Regence

Medical Policy Manual Genetic Testing, Policy No. 13

KRAS, NRAS, and BRAF Variant Analysis and MicroRNA Expression Testing for Colorectal Cancer

Effective: July 1, 2024

Next Review: December 2024
Last Review: June 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Variants in the *KRAS*, *NRAS*, and *BRAF* genes can substantially reduce the efficacy of certain antibody-based therapies for metastatic colon cancer. Testing for such variants can help to guide treatment decisions.

MEDICAL POLICY CRITERIA

I. *KRAS*, *NRAS*, and *BRAF* variant analysis may be considered **medically necessary** for treatment selection in patients with metastatic, unresectable, or advanced colorectal cancer.

II. *KRAS*, *NRAS*, and *BRAF* variant analysis is considered **investigational** for colorectal cancer that is not metastatic, unresectable, or advanced.

III. MicroRNA expression testing to predict anti-EGFR therapy response, including but not limited to the miR-31now™ test, is considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF GENETIC TESTING DOCUMENTATION

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or mutations being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test
    - History and physical exam
    - Conventional testing and outcomes
    - Conservative treatment provided, if any

CROSS REFERENCES

1. Genetic Testing for Lynch Syndrome and APC-associated and MUTYH-associated Polyposis Syndromes, Genetic Testing, Policy No. 06
2. Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening, Genetic Testing, Policy No. 12
3. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
4. BRAF Genetic Testing To Select Melanoma or Glioma Patients for Targeted Therapy, Genetic Testing, Policy No. 41
5. Molecular Analysis for Targeted Therapy of Non-Small Cell Lung Cancer (NSCLC), Genetic Testing, Policy No. 56
6. Expanded Molecular Testing of Cancers to Select Targeted Therapies, Genetic Testing, Policy No. 83
7. Serologic Genetic and Molecular Screening for Colorectal Cancer, Genetic Testing, Policy No. 86

BACKGROUND

Cetuximab (Erbitux®) and panitumumab (Vectibix®) are monoclonal antibodies that bind to the epidermal growth factor receptor (EGFR), preventing binding and activation of downstream signaling pathways vital for cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization.

The *KRAS* gene can harbor oncogenic variants that may result in tumor resistance to therapies that target the epidermal growth factor receptor (EGFR). *KRAS* variants are found in approximately 30–50% of colorectal cancer tumors and are common in other tumor types.

The *NRAS* gene can harbor variants in codons 12, 13 and 61 that constitutively activate the EGFR-mediated signaling pathway similar to variants in *KRAS*. Thus, the *NRAS* oncogene may also have an impact on outcomes of anti-EGFR treatments for advanced colorectal cancer. Although *NRAS* variants account for some 15% of all *RAS* variants, they are rare compared to *KRAS* variants and are found in perhaps 2-7% % of all CRC. As a consequence of the low prevalence of *NRAS* variants, it is difficult to assess their effect on cancer behavior or therapy.

BRAF encodes a protein kinase and is involved in intracellular signaling and cell growth and is

a principal downstream effector of *KRAS*. *BRAF* variants occur in less than 10-15% of colorectal cancers.

It has been shown that patients with a *KRAS* mutant tumor do not respond to cetuximab or panitumumab. However, there are still patients with *KRAS* wild-type tumors that do not respond to these agents, suggesting that other factors, such as alterations in other EGFR effectors could drive resistance to anti-EGFR therapy, and therefore, *BRAF* variants are now increasingly being investigated in metastatic colorectal cancer. *KRAS* and *BRAF* variants are considered to be mutually exclusive.

REGULATORY STATUS

Most *KRAS*, *NRAS*, and *BRAF* variant and microRNA tests using PCR methodology are commercially available as laboratory-developed tests. Such tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA). Premarket approval from the U.S. Food and Drug Administration (FDA) is not required when the assay is performed in a laboratory that is licensed by CLIA for high-complexity testing.

Two companion diagnostic tests for KRAS variant analysis have been premarket approval from the FDA:

- "The cobas® KRAS Mutation Test, for use with the cobas® 4800 System, [which] is a real-time PCR [polymerase chain reaction] 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."[1]

- "The 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."[1]

In 2015, the FDA prescribing information for panitumumab was updated to indicate that panitumumab was not indicated for treatment in colorectal cancer patients with variants in exon 2, 3, or 4 of either *KRAS* or *NRAS* in combination with oxaliplatin-based chemotherapy.

In June 2022, FDA granted accelerated approval to dabrafenib (Tafinlar) in combination with trametinib (Mekinist) for the treatment of adult and pediatric patients six 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 colorectal cancer because of known intrinsic resistance to BRAF inhibition

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[2] is used to describe variants found

in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

The focus of the scientific evidence is on evidence related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

For *KRAS, NRAS,* and *BRAF* testing in individuals with metastatic, unresectable, or advanced colorectal cancer, the evidence includes FDA-approved therapeutics with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher, and evidence reviews below for these genes will not be updated.

KRAS

Agency for Healthcare Research and Quality (AHRQ) Technology Assessment[3]

In 2010, AHRQ conducted a systematic review of the published evidence on *KRAS* variant testing and its ability to predict patient response to treatment with the anti-EGFR antibodies cetuximab and panitumumab. Forty-seven publications of *KRAS* variant testing met the eligibility criteria and were included in the review (45 in metastatic setting and two in neo-adjuvant setting). The review of evidence identified both small, retrospective studies and randomized controlled trials (RCTs). The assessment concluded that there is substantial and consistent evidence that *KRAS* testing can predict response to anti-EGFR therapy in colorectal cancer patients, and that,

> "For all outcomes assessed, patients with *KRAS* mutations were less likely to experience benefit with anti-EGFR antibody treatment, compared to patients whose tumors were wild-type for *KRAS* mutations. The direction of the association is consistent for overall mortality, disease progression and treatment failure by radiologic imaging."

BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment

The 2008 BlueCross BlueShield Association TEC Assessment concluded that the data are sufficient to demonstrate both the analytical and clinical validity of *KRAS* variant testing.[4] The evidence from five randomized trials and five single-arm studies is sufficient to indicate that metastatic colorectal cancer patients with mutated *KRAS* tumors do not respond to anti-EGFR monoclonal antibody therapy (either as monotherapy or in combination with other treatment regimens), do not derive survival benefit, and may experience decreased progression-free survival. Identifying patients whose tumors express mutated *KRAS* avoids exposing them to ineffective drugs, avoids exposure to unnecessary drug toxicities, and expedites the use of the best available alternative therapy.

Several studies published after the TEC and AHRQ assessments, including a meta-analysis and systematic review, continue to support the above findings.[5-12]

NRAS

A 2014 meta-analysis evaluated the predictive value of *NRAS* variants on clinical outcomes of anti-EGFR therapy in CRC[13] and included data from three nonrandomized studies.[14-16] The investigators suggest that the pooled analyses showed a trend towards poor objective response based on 17 events, but with significant effects on progression free survival (PFS) (hazard ratio [HR] 2.30, 95% CI 1.30 to 4.07) and overall survival (OS) (HR 1.85, 95% CI 1.23 to 2.78) among patients with wild-type *KRAS*. These results are limited by the small pool of variants, with studies reporting a prevalence of 2.2-5%.

Sorich (2015) published a systematic review and meta-analysis of nine RCTs that included 5948 metastatic colorectal cancer patients evaluated for *KRAS* exon 2 variants and new *RAS* variants, which were defined as variants in exons 3 and 4 of *KRAS* and exons 2, 3, and 4 of *NRAS*.[17] The prevalence of *NRAS* exon 2, 3, and 4 variants ranged from 0.5% to 4.8% and was similar to the prevalence of *KRAS* exon 3 and 4 variants, which ranged from 4.3% to 6.7% of tumors. Pooled data indicated that tumors without *KRAS* exon 2 variants or new *RAS* variants were found to have significantly superior PFS ($p<0.001$) and OS ($p=0.008$) with anti-EGFR monoclonal antibody (mAb) treatment compared to tumors with these variants. In addition, there were no differences noted in the PFS or OS of tumors with *KRAS* exon 2 variants when compared to new *RAS* variants. These results were consistent between different anti-EGFR mAb agents, lines of therapy, and chemotherapy. No PFS or OS benefit was observed with the use of anti-EGFR mAb agents in tumors with *KRAS* exon 2 variants or new *RAS* variants ($p>0.05$). Based on these results, authors concluded that approximately 53% of metastatic colorectal tumors (~42% with *KRAS* exon 2 and ~11% with new *RAS* variants) are unlikely to have a positive response to anti-EGFR mAb therapy. Results from this pooled data analysis suggest *NRAS* variant results may be used to guide treatment decisions in patients with metastatic colorectal tumors, as patients with *NRAS* variants are unlikely to benefit from anti-EGFR mAb therapy.

A systematic review and meta-analysis by Lin (2016) evaluated the efficacy of cetuximab-based chemotherapy according to *RAS* and *BRAF* variant subgroups in nine studies.[12] Cetuximab was associated with longer overall survival in tumors that had no variants in exon 2 of *KRAS* ($p=0.004$), tumors with wild-type (exons 2, 3, and 4) *KRAS*/*NRAS* ($p=0.0002$). There were no significant differences in OS or PFS between tumors with *KRAS* exon 2 variants and other exon 2, 3, or 4 *KRAS* or *NRAS* variants.

Additional studies published since the systematic reviews have shown similar differences in response to EGFR inhibitors according to *RAS* variant status.[18]

BRAF

Systematic Reviews

Pietrantonio (2015) published a systematic review and meta-analysis of randomized trials that compared cetuximab or panitumumab plus chemotherapy compared to standard therapy or best supportive care in patients with advanced colorectal cancer that have a *BRAF* variant.[19] Pooled results were reported for the efficacy of anti-EGFR-based therapy according to variant status as a first-line, second-line or refractory setting. Nine phase III trials and one phase II trial with a total of 463 patients with metastatic colon cancer were analyzed. Treatment with cetuximab or panitumumab did not significantly improve PFS (HR 0.88, 95% CI 0.67 to 1.14), OS (HR 0.91, 95% CI 0.62 to 1.34), or overall response rates (RR 1.31, 95% CI 0.83 to 2.08) compared to the control groups.

Rowland (2015) also published a systematic review and meta-analysis RCTs which evaluated the impact of *BRAF* variant status upon anti-EGFR mAb treatment outcomes in patients with metastatic colorectal cancer.[20] Seven RCTs met inclusion criteria for OS and eight studies met inclusion criteria for PFS. Pooled data indicated that cetuximab and panitumumab did not improve PFS (HR 0.86, 95% CI 0.61 to 1.21) or OS (HR 0.97, 95% CI 0.67 to 1.41) in patients with *BRAF* variants.

Other Studies

An updated analysis of the CRYSTAL trial reported increased follow-up time and an increased number of patients evaluable for tumor *KRAS* status and considered the clinical significance of the tumor variant status of *BRAF* in the expanded population of patients with *KRAS* wild-type tumors.[8] The impact of *BRAF* tumor variant status in relation to the efficacy of the chemotherapy regimen consisting of cetuximab plus folinic acid (leucovorin), 5-FU, and irinotecan (FOLFIRI) was examined in the population of patients with *KRAS* wild-type disease (n=625). There was no evidence of an independent treatment interaction by tumor *BRAF* variant status. The authors concluded that *BRAF* variant status was not predictive of treatment effects of cetuximab plus FOLFIRI but that *BRAF* tumor variant was a strong indicator of poor prognosis for all efficacy end points compared with those whose tumors were wild-type. Other studies have been published that report mixed results.[8, 21-29]

The data regarding the utility of variant testing as a predictive marker which informs the use of anti-EGFR mAb is less substantial for *BRAF* testing than for *KRAS* or *NRAS* testing. However, the evidence suggests that *BRAF* variant testing may be useful in directing treatment decisions, as anti-EGFR therapies do not improve PFS or OS in metastatic colorectal cancer patients with *BRAF* variants.

MICRORNA

Several studies have evaluated the association between the expression of the miR-31-3p microRNA and colorectal cancer progression in patients treated with anti-EGFR therapies.[30-34] For example, an industry-sponsored study published by Laurent-Puig (2018) reported that individuals with low miR-31-3p expression derived more benefit from cetuximab than bevacizumab (PFS HR 0.74, 95% CI 0.55 to 1.00, p=0.05; OS HR 0.61, 95% CI 0.41 to 0.88, p<0.01).[30] However, no studies have assessed the use of microRNA expression test results to guide treatment decisions or impact health outcomes.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN)[35] guidelines (v.4.2024) on the treatment of colon cancer make the following recommendation regarding *KRAS*, *NRAS*, and *BRAF* variant testing:

> "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 (exons 2, 3, and 4) or *NRAS* mutation (exons 2, 3, and 4) should not be treated with either cetuximab or panitumumab, unless given as part of a regimen targeting a *KRAS* G12C mutation. *BRAF* V600E mutation makes

response to panitumumab or cetuximab highly unlikely unless given with a *BRAF* inhibitor."

The guidelines did not discuss microRNA testing.

SUMMARY

There is enough evidence to show that cetuximab and panitumumab are not effective treatments for colorectal cancers with *KRAS*, *NRAS* or *BRAF* variants. Clinical guidelines based on research recommend testing patients with metastatic colorectal cancer for variants in the *KRAS*, *NRAS*, and *BRAF* genes to help with treatment decisions. Therefore, *KRAS*, *NRAS* and *BRAF* variant analysis may be considered medically necessary to predict nonresponse to anti-EGFR monoclonal antibodies in the treatment of metastatic colorectal cancer.

Anti-EGFR monoclonal antibodies are approved to treat advanced forms of colorectal cancer. These therapies are not approved for patients with non-metastatic, resectable colorectal cancer. Therefore, *KRAS*, *NRAS*, and *BRAF* variant analysis is considered investigational for colorectal cancer that is not metastatic, unresectable, or advanced.

There is not enough research to show that testing for microRNA expression can improve treatment decisions or health outcomes for patients with colorectal cancer. In addition, there are no clinical guidelines based on research that recommend microRNA testing for these patients. Therefore, microRNA expression testing to predict anti-EGFR therapy response, including but not limited to the miR-31now™ test, is considered investigational.

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CODES

Codes	Number	Description
CPT	0069U	Oncology (colorectal), microRNA, RT-PCR expression profiling of miR-31-3p, formalin-fixed paraffin-embedded tissue, algorithm reported as an expression score
	0111U	Oncology (colon cancer), targeted KRAS (codons 12, 13, and 61) and NRAS (codons 12, 13, and 61) gene analysis utilizing formalin-fixed paraffin-embedded tissue
	0471U	Oncology (colorectal cancer), qualitative real-time PCR of 35 variants of KRAS and NRAS genes (exons 2, 3, 4), formalinfixed paraffin-embedded (FFPE), predictive, identification of detected mutations
	81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
	81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)
	81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)
	81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)
	81403	Molecular pathology procedure, Level 4
	81404	Molecular pathology procedure, Level 5
HCPCS	None	

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