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Testing for Colorectal Cancer Management

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Line(s) of Business: HMO; PPO; QUEST Integration; Medicare; FEP	**Precertification:** Refer to the GTM Utilization Review Matrix

POLICY DESCRIPTION | RELATED POLICIES | INDICATIONS AND/OR LIMITATIONS OF COVERAGE | TABLE OF TERMINOLOGY | SCIENTIFIC BACKGROUND | GUIDELINES AND RECOMMENDATIONS | APPLICABLE STATE AND FEDERAL REGULATIONS | APPLICABLE CPT/HCPCS PROCEDURE CODES | EVIDENCE-BASED SCIENTIFIC REFERENCES | REVISION HISTORY

I. Policy Description

Colorectal cancer (CRC) involves the accumulation of genetic and epigenetic modifications within pathways that regulate proliferation, apoptosis, and angiogenesis resulting in carcinoma of the colon and rectum.[1] Tumors originate in adenomas or flat dysplasia and evolve into different morphologic patterns with invasion and expansion.[2]

~~Monoclonal antibodies that bind the epidermal growth factor receptor (*EGFR*), such as cetuximab, and block its activation have led to significant clinical benefits for metastatic colorectal cancer (mCRC) patients.[3] Mutations in downstream effectors of the *EGFR* pathway have been associated with resistance to *EGFR* antibody chemotherapies.[4,5]~~

For guidance on microsatellite instability or tumor mutational burden testing in colorectal cancer, please refer to AHS-M2178- Microsatellite Instability and Tumor Mutational Burden Testing.

II. Related Policies

Policy Number	Policy Title
AHS-G2054	Liquid Biopsy
AHS-G2181	Colorectal Cancer Screening
AHS-M2004	Lynch Syndrome
AHS-M2024	Genetic Testing for Polyposis Syndromes
AHS-M2029	Molecular Testing for Cutaneous Melanoma
AHS-M2178	Microsatellite Instability and Tumor Mutational Burden Testing

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

1) For all individuals with suspected or proven metastatic colorectal cancer, ~~*KRAS, NRAS,* and *BRAF* mutation genotyping of the primary or the metastatic tumor **MEETS**~~tissue- or blood-based single

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gene or multigene panel testing (see Note 1) and HER2 overexpression/amplification testing **MEET COVERAGE CRITERIA**.

~~2) For individuals with metastatic colorectal cancer for whom tumor tissue testing did not identify a mutation in *KRAS, NRAS,* **or** *BRAF*, HER2 amplification testing **MEETS COVERAGE CRITERIA**.~~

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

~~3) For all other situations not described above, testing for *KRAS, NRAS,* and *BRAF* mutations **DOES NOT MEET COVERAGE CRITERIA**.~~

~~4)~~2)For all other situations ~~and/or mutations~~ not described above, genotyping of the colorectal cancer tumor **DOES NOT MEET COVERAGE CRITERIA.**

~~5)~~3)To determine the prognosis of stage II colon cancer following surgery, gene expression profiling (e.g., ColDx, Coloprint, Oncotype DX Colon Cancer Assay) **DOES NOT MEET COVERAGE CRITERIA.**

NOTES:

Note 1: When multigene panel testing is performed in individuals with colon cancer, the panel should at minimum include the following: *BRAF, KRAS, NRAS, NTRK1/2/3, POLE/POLD1,* and *RET.* When tissue-based testing is performed, it is recommended that testing should be performed on the metastasis.

Note 2: For two or more gene tests being run on the same platform, please refer to AHS-R2162-Reimbursement Policy.

IV. Table of Terminology

Term	Definition
ASCO	American Society of Clinical Oncology
ACS	American Cancer Society
BRAF	*B-Raf proto-oncogene*
CEA	Carcinoembryonic antigen
CLIA-1988	Clinical Laboratory Improvement Amendments of 1988
CNA	Copy number alteration
CRC	Colorectal cancer
ctDNA	Circulating tumor deoxyribonucleic acid
DFS	Disease free survival
dMMR	Deficient MMR
EGAPP	Evaluation of Genomic Applications in Practice and Prevention
EGFR	*Epidermal growth factor receptor*
ERBB2	*Erb-B2 Receptor Tyrosine Kinase 2*
ESCP	European Society of Coloproctology

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ESMO	European Society for Medical Oncology
EWG	European Working Group
1F1CDx	Foundation One Cdx
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FISH	Fluorescence in-situ hybridization
FOLFOX4	5-fluorouracil, leucovorin, and oxaliplatin
HER2	Human epidermal growth factor receptor 2
HR	Hazard ~~ratios~~ratio
ICI	Immune checkpoint inhibition
IHC	Immunohistochemistry
KRAS	*Kirsten rat sarcoma*
~~LDTs~~LDT	Laboratory-developed ~~tests~~ test
~~mAbs~~mAb	Monoclonal ~~antibodies~~ antibody
mCRC	Metastatic colorectal cancer
MGPT	Multigene panel testing
MMR	Mismatch repair
MMR-P	Mismatch repair proficient
MPFS	Median progression-free survival
MSI	Microsatellite instability
NCCN	National Comprehensive Cancer Network
NGS	Next-generation sequencing
NICE	National Institute for Health and Care Excellence
NRAS	*Neuroblastoma rat sarcoma virus*
NSABP	National Surgical Adjuvant Breast and Bowel Project
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PCO	Provisional clinical opinion
PCR	Polymerase chain reaction
PFS	Progression-free survival rate
PIK3CA	*Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha*
PL	Plasma
PTEN	*Phosphatase and TENsin homolog deleted on chromosome 10*
QALY	Quality-adjusted life year
RAF	*Rapidly accelerated fibrosarcoma*
RAS	*Rat sarcoma virus*
RS	Recurrence score
T	Tissue
TMB	Tumor mutational burden
WT	Wild-type

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V. Scientific Background

Colorectal cancer (CRC) is the third leading cause of cancer-related deaths in the United States following lung cancer. The American Cancer Society (ACS) estimates ~~107,320~~108,860 new cases of colon cancer and ~~46,950~~49,990 new cases of rectal cancer for ~~2025~~2026. Overall, there is about a one in twenty-four or twenty-six lifetime risk of developing colorectal cancer based on gender.[63] Metastatic colorectal cancer (mCRC), which occurs in 22% of patients with colorectal cancer, has a significantly poorer prognosis than colorectal cancer that has not metastasized. The five-year survival is 14% in patients with distant metastases from CRC, as compared to 71% for all CRC patients.[~~7,8~~4,5]

Approximately one-quarter of the patients with colon cancer present with stage II disease.[~~9~~6] The current National Comprehensive Cancer Network (NCCN) guidelines include adjuvant chemotherapy as a treatment option in this setting, particularly for high-risk stage II patients, as determined by clinical and pathological parameters.[~~10~~7] Although some of the routinely used parameters for estimating recurrence risk, such as T-stage and mismatch repair (MMR) status, are well established, they may not be reliable predictors of recurrence risk in this population.[~~11-16~~8-13]

Certain mutations may affect treatment of CRC. For example, the activation of the EGFR signaling cascade is associated with colon tumorigenesis;[~~17~~14] therefore, medications such as cetuximab or panitumumab that target the *EGFR* pathway may be used in treatment of CRC. However, activating mutations in the *KRAS* oncogene will cause anti-*EGFR* resistance since these mutations can result in a constitutively active pathway, even with anti-*EGFR* treatment.[~~18~~15] 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.[~~19~~16] 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 five percent of colorectal cancer cases are found to overexpress *HER2*.[~~18~~15]

Another component of the RAS signaling pathway, *BRAF*, has also been found to affect anti-*EGFR* treatment. *BRAF* V600E mutations may also confer a lack of response to anti-*EGFR* treatment even when paired with a wild-type RAS oncogene. Mutations in this region occur in less than 10% of sporadic CRCs, and the mutation at position 600 is the primary polymorphism found in CRC. Non-V600 *BRAF* mutations are rarer (composing about 2.2% of patients with metastatic CRC) and confer a generally better prognosis than their V600 mutated counterparts; a study found non-V600 genotypes to lead to better median overall survival and fewer high-grade tumors.[~~20~~17]

Proprietary Testing

Gene expression assays have been commercially produced to predict prognosis of colon cancer. The 12-gene Oncotype DX Colon Cancer Assay (Genomic Health, Inc., Redwood City, CA) is a reverse transcriptase polymerase chain reaction–based assay that provides a Recurrence Score (RS) result.[~~21~~18] This test assesses the activity level of 12 genes (seven cancer-related genes, five reference genes), and this gene expression is scored from 1-100. This test is intended for resected stage II, MMR-P or stage III A/B colon cancer. Low risk is a score under 30, moderate risk is 31-40, and higher risk is ≥41.[~~22,23~~19,20]

The ColDx assay (Almac Diagnostics, Craigavon, Northern Ireland) uses microarray technology for assessing the gene expression of 634 genes to stratify patients into low and high recurrence risk

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groups.[24~~21~~] ColDx identified 73 high-risk patients with a hazard ratio of 2.62 during cross validation. In an independent validation, the assay identified high-risk patients with a hazard ratio of 2.53.[25~~22~~]

ColoPrint (Agendia, Amsterdam, The Netherlands) is a gene expression classifier that uses whole-genome expression data of 18 key genes to distinguish patients with low versus high-risk of disease relapse. In a study using 206 fresh frozen tumor tissue samples from 188 patients with stage I through IV CRC, ColoPrint classified "60% of patients as low risk and 40% as high risk," and was "superior to American Society of Clinical Oncology criteria in assessing the risk of cancer recurrence without prescreening for microsatellite instability."[26~~23~~] In a study of 416 stage II colon cancer patients, "ColoPrint identified 63% of patients as low risk with a 5-year ROR of 10%, whereas high-risk patients (37%) had a 5-year ROR of 21%." Alternatively, the 2013 NCCN clinical risk factors could not distinguish low and high-risk patients.[27~~24~~]

Analytical Validity

~~Cenaj, et al. (2019) evaluated the correlation between "*ERBB2* amplification by next-generation sequencing (NGS) with HER2 overexpression by immunohistochemistry." NGS was performed on specimens with 20% or more tumor, and 1300 cases of colorectal cancer were included. *ERBB2* amplification was detected in two percent of cases. HER2 amplification was examined in "15 cases with *ERBB2* amplification (six or more copies), 10 with low gain (three to five copies), and 77 copy neutral." *ERBB2* amplification was found to have perfect concordance with HER2 immunochemistry at H-scores of 105 or more. Further, *ERBB2* amplification was found to inversely correlate with RAS/RAF mutations. The authors concluded that "NGS-detected *ERBB2* amplification highly correlates with HER2 overexpression in CRC," which may support authors' original hypothesis that ERBB2 amplification/overexpression may predict response to HER2 inhibitors.[28]~~

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 ($P > 0.05$)."[29~~25~~] 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.

Formica, et al. (2020) examined tumor tissue (T) mutational analysis in terms of discordance with circulating tumor DNA (ctDNA) obtained by liquid biopsy from plasma (PL) and assessed through real-time polymerase chain reaction (PCR). Despite finding concordance for patients with *BRAF* mutations between the tissue and plasma samples, 20% of patients were *RAS* discordant. Mutations identified from ctDNA were able to refine the prognosis determined by tissue samples. "*RAS* wild type in T and mutated in PL had significantly shorter PFS than concordant *RAS* wild type in T and PL: mPFS [median progression free survival] 9.6 vs. 23.3 months, respectively, $p = 0.02$. Patients RAS mutated in T and wild type in PL had longer PFS than concordant RAS mutated in T and PL: 24.4 vs. 7.8 months, respectively, $p = 0.008$." This raises a limitation to using tumor tissue as the mainstay for mutational analysis and considering

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combining with or replacing tumor tissue genotyping with plasma ctDNA as a measure of prognosis going forward.[30][26]

~~Pinheiro, et al. (2022) studied the analytical validity of using ctDNA as a possible strategy to analyze *KRAS* and *NRAS* mutations from patients with metastatic colorectal cancer. The BEAMing Digital PCR (OncoBEAM) and Idylla ctDNA qPCR were compared and the concordance rate was reported. Blood samples from 47 mCRC patients were tested and the overall agreement and concordance rate were noted. "The overall agreement between tumor tissue and ctDNA analyses was 83% and 78.7% using the OncoBEAM and Idylla assays, respectively, with the concordance being 96.2% and 88.5% in naive treatment patients. The overall agreement between OncoBEAM and Idylla ctDNA analyses was 91.7%."[31] The authors conclude that Idylla ctDNA qPCR method is a cheaper alternative with equivalent performance in comparison to the OncoBEAM assay. Analysis of ctDNA can be used to detect "RAS mutations in plasma, either at diagnosis or after progression when considering anti-EGFR treatment rechallenge."[31]~~

Clinical Utility and Validity

In a meta-analysis by Xu, et al. (2013), a total of 2875 patients were evaluated, with 246 patients having *BRAF* mutations. The objective response rate (ORR) to *EGFR* therapy was 18.4% (40/217) in mutant *BRAF* group and 41.7% (831/1993) in the wild-type *BRAF* group. The overall risk ratio for the ORR of *BRAF* mutations compared to wild-type *BRAF* patients was 0.58. The median progression-free survival (hazard ratio 2.98) and overall survival (hazard ratio: 2.85) were significantly shorter of patients with *BRAF* mutations compared to patients with wild-type *BRAF* mutations.[32][27]

~~Douillard, et al. (2013) evaluated the effect of panitumumab plus oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) compared to just FOLFOX4 on patients with varying RAS and *BRAF* mutations. A total of 639 patients with metastatic CRC without mutations in *KRAS* exon 2 had at least one of the following: *KRAS* exon 3 or 4; *NRAS* exon 2, 3, or 4; or *BRAF* exon 15. A total of 228 patients had neither RAS nor *BRAF* mutations, and this group was evaluated to have better survival metrics with panitumumab plus FOLFOX4 than the group with just FOLFOX4 (median of 10.8 months progression-free survival and 28.3 months overall survival for panitumumab group vs 9.2 and 20.9 respectively for the group without). However, 296 patients with either a *RAS* or *BRAF* mutation were treated with panitumumab plus FOLFOX4, and this group's survival metrics were lower than the group only treated with FOLFOX4. The *RAS/BRAF* group treated with panitumumab plus FOLFOX4 had a median of only 7.3 months progression-free survival and 15.3 months overall survival vs 8.0 and 18.0 for the 305 patients treated with only FOLFOX4). The authors concluded that additional RAS mutations predicted a lack of response to panitumumab plus FOLFOX4.[33]~~

~~Therkildsen, et al. (2014) performed a meta-analysis of the clinical impact of anti-*EGFR* treatment on patients with *KRAS*, *NRAS*, and *BRAF* mutations (as well as *PIK3CA* and *PTEN*). A total of 22 studies (2395 participants) were evaluated. Odds ratios for objective response rate (ORR) and hazard ratios (HR) for progression-free survival rate (PFS) and overall survival (OS) were calculated. Mutations in *KRAS* exons 3 and 4 and *BRAF* predicted poor ORR (0.26 and 0.29 respectively), *KRAS*, *NRAS*, and *BRAF* mutations all led to significantly lower progression-free survival (HR = 2.19, 2.30, and 2.95 respectively) and significantly lower overall survival (HR = 1.78, 1.85, and 2.52 respectively).[17]~~

Rebersek, et al. (2019) investigated the impact of molecular biomarkers on survival and response to first-line therapy in metastatic colorectal cancer patients. The study included 154 patients with 42% harboring *KRAS* mutations and 3% harboring *BRAF* mutations. Median overall survival was found to be

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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.[34]28

Sartore-Bianchi, et al. (2019) investigated the effect of *HER2* positivity on anti-*EGFR* treatment. A total of 100 patients HER2-positive (of 1485 wild-type *KRAS* exon 2 patients) with metastatic colorectal cancer were included. The authors found that HER2-positive patients had more frequent lung metastases (odds ratio [OR] = 2.04) and higher tumor burden (OR = 1.48). The 79 *HER2*-positive patients given anti-*EGFR* treatment were also found to have poorer clinical outcomes, with lower objective response rate (31.2% compared to 46.9% for all others) and lower progression-free survival (5.7 months vs seven months). The authors concluded that HER2 testing should be offered because "occurrence of this biomarker is unlikely to be predicted based on main clinicopathological features."[35]29

~~The prognostic benefit was corroborated by Chang, et al. (2021), who found that the *BRAF* gene mutation was "associated with cancer thrombosis in blood vessels" and was "negatively correlated with the OS [overall survival] rate of CRC patients" in their patient population (n=410) from Central China.[36] Like Fan, et al. (2021), *KRAS* also had the greatest mutation rate at 47.56% in this study, showing more awareness needed for tissue genotyping for mCRC.[29,36]~~

Loree, et al. (2021) characterized the clinical prevalence of atypical *KRAS/NRAS* mutations in metastatic colorectal cancer. The authors evaluated tissue and DNA samples from 9,485 patients to characterize atypical *RAS* variants using an in vitro cell-based assay, studying the signaling changes across mutations. According to the results, "*KRAS* exon 2, extended *RAS*, and atypical *RAS* mutations were noted in 37.8%, 9.5%, and 1.2% of patients, respectively. Among atypical variants, *KRAS* L19F, Q22K, and D33E occurred at prevalence ≥0.1%, whereas no *NRAS* codon 117/146 and only one *NRAS* codon 59 mutation was noted. Atypical *RAS* mutations had worse overall survival than *RAS/BRAF* wild-type mCRC." Of the 57 atypical *RAS* variants, 18 (31.6%) had signaling below wild-type, 23 (40.4%) had signaling between wild-type and activating control, and 16 (28.1%) were hyperactive beyond the activating control. The authors concluded that "*KRAS* L19F, Q22K, D33E, and T50I are more prevalent than many guideline-included RAS variants and functionally relevant."[37]30

Benavides, et al. (2022) studied how effective liquid biopsy-tailored assays were in identifying guideline-recommended biomarkers, including *RAS* and *BRAF*, in comparison to standard of care tissue genotyping for patients newly diagnosed with mCRC. To quantify the effectivity of liquid biopsy assays for biomarkers, the researchers utilized the Guardant360 for comprehensive ctDNA analysis, and OncoBEAM for targeted RAS and BRAF analysis. Among the 155 patients included in this prospective study, physician discretion standard of care tissue genotyping identified guideline-recommended biomarkers in 52.9% of patients, in comparison to the 56.8% from the comprehensive Guardant360 ctDNA analysis and 44.5% from targeted ctDNA analysis by OncoBEAM. An additional 19.5% more samples were included in the ctDNA assays "by rescuing those without tissue results either due to tissue insufficiency, test failure, or false negatives." The complete processing of ctDNA assays was faster (10 days versus 27 days on median) and maintained accuracy even 10 days after sample collection (52.0% vs 10.2%). This could allow inclusion of ctDNA genotyping in the care of patients with mCRC and could enable accelerated personalized treatment regimens for patients with the quick turnaround and comparable results to current practices.[38]31

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~~Several studies have evaluated the impact of the gene expression profiling on clinical decision making in certain colon cancer subgroups. Brenner, et al. (2016) assessed the clinical impact of the 12-gene Colon Cancer Recurrence Score Assay in treatment of T3 mismatch repair proficient (MMR-P) stage II colon cancer. Out of 269 patients, 102 patients had their treatment changed because of the assay's results. The authors concluded that testing significantly impacted adjuvant treatment decisions in clinical practice.[39]~~

Cartwright, et al. (2014) performed a web-based survey evaluating the impact of the 12-gene Colon Cancer Recurrence Score Assay in stage II colon cancer patients. The authors surveyed 346 oncologists about their use of the Oncotype DX assay; the survey included questions about courses of treatment before and after using the assay and the stage of cancer their patient had. The authors found that 29% of treatment recommendations were changed for patients receiving Recurrence Score testing.[40] ~~Srivastava, et al. (2014) conducted a prospective study assessing the impact of recurrence score results on physician recommendations regarding adjuvant chemotherapy in T3 MMR-P stage II colon cancer patients. A total of 141 patients were eligible for analysis, and the study concluded that treatment recommendation changes were made for 63 (45%) of patients.[41]~~[32]

~~Chang, et al. (2020) reviewed the "entire database" of the OncoType Colon Recurrence Score test to identify any age-related differences in Recurrence Score (RS) and single-gene results. A total of 20478 Stage II and IIIA/B colon cancer patients were included. RS results were categorized into low, medium, and high risk, and single-gene results were organized by median and interquartile ranges. In total, 72.5% of all patients and 72.6% of patients under 40 years old were found to have a low risk RS. However, there were no significant differences in either RS or single-gene results among the four age groups (<40, 40-54, 55-64, >65). Young-onset cancer was also not found to differ by gene expression in individual RS genes. Overall, most patients in stages II or III colon cancer were found to have low risk disease per the Oncotype assay.[42]~~

Allar, et al. (2022) evaluated how the OncoType Colon Recurrence Score influences clinical practice. The study included 105 patients with stage IIa colon cancer and investigated the association between the RS and the decision to offer adjuvant chemotherapy after resection. Fifty-two patients underwent RS testing, seven (13%) of whom received adjuvant chemotherapy. The authors found no significant effect or clear association of RS on the odds of undergoing chemotherapy. The authors conclude that "RS was not associated with the decision to start adjuvant chemotherapy" and suggest that "the RS should not be obtained in patients with stage IIa colon cancer."[43][33]

Chaudhari and Issa (2022) conducted a study to compare the cost-effectiveness of various genomic tests used to prognosticate stage II colorectal cancer patients. The researchers compared a 12-gene assay, 18-gene expression assay, 482-gene signature assay, and Immunoscore assay in a hypothetical cohort to investigate recurrence risk and death. Using a Markov model, the authors found that "the cost of the Immunoscore assay strategy in stage II colorectal cancer patients was estimated to be US $23,564 with a gain of 3.903 quality-adjusted life years (QALYs) as compared with the 12-gene assay strategy at US $24,545 and 3.903 QALYs; the 18-gene assay strategy at US $28,374 and 3.623 QALYs; and the 482-gene signature treatment strategy at US $33,315 with 3.704 QALYs." This, along with further analysis, led to the conclusion that the Immunoscore assay may be the "dominant strategy," in that it may reduce costs associated with treatment in long-term, but for the gene expression signature assays alone, the 12-gene assay may generate more cost savings than the 18-gene expression assay, equivalent to $3900.[44][34]

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Aoki, et al. (2023) studied the validity of NGS-based ctDNA genotyping for *RAS* and *BRAF* V600E mutation assessment to guide therapy for metastatic colorectal cancer. The study included 212 mCRC patients. The authors compared NGS-cased ctDNA genotyping results with the results of validated PCR-based tissue testing, specifically looking at the concordance rate, sensitivity, and specificity. For *RAS,* the concordance rate was 92.5%, the sensitivity was 88.7%, and the specificity was 97.2%. For *BRAF* V600E, the concordance rate was 96.2%, the sensitivity was 88.0%, and the specificity was 97.3%. The authors then investigated efficacy of anti-EGFR and BRAF-targeted therapies based on ctDNA results. The progression-free survival pf anti-EGFT therapy was 12.9 months, and the progression-free survival of BRAF-targeted treatment was 3.7 months. The authors concluded that "ctDNA genotyping effectively detected RAS/BRAF mutations" and "clinical outcomes support ctDNA genotyping for determining the use of anti-EGFR and BRAF-targeted therapies in patients with mCRC."[4535]

VI. Guidelines and Recommendations

American Society of Clinical Oncology (ASCO)

The ASCO published an endorsement of the College of American Pathologist Guidelines, recommending:

- "For patients with CRC, being considered for immune checkpoint inhibitor therapy, pathologists should use MMR-immunohistochemistry (IHC) and/or microsatellite instability (MSI) by polymerase chain reaction (PCR) for the detection of DNA MMR defects. Although MMR-IHC or MSI by PCR is preferred, pathologists may use a validated MSI by next-generation sequencing (NGS) assay for the detection of DNA MMR defects. Note: MSI by NGS assay must be validated against MMR-IHC or MSI by PCR and must show equivalency. (Strong recommendation)."
- "For all cancer patients being considered for immune checkpoint inhibitor therapy based on defective MMR, pathologists should not use tumor mutation burden (TMB) as a surrogate for the detection of DNA MMR defects. If a tumor is identified as TMB-high, pathologists may perform IHC and/or MSI by PCR to determine if high TMB is secondary to MMR deficiency. (Strong recommendation)."
- "For cancer patients being considered for immune checkpoint inhibitor therapy, if a MMR deficiency consistent with Lynch syndrome is identified in the tumor, pathologists should communicate this finding to the treating physician. (Strong recommendation)."[4636]

Similar to the guideline above, in 2024 ASCO released management of locally advanced rectal cancer guidelines and included the following recommendation:

- "Patients with locally advanced rectal cancer should be assessed for MSI or MMR status prior to commencement of treatment (good practice statement)."[4737]

American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology

These joint guidelines focus on "Molecular Biomarkers for the Evaluation of Colorectal Cancer." They list the following recommendations for *KRAS*, *NRAS*, and *BRAF* for CRC:

- "Patients with CRC considered for anti-*EGFR* therapy must receive RAS mutational testing. Mutational analysis should include *KRAS* and *NRAS* codons 12, 13 of exon 2; 59, 61 of exon 3; and 117 and 146 of exon 4 (expanded or extended RAS)."

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- "*BRAF* p.V600 (*BRAF* c. 1799 [p.V600]) mutational analysis should be performed in CRC tissue in patients with CRC for prognostic stratification."
- "There is insufficient evidence to recommend *BRAF* c.1799 p.V600 mutational status as a predictive molecular biomarker for response to anti-*EGFR* inhibitors."~~5~~38

The joint guidelines state that further research is required to study the clinical validity and utility of gene expression profiling assays in colon cancer patients.~~5~~38

National Comprehensive Cancer Network (NCCN)

The guidelines version ~~1.2025~~1.2026 recommends that "all patients with metastatic ~~colorectal cancer~~CRC should have tumor genotyped for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations individually or as part of ~~a next-generation sequencing (NGS) panel (preferred)~~MGPT [multigene panel testing] at initial diagnosis of metastatic disease. Patients with any known *KRAS* mutation (exons 2, 3, and 4) or *NRAS* mutation (exons 2, 3, and 4) should not be treated with either cetuximab or panitumumab, unless given as part of a regimen targeting a *KRAS* G12C mutation. *BRAF* V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a BRAF inhibitor."

The NCCN guidelines state that testing for *KRAS*, *NRAS* and *BRAF* mutations should be performed only in laboratories that are CLIA-1988 certified as qualified to perform "~~high-complexity~~high-complexity clinical laboratory (molecular pathology) testing." ~~Testing can be performed on formalin-fixed paraffin-embedded tissue (preferred) or blood-based assay.~~"No specific methodology is recommended."

The NCCN further states that "testing can be performed on the primary CRCs and/or the metastasis, as literature has shown that the *KRAS, NRAS*, and *BRAF* mutations are similar in both specimen types."

The *BRAF* genotyping of tumor tissue is recommended at stage IV disease. ~~Allele-specific PCR, NGS, or immunohistochemistry (IHC) may be used to determine *BRAF* status.~~

The NCCN notes that "HER2 is rarely amplified/overexpressed in CRC (approximately 3% overall), but the prevalence is higher in RAS/BRAF–wild-type tumors (reported at 5%–14%)." "HER2-targeted therapies are now recommended in patients with tumors that are *RAS/BRAF* wild-type and with HER2 overexpression." Therefore, the NCCN now recommends testing for HER2 amplifications in patients with metastatic CRC. However, *HER2* testing is not indicated in patients with known ~~*KRAS/NRAS*~~*RAS* or *BRAF* mutations.~~10~~7

Routine *EGFR* testing is not recommended.~~10~~7

Overall, in patients with suspected or proven mCRC, the NCCN recommends "~~molecular~~Biomarker testing ordered as rapidly as possible following diagnosis, including: ~~*RAS*~~*KRAS, NRAS,* and *BRAF* V600E mutations; HER2 ~~amplifications~~(*ERBB2*) overexpression/amplification; MMR or MSI status (if not previously done). Testing should be conducted as part of ~~broad molecular profiling~~multigene panel testing (MGPT), which would identify rare and actionable mutations and gene fusions such as *POLE/POLD1*, *RET*, and *NTRK 1/2/3*."~~10~~7

Regarding the OncoType DX colon cancer assay, the NCCN remarks that clinical validation in patients with stages II or III cancer from the QUASAR and NSABP clinical trials shows that "recurrence scores are prognostic for recurrence, DFS [disease free survival], and OS [overall survival] in stage II and stage III colon cancer but are not predictive of benefit to adjuvant therapy." ColoPrint, an 18-gene classifier for

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recurrence risk, was also found to independently predict recurrence risk and is currently being validated to predict 3-year relapse rates in patients with stage II colon cancer in a prospective trial. Similarly, ColDx, a microarray based multigene assay, was found to independently predict recurrence risk. However, despite these tests' ability to further inform risk of recurrence, the panel questions the value added. The panel also noted that "evidence of predictive value in terms of the potential benefit of chemotherapy is lacking" and that "there are insufficient data to recommend the use of multigene assays, Immunoscore, or post-surgical ctDNA to estimate risk of recurrence or determine adjuvant therapy."~~10~~7

European Society for Medical Oncology (ESMO)

In its 2023 guidelines with some September 2024 updates, ESMO recommends the following for mCRC genetic testing:

- "Determining the *RAS* mutational testing on a tumour biopsy [I, A] (or through a liquid biopsy in case no tumour sample is available [II, B]) is mandatory to guide the best treatment decision.
- Testing for mismatch repair (MMR) status and *KRAS, NRAS* exon 2, 3, and 4 as well as *BRAF* mutations is recommended in all patients at the time of mCRC diagnosis [I, A]
- *RAS* testing is mandatory before treatment with anti-EGFR mAbs and can be carried out on either the primary tumour or other metastatic sites [III, A]
- *BRAF* V600E mutations [ESCAT: I-A] status should be assessed simultaneously with the evaluation of RAS, for prognostic assessment [I, B] and for the option of treatment with targeted therapy.
- DMMR/MSI-H [ESCAT: I-A, if detection by NGS] testing in metastatic colorectal cancer can assist in genetic counselling for Lynch syndrome [II, B]
  , and is recommended as the initial molecular work-up in metastatic disease for its predictive value for the use of immune checkpoint inhibitors [I, A].
- Identification of HER2 overexpression (by IHC) and/or HER2 amplification [ESCAT: II-B] is recommended in RAS-wt patients to detect those who may benefit from targeted therapy."~~8,9~~39,40

In 2025, EMSO updated the metastatic colorectal cancer living guideline. The guidelines recommend:

- "Testing for MMR status [if detection by NGS] and KRAS, NRAS exon 2, 3 and 4 and BRAF mutation is recommended in all patients at the time of metastatic colorectal cancer diagnosis."
- "RAS testing is mandatory before treatment with anti-EGFR monoclonal antibodies and can be carried out on either the primary tumour or other metastatic sites."
- "BRAF V600E mutations status should be assessed simultaneously with the evaluation of RAS, for prognostic assessment and for the option of treatment with targeted therapy."
- "DMMR/MSI-H [if detection by NGS] testing in metastatic colorectal cancer can assist in genetic counselling for Lynch syndrome, and is recommended as the initial molecular work-up in metastatic disease for its predictive value for the use of immune checkpoint inhibitors."
- "Identification of HER2 overexpression (by IHC) and/or HER2 amplification is recommended in RAS-wt patients to detect those who may benefit from targeted therapy."
- "When multigene tumour NGS is available and applicable, testing for KRAS G12C, and POLE mutations as well as for genomic aberrations for which targeted therapeutics are approved in tumour-agnostic indications [NTRK fusions, RET fusions, TMB-H] is advised."
- "Testing of other biomarkers including ALK and ROS1 gene fusions [ESCAT: III-A], mutations of PIK3CA and HER2 activating mutations is not recommended outside clinical trials."

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- "Testing for dihydropyrimidine dehydrogenase deficiency must be conducted before initiating 5-FU-based chemotherapy."[41]

With regards to localized colon cancer, ESMO states that "besides MSI status, other genetic markers, e.g. *RAS* and *BRAF* mutations are not recommended for the routine assessment of risk of recurrence in non-metastatic patients, based on their lack of utility in the adjuvant decision-making process."[~~50~~42]

In ~~their newly released~~2023 guidelines, ESMO does not provide recommendations for using gene expression profiling assays for prognosticating patients with stage II colon cancer.[~~48~~39]

Choosing Wisely Canada

Choosing Wisely Canada lists "sixteen tests and treatments to question" in their oncology recommendations. In this list, they recommend: "Don't perform routine colonoscopic surveillance every year in patients following their colon cancer surgery; instead, frequency should be based on the findings of the prior colonoscopy and corresponding guidelines."[~~51~~43] The guideline goes on to add that "typical colonoscopic surveillance following colon cancer surgery consists of a colonoscopy at one year; thereafter it should not typically exceed every 3 years following detection of an advanced polyp, or every 5 years following a normal exam or one showing small polyps."[~~51~~43]

Research Committee and the Guidelines Committee of the European Society of Coloproctology (ESCP)

This systematic review was performed by the committee to assess the consensus levels "in guidelines from member countries of the European Society of Coloproctology, with supporting evidence." This review focuses on follow-up strategies for patients "after treatment with curative intent of nonmetastatic colorectal cancer."[~~52~~44]

In this review, the committee concluded that "laboratory tests other than CEA [carcinoembryonic antigen] should not be part of follow-up," although it noted that only eight of 21 guidelines reviewed addressed this topic.[~~52~~44]

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

Cetuximab and panitumumab have FDA marketing approval for treatment of metastatic colorectal cancer in the refractory disease setting, and ongoing studies are investigating the use of these *EGFR*

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inhibitors as monotherapy and as part of combination therapy in first, second, and subsequent lines of therapy.

On May 23, 2014, the FDA approved therascreen *KRAS* RGQ PCR Kit is a real-time qualitative PCR assay used on the Rotor-Gene Q MDx instrument for the detection of seven somatic mutations in the human *KRAS* oncogene, using DNA extracted from formalin-fixed paraffin-embedded (FFPE), colorectal cancer (CRC) tissue. The therascreen *KRAS* RGQ PCR Kit is intended to aid in the identification of CRC patients for treatment with Erbitux (cetuximab) and Vectibix (panitumumab) based on a *KRAS* no mutation detected test result.[~~53~~45]

On May 7, 2015, the FDA approved cobas *KRAS* Mutation Test, for use with the cobas® 4800 System. Cobas is a real-time PCR test for the detection of seven somatic mutations in codons 12 and 13 of the *KRAS* gene in DNA derived from formalin-fixed paraffin-embedded human colorectal cancer (CRC) tumor tissue. The test is intended to be used as an aid in the identification of CRC patients for whom treatment with Erbitux (cetuximab) or with Vectibix (panitumumab) may be indicated based on a no mutation detected result.[~~54~~46]

On June 29, 2017, the FDA approved PraxisTM Extended RAS Panel as a qualitative in vitro diagnostic test using targeted high throughput parallel sequencing for the detection of 56 specific mutations in RAS genes [*KRAS* (exons 2, 3, and 4) and *NRAS* (exons 2, 3, and 4)] in DNA extracted from FFPE colorectal cancer (CRC) tissue samples. The Praxis™ Extended RAS Panel is indicated to aid in the identification of patients with colorectal cancer for treatment with Vectibix (panitumumab) based on a no mutation detected test result. The test is intended to be used on the Illumina MiSeqDx instrument.[~~55~~47]

On November 30, 2017, the FDA approved FoundationOne CDx, which is a next-generation sequencing oncology panel. From the FDA website: "FoundationOne CDx™ (F1CDx) is a next-generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels) and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from FFPE tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed Table 1 in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for cancer patients with solid malignant neoplasms. The F1CDx test is a single-site assay performed at Foundation Medicine, Inc."[~~55~~47]

In 2021, the ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) was approved. O/RDx-LCCA is a highly accurate FDA approved IVD assay for the detection of clinically relevant KRAS variants in CRC and EGFR variants in and determination of approved therapy. "The device is a qualitative next generation sequencing based in vitro diagnostic test that uses amplicon-based target enrichment technology for detection of single nucleotide variants (SNVs) and deletions in 2 genes from DNA isolated from FFPE non-small cell lung cancer (NSCLC) and colorectal cancer (CRC) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients with NSCLC or CRC who may benefit from treatment with the targeted therapies."[~~56~~48]

VIII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to

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discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status.

HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

Genetic testing is covered for level 1 or 2A recommendations of the National Comprehensive Cancer Network (NCCN and in accordance with Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, the Hawaii Administrative Rules (HAR 1700.1-42).

IX. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
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)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81445	Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis
81455	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, 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
81479	Unlisted molecular pathology procedure
81525	Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score
81599	Unlisted multianalyte assay with algorithmic analysis

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0111U	Oncology (colon cancer), targeted KRAS (codons 12, 13, and 61) and NRAS (codons 12, 13, and 61) gene analysis utilizing formalin-fixed paraffin-embedded tissue Proprietary test: Praxis ™ Extended RAS Panel Lab/Manufacturer: Illumina
0471U	Oncology (colorectal cancer), qualitative real-time PCR of 35 variants of KRAS and NRAS genes (exons 2, 3, 4), formalin-fixed paraffin-embedded (FFPE), predictive, identification of detected mutations Proprietary test: CRCdx® RAS Mutation Detection Kit Lab/~~Manufacturera~~Manufacturer: EntroGen, Inc
0498U	Oncology (colorectal), next-generation sequencing for mutation detection in 43 genes and methylation pattern in 45 genes, blood, and formalin-fixed paraffin-embedded (FFPE) tissue, report of variants and methylation pattern with interpretation Proprietary test: ~~OptiSeqTM~~OptiSeq™ Colorectal Cancer NGS Panel Lab/Manufacturer: DiaCarta, Inc

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

X. Evidence-based Scientific References

~~1. Bardhan K, Liu K. Epigenetics and colorectal cancer pathogenesis. *Cancers*. Jun 2013;5(2):676-713. doi:10.3390/cancers50206761.~~ 1. Bardhan K, Liu K. Epigenetics and colorectal cancer pathogenesis. *Cancers*. 2013;5(2):676-713. doi:10.3390/cancers5020676

~~2. Compton C. Pathology and prognostic determinants of colorectal cancer. Updated February 28, 2025.~~ 2. Compton C. Pathology and prognostic determinants of colorectal cancer. Updated February 19, 2026. https://www.uptodate.com/contents/pathology-and-prognostic-determinants-of-colorectal-cancer

~~3. De Roock W, Claes B, Bernasconi D, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. *The Lancet Oncology*. Aug 2010;11(8):753-62. doi:10.1016/s1470-2045(10)70130-3~~

~~4. 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 anti-epidermal growth factor receptor monoclonal antibody therapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Apr 20 2009;27(12):2091-6. doi:10.1200/jco.2009.21.9170~~

~~5. 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 American Society of Clinical Oncology. *The Journal of molecular diagnostics : JMD*. Mar 2017;19(2):187-225. doi:10.1016/j.jmoldx.2016.11.001~~

~~6. ACS. Key Statistics for Colorectal Cancer. Updated January 16, 2025.~~ 3. ACS. Key Statistics for Colorectal Cancer. https://www.cancer.org/cancer/colon-rectal-cancer/about/key-statistics.html

~~7. Wang J, Li S, Liu Y, Zhang C, Li H, Lai B. Metastatic patterns and survival outcomes in patients with stage IV colon cancer: A population-based analysis. *Cancer Med*. Jan 2020;9(1):361-373. doi:10.1002/cam4.2673~~ 4. Wang J, Li S, Liu Y, Zhang C, Li H, Lai B. Metastatic patterns and survival outcomes in patients with stage IV colon cancer: A population-based analysis. *Cancer Med*. 2020;9(1):361-373. doi:10.1002/cam4.2673

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8. El-Deiry WS, Vijayvergia N, Xiu J, et al. Molecular profiling of 6,892 colorectal cancer samples suggests different possible treatment options specific to metastatic sites. *Cancer biology & therapy*. 2015;16(12):1726-37. doi:10.1080/15384047.2015.11133565. El-Deiry WS, Vijayvergia N, Xiu J, et al. Molecular profiling of 6,892 colorectal cancer samples suggests different possible treatment options specific to metastatic sites. *Cancer biology & therapy*. 2015;16(12):1726-37. doi:10.1080/15384047.2015.1113356
9. Kopetz S. Adjuvant Chemotherapy for Stage II Colon Cancer. 6. Kopetz S. Adjuvant Chemotherapy for Stage II Colon Cancer. https://pubmed.ncbi.nlm.nih.gov/18494354/
10. NCCN. NCCN Clinical Practice Guidelines in Oncology; Colon Cancer v1.2025. Updated April 24, 2025. 7. NCCN. NCCN Clinical Practice Guidelines in Oncology; Colon Cancer v1.2026. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf
11. Harris EI, Lewin DN, Wang HL, et al. Lymphovascular invasion in colorectal cancer: an interobserver variability study. *The American journal of surgical pathology*. Dec 2008;32(12):1816-21. doi:10.1097/PAS.0b013e318181608338. Harris EI, Lewin DN, Wang HL, et al. Lymphovascular invasion in colorectal cancer: an interobserver variability study. *The American journal of surgical pathology*. 2008;32(12):1816-21. doi:10.1097/PAS.0b013e3181816083
12. Venook AP, Niedzwiecki D, Lopatin M, et al. Biologic determinants of tumor recurrence in stage II colon cancer: validation study of the 12-gene recurrence score in cancer and leukemia group B (CALGB) 9581. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. May 10 2013;31(14):1775-81. doi:10.1200/jco.2012.45.10969. Venook AP, Niedzwiecki D, Lopatin M, et al. Biologic determinants of tumor recurrence in stage II colon cancer: validation study of the 12-gene recurrence score in cancer and leukemia group B (CALGB) 9581. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2013;31(14):1775-81. doi:10.1200/jco.2012.45.1096
13. Gray RG, Quirke P, Handley K, et al. Validation study of a quantitative multigene reverse transcriptase-polymerase chain reaction assay for assessment of recurrence risk in patients with stage II colon cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Dec 10 2011;29(35):4611-9. doi:10.1200/jco.2010.32.873210. Gray RG, Quirke P, Handley K, et al. Validation study of a quantitative multigene reverse transcriptase-polymerase chain reaction assay for assessment of recurrence risk in patients with stage II colon cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2011;29(35):4611-9. doi:10.1200/jco.2010.32.8732
14. Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jul 10 2010;28(20):3219-26. doi:10.1200/jco.2009.27.182511. Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2010;28(20):3219-26. doi:10.1200/jco.2009.27.1825
15. Ribic CM, Sargent DJ, Moore MJ, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *The New England journal of medicine*. Jul 17 2003;349(3):247-57. doi:10.1056/NEJMoa02228912. Ribic CM, Sargent DJ, Moore MJ, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *The New England journal of medicine*. 2003;349(3):247-57. doi:10.1056/NEJMoa022289
16. Gunderson LL, Jessup JM, Sargent DJ, Greene FL, Stewart AK. Revised TN categorization for colon cancer based on national survival outcomes data. *Journal of clinical oncology : official journal of the*

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American Society of Clinical Oncology. Jan 10 2010;28(2):264-71. doi:10.1200/jco.2009.24.095213. Gunderson LL, Jessup JM, Sargent DJ, Greene FL, Stewart AK. Revised TN categorization for colon cancer based on national survival outcomes data. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2010;28(2):264-71. doi:10.1200/jco.2009.24.0952

17. Therkildsen C, Bergmann TK, Henrichsen-Schnack T, Ladelund S, Nilbert M. The predictive value of KRAS, NRAS, BRAF, PIK3CA and PTEN for anti-EGFR treatment in metastatic colorectal cancer: A systematic review and meta-analysis. review-article. 23 Jun 2014 2014;doi:10.3109/0284186X.2014.89503614. Therkildsen C, Bergmann TK, Henrichsen-Schnack T, Ladelund S, Nilbert M. The predictive value of KRAS, NRAS, BRAF, PIK3CA and PTEN for anti-EGFR treatment in metastatic colorectal cancer: A systematic review and meta-analysis. review-article. 2014;doi:10.3109/0284186X.2014.895036
18. Clark JW, Sanoff HK. Initial systemic therapy for metastatic colorectal cancer. Updated April 10, 2025. 15. Clark JW, Sanoff HK. Initial systemic therapy for metastatic colorectal cancer. Updated March 17, 2026. https://www.uptodate.com/contents/initial-systemic-therapy-for-metastatic-colorectal-cancer
19. Frucht H, Lucas AL. Molecular genetics of colorectal cancer. Updated November 20, 2024. 16. Frucht H, Lucas AL. Molecular genetics of colorectal cancer. Updated November 20, 2024. https://www.uptodate.com/contents/molecular-genetics-of-colorectal-cancer
20. Jones JC, Renfro LA, Al-Shamsi HO, et al. (Non-V600) BRAF Mutations Define a Clinically Distinct Molecular Subtype of Metastatic Colorectal Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Aug 10 2017;35(23):2624-2630. doi:10.1200/jco.2016.71.439417. Jones JC, Renfro LA, Al-Shamsi HO, et al. (Non-V600) BRAF Mutations Define a Clinically Distinct Molecular Subtype of Metastatic Colorectal Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2017;35(23):2624-2630. doi:10.1200/jco.2016.71.4394
21. O'Connell MJ, Lavery I, Yothers G, et al. Relationship between tumor gene expression and recurrence in four independent studies of patients with stage II/III colon cancer treated with surgery alone or surgery plus adjuvant fluorouracil plus leucovorin. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Sep 01 2010;28(25):3937-44. doi:10.1200/jco.2010.28.953818. O'Connell MJ, Lavery I, Yothers G, et al. Relationship between tumor gene expression and recurrence in four independent studies of patients with stage II/III colon cancer treated with surgery alone or surgery plus adjuvant fluorouracil plus leucovorin. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2010;28(25):3937-44. doi:10.1200/jco.2010.28.9538
22. Oncotype. About the Oncotype DX Colon Recurrence Score Test. 19. Oncotype. Oncotype DX Colon Recurrence Score® test. https://www.oncotypeiq.com/en-US/colon-cancer/healthcare-professionals/oncotype-dx-colon-recurrence-score/about-the-test
23. Oncotype. Interpreting the Results. 20. Oncotype. Explore the Results. https://www.oncotypeiq.com/en-US/colon-cancer/healthcare-professionals/oncotype-dx-colon-recurrence-score/interpreting-the-results
24. Almac Group. ColDx. 21. Almac Group. ColDx. https://www.almacgroup.com/diagnostics/portfolio-overview/coldx/
25. Kennedy RD, Bylesjo M, Kerr P, et al. Development and independent validation of a prognostic assay for stage II colon cancer using formalin-fixed paraffin-embedded tissue. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Dec 10 2011;29(35):4620-6. doi:10.1200/jco.2011.35.449822. Kennedy RD, Bylesjo M, Kerr P, et al. Development and independent validation of a prognostic assay for stage II colon cancer using formalin-fixed paraffin-

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embedded tissue. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2011;29(35):4620-6. doi:10.1200/jco.2011.35.4498

26. Salazar R, Roepman P, Capella G, et al. Gene expression signature to improve prognosis prediction of stage II and III colorectal cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jan 1 2011;29(1):17-24. doi:10.1200/jco.2010.30.107723. Salazar R, Roepman P, Capella G, et al. Gene expression signature to improve prognosis prediction of stage II and III colorectal cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2011;29(1):17-24. doi:10.1200/jco.2010.30.1077
27. Kopetz S, Tabernero J, Rosenberg R, et al. Genomic classifier ColoPrint predicts recurrence in stage II colorectal cancer patients more accurately than clinical factors. *Oncologist*. Feb 2015;20(2):127-33. doi:10.1634/theoncologist.2014-032524. Kopetz S, Tabernero J, Rosenberg R, et al. Genomic classifier ColoPrint predicts recurrence in stage II colorectal cancer patients more accurately than clinical factors. *Oncologist*. 2015;20(2):127-33. doi:10.1634/theoncologist.2014-0325
28. Cenaj O, Ligon AH, Hornick JL, Sholl LM. Detection of ERBB2 Amplification by Next-Generation Sequencing Predicts HER2 Expression in Colorectal Carcinoma. *Am J Clin Pathol*. Jun 5 2019;152(1):97-108. doi:10.1093/ajcp/aqz03125. 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
29. 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.i11.245826.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. *J Clin Med*. 2020;10(1):87. doi:10.3390/jcm10010087
30. 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. *J Clin Med*. 2020;10(1):87. doi:10.3390/jcm1001008727. Xu Q, Xu AT, Zhu MM, Tong JL, Xu XT, Ran ZH. Predictive and prognostic roles of BRAF mutation in patients with metastatic colorectal cancer treated with anti-epidermal growth factor receptor monoclonal antibodies: a meta-analysis. *Journal of digestive diseases*. 2013;14(8):409-16. doi:10.1111/1751-2980.12063
31. Pinheiro M, Peixoto A, Rocha P, et al. KRAS and NRAS mutational analysis in plasma ctDNA from patients with metastatic colorectal cancer by real-time PCR and digital PCR. *International Journal of Colorectal Disease*. 2022/04/01 2022;37(4):895-905. doi:10.1007/s00384-022-04126-628. 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*. 2019;53(1):85-95. doi:10.2478/raon-2019-0013
32. Xu Q, Xu AT, Zhu MM, Tong JL, Xu XT, Ran ZH. Predictive and prognostic roles of BRAF mutation in patients with metastatic colorectal cancer treated with anti-epidermal growth factor receptor monoclonal antibodies: a meta-analysis. *Journal of digestive diseases*. Aug 2013;14(8):409-16. doi:10.1111/1751-2980.1206329. Sartore-Bianchi A, Amatu A, Porcu L, et al. HER2 Positivity Predicts Unresponsiveness to EGFR-Targeted Treatment in Metastatic Colorectal Cancer. *Oncologist*. 2019;24(10):1395-1402. doi:10.1634/theoncologist.2018-0785
33. Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *The New England journal of medicine*. Sep 12 2013;369(11):1023-34. doi:10.1056/NEJMoa130527530. Loree JM, Wang Y, Syed MA, et al. Clinical and Functional

Confidential and Proprietary Information of Avalon Health Services, LLC, d/b/a Avalon Healthcare Solutions. All Rights Reserved.

Characterization of Atypical KRAS/NRAS Mutations in Metastatic Colorectal Cancer. *Clinical Cancer Research*. 2021;27(16):4587-4598. doi:10.1158/1078-0432.Ccr-21-0180

34. 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*. Mar 3 2019;53(1):85-95. doi:10.2478/raon-2019-0013
31. Benavides M, Alcaide-Garcia J, Torres E, et al. Clinical utility of comprehensive circulating tumor DNA genotyping compared with standard of care tissue testing in patients with newly diagnosed metastatic colorectal cancer. *ESMO Open*. 2022;7(3):100481. doi:10.1016/j.esmoop.2022.100481
35. Sartore-Bianchi A, Amatu A, Porcu L, et al. HER2 Positivity Predicts Unresponsiveness to EGFR-Targeted Treatment in Metastatic Colorectal Cancer. *Oncologist*. Oct 2019;24(10):1395-1402. doi:10.1634/theoncologist.2018-0785
32. Cartwright T, Chao C, Lee M, et al. Effect of the 12-gene colon cancer assay results on adjuvant treatment recommendations in patients with stage II colon cancer. *Current medical research and opinion*. 2014;30(2):321-8. doi:10.1185/03007995.2013.855183
36. Chang XN, Shang FM, Jiang HY, et al. Clinicopathological Features and Prognostic Value of KRAS/NRAS/BRAF Mutations in Colorectal Cancer Patients of Central China. *Curr Med Sci*. Feb 2021;41(1):118-126. doi:10.1007/s11596-021-2326-1
33. Allar BG, Messaris E, Poylin VY, Schlechter BL, Cataldo TE. Oncotype DX testing does not affect clinical practice in stage IIa colon cancer. *Med Oncol*. 2022;39(5):59. doi:10.1007/s12032-022-01660-9
37. Loree JM, Wang Y, Syed MA, et al. Clinical and Functional Characterization of Atypical KRAS/NRAS Mutations in Metastatic Colorectal Cancer. *Clinical Cancer Research*. 2021;27(16):4587-4598. doi:10.1158/1078-0432.Ccr-21-0180
34. Chaudhari VS, Issa AM. Cost-effectiveness of precision molecular diagnostic tests for stage II colorectal cancer. *Ann Transl Med*. 2022;10(23):1260. doi:10.21037/atm-2022-77
38. Benavides M, Alcaide-Garcia J, Torres E, et al. Clinical utility of comprehensive circulating tumor DNA genotyping compared with standard of care tissue testing in patients with newly diagnosed metastatic colorectal cancer. *ESMO Open*. Jun 2022;7(3):100481. doi:10.1016/j.esmoop.2022.100481
35. Aoki Y, Nakamura Y, Denda T, et al. Clinical Validation of Plasma-Based Genotyping for RAS and BRAF V600E Mutation in Metastatic Colorectal Cancer: SCRUM-Japan GOZILA Substudy. *JCO Precis Oncol*. 2023;7:e2200688. doi:10.1200/po.22.00688
39. Brenner B, Geva R, Rothney M, et al. Impact of the 12-Gene Colon Cancer Assay on Clinical Decision Making for Adjuvant Therapy in Stage II Colon Cancer Patients. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Jan 2016;19(1):82-7. doi:10.1016/j.jval.2015.08.013
36. Vikas P, Messersmith H, Compton C, et al. Mismatch Repair and Microsatellite Instability Testing for Immune Checkpoint Inhibitor Therapy: ASCO Endorsement of College of American Pathologists Guideline. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2023;41(10):1943-1948. doi:10.1200/jco.22.02462
40. Cartwright T, Chao C, Lee M, et al. Effect of the 12-gene colon cancer assay results on adjuvant treatment recommendations in patients with stage II colon cancer. *Current medical research and opinion*. Feb 2014;30(2):321-8. doi:10.1185/03007995.2013.855183
37. Scott AJ, Kennedy EB, Berlin J, et al. Management of Locally Advanced Rectal Cancer: ASCO Guideline. *Journal of Clinical Oncology*. 2024;42(28):3355-3375. doi:10.1200/jco.24.01160
41. Srivastava G, Renfro LA, Behrens RJ, et al. Prospective multicenter study of the impact of oncotype DX colon cancer assay results on treatment recommendations in stage II colon cancer patients. *Oncologist*. May 2014;19(5):492-7. doi:10.1634/theoncologist.2013-0401
38. 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

Confidential and Proprietary Information of Avalon Health Services, LLC, d/b/a Avalon Healthcare Solutions. All Rights Reserved.

Molecular Pathology, and American Society of Clinical Oncology. *The Journal of molecular diagnostics : JMD*. 2017;19(2):187-225. doi:10.1016/j.jmoldx.2016.11.001

42. Chang GJ, You YNY, Russell CA, et al. Young-Onset Colon Cancer and Recurrence Risk By Gene Expression. *J Natl Cancer Inst*. Feb 10 2020;doi:10.1093/jnci/djaa019
39. Cervantes A, Adam R, Roselló S, et al. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34(1):10-32. doi:10.1016/j.annonc.2022.10.003
43. Allar BG, Messaris E, Poylin VY, Schlechter BL, Cataldo TE. Oncotype DX testing does not affect clinical practice in stage IIa colon cancer. *Med Oncol*. Feb 12 2022;39(5):59. doi:10.1007/s12032-022-01660-9
44. Chaudhari VS, Issa AM. Cost-effectiveness of precision molecular diagnostic tests for stage II colorectal cancer. *Ann Transl Med*. Dec 2022;10(23):1260. doi:10.21037/atm-2022-77
45. Aoki Y, Nakamura Y, Denda T, et al. Clinical Validation of Plasma-Based Genotyping for RAS and BRAF V600E Mutation in Metastatic Colorectal Cancer: SCRUM-Japan GOZILA Substudy. *JCO Precis Oncol*. Jun 2023;7:e2200688. doi:10.1200/po.22.00688
46. Vikas P, Messersmith H, Compton C, et al. Mismatch Repair and Microsatellite Instability Testing for Immune Checkpoint Inhibitor Therapy: ASCO Endorsement of College of American Pathologists Guideline. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Apr 1 2023;41(10):1943-1948. doi:10.1200/jco.22.02462
47. Scott AJ, Kennedy EB, Berlin J, et al. Management of Locally Advanced Rectal Cancer: ASCO Guideline. *Journal of Clinical Oncology*. 2024;42(28):3355-3375. doi:10.1200/jco.24.01160
48. Cervantes A, Adam R, Roselló S, et al. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. Jan 2023;34(1):10-32. doi:10.1016/j.annonc.2022.10.003
49. ESMO. ESMO Metastatic Colorectal Cancer Living Guideline.
40. ESMO. ESMO Metastatic Colorectal Cancer Living Guideline. https://www.esmo.org/living-guidelines/esmo-metastatic-colorectal-cancer-living-guideline
41. EMSO. Diagnosis, Pathology and Molecular Biology. https://www.esmo.org/guidelines/living-guidelines/esmo-metastatic-colorectal-cancer-living-guideline/diagnosis
50. Argilés G, Tabernero J, Labianca R, et al. Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. Oct 2020;31(10):1291-1305. doi:10.1016/j.annonc.2020.06.022
42. Argilés G, Tabernero J, Labianca R, et al. Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;31(10):1291-1305. doi:10.1016/j.annonc.2020.06.022
51. Choosing Wisely Canada. Sixteen Tests and Treatments to Question Updated May 2024.
43. Choosing Wisely Canada. Sixteen Tests and Treatments to Question https://choosingwiselycanada.org/recommendation/oncology/
52. Bastiaenen VP, Hovdenak Jakobsen I, Labianca R, et al. Consensus and controversies regarding follow-up after treatment with curative intent of nonmetastatic colorectal cancer: a synopsis of guidelines used in countries represented in the European Society of Coloproctology. *Colorectal Dis*. Apr 2019;21(4):392-416. doi:10.1111/codi.14503
44. Bastiaenen VP, Hovdenak Jakobsen I, Labianca R, et al. Consensus and controversies regarding follow-up after treatment with curative intent of nonmetastatic colorectal cancer: a synopsis of guidelines used in countries represented in the European Society of Coloproctology. *Colorectal Dis*. 2019;21(4):392-416. doi:10.1111/codi.14503
53. FDA. Summary of Safety and Effectiveness Data (SSED).
45. FDA. Summary of Safety and Effectiveness Data (SSED). https://www.accessdata.fda.gov/cdrh_docs/pdf11/P110027B.pdf
54. FDA. Summary of Safety and Effectiveness Data (SSED).
46. FDA. Summary of Safety and Effectiveness Data (SSED). https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140023B.pdf

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~~55. FDA. Summary of Safety and Effectiveness Data (SSED).~~ 47. FDA. Summary of Safety and Effectiveness Data (SSED). https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160038B.pdf
~~56. FDA. ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA).~~ 48.FDA. ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA).
https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pma&id=454588

XI. Revision History

Revision Date	Summary of Changes
06/03/2026	Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: Based on NCCN guideline updates, CC1 edited to allow single gene and multigene panel testing in suspected or proven mCRC and HER2 overexpression/amplification as a first line test results in removal of CC2 and movement of HER2 recommendations into newly formatted CC1. Now reads: "1) For all individuals with suspected or proven metastatic colorectal cancer, tissue- or blood-based single gene or multigene panel testing (see Note 1) and HER2 overexpression/amplification testing MEET COVERAGE CRITERIA." CC3 removed to align with changes to CC1 Removed "and/or mutations" from former CC4, now CC2. Now reads: "2) For all other situations not described above, genotyping of the colorectal cancer tumor DOES NOT MEET COVERAGE CRITERIA." Former CC5, now CC3: Added "(e.g., ColDx, Coloprint, Oncotype DX Colon Cancer Assay)" as examples of gene expression profiling. New Note 1 to define the minimum gene set for CRC multigene panel testing. Added CPT code 81445, 81455

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