INSTRUCTIONS FOR USE
This protocol provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Evidence of Coverage (EOC)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this protocol. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Protocol. Other Protocols, Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Protocols, Policies and Guidelines as necessary. This protocol is provided for informational purposes. It does not constitute medical advice. This policy does not govern Medicare Group Retiree members.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

COMMERCIAL AND MEDICAID COVERAGE RATIONALE

MCG™ Guidelines 21st edition A-0773
Colorectal Cancer – KRAS and NRAS Genes

Clinical indications for procedure
- KRAS and NRAS gene testing may be indicated when ALL of the following are present:
  o Metastatic colorectal cancer
  o Anti-epidermal growth factor receptor (EGFR) therapy is being considered.
Inconclusive or Non-Supportive Evidence
For multigene somatic mutation panels, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. The clinical utility of multigene somatic mutation panels has not been evaluated, and some of the mutations tested (eg, PIK3CA, BRAF) do not inform treatment decisions.

**End of MCG**

The National Comprehensive Cancer Network (NCCN) strongly recommends KRAS genotyping of tumor tissue in all patients with metastatic colorectal cancer. Patients with any known KRAS mutation (exon 2 or non-exon 2) should not be treated with either cetuximab or panitumumab, either alone or in combination with other anticancer agents (NCCN, 2017).

Additional Information
Please refer to the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium for additional information and specific indications for treatment with cetuximab and panitumumab.

**MEDICARE COVERAGE RATIONALE**

Medicare does not have a National Coverage Determination (NCD) for the use of KRAS mutation analysis. There is a Local Coverage Determination for Nevada for Molecular Diagnostic Tests (MDT) (L35160). Accessed August 2017

**MolDX: Molecular Diagnostic Tests (MDT) (L35160)**

**Coverage Indications, Limitations, and/or Medical Necessity**
This coverage policy provides the following information:
- defines tests required to register for a unique identifier
- defines tests required to submit a complete technical assessment (TA) for coverage determination
- defines the payment rules applied to covered tests that are not reported with specific CPT codes
- lists some examples of specific covered tests that have completed the registration and TA process and meet Medicare’s reasonable and necessary criteria for coverage. This listing is not inclusive.

Tests evaluated through the application process and/or technical assessment will be reviewed to answer the following questions:
- Is the test performed in the absence of clinical signs and symptoms of disease?
- Will the test results provide the clinician with information that will improve patient outcomes and/or change physician care and treatment of the patient?
- Will the test results confirm a diagnosis or known information?
- Is the test performed to determine risk for developing a disease or condition?
- Will risk assessment change management of the patient?
- Is there a diagnosis specific indication to perform the test?
- Is the test performed to measure the quality of a process or for Quality Control/Quality Assurance (QC/QA), i.e., a test to ensure a tissue specimen matches the patient?
MDT Policy Specific Definitions

MDT: Any test that involves the detection or identification of nucleic acid(s) (DNA/RNA), proteins, chromosomes, enzymes, cancer chemotherapy sensitivity and/or other metabolite(s). The test may or may not include multiple components. A MDT may consist of a single mutation analysis/identification, and/or may or may not rely upon an algorithm or other form of data evaluation/derivation.

LDT: Any test developed by a laboratory developed without FDA approval or clearance.

Applicable Tests/Assays
In addition to the MDT definition, this coverage policy applies to all tests that meet at least one of the following descriptions:
• All non-FDA approved/cleared laboratory developed tests (LDT)
• All modified FDA-approved/cleared kits/tests/assays
• All tests/assays billed with more than one CPT code to identify the service, including combinations of method-based, serology-based, and anatomic pathology codes
• All tests that meet the first three bullets and are billed with an NOC code

Covered Tests
The following tests have completed the MolDX Program application review and/or technical assessment and meet Medicare reasonable and necessary criteria:
• Afirma™
• Allomap
• Avise PG
• Cancer TYPE ID
• cobas® 4800 BRAF V600
• cobas® EGFR
• ConfirmMDx Epigenetic Molecular Assay
• Corus® CAD
• HERmark®
• MammaPrint™
• Oncotype DX® Breast
• Oncotype DX® Colon
• Progensa® PCA3
• therascreen EGFR
• therascreen KRAS
• Tissue of Origin
• THXID™BRAF V600E/K Test
• Vectra™ DA
• Vysis

Other tests/assays may be covered by separate Noridian policy. In addition the CPT codes listed under Group 1 are covered. If a test is not listed, it may be covered under separate Noridian policy or it has not been approved for coverage as it has either not been vetted by the MolDx contractor
For Medicare and Medicaid Determinations Related to States Outside of Nevada:
Please review Local Coverage Determinations that apply to other states outside of Nevada using http://www.cms.hhs.gov/mcd/search.

Important Note: Please also review local carrier Web sites in addition to the Medicare Coverage database on the Centers for Medicare & Medicaid Services’ Web site.

BACKGROUND

KRAS and NRAS genes are oncogenes that, when mutated, have the potential to cause normal cells to become cancerous (MCG, 2016). Some patients with advanced colorectal cancer have tumors with a mutation in the KRAS gene. This mutation may affect how the tumor responds to certain therapies that inhibit the epidermal growth factor receptor (EGFR) – namely cetuximab (Erbitux®) and panitumumab (Vectibix®). These newer therapies are monoclonal antibodies that interfere with the cancer’s ability to grow and metastasize. KRAS mutation testing is performed to predict an individual’s response to these therapies.

CLINICAL EVIDENCE

The available clinical evidence is sufficient to show the clinical validity and utility of KRAS mutation testing in guiding therapy selection for patients with metastatic colorectal cancer.

An Agency for Healthcare Research and Quality (AHRQ) report on selected pharmacogenetic tests concluded that a substantial body of evidence suggests that testing for KRAS mutations predicts differential response to anti-EGFR therapy in colorectal cancer patients (AHRQ, 2010).

Lin et al. (2011) performed a systematic review and meta-analysis of randomized controlled trials in metastatic colorectal cancer that evaluated chemotherapy regimens with and without anti-EGFR therapy. Outcomes included progression-free survival (PFS), median overall survival (OS) and predictive test performance. In pooled data from 8 trials with 5325 patients, the addition of anti-EGFR treatment to standard chemotherapy improved PFS for those with wild-type, but not mutant KRAS status.

Adelstein et al. (2011) systematically reviewed the evidence for KRAS status as a predictive biomarker in metastatic colorectal cancer (CRC). Eleven studies (8924 patients) were selected from 198 reports. Two studies assessed anti-EGFR antibodies as monotherapy and nine their use with chemotherapy. KRAS status was reported in 7555 cases. The authors found a significant treatment effect interaction between KRAS status and the addition of anti-EGFR antibodies to standard treatment for PFS and a response rate difference. Further evidence is needed to determine whether this is true for all chemotherapy partners and all clinical circumstances.

The randomized phase II OPUS (Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer) study showed that tumor KRAS mutation status was predictive for outcome in patients receiving cetuximab plus FOLFOX-4 (oxaliplatin/5-fluorouracil/folinic acid) as first-line therapy for metastatic colorectal cancer (mCRC). The biomarker analysis was extended through the use of additional DNA samples extracted from stained tissue sections. KRAS and BRAF tumor
mutation status was determined for new (and for BRAF, existing) samples using a PCR technique. Clinical outcome was reassessed according to mutation status. Of 315 KRAS evaluable patient samples (93%), 179 tumors (57%) were KRAS wild type. Eleven of 309 (4%) KRAS/BRAF evaluable tumors (all KRAS wild type) carried BRAF mutations. The addition of cetuximab to FOLFOX-4 significantly improved progression-free survival and response in patients with KRAS wild-type tumors. A favorable effect on survival was also observed. These results confirm the efficacy of cetuximab plus FOLFOX-4 in the first-line treatment of patients with KRAS wild-type mCRC and confirm KRAS mutation status as an effective predictive biomarker. The small number of tumors with BRAF mutations precluded the drawing of definitive conclusions concerning the predictive or prognostic utility of this biomarker (Bokemeyer et al., 2011).

A meta-analysis of 2188 metastatic colorectal cancer (mCRC) patients strongly suggests that KRAS mutations represent adverse predictive and prognostic biomarkers for tumor response and survival in mCRC patients treated with cetuximab. Patients with tumors that harbor mutant-type KRAS are more likely to have a worse response, progression-free survival and overall survival when treated with cetuximab (Qiu et al. 2010).

In the CRYSTAL trial, Van Cutsem et al. (2009) investigated the efficacy of cetuximab plus irinotecan, fluorouracil, and leucovorin (FOLFIRI) as first-line treatment for metastatic colorectal cancer and sought associations between the mutation status of the KRAS gene in tumors and clinical response to cetuximab. Patients with epidermal growth factor receptor-positive colorectal cancer with unresectable metastases were randomly assigned to receive FOLFIRI either alone or in combination with cetuximab. The primary end point was progression-free survival. A total of 599 patients received cetuximab plus FOLFIRI, and 599 received FOLFIRI alone. There was no significant difference in the overall survival between the two treatment groups. There was a significant interaction between treatment group and KRAS mutation status for tumor response but not for progression-free survival or overall survival. The authors concluded that first-line treatment with cetuximab plus FOLFIRI, as compared with FOLFIRI alone, reduced the risk of progression of metastatic colorectal cancer. The benefit of cetuximab was limited to patients with KRAS wild-type tumors.

Van Cutsem et al. (2011) performed an updated survival analysis, including additional patients analyzed for tumor mutation status. Patients were randomly assigned to receive FOLFIRI with or without cetuximab. Clinical outcome according to the tumor mutation status of KRAS and BRAF was assessed in the expanded patient series. The percentage of patients analyzed for tumor KRAS status was increased from 45% to 89%, with mutations detected in 37% of tumors. The addition of cetuximab to FOLFIRI in patients with KRAS wild-type disease resulted in significant improvements in overall survival (median, 23.5 v 20.0 months), progression-free survival (median, 9.9 v 8.4 months) and response (rate 57.3% v 39.7%) compared with FOLFIRI alone. Significant interactions between KRAS status and treatment effect were noted for all key end points. KRAS mutation status was confirmed as a powerful predictive biomarker for the efficacy of cetuximab plus FOLFIRI. The authors concluded that the addition of cetuximab to FOLFIRI as first-line therapy improves survival in patients with KRAS wild-type mCRC.

Tol et al. (2009) reported the results of the CAIRO2 trial, a multicenter open-label, randomized, phase III trial involving 755 patients with previously untreated metastatic colorectal cancer who were randomized to capecitabine, oxaliplatin, and bevacizumab (CB regimen, 378 patients) or the same
regimen plus weekly cetuximab (CBC regimen, 377 patients). The primary end point, progression-free survival was reached in 293 patients in the CB group and 316 patients in the CBC group. The addition of cetuximab significantly decreased the median progression-free survival (10.7 months in the CB group and 9.4 months in the CBC group). The overall survival (20.3 months vs. 19.4 months) and response rates (50.0% vs. 52.7%) did not differ significantly in the two groups. The mutation status of the KRAS gene was evaluated in 528 tumors. An activating KRAS mutation was found in 206 tumors (39.6%); 108 from patients in the CB group and 98 from patients in the CBC group. Cetuximab-treated patients with mutated-KRAS tumors had significantly shorter progression-free survival than cetuximab-treated patients with wild-type-KRAS tumors (8.1 vs. 10.5 months). As compared with patients with mutated-KRAS tumors in the CB group, cetuximab-treated patients with mutated-KRAS tumors had significantly shorter progression-free survival (8.1 vs. 12.5 months) and overall survival (17.2 vs. 24.9 months). Among patients with wild-type-KRAS tumors, there was no significant difference in progression-free survival between the two treatment groups. Among patients treated with cetuximab, the response rate was significantly lower in those with KRAS mutations than in those with wild-type-KRAS tumors (45.9% vs. 61.4%), whereas no significant difference was observed in the CB group (59.2% vs. 50.0%).

Karapetis et al. (2008) analyzed tumor samples obtained from 394 of 572 patients (68.9%) with colorectal cancer enrolled into the CO.17, a randomized trial conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) in collaboration with the Australasian Gastro-Intestinal Trials Group (AGITG) in patients that had not responded to advanced chemotherapy and were treated with cetuximab monotherapy. Of the tumors evaluated for KRAS mutations, 42.3% had at least one mutation in exon 2 of the gene. The effectiveness of cetuximab was significantly associated with KRAS mutation status. In patients with wild-type KRAS tumors, treatment with cetuximab as compared with supportive care alone significantly improved overall survival (median, 9.5 vs. 4.8 months; hazard ratio for death, 0.55) and progression-free survival (median, 3.7 months vs. 1.9 months; hazard ratio for progression or death, 0.40). Among patients with mutated KRAS tumors, there was no significant difference between those who were treated with cetuximab and those who received supportive care alone with respect to overall survival (hazard ratio, 0.98) or progression-free survival (hazard ratio, 0.99). In the group of patients receiving best supportive care alone, the mutation status of the KRAS gene was not significantly associated with overall survival (hazard ratio for death, 1.01).

Amado et al. (2008) performed a subgroup analysis of KRAS tumor mutations in a patient population that had been previously randomized to panitumumab versus best supportive care (BSC) as third-line therapy for chemotherapy-refractory metastatic colorectal cancer. Of the 463 patients in the original phase III study (Van Cutsem 2007), 427 (92%) were included in the KRAS subgroup mutation analysis. KRAS mutations were found in 43% of patients. The treatment effect on progression-free survival (PFS) in the wild-type (WT) KRAS group (hazard ratio, 0.45) was significantly greater than in the mutant group (hazard ratio, 0.99). Median PFS in the WT KRAS group was 12.3 weeks for panitumumab and 7.3 weeks for BSC. Response rates to panitumumab were 17% and 0%, for the WT and mutant groups, respectively. WT KRAS patients had longer overall survival (HR, 0.67 to 0.82 treatment arms combined). Consistent with longer exposure, more grade 3 treatment-related toxicities occurred in the WT KRAS group. No significant differences in toxicity were observed between the WT KRAS group and the overall population.
Lievre et al. (2008) analyzed 89 metastatic colorectal cancer patients treated with cetuximab after treatment failure with irinotecan-based chemotherapy for KRAS mutation. A KRAS mutation was present in 27% of the patients and was associated with resistance to cetuximab (0% vs 40% of responders among the 24 mutated and 65 nonmutated patients, respectively) and a poorer survival (median PFS: 10.1 vs. 31.4 weeks in patients without mutation; median OS: 10.1 vs. 14.3 months in patients without mutation). In an earlier study Lievre et al. (2006) screened tumors from 30 metastatic colorectal cancer patients for KRAS. A KRAS mutation was found in 13 tumors (43%) and was significantly associated with the absence of response to cetuximab (KRAS mutation in 0% of the 11 responder patients vs. 68.4% of the 19 nonresponder patients). The overall survival of patients without KRAS mutation in their tumor was significantly higher compared with those patients with a mutated tumor (median, 16.3 vs. 6.9 months).

Freeman et al. (2008) evaluated the association of KRAS, BRAF and PIK3CA gene mutations with tumor resistance to panitumumab alone. From 3 phase II panitumumab metastatic colorectal cancer (mCRC) studies, 62 of 533 patient samples were available. Of the 62 samples, 24 (38.7%) harbored a KRAS mutation, and 38 (61.3%) were wild type. In the wild-type KRAS group, 11% of patients had a partial response (PR), 53% had stable disease (SD), and 37% had progressive disease (PD). In the mutant KRAS group, 21% of patients had SD, and 79% of patients had PD; there were no responses. The absence of a KRAS mutation was associated with response to panitumumab. Four patients had a V600E BRAF mutation, and 2 patients had a PIK3CA mutation. These data suggest that patients with mCRC with activating KRAS mutations are less likely to respond to panitumumab alone. The small sample size limits the ability to define a predictive role of PIK3CA and BRAF mutations for panitumumab treatment.

Di Fiore et al. (2007) treated 59 patients with a chemotherapy-refractory metastatic colon cancer with cetuximab plus chemotherapy. A KRAS mutation was detected in 22 out of 59 tumors (37%). No KRAS mutation was found in the 12 patients with clinical response. KRAS mutation was associated with disease progression and time to progression (TTP) was significantly decreased in mutated KRAS patients (3 months vs. 5.5 months).

De Roock et al. (2008) studied the KRAS mutation status of 113 patients with irinotecan refractory metastatic colorectal cancer treated with cetuximab enrolled in four clinical trials (EVEREST, BOND, SALVAGE, and BABEL) from four Belgian centers. KRAS mutations were detected in 46 of 113 (40.7%) tumors. A predictive model for objective response (OR), progression-free survival (PFS) and overall survival (OS) was constructed using logistic and Cox regression. OR was seen in 27 of 66 KRAS wild-type (WT) patients versus 0 of 42 in KRAS mutants. Median OS was significantly better in KRAS WT versus mutants (43.0 weeks vs. 27.3 weeks).

Linardou et al. (2008) performed a systematic review of articles pertaining to KRAS mutational status in patients with non-small cell lung cancer (NSCLC) treated with tyrosine-kinase inhibitors (TKI), and patients with metastatic colorectal cancer (mCRC) treated with any anti-EGFR-based regimens. The authors selected 8 studies for a meta-analysis involving 817 patients with 306 mutated KRAS genes (37.4%). The data analysis showed that the presence of KRAS mutation predicted lack of response to treatment with anti-EGFR monoclonal antibodies (e.g., panitumumab or cetuximab), whether as stand-alone therapy or in combination with chemotherapy with a sensitivity of 0.47, a specificity of 0.93, a positive likelihood ratio (+LR) of 6.82, and a negative likelihood ratio (-LR) of 0.57. The authors
stated that this analysis provides empirical evidence that KRAS mutations are highly specific negative predictors of response to anti-EGFR monoclonal antibodies alone or in combination with chemotherapy in patients with mCRC. The low sensitivity and relatively high -LR of KRAS mutations for determining nonresponsiveness clearly shows that additional mechanisms of resistance to EGFR inhibitors exist.

Etienne-Grimaldi et al. (2008) analyzed the effect of KRAS mutations in 93 stage IV colorectal cancer patients with unresectable measurable liver metastasis treated exclusively with 5-FU therapy. Thirty-six of 93 (38.7%) metastases were KRAS mutated. Mutated primary tumors (16 of 48) matched perfectly with mutated metastases. The objective response rate was 37%: 44.4% in KRAS mutated versus 32.1% in wild-type KRAS metastasis. The authors concluded that based on the study data any predictive and/or prognostic value of KRAS mutations in treatments combining anti-EGFR monoclonal antibodies with 5-FU should be exclusively linked to the anti-EGFR agent.

A Blue Cross Blue Shield Association Technology Evaluation Center (TEC) report concluded that the evidence is sufficient to show the clinical validity of KRAS mutation testing and its clinical utility in guiding therapy selection for patients with metastatic colorectal cancer. Patients with mutated KRAS tumors in the setting of metastatic colorectal cancer do not respond to anti-EGFR monoclonal antibody therapy, do not derive survival benefit and may experience decreased progression-free survival (BCBS TEC, 2009).

The National Comprehensive Cancer Network (NCCN) states the following regarding KRAS mutation testing:

- Mutations in codons 12 and 13 in exon 2 of the coding region of the KRAS gene predict lack of response to therapy with cetuximab or panitumumab.
- KRAS mutation testing should be performed in laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform molecular pathology testing. No specific methodology is recommended.
- KRAS mutation testing can be performed on the primary colorectal cancers and/or the metastasis.

NCCN strongly recommends KRAS genotyping of tumor tissue in all patients with metastatic colorectal cancer. Patients with known codon 12 or 13 KRAS mutations should not be treated with either cetuximab or panitumumab as the mutations predict a lack of response to these drugs (NCCN, 2017).

According to the NCCN Drugs & Biologics Compendium, cetuximab and panitumumab are only recommended for patients with tumors that express the wild-type KRAS gene (NCCN, 2017).

**Professional Societies**

**American Society of Clinical Oncology (ASCO)**

In a Provisional Clinical Opinion (PCO), ASCO states that based on systematic reviews of the relevant literature, all patients with metastatic colorectal carcinoma who are candidates for anti-EGFR antibody therapy should have their tumor tested for KRAS mutations in a CLIA-accredited laboratory. If a KRAS mutation in codon 12 or 13 is detected, then patients with metastatic colorectal carcinoma should not receive anti-EGFR antibody therapy as part of their treatment (Allegra, 2009).
College of American Pathologists (CAP)
A CAP Perspectives on Emerging Technology (POET) report states that KRAS mutations can be detected in approximately 30-40% of all patients with CRC. Although no level I evidence has been published, multiple studies with strong level II evidence have convincingly shown that patients with KRAS mutations in codons 12 or 13 do not benefit from anti-EGFR therapy with cetuximab or panitumumab. In contrast, about 40% of patients with metastatic colorectal cancer unresponsive to other therapies, and who lack a KRAS mutation, show a partial response with these agents. These findings suggest that only patients without KRAS mutations should be eligible to receive these therapies (CAP, 2009).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

KRAS mutation analysis using polymerase chain reaction (PCR) methodology is commercially available as a laboratory-developed test. Such tests are regulated under 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.

In July 2009, the labeling for both cetuximab and panitumumab was updated to include information on KRAS mutation status. The labels now state that retrospective subset analyses of metastatic or advanced colorectal cancer trials have not shown a treatment benefit for Erbitux in patients whose tumors had $KRAS$ mutations in codon 12 or 13, codons 59 and 61 and codons 17 and 146 or for Vectibix in patients with KRAS mutations in codon 12 or 13. Use of these drugs is not recommended for the treatment of colorectal cancer with these mutations or if the results of the KRAS mutation tests are unknown. See the following websites for details.

Erbitux® (cetuximab)

Vectibix™ (panitumumab)

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

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<th>CPT® Codes</th>
<th>Description</th>
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<td>81275</td>
<td>KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)</td>
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<tr>
<td>81276</td>
<td>KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)</td>
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<td>Molecular pathology procedure, Level 4</td>
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<td>81404</td>
<td>Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)</td>
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<td>81405</td>
<td>Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons), regionally targeted cytogenomic array analysis</td>
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<td>88363</td>
<td>Examination and selection of retrieved archival (i.e., previously diagnosed) tissue(s) for molecular analysis (e.g., KRAS mutational analysis)</td>
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*CPT® is a registered trademark of the American Medical Association.*

**REFERENCES**


### PROTOCOL HISTORY/REVISION INFORMATION

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The foregoing Health Plan of Nevada/Sierra Health & Life Health Operations protocol has been adopted from an existing UnitedHealthcare coverage determination guideline that was researched, developed and approved by the UnitedHealthcare Coverage Determination Committee.