Healthy Blue

Medical Policy

Subject:	Gene Expression Profiling for Colorectal Cancer		
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Description/Scope

This document addresses the use of gene expression profiling (GEP) to manage colorectal cancer (CRC), such as predicting the likelihood of the development of CRC or the recurrence of the disease in individuals with a history of CRC.

Position Statement

Investigational and Not Medically Necessary:

Gene expression profiling as a technique for colorectal cancer (CRC) risk assessment or management is considered **investigational and not medically necessary** for all indications, including but not limited to its use for predicting the likelihood of the development of CRC as well as the likelihood of disease recurrence in individuals with a history of CRC.

Rationale

Excluding skin cancers, CRC is the third most frequently diagnosed cancer in the United States. It has been estimated that as many as 101,420 new cases of colon cancer and 44,180 new cases of rectal cancer will be diagnosed in the United States in 2019. Approximately 51,020 individuals will die from the disease. Several professional associations and societies recommend routine screening for CRC for the early detection and removal of early-stage cancers or precancerous polyps as a means of improving overall survival. In spite of current recommendations and the knowledge that screening may improve survival, many individuals do not adhere to the current screening guidelines. Researchers have been exploring the use of more high-sensitivity screening tools that may be considered more acceptable to individuals who are eligible for CRC screening. It has been theorized that the availability of less invasive screening tests would increase compliance with CRC screening recommendations (ACS, 2019).

Surgery is the primary treatment for colon cancer and results in cure in approximately 50% of the individuals who undergo surgery for colon cancer. Recurrence following surgery is a major concern and is frequently the ultimate cause of death. While adjuvant chemotherapy is recommended in individuals with stage III colon cancer, its role in stage II disease is unclear. It has been estimated that in treating 100 stage II individuals with adjuvant chemotherapy, 3-4 will benefit, while others will suffer significant adverse effects. Identification of individuals who

are most likely to experience a recurrence of disease would help practitioners identify those individuals who might benefit from adjuvant therapy after surgery.

Gene expression profiling (GEP) assays are being investigated as a tool for identifying those individuals who may be considered at increased risk for the development of CRC as well as identifying individuals with a history of CRC who may be at greater risk for a recurrence of the disease and who might benefit from adjuvant therapy after surgery. Several GEP assays are available through CLIA-certified laboratories. The number of gene signatures explored varies, depending upon the assay used, and may range from as few as five to as many as several hundred (Black, 2012).

Risk of Developing CRC
ColonSentry® (Innovative Diagnostic Laboratory, [Richmond, VA]) is a blood-based test that measures the expression of seven genes: annexin A3 (ANXA3); C-type lectin domain family 4, member D (CLEC4D); lamin B1 (LMNB1); proline-rich gamma-carboxyglutamic acid protein 4 (PRRG4); tumor necrosis factor-alpha-induced protein 6 (TNFAIP6); vanin1 (VNN1); and interleukin 2 receptor, beta (IL2RB). The gene expression results are used to determine the relative risk (expressed as multiples of the average risk) of having CRC. Based on information from the manufacturer, individuals identified as having an increased current risk of CRC should undergo a colonoscopy. Individuals identified as having a decreased current risk of CRC should discuss repeat screening options with their physician at regular intervals. The ColonSentry test is marketed as a molecular diagnostic risk assessment test rather than a cancer detection test.

The evolution of the development of the ColonSentry test is captured in the following articles by Marshall (2010), Yip (2010) and Chen (2013). Marshall and colleagues (2010) analyzed 196 gene expression profiles to select candidate CRC biomarkers. Quantitative transcriptase polymerase chain reaction (qRT-PCR) was carried out on 642 samples to develop a seven-gene biomarker panel using 112 CRC/120 controls (training set) and 202 CRC/208 controls (independent, blind test set). Panel performance characteristics and disease prevalence were then used to develop a scale assessing an individual's current risk of having CRC based on his/her gene signature. The seven-gene panel (ANXA3, CLEC4D, LMNB1, PRRG4, TNFAIP6, VNN1 and IL2RB) differentiated CRC in the training set (area under the receiver-operating-characteristic curve [ROC AUC], 0.80; accuracy, 73%; sensitivity, 82%; specificity 64%). The independent blind test set corroborated performance (ROC AUC, 0.80; accuracy, 71%; sensitivity, 72%; specificity, 70%). Individual gene profiles were compared to the population results and utilized to calculate the current relative risk for CRC. The authors concluded that the GEP test makes it possible to identify clinically meaningful reference points that can assist individuals and physicians in CRC screening decision making.

Yip and colleagues (2010) utilized qRT-PCR to analyze gene expression of the seven biomarkers (ANXA3, CLEC4D, TNFAIP6, LMNB1, PRRG4, VNN1 and IL2RB) as compared with controls. Blood samples were collected from a total of 210 subjects (99 CRC and 111 controls from the Malaysian population) and total blood RNA was isolated and subjected to qRT-PCR and data analysis. The logistic regression analysis of the seven-gene panel had an area under the curve (AUC) of 0.76 (95% confidence interval: 0.70 to 0.82), 77% specificity, 61% sensitivity and 70% accuracy. The authors concluded that the seven-gene panel is capable of discriminating CRC from controls in blood samples drawn from the study population.

Chao and colleagues (2013) further validated the seven-gene panel by assessing its effectiveness for the detection of left- and right-sided CRC lesions in participants from the United States and Canada. Case samples consisted of blood samples taken from individuals with colonoscopy-confirmed CRC who had not undergone CRC treatment. Institutional pathologists established cancer stage according to the American Joint Committee on Cancer (AJCC) Tumor, Node, and Metastases (TNM) staging system. Controls consisted of samples from participants with no pathology at colonoscopy. Results were evaluated for 328 control samples and 314 participants with CRC (left-sided: TNM I, 65; TNM II, 57; TNM III, 60; TNM IV, 17; unknown, 9; right-sided: TNM I, 28; TNM II, 29; TNM III, 38; TNM IV, 12; unknown, 1 and including 2 samples with both left and right lesions). Blood samples were obtained prior to clinical staging and therapy. Of the study population, most of the CRC participants had localized disease (stages I and II, 58%); regional (stage III) and systemic (stage IV) disease represented 32% and 9%, respectively. The gene expression panel detected left-sided (74%, 154/208) and right-sided (85%, 92/108) lesions with an overall sensitivity of 78% (215/316) and a specificity of 66% (215/328). Treatable (stages I to III) cancer was detected with left-sided lesion sensitivity of 76% (138/182) and right-sided sensitivity of 84% (80/95). The authors concluded that the seven-gene biomarker panel detected right-sided CRC lesions across all cancer stages with a sensitivity that is at least equal to that for left-sided lesions.

There are insufficient data on the analytical validity, clinical validity, and clinical utility of the ColonSentry test to recommend the inclusion of the ColonSentry test as a CRC screening test. No current evidence-based guidelines from medical professional organizations were identified which recommend the use of the ColonSentry for any indication.

Recurrence of CRC Cancer
Oncotype DX® Colon Cancer Assay (Genomic Health, Inc., Redwood City, CA) is purported to predict the likelihood of disease recurrence in individuals with stage II colon cancer following surgery. The Oncotype DX Colon Cancer Assay utilizes a colon cancer sample to analyze the expression of 12 genes (7 colon cancer genes and 5 reference genes.) The test results are reported as a quantitative Recurrence Score® (RS) result, a score between 0 and 100 that correlates with the likelihood of an individual's chances of experiencing a recurrence of the cancer. The RS includes seven genes identified as consistently and significantly associated with recurrence-free interval (RFI). The manufacturer of the Oncotype DX Colon Cancer Assay recommends that the test be performed after colon resection, but before decisions are made regarding adjuvant treatments.

The QUASAR (Quick and Simple and Reliable) clinical validation study assessed the recurrence risk and benefits from adjuvant fluoropyrimidine chemotherapy versus surgery alone. Tumor specimens were retrieved from 2197 (68%) of the 3239 subjects who had curatively resected colorectal cancers and who were randomly assigned to either chemotherapy or to surgery alone in the QUASAR study. Of these 2197 individuals, 1490 (68%) were confirmed by pathologic review to have stage II colon cancer and 1436 were determined to be eligible samples. Of the eligible samples, 1399 underwent full pathologic examination and 1307 underwent tissue microarray analysis. An RS and a treatment score (TS) were calculated from gene expression levels of 13 cancer-related genes (7 recurrence genes and 6 treatment benefit genes) and from 5 reference genes with prespecified algorithms. Cox proportional hazards regression models and log-rank methods were used to analyze the relationship between the RS

and risk of recurrence in subjects treated with surgery alone and between the TS and benefits of chemotherapy. The recurrence risk increased as the RSs increased, with an average recurrence risk at 3 years of 12%, 18% and 22% in the pre-defined low, intermediate and high recurrence risk groups, respectively. The study findings suggest that the RS provides a continuous measure of recurrence risk at 3 years, ranging from a lowest risk of 9-11% to a highest risk of 25-27%. The authors acknowledged that some of the limitations of the study included the fact that tumor specimens were retrieved from only 68% of the participants and the proportion of participants with at least 12 nodes examined (approximately 38%) is lower than that observed in modern clinical practice (Gray, 2011).

Yothers and colleagues (2013) reported the results of an independent prospectively designed study using archived specimens (n=892) from the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 clinical trial. The study assessed the clinical validity of the Oncotype DX continuous RS. Archived specimens were obtained from individuals with stage II and III colon cancer who were randomly assigned to fluorouracil (FU) or FU plus oxaliplatin. The primary endpoint was RFI. Recurrence at death found on autopsy was considered a recurrence event. Data were analyzed by Cox regression adjusting for stage and treatment. Of the 892 participants, 31/264 with stage II and 214/628 with stage III colon cancer experienced a recurrence of the disease. The continuous RS was significantly associated with RFI and significantly predicted recurrence ($p<0.001$), disease-free ($p<0.001$) and overall survival ($p<0.001$). The Recurrence score predicted recurrence risk ($p=0.001$) after adjustment for mismatch repair, stage, nodes examined, grade and treatment. While the relative benefit of oxaliplatin was similar across the range of RS (interaction $p=0.48$), the absolute benefit of oxaliplatin increased with higher scores, especially in individuals with stage II and IIIA/b disease.

Venook and colleagues (2013) carried out a prospectively designed validation study which investigated the use of the twelve-gene RS on tumor specimens from participants included in the Cancer and Leukemia Group B (CALGB) 9581 study, a randomized, phase III clinical trial of adjuvant edrecolomab antibody therapy in individuals with surgically resected stage II colon cancer. The CALGB study excluded individuals with high-risk factors such as perforation or obstruction; therefore, the study population represented a group with a relatively low risk of colon cancer recurrence. The primary study endpoint was RFI. Among participants with stage T3 disease (colon cancer that has not metastasized to nearby organs), with intact mismatch repair ability, those the multi-gene expression test deemed to be at high risk had an average 5-year recurrence risk of 21% and those the test determined to be at low risk had an average recurrence risk of 13%. The RS was the strongest predictor of disease recurrence independent of other factors, such as T-stage, number of nodes examined, tumor grade, mismatch repair status and lymphovascular invasion.

Srivastava and colleagues (2014) carried out a multicenter prospective case series to evaluate the impact of OncotypeDX Colon on physician recommendations for adjuvant chemotherapy for the treatment of 141 individuals with resected, T3, mismatch repair-proficient (MMR-P) stage II colon cancer. The participants' tumor specimens were assessed by the RS test (qRT-PCR) and mismatch repair (immunohistochemistry). For each participant, the physician's recommended postoperative treatment plan of observation, fluoropyrimidine monotherapy, or combination therapy with oxaliplatin was recorded before and after the RS and mismatch repair results were made available. Treatment recommendations were modified for 63 (45%; 95% confidence interval [CI], 36%-53%) of the participants with intensity diminishing for 47 (33%) and increasing for 16 (11%). Following review of RS results

by the physician and the participant, recommendations for chemotherapy decreased from 73 participants (52%) to 42 (30%), Increased treatment intensity was more frequently seen at higher RS values, and decreased intensity was seen at lower values (p=0.011).

ColoPrint® (Agendia, BV, Amsterdam, Holland) is a microarray-based, 18 GEP designed to predict the risk of distant recurrence of the disease in individuals with stage II and III colon cancer. The ColoPrint test determines the risk of recurrence independent of other risk factors such as T stage, perforation, and tumor grade. Higher recurrence scores are associated with shorter time to progression and shorter overall survival.

Salazar and colleagues (2011) discuss the development of the ColoPrint test in which a total of 188 samples were prospectively collected from individuals undergoing surgery for stage I to IV colorectal cancer. RNA was separated from fresh tissue frozen in liquid nitrogen, labeled and hybridized to customized whole-genome oligonucleotide high-density microarrays. A nearest mean classifier was created using a cross-validation procedure to score all genes for their association with 5-year distant metastasis-free survival. From this pool of genes, an optimal set of 18 nonredundant genes was identified and used to construct a prognostic classifier (ColoPrint). The signature was validated on an independent set of 206 samples from individuals with stage I, II, and III colorectal cancer. The signature classified 60% of individuals as low risk and 40% as high risk. Five-year relapse-free survival rates were 87.6% (95% CI, 81.5% to 93.7%) and 67.2% (95% CI, 55.4% to 79.0%) for low- and high-risk subjects, respectively. In individuals with stage II disease, the hazard ratio between the low and high groups was 3.34 (p=0.017).

In another study conducted by Salazar (2012), the assay was further validated in a pooled analysis of 320 individuals with stage II colon cancer. Of this group, 227 were identified as a T3/MSS subset. In the T3/MSS subset, individuals classified as low risk and high risk had 3-year recurrence-free survival rates of 91% (86-96%) and 73% (63%-83%) (p=0.002), respectively. The results of this study have been published only in abstract form.

Maak and colleagues (2013) conducted a subsequent study to validate the ability of ColoPrint to assess the recurrence risk in individuals with stage II colon cancer and assist in treatment decisions. Clinical validation of the ColoPrint assay was performed on 135 individuals who underwent curative resection for stage II colon cancer. Fresh-frozen tissue, microsatellite instability status, clinical parameters, and follow-up data (median 8.4 years) were collected. Five-year distant metastasis-free survival was 95% for individuals classified as low risk by ColoPrint and 80% for individuals classified as high risk.

At least one clinical trial (A Prospective Study for the Assessment of Recurrence Risk in Stage II Colon Cancer Patients Using ColoPrint [PARSC]) is underway. In this trial (NCT00903565), researchers seek to further validate the ability of the ColoPrint test to predict 3-year relapse rates in individuals with stage II colon cancer (Agendia, 2017).

Colorectal Cancer DSA® (Almac Diagnostics, Craigavon, UK) is a microarray-based GEP for assessing the risk of CRC recurrence within 5 years following the surgical removal of the primary tumor. At least one clinical trial for the Colorectal Cancer DSA test (Kennedy, 2011) has been completed.

GeneFx Colon® (Precision Therapeutics, Pittsburgh, PA) is a 634-transcript DNA microarray-based gene signature developed for stage II colon cancer using formalin-fixed and paraffin-embedded (FFPE) specimens. Following surgery, GeneFx Colon assesses the individual's risk of recurrence within 5 years.

OncoDefender-CRC® (Everist Genomics, Ann Arbor, MI) is a five-gene assay used to assess the risk of recurrence of cancer in individuals previously treated with surgical resection of stage I or II colon cancer or stage I rectal cancer. Lenehan and colleagues (2012) reported on the development of the OncoDefender. The archived FFPE primary adenocarcinoma tissues of 74 individuals with CRC were used for training/test sets. Of this group, 15 individuals had stage I CRC; 59 had stage II CRC; 60 had colon cancer and 14 had rectal cancer. For external validation, FFPE tissues were obtained from 264 individuals (49 with stage I CRC and 215 with stage II colon cancer) from 18 hospitals in four countries. None of the individuals had received neoadjuvant/adjuvant therapy. A proprietary genetic programming which analyzed the expression profiles for 225 prespecified tumor genes was used to create a 36-month recurrence risk signature. The test appeared to differentiate participants at high versus low risk of recurrence with a hazard ratio of 1.63, p=0.031. Sensitivity and specificity of the assay was compared to National Comprehensive Cancer Network (NCCN) guidelines and demonstrated similar sensitivity (69% vs. 73%) with improved specificity (48% vs. 26%). However, several findings considered to be high-risk by the NCCN (lymphovascular invasion and bowel obstruction/perforation) demonstrated higher hazard ratios than observed using the molecular signature. Also, isolated performance of the test in individuals with stage II colon cancer was not reported.

A technical brief published by the Agency for Healthcare Research and Quality (AHRQ) focused on the use of GEP tests for both prognostic and predictive outcomes. In this brief, prognostic outcomes relate to disease prognosis such as recurrence of tumor or survival (disease-free survival). In contrast, the use of GEP assays for predictive outcomes correlates the GEP result with benefit (reduced recurrence rate and improved survival) from adjuvant chemotherapy. The authors concluded that: "while information is emerging about use of GEP assays to inform the decision about use of adjuvant chemotherapy in stage II colon cancer, studies to date have not provided the type of information needed to address major uncertainties" (Black, 2012).

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

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

Pugh (2017) retrospectively evaluated miR-31-3p expression in primary tumor samples from a group of 149 subjects with KRAS wild-type advanced metastatic CRC (mCRC) treated with oxaliplatin/irinotecan plus fluorouracil chemotherapy with (n=78) or without (n=71) cetuximab. The authors reported that progression-free survival (PFS) and overall survival (OS) were not significantly different between miR-31-3p expression groups across the whole study population. However, in the cetuximab treated group, the low-expression group had longer PFS vs. the mid- and high-expression groups (p=0.049). OS was reported to not be significantly different between the miR-31-3p expression groups in the whole modified intent-to-treat population (p=0.86), in the chemotherapy alone arm (p=0.62), or in the chemotherapy plus cetuximab arm (p=0.85). Likewise, no differences were reported in objective response rates (p=0.59, p=0.61, and p=1.0, respectively). Subjects treated with cetuximab with mid and high expression of miR-31-3p had shorter PFS compared to the chemotherapy alone group (12.3 months vs. 26.7 months, p=0.005). This difference was not seen in the low-expression group (20.3 vs. 18.9 months, p=0.91). Similar results were found with regard to OS, with the mid- and high-expression groups treated with cetuximab having significantly lower OS vs. those in the chemotherapy alone group (hazard ratio [HR],2.5, p=0.06), and no differences found in the low-expression group (HR,1.6, p=0.49). No differences between treatment groups or expression groups were reported with regard to objective response rates (p=0.22 and p=0.77, respectively). Multivariate analysis demonstrated that the miR-31-3p expression group was a significant predictive factor for PFS in the cetuximab treated group (low expression vs. mid and high, HR, 2.1, p=0.05). The authors concluded that subjects in the low-expression group were not harmed by the addition of cetuximab.

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

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

The miR-31now™ assay (GoPath laboratories, LLC, Buffalo Grove, IL) has been proposed to leverage the findings reported by Pugh (2017) and Laurent-Puig (2018) in the clinical setting to identify the most appropriate therapeutic

strategy for RAS wild type patients with mCRC. At this time there are no prospective published, peer-reviewed studies investigating the use of the miR-31now test for this use, and further investigation is warranted.

With regards to multigene assays, the NCCN guidelines on colon cancer provide the following conclusion:

> The information from these tests can further inform the risk of recurrence over other risk factors, but the panel questions the value added. Furthermore, there is no evidence of predictive value in terms of the potential benefit of chemotherapy to any of the available multigene assays. The panel believes that there are insufficient data to recommend the use of multigene assays to determine adjuvant therapy (NCCN, 2020).

In summary, much of the scientific literature for this topic primarily addresses the diagnostic validity and clinical validity of these tests, that is, the ability of the test to detect specific gene variants and the possible association of those variants with development or recurrence of colon cancer. Thus far, there is no information in the published peer-reviewed medical literature demonstrating the clinical utility of GEP assays to improve outcomes in individuals at risk for or with a history of colon cancer.

Background/Overview

Cancer of the colon is a highly treatable and often curable disease when the cancer is detected early. While surgery is the primary treatment for colon cancer, the possibility of a recurrence of the disease is an ongoing concern for health care practitioners and affected individuals. GEP is being investigated as a technique for identifying those individuals who may be at greater risk for the development or the recurrence of colon cancer and who might benefit from adjuvant therapy after surgery.

Definitions

Colon cancer: Cancer originating in the tissues of the colon (the longest part of the large intestine); most colon cancers are adenocarcinomas that begin in cells that make and release mucus and other fluids.

Gene expression profile/profiling (GEP): The individual pattern of expression of a panel of genes that is regarded as a "signature" for that tissue; a major determinant of the biology of both normal and malignant cells. It is also known as gene expression patterns or signatures.

Metastatic: The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.

Rectal cancer: Cancer originating in tissues of the rectum (the last several inches of the large intestine closest to the anus).

TNM (tumor size, nodal involvement, and metastasis) classification: A classification system used for characterizing the size and location of cancer.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

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 Oncotype DX Colon Cancer Assay, Genomic Health
81599	Unlisted multianalyte assay with algorithmic analysis [when specified as gene expression testing for colorectal cancer]
84999	Unlisted chemistry procedure [when specified as gene expression testing for colorectal cancer]
0069U	Oncology (colorectal), microRNA, RT-PCR expression profiling of miR-31-3p, formalin-fixed paraffin-embedded tissue, algorithm reported as an expression score miR-31now™, GoPath Laboratories, GoPath Laboratories

ICD-10 Diagnosis

	All diagnoses, including but not limited to the following:
C18.0-C18.9	Malignant neoplasm of colon
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C78.5	Secondary malignant neoplasm of large intestine and rectum
D01.0-D01.2	Carcinoma in situ of colon, rectosigmoid junction, rectum
Z85.038	Personal history of other malignant neoplasm of large intestine
Z85.048	Personal history of other malignant neoplasm of rectum, rectosigmoid junction, and anus

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2. 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. J Clin Oncol. 2011; 29(35):4611-4619.
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Government Agency, Medical Society, and Other Authoritative Publications:

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Websites for Additional Information

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	11/05/2020	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Rationale, References and Websites for Additional Information sections.
Reviewed	11/07/2019	MPTAC review. Updated Rationale, References and Websites for Additional Information sections.
Reviewed	01/24/2019	MPTAC review.
Reviewed	01/16/2018	Hematology/Oncology Subcommittee review. Updated Rationale, References, Websites for Additional Information and Index sections.
	09/20/2018	Updated Coding section with 10/01/2018 CPT changes; added 0069U.
Reviewed	05/03/2018	MPTAC review.
Reviewed	05/02/2018	Hematology/Oncology Subcommittee review. The document header wording updated from "Current Effective Date" to "Publish Date." Updated Rationale, References, Websites for Additional Information and History sections of the document.

Reviewed	05/04/2017	MPTAC review.
Reviewed	05/03/2017	Hematology/Oncology Subcommittee review. Updated Rationale and References sections of the document.
Reviewed	05/05/2016	MPTAC review.
Reviewed	05/04/2016	Hematology/Oncology Subcommittee review. Updated Rationale and References sections of the document.
	01/01/2016	Updated Coding section with 01/01/2016 CPT changes; removed ICD-9 codes.
Revised	05/07/2015	MPTAC review.
Revised	05/06/2015	Hematology/Oncology Subcommittee review. Changed title to Gene Expression Profiling for Colorectal Cancer. Information on ColonSentry added to document. Revised Position Statement and updated the Rationale, Coding, References and Index sections of the document.
Reviewed	05/15/2014	MPTAC review.
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	01/01/2013	Updated Coding section with 01/01/2013 CPT changes.
Reviewed	05/10/2012	MPTAC review.
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New	08/19/2010	MPTAC review. Initial document development.