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. 154 patients were included, 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, Mesti, Boc, & Ocvirk, 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).

Cenaj et al 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, Ligon, Hornick, & Sholl, 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.

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).

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).

Food and Drug Administration (FDA, 2009, 2012)

As per FDA requirements, the Erbitux (cetuximab) package insert (FDA, 2012) indicates that the drug is to be used for "K-Ras mutation-negative (wild-type), *EGFR*-expressing, metastatic colorectal cancer as determined by FDA-approved tests." Similarly, the Vectibix (panitumumab) package insert (FDA, 2009) states that "Use of Vectibix is not recommended for the treatment of colorectal cancer with these [*KRAS*] mutations."

American Society of Clinical Oncology (ASCO) (Chiorean et al., 2020; Sepulveda et al., 2017)

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).

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).

National Comprehensive Cancer Network (NCCN, 2021)

The guidelines v.2.2021 recommend that "all patients with metastatic colorectal cancer should have tumor tissue 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, 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. No specific methodology is recommended (e.g. sequencing, hybridization).

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. *HER2*-targeted therapies are now recommended in patients with HER2 overexpression. Therefore, the NCCN now recommends testing for *HER2* amplifications in patients with metastatic CRC. However, *HER2* testing is not required in patients with known *KRAS*/*NRAS* or *BRAF* mutations, and the NCCN states that anti HER2 therapy is only indicated in HER2-positive tumors that are also *RAS* and *BRAF* wild type (NCCN, 2021).

Routine *EGFR* testing is not recommended (NCCN, 2021).

Overall, the NCCN states that "determination of tumor gene status for *KRAS*/*RAS* and *BRAF* mutations, as well as *HER2* amplifications, are recommended for patients with mCRC" (NCCN, 2021).

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (EWG)

The EWG determined that, "for patients with metastatic colorectal cancer (mCRC) who are being considered for treatment with cetuximab or panitumumab, there is convincing evidence to recommend clinical use of *KRAS* mutation analysis to determine which patients are *KRAS* mutation positive and therefore unlikely to benefit from these agents before initiation of therapy (EGAPP, 2013)." However, the EWG "found insufficient evidence to recommend for or against *BRAF* V600E testing for the same clinical scenario," and "the level of certainty for *BRAF* V600E testing to guide anti-epidermal growth factor receptor (*EGFR*) therapy was deemed low (EGAPP, 2013)."

European Society for Medical Oncology (ESMO, 2016)

ESMO states that RAS mutational testing should be done at the time of diagnosing metastatic CRC and that RAS testing is mandatory before treatment with cetuximab and panitumumab. ESMO notes that RAS analysis should include "at least *KRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61, 117 and 146) and *NRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61 and 117)". ESMO also recommends that *BRAF* mutational status be assessed alongside RAS (Van Cutsem et al., 2016).

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).

National Institute for Health and Care Excellence (NICE, 2020)

NICE recommends testing for *RAS* and *BRAF* V600E mutations in all people with metastatic colorectal cancer suitable for systemic anti-cancer treatment (NICE, 2020).

American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology (Sepulveda et al., 2017)

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).

State and Federal Regulations, as applicable

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).

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: 0111U, 81210, 81275, 81276, 81311, 81403, 81405, 88363

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

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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

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)