Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 11/1/24**
(See policy history boxes for previous effective dates)

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

According to estimates by the National Cancer Institute, in 2023 over 153,000 new cases of colorectal cancer will be diagnosed in the U.S., and nearly 53,000 people will die of this cancer.[1] Five-year survival estimates are around 65%. Disparities in colorectal cancer outcomes have been identified in different subgroup classifications based on race and ethnicity, age, socioeconomic status, insurance access, geography, and environmental exposures. For example, in the U.S. between 2012-2016, mortality rates were highest among non-Hispanic Black patients (incidence rate of 45.7 per 100,000), which were 20% and50% higher than rates among non-Hispanic White and Asian patients, respectively. Additionally, non-Hispanic Black patients may have limited opportunities for therapeutic interventions due to experiencing higher inequities in comorbidities.[2]

Colorectal cancer is classified as stage 2 the primary tumor extends into or through the layers of 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. After surgery, the prognosis is good, with survival rates of 75% to 80% at 5 years.[3] A Cochrane review by Figueredo et al (2008), assessing 50studies of adjuvant therapy versus surgery alone in stage II patients, found a small though statistically significant absolute benefit of chemotherapy for disease-free survival but not for overall survival. Therefore, adjuvant chemotherapy with 5-fluorouracil (5-FU), capecitabine, CAPEOX (capecitabine and oxaliplatin), or FOLFOX (5-FU and oxaliplatin) is recommended only for resected patients with high-risk stage II disease (i.e., those with poor prognostic features).[4]

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.[4] Gene expression profiling (GEP) and circulating tumor DNA (ctDNA) tests are intended to facilitate identifying stage II patients most likely to experience recurrence after surgery and most likely to benefit from additional treatment.

Of interest, a 2010 review by Vilar and Gruber, has noted that microsatellite instability (MSI) and mismatch repair (MMR) deficiency in colon cancer may represent confounding factors to be considered in treatment.[5] 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®
- Guardant Reveal™

Medical Policy Statement

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

Inclusionary and Exclusionary Guidelines

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	0340U	0368U		

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 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 individuals 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.[7] 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.[8] 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. Recurrence-free Survival 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)	393	5	177 (45)	91 (89 to 93)	216 (55)	82 (79 to 85)

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

Oncotype DX® Colon Recurrence Score

O'Connell et al (2010) described the development of a 12-gene expression test, Oncotype DX® colon cancer test.[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 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.[10] 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 Colon Validation Study Characteristics

Study; Trial	Design	N	Colon Cancer, n		Randomized Treatments	
			Stage II	Stage III	Intervention	Comparator
Gray et al (2011)[,]; QUASAR	RCT	3239	1436		Adjuvant chemotherapy	Surgery alone
Venook et al (2013); CALGB 9581	RCT	1713	690		Edrecolomab	Observation
Yothers et al (2013); NASBP C-07 R	RCT	2409	264		5-fluorouracil plus leucovorin with oxaliplatin	5-fluorouracil plus leucovorin without oxaliplatin
Reimers et al (2014); TME	RCT	1861	130[a]	167[a]	Radiotherapy	No radiotherapy
Yamanaka et al (2016); SUNRISE	Cohort	1487	247	350	Not applicable	

CALGB 9581: Cancer and Leukemia Group B 9581 trial; 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.[11] 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.[12] 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

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

Reimers et al (2014)[13] conducted a retrospective study using prospectively collected tumor specimens from the Dutch total mesenteric excision (TME) trial[15] in patients with resectable

colon cancer. Reimers used available tumor tissue from 569 stage 2 and stage 3 patients randomized to surgery alone.[13] 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.[14] 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; $p<0.001$).

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.[16] 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.[17] 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.[18] 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.[19] 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.[20,21] Cartwright performed a retrospective study predicting that test results may lead to reductions in treatment intensity in a percentage of patients.[20] Srivastava et al (2014) performed a prospective study that directly demonstrated reductions in treatment intensity in a percentage of patients.[21]

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: Gene Expression Profile Testing

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

Populations
The relevant population of interest are individuals 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
Four nonrandomized studies, 3 of which were noncomparative, examined the association of Signatera testing to prognosis in individuals with colorectal cancer (CRC). They differed in their

study designs, populations (e.g., stage of disease), frequency and timing of standard care, outcome measures, and timing of follow up. Three studies evaluated the association between positive ctDNA results and prognosis in CRC. These studies did not provide comparisons of ctDNA testing to standard methods of risk stratification for therapy selection, monitoring response to therapy, or early relapse detection. One retrospective study compared Signatera testing to other surveillance strategies in individuals with resected colorectal cancer.[22] There are no randomized controlled trials, and no studies in which Signatera testing was used to guide treatment decisions.

Reinert et al (2019) enrolled 125 patients with Stage I-III colon cancer in a validation study of the Signatera assay.[23] 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.

Henriksen et al (2022) assessed the added benefit of serial ctDNA analysis; with samples taken at diagnosis, following surgery, during adjuvant therapy, and at follow up.[24]

Loupakis et al (2021) evaluated the association of ctDNA with Signatera on survival outcomes in 112 individuals who had undergone resection for metastatic (stage IV) CRC.[25] The study included an analysis of the sensitivity of Signatera testing to digital droplet PCR testing but not to standard methods to identify recurrence, such as CEA and imaging.

Fakih et al (2022) directly compared Signatera testing to other surveillance strategies in individuals with resected CRC in a retrospective observational study.[26] This study was unique in that it used NCCN recommended guidelines for surveillance and ctDNA testing was performed at the same interval as standard surveillance with CEA and imaging. Test characteristics for Signatera were not significantly different from standard imaging techniques. Estimates were imprecise, with wide confidence intervals.

Study limitations are shown in Tables 4 and 5. Major limitations include a lack of comparison to tests used for the same purpose, imprecise estimates due to small sample sizes, and clinical heterogeneity of study populations.

Table 1. Nonrandomized Studies of Signatera Testing in Colorectal Cancer - Study Characteristics

Study	Test Purpose	Study Population	Setting	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
Reinert et al (2019)	1. Risk stratification 2. Monitoring response to adjuvant chemotherapy 3. Early relapse detection	130 individuals with stages I to III CRC; treated from May 1, 2014 to January 31, 2017	Multicenter, Denmark	CEA and CT imaging	2 or more variants detected out of 16	Before and after surgery, during and after adjuvant chemotherapy, and during surveillance Sample at Day 30 following surgery; individuals were	Yes

						followed up for a median of 12.5 months	
Henriksen et al (2022)	1. Risk stratification 2. Monitoring response to adjuvant chemotherapy 3. Early relapse detection Assessed added benefit of serial measurements	168 individuals with stage III CRC treated with curative intent between 2014 and 2019	Multicenter, Spain and Denmark	CEA analysis-thresholds set according to national guidelines and CT imaging	ctDNA detected-greater or equal to 2 variants detected out of 16	Median sampling 2 weeks after surgery (IQR, 2 to 4 weeks); postoperative plasma samples (within 2-4 weeks) prior. Plasma samples were also collected during and after adjuvant therapy; individuals were followed up for a median of 35 months.	Yes
Loupakis et al (2021)	1. Risk stratification following surgery	112 individuals with stage IV CRC who had undergone resection with curative intent as part of the PREDATOR clinical trial	Italy	Radiological imaging	ctDNA detected-greater or equal to 2 variants detected out of 16	Plasma samples collected at the first time point and at the time of radiologic evidence of progressive disease or at the last follow-up; individuals were followed for a median of 10.7 months	Yes
Fakih et al (2022)		48 individuals with stage II to IV CRC who underwent surveillance with Signatera and underwent curative resections between 2019 and 2021	US, single center, retrospective	Confirmed recurrence, defined as a positive ctDNA finding or a finding on imaging confirmed by biopsy, CEA level elevation, or subsequent tumor radiographic dynamics	Any positive assay finding more than 4 weeks after definitive surgery	Standard surveillance strategy included ctDNA every 3 months for 2 years and then every 6 months for 3 years. CEA at the same interval as the ctDNA assay. Imaging studies performed within NCCN guidelines and included yearly CT scans for 5 years for low-risk stage II disease and every 6 months for 2 years and then every year for 3 years for high-risk stage II and III disease. Imaging studies	No

						were performed every 3 months for 2 years and then every 6 months for 3 years for resected stage IV disease.	

CEA: carcinoembryonic antigen; CRC: colorectal cancer; CT: computerized tomography; IQR: interquartile range; NCCN: National Comprehensive Cancer Network.

Table 2. Recurrence Rates by Risk Category in Nonrandomized Studies of Signatera in Colorectal Cancer

Study	Mean Recurrence Rate (95% CI)	
	ctDNA Positive	**ctDNA Negative**
Reinert et al (2019)	7/10; 70% (34.2% to 93.1%)	10/84; 11.9% (6.3% to 20.1%)
Hazard ratio for recurrence following surgery (95% CI)	7.2 (2.7 to 19.0); p<.001	
Hazard ratio for recurrence following adjuvant chemotherapy (95% CI)	17.5 (5.4 to 56.5); p<.001	
Henriksen et al (2022)	16/20 (80%)	22/120 (18%)
Hazard ratio for RFS (95% CI)	7.0 (3.7 to 13.5); p<.001	
Loupakis et al (2021)	59/61 (96.7%)	NR/51 Number with recurrences not reported; 49 of 51 were alive at data cutoff
Hazard ratio for RFS (95% CI)	5.8 (3.5 to 9.7); p<.001	
Hazard ratio for OS (95% CI)	16.0 (3.9 to 68.0); p<.001	

CI: confidence interval; ctDNA: circulating tumor DNA; NR: not reported; RFS: recurrence-free survival.

Table 3. Retrospective Comparison of Signatera to Other Surveillance Strategies in Resected Colorectal Cancer

Study	Sensitivity	Specificity	PPV	NPV	Median Time to Recurrence, months
Fakih et al (2022)					
Signatera Testing	53.3 (27.4 to 77.7)	100 (87.0 to 100)	100 (59.8 to 100)	82.5 (66.6 to 92.1)	14.3
Imaging	60.0 (32.9 to 82.5)	96.9 (82.5 to 99.8)	90.0 (54.1 to 99.5)	84.2 (68.1 to 93.4)	15.0
CEA	20.0 (5.3 to 48.6)	90.9 (74.5 to 97.6)	50.0 (13.9 to 86.1)	71.4 (55.2 to 83.8)	Not assessed
CEA plus imaging	73.3 (44.8 to 91.1)	87.9 (70.9 to 96.0)	73.3 (44.8 to 91.1)	87.9 (70.9 to 96.0)	15.0

P-value Signatera vs. imaging Signatera vs. imaging plus CEA Signatera vs. CEA	>.99 .55 .13	>.99 .13 .25	not assessed	not assessed	.45 .79 not assessed

CEA: carcinoembryonic antigen; CI: confidence interval; ctDNA: circulating tumor DNA; NPV: negative predictive value; PPV: positive predictive value; RFS: recurrence-free survival.

Table 4. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Reinert et al (2019)	1. Included individuals with stage I through III colorectal cancer		3. No comparator	1. Overall survival not assessed	1. Follow up for recurrence was under 3 years (median 12.5 months)
Henriksen et al (2022)			3. No comparator		1. Follow up for recurrence was under 3 years (median 35 months)
Loupakis et al (2021)			3. No comparator		1. Follow up for recurrence was under 3 years (median 10.7 months)
Fakih et al (2022)				1. Survival outcomes 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 5. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Reinert et al (2019)	1. individual selection not described					Multiple subgroup analyses, small numbers of individuals with positive ctDNA tests.
Henriksen et al (2022)			2. Standard-of-care imaging frequency differed between the Spanish (every 6			Small numbers of individuals with positive ctDNA tests.

			months) and Danish (at month 12 and 36) cohort.			
Loupakis et al (2021)						Small numbers of individuals with positive ctDNA tests.
Fakih et al (2022)						

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.

Colvera Assay

Three cohort studies have reported an association between positive ctDNA results and risk of recurrence of colon cancer (Tables 8 and 9).[26-28] 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.[29] 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.[30] 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.[31] 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.[32] 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 Observational 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)	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)	Prospective cohort	Colvera assay	None	172	Single sample collected within 12 months of surgical resection	NR	NR	NR	NR
Symonds et al (2020)	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)	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)	7/28	16/144
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)	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)	1. Included patients with any stage of colon cancer			1. Overall survival not assessed	
Murray et al (2018)	1. Included patients with any stage of colon cancer		3. No comparator		
Symonds et al (2020)	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[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Young et al (2016)						
Murray et al (2018)	1. Patient selection not described		1. Timing of sample collection could be any time within 12 months			2. Not compared to other tests

			following surgery			
Symonds et al (2020)	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.

Guardant Reveal

Parikh et al (2021) evaluated a plasma-only ctDNA assay integrating genomic and epigenomic cancer signatures to enable tumor-uninformed MRD detection.[33] A total of 252 prospective serial plasma specimens from 103 patients with colorectal cancer undergoing curative-intent surgery were analyzed and correlated with recurrence. Of 103 patients, 84 [stage I (9.5%), II (23.8%), III (47.6%), IV (19%)] had evaluable plasma drawn after completion of definitive therapy, defined as surgery only (*n* = 39) or completion of adjuvant therapy (*n* = 45). In "landmark" plasma drawn 1-month (median, 31.5 days) after definitive therapy and >1 year follow-up, 15 patients had detectable ctDNA, and all 15 recurred [positive predictive value (PPV), 100%; HR, 11.28 (*P* < 0.0001)]. Of 49 patients without detectable ctDNA at the landmark timepoint, 12 (24.5%) recurred. Landmark recurrence sensitivity and specificity were 55.6% and 100%. Incorporating serial longitudinal and surveillance (drawn within 4 months of recurrence) samples, sensitivity improved to 69% and 91%. Integrating epigenomic signatures increased sensitivity by 25%–36% versus genomic alterations alone. Notably, standard serum carcinoembryonic antigen levels did not predict recurrence [HR, 1.84 (*P* = 0.18); PPV = 53.9%].

Section Summary: Circulating Tumor DNA Testing

Several observational studies reported an association between positive ctDNA results using the Signatera assay, Colvera assay or Guardant Reveal 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. 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.

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 12.

Table 8. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04264702[a]	BESPOKE Study of ctDNA Guided Therapy in Colorectal Cancer	1788	Feb 2026
NCT04068103	Circulating Tumor DNA Testing in Predicting Treatment for Patients With Stage IIA Colon Cancer After Surgery	1,408	Apr 2027
NCT04120701	Circulating Tumor DNA Based Decision for Adjuvant Treatment in Colon Cancer Stage II	1,980	Jan 2028
NCT04761783[a]	BESPOKE Study of ctDNA Guided Immunotherapy	1539	May 2025
NCT04264702[a]	BESPOKE Study of ctDNA Guided Therapy in Colorectal Cancer	2000	Jan 2025
NCT04786600[a]	A Phase II Randomized Therapeutic Optimization Trial for Subjects With Refractory Metastatic Colorectal Cancer Using ctDNA: Rapid 1 Trial	78	May 2025
NCT05178576[a]	A Single Arm Phase II Study to Evaluate Treatment With Gevokizumab in individuals With Stage II/III Colon Cancer Who Are ctDNA-positive After Curative Surgery and Adjuvant Chemotherapy	31	Nov 2025
NCT04920032[a]	Proof of Concept Study of ctDNA Guided Change in Treatment for Refractory Minimal Residual Disease in Colon Adenocarcinomas	22	Dec 2025
NCT05059444	ORACLE: observation of residual cancer with liquid biopsy evaluation	1000	Feb 2028
NCT05674422	GEMCAD-REVEAL study—circulating tumor DNA as a predictor of relapse in patients with locally advanced recal cancer (REVEAL)	120	Jul 2026
NCT05904665	Circulating Tumor DNA Methylation Guided Postoperative Follow-up Strategy for High-risk Stage II/III Colorectal Cancer: a Multicenter, Prospective, Randomized Controlled Cohort Study (FIND Trial)	526	Jun 2028
NCT05529615	Circulating Tumor DNA Guided Adjuvant Chemotherapy for Colon Cancer: A Prospective, Multicenter, Open-label, Randomized Controlled Clinical Trial	2684	Jul 2029
NCT04084249	Implementing Non-invasive Circulating Tumor DNA Analysis to Optimize the Operative and Postoperative Treatment for Patients With Colorectal Cancer -Intervention Trial 2	340	Jun 2028

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

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network
Current clinical practice guidelines from the NCCN (v.4.2024) on colon cancer state "the panel believes that there are insufficient data to recommend the use of multigene assays, Immunoscore, or post-surgical ctDNA to estimate risk of recurrence or determine adjuvant therapy. ESMO (European Society for Medical Oncology) has released similar recommendations regarding these assays, stating that their role in predicting chemotherapy benefit is uncertain. The NCCN Panel encourages enrollment in clinical trials to help with the generation of additional data on these assays."[4]

American Society of Clinical Oncology
In 2022, the American Society of Clinical Oncology published updated guidance on adjuvant chemotherapy for stage II coloncancer.27, The guideline stated that there was insufficient evidence on the predictive value of ctDNA to warrant a recommendation, but that a recommendation may be possible in the future if prospective data becomes available.

National Cancer Institute
In 2020, an expert panel of the National Cancer Institute (the Colon and Rectal-Anal Task Forces) published a white paper on the use of ctDNA in colorectal cancer.[28] For nonmetastatic colorectal cancer, the paper stated that ctDNA after surgery or completion of adjuvant therapy is highly associated with disease recurrence and can be used as a marker of minimal residual disease.

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: 02/01/2024.

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 (L38835): Minimal Residual Disease Testing for Cancer. Effective on or after 10/26/23.

Coverage Indications, Limitations, and/or Medical Necessity

This Medicare contractor will provide limited coverage for minimally invasive molecular deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) tests that detect minimal residual disease (MRD) in patients with a personal history of cancer.
This Contractor provides limited coverage for MRD testing in cancer when ALL of the following are true:

1. If Next-Generation Sequencing (NGS) methodology is used in testing, the conditions set by NCD 90.2 are fulfilled (summarized: the patient has advanced cancer; plans on being treated for said cancer, and has not been previously 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 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 National Comprehensive Cancer Network (NCCN) or other established guidelines as a condition that requires a definitive change in patient management.
4. The test is demonstrated to identify molecular recurrence or progression before there is clinical, biological, or radiographical evidence of recurrence or progression AND demonstrates sensitivity and specificity of subsequent recurrence or progression comparable with or superior to radiographical or other evidence (as per the standard of care for monitoring a given cancer type) of recurrence or progression.
5. To be reasonable and necessary, it must also be medically acceptable that the test being utilized precludes other surveillance or monitoring tests intended to provide the same or similar information unless they either (a) are required to follow-up or confirm the findings of this test or (b) are medically required for further assessment and management of the patient.
6. If the test is to be used for monitoring a specific therapeutic response, it must demonstrate the clinical validity of its results in published literature for the explicit management or therapy indication (allowing for the use of different drugs within the same therapeutic class, so long as they are considered ‘equivalent and interchangeable’ *for the purpose of MRD testing*, as determined by national or society guidelines).

7. Clinical validity (CV) of any analytes (or expression profiles) measured must be established through a study published in the peer-reviewed literature for the intended use of the test in the intended population.
8. The test is being used (a) in a patient who is part of the population in which the test was analytically validated and (b) according to the intended use of the test.
9. The MRD test [(unless it is a Food and Drug Administration (FDA)-approved and established standard-of-care single-gene polymerase chain reaction (PCR)] satisfactorily completes a technical assessment (TA) that will evaluate and confirm that the analytical validity, clinical validity, and clinical utility criteria set in this policy are met to establish the test as Reasonable and Necessary.
10. Tests utilizing a similar methodology or evaluating a similar molecular analyte to a test for which there is a generally accepted testing standard or for which existing coverage exists must demonstrate equivalent or superior test performance (i.e., sensitivity and/or specificity) when used for the same indication in the same intended-use population.

MRD testing often requires 2 types of assays to be performed as part of the service. First, a sample is taken from tumor diagnostic material to establish a baseline (solid and/or liquid) tumor signature as defined by the test methodology. This is followed by a series of assays run on a minimally invasive specimen (i.e., liquid biopsy or bone marrow aspirate) to detect the presence or recurrence of tumor based on the measured biomarkers, expression, or other analytes over various timepoints. Other approaches are also acceptable, based on the validity established for the individual test comprising the service. 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 timepoint may constitute a single test. In such patients, the frequency of MRD testing is in accordance with national or society guidelines or recommendations.

For patients with or without cancer (as defined above), established standard-of-care MRD tests using single-gene PCR (i.e., BCR-ABL1) are covered under this policy according to testing schedules outlined in national (i.e., NCCN) or society guidelines.

MRD testing in accordance with this policy can be performed using PCR and/or sequencing-based technologies and is not restricted to a single type of biological material or defined number of genes.

(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 July 2024, 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.
5/1/23	3/29/23		Received materials from Natera for reconsideration of coverage for testing with signatera, a Payer Dossier was sent for review and was discussed. Rationale updated. No change in policy status. Added code 0368U as E/I. (ds)

11/1/23	8/15/23		Added code 0340U as E/I. Guardant reveal test added to policy as E/I. References added. Vendor managed: N/A. (ds)
11/1/24	8/20/24		Routine policy maintenance, no change in policy status. Vendor managed: N/A (ds)

Next Review Date: 3rd Qtr. 2025

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.