Medical Policy

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Title: Multigene Expression Assay for Predicting Recurrence in Colon Cancer

Professional
Original Effective Date: March 4, 2016
Revision Date(s): March 4, 2016; October 12, 2016; September 28, 2017; October 1, 2018
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Populations	Interventions	Comparators	Outcomes
Individuals: • With stage II or III colon cancer	Interventions of interest are: • Gene expression profile testing	Comparators of interest are: • Risk prediction based on clinicopathologic factors	Relevant outcomes include: • Disease-specific survival • Test accuracy • Test validity • Change in disease status

DESCRIPTION

Gene expression profiling (GEP) tests have been developed and reported for use as prognostic markers in stage II or stage III colon cancer to help identify patients who are at high risk for recurrent disease and could be candidates for adjuvant chemotherapy.

OBJECTIVE

The objective of this policy is to determine whether gene expression profile testing improves the net health outcome in individuals with stage II or III colon cancer who are being considered for adjuvant chemotherapy.

BACKGROUND

Colon Cancer

According to estimates by the National Cancer Institute, in 2018 over 140,000 new cases of colorectal cancer will be diagnosed in the United States, and over 50,600 people will die of this cancer.[1] Five-year survival estimates are around 65%.

Treatment

Of patients with stage II colon cancer, 75% to 80% are cured by surgery alone, and the absolute benefit of chemotherapy for the overall patient population is small. Patients most likely to benefit from chemotherapy are difficult to identify by standard clinical and pathologic risk factors. Genomic tests are intended to be used as an aid for identifying stage II patients most likely to experience recurrence after surgery and most likely to benefit from additional treatment.

Colorectal cancer is classified as stage II (also called Dukes B) when it has spread outside the colon and/or rectum to nearby tissue but is not detectable in lymph nodes (stage III disease, also called Dukes C) and has not metastasized to distant sites (stage IV disease). Primary treatment is surgical resection of the primary cancer and colonic anastomosis. After surgery prognosis is good, with survival rates of 75% to 80% at 5 years.[2] A 2008 meta-analysis of 50 studies of adjuvant therapy versus surgery alone in stage II patients found statistically significant, although small, absolute benefit of chemotherapy for disease-free survival (DFS) but not for overall survival.[2] Therefore, adjuvant chemotherapy with 5-fluorouracil or capecitabine is recommended only as an option for resected patients with high-risk stage II disease (ie, those with poor prognostic features).[3]

However, clinical and pathologic features used to identify high-risk disease are not well-established, and patients for whom benefits of adjuvant chemotherapy would most likely outweigh harms cannot be identified with certainty. The current system relies on a variety of factors, including tumor substage IIB (T4A tumors that invade the muscularis propria and extend into pericolorectal tissues) or IIC (T4B tumors that invade or are adherent to other organs or structures), obstruction or bowel perforation at initial diagnosis, an inadequately low number of sampled lymph nodes at surgery (≤12), histologic features of aggressiveness, a high preoperative carcinoembryonic antigen level, and indeterminate or positive resection margins.[3]

Of interest, a recent review has noted that microsatellite instability (MSI) and mismatch repair (MMR) deficiency in colon cancer may represent confounding factors to be considered in treatment.[4] These factors may identify a small proportion (15%-20%) of

the population with improved DFS who may derive no benefit or may exhibit deleterious effects from adjuvant fluorouracil/leucovorin-based treatments. Patient MSI and MMR status may be critically important in how to study, interpret, and use a particular GEP test.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Multigene expression assay testing for predicting recurrent colon cancer is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Gene expression profiling tests for colon cancer currently commercially available include:

- ColoPrint® 18-Gene Colon Cancer Recurrence Assay (Agendia)
- GeneFx™ Colon (Helomics Therapeutics; also known as ColDx, Almac Diagnostics)
- OncoDefender-CRC™ (Everist Genomics)
- Oncotype DX® Colon Recurrence Score (Genomic Health).

POLICY

Gene expression assays for determining the prognosis of stage II or stage III colon cancer following surgery are considered **experimental / investigational**.

Policy Guidelines

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

RATIONALE

An updated literature search was performed using the MEDLINE database for the period through June 7, 2018.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Stage II or III Colon Cancer

Clinical Context and Test Purpose

The purpose of prognostic testing of diagnosed disease is to predict natural disease course (eg, aggressiveness, risk of recurrence, death). This type of testing uses gene expression of affected tissue to predict the course of the disease.

The question addressed in this evidence review is: Does prognostic testing using the gene expression profile (GEP) tests described below in individuals diagnosed with stage II or stage III colon cancer improve the net health outcome?

The specific clinical context of each test is described briefly in the following section. The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is patients who have undergone surgery for stage II or stage III colon cancer and are being evaluated for adjuvant chemotherapy.

Interventions

The interventions of interest are GEP testing with the ColoPrint 18-Gene Colon Cancer Recurrence Assay, GeneFx Colon (ColDx), OncoDefender-CRC, and Oncotype DX Colon Recurrence Score.

Comparator

The comparator of interest is standard care without prognostic testing. The current standard of care is not to provide adjuvant chemotherapy to patients with stage II colon cancer and to administer adjuvant chemotherapy routinely to patients with stage III colon cancer.

Outcomes

The outcomes of interest are recurrence risk, recurrence-free survival, and overall survival at follow-up in patients classified as low risk, medium risk, or high risk by GEP.

Time

The time of interest is 5 to 10 years after surgical resection to assess colon cancer recurrence.

Setting

These tests are offered commercially through various manufacturers and would be performed on tumor tissue after surgical resection.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

ColoPrint 18-Gene Colon Cancer Recurrence Assay

Salazar et al (2011) described the development of an 18-gene expression test called the ColoPrint 18-Gene Colon Cancer Recurrence Assay.[5] A total of 188 samples were prospectively collected from patients with colorectal cancer (CRC). RNA was isolated from fresh tissue frozen in liquid nitrogen, labeled and hybridized to customized whole-genome oligonucleotide high-density microarrays. A cross-validation procedure was performed on 33,834 gene probes that showed variation across the training samples. They were scored for their association with 5-year distant metastasis-free survival. From this pool of genes, an optimal set of 18 nonredundant probes was identified and used to construct classification scores for the test. Results were dichotomized into a 2-category, low- and high-risk, scoring system.

In a small independent validation study, Salazar et al (2011) used a patient cohort of 206 patients. However, only 56% represented stage II tumors.[6] Risk classification and survival are shown in Table 1 for the patients with stage II disease in this study.

Maak et al (2013) conducted a subsequent validation study in fresh-frozen tumor samples from patients who had undergone curative resection for stage II colon cancer.[7] Mismatch repair status, clinical parameters, and follow-up data (median, 8.4 years) were collected. Five-year distant metastasis-free survival for patients classified as low risk and high risk is shown in Table 1. Information about net reclassification and clinical utility was not provided.

Table 1. RFS in Patients with Stage II Colon Cancer Assessed with ColoPrint

Study	N	Follow-Up, y	Low Risk, %	Mean RFS for Low Risk, %	High Risk, %	Mean RFS for High Risk, %
Salazar et al (2011)[6]	115	5	63.2	90.9	36.8	73.9
Maak et al (2013)[7]	135	8.4[a]		95		80

RFS: recurrence-free survival.
[a] Median.

Kopetz et al (2015) reported on a pooled analysis of 416 patients with stage II colon cancer from independent cohorts in the United States, Spain, Italy, Austria, and Germany.[8] Investigators compared the prognostic ability of ColoPrint with National Comprehensive Cancer Network (NCCN) risk prediction based on clinicopathologic factors (T4; high-grade tumor; lymphovascular or perineural invasion; perforation or obstruction; <12 lymph nodes examined; positive margins). Recurrence risk at a mean 81 months (range, 56 to 178) is shown in Table 2. Statistical comparison of the risk models (eg, using a likelihood ratio test and/or receiver operating characteristic curves) and comparison of classifications by survival outcomes (ie, reclassification analysis) were not provided. Further, a 5-year recurrence risk as high as 14% in patients classified as low risk by ColoPrint may be too high for some patients to consider forgoing chemotherapy.

Table 2. ColoPrint and NCCN Risk Prediction and RR in Patients with Stage II Colon Cancer

Study	Risk Prediction	Low Risk, n (%)	Mean RR for Low Risk (95% CI)	High Risk, n (%)	Mean RR for High Risk (95% CI)
Kopetz et al (2015)[8]	ColoPrint	263 (63)	10 (7 to 14)	153 (37)	21 (14 to 28)
	NCCN	236 (57)	13 (9 to 18)	180 (43)	15 (10 to 20)

CI: confidence interval; NCCN: National Comprehensive Cancer Network; RR: recurrence risk.

GeneFx Colon

Kennedy et al (2011) reported on the development of a 634-probe set signature.[9] A training set of 215 patients (142 low-risk, 73 high-risk) was identified based on 5-year disease-free survival. The assay was performed using DNA-microarray analysis of formalin-fixed, paraffin-embedded (FFPE) samples. Cross-validation studies were used to select an optimal transcript signature for prognostic classification.

Independent validation was performed by Kennedy et al (2011) on 144 patients enriched for recurrence (85 low-risk, 59 high-risk) using the threshold score identified in the training set.[9] The signature in this convenience sample of patients predicted disease recurrence with a hazard ratio (HR) of 2.53 ($p<0.001$) in the high-risk group. The signature also predicted cancer-related death with an HR of 2.21 ($p<0.001$) in the high-risk group. The authors also noted plans for an additional retrospective validation of the test in a large cohort of stage II colon cancer samples collected.

Niedzwiecki et al (2016) reported on the recurrence-free interval for 393 of 1738 patients treated in the Cancer and Leukemia Group B 9581 (CALGB 9581) trial.[10] Treatment in CALGB 9581 was with an experimental monoclonal antibody (edrecolomab) or observation; there was no significant survival benefit from the experimental treatment. Of 901 eligible patients with available tissue, a randomized sample of 514 patients was selected. The final analysis included 360 patients in the randomized cohort (58 events) and 33 nonrandomly selected events that had samples successfully analyzed. The investigators hypothesized that the high failure rate was due to the long interval between sample collection and analysis (mean, 13.2 years). Table 3 provides recurrence scores for patients categorized as low risk and high risk. After adjusting for prognostic variables that included mismatch repair deficiency, patients categorized as high risk by GeneFx had a significantly worse recurrence-free interval in unadjusted analysis (HR=2.13; 95% CI, 1.3 to 3.5; $p<0.01$). However, in multivariate analysis, the GeneFx risk score was marginally associated with overall survival (HR=1.74; 95% CI, 0.97 to 3.1; $p=0.06$). For the 271 samples analyzed by both GeneFx and Oncotype DX (see below), there was a weak correlation in continuous scores (R=0.18).

Table 3. RFS in Patients with Stage II Colon Cancer Assessed with GeneFx

Study	N	Follow-Up, y	Low Risk, n (%)	Mean RFS for Low Risk (95% CI)	High Risk, n (%)	Mean RFS for High Risk (95% CI)
Niedzwecki et al (2016)[10]	393	5	177 (45)	91 (89 to 93)	216 (55)	82 (79 to 85)

CI: confidence interval; RFS: recurrence-free survival.

OncoDefender-CRC

Lenehan et al (2012) reported on the development of a 5-gene test called OncoDefender.[11] A total of 417 cancer-associated genes were preselected for the study of archived FFPE primary adenocarcinoma tissues from 74 patients with CRC (15 with stage I disease, 59 with stage II disease; 60 with a colon cancer, 14 with rectal cancer). Patients were divided into a training set and a test set. Cross-validation was performed to estimate the ability of the classifier to generalize to unseen samples. The most important feature of gene fitness was the area under the receiver operating characteristic curve for each gene.

In addition, Lenehan performed external validation on 251 patients with stage I and II colon cancer obtained from an international study set. Patient dropout from the set of archived samples used was substantial; only 264 (55%) of 484 patients with lymph node–negative CRC satisfied the initial clinicopathologic screening. This included a mix of patients with both rectal and colon cancer (stages I and II). The test appeared to distinguish patients at high vs low risk of recurrence (HR=1.63; p=0.031). Sensitivity and specificity of OncoDefender were compared with NCCN guidelines and showed similar sensitivity (69% vs 73%), with improved specificity (48% vs 26%). However, the isolated performance of the test in patients with stage II colon cancer was not reported, and several NCCN high-risk findings (bowel obstruction or perforation and lymphovascular invasion) demonstrated higher HRs than observed with the molecular signature. The study alluded to but did not directly address clinical utility.

Oncotype DX Colon Recurrence Score

O'Connell et al (2010) described the development of a 12-gene expression test called Oncotype DX Colon Recurrence Score.[12] A total of 761 candidate genes of possible prognostic value for recurrence or of possible predictive value for treatment were examined by correlating the genes in tumor samples with clinical outcomes in 1851 patients who had surgery with or without adjuvant 5-fluorouracil-based chemotherapy. Gene expression was quantified from microdissected, FFPE primary colon cancer tissue. Of the 761 candidate genes, multivariate analysis (including disease severity, stage, and nodal involvement) reduced the gene set to a 7-gene prognostic signature and a separate 6-gene predictive signature. Five reference genes also are included in the assay.

Tables 4 and 5 summarize the characteristics and results of several validation studies. External validation of the algorithm was first reported by Gray et al (2011), who used FFPE primary tumor samples from patients with stage II colon cancer who had participated in the Quick and Simple and Reliable study.[13] The relation between the 7-gene recurrence score and risk of recurrence was statistically significant, with 3-year risk of recurrence for predefined low-, intermediate-, and high-risk groups as shown in Table 5. In the surgery-alone group, the HR for recurrence in the high-risk group compared with the low-risk group was 1.47 (95% CI, 1.01 to 2.14, p=0.046).

Table 4. Oncotype DX Colon Validation Study Characteristics

Study; Trial	Design	N	Colon Cancer, n		Randomized Treatments	
			Stage II	Stage III	Intervention	Comparator
Gray et al (2011)[13]; QUASAR	RCT	3239	1436		Adjuvant chemotherapy	Surgery alone
Venook et al (2013)[14]; CALGB 9581	RCT	1713	690		Edrecolomab	Observation
Yothers et al (2013)[15]; NASBP C-07 R	RCT	2409	264		FULV with oxaliplatin	FULV without oxaliplatin
Reimers et al (2014)[16]; TME	RCT	1861	130[a]	167[a]	Radiotherapy	No radiotherapy
Yamanaka et al (2016)[17]; SUNRISE	Cohort	1487	247	350	Not applicable	

CALGB 9581: Cancer and Leukemia Group B 9581 trial; FULV: 5-fluorouracil plus leucovorin; NASBP C-07: National Surgical Adjuvant Breast and Bowel Project; QUASAR: Quick and Simple and Reliable; RCT: randomized controlled trial; TME: Dutch total mesenteric excision trial.
[a] Rectal.

Venook et al (2013) reported on a validation study using tumor tissue from patients with stage II colon cancer who had participated in the randomized CALGB 9581 trial.[14] The investigators

selected samples stratified by treatment group from those who had tumor tissue available (40% of the original patient sample). They used recurrence score cut points of 29 and 39 to determine low-, intermediate-, and high-risk groups (see Table 5); these values differ from the cut points of 30 and 41 validated in the Quick and Simple and Reliable study (previously described). In multivariate analysis, every 25-unit change in recurrence score was associated with recurrence independent of tumor stage, tumor grade, mismatch repair status, presence or absence of lymphovascular invasion, and the number of nodes assessed.

Yothers et al (2013) conducted a validation study using tumor tissue from 264 patients with stage II colon cancer who had participated in the National Surgical Adjuvant Breast and Bowel Project C-07 trial.[15] The National Surgical Adjuvant Breast and Bowel Project C-07 randomized 2409 patients with stage II (28%) or stage III (72%) colon cancer to adjuvant chemotherapy with 5-fluorouracil plus leucovorin or oxaliplatin plus 5-fluorouracil plus leucovorin. For the randomly selected sample of 50% of patients with stage II colon cancer, estimated 5-year recurrence risks (adjusted for treatment) are shown in Table 5. Five-year recurrence risk, estimated by Kaplan-Meier analysis, was reduced in high-risk patients who received oxaliplatin (9%; 95% CI, 3% to 25%) compared with those who did not (23%; 95% CI, 12% to 42%), but this difference was not observed in low- or intermediate-risk patients. However, CIs for these estimates were wide due to small numbers of patients and events in each risk group. For all stage III patients in any risk class, adjusted 5-year recurrence risk estimates exceeded 15%.

Table 5. Recurrence Rates by Risk Category for the Oncotype DX Colon Recurrence Risk Score

Study	Trial	Risk Prediction, y	Mean Recurrence Rate (95% CI), %		
			Low Risk	Medium Risk	High Risk
Gray et al (2011)[13]	QUASAR	3	12	18	22
Venook et al (2013)[14]	CALGB 9581	5	12 (10 to 15)	15 (12 to 17)	18 (14 to 22)
Yothers et al (2013)[15]	NASBP C-07	5	9 (6 to 13)	13 (8 to 17)	18 (12 to 25)
Reimers et al (2014)[16]	TME stage II cohort (rectal)	5	11 (6 to 22)	27 (16 to 46)	43 (29 to 65)
Yamanaka et al (2016)[17]	SUNRISE stage II cohort	5	9 (7 to 12)	14 (11 to 17)	19 (13 to 24)
	SUNRISE stage III cohort	5	20 (14 to 25)	29 (23 to 35)	38 (29 to 47)

CALGB 9581: Cancer and Leukemia Group B 9581 trial; CI: confidence interval; NASBP C-07: National Surgical Adjuvant Breast and Bowel Project; QUASAR: Quick and Simple and Reliable; TME: Dutch total mesenteric excision trial.

Reimers et al (2014)[16] conducted a retrospective study using prospectively collected tumor specimens from the Dutch total mesenteric excision trial[18] in patients with resectable rectal cancer. Reimers used available tumor tissue from 569 stage II and III patients randomized to surgery alone. Among 130 patients with stage II rectal cancer, Oncotype DX Colon classified 63 (49%) patients as low-risk, 37 (28%) patients as intermediate-risk, and 30 (23%) patients as high-risk. Five-year Kaplan-Meier recurrence risk estimates in the low-, intermediate-, and high-risk groups are shown in Table 5. Oncotype DX Colon risk classification and estimated recurrence risks for patients with stage III rectal cancer were not reported.

The SUNRISE study, as reported by Yamanaka et al (2016), evaluated tissue samples from consecutive patients with stage II and stage III colon cancer who had been treated with surgery

alone.[17] Surgery was the standard of care at hospitals in Japan during the study period 2000 to 2005. From the total cohort of 1487 patients, samples were randomly selected from patients who had or did not have a recurrence, in a 1:2 ratio. The final number of patients studied was 597; 202 patients had disease recurrence, and 395 had no recurrence. As shown in Table 5, the risk of recurrence in patients with stage III colon cancer with a low-risk score was similar to patients with stage II disease and a high-risk score and exceeded 15%. When adjusted for disease stage, a 25-unit increase in the recurrence score had an HR of 2.05 (95% CI, 1.47 to 2.86; p<0.001).

Section Summary: Clinically Valid

Several validation studies of GEP testing for colon cancer have reported that testing provides prognostic information on the risk of recurrence. Some studies have reported that GEP testing offers prognostic information in a multivariate analysis. Other data have suggested that GEP testing may provide modest incremental prognostic information over the standard prognostic workup, including the NCCN risk prediction model. Patients with a low recurrence score have a lower risk of recurrence and patients with a high-risk score have a higher risk of recurrence. However, the increase in recurrence risk for a high-risk score is small, and it is uncertain whether the degree of increase is sufficient to intensify management.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

A technical brief by Black et al (2012), conducted for the Agency for Healthcare Research and Quality, reviewed the clinical evidence for GEP testing in predicting outcomes, including the benefit from adjuvant chemotherapy, in patients with stage II colon cancer.[19] The 4 commercially available assays reviewed herein were included in the brief. No prospective studies were identified that assessed change in the net health outcome with use of a GEP assay, and no studies were identified that used a net reclassification analysis and subsequently evaluated the impact of the reclassification on the net health outcome. Additionally, evidence was limited on the reproducibility of test findings, indications for GEP testing in stage II patients, and whether results of GEP assays can stratify patients into groups with clinically meaningful differences in recurrence risk. No studies have been identified in subsequent literature updates that evaluated the impact of GEP testing on recurrence in patients with stage II or III colon cancer.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. A chain of evidence may be developed, which addresses 2 key questions.

1. Does the use of GEP testing of colon cancer risk in individuals with stage II or stage III colon cancer lead to a change in management regarding use of adjuvant chemotherapy?
2. Do those management changes improve health outcomes?

Several studies have documented changes in management following GEP testing for colon cancer. For example, Brenner et al (2016) published a retrospective study of the association between Oncotype DX Colon Recurrence Score and management decisions.[20] The study included 269 patients from a health plan who had stage II colon cancer, mismatch repair proficient status, and Oncotype DX Colon Recurrence Score. The primary outcome measure was change in management that occurred following Oncotype DX Colon testing. Patients were classified as having either an increase in the intensity of surveillance or treatment, a decrease in the intensity of surveillance or treatment, or no change. A change in management following testing was found for 102 (38%) of 269 patients. Of the 102 patients with management changes, 76 patients had a decrease and 26 had an increase in treatment intensity. More patients who had a low recurrence score had a decrease in the intensity of management, and more patients with a high recurrence score had an increase in intensity.

Cartwright et al (2014) and Srivastava et al (2014) have also published studies showing the effect of Oncotype DX Colon results on treatment recommendations made using traditional risk classifiers in patients with stage II colon cancer.[21,22] Cartwright et al (2014) performed a retrospective study predicting that test results might lead to reductions in treatment intensity in a percentage of patients.[21] Srivastava et al (2014) performed a prospective study that directly demonstrated reductions in treatment intensity in a percentage of patients.[22]

This type of study does not determine whether patient outcomes are improved as a consequence of the changes in management, and there are no well-defined treatment protocols that differ according to the risk of recurrence within stage II or within stage III colon cancer.

Section Summary: Clinically Useful
Some studies have reported management changes following GEP testing. However, these studies did not report clinical outcomes, and there is no direct evidence to determine whether GEP testing improves health outcomes. A chain of evidence might be constructed if there was evidence that changes in management for patients with stage II colon cancer improved health outcomes. The intensity of surveillance and management may be impacted by results of GEP testing, but the evidence to demonstrate that a change in management improved health outcomes is weak and not definitive. Therefore, the evidence does not demonstrate clinical utility.

SUMMARY OF EVIDENCE

For individuals who have stage II or III colon cancer who receive GEP testing, the evidence includes development and validation studies and decision-impact studies. Relevant outcomes are disease-specific survival, test accuracy and validity, and change in disease status. The available evidence has shown that GEP testing for colon cancer can improve risk prediction, particularly the risk of recurrence in patients with stage II or III colon cancer. However, the degree of difference in risk conferred by the test is small. Evidence to date does not permit conclusions on whether GEP classification is sufficient to modify treatment decisions in stage II or III patients. Studies showing management changes as a consequence of testing have not demonstrated whether such changes improve outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

PRACTICE GUIDELINES AND POSITION STATEMENTS

Current clinical practice guidelines from the National Comprehensive Cancer Network (v. 2.2018) on colon cancer state that "there is insufficient data to recommend the use of multigene assays to determine adjuvant therapy" in patients with stage II or III colon cancer.[3]

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT00903565[a]	A Prospective Study for the Assessment of Recurrence Risk in Stage II Colon Cancer Patients Using ColoPrint (PARSC)[20]	1200	Dec 2019

NCT: national clinical trial. [a] Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy 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. 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.

CPT/HCPCS

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
84999	Unlisted chemistry procedure
88299	Unlisted cytogenetic study

- There is a CPT code specific to Oncotype DX Colon Cancer Assay: 81525
- If the test is a multianalyte assay with algorithmic analysis (MAAA), it would be reported with the unlisted MAAA code: 81599.
- Otherwise, it would likely be reported using an unlisted code such as: 84999 or 88299.

Diagnoses

Experimental / Investigational for all diagnoses related to this medical policy.

REVISIONS

03-04-2016	Policy added to the bcbsks.com web site on 02-03-2016.
10-12-2016	Updated Description section.
	Updated Rationale section.
	In Coding section:

	▪ Revised coding bullets.
	Updated References section.
09-28-2017	Updated Description section.
	In Policy section: ▪ Removed Policy Guidelines.
	Updated Rationale section.
	In Coding section: ▪ Updated Coding bullets.
	Updated References section.
10-01-2018	Updated Description section.
	In Policy section: ▪ Added Policy Guidelines.
	Updated Rationale section.
	Updated References section.
	Removed Appendix section.

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