Medical Policy Manual Laboratory, Policy No. 76

Multianalyte and Gene Expression Assays for Predicting Recurrence in Colon Cancer

Effective: October 1, 2023

Next Review: August 2024
Last Review: August 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Several tests using gene expression profile (GEP) or multi-analyte algorithmic analyses have been developed for use as prognostic markers in stage I through stage III colon cancer and are proposed to help identify patients who are at high risk for recurrent disease and to identify good candidates for adjuvant chemotherapy.

MEDICAL POLICY CRITERIA

Multianalyte and gene expression assays are considered **investigational** for determining the prognosis of stage II and stage III colon cancer, including but not limited to the following genetic tests:

A. ColonPRS®
B. ColoPrint®
C. Genefx® Colon
D. Immunoscore®
E. OncoDefender™-CRC

F. Oncotype DX® colon cancer test

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening, Genetic Testing, Policy No. 12
2. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
3. Serologic Genetic and Molecular Screening for Colorectal Cancer, Genetic Testing, Policy No. 86
4. Investigational Gene Expression and Multianalyte Testing, Laboratory, Policy No. 77

BACKGROUND

Assays that are currently being marketed for clinical use in the United States include: ColoPrint®, Agendia; Genefx Colon®, Precision Therapeutics; OncoDefender™-CRC (colon and rectal cancer), Everist Genomics; Oncotype DX® colon cancer test, Genomic Health, Inc.; and Immunoscore®, Veracyte (previously HalioDx).

Colorectal cancer (CRC) is classified as stage I when it is localized and stage II (also called Dukes B) when it has spread outside the colon and/or rectum to nearby tissue, but is not detectable in the lymph nodes (stage III, also known as Dukes C) and has not metastasized to distant sites (stage IV). The primary treatment for stage II CRC is surgical resection of the primary cancer and colonic anastomosis. After surgery the prognosis is very good, with survival rates of 75% to 80% at five years.[1] Meta-analysis of several trials of adjuvant therapy vs. surgery alone in stage II patients found statistically significant, although small, absolute benefit of chemotherapy for disease-free survival (DFS) but not for overall survival (OS).[1] Therefore, adjuvant chemotherapy is recommended only as an option for resected patients with high-risk stage II disease (i.e., those with poor prognostic features).[2]

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. Those patients who are most likely to benefit from chemotherapy are difficult to identify by standard clinical and pathological risk factors. Genomic and multianalyte tests are primarily intended to be used as an aid in identifying those stage II and stage III patients most likely to experience recurrence after surgery and therefore those most likely to benefit from additional treatment.

However, the clinical and pathologic features used to identify high-risk disease are not well-established, and patients for whom benefits of adjuvant chemotherapy would most likely outweigh harms cannot be identified with certainty. The current diagnostic system relies on a variety of factors, including tumor substage IIB (T4A tumors that invade the muscularis propria and extend into pericolorectal tissues) or IIC (T4B tumors that invade or are adherent to other organs or structures), obstruction or bowel perforation at initial diagnosis, an inadequately low number of sampled lymph nodes at surgery (≤12), histologic features of aggressiveness, a high preoperative carcinoembryonic antigen level, and indeterminate or positive resection margins.[2]

Of interest, a recent review has noted that microsatellite instability and mismatch repair (MMR) deficiency in colon cancer may represent confounding factors to be considered in treatment.[3] The finding of these factors may identify a small population (15% to 20%) of the population with improved DFS who may derive no benefit or may exhibit deleterious effects from adjuvant

fluorouracil/leucovorin based treatments. The status of patients with regard to these findings may be of critical important in how to study, interpret, and use a particular gene expression profile test.

REGULATORY STATUS

To date, no gene expression or multianalyte test for evaluation of prognosis in stage I, II, or III colon cancer has been cleared for marketing by the U.S. Food and Drug Administration (FDA). These tests are offered as laboratory-developed assays in Clinical Laboratory Improvement Amendment (CLIA)-licensed laboratories operated by each company and currently do not require FDA premarket review as a result of enforcement discretion.

EVIDENCE SUMMARY

The evidence for the use of prognostic gene expression profile (GEP) tests or multianalyte tests with algorithmic analyses (MAAA) in patients who have colon cancer includes development and validation studies. Relevant outcomes are disease-specific survival, test accuracy, test validity, and change in disease status. To date, no studies have compared the clinical decisions made as a result of these tests to decisions made based on existing methods of risk analysis. In addition, no clinical utility studies have been published that prospectively evaluate health outcomes in patients managed with and without the utilization of GEP or MAAA tests to predict colon cancer recurrence. Further, the clinician's ability to assess individualized risk and predict response to adjuvant therapy based upon such testing, in patients with colon cancer, has not been demonstrated in the literature. Therefore, the impact of the test results on improved patient outcomes or patient management is still unknown.

Randomized controlled trials (RCTs) comparing health outcomes in patients with colon cancer who are managed with versus without GEP or MAAA assays are necessary in order to reliably establish the clinical utility of the assay in question.

TECHNOLOGY ASSESSMENTS

A 2017 evidence report conducted for the Washington State Health Care Authority reviewed the clinical utility of gene expression profile tests for cancer, including ColoPrint® and Oncotype DX® for stage II or III colon cancer.[4] The researchers identified no clinical utility studies with mortality, morbidity, or harms outcomes.

The Agency for Healthcare Research and Quality (AHRQ) published a Technology Assessment on the value and performance of molecular tests for common cancers in 2014. This assessment complements but does not replace the 2012 AHRQ Technology Brief that focussed specifically on colon cancer expression profiling assays. The 2014 assessment includes additional studies on the clinical utility of one of the commercially available assays, Oncotype DX®. Both AHRQ publications are summarized below.

The Technology Assessment published by the AHRQ in May 2014[5] reviewed the prognostic value and test performance of several molecular pathology tests for common cancers. One of the commercially available assays described in this policy, Oncotype DX® Colon, was reviewed in this assessment. One study was reviewed that addressed analytic validity and precision of this test but did not address reproducibility. This study was performed by a laboratory affiliated with Genomic Health, the company that developed Oncotype DX®. One cohort study was reviewed that addressed recurrence risk, but not survival or other measures.

Three studies addressed the clinical utility of Oncotype DX® Colon: one cross-sectional study, one uncontrolled trial and one cohort study. None of these studies met AHRQ's risk of bias standard and were reported as not having reliable data to inform conclusions regarding the impact of the assay on decisions regarding treatment.

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 II colon cancer.[6] Two of the commercially available assays described in this policy were reviewed; Oncotype DX® Colon Cancer and ColoPrint®. No prospective studies were identified that assessed change in net health outcome with use of a GEP assay. Furthermore, no studies were identified that used a net reclassification analysis and subsequently evaluated the impact of the reclassification on net health outcome. Additionally, the evidence was limited regarding the reproducibility of test findings, indications for GEP testing in stage II patients, and whether or not results of GEP assays can stratify patients into clinically meaningful groups.

SYSTEMATIC REVIEWS

A systematic review by Sun (2019) evaluated the prognostic value of the Immunoscore® assay for patients with colorectal cancer using data from eight studies (total n=4,689).[7] Six of the studies included patients with colorectal cancer, while one study each included patients with rectal cancer and colon cancer. The median follow-up in these studies ranged from 36 to 110 months, however three studies did not include accurate follow-up data. In the meta-analysis, low Immunoscore® was associated with lower OS (hazard ratio [HR] 1.74, 95% confidence interval [CI] 1.43 to 2.13) and studies had a moderate degree of heterogeneity (p=0.002, I^2=67.1%) for this outcome. Similarly, low scores were associated with lower DFS (HR 1.82, 95% CI 1.64 to 2.03) with a low degree of heterogeneity (p=0.120, I^2=40.7%). The quality of the included studies was not assessed.

NONRANDOMIZED STUDIES

ColonPRS®

Van Laar (2010) reported on a 163-gene expression test using data from 232 colon cancer patients across all stages (I to IV) of disease.[8] Patients were stratified into high risk and low risk, and a second validation test was performed in 33 stage II and 27 stage III patients. Gene expression classification was reported to show a statistically significant decrease in five-year DFS in low-risk stage II patients and a trend toward a statistically significant decrease in low-risk stage III patients. The assay described in this study, ColonPRS® (ChipDx), was originally marketed by Signal Genetics for research use only but is no longer available.

ColoPrint®

Kopetz (2015) reported a pooled analysis of patients with stage II colon cancer from independent cohorts in the United States, Spain, Italy, Austria, and Germany.[9] Of 416 patients in the pooled dataset, 124 (30%) received adjuvant 5-fluorouracil (5-FU)–based chemotherapy. Investigators compared the prognostic ability of ColoPrint® with National Comprehensive Cancer Network (NCCN) risk prediction based on clinicopathologic factors (T4; high-grade tumor; lymphovascular or perineural invasion; perforation or obstruction; <12 lymph nodes examined; and positive margins). ColoPrint® classified 263 patients (63%) as low risk and 153

patients (37%) as high risk. NCCN classified 236 patients (57%) as low risk and 180 patients (43%) as high risk. At median follow-up of 81 months (range, 56 to 178 months), five-year recurrence risks in ColoPrint® low- and high-risk groups were 10% (95% CI 7% to 14%) and 21% (95% CI 14% to 28%), respectively. In NCCN low- and high-risk groups, five-year recurrence risks were 13% (95% CI 9% to 18%) and 15% (95% CI 10% to 20%), respectively. Statistical comparison of the risk models (e.g., use of a likelihood ratio test and/or receiver operating characteristic [ROC] curves) and comparison of classifications by survival outcomes (i.e., reclassification analysis) were not provided. Further, a five-year recurrence risk as high as 14% in patients classified as low risk by ColoPrint® may be too high for some patients to consider foregoing chemotherapy.

In a 2013 validation study, ColoPrint® was used to evaluate the risk of cancer recurrence and assist in treatment decisions in 135 stage II patients who had undergone curative resection for stage II colon cancer. ColoPrint® identified most stage II patients (73.3%) as low risk.[10] The five-year distant-metastasis free survival was 94.9% for low-risk patients and 80.6% for high-risk patients. In multivariable analysis, ColoPrint® was the only significant parameter to predict the development of distant metastasis. Authors concluded that ColoPrint® was able to predict the development of distant metastasis of patients with stage II colon cancer and facilitate the identification of patients who may be safely managed without chemotherapy. Information about net reclassification and clinical utility was not provided, since treatment decisions were not compared to decisions that would have been made in the absence of genetic testing.

Salazar (2011) described the development of an 18-gene expression test (the ColoPrint® test).[11] A total of 188 samples were prospectively collected from patients with colorectal cancers. From this pool of genes, an optimal set of 18 non-redundant probes were identified. These were used to construct the classification scores used in the test. Results were dichotomized into a two-category system identified as high-risk and low-risk scores. In a nested small independent validation study, using a patient cohort of 206, 60% of patients were identified as low risk and 40% as high risk. However, the population studied was a mixture of patients of different disease stages with 55% and 30% representing stage II and stage III tumors, respectively. In the evaluation of patients with stage II disease, 63.2% were classified as low risk (with a five-year recurrence-free survival of 90.9%) and 36.8% were classified as high risk (with five-year recurrence-free survival of 73.9%). In the evaluation of patients with stage III disease, the five-year rate of recurrence-free survival was 78.2% and 47.2% for low-risk and high-risk patients, respectively.

Genefx Colon® (also known as ColDx)

Niedzwiecki (2016) reported on the recurrence-free interval for 393 patients out of 1,738 treated in the Cancer and Leukemia Group B 9581 (CALGB 9581) trial.[12] Treatment in CALGB 9581 was with an experimental monoclonal antibody (edrecolomab) or observation; there was no significant survival benefit of the experimental treatment. Of 901 eligible patients with available tissue, a randomized sample of 514 patients was selected. Final analysis included 360 patients in the randomized cohort (58 events) and 33 nonrandomly selected events that had samples that were successfully analyzed. The investigators hypothesized that the high failure rate was due to the long interval between sample collection and analysis (mean, 13.2 years). The proportion of patients with a five-year recurrence free survival was 91% (95% CI 89% to 93%) for those categorized as low risk (n=177) and 82% (95% CI 79% to 85%) for those categorized as high risk (n=216). After adjustment for prognostic variables that included mismatch repair deficiency, patients categorized as high risk by ColDx had

significantly worse regression-free interval in unadjusted analysis (hazard ratio [HR] 2.13, 95% CI 1.3 to 3.5, p<0.01). However, in multivariate analysis the ColDx risk score was marginally associated with OS (HR 1.74, 95% CI 0.97 to 3.1, p=0.06). For the 271 samples analyzed by both ColDx and Oncotype DX® (see below), there was little correlation in continuous scores (R = 0.18).

Kennedy (2011) reported on the development of a 634-probe set signature.[13] A training set of 215 patients (142 low risk and 73 high risk) were identified based on DFS at five years. Independent validation was performed on 144 patients enriched for recurrence (85 low-risk and 59 high-risk patients) using the threshold score identified in the training set. The signature in this convenience sample of patients predicted disease recurrence in the high-risk group. The signature also predicted cancer-related death in the high-risk group.

Immunoscore®

Since the publication of the systematic review described above, the Immunoscore® assay has been evaluated in several non-randomized studies and in studies using samples collected from randomized trials of adjuvant therapy.

Mlecnik (2023) evaluated the Immunoscore® in tumors from 1,885 AJCC/UICC-TNM Stage I/II colon cancer patients in a multicenter study with sites in Canada, the USA, Europe, and Asia.[14] At five years, recurrence-free rates for those with low, intermediate, and high Immunoscore® were 78.4% (95% CI 74.4 to 82.6), 88.1% (95% CI 85.7 to 90.4), and 93.4% (95% CI 91.1 to 95.8), respectively.

Sinicrope (2020) published an industry-sponsored analysis of data from a phase 3 randomized trial of adjuvant FOLFOX ± cetuximab in patients with resected stage III colon adenocarcinoma.[15] From the FOLFOX-only arm of the trial, 559 patients with Immunoscore® results were included in the study and 529 contributed data for the clinical prediction models. In this analysis, low Immunoscore® was associated with lower DFS (HR 1.69, 95% CI 1.22 to 2.33, p=0.001) in a model that included age, tumor location, tumor stage, and *BRAF/KRAS* and MMR status, with a three-year DFS of 66.6% for those with a low score compared with 82.6% for those with a high score.

In a similar study by the same group, 600 tumor samples from the infusional fluorouracil, leucovorin, and oxaliplatin arm of the NCCTG N0147 trial were tested using Immunoscore®.[16] Of the 559 that had Immunoscore® results, 53.5% were classified clinically as low-risk (T1-3 N1) and the rest (46.5%) were classified clinically as high-risk (T4 or N2). In both low and high clinical risk groups, Immunoscore®-low results were associated with reduced five-year DFS compared with Immunoscore®-high results (77.5% vs. 91.8% for the clinically low-risk patients, and 55.3% vs. 70.3% for the clinically high-risk patients).

Similarly, Pagès (2020) published an analysis of the Immunoscore® in patients from the IDEA France PRODIGE-GERCOR study.[17] The study was designed to compare outcomes in patients with stage III colon cancer randomized to either three or six months of adjuvant chemotherapy with fluoropyrimidines and oxaliplatin following surgery. There were 1,322 (65.8%) patients from the modified intention to treat population of that trial included in the study. The three-year DFS was 66.80% (95% CI 62.23 to 70.94) for patients with low Immunoscore® and 77.14% (95% CI 73.50 to 80.35) for those with intermediate/high scores. For patients with intermediate/high scores, the six-month chemotherapy regimen (mFOLFOX6) was associated with improved DFS as compared with the three-month regimen (HR 0.528,

95% CI 0.372 to 0.750; p=0.0004). No differential benefit for the longer chemotherapy treatment was seen in those with a low score. These results were statistically significant for both clinically high and low risk tumors.

A multi-center cohort validation study published by Mlecnik (2020) evaluated the association between the Immunoscore® and time to recurrence (TTR), OS, and DFS in 763 patients with stage III colon cancer.[18] Both untreated patients and those treated with adjuvant chemotherapy, but not immunotherapy, were included. In this group, there were 251 relapses and 342 deaths. Five-year recurrence rates were 30.6%, 36.8%, and 50.4% for high, intermediate, and low Immunoscore®. Chemotherapy treatment was associated with TTR in those with intermediate and high scores, but not low scores.

OncoDefender®

Lenehan (2012) reported on the development of a five-gene test, the OncoDefender®.[19] A total of 417 cancer-associated genes were preselected for study in archived formalin-fixed, paraffin-embedded primary adenocarcinoma tissues of 74 patients with colorectal cancer (15 with stage I disease and 59 with stage II disease; 60 with colon and 14 with rectal cancer). Patients were divided into a training set and a testing set. Cross validation was performed to estimate the ability of the classifier to generalize to unseen samples. The most important feature of gene fitness was the area under the ROC curve observed for each gene.

As part of the same study, an external validation test was performed on 251 patients with stage I and II colon cancer obtained from an international study set. Patient drop-out from the archived sample banks used was substantial; only 264 (55%) of 484 patients with lymph-node negative CRC satisfied the initial clinicopathologic screening. This included a mix of patients with both rectal and colon cancer (stage I and II). The test appeared to distinguish patients at high- versus low-risk of recurrence with a hazard ratio of 1.63, p=0.031. Sensitivity and specificity of the OncoDefender® was compared to National Comprehensive Cancer Network (NCCN) guidelines and showed similar sensitivity (69% vs. 73% with improved specificity 48% vs. 26%). However, isolated performance of the test in patients with stage II colon cancer was not reported, and several NCCN high-risk findings (bowel obstruction/perforation, and lymphovascular invasion) demonstrated higher hazard ratios than observed using the molecular signature. The study alluded to but did not directly address clinical utility.

Oncotype DX®

The SUNRISE study, published by Yamanaka (2016) evaluated tissue samples from consecutive patients with stage II and stage III colon cancer who had been treated with surgery alone.[20] This was the standard of care at hospitals in Japan during the study period 2000 to 2005. From the total cohort of 1,487 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. The risk of recurrence in patients with stage III colon cancer with a low-risk score (20%) was similar to that of patients with stage II disease and a high-risk score (19%) 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).

Reimers (2014) conducted a retrospective study using prospectively collected tumor specimens from the Dutch total mesenteric excision (TME) trial[21] in patients with resectable colon cancer.[22] The authors used available tumor tissue from 569 stage II and stage III

patients randomized to surgery alone; only 297 specimens (52%) were included in their analysis. Among patients with stage II rectal cancer (n=130), Oncotype DX® classified 63 patients (49%) as low risk, 37 patients (28%) as intermediate risk, and 30 patients (23%) as high risk. At median follow-up of 12 years (range 1 to 14 years[23]), five-year Kaplan-Meier recurrence risk estimates in the low-, intermediate-, and high-risk groups were 12% (95% CI 6 to 24), 29% (95% CI 17 to 47), and 53% (95% CI 35 to 73), respectively. The authors concluded that a five-year recurrence risk as high as 24% in patients classified as low risk by Oncotype DX® is likely too high to meaningfully inform clinical treatment decision making in patients with stage II colon cancer. Oncotype DX® risk classification and estimated recurrence risks for patients with stage III rectal cancer were not reported.

Venook (2013) conducted a validation study using tumor tissue from 690 patients with stage II colon cancer who had participated in the Cancer and Leukemia Group B (CALGB) 9581 trial.[24] The trial randomized 1,713 patients with stage II colon cancer to treatment with edrecolomab, an experimental monoclonal antibody, or observation. DFS and OS did not differ between treatment groups. Selected samples were stratified by treatment group from those who had tumor tissue available (40% of the original patient sample). The authors used Oncotype DX® 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 five-year recurrence risk was 12% (95% 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.

A validation study by Yothers (2013) used tumor tissue from 264 patients with stage II colon cancer who had participated in the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial.[25] A total of 2,409 patients with stage II (28%) or stage III (72%) colon cancer were randomized to adjuvant chemotherapy with 5-FU plus leucovorin (FULV) or oxaliplatin plus FULV (FLOX). Authors randomly selected 50% of patients who had tissue available (total of 892 tissue samples), 264 of whom (30%) had stage II cancer. For these patients, estimated five-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 five-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 in each risk group. For all stage III patients in any risk class, adjusted five-year recurrence risk estimates exceeded 15%.

The development of the 12-gene expression test is described in an article by O'Connell (2010).[26] 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-FU-based chemotherapy. Gene expression was quantitated from microdissected fixed paraffin-embedded primary colon cancer tissue. Of the 761 candidate genes surveyed, a multivariate analysis including disease severity, stage, and nodal involvement, reduced the genes to a significant seven-gene prognostic signature and a separate six-gene predictive signature. Five reference genes were also included in the assay. External validation of the

algorithm in an independent study, the Quick and Simple and Reliable (QUASAR) study was reported in 2011.[27] The relationship between the seven-gene test's recurrence score and risk of recurrence was found to be statistically significant with the three-year risk of recurrence for predefined low-, intermediate-, and high-risk groups to be 12%, 18%, and 22%, respectively. No relationship was identified comparing the six-gene treatment score results with benefit from chemotherapy.

Several studies have documented changes in management following GEP testing with the Oncotype DX® Colon Cancer Assay. For example, Oki (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.[28] 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 (2016) published a retrospective study of the association between Oncotype DX® recurrence score and management decisions.[29] There were 269 patients from one health plan included who had stage II colon cancer, mismatch repair 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 102/269 patients (38%). Of the 102 patients with management changes, there were 76 cases in which the intensity of management was decreased and 26 patients in whom the intensity 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. This study did not determine whether patient outcomes were improved because of the changes in management.

Renfro (2016) reported on a prospective evaluation of Oncotype DX®'s influence on patient treatment decisions, physician confidence, and concordance between physicians and patients.[30] Of 221 consecutive patients enrolled, 139 stage IIA mismatch repair-proficient patients were evaluated for the patient-reported analyses and 150 patients were evaluated for the physician-reported analyses. Before the assay, 46% of the patients chose observation and 41% were undecided. After the assay, 75% chose observation and 0% were undecided. After the assay, 94% of the defined treatment decisions were concordant between patients and physicians compared with 60% before the assay. Physicians reported the assay influenced their treatment decisions and increased confidence in their treatment recommendations for 69% and 84% of patients, respectively. Most patients (86%) reported that the assay influenced their treatment decisions.

Srivastava (2014) also evaluated the impact of the Oncotype DX® results on treatment recommendations made according to traditional risk classifiers in stage II colon cancer patients.[31] For each patient, the physician's recommended postoperative treatment plan of observation, fluoropyrimidine monotherapy, or combination therapy with oxaliplatin was recorded before and after the recurrence score and mismatch repair results were provided. Of the 221 stage IIA patients enrolled, 141 had T3 MMR-P tumors and were eligible for analysis.

Authors reported treatment recommendations changed for 63 patients (45%) with the use of Oncotype DX recurrence scores; however, whether these treatment changes impacted patient survival or recurrence outcomes was not reported.

Cartwright (2014) conducted a cross sectional survey regarding the clinical utility of the Oncotype DX® assay with US medical oncologists who had ordered the assay in the first two years of commercial availability.[32] Before assay, treatment recommendations were specified for 92 (79%) patients, and of these, the assay changed recommendations for 27 patients (29%). However, limited utility can be derived from this study due to its retrospective nature and the limited time frame in which the data was accumulated.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)

NCCN clinical practice guidelines for colon cancer (v.2.2023) the following regarding multigene assays and Immunoscore®:[2]

"[T]he information from these tests can further inform the risk of recurrence over other risk factors, but the panel questions the value added. Furthermore, evidence of predictive value in terms of the potential benefit of chemotherapy is lacking. Therefore, 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."

SUMMARY

There is not enough research to show if gene expression profile (GEP) tests or multianalyte assays with algorithmic analysis (MAAA) for colon cancer can lead to improved health outcomes for patients. Also, clinical guidelines based on research do not recommend GEP or MAAA testing. Therefore, use of any GEP or MAAA test is considered investigational for determining prognosis or predicting disease recurrence in patients with colon cancer.

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CODES

Codes	Number	Description
CPT	0261U	Oncology (colorectal cancer), image analysis with artificial intelligence assessment of 4 histologic and immunohistochemical features (CD3 and CD8 within tumor-stroma border and tumor core), tissue, reported as immune response and recurrence-risk score
	81479	Unlisted molecular pathology procedure
	81525	Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score
	81599	Unlisted multianalyte assay with algorithmic analysis
	84999	Unlisted chemistry procedure
	88299	Unlisted cytogenetic study
HCPCS	None	

Date of Origin: *August 2021*