Medical Policy

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***Current Policy Effective Date: 5/1/22**
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Title: Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer (e.g., Coloprint, Colon PRS, GeneFx, OncoDefender, Oncotype Dx® Colon Cancer Test)

Description/Background

COLON CANCER

Of patients with stage II colon cancer, 75–80% are cured by surgery alone, and the absolute benefit of chemotherapy for the 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 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 (stage 3 disease) and has not metastasized to distant sites (stage 4 disease). Primary treatment is surgical resection of the primary cancer and colonic anastomosis.

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. Gene expression profiling and circulating tumor DNA tests are intended to facilitate identifying stage II patients most likely to experience recurrence after surgery and most likely to benefit from additional treatment.

However, clinical and pathologic features used to identify high-risk disease are not well established, and the patients for whom the benefits of adjuvant chemotherapy would most likely outweigh the harms cannot be identified with certainty. The current system relies on the use of 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 the presence of indeterminate or positive resection margins.[3]

Of interest, a 2010 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 Improvement Act (CLIA). Multigene expression assay testing and circulating tumor DNA (ctDNA) 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 profile and ctDNA tests for colon cancer currently commercially available include:

- GeneFx™ Colon (Helomics)
- Oncotype DX® Colon Recurrence Score (Genomic Health).
- Signatera™ ctDNA test (Natera)
- Colvera®

Medical Policy Statement

Gene expression assays for determining the prognosis of stage 2 or stage 3 colon cancer following surgery are considered experimental/investigational. The peer reviewed medical literature has not yet shown that these tests have been scientifically demonstrated to improve patient clinical outcomes.

Circulating tumor DNA assays for determining the prognosis of stage II or III colon cancer following surgery are considered **investigational**.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

81525	81599	84999	88299	0229U
81479				

Note: The Oncotype Dx colon cancer assay is the only multigene assay covered for Medicare Advantage and BCNA members. None of the other assays are covered for these Medicare groups. There is no coverage for any of these assays for commercial members.

Rationale

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.

GENE EXPRESSION PROFILE TESTING

Clinical Context and Test Purpose
The purpose of prognostic testing of diagnosed disease is to predict natural disease course (e.g., aggressiveness, the 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 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 **PICOs** elements were used to select literature to inform this review.

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

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

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.

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

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).

Review of Evidence

GeneFx Colon®:
Kennedy et al (2011) reported on the development of a 634-probe set signature.[6] A training set of 215 patients (143 low risk and 73 high risk) was identified based on 5-year DFS. The assay was performed using DNA-microarray analysis of formalin-fixed paraffin-embedded samples. Cross-validation studies were used to select an optimal transcript signature for prognostic classification. Independent validation was performed on 144 patients enriched for recurrence (85 low-risk and 59 high-risk) using the threshold score identified in the training set. 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.

In 2016, Niedzwiecki et al reported on the recurrence-free interval for 393 patients of 1738 treated in the Cancer and Leukemia Group B 9581 (CALGB 9581) trial.[7] 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. 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). Recurrence scores in patients categorized as low risk and high risk are shown in Table 3. After adjusting for prognostic variables that included mismatch repair deficiency, patients categorized as high risk by GeneFx had a 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 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 1. RFS in Patients with Stage II Colon Cancer Assessed with GeneFx

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)[7]	5	393	177 (45)	91 (89 to 93)	216 (55)	82 (79 to 85)

CI: confidence interval; RFS: recurrence-free survival

Oncotype DX® Colon Recurrence Score

O'Connell et al (2010) described the development of a 12-gene expression test, Oncotype DX® colon cancer test.[8] 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 the clinical outcomes seen in 1,851 patients who had surgery with or without adjuvant 5-fluorouracil (5-FU)-based chemotherapy. Gene expression was quantitated from microdissected fixed paraffin-embedded 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 are also included in the assay.

There have been several validation studies, with data summarized in Tables 2 and 3.External validation of the algorithm was reported by Gray et al (2011) in an independent study using fixed paraffin-embedded primary tumor samples from patients with stage 2 colon cancer who had participated in the Quick and Simple and Reliable (QUASAR) study of adjuvant chemotherapy versus surgery alone.[9] The relationship between the 7-gene recurrence score and risk of recurrence was found to be statistically significant with the 3-year risk of recurrence for predefined low-, intermediate-, and high-risk groups as shown in Table 4. 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 2. Oncotype DX Validation Study Characteristics

Author (year)	Study	Study Design	N	Colon Cancer, n		Randomized Comparators
				Stage II	Stage III	
Gray et al (2011)[9]	QUASAR	RCT	3239	1436		• Adjuvant chemotherapy • Surgery alone
Venook et al (2013)[10]	CALGB 9581	RCT	1713	690		• Edrecolomab • Observation
Yothers et al (2013)[11]	NASBP C-07 R	RCT	2409	264		• FULV with oxaliplatin • FULV without oxaliplatin
Reimers et al (2014)[12]	TME	RCT	1861	130[a]	167[a]	• Radiotherapy • No radiotherapy
Yamanaka et al (2016)[13]	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) conducted a validation study using tumor tissue from 690 patients with stage 2 colon cancer who had participated in the Cancer and Leukemia Group B (CALGB) 9581 trial.[10] CALGB 9581 randomized 1713 patients with stage 2 colon cancer to treatment with edrecolomab, an experimental monoclonal antibody, or observation; DFS and overall survival did not differ between treatment groups. Venook et al selected samples stratified by treatment group from those who had tumor tissue available (40% of the original patient sample). The authors used recurrence score cut points of 29 and 39 to determine low-, intermediate-, and high-risk groups; these values differ from the cut points of 30 and 41 validated in the QUASAR study previously described. Estimated 5-year recurrence risk was 12% (95% confidence interval [CI], 10 to 15), 15% (95% CI, 12 to 17), and 18% (95% CI, 14 to 22) in the low-, intermediate-, and high-risk groups, respectively. 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 2 colon cancer who had participated in the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial.[11] NSABP C-07 randomized 2409 patients with stage 2 (28%) or stage 3 (72%) colon cancer to adjuvant chemotherapy with 5-FU plus leucovorin (FULV) or oxaliplatin plus FULV (FLOX). Yothers et al randomly selected 50% of patients who had tissue available (total of 892 tissue samples), 264 of whom (30%) had stage 2 cancer. For these patients, estimated 5-year recurrence risks adjusted for treatment (FULV vs. FLOX) were 9% (95% CI, 6 to 13) in the Oncotype-defined low-risk group, 13% (95% CI, 8 to 17) in the intermediate-risk group, and 18% (95% CI, 12 to 25) in the high-risk group. Five-year recurrence risk was reduced in high-risk patients who received oxaliplatin compared with those who did not (Kaplan-Meier estimated 5-year recurrence risk, 9% [95% CI, 3 to 25] FLOX vs. 23% [95% CI, 12 to 42] FULV), 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 3 patients in any risk class, adjusted 5-year recurrence risk estimates exceeded 15%.

Table 3. Recurrence Rates by Risk Category for the Oncotype DX Colon Recurrence Risk Score

			Mean Recurrence Rate (95% CI), %		
Author (year)	**Study**	**Risk Prediction, y**	**Low Risk**	**Medium Risk**	**High Risk**
Gray et al (2011)[9]	QUASAR	3	12	18	22
Venook et al (2013)[10]	CALGB 9581	5	12 (10 TO 15)	15 (12 TO 17)	18 (14 TO 22)
Yothers et al (2013)[11]	NASBP C-07	5	9 (6 to 13)	13 (8 to 17)	18 (12 to 25)
Reimers et al (2014)[12]	TME stage II cohort (rectal)	5	11 (6 to 22)	27 (16 to 46)	43 (29 to 65)
Yamanaka et al (2016)[13]	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)[12]conducted a retrospective study using prospectively collected tumor specimens from the Dutch total mesenteric excision (TME) trial[18] in patients with resectable colon cancer. Reimers used available tumor tissue from 569 stage 2 and stage 3 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 5. Oncotype DX 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.[13] 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: Clinically Valid
Several validation studies of GEP for colon cancer have reported that testing provides prognostic information on the risk of recurrence. 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, published by the Agency for Healthcare Research and Quality (AHRQ) in December 2012 reviewed the clinical evidence for the use of gene expression profiling for predicting outcomes, including benefit from adjuvant chemotherapy, in patients with stage 2 colon cancer.[15] The 4 assays reviewed earlier that are commercially available for clinical use 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 regarding the reproducibility of test findings, indications for GEP testing in stage 2 patients, and whether results of GEP assays can stratify

patients into groups defined by 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.

A more recent evidence report conducted for the Washington State Health Care Authority (2017) reviewed the clinical utility of gene expression profile tests for cancer, including ColoPrint and Oncotype DX for stage II or III colon cancer.[16] The researchers identified no clinical utility studies with mortality, morbidity, or harms outcomes.

Chain of Evidence

Indirect evidence for the 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, Oki et al (2021) published a prospective observational study in Japan examining the impact of Oncotype Dx Colon Recurrence Score on management decisions for patients with stage II and stage IIIA/IIIB colon cancer.[17,] The study included 275 patients; 97 patients had stage II colon cancer, and 178 had stage IIIA/IIIB disease. Oncotype Dx Colon Recurrence Score changed treatment decisions in 39.6% of patients. Treatment was decreased in intensity in 32% of study patients (n=88), and increased in intensity for 7.6% of study patients (n=21). Patients with stage IIIA/IIIB cancer had treatment recommendations changed more frequently than patients with stage II cancer (44.9% vs. 29.9%; p=.0148). Similarly, Brenner et al (2016) published a retrospective study of the association between Oncotype DX recurrence score and management decisions.[18] There were 269 patients from 1 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) published studies showing the effect of Oncotype DX® results on treatment recommendations made according to traditional risk classifiers in patients with stage 2 colon cancer.[19,20] Cartwright performed a retrospective study predicting that test results may lead to reductions in treatment intensity in a percentage of patients.[19] Srivastava et al (2014) performed a prospective study that directly demonstrated reductions in treatment intensity in a percentage of patients.[20]

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 do not report clinical outcomes and cannot 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.

Circulating Tumor DNA Testing

Clinical Context and Test Purpose
The purpose of prognostic testing of diagnosed disease is to predict natural disease course (e.g., aggressiveness, risk of recurrence, death). This type of testing uses circulating tumor DNA (ctDNA) testing of blood to predict the course of the disease.
The question addressed in this evidence review is: Does prognostic testing using the ctDNA test described below in individuals diagnosed with stage II or stage III colon cancer improve the net health outcome?

The following **PICO** was used to select literature to inform this review.

Populations
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 or who are being monitored for risk of relapse following treatment.

Interventions
The intervention of interest is ctDNA testing with the Signatera assay. Signatera is designed to detect molecular residual disease in the blood. Tumor tissue obtained from either a diagnostic biopsy or surgically resected tissue is used to identify 16 single nucleotide variants found in the tumor but not in normal tissue. Once the tumor has been definitively treated, a custom assay of 16 tumor-specific clonal, somatic variants is generated for the patient and the resulting tumor signature is monitored throughout the patient's disease course.

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. Current NCCN guidelines also recommend surveillance with carcinoembryonic antigen and imaging after curative colorectal cancer surgery.

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.

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

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).

Signatera Assay

Two cohort studies, one that used the Signatera assay, reported an association between positive ctDNA results and risk of recurrence of colon cancer (Tables 4 and 5).

Reinert et al (2019) enrolled 125 patients with Stage I-III colon cancer in a validation study of the Signatera assay.[21] Plasma samples were collected before surgery, at 30 days following surgery, and every 3 months for up to 3 years. The recurrence rate at 3 years was 70% in patients with a positive ctDNA test (7 of 10) compared to 11.9% (10 of 84) of those with a negative ctDNA test. In multivariate analyses, ctDNA status was associated with recurrence after adjusting for clinicopathological risk factors including stage, lymphovascular invasion, and microradical resection status.

Table 4. Signatara Circulating Tumor DNA Study Characteristics

Study; Trial	Design	Detection Method	N	Data Collection	Colon Cancer, n		
					Stage I	Stage II	Stage III
Reinert et al (2019)[24]	Cohort	Signatera Assay	125	Day 30 following surgery, up to 3 years	5	39	81

N: sample size

Table 5. Recurrence Rates by Risk Category for Signatera Circulating Tumor DNA

Study	Mean Recurrence Rate (95% CI)	
	CtDNA Positive	ctDNA Negative
Reinert et al (2019)[24]	7/10 70% (34.2% - 93.1%)	10/8411.9% (6.3% - 20.1%)
Hazard Ratio for RFS (95% CI)	7.2 (2.7-19.0); *P* <.001	

CI: confidence interval; ctDNA: circulating tumor DNA; RFS: recurrence-free survival

Table 6. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Reinert et al (2019)[21,]	1. Included patients with stage I through III colon cancer		3. No comparator	1. Overall survival not assessed	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
ctDNA: circulating tumor DNA.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss

to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Table 7. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Deliver of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Reinert et al (2019)[21]	1. Patient selection not described					Multiple subgroup analyses, small numbers of patients with positive ctDNA tests.

Colvera Assay

Three cohort studies have reported an association between positive ctDNA results and risk of recurrence of colon cancer (Tables 8 and 9).[22,23,24,] Limitations of these studies are described in Tables 10 and 11.

Young et al (2016) enrolled 122 patients with colorectal cancer who had no evidence of residual disease after initial therapy.[22,] In this study, a positive ctDNA test was associated with an increased risk of recurrence. Blood samples were also tested for CEA, and a positive CEA test was also found to be significantly associated with an increased risk of recurrence. Among the 28 patients who had recurrent disease, 9 patients (32%) had a positive CEA test, while 19 (68%) had a positive ctDNA test (p=.002). Among the 94 patients without clinically detectable recurrence, CEA was positive in 6 patients (6%) and ctDNA test was positive in 12 (13%; p=.210). The positive predictive values of ctDNA and CEA were 61.3% and 60%, respectively. The negative predictive values were 90.1% and 82.2%, respectively.

Murray et al (2018) enrolled 172 patients with invasive colorectal cancer with plasma samples collected within 12 months after surgery.[23,] In this study, multivariate analysis found that risk of recurrence was increased among patients who had positive ctDNA tests following surgery. Risk of colorectal cancer-related death was also increased among patients who had a positive ctDNA test following surgery, but multivariate analysis could not be performed for this outcome due to the low number of events.

Symonds et al (2020) examined the association between a positive Colvera test result and recurrence of colorectal cancer in 144 patients who had no evidence of residual disease after surgical resection and/or neoadjuvant chemotherapy.[24,] Blood samples were also tested for CEA, and the association between a positive CEA test and recurrent colorectal cancer was assessed. A positive Colvera test was an independent predictor of recurrence, while a positive CEA test was not found to be a significant predictor of recurrence after adjusting for other predictors of recurrence (e.g., stage at primary diagnosis). Sensitivity of the Colvera assay for detecting recurrence was significantly greater than the sensitivity of CEA (66% vs. 31.9%, p=.001), but specificity was not significantly different (97.9% vs. 96.4%, p=1.000). The positive predictive value was not significantly different for Colvera and CEA (94.3% vs. 83.3%, p=.262), but the negative predictive value was significantly greater for Colvera (84.4% vs. 71.7%, p<.001).

Musher et al (2020) conducted an additional prospective cross-sectional observational study in patients undergoing surveillance after definitive therapy for stage II or III colorectal cancer.[25] Samples were collected within 6 months of planned radiologic surveillance imaging and tested using the Colvera assay and a CEA assay. A total of 322 patients were included, with 27 experiencing recurrence and 295 not experiencing recurrence. The sensitivities of Colvera and CEA for detecting colorectal cancer recurrence using a single time-point blood test were 63% (17/27) and 48.1% (13/27), respectively (p=.046). The specificities of single time-point Colvera and CEA were 91.5% and 96.3%, respectively (p=.012).

Table 8. Colvera Assay Observtional Study Characteristics

Study	Design	Detection Method	Comparator Test	N	Data Collection	Colon Cancer, n			
						Stage I	Stage II	Stage III	Stage IV
Young et al (2016)[22]	Cross-sectional observational	Colvera assay	CEA	122[a]	Sample collected 12 months prior to or 3 months after complete investigational assessment of recurrence status	28	40	47	6
Murray et al (2018)[23]	Prospective cohort	Colvera assay	None	172	Single sample collected within 12 months of surgical resection	NR	NR	NR	NR
Symonds et al (2020)[24]	Cross-sectional observational	Colvera assay	CEA	144	Single sample collected at time of recurrence or within 12 months of surveillance imaging	21	50	62	11

CEA: carcinoembryonic antigen; ctDNA: circulating tumor DNA; NR: not reported.
[a]1 patient in this study had unstaged primary cancer.

Table 9. Recurrence Rates by Risk Category for Colvera Assay

Study	Recurrence Rate (95% CI)
Young et al (2016)[22]	28/122
Positive vs. negative Colvera odds ratio for recurrence (95% CI)	14.4 (5.4 to 38.7; p<.001)
Positive vs. negative CEA odds ratio for recurrence (95% CI)	6.9 (2.3 to 21.1; p=.001)
	ctDNA Positive *ctDNA Negative*
Murray et al (2018)[23]	7/28
Positive vs. negative Colvera hazard ratio for recurrence (95% CI)	3.8 (1.5 to 9.5; p=.004)
Positive vs. negative Colvera hazard ratio for colorectal cancer-related death (95% CI)	6.6 (1.9 to 22.8)
Symonds et al (2020)[24]	50/144
Positive vs. negative Colvera adjusted odds ratio for recurrence (95% CI)	155.7 (17.9 to 1360.6; p<.001)
Positive vs. negative CEA adjusted odds ratio for recurrence (95% CI)	2.5 (0.3 to 20.6; p=.407)

CEA: carcinoembryonic antigen; CI: confidence interval; ctDNA: circulating tumor DNA.

Table 10. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Young et al (2016)[22,]	1. Included patients with any stage of colon cancer			1. Overall survival not assessed	
Murray et al (2018)[23,]	1. Included patients with any stage of colon cancer		3. No comparator		
Symonds et al (2020)[24,]	1. Included patients with any stage of colon cancer			1. Overall survival not assessed	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 11. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[e]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Young et al (2016)[22]						
Murray et al (2018)[23]	1. Patient selection not described		1. Timing of sample collection could be any time within 12 months following surgery			2. Not compared to other tests
Symonds et al (2020)[24]	1. Patient selection not described					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Section Summary

Several observational studies reported an association between positive ctDNA results using the Signatera assay or Colvera assay and risk of recurrence of colon cancer. While these

studies showed an association between ctDNA results and risk of recurrence, they are limited by their observational design and relatively small numbers of patients with positive results. Management decisions were not based on ctDNA test results. There are no controlled studies of management changes made in response to ctDNA test results compared to other risk factors, and no studies showing whether testing improved outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUMMARY OF EVIDENCE

For individuals who have stage II or III colon cancer who receive gene expression profiling (GEP) testing, the evidence includes development and validation studies and 1 decision-impact study. Relevant outcomes are disease-specific survival, test accuracy and validity, and change in disease status. The available evidence has shown that GEP tests 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.

For individuals who have stage II or III colon cancer who receive circulating tumor DNA (ctDNA) testing, the evidence includes cohort studies. Relevant outcomes are disease-specific survival, test accuracy and validity, and change in disease status. several cohort studies have reported an association between positive ctDNA results and risk of recurrence of colon cancer. While these studies showed an association between ctDNA results and risk of recurrence, they are limited by their observational design and relatively small numbers of patients with positive results. Management decisions were not based on ctDNA test results. There are no controlled studies of management changes made in response to ctDNA test results compared to other risk factors, and no studies showing whether testing improved outcomes.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

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

Table 8. Summary of Key Trials

NCT. No.	Trial Name	Planned Enrollment	Completion Date
Unpublished			
NCT00903565[a]	A Prospective Study for the Assessment of Recurrence Risk in Stage II Colon Cancer Patients Using ColoPrint (PARSC)	1200	Dec 2019
Ongoing			
NCT04264702[a]	BESPOKE Study of ctDNA Guided Therapy in Colorectal Cancer	1000	Jun 2024

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network
Current clinical practice guidelines from the NCCN (v.3.2021) on colon cancer state that data are insufficient “to recommend the use of multigene assays to determine adjuvant therapy” in patients with stage 2 or 3 colon cancer.[3]

The guidelines do not comment on circulating tumor DNA testing to guide decision about adjuvant chemotherapy, but state, "Research into additional possible predictive markers may allow for more informed decision-making int the future."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Government Regulations

National:

There is no National Coverage Determination (NCD) on this topic. In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Local:

Local Coverage Article: MolDX: Oncotype Dx® Colon Cancer assay Update (A55231). Revision effective date: 11/25/2021.

The **ONCOTYPE** DX® Colon Cancer Assay, developed to predict the recurrence risk for patients with Stage II colon cancer, has been assigned a unique identifier. To bill an **ONCOTYPE** DX Colon service, please provide the following claim information:

- CPT code 81525-Oncology (colon), mRNA gene expression of 12 genes
- Enter “1” in the Days/Unit field
- Labs may either use the SV101-7 or SV202-7 (preferred) or the NTE field to submit this required information.
- Enter the appropriate DEX Z-Code™ Identifier adjacent to the CPT code in the comment/narrative field for the following Part B claim field/types:
    - Loop 2400 or SV101-7 for the 5010A1 837P
    - Box 19 for paper claim.
- Enter the appropriate DEX Z-Code™ identifier adjacent to the CPT code in the comment/narrative field for the following Part A claim field/types:
    - Line SV202-7 for 837I electronic claim
    - Block 80 for the UB04 claim form
- Select the appropriate ICD-10-CM code:

Local Coverage Determination (L38305): Minimal Residual Disease Testing for colorectal Cancer. Effective on or after 10/19/2020.

Coverage Indications, Limitations, and/or Medical Necessity

This Medicare contractor will provide limited coverage for ctDNA tests that detect minimum residual disease (MRD) in patients with a personal history of colorectal cancer.
Specifically, the enclosed evidentiary review is focused on the **SIGNATERA** molecular residual disease assessment test, from here on called "**SIGNATERA**," (Natera, Inc, San Carlos, CA).
Other tests that demonstrate equivalent analytical and clinical validity as part of a comprehensive technical assessment (TA) will similarly attain coverage for indications that are supported by the evidence and intended use within scope of this policy.
This Contractor provides limited coverage for MRD testing in cancer when:

1. The conditions set by NCD90.2 are fulfilled if NGS methodology is utilized (summarized: the patient has advanced cancer; plans on being treated for said cancer, and has not been previously been tested with the same test for the same genetic content) or are not applicable (the patient does not have cancer as defined below)
2. The patient has a personal history of colorectal cancer, the type and staging of which is within the intended use of the MRD test
3. The identification of recurrence or progression of disease within the intended use population of the test is identified in the NCCN Guidelines as a condition that requires a definitive change in patient management
4. The test is demonstrated to identify recurrence or progression before there is clinical or radiographical evidence of recurrence or progression; and demonstrates sensitivity and specificity comparable with radiographical evidence of recurrence. For colorectal cancer, it must have a sensitivity at least equivalent to and specificity that is significantly better than serial CEA monitoring OR demonstrate equivalence with another ctDNA MRD test that has demonstrated this measuring the same analytes. Test performance must be similar to established MRD tests including **SIGNATERA**
5. The test satisfactorily completes a technical assessment that will review and confirm the analytical and clinical validity of the test

MRD testing often requires two types of assays to be performed as part of the service. First, a sample is taken from tumor diagnostic material to establish a baseline tumor signature as defined by the test methodology. This is followed by a series assays run on blood to detect the presence or recurrence of tumor based on the measured biomarkers, expression, or other analytes over various timepoints. This series of assays comprises a single test when the patient is known to have cancer. When the patient is NOT known to have cancer (specifically when there is no clinical, radiographical, or other biological evidence that tumor cells remain post treatment and subsequently the patient is no longer being subjected to therapeutic interventions for cancer), a second kind of test may exist wherein a single additional timepoint may constitute a single test.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing to Determine the Prognosis of Breast Cancer Patients
- Genetic Testing for Inherited Susceptibility to Colon Cancer

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2022, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/1/11	4/19/11	5/3/11	Joint policy established
1/1/13	10/16/12	10/16/12	Routine maintenance. Rationale and references updated. No change in policy status.
1/1/14	10/15/13	10/25/13	Routine maintenance. No change in policy status.
3/1/15	12/9/14	12/29/14	Routine maintenance. Updated references and rationale. No change in policy status.
5/1/16	2/16/16	2/16/16	Routine maintenance. Added CPT code 81525
5/1/17	2/21/17	2/21/17	Routine maintenance. Updated rationale and added reference # 31.
5/1/18	2/20/18	2/20/18	Routine policy maintenance. Updated rationale and added references 23 & 29. No change in policy status.
5/1/19	2/19/19		Routine policy maintenance. No change in policy status.
5/1/20	2/18/20		Routine policy maintenance. No change in policy status. Updated government section.
5/1/21	4/1/21		Title revised, added “Circulating tumor DNA assays for determining the prognosis of stage II or III colon cancer following surgery are considered investigational” to MPS. Added code 0229U as E/I. Added references 24, 28 and 29.
5/1/22	2/15/22		Rationale updated. No change in policy status.

Next Review Date: 1st Qtr. 2023

BLUE CARE NETWORK BENEFIT COVERAGE POLICY: GENE EXPRESSION PROFILE TESTING AND CIRCULATING TUMOR DNA TESTING FOR PREDICTING RECURRENCE IN COLON CANCER (E.G., COLOPRINT, COLON PRS, GENEFX, ONCODEFENDER, ONCOTYPE DX® COLON CANCER TEST)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines: (BCNA only)

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- Services must be performed by a BCN-contracted provider, if available.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.