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, 2017; Sepulveda et al., 2017).

Related Policies
Molecular Panel Testing of Cancers to Identify Targeted Therapy AHS – M2109

***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.
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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

Literature Review

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).

The pathogenesis of CRC involves the accumulation of genetic and epigenetic modifications within pathways that regulate proliferation, apoptosis, and angiogenesis (Fearon & Vogelstein, 1990). The activation of the epidermal growth factor receptor (EGFR) signaling cascade is well known to lead to colon tumorigenesis (Therkildsen, Bergmann, Henrichsen-Schnack, Ladelund, & Nilbert, 2014). Mutations within the RAS and BRAF oncogenes located downstream to EGFR within this pathway lead to its constitutive activation, even if the EGFR is blocked. Consequently, tumors with mutated KRAS are unresponsive to anti-EGFR therapy. Therefore, testing for mutational status as a negative predictive factor for anti-EGFR therapy has become part of routine pathological evaluation for CRC (Frucht, 2017).

Analytic validity:

There is adequate evidence that KRAS mutation analysis reliably and accurately detects common mutations (codons 12 and 13), whereas evidence was inadequate for less frequent KRAS mutations (e.g., codon 61). There is also adequate evidence that testing for BRAF V600E accurately and reliably detects the mutation (EGAPP, 2013).

Clinical validity:

For KRAS mutation analysis, the EWG found convincing evidence for association with treatment response to anti-EGFR therapy (EGAPP, 2013).

For BRAF V600E mutation testing, BRAF mutation is associated with poor response to anti-EGFR therapy. In a meta-analysis by Xu et al (Xu et al., 2013) objective response rate of EGFR therapy was 18.4% (40/217) in mutant BRAF group and 41.7% (831/1993) in the wild-type BRAF group.

A consortium analysis by De Roock et al (De Roock et al., 2010) confirmed the negative effect of KRAS mutations on outcome after cetuximab, and showed that BRAF mutations are significantly associated with a low response rate.

Clinical utility: For KRAS mutation analysis, the EWG found adequate evidence that improved health outcomes are achieved by avoiding ineffective chemotherapy and potential side effects and expediting access to the next most effective treatment (EGAPP, 2013). Objective response rates could be improved by additional genotyping of BRAF mutations in a KRAS wild-type population (De Roock et al., 2010).
Applicable Federal Regulations

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 thesrascreen® KRAS RGQ PCR Kit is a real-time qualitative PCR assay used on the RotorGene 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 thesrascreen® 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.

On May 7, 2015 the FDA approved cobas® KRAS Mutation Test, for use with the cobas® 4800 System, 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.

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.

Other KRAS, NRAS, and BRAF mutation analyses are considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories.

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).

As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

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 “Vectibix is not indicated for the treatment of patients with KRAS mutation-positive mCRC or for whom KRAS mCRC status is unknown."

In 2015, the American Society of Clinical Oncology (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” (Allegra et al., 2016). The PCO 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).

The National Comprehensive Cancer Network (NCCN, 2018) guidelines v.2.2018 recommend that “all patients with metastatic colorectal cancer should have tumor tissue genotyped for RAS (KRAS and NRAS) and BRAF mutations. Patients with any known KRAS mutation (exon 2 3 or 4) or NRAS (exon
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2-3 or 4) mutation should not be treated with either cetuximab or panitumumab. BRAF V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with BRAF inhibitor” (NCCN, 2017). The NCCN guidelines state that testing for KRAS, NRAS and BRAF mutations should be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) 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 “The testing can be performed on formalin-fixed or paraffin-embedded tissue. The 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.”

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (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 antiepidermal growth factor receptor (EGFR) therapy was deemed low.”

 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, 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


**For Policy Titled: Tumor Tissue Mutation Analysis in Colorectal Cancer**

Specialty Matched Consultant Advisory Panel 8/2019

Medical Director review 8/2019
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)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.