# KRAS/NRAS and BRAF Mutation Analysis

Wellmark Blue Cross and Blue Shield is an Independent Licensee of the Blue Cross and Blue Shield Association.

**Medical Policy #: 02.04.20**
**Original Effective Date:** October 2008
**Reviewed:** January 2022
**Revised:** January 2022

**NOTICE: This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.**

**Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations, or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.**

**This Medical Policy document describes the status of medical technology at the time the document was developed. Since that time, new technology may have emerged, or new medical literature may have been published. This Medical Policy will be reviewed regularly and be updated as scientific and medical literature becomes available; therefore, policies are subject to change without notice.**

## DESCRIPTION

### BRAF

BRAF is a gene found on chromosome seven that encodes a protein also called BRAF. This protein plays a role in cell growth by sending signals inside the cell promoting, among other functions, cell division.

A BRAF mutation is a spontaneous change in the BRAF gene that makes it work incorrectly. A mutation causes the gene to turn on the protein and keep it on, which means certain cells get ongoing signals to keep dividing and no instructions on when to stop. This can lead to development of a tumor. One of the most common types is the BRAF V600E mutation.

Some mutations in BRAF cause cancer in combination with additional mutations or other factors. BRAF mutations can also cause cancers to grow more quickly than they would otherwise, either alone or in combination with additional mutations. BRAF are frequent drivers in colorectal cancer, gliomas, hairy cell leukemia, histiocytic neoplasms,

melanoma and pancreatic cancer. Different mutations in BRAF may be sensitive to different targeted therapies. Some mutations in BRAF aren't sensitive to any targeted therapies.

**KRAS**
The KRAS gene provides instructions for making a protein called K-Ras that is part of a signaling pathway known as the RAS/MAPK pathway. The protein relays signals from outside the cell to the cell's nucleus. These signals instruct the cell to grow and divide (proliferate) or to mature and take on specialized functions (differentiate). The K-Ras protein is a GTPase, which means it converts a molecule called GTP into another molecule called GDP. In this way the K-Ras protein acts like a switch that is turned on and off by the GTP and GDP molecules. To transmit signals, it must be turned on by attaching (binding) to a molecule of GTP. The K-Ras protein is turned off (inactivated) when it converts the GTP to GDP. When the protein is bound to GDP, it does not relay signals to the cell's nucleus.

The KRAS gene belongs to a class of genes known as oncogenes. When mutated, oncogenes have the potential to cause normal cells to become cancerous. KRAS mutations are present in approximately 25% of tumors, making them one of the most common gene mutations linked to cancer. They are frequent drivers in non-small cell lung cancer (NSCLC), colorectal cancer and pancreatic cancer.

**NRAS**
The NRAS gene provides instructions for making a protein called N-Ras that is involved primarily in regulating cell division. Through a process known as signal transduction, the protein relays signals from outside the cell to the cell's nucleus. These signals instruct the cell to grow and divide (proliferate) or to mature and take on specialized functions (differentiate). The N-Ras protein is a GTPase, which means it converts a molecule called GTP into another molecule called GDP. The N-Ras protein acts like a switch, and it is turned on and off by the GTP and GDP molecules. To transmit signals, the N-Ras protein must be turned on by attaching (binding) to a molecule of GTP. The N-Ras protein is turned off (inactivated) when it converts the GTP to GDP. When the protein is bound to GDP, it does not relay signals to the cell's nucleus.

The NRAS gene belongs to a class of genes known as oncogenes. When mutated, oncogenes have the potential to cause normal cells to become cancerous. The majority (97%) of mutations involve codons 12, 13, and 61. NRAS mutational status is useful in guiding therapy in patients with certain cancers including colon cancer and anal cancer.

**Colorectal Cancer**
Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2022, an estimated 106,180 new cases of colon cancer and 44,850 new cases of rectal cancer will occur. An estimated 52,580 people will die of colon and rectal cancer combined.

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; 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 antiEGFR treatment. 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. 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.

Another component of the RAS signaling pathway, BRAF, has also been found to affect antiEGFR 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.

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.

Rebersek et al. (2019) 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.

**Praxis Extended RAS Panel**
The Praxis Extended RAS Panel (Illumina) is an FDA approved next generation sequencing (NGS) panel evaluating RAS mutations KRAS/NRAS in metastatic colorectal cancer using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) colorectal cancer (CRC) tissue samples to determine patient eligibility for treatment with panitumumab (vectibix).

The FDA labeling for panitumumab (vectibix) includes the following: Vectibix is an epidermal growth factor receptor (EGFR) antagonist indicated for the treatment of wild-type RAS (defined as wild-type in both KRAS and NRAS as determined by an FDA-approved test for this use) metastatic colorectal cancer (mCRC). Limitation of Use: Vectibix is not indicated for the treatment of patients with RAS-mutant mCRC or for whom RAS mutation status is unknown.

In the FDA summary of safety and effectiveness data (SSED) regarding Praxis Extended RAS Panel: 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. The safety and effectiveness of the Praxis Extended RAS Panel was evaluated in a retrospective study designed to demonstrate that the Praxis Extended RAS Panel correctly detects the presence of 56 RAS mutants in CRC patients for the purpose of clinically validating the use of the test companion diagnostic test for panitumumab (Vectibix®). Patients without KRAS mutations may benefit from treatment with panitumumab. In conclusion, given the available information above, the data support the use of the Illumina Praxis Extended RAS Panel as an aid in the identification of patients eligible for treatment with panitumumab, and the probable benefits outweigh the probable risks.

The current NCCN guideline for colon and rectal cancer include the following:

**Principles of Pathologic Review**

- All patients with metastatic colorectal cancer should have tumor tissue genotyped for RAS (KRAS and NRAS) and BRAF mutation individually or as part of an NGS panel. Patient 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.
- BRAF B600E mutation testing via immunohistochemistry is also an option.
- 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 testing can be performed on formalin-fixed 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 in similar in both specimen types.

**Summary of Evidence**
Based on review of the available peer reviewed medical literature and current NCCN guidelines mutation analysis for patients with metastatic colorectal cancer should have tumor tissue genotyped for RAS (KRAS and NRAS) and BRAF mutation individually or as part of an NGS panel. Patient 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 evidence is sufficient to determine the effects of the technology on net health outcomes.

**Response to Treatment Using MicroRNAs (miRNAs) in Colorectal Cancer**
MicroRNAs (miRNAs) represent a recently detected class of small (typically 22 nucleotides), non-coding RNA molecules that play a key role in RNA silencing and post-transcriptional regulation of gene expression. MicroRNAs have also been associated with a number of diseases including but not limited to various cancers, neurological and cardiac diseases. MicroRNA expression levels are being investigated as possible diagnostic and prognostic biomarkers as well as predictors of drug response (Laurent-Puig, 2018).

Evidence has identified the potential of microRNA (miR) expression as a diagnostic, prognostic or predictive biomarker in various cancers, including CRC. Several miRs, miR-31, miR-31-3p, and miR-31-5p have been investigated for their association with advanced CRC and poor response to anti-EGFR therapy (Manceau, 2014; Moshakhani, 2012; Mlcochova, 2015).

Pugh (2017) retrospectively evaluated miR-31-3p expression in primary tumor samples from a group of 149 subjects with KRAS wild-type advanced metastatic CRC (mCRC) treated with oxaliplatin/irinotecan plus fluorouracil chemotherapy with (n=78) or without (n=71) cetuximab. The authors reported that progression-free survival (PFS) and overall survival (OS) were not significantly different between miR-31-3p expression groups across the whole study population. However, in the cetuximab treated group, the low-expression group had longer PFS vs. the mid- and high-expression groups (p=0.049). OS was reported to not be significantly different between the miR-31-3p expression groups in the whole modified intent-to-treat population (p=0.86), in the chemotherapy alone arm (p=0.62), or in the chemotherapy plus cetuximab arm (p=0.85). Likewise, no differences were reported in objective response rates (p=0.59, p=0.61, and p=1.0, respectively). Subjects treated with cetuximab with mid and high expression of miR-31-3p had shorter PFS compared to the chemotherapy alone group (12.3 months vs. 26.7 months, p=0.005). This difference was not seen in the low-expression group (20.3 vs. 18.9 months, p=0.91). Similar results were found with regard to OS, with the mid- and high-expression groups

treated with cetuximab having significantly lower OS vs. those in the chemotherapy alone group (hazard ratio [HR],2.5, p=0.06), and no differences found in the low-expression group (HR,1.6, p=0.49). No differences between treatment groups or expression groups were reported with regard to objective response rates (p=0.22 and p=0.77, respectively). Multivariate analysis demonstrated that the miR-31-3p expression group was a significant predictive factor for PFS in the cetuximab treated group (low expression vs. mid and high, HR, 2.1, p=0.05). The authors concluded that subjects in the low-expression group were not harmed by the addition of cetuximab.

In a retrospective study, researchers investigated the predictive role of miR-31-3p expression testing in 340 subjects with RAS Exon-2 wild-type mCRC who received first line treatment with FOLFIRI plus either cetuximab (n=164) or bevacizumab (n=176). Expression of miR-31-3p was determined to be either high or low for both treatment groups. The analysis resulted in the findings that individuals with low miR-31-3p expression had longer PFS and OS than those with high expression (PFS: 11.1 vs. 7.8 months; HR, 1.43; p<0.001; OS: 30.3 vs. 20.3 months; HR, 1.76; p<0.01). Additionally, miR-31-3p alone as a quantitative variable was a prognostic factor for both PFS and OS (p<0.01 for both). The low-expression group who received FOLFIRI plus cetuximab had PFS and OS benefits (p=0.005 and p<0.01, respectively). Compared to the low-expression group receiving treatment with bevacizumab, the cetuximab group had a median PFS benefit of 1.3 months and a median OS benefit of 12 months. In the high-expression group, treatment with cetuximab or bevacizumab provided no OS or PFS benefits. In a multivariate analysis miR-31-3p expression level was predictive of both PFS and OS. While the authors concluded that the study "suggests that MiR-31-3p expression level is a useful biomarker to further personalize the treatment of mCRC", they also acknowledged that "additional studies are warranted to determine whether similar findings would be observed in patients with mCRC treated in first line with FOLFOX plus EGFR-antibody therapy" (Laurent-Puig, 2018).

Although early studies suggest miR-31-3p expression may be a useful predictor of clinical outcomes in individuals with mCRC, additional prospective, controlled studies demonstrating that the results of miR-31-3p expression testing are able to guide therapy and result in improved clinical outcomes are needed.

The miR-31now™ assay (GoPath laboratories, LLC, Buffalo Grove, IL) has been proposed to leverage the findings reported by Pugh (2017) and Laurent-Puig (2018) in the clinical setting to identify the most appropriate therapeutic strategy for RAS wild type patients with mCRC. At this time there are no prospective published, peer-reviewed studies investigating the use of the miR-31now test for this use, and further investigation is warranted. The evidence is insufficient to determine the effects of the technology on net health outcomes.

**BRAF, KRAS and NRAS Mutational Analysis in Other Cancers**

Based on review of the peer reviewed medical literature and current NCCN guidelines BRAF, KRAS and NRAS mutation testing are supported as identified below in the Policy

section when indicated as medically necessary. The evidence is sufficient to determine the effects of the technology on net health outcomes.

Based on review of the peer reviewed medical literature and current NCCN guidelines BRAF, KRAS and NRAS mutation testing will be considered investigational per the Policy below as the evidence is insufficient to determine the effects of the technology on net health outcomes.

**Expanded Genetic Panels (51 or more genes)**
Based on review of the available peer reviewed medical literature and current NCCN guidelines mutation analysis for patients with certain cancers (see Policy) should have tumor tissue genotyped for RAS (KRAS and NRAS) and BRAF mutations. However, utilization of expanded genetic panels (51 or more genes) for any indications based on the peer reviewed medical literature is insufficient in demonstrating the clinical utility and how this expanded genetic panel testing (51 or more genes) impacts patient management. Also, clinical validity of expanded genetic panels (51 or more genes) is incomplete and may be considered excessive because it is not possible to determine the clinical validity of the panel as a whole. The evidence is insufficient in determining the technology improves net health outcomes to include changes in clinical management

**Practice Guidelines and Position Statements**

**National Comprehensive Cancer Network (NCCN)**

**Colon Cancer Version 3.2021**

**Principles of Pathologic Review**

- All patients with metastatic colorectal cancer should have tumor tissue genotyped for RAS (KRAS and NRAS) and BRAF mutation individually or as part of an NGS panel. Patient 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.
- BRAF V600E mutation testing via immunohistochemistry is also an option.
- 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 testing can be performed on formalin-fixed 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 in similar in both specimen types.

**Anal Carcinoma Version 2.2021**
There has also been interest in the use of biologic therapies for the treatment of anal cancer. Because KRAS mutations to be very rare in anal cancer, the use of an EGFR inhibitor such as cetuximab has been considered to be a promising avenue of investigation.

**B-Cell Lymphomas Version 5.2021**

**Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms**
(To be used in conjunction with clinical and morphologic correlation)

**B-cell Antigen Positive (CD19, CD20, CD79a, PAX5)**

- Genetic testing
    - BCL2, BCL6, CCND1, MYC, ALK, MYD88, BRAF, IG rearrangement

B-Cell Neoplasms

- Small cells: to include the following for confirmation of mutant protein:
    - Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)
    - Mantel cell lymphoma (MCL)
    - Splenic marginal zone lymphoma (SMZL)
    - Lymphoplasmacytic lymphoma (LPL)
    - Extranodal marginal zone lymphoma (EMZL) (MALT lymphoma)
    - Nodal marginal zone lymphoma (NMZL)
    - Follicular lymphoma (FL)
    - Pediatric – type follicular lymphoma (PTFL)

**Hairy Cell Leukemia Version 1.2022**
In the diagnosis may be useful under certain circumstances: ICH or molecular analysis to detect BRAF V600E mutation for cases that do not have cHCL immunophenotype.

HCL-Varian characteristically CD25-, CD123-, annexin A-1-, and negative for BRAF V600E mutations. This helps to distinguish the variant from cHCL.

The BRAF V600E mutation was reported in the majority of patients with classic HCL. Targeted sequencing has also identified recurrent mutations in several other genes (e.g., CDKN1B in classic HCL; MAP2K1 and CCND3 in HCL-variant). BRAF V600E mutation was absent in 10% to 20% of B-cell lymphoproliferative neoplasms with a classic HCL phenotype expression IGHV-34 rearrangement and also in call cases of HCL-variant. A high frequency of MPK2K1 mutations were reported in HCL-variant and in classic HCL with IGHV4-34 rearrangement.

Immunophenotyping is the primary methodology used to distinguish classic HCL from HCL-variant, though the role of molecular analysis is rapidly expanding. BRAF V600E mutation may serve as a reliable molecular marker to distinguish classic HCL from HCL-variant and other B-cell leukemias or lymphomas, and MAPK1 mutation analysis may be useful to distinguish HCL-variant from classic HCL in BRAF mutation-negative cases.

IHC or molecular studies for BRAF V600e mutation are useful for the distinction of classic HCL from HCL-variant and other splenic B-cell lymphomas.

**Melanoma: Cutaneous Version 1.2022**

**Principles of Molecular Testing**
Specific mutations (BRAF, NRAS, KIT) and implications

- BRAF mutations are most commonly found in the 600$^{th}$ codon (V600), most frequently V600E (80%), but also including V600K (15%) and V600R/M/D/G 5%
    - BRAF V600 mutations are associated with sensitivity to BRAF inhibitors, Available evidence suggests that BRAF inhibitors should not be used in patients without activating mutations in BRAF.
    - BRAF V600 mutations are also associated with sensitivity to MEK inhibitors.
    - Clinical trials have shown that the combination of BRAF and MEK inhibitors are superior to either agent alone in patients with BRAF V600 mutations.
    - Extensive clinical trial data have shown that compared with BRAF V600E, patients with BRAF V600K-mutated metastatic melanoma may have slightly lower response/benefit when treated with BRAF $\pm$ MEK inhibitors. Less frequent mutations affecting codon 600 (including V600R/M/D/G) also may benefit from these therapies.

- BRAF mutation testing is recommended for patients with stage III at high risk for recurrence for whom future BRAF-directed therapy may be an option.
- If BRAF single-gene testing was the initial test performed, and is negative, clinicians should strongly consider larger NGS panels to identify other potential genetic targes (e.g., KIT, BRAF non-V600).

**Histiocytic Neoplasms Version 2.2021**

**Langerhans Cell Histiocytosis and Erdheim-Chester Disease**
As part of the workup/evaluation the tissue biopsy should include BRAF V600E (VE1) immunohistochemistry (IHC). Targeted-capture, next generation sequencing (NGS) in BRAF V600E wild-type or equivocal cases for mutations in the MAPK pathway such as ARAF, NRAS, KRAS, MPA2K1, and PIK3CA, or gene fusion assay.

**Pathologic Analysis of Histiocytic Neoplasms**
Immunohistochemistry (IHC) analysis plays an important role in the diagnosis and should be carried out when a histiocytic neoplasm is suspected. The basic IHC panel should include CD163/CD68, S100, CD1a, langerin/CD, cyclin D1, and factor XIIa as indicated. BRAF V600E (VE1) IHC is recommended for LCH and ECD. IHC analysis can be helpful in the broad differential diagnosis of histiocytosis, including varied entities such as composite IgG4-related disease and B-cell lymphoma, as well as infection, fat necrosis, and idiopathic retroperitoneal fibrosis.

Next generation sequencing (NGS) of tumor tissue for identification of mutations in the RAS/RAF/MAPK/ERK and PI3K/AKT pathway genes can be instrumental in the diagnosis of histiocytic neoplasms and can also inform systemic therapy decision-making. Additionally, fusion testing should include BRAF, ALK, and NTRK1 rearrangements. If fusion panel testing is unavailable, then IHC or fluorescence in situ hybridization (FISH) may be used to evaluate for ALK rearrangements. Molecular testing can be done either in a stepwise fashion or in parallel, depending on clinical indication and institutional protocol. If a specific histiocytic disorder is suspected, then stepwise testing should be tailored based on the mutations know to be associated with that disorder.

**Gastrointestinal Stromal Tumors Version 1.2022**

**Principles of Mutation Testing**
All GISTs lacking a KIT or PDGFRA mutation should be tested for SDH deficiency and alternative driver mutations using next-generation sequencing (NGS). In addition, alternative driver mutations using NGS (e.g., BRAF, NF1, NTRK, and FGFR fusions) should be performed for potential identification of a targeted therapy.

**Small Bowel Adenocarcinoma Version 2.2021**

**Genetic Alterations in SBA**
Emerging research has shown that SBA has a distinct genetic profile, which sets it apart from CRC or gastroesophageal cancers, the two cancer types SBA is the most often likened to. While KRAS and TP53 alterations are frequently identified in both SBA and CRC, APC mutations are significantly less common in SBA (27% in SBA vs. 76% in CRC; $P < .001$) Considering the near ubiquity of APC mutation and its well-established role in CRC carcinogenesis, the suggests that neoplastic transformation in SBA is unique compared to CRC.

SMAD4 and CDKN2A mutations are more commonly seen compared to gastroesophageal cancers and CRC. Though BRAF mutations occur at a similar rate as seen in CRC, only 10% of BRAF-mutant SBAs have a V600E alteration, compared with >70% in BRAF-mutant CRC. Importantly, human epidermal growth factor receptor 2 (HER2) alterations, MSI-H/dMMR, programmed death-ligand 1 (PD-1) expression, and high tumor mutational burned are enhanced in SBA compared to CRC, and may reveal

greater importance of targeted or immunotherapeutic treatments compared to current CRC treatment algorithms.

**Central Nervous System Cancer Version 2.2021**

**Principals of Brain and Spinal Cord Tumor Systemic Therapy**

**Adult Low-Grade (WHO Grade 1 or 2) Glioma**

| | **Useful in Certain Circumstances** |
|---|---|
| Adjuvant Treatment | • PA, PDX, ganglioglioma if BRAF V600E activation mutation<br>▪ BRAF/MEK inhibitors:<br>o Debrafenib/trametinib<br>o Vemurafenib/cobimetinib |
| Recurrent or Progressive Disease | • BRAF V600E activation mutation<br>▪ BRAF/MEK inhibitors:<br>o Debrafenib/trametinib<br>o Vemurafenib/cobimetinib<br>▪ MEK inhibitor<br>o Selumetinib (for PA with BRAF fusion or BRAF V600E activating mutation) |

**Anaplastic Gliomas**

| | **Useful in Certain Circumstances** |
|---|---|
| Recurrence Therapy | • BRAF V600E activation mutation<br>▪ BRAF/MEK inhibitors:<br>o Debrafenib/trametinib<br>o Vemurafenib/cobimetinib |

**Glioblastoma**

| | **Useful in Certain Circumstances** |
|---|---|
| Recurrence Therapy | • BRAF V600E activation mutation<br>▪ BRAF/MEK inhibitors:<br>o Debrafenib/trametinib<br>o Vemurafenib/cobimetinib |

**Pancreatic Cancer Version 2.2021**

Tumor/somatic gene profiling is recommended for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify uncommon mutations. Consider specifically testing for actional somatic findings

including, but not limited to fusions (ALK, NRG1, NTRK, ROS1) mutations (BRAF, BRCA 1/2, HER2, KRAS, PALB2), and MMR deficiency (detected by tumor IHC, PCR or NGS). Testing on tumor tissue is preferred.

**Biopsy**
Evolving changes in molecular analysis of pancreatic cancer have led some institutions to attempt to procure additional tumor-rich, formalin-fixed, paraffin-embedded tissue to bank for future genomic studies. Several methods can be used to obtain such tissue samples, including core biopsy, but the panel believes that core biopsies should not replace EUS-guided FNA. Some of the most common somatic mutations in pancreatic cancer are KRAS, TP53, CDKN2A, and SMAD4. Molecularly targeted therapies for pancreatic cancer are being developed and investigated.

**Rectal Cancer Version 2.2021**

**Principles of Pathologic Review**

- All patients with metastatic colorectal cancer should have tumor tissue genotyped for RAS (KRAS and NRAS) and BRAF mutation individually or as part of an NGS panel. Patient 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.
- BRAF V600E mutation testing via immunohistochemistry is also an option.
- 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 testing can be performed on formalin-fixed 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 in similar in both specimen types.

**Breast Cancer Version 2.2022**
The current NCCN guideline does not indicate mutation analysis for breast cancer using BRAF, KRAS or NRAS in diagnosis, treatment, or monitoring.

**Prostate Cancer Version 3.2022**
The current NCCN guideline does not indicate mutation analysis for prostate cancer using BRAF, KRAS or NRAS in diagnosis, treatment, or monitoring.

**Small Cell Lung Cancer Version 2.2022**
The current NCCN guideline does not indicate mutation analysis for small cell lung cancer using BRAF, KRAS or NRAS in diagnosis, treatment, or monitoring.

**American Society of Clinical Oncology (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.

**American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology (2017)**

**Guideline Statements**
Colorectal carcinoma patients being considered for anti-epidermal growth factor receptor (EGFR) therapy must receive RAS (rat sarcoma viral oncogene homolog) mutational testing. Mutational analysis should include KRAS (Kirsten rat sarcoma viral oncogene homolog) and NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) codons 12, 13 of exon 2; 59, 61 of exon 3; and 117 and 146 of exon 4 ("expanded" or "extended" RAS) (Type: recommendation; Strength of Evidence: convincing/adequate, benefits outweigh harms; Quality of Evidence: high/intermediate).

BRAF (V-raf murine sarcoma viral oncogene homolog B1) p.V600 (BRAF c. 1799 [p.V600]) position mutational status is recommended for prognostic stratification in selected patients with CRC (Recommendation 2a) and that there is insufficient evidence to recommend BRAF pV600 mutational status as a predictive molecular biomarker for response to anti-EGFR inhibitors (Recommendation 4).

BRAF p.V600 mutational analysis should be performed in deficient mismatch repair (MMR) tumors with loss of MLH1 (MutL homolog 1) to evaluate for Lynch syndrome risk. Presence of a BRAF mutation strongly favors a sporadic pathogenesis. The absence of BRAF mutation does not exclude risk of Lynch syndrome (Type: recommendation; Strength of Evidence: adequate/inadequate, balance of benefits and harms; Quality of Evidence: intermediate/low).

**Regulatory Status**
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. KRAS, NRAS, and BRAF variant analyses using polymerase chain reaction methodology are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed under the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test. No liquid biopsy test is currently FDA approved to select treatment for patients with metastatic colorectal cancer.

# PRIOR APPROVAL

Not applicable.

# POLICY

**See related policies:**

- 02.04.65 Molecular Markers in Fine Needle Aspirates of the Thyroid
- 02.04.78 Molecular Analysis for Targeted Therapy of Non-Small Cell Lung Cancer
- 02.04.79 Circulating Tumor DNA for Management of Non-Small Cell Lung Cancer (Liquid Biopsy)
- 02.04.16 Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsies)
- 02.04.63 Expanded Genetic Panels to Identify Targeted Cancer Therapy

**Anal Cancer**
Analysis of KRAS and NRAS status is considered **medically necessary** to predict treatment response to the anti-EGFR monoclonal antibody cetuximab (Erbitux), or panitumumab (Vectibix) in individuals with anal carcinoma prior to initiation of cetuximab (Erbitux) or panitumumab (Vectibix).

**B-Cell Lymphomas**
BRAF sequencing may be considered **medically necessary** in B-cell neoplasms i.e., small cell neoplasms to include the following for confirmation of mutant protein (Annexin A1):

- Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)
- Mantel cell lymphoma (MCL)
- Splenic marginal zone lymphoma (SMZL)
- Lymphoplasmacytic lymphoma (LPL)
- Extranodal marginal zone lymphoma (EMZL) (MALT lymphoma)
- Nodal marginal zone lymphoma (NMZL)
- Follicular lymphoma (FL)
- Pediatric – type follicular lymphoma (PTFL)

**Colorectal Cancer**
KRAS, NRAS, and BRAF V600E mutation tumor analysis may be considered **medically necessary** to predict nonresponse to cetuximab and panitumumab in the treatment of metastatic (Stage IV) colorectal cancer prior to the initiation of therapy.

The Praxis Extended RAS panel (0111U) (tissue analysis, for consideration of panitumumab [vectibix]) in the treatment of metastatic stage IV colorectal cancer may be considered **medically necessary** prior to initiation of therapy.

The miR-31now™ (0069U) microRNA, RT-PCR expression profiling for colorectal cancer is considered **investigational,** because the evidence is insufficient to determine the effects of the technology on net health outcomes.

**Gastrointestinal Stromal Tumor (GIST)**
BRAF mutation analysis as an alternative driver mutation in an individual with a diagnosis of gastrointestinal stromal tumors (GISTs) lacking KIT or PDGFRA mutations may be considered **medically necessary** for potential identification of targeted therapy prior to initiation of therapy.

**Glioma**
BRAF sequencing BRAF or BRAF V600E mutation analysis in gliomas may be considered **medically necessary** for the following indications:

- Adult low grade (WHO Grade 1 or 2) glioma
    - For management decisions related to adjuvant treatment related to BRAF/MEK inhibitors (dabrafenib/trametinib or vermurafenib/cobimetinib) prior to initiation of therapy; **or**
    - Management decisions for recurrent or progressive disease related BRAF/MEK inhibitors (dabrafenib/trametinib or vermurafenib/cobimetinib) or MEK inhibitor (selumetnib) prior to initiation of therapy.
- Anaplastic glioma for management decisions for recurrence therapy for BRAF/MEK inhibitors (dabrafenib/trametinib or vermurafenib/cobimetinib) prior to initiation of therapy.
- Glioblastoma for management decisions related to recurrence therapy for BRAF/MEK inhibitors (dabrafenib/trametinib or vermurafenib/cobimetinib) prior to initiation of therapy.

**Hairy Cell Leukemia**
BRAF V600E mutation analysis may be considered **medically necessary** to distinguish classical hairy cell leukemia (cHCL) from HCL-variant and other B-Cell leukemias or lymphomas.

**Histiocytic Neoplasms (Langerhans Cell Histiocytosis and Erdheim-Chester Disease**
BRAF V600E, NRAS and KRAS mutation analysis for Langerhans Cell Histiocytosis (LCH) or Erdheim-Chester Disease may be considered **medically necessary** in the diagnosis when one of these histiocytic neoplasms is suspected.

**Melanoma: Cutaneous**
BRAF mutation analysis with a diagnosis of **stage III or IV metastatic or unresectable melanoma** to predict nonresponse to nivolumab, pembrolizumab, vemurafenib, dabrafenib plus trametinib may be considered **medically necessary** prior to initiation of therapy.

**Pancreatic Cancer**
BRAF and KRAS mutations may be considered medically necessary using tumor tissue for patients with locally advanced or metastatic disease who are candidates for anti-cancer therapy to identify uncommon mutations prior to initiation of therapy.

KRAS, NRAS or BRAF mutation analysis not meeting the above criteria and for the following indications, is considered **investigational,** because the evidence is insufficient to determine the effects of the technology on net health outcomes.

- Benign Neoplasms
- Breast Cancer
- Lung Cancers except NSCLC (see the above related medical policies)
- Prostate Cancer
- Small bowel adenocarcinoma

**Expanded Genetic Panels (51 or more genes)**
Expanded genetic panels (51 or more genes, 81455) for the analysis of RAS (KRAS and NRAS) and BRAF mutations is considered **investigational** for any indication, because utilization of expanded genetic panels (51 or more genes) for any indications based on the peer reviewed medical literature is insufficient in demonstrating the clinical utility and how this expanded genetic panel testing (51 or more genes) impacts patient management. Also, clinical validity of expanded genetic panels (51 or more genes) is incomplete and may be considered excessive because it is not possible to determine the clinical validity of the panel as a whole. The evidence is insufficient in determining the technology improves net health outcomes to include changes in clinical management.

# PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 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)
  81406 Molecular pathology procedure level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons) ACADVL (acyl-CoA dehydrogenase, very long chain) (e.g., very long chain acyl-coenzyme A dehydrogenase deficiency), full gene sequence ACTN4 (actinin, alpha 4) (e.g., focal segmental glomerulosclerosis), full gene sequence

AFG3L2 (AFG3 ATPase family gene 3-like 2 [S. cerevisiae]) (e.g., spinocerebellar ataxia), full gene sequence AIRE (autoimmune regulator) (e.g., autoimmune polyendocrinopathy syndrome type 1), full gene sequence ALDH7A1 (aldehyde dehydrogenase 7 family, member A1) (e.g., pyridoxine-dependent epilepsy), full gene sequence ANO5 (anoctamin 5) (e.g., limb-girdle muscular dystrophy), full gene sequence ANOS1 (anosmin-1) (e.g., Kallmann syndrome 1), full gene sequence APP (amyloid beta [A4] precursor protein) (e.g., Alzheimer disease), full gene sequence ASS1 (argininosuccinate synthase 1) (e.g., citrullinemia type I), full gene sequence ATL1 (atlastin GTPase 1) (e.g., spastic paraplegia), full gene sequence ATP1A2 (ATPase, Na+/K+ transporting, alpha 2 polypeptide) (e.g., familial hemiplegic migraine), full gene sequence ATP7B (ATPase, Cu++ transporting, beta polypeptide) (eg, Wilson disease), full gene sequence BBS1 (Bardet-Biedl syndrome 1) (e.g., Bardet-Biedl syndrome), full gene sequence BBS2 (Bardet-Biedl syndrome 2) (e.g., Bardet-Biedl syndrome), full gene sequence BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (e.g., maple syrup urine disease, type 1B), full gene sequence BEST1 (bestrophin 1) (eg, vitelliform macular dystrophy), full gene sequence BMPR2 (bone morphogenetic protein receptor, type II [serine/threonine kinase]) (e.g., heritable pulmonary arterial hypertension), full gene sequence BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, Noonan syndrome), full gene sequence BSCL2 (Berardinelli-Seip congenital lipodystrophy 2 [seipin]) (eg, Berardinelli-Seip congenital lipodystrophy), full gene sequence BTK (Bruton agammaglobulinemia tyrosine kinase) (e.g., X-linked agammaglobulinemia), full gene sequence CACNB2 (calcium channel, voltage-dependent, beta 2 subunit) (eg, Brugada syndrome), full gene sequence CAPN3 (calpain 3) (e.g., limb-girdle muscular dystrophy [LGMD] type 2A, calpainopathy), full gene sequence CBS (cystathionine-beta-synthase) (eg, homocystinuria, cystathionine beta-synthase deficiency), full gene sequence CDH1 (cadherin 1, type 1, E-cadherin [epithelial]) (eg, hereditary diffuse gastric cancer), full gene sequence CDKL5 (cyclin-dependent kinase-like 5) (e.g., early infantile epileptic encephalopathy), full gene sequence CLCN1 (chloride channel 1, skeletal muscle) (e.g., myotonia congenita), full gene sequence CLCNKB (chloride channel, voltage-sensitive Kb) (e.g., Bartter syndrome 3 and 4b), full gene sequence CNTNAP2 (contactin-associated protein-like 2) (e.g., Pitt-Hopkins-like syndrome 1), full gene sequence COL6A2 (collagen, type VI, alpha 2) (e.g., collagen type VI-related disorders), duplication/deletion analysis CPT1A (carnitine palmitoyltransferase 1A [liver]) (e.g., carnitine palmitoyltransferase 1A [CPT1A] Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons) ACADVL (acyl-CoA dehydrogenase, very long chain) (e.g., very long chain acyl-coenzyme A dehydrogenase deficiency), full gene sequence ACTN4 (actinin, alpha 4) (e.g., focal segmental glomerulosclerosis), full gene sequence AFG3L2 (AFG3 ATPase family gene 3-like 2 [S. cerevisiae]) (e.g., spinocerebellar ataxia), full gene sequence AIRE (autoimmune regulator) (e.g., autoimmune polyendocrinopathy syndrome type 1), full gene sequence ALDH7A1 (aldehyde dehydrogenase 7

family, member A1) (e.g., pyridoxine-dependent epilepsy), full gene sequence ANO5 (anoctamin 5) (e.g., limb-girdle muscular dystrophy), full gene sequence ANOS1 (anosmin-1) (e.g., Kallmann syndrome 1), full gene sequence APP (amyloid beta [A4] precursor protein) (e.g., Alzheimer disease), full gene sequence ASS1 (argininosuccinate synthase 1) (e.g., citrullinemia type I), full gene sequence ATL1 (atlastin GTPase 1) (e.g., spastic paraplegia), full gene sequence ATP1A2 (ATPase, Na+/K+ transporting, alpha 2 polypeptide) (e.g., familial hemiplegic migraine), full gene sequence ATP7B (ATPase, Cu++ transporting, beta polypeptide) (e.g., Wilson disease), full gene sequence BBS1 (Bardet-Biedl syndrome 1) (e.g., Bardet-Biedl syndrome), full gene sequence BBS2 (Bardet-Biedl syndrome 2) (e.g., Bardet-Biedl syndrome), full gene sequence BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, maple syrup urine disease, type 1B), full gene sequence BEST1 (bestrophin 1) (eg, vitelliform macular dystrophy), full gene sequence BMPR2 (bone morphogenetic protein receptor, type II [serine/threonine kinase]) (eg, heritable pulmonary arterial hypertension), full gene sequence BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, Noonan syndrome), full gene sequence BSCL2 (Berardinelli-Seip congenital lipodystrophy 2 [seipin]) (eg, Berardinelli-Seip congenital lipodystrophy), full gene sequence BTK (Bruton agammaglobulinemia tyrosine kinase) (eg, X-linked agammaglobulinemia), full gene sequence CACNB2 (calcium channel, voltage-dependent, beta 2 subunit) (eg, Brugada syndrome), full gene sequence CAPN3 (calpain 3) (eg, limb-girdle muscular dystrophy [LGMD] type 2A, calpainopathy), full gene sequence CBS (cystathionine-beta-synthase) (eg, homocystinuria, cystathionine beta-synthase deficiency), full gene sequence CDH1 (cadherin 1, type 1, E-cadherin [epithelial]) (eg, hereditary diffuse gastric cancer), full gene sequence CDKL5 (cyclin-dependent kinase-like 5) (eg, early infantile epileptic encephalopathy), full gene sequence CLCN1 (chloride channel 1, skeletal muscle) (eg, myotonia congenita), full gene sequence CLCNKB (chloride channel, voltage-sensitive Kb) (eg, Bartter syndrome 3 and 4b), full gene sequence CNTNAP2 (contactin-associated protein-like 2) (eg, Pitt-Hopkins-like syndrome 1), full gene sequence COL6A2 (collagen, type VI, alpha 2) (eg, collagen type VI-related disorders), duplication/deletion analysis CPT1A (carnitine palmitoyltransferase 1A [liver]) (eg, carnitine palmitoyltransferase 1A [CPT1A] deficiency), full gene sequence CRB1 (crumbs homolog 1 [Drosophila]) (eg, Leber congenital amaurosis), full gene sequence CREBBP (CREB binding protein) (eg, Rubinstein-Taybi syndrome), duplication/deletion analysis DBT (dihydrolipoamide branched chain transacylase E2) (eg, maple syrup urine disease, type 2), full gene sequence DLAT (dihydrolipoamide S-acetyltransferase) (eg, pyruvate dehydrogenase E2 deficiency), full gene sequence DLD (dihydrolipoamide dehydrogenase) (eg, maple syrup urine disease, type III), full gene sequence DSC2 (desmocollin) (eg, arrhythmogenic right ventricular dysplasia/cardiomyopathy 11), full gene sequence DSG2 (desmoglein 2) (eg, arrhythmogenic right ventricular dysplasia/cardiomyopathy 10), full gene sequence DSP (desmoplakin) (eg, arrhythmogenic right ventricular dysplasia/cardiomyopathy 8), full gene sequence

EFHC1 (EF-hand domain [C-terminal] containing 1) (eg, juvenile myoclonic epilepsy), full gene sequence EIF2B3 (eukaryotic translation initiation factor 2B, subunit 3 gamma, 58kDa) (eg, leukoencephalopathy with vanishing white matter), full gene sequence EIF2B4 (eukaryotic translation initiation factor 2B, subunit 4 delta, 67kDa) (eg, leukoencephalopathy with vanishing white matter), full gene sequence EIF2B5 (eukaryotic translation initiation factor 2B, subunit 5 epsilon, 82kDa) (eg, childhood ataxia with central nervous system hypomyelination/vanishing white matter), full gene sequence ENG (endoglin) (eg, hereditary hemorrhagic telangiectasia, type 1), full gene sequence EYA1 (eyes absent homolog 1 [Drosophila]) (eg, branchio-oto-renal [BOR] spectrum disorders), full gene sequence F8 (coagulation factor VIII) (eg, hemophilia A), duplication/deletion analysis FAH (fumarylacetoacetate hydrolase [fumarylacetoacetase]) (eg, tyrosinemia, type 1), full gene sequence FASTKD2 (FAST kinase domains 2) (eg, mitochondrial respiratory chain complex IV deficiency), full gene sequence FIG4 (FIG4 homolog, SAC1 lipid phosphatase domain containing [S. cerevisiae]) (eg, Charcot-Marie-Tooth disease), full gene sequence FTSJ1 (FtsJ RNA methyltransferase homolog 1 [E. coli]) (eg, X-linked mental retardation 9), full gene sequence FUS (fused in sarcoma) (eg, amyotrophic lateral sclerosis), full gene sequence GAA (glucosidase, alpha; acid) (eg, glycogen storage disease type II [Pompe disease]), full gene sequence GALC (galactosylceramidase) (eg, Krabbe disease), full gene sequence GALT (galactose-1-phosphate uridylyltransferase) (eg, galactosemia), full gene sequence GARS (glycyl-tRNA synthetase) (eg, Charcot-Marie-Tooth disease), full gene sequence GCDH (glutaryl-CoA dehydrogenase) (eg, glutaricacidemia type 1), full gene sequence GCK (glucokinase [hexokinase 4]) (eg, maturity-onset diabetes of the young [MODY]), full gene sequence GLUD1 (glutamate dehydrogenase 1) (eg, familial hyperinsulinism), full gene sequence GNE (glucosamine [UDP-N-acetyl]-2-epimerase/N-acetylmannosamine kinase) (eg, inclusion body myopathy 2 [IBM2], Nonaka myopathy), full gene sequence GRN (granulin) (eg, frontotemporal dementia), full gene sequence HADHA (hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase [trifunctional protein] alpha subunit) (eg, long chain acyl-coenzyme A dehydrogenase deficiency), full gene sequence HADHB (hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase [trifunctional protein], beta subunit) (eg, trifunctional protein deficiency), full gene sequence HEXA (hexosaminidase A, alpha polypeptide) (eg, Tay-Sachs disease), full gene sequence HLCS (HLCS holocarboxylase synthetase) (eg, holocarboxylase synthetase deficiency), full gene sequence HMBS (hydroxymethylbilane synthase) (eg, acute intermittent porphyria), full gene sequence HNF4A (hepatocyte nuclear factor 4, alpha) (eg, maturity-onset diabetes of the young [MODY]), full gene sequence IDUA (iduronidase, alpha-L-) (eg, mucopolysaccharidosis type I), full gene sequence INF2 (inverted formin, FH2 and WH2 domain containing) (eg, focal segmental glomerulosclerosis), full gene sequence IVD (isovaleryl-CoA dehydrogenase) (eg, isovaleric acidemia), full gene sequence JAG1 (jagged 1) (eg, Alagille syndrome), duplication/deletion analysis JUP (junction plakoglobin) (eg, arrhythmogenic

right ventricular dysplasia/cardiomyopathy 11), full gene sequence KCNH2 (potassium voltage-gated channel, subfamily H [eag-related], member 2) (eg, short QT syndrome, long QT syndrome), full gene sequence KCNQ1 (potassium voltage-gated channel, KQT-like subfamily, member 1) (eg, short QT syndrome, long QT syndrome), full gene sequence KCNQ2 (potassium voltage-gated channel, KQT-like subfamily, member 2) (eg, epileptic encephalopathy), full gene sequence LDB3 (LIM domain binding 3) (eg, familial dilated cardiomyopathy, myofibrillar myopathy), full gene sequence LDLR (low density lipoprotein receptor) (e.g. familial hypercholesterolemia) full gene sequence, *LEPR (leptin receptor*(eg, obesity with hypogonadism), full gene sequence, *LHCGR (luteinizing hormone/choriogonadotropin receptor)* (eg, precocious male puberty), full gene sequence, *LMNA (lamin A/C)* (eg, Emery-Dreifuss muscular dystrophy [EDMD1, 2 and 3] limb-girdle muscular dystrophy [LGMD] type 1B, dilated cardiomyopathy [CMD1A], familial partial lipodystrophy [FPLD2]), full gene sequence, *LRP5 (low density lipoprotein receptor-related protein 5)* (eg, osteopetrosis), full gene sequence, *MAP2K1 (mitogen-activated protein kinase 1)* (eg, cardiofaciocutaneous syndrome), full gene sequence, *MAP2K2 (mitogen-activated protein kinase 2)* (eg, cardiofaciocutaneous syndrome), full gene sequence, *MAPT (microtubule-associated protein tau)* (eg, frontotemporal dementia), full gene sequence, *MCCC1 (methylcrotonoyl-CoA carboxylase 1 [alpha])* (eg, 3-methylcrotonyl-CoA carboxylase deficiency), full gene sequence, *MCCC2 (methylcrotonoyl-CoA carboxylase 2 [beta])* (eg, 3-methylcrotonyl carboxylase deficiency), full gene sequence, *MFN2 (mitofusin 2)* (eg, Charcot-Marie-Tooth disease), full gene sequence, *MTM1 (myotubularin 1)* (eg, X-linked centronuclear myopathy), full gene sequence, *MUT (methylmalonyl CoA mutase)* (eg, methylmalonic acidemia), full gene sequence, *MUTYH (mutY homolog [E. coli])* (eg, MYH-associated polyposis), full gene sequence, *NDUFS1 (NADH dehydrogenase [ubiquinone] Fe-S protein 1, 75kDa [NADH-coenzyme Q reductase])* (eg, Leigh syndrome, mitochondrial complex I deficiency), full gene sequence, ***NF2*** *(neurofibromin 2 [merlin])* (eg, neurofibromatosis, type 2), full gene sequence, *NOTCH3 (notch 3)* (eg, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL]), targeted sequence analysis (eg, exons 1-**23**), *NPC1 (Niemann-Pick disease, type C1)* (eg, Niemann-Pick disease), full gene sequence, *NPHP1 (nephronophthisis 1 [juvenile])* (eg, Joubert syndrome), full gene sequence, *NSD1 (nuclear receptor binding SET domain protein 1)* (eg, Sotos syndrome), full gene sequence, *OPA1 (optic atrophy 1)* (eg, optic atrophy), duplication/deletion analysis, *OPTN (optineurin)* (eg, amyotrophic lateral sclerosis), full gene sequence, *PAFAH1B1 (platelet-activating factor acetylhydrolase 1b, regulatory subunit 1 [45kDa])* (eg, lissencephaly, Miller-Dieker syndrome), full gene sequence, *PAH (phenylalanine hydroxylase)* (eg, phenylketonuria), full gene sequence, *PALB2 (partner and localizer of BRCA2)* (eg, breast and pancreatic cancer), full gene sequence, *PARK2 (Parkinson protein 2, E3 ubiquitin protein ligase [parkin])* (eg, Parkinson disease), full gene sequence, *PAX2 (paired box 2)* (eg, renal coloboma syndrome), full gene sequence, *PC (pyruvate carboxylase)* (eg, pyruvate carboxylase

deficiency), full gene sequence, *PCCA (propionyl CoA carboxylase, alpha polypeptide)* (eg, propionic acidemia, type 1), full gene sequence, *PCCB (propionyl CoA carboxylase, beta polypeptide)* (eg, propionic acidemia), full gene sequence, *PCDH15 (protocadherin-related **15**)* (eg, Usher syndrome type 1F), duplication/deletion analysis, *PCSK9 (proprotein convertase subtilisin/kexin type 9)* (eg familial hypercholesterolemia), full gene sequence, *PDHA1 (pyruvate dehydrogenase [lipoamide] alpha 1)* (eg, lactic acidosis), full gene sequence, *PDHX (pyruvate dehydrogenase complex, component X)* (eg, lactic acidosis), full gene sequence, *PHEX (phosphate-regulating endopeptidase homolog, X-linked)* (eg, hypophosphatemic rickets), full gene sequence, *PKD2 (polycystic kidney disease 2 [autosomal dominant])* (eg, polycystic kidney disease), full gene sequence, *PKP2 (plakophilin 2)* (eg, arrhythmogenic right ventricular dysplasia/cardiomyopathy 9), full gene sequence, *PNKD* (eg, paroxysmal nonkinesigenic dyskinesia), full gene sequence, *POLG (polymerase [DNA directed], gamma)* (eg, Alpers-Huttenlocher syndrome, autosomal dominant progressive external ophthalmoplegia), full gene sequence, *POMGNT1 (protein O-linked mannose beta1, 2-N acetylglucosaminyltransferase)* (eg, muscle-eye-brain disease, Walker-Warburg syndrome), full gene sequence, *POMT1 (protein-O-mannosyltransferase 1)* (eg, limb-girdle muscular dystrophy [LGMD] type 2K, Walker-Warburg syndrome), full gene sequence, *POMT2 (protein-O-mannosyltransferase 2)* (eg, limb-girdle muscular dystrophy [LGMD] type 2N, Walker-Warburg syndrome), full gene sequence, *PPOX (protoporphyrinogen oxidase)* (eg, variegate porphyria), full gene sequence, *PRKAG2 (protein kinase, AMP-activated, gamma 2 non-catalytic subunit)* (eg, familial hypertrophic cardiomyopathy with Wolff-Parkinson-White syndrome, lethal congenital glycogen storage disease of heart), full gene sequence, *PRKCG (protein kinase C, gamma)* (eg, spinocerebellar ataxia), full gene sequence, *PSEN2 (presenilin 2[Alzheimer's disease 4])* (eg, Alzheimer's disease), full gene sequence, *PTPN11 (protein tyrosine phosphatase, non-receptor type **11**)* (eg, Noonan syndrome, LEOPARD syndrome), full gene sequence, *PYGM (phosphorylase, glycogen, muscle)* (eg, glycogen storage disease type V, McArdle disease), full gene sequence, *RAF1 (v-raf-1 murine leukemia viral oncogene homolog 1)* (eg, LEOPARD syndrome), full gene sequence, *RET (ret proto-oncogene)* (eg, Hirschsprung disease), full gene sequence, *RPE65 (retinal pigment epithelium-specific protein 65kDa)* (eg, retinitis pigmentosa, Leber congenital amaurosis), full gene sequence, *RYR1 (ryanodine receptor 1, skeletal)* (eg, malignant hyperthermia), targeted sequence analysis of exons with functionally-confirmed mutations, *SCN4A (sodium channel, voltage-gated, type IV, alpha subunit)* (eg, hyperkalemic periodic paralysis), full gene sequence, *SCNN1A (sodium channel, nonvoltage-gated 1 alpha)* (eg, pseudohypoaldosteronism), full gene sequence, *SCNN1B (sodium channel, nonvoltage-gated 1, beta)* (eg, Liddle syndrome, pseudohypoaldosteronism), full gene sequence, *SCNN1G (sodium channel, nonvoltage-gated 1, gamma)* (eg, Liddle syndrome, pseudohypoaldosteronism), full gene sequence, *SDHA (succinate dehydrogenase complex, subunit A, flavoprotein [Fp])* (eg, Leigh syndrome, mitochondrial complex II deficiency),

full gene sequence, *SETX (senataxin)* (eg, ataxia), full gene sequence, *SGCE (sarcoglycan, epsilon)* (eg, myoclonic dystonia), full gene sequence, *SH3TC2 (**SH3** domain and tetratricopeptide repeats 2)* (eg, Charcot-Marie-Tooth disease), full gene sequence, *SLC9A6 (solute carrier family 9 [sodium/hydrogen exchanger], member 6)* (eg, Christianson syndrome), full gene sequence, *SLC26A4 (solute carrier family **26**, member 4)* (eg, Pendred syndrome), full gene sequence, *SLC37A4 (solute carrier family **37** [glucose-6-phosphate transporter], member 4)* (eg, glycogen storage disease type Ib), full gene sequence, *SMAD4 (SMAD family member 4)* (eg, hemorrhagic telangiectasia syndrome, juvenile polyposis), full gene sequence, *SOS1 (son of sevenless homolog 1)* (eg, Noonan syndrome, gingival fibromatosis), full gene sequence, *SPAST (spastin)* (eg, spastic paraplegia), full gene sequence, *SPG7 (spastic paraplegia 7 [pure and complicated autosomal recessive])* (eg, spastic paraplegia), full gene sequence, *STXBP1 (syntaxin-binding protein 1)* (eg, epileptic encephalopathy), full gene sequence, *TAZ (tafazzin)* (eg, methylglutaconic aciduria type 2, Barth syndrome), full gene sequence, *TCF4 (transcription factor 4)* (eg, Pitt-Hopkins syndrome), full gene sequence, *TH (tyrosine hydroxylase)* (eg, Segawa syndrome), full gene sequence, *TMEM43 (transmembrane protein **43**)* (eg, arrhythmogenic right ventricular cardiomyopathy), full gene sequence, *TNNT2 (troponin T, type 2 [cardiac])* (eg, familial hypertrophic cardiomyopathy), full gene sequence, *TRPC6 (transient receptor potential cation channel, subfamily C, member 6)* (eg, focal segmental glomerulosclerosis), full gene sequence, *TSC1 (tuberous sclerosis 1)* (eg, tuberous sclerosis), full gene sequence, *TSC2 (tuberous sclerosis 2)* (eg, tuberous sclerosis), duplication/deletion analysis, *UBE3A (ubiquitin protein ligase **E3A**)* (eg, Angelman syndrome) full gene sequence, *UMOD (uromodulin)* (eg, glomerulocystic kidney disease with hyperuricemia and isosthenuria), full gene sequence, *VWF (von Willebrand factor)* (von Willebrand disease type 2A), extended targeted sequence analysis (eg, exons **11**-**16**, **24**-**26**, **51**, **52**), *WAS (Wiskott-Aldrich syndrome [eczema-thrombocytopenia])* (eg, Wiskott-Aldrich syndrome), full gene sequence

- 81455 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
- 81456 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis

- 0111U Oncology (colon cancer), targeted KRAS (codons 12, 13, and 61) and NRAS (codons 12, 13, 61) gene analysis using formalin-fixed-paraffin-embedded tissue (Praxis™ Extended RAS Panel Test)
- 0069U Oncology (colorectal), microRNA, RT-PCR expression profiling of miR-31-3p, formalin-fixed paraffin-embedded tissue, algorithm reported as an expression score (miR-31now™)

# SELECTED REFERENCES


- Amado RG, Wolf M, Peeters M et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008; 26(10):1626-34.
- Linardou H, Dahabreh IJ, Kanaloupiti D et al. Assessment of somatic k-RAS mutations as a mechanism associated with resistance to EGFR-targeted agents: a systematic review and meta-analysis of studies in advanced non-small-cell lung cancer and metastatic colorectal cancer. Lancet Oncology 2008 Sept 17. [Epub ahead of print].
- Lievre A, Bachet JB, Boige V et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. J Clin Oncol 2008; 26(3):374-9.
- Van Cutsem E, Peeters M, Siena S et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 2007; 25(13):1658-64.
- Khambata-Ford S, Garrett CR, Meropol NJ et al. Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. J Clin Oncol 2007; 25(22):3230-7.
- Punt CJ, Tol J, Rodenburg CJ et al. Randomized phase III study of capecitabine, oxaliplatin, and bevacizumab with or without cetuximab in advanced colorectal cancer (ACC), the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG). J Clin Oncol 2008; 26(15 suppl); abstract LBA4011.
- De Roock W, Piessevaux H, De Schutter J et al. KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab. Ann Oncol. 2008 Mar;19(3):508-15. [E-pub 2007 Nov 12].
- Peeters M, Balfour J, Arnold D. Review Article: Panitumumab- A fully human anti-EGFR monoclonal antibody for treatment of metastatic colorectal cancer. Aliment Pharmacol Ther. 2008;28(3):269-81.
- Amado RG, Wolf M, Peeters M et al. Wild-Type KRAS is required for Panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol. 2008 Apr 1; 26(10):1626-34.

- Karapetis CS, Khambata-Ford S, Jonker DJ et al. K-ras Mutations and Benefit from Cetuximab in Advanced Colorectal Cancer. N Engl J Med 2008 Oct 23;359 (17):1757-65.
- Price TJ, Hardingham JE, Lee CK et al. Impact of KRAS and BRAF gene mutation status on outcomes from the phase III AGITG MAX Trial of capecitabine alone or in combination with bevacizumab and mitomycin in advanced colorectal cancer. J Clin Oncol 2011;29(19): 2675-82.
- Dahabreh IJ, Terasawa T, Castaldi PJ et al. Systematic review: Anti-epidermal growth factor receptor treatment effect modification by KRAS mutations in advanced colorectal cancer. Ann Intern med. 2011;154:37-49.
- Santini D, Spoto C, Loupakis F et al. High concordance of BRAF status between primary colorectal tumours and related metastatic sites: implications for clinical practice. Ann Oncol 2012; 21:1565.
- Mao C, Liao RY, Qiu LX et al. BRAF V600E mutation and resistance to anti-EGFR monoclonal antibodies in patients with metastatic colorectal cancer: a meta-analysis. Mol Biol Rep 2011;38(4):2219-23.
- Maughan TS, Adams RA, Smith CG et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomized phase 3 MRC COIN trial. Lancet 2011;377(9783):2103-14.
- NCCN Clinical Practice Guidelines in Oncology™. Colon cancer. Version 3.2021 Cancer Network, Inc. Also available at https://www.nccn.org
- NCCN Clinical Practice Guidelines in Oncology™. Rectal cancer. Version 2.2021 Cancer Network, Inc. Also available at https://www.nccn.org
- NCCN Clinical Practice Guidelines in Oncology™. Anal Carcinoma. Version 2.2021 Cancer Network, Inc. Also available at https://www.nccn.org
- NCCN Clinical Practice Guidelines in Oncology™. Melanoma: Cutaneous Version 1.2022 Cancer Network, Inc. Also available at https://www.nccn.org
- NCCN Clinical Guidelines in Oncology. Acute Lymphoblastic Leukemia. Version 1.2021 Cancer Network, Inc. Also available at https://www.nccn.org
- NCCN Clinical Practice Guidelines in Oncology™. Hairy Cell Leukemia. Version 1.2022 Cancer Network, Inc. Also available at https://www.nccn.org
- NCCN Clinical Practice Guidelines in Oncology™. Soft Tissue Sarcoms/Gastrointestinal Stromal Tumors (GIST). Version 1.2022 Cancer Network, Inc. Also available at https://www.nccn.org
- NCCN Clinical Practice Guidelines in Oncology™. Small Bowel Adenocarcinoma Version 2.2021 Cancer Network, Inc. Also available at https://www.nccn.org
- NCCN Clinical Practice Guidelines in Oncology™. Central Nervous System Cancer Version 2.2021 Cancer Network, Inc. Also available at https://www.nccn.org
- NCCN Clinical Practice Guidelines in Oncology™ Pancreatic Adenocarcinoma Version 2.2021. Also available at https://www.nccn.org
- NCCN Clinical Practice Guidelines in Oncology™. Breast Cancer Version 2.2022. Also available at https://www.nccn.org

- NCCN Clinical Practice Guidelines in Oncology™. Small Cell Lung Cancer Version 2.2022. Also available at https://www.nccn.org
- NCCN Clinical Practice Guidelines in Oncology™. Prostate Cancer Version 3.2022. Also available at https://www.nccn.org
- NCCN Clinical Practice Guidelines in Oncology™. Histiocytic Neoplasms Version 2.2021. Also available at https://www.nccn.org
- Bokemeyer C., Cutsem E.V., Rougier P., Ciardiello F., Heeger S., Schlichting M., Celik I., Kohne C.-H. Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: Pooled analysis of the CRYSTAL and OPUS randomised clinical trials (2012) European *Journal of Cancer*, 48 (10) , pp. 1466-1475
- Cushman-Vokoun AM. Stover DG et al. Clinical Utility of KRA*S and BRAF Mutations in a* Cohort of Patients With Colorectal Neoplasms Submitted for Microsatellite Instability Testing. (2013) Clinical Colorectal Cancer epub ahead of print.
- Lindeman NI, Cagle PT, Beasley MB, Chitale DA, Dacic S, Giaccone G, Jenkins RB, Kwiatkowski DJ, Saldivar JS, Squire J, Thunnissen E, Ladanyi M. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors. Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer [trunc]. Arch Pathol Lab Med. 2013 Jun;137(6):828-860.
- American College of Medical Genetics and Genomics, Recommendations from the EGAPP Working Group: can testing of tumor tissue for mutations in EGFR pathway downstream effector genes in patients with metastatic colorectal cancer improve health outcomes by guiding decisions regarding anti-EGFR therapy? Genetics in Med. 2013 July:15(7): 517-527.
- Allegra CJ, Jessup JM, Somerfield MR, et al. American Society of Clinical Oncology provisional clinical opinion: testing for KRAS gene mutations in patients with metastatic colorectal carcinoma to predict response to antiepidermal growth factor receptor monoclonal antibody therapy. J Clin Oncol 2009;27:2091–2096.
- AHRQ Tech Assessment, Technology assessment of molecular pathology testing for the estimation of prognosis for common cancers. May 29, 2014. Available at: https://www.cms.gov/Medicare/Coverage/DeterminationProcess/Downloads/id94TA.pdf.
- Klingbiel D, Tejpar S. Microsatellite instability and BRAF and KRAS mutations in Stage III colon cancer. Jama Oncology January 14, 2016; doi:10.1001/jamaoncol.2015.5226
- Shea M, et al. Management of advanced non-small cell lung cancers with known mutations or rearrangements: latest evidence and treatment approaches. Ther Adv Respir Dis 2016 Apr;10(2):113-29.
- Barone C, Pinto C, Normanno N, Capussotti L, Cognetti F, et al. (2014) KRAS Early Testing: Consensus Initiative and Cost-Effectiveness Evaluation for Metastatic Colorectal Patients in an Italian Setting. PLoS ONE 9(1): e85897. doi:10.1371/journal.pone.0085897

- F Sahm, D Capper, M Preusser , etal : BRAFV600E mutant protein is expressed in cells of variable maturation in Langerhans cell histiocytosis Blood 120: e28–e34,2012
- T Satoh, A Smith, A Sarde , etal : B-RAF mutant alleles associated with Langerhans cell histiocytosis, a granulomatous pediatric disease PLoS One 7: e33891,2012
- J Haroche, F Charlotte, L Arnaud , etal : High prevalence of BRAF V600E mutations in Erdheim-Chester disease but not in other non-Langerhans cell histiocytoses Blood 120: 2700– 2703,2012
- Stempel, J., Alvaraz, J., et. al. Erdheim-Chester disease, moving away from the orphan diseases: A case report. *Resp.Medicine Case Reports,* 2017, 55-58. doi.org/10.1016/j.rmcr.2016.11.013
- Lech et al. Colorectal cancer tumour markers and biomarkers: Recent therapeutic advances. World J Gastroenterol 2016. 22(5):1745-55.
- Mao et al. Concordant analysis of KRAS, BRAF, PIK3CA mutations, and PTEN expression between primary colorectal cancer and matched metastases. Sci Rep 2015. 5:8065.
- Molecular biomarkers for the evaluation of colorectal cancer: guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology. (May 2017) Available at: https://www.guideline.gov
- Poulos RC, Wong YT, Ryan R, Pang H, Wong JWH. Analysis of 7,815 cancer exomes reveals associations between mutational processes and somatic driver mutations. PLoS Genet. 2018 Nov 9;14(11):e1007779. doi: 10.1371/journal.pgen.1007779. eCollection 2018 Nov
- Caiola E, Falcetta F, Giordano S, Marabese M, Garassino MC, Broggini M, Pastorelli R, Brunelli L. Co-occurring **KRAS mutation**/LKB1 loss in non-small cell lung cancer cells results in enhanced metabolic activity susceptible to caloric restriction: an in vitro integrated multilevel approach. J Exp Clin Cancer Res. 2018 Dec 4;37(1):302. doi: 10.1186/s13046-018-0954-5.
- Christensen TD, Palshof JA, Larsen FO, Poulsen TS, Høgdall E, Pfeiffer P, Jensen BV, Yilmaz MK, Nielsen D. Associations between primary tumor RAS, BRAF and PIK3CA mutation status and metastatic site in patients with chemo-resistant metastatic colorectal cancer. Acta Oncol. 2018 Aug;57(8):1057-1062. doi: 10.1080/0284186X.2018.1433322. Epub 2018 Jan 30.
- Saeed, O., Lopez-Beltran, A., et al. RAS genes in colorectal carcinoma: pathogenesis, testing guidelines, and treatment implications. J Clin. Path. (2019), 72:135-139.
- Li G, Pavlick D, Chung JH, et al. Genomic profiling of cell-free circulating tumor DNA in patients with colorectal cancer and its fidelity to the genomics of the tumor biopsy. J Gastrointest Oncol 2019. http://jgo.amegroups.com/article/view/29063.
- Lokhandwala PM, Tseng LH, Rodriguez E, et al. Clinical mutational profiling and categorization of BRAF mutations in melanomas using next generation sequencing. BMC Cancer. 2019;19(1):665. Published 2019 Jul 5. doi:10.1186/s12885-019-5864-1

- Laurent-Puig P, Paget-Bailly S, Vernerey D, et al. Evaluation of miR 31 3p as a biomarker of prognosis and panitumumab benefit inRAS-wt advanced colorectal cancer (aCRC): Analysis of patients (pts) from the PICCOLO trial (abstract). J Clin Oncol. 2015; 33 (Suppl. 15): 3547
- Sartore-Bianchi, A., Amatu, A., Porcu, L., Ghezzi, S., Lonardi, S., Leone, F., . . . Siena, S. (2019). HER2 Positivity Predicts Unresponsiveness to EGFR-Targeted Treatment in Metastatic Colorectal Cancer. Oncologist, 24(10), 1395-1402. doi:10.1634/theoncologist.2018-0785
- Sepulveda AR, Hamilton SR, Allegra CJ, et al. Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology. J Clin Oncol. May 01, 2017;35(13):1453-1486. PMID 28165299
- Mosakhani N, Lahti L, Borze I, et al. MicroRNA profiling predicts survival in anti-EGFR treated chemorefractory metastatic colorectal cancer patients with wild-type KRAS and BRAF. Cancer Genet. 2012; 205(11):545-551.
- Pugh S, Thiébaut R, Bridgewater J, et al. Association between miR-31-3p expression and cetuximab efficacy in patients with KRAS wild-type metastatic colorectal cancer: a post-hoc analysis of the New EPOC trial. Oncotarget. 2017; 8(55):93856-93866.
- Manceau G, Imbeaud S, Thiébaut R, et al. Hsa-miR-31-3p expression is linked to progression-free survival in patients with KRAS wild-type metastatic colorectal cancer treated with anti-EGFR therapy. Clin Cancer Res. 2014; 20(12):3338-3347
- Laurent-Puig P, Grisoni ML, Heinemann V, et al. Validation of miR-31-3p expression to predict Cetuximab efficacy when used as first-line treatment in RAS Wild-Type metastatic colorectal cancer. Clin Cancer Res. 2019; 25(1):134-141.
- Chang, X. N., Shang, F. M., Jiang, H. Y., et.al. Clinicopathological Features and Prognostic Value of KRAS/NRAS/BRAF Mutations in Colorectal Cancer Patients of Central China. Curr Med Sci, 2021 41(1), 118-126. doi:10.1007/s11596-021-2326-1
- Chiorean, E. G., Nandakumar, G., Fadelu, T., et. al. Treatment of Patients with Late-Stage Colorectal Cancer: ASCO Resource-Stratified Guideline. JCO Global Oncology (6), 414-438. Doi:10.1200/JGO.19.00367
- Fan, J.-Z., Wang, G.-F., Cheng, X.-B., et.al. Relationship between mismatch repair protein, RAS, BRAF, PIK3CA gene expression and clinicopathological characteristics in elderly colorectal cancer patients. World J Clin Cases 2021, 9(11), 2458-2468. doi:10.12998/wjcc. v9.i11.2458
- FDA Vectibix Package Insert. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125147s080lbl.pdf
- FDA Summary of Safety and Effectiveness for Praxis Extended RAS Panel
- Formica, V., Lucchetti, J., Doldo, E., et, al. Clinical Utility of Plasma KRAS, NRAS and BRAF Mutational Analysis with Real Time PCR in Metastatic Colorectal Cancer Patients-The Importance of Tissue/Plasma Discordant Cases. Journal of clinical medicine, 10(1), 87. Doi:10.3390/jcm10010087

- Rebersek, M., Mesti, T., Boc, M., & Ocvirk, J. Molecular biomarkers and histological parameters impact on survival and response to first- line systemic therapy of metastatic colorectal cancer patients. Radiol Oncol, 53(1), 85-95. doi:10.2478/raon-2019-0013
- Praxis Extended RAS Panel. Also available at https://www.illumina.com/products/by-type/ivd-products/extended-ras-panel.html


| POLICY HISTORY | | |
|---|---|---|
| **Date** | **Reason** | **Action** |
| January 2022 | Annual Review | Policy Revised |
| January 2021 | Annual Review | Policy Revised |
| January 2020 | Annual Review | Policy Revised |
| September 2019 | Interim Review | Policy Revised |
| March 2019 | Annual Review | Policy Revised |
| January 2019 | Interim Review | Policy Revised |
| July 2018 | Interim Review | Policy Revised |
| March 2018 | Annual Review | Policy Revised |
| December 2017 | Interim Review | Policy Revised |
| March 2017 | Annual Review | Policy Revised |
| March 2016 | Annual Review | Policy Revised |
| April 2015 | Annual Review | Policy Revised |
| May 2014 | Annual Review | Policy Revised |
| July 2013 | Annual Review | Policy Revised |
| May 2013 | Interim Review | Policy Revised |
| August 2012 | Annual Review | Policy Renewed |
| August 2011 | Annual Review | Policy Renewed |

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

*CPT® is a registered trademark of the American Medical Association.