



Kansas City

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Multigene Expression Assay for Predicting Recurrence in Colon Cancer

Policy Number: 2.04.61
Origination: 8/2010

Last Review: 10/2018
Next Review: 10/2019

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for multigene expression assay for predicting recurrence in colon cancer. This is considered investigational.

When Policy Topic is covered

Not Applicable

When Policy Topic is not covered

Gene expression assays for determining the prognosis of stage 2 or stage 3 colon cancer following surgery are considered **investigational**.

Considerations

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 PG2). 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 PG3 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

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

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 Unlisted chemistry procedure

88299 Unlisted cytogenetic study

There is a CPT code specific to Oncotype DX Colon Cancer Assay:

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.

Description of Procedure or Service

Populations	Interventions	Comparators	Outcomes
Individuals: • With stage 2 or	Interventions of interest are:	Comparators of interest are:	Relevant outcomes include: • Disease-specific survival

stage 3 colon cancer	<ul style="list-style-type: none"> • Gene expression profiling tests 	<ul style="list-style-type: none"> • Risk prediction based on clinicopathologic factors 	<ul style="list-style-type: none"> • Test accuracy • Test validity • Change in disease status
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Gene expression profiling (GEP) tests have been developed and reported for use as prognostic markers in stage 2 or stage 3 colon cancer to help identify patients who are at high risk for recurrent disease and could be candidates for adjuvant chemotherapy.

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 is insufficient to 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 do not demonstrate whether such changes improve outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Background

Of patients with stage 2 colon cancer, 75-80% 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 pathological risk factors. Genomic tests are intended to be used as an aid for identifying stage 2 patients most likely to experience recurrence after surgery and most likely to benefit from additional treatment.

Colorectal cancer is classified as stage 2 when it has spread outside the colon and/or rectum to nearby tissue but is not detectable in lymph nodes and has not metastasized to distant sites (also called Dukes B). 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.¹ A 2008 meta-analysis of 50 studies of adjuvant therapy versus surgery alone in stage 2 patients found statistically significant, although small, absolute benefit of chemotherapy for disease-free survival but not for overall survival.¹ Therefore, adjuvant chemotherapy with 5-fluorouracil (5-FU) or capecitabine is recommended only as an option for resected patients with high-risk stage 2 disease (ie those with poor prognostic features).²

However, clinical and pathological 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 sub-stage 2B (T4A tumors that invade the muscularis propria and extend into pericolorectal tissues) or 2C (T4B tumors that invade or are adherent to other organs or structures), obstruction or bowel perforation at initial diagnosis, inadequately low number of

sampled lymph nodes at surgery (12 or less); histological features of aggressiveness, a high preoperative carcinoembryonic antigen level, and indeterminate or positive resection margins.²

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.³ These factors may identify a small proportion (15% to 20%) of the population with improved disease-free survival 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 gene expression profile (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 Improvement Act (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 these tests.

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

- ColoPrint® 18-Gene Colon Cancer Recurrence Assay (Agendia)
- GeneF_x™ Colon (Helomics), also known as ColD_x)
- OncoDefender-CRC™ (Everist Genomics)
- Oncotype DX® Colon Recurrence Score (Genomic Health).

Rationale

This evidence review was created in March 2010 and has been updated regularly with literature searches of the MEDLINE database. The most recent literature update was performed through June 22, 2017. The review addresses BCBSA genetic testing category 1b (prognostic testing of an affected individual's germline to benefit the individual; see Appendix Table 1 for genetic testing categories).

Validation of genotyping to improve treatment outcomes is a multistep process. In general, important steps in the validation process address the following:

- **Analytic validity** measures technical performance (ie, whether the test accurately and reproducibly detects gene markers of interest).
- **Clinical validity** measures the strength of associations between selected genetic markers and clinical status.
- **Clinical utility** determines whether the use of genotyping for specific genetic markers to guide treatment decisions improves patient outcomes (eg, survival or adverse event rates) compared with standard treatment without genotyping.

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 disease. The criteria under which prognostic testing may be considered clinically useful are as follows:

- An association of the marker with the natural history of the disease has been established; and
- Clinical utility of identifying the variant has been established, eg, by demonstrating that testing will lead to changes in clinical management of the condition or changes in surveillance.

The question addressed in this evidence review is: Does prognostic testing using the gene expression profiling (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 is gene expression profiling (GEP) 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.

Analytic Validity

Many GEP assays have been developed and reported as prognostic markers in stage II colon cancer since 2004.⁴⁻¹⁹ Four are currently offered commercially in the United States (ColoPrint 18-Gene Colon Cancer Recurrence Assay, GeneFx Colon, OncoDefender-CRC, Oncotype DX Colon Recurrence Score).

Information on specimen type, sample handling, and technique used for GEP, has been reported for many of these assays.

Clinical Validity

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.⁽¹⁶⁾ 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.

A small independent validation study by Salazar et al (2011) used a patient cohort of 206 patients, however, only 56% represented stage II tumors.⁽¹⁶⁾ Risk classification and survival are shown in table x 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.⁽²⁰⁾ Mismatch repair (MMR) 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 are 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

Author (Year)	Follow-Up, y	N	Low Risk, %	Mean RFS for Low Risk, %	High Risk, %	Mean RFS for High Risk, %
Salazar et al (2011) ¹⁶	5	115	63.2	90.9	36.8	73.9
Maak et al	8.4a	135		95		80

(2013)20

RFS: recurrence-free survival. a Median.

In 2015, Kopetz et al(21) reported a pooled analysis of 416 patients with stage II colon cancer from independent cohorts in the United States, Spain, Italy, Austria, and Germany. 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; and 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 [ROC] 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 foregoing chemotherapy.

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

Author (Year)	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)21	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.(15) A training set of 215 patients (142 low risk, 73 high risk) was identified based on 5-year DFS. 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 in 2011 on 144 patients enriched for recurrence (85 low risk, 59 high risk) using the threshold score identified in the training set.(15) 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 noted that additional retrospective validation of the test in a large cohort of stage II colon cancer samples collected as part of a clinical trial was planned.

In 2016, Niedzwiecki reported recurrence free interval from 393 patients out of 1738 treated in the Cancer and Leukemia Group B 9581 (CALGB 9581) trial.(22) Treatment in CALGB 9581 was with an experimental monoclonal antibody (edrecolomab) or observation; there was no significant survival benefit of the experimental treatment. Of 901 eligible patients with available tissue, a

randomized sample of 514 patients was selected. Final analysis included 360 patients in the randomized cohort (58 events) and 33 nonrandomly selected events that had samples that were 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). Recurrence scores in patients categorized as low risk and high risk are shown in Table 3. After adjustment for prognostic variables that included mismatch repair deficiency, patients categorized as high risk by GeneF_x had significantly worse regression-free interval in unadjusted analysis (HR=2.13; 95% CI, 1.3 to 3.5; p<0.01). However, in multivariate analysis the GeneF_x 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 GeneF_x and Oncotype DX (see below), there was little correlation in continuous scores ($R=0.18$).

Table 3. RFS in Patients With Stage II Colon Cancer Assessed With GeneF_x

Author (Year)	Follow-Up, y	N	Low Risk, n (%)	Mean RFS for Low Risk (95% CI)	High Risk, n (%)	Mean RFS for High Risk (95% CI)
Niedzwecki et al (2016) ²²	5	393	177 (45)	91 (89 to 93)	216 (55)	82 (79 to 85)

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

OncoDefender-CRC

Lenahan et al (2012) reported on their development of a 5-gene test, OncoDefender.⁽²³⁾ A total of 417 cancer-associated genes were preselected for study in archived FFPE primary adenocarcinoma tissues of 74 patients with CRC (15 with stage I disease, 59 with stage II disease; 60 with colon, 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 ROC curve for each gene.

External validation (2012) was performed on 251 patients with stage I and II colon cancer obtained from an international study set.⁽²³⁾ 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 with an HR of 1.63 (p=0.031). Sensitivity and specificity of OncoDefender was compared with NCCN guidelines and showed similar sensitivity (69% vs 73%), with improved specificity (48% vs 26%). However, 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, Oncotype DX Colon Recurrence Score.(9) 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-FU-based chemotherapy. Gene expression was quantified from microdissected, FFPE primary colon cancer tissue. Of 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.

There have been several validation studies. These are summarized in Tables 4 and 5.

External validation of the algorithm was first reported by Gray et al in 2011, who used FFPE primary tumor samples from patients with stage II colon cancer who had participated in the Quick and Simple and Reliable (QUASAR) study.(24) 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 4. In the surgery alone group, the hazard ratio 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 Validation Study Characteristics

Author (Year)	Study	Study Design	N	Randomized Comparators	Stage II Colon Cancer, n	Stage III Colon Cancer, n
Gray et al (2011)24	QUASAR	RCT	3239	<ul style="list-style-type: none"> ▪ Adjuvant chemotherapy ▪ Surgery alone 	1436	
Venook et al (2013)25	CALGB 9581	RCT	1713	<ul style="list-style-type: none"> ▪ Edrecolomab ▪ Observation 	690	
Yothers et al (2013)26	NASBP C-07 R	RCT	2409	<ul style="list-style-type: none"> ▪ FULV with oxaliplatin ▪ FULV without oxaliplatin 	264	
Reimers et al (2014)27	TME	RCT	1861	<ul style="list-style-type: none"> ▪ Radiotherapy ▪ No radiotherapy 	130a	167a
Yamanaka et al (2016)28	SUNRISE	Cohort	1487		247	350

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 (TME) trial. a Rectal.

In 2013, Venook et al reported a validation study using tumor tissue from patients with stage II colon cancer who had participated in the randomized CALGB 9581 trial.(25) 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 (Table 4); these values differ from the cut points of 30 and 41 validated in the QUASAR study previously described. In multivariate analysis, every 25-unit change in recurrence score was associated with recurrence independent of tumor stage, tumor grade, MMR status, presence or absence of lymphovascular invasion, and 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 (NSABP) C-07 trial.(26) NSABP C-07 randomized 2409 patients with stage II (28%) or stage III (72%) colon cancer to adjuvant chemotherapy with 5-fluorouracil plus leucovorin (FULV) or oxaliplatin plus FULV (FLOX). 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, confidence intervals 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 With 3-Level Oncotype DX Colon Cancer Recurrence Risk Score

Author (year)	Study	Risk Prediction, y	Mean Recurrence Rate for Low Risk (95% CI), %	Mean Recurrence Rate for Medium Risk (95% CI), %	Mean Recurrence Rate for High Risk (95% CI), %
Gray et al (2011)24	QUASAR	3	12	18	22
Venook et al (2013)25	CALGB 9581	5	12 (10 to 15)	15 (12 to 17)	18 (14 to 22)
Yothers et al (2013)26	NASBP C-07	5	9 (6 to 13)	13 (8 to 17)	18 (12 to 25)
Reimers et al (2014)27	TME stage II cohort (rectal)	5	11 (6 to 22)	27 (16 to 46)	43 (29 to 65)
Yamanaka et al (2016)28	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 (TME) trial.

Reimers et al (2014)(27) conducted a retrospective study using prospectively collected tumor specimens from the Dutch total mesenteric excision (TME) trial(29) 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 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 x.(30) Oncotype DX risk classification and estimated recurrence risks for patients with stage III rectal cancer were not reported.

The SUNRISE study (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.(28) This 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: Clinical Validity

Several validation studies of GEP 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 suggest that GEP testing may provide modest incremental prognostic information over the standard prognostic work-up, including the NCCN risk prediction model. Generally, 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.

Clinical Utility

Clinical utility is defined as how the results of the prognostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

A technical brief, published by the Agency for Healthcare Research and Quality in 2012, reviewed the clinical evidence for GEP in predicting outcomes, including benefit from adjuvant chemotherapy, in patients with stage II colon cancer.(31) The 4 commercially available assays reviewed herein were included in the brief. No prospective studies were identified that assessed change in 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 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.

Direct evidence for the clinical utility of GEP testing to improve health outcomes is lacking. Therefore, 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 been published that document changes in management following GEP testing for colon cancer.

In 2016, Brenner et al published a retrospective study of the association between Oncotype DX recurrence score and management decisions.(32) There were 269 patients from a health plan included who had stage II colon cancer, MMR proficient status, and Oncotype DX recurrence scores. The primary outcome measures were changes in management that occurred following Oncotype DX testing. Patients were classified as having either an increase in the intensity of surveillance/treatment, a decrease in the intensity of surveillance/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, there were 76 patients in whom the intensity of management was decreased and 26 in whom it was increased. More patients who had a low recurrence score had a decrease in 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 results on treatment recommendations made according to traditional risk classifiers in patients with stage II colon cancer.(33,34)

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 risk of recurrence within stage II or within stage III colon cancer.

Section Summary: Clinical Utility

Some studies have reported management changes following GEP testing. However, these studies do 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 leads to an improvement

in 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 is insufficient to 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 do not demonstrate whether such changes improve outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

Current clinical practice guidelines from the National Comprehensive Cancer Network (v.2.2017) 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.(2)

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

MEDICARE NATIONAL COVERAGE

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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			
NCT00903565a	A Prospective Study for the Assessment of Recurrence Risk in Stage II Colon Cancer Patients Using ColoPrint (PARSC)35	1200	Dec 2017

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

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Billing Coding/Physician Documentation Information

- 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

ICD-10 Codes

- C18.0-** Malignant neoplasm of colon code range
- C18.9**

C19 Malignant neoplasm of rectosigmoid junction
Z85.030, Personal history of malignant neoplasm of large intestine codes
Z85.038

Additional Policy Key Words

N/A

Policy Implementation/Update Information

8/1/10 New policy; considered investigational.
8/1/11 No policy statement changes.
8/1/12 No policy statement changes.
10/1/12 No policy statement changes.
10/1/13 Policy statement clarified to remove specific brand name for the test; considered investigational for all versions of the test.
10/1/14 No policy statement changes.
3/1/15 Removed CPT 84999, 88299 and added CPT 81599.
10/1/15 Stage 3 colon cancer added to investigational policy statement.
10/1/16 No policy statement changes.
10/1/17 No policy statement changes.
10/1/18 No policy statement changes.

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