Genetic Testing for Predicting Recurrence of Colon Cancer

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DESCRIPTION

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

Immunoscore is a biomarker (immunohistochemical staining of colon cancer tissue) that measures the response of a patient's immune system to a tumor. Immunoscore allows the quantification of two T-cell subsets (CD3 and CD8) in two tumor regions (core and invasive margin tumors). When used with TNM scoring which is the method clinicians use to assign staging to a disease and appears to be a promising way to predict an individual's risk of recurrence, which may help develop a personalized treatment plan. The scores provided by Immunoscore can be high or low. A high level of immune cell infiltration (Immunoscore-High) indicates that a patient's immune system is active and

fighting a tumor and indicates a lower risk for recurrence. A low Immunoscore (Immunoscore-Low) indicates that an individual's immune system is not as active in controlling the tumor and suggests a higher risk for recurrence.

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. The American Cancer Society estimates the following for colorectal cancer cases in the United States for 2022:

- 151,030 new cases of colon cancer
- 44,850 new cases of rectal cancer
- 52,580 estimated deaths of colorectal cancer

Stage II or III Colon Cancer

Clinical Context and Test Purpose
The purpose of prognostic testing of diagnosed disease is to predict natural disease course (e.g., aggressiveness, risk of recurrence, death). This type of testing uses gene expression profiling (GEP) of affected tissue to predict the course of the disease.

Immunoscore is a biomarker that measures the response of a patient's immune system to a tumor to predict the course of the disease.

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

Interventions
The interventions of interest are gene expression profiling (GEP) assays with Oncotype DX Colon Recurrence Score, ColoPrint 18-Gene Colon Cancer Recurrence Assay, GeneFx Colon (ColDx), and OncoDefender-CRC.

Immunoscore biomarker indicating if the individual's immune system is active in fighting the tumor and indicates a low or high-risk score for recurrence.

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 of 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 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 gene expression (GEP).

The time of interest is 3 to 5 years after surgical resection to assess colon cancer recurrence, given that the majority of colon cancer recurrences occur within the first 3 years after surgical resection of the primary tumor and approximately 95% in the first 5 years.

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

Staging
The tumor, node, metastasis (TNM) staging system of the combined American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) is the preferred staging system for colorectal cancer (CRC).

In the 8th edition of the AJCC Staging Manual, T1 tumors involve the submucosa; T2 tumors penetrate through the submucosa into the muscularis propria; T3 tumors penetrate through the muscularis propria; T4a tumors directly penetrate to the surface of the visceral peritoneum; and T4b tumors directly invade or are adherent to other organs or structures. Regional lymph node classification includes N1a (1 positive lymph node); N1b (2-3 positive lymph nodes), N2a (4-9 positive lymph nodes); and N2b (7 or more positive lymph nodes). In addition, tumor deposit(s) in the subserosa mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal metastasis (i.e., satellite tumor nodules) have been classified as N1c. Metastatic disease is classified as M1a when metastases that are limited to only one site/solid organ (including to lymph nodes outside the primary tumor regional drainage area) are positive. M1b is used for metastases to multiple distant sites or solid organs, exclusive of peritoneal carcinomatosis. The 8th edit of the AJCC Cancer Staging Manual includes the M1c category for peritoneal carcinomatosis with or without blood-borne metastasis to visceral organs.

Stage II Colorectal Cancer

Stage	TNM	Description
IIA	T3, N0, M0	T3 = Tumor invades through muscularis propria into pericolorectal tissues N0 = No regional lymph node metastasis MO = No distant metastasis by imaging; no evidence of

		tumor in distant sites or organs
IIB	T4a, N0, M0	T4a = Tumor invades through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum) N0 = No regional lymph node metastasis M0 = No distant metastasis by imaging; no evidence of tumor in distant sites or organs
IIC	T4b, N0, M0	T4b = Tumor directly invades or adheres to adjacent organs or structures N0 = No regional lymph node metastasis M0 = No distant metastasis by imaging; no evidence of tumor in distant sites or organs

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 stage (tumors that invade the muscularis propria and extend into pericolorectal tissues; 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 ($\leq$ 12), histologic features of aggressiveness, an high preoperative carcinoembryonic antigen level, and indeterminate or positive resection margins.

Stage III Colon Cancer

Stage	TNM	Description
IIIA	T1, N2a, M0	T1 = Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria) N2a = Four to six regional lymph nodes are positive M0 = No distant metastasis by imaging; no evidence of tumor in distant sites or organs
	T1-2, N1/N1c, M0	T1 = Tumor invades submucosa (through the muscularis mucosa but not into the muscularis propria) T2 = Tumor invades the muscularis propria N1 = One to three regional lymph nodes are positive (tumor in lymph nodes measuring $\geq$ 0.2 mm); or any number of tumor deposits are present and all identifiable lymph nodes are negative N1c = No regional lymph nodes are positive, but there are tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic, or perirectal/mesorectal tissues M0 = No distant metastasis by imaging; no evidence of tumor in distant sites or organs
IIIB	T1-T2, N2b, M0	T1 = Tumor invades submucosa (through the muscularis mucosa but not into the muscularis propria)

		T2 = Tumor invades the muscularis propria N2b = seven or more regional lymph nodes are positive M0 = No distant metastasis by imaging; no evidence of tumor in distant sites or organs
	T2-T3, N2a, M0	T2 = Tumor invades the muscularis propria T3 = Tumor invades through the muscularis propria into pericolorectal tissues N2a = Four to six regional lymph nodes are positive M0 = No distant metastasis by imaging; no evidence of tumor in distant sites or organs
	T3-T4a, N1/N1c, M0	T3 = Tumor invades through the muscularis propria into pericolorectal tissues T4 = Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure • T4a = Tumor invades through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the

		surface of the visceral peritoneum) N1 = One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥ 0.2 mm); or any number of tumor deposits are present and all identifiable lymph nodes are negative N1c = No regional lymph nodes are positive, but there are tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic, or perirectal/mesorectal tissues M0 = No distant metastasis by imaging; no evidence of tumor in distant sites or organs
IIIC	T3-T4a, N2b, M0	T3 = Tumor invades through the muscularis propria into pericolorectal tissues T4 = Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure • T4a = Tumor invades through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)

		N2b = Seven or more regional lymph nodes are positive M0 = No distant metastasis by imaging; no evidence of tumor in distant sites or organs
	T4a, N2a, M0	T4a = Tumor invades through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum) N2a = Four to six regional lymph nodes are positive M0 = No distant metastasis by imaging; no evidence of tumor in distant sites or organs
	T4b, N1-N2, M0	T4b = Tumor directly invades or adheres to adjacent organs or structures N1 = One to three regional lymph nodes are positive (tumor in lymph nodes measuring $\geq$ 0.2 mm); or any number of tumor deposits are present and all identifiable lymph nodes are negative • N1a = One regional lymph node is positive • N1b = Two or three regional lymph nodes are positive

		• N1c = No regional lymph nodes are positive, but there are tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic, or perirectal/mesorectal tissues N2 = Four or more regional lymph nodes are positive • N2a = Four to six regional lymph nodes are positive • N2b = Seven or more regional lymph nodes are positive M0 = No distant metastasis by imaging; no evidence of tumor in distant sites or organs

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

ColoPrint 18-Gene Colon Cancer Recurrence Assay
In 2015, Kepetz et. al. reported on a pooled analysis of 416 patients with stage II colon cancer from five different hospitals in Europe and one hospital in the United States. ColoPrint was compared with clinical risk factors described in the National Comprehensive Cancer Network (NCCN) 2013 Guidelines for Colon Cancer (T4; high grade tumor; lymphovascular or perineural invasion; perforation or obstruction; <12 lymph nodes examined; positive margins). Median follow-up was 81 months. Most patients (70%) did not receive adjuvant chemotherapy. Risk of relapse (ROR) was defined as survival until first event of recurrence or death from cancer. In the pooled stage II data set, ColoPrint identified 63% of patients as low risk with a 5-year ROR of 10%, whereas high-risk patients (37%) had a 5-year ROR of 21%, with a hazard ratio (HR) of 2.16 (p = .004). This remained significant in a multivariate model that included number of lymph nodes retrieved and microsatellite instability. In the T3 microsatellite-stable subgroup (n = 301), ColoPrint classified 59% of patients as low risk with a 5-year ROR of 9.9%. High-risk patients (31%) had a 22.4% ROR (HR: 2.41; p = .005). In

contrast, the NCCN clinical high-risk factors were unable to distinguish high- and low-risk patients (15% vs. 13% ROR; p = .55). Thirty percent (30%) of patients received adjuvant 5-FU based chemotherapy. The decision to administer adjuvant chemotherapy as correlated with cohort site, year, and clinical risk factors but was not correlated with ColoPrint results, which were not available to the treating physicians. The outcome of patients was not improved by chemotherapy (p = 0.88). Patients who did not receive chemotherapy had a 5-year ROR of 13.8% (95% CI: 9.7% – 17.9%), whereas patients who received therapy had a 5-year ROR of 14.8% (95% CI: 8.5% – 21.1%). Although there was no difference in the outcomes of patients treated or not treated with adjuvant therapy, conclusions are limited based on these findings because patients were not treated within a randomized clinical trial and the potential benefit of chemotherapy may be too small (3%–5%) to be detected in this limited data set.

GeneFx Colon (Also Known as ColDx)

Niedzwiecki et. al. (2016) reported on the association between results of a gene expression signature assay (ColDx also known as GeneFx Colon) and recurrence free interval in patients with stage II colon cancer in Cancer and Leukemia Group B 9581 as part of the Alliance phase III trial. C9581 evaluated edrecolomab versus observation in patients with stage II CC and reported no survival benefit. Under an initial case-cohort sampling design, a randomly selected sub cohort (RS) comprised 514 patients from 901 eligible patients with available tissue. Forty-nine additional patients with recurrence events were included in the analysis. Final analysis comprised 393 patients: 360 RS (58 events) and 33 non-RS events. Risk status was determined for each patient by ColDx. The Self-Prentice method was used to test the association between the resulting ColDx risk score and RFI (recurrence free interval) adjusting for standard prognostic variables. Fifty-five percent of patients (216 of 393) were classified as high risk. After adjustment for prognostic variables that included mismatch repair (MMR) deficiency, ColDx high-risk patients exhibited significantly worse RFI (multivariable hazard ratio, 2.13; 95% CI, 1.3 to 3.5; P < .01). Age and MMR status were marginally significant. RFI at 5 years for patients classified as high risk was 82% (95% CI, 79% to 85%), compared with 91% (95% CI, 89% to 93%) for patients classified as low risk. In the subset of 271 patients for whom data are available from both assays (OncotypeDX and ColDx), there is low correlation between the continuous scores (R = 0.18). Although there is some overlap, it does not seem that the signatures are measuring the same thing or identifying the same patients at high risk. Further analysis is being conducted in this patient subset.

OncoDefender-CRC

Lenehan et. al. (2012) reported on the development and validation of a tumor derived 5-gene prognostic signature (OncoDefender-CRC) for recurrence of lymph node-negative invasive colorectal carcinoma (CRC). A total of 417 cancer-associated genes were preselected for the study of archived FFPE (formalin-fixed paraffin-embedded) primary adenocarcinoma tissues from 74 patients with CRC (15 with stage I disease and 59 with stage II disease). Patients were divided into a training set and a test set. In addition, FFPE tissues were retrieved from 49 patients with stage I CRC and 215 patients with stage II colon cancer for an External Validation (EV) Set (n = 264) from 18 hospitals in 4

countries. No patients had received neoadjuvant/adjuvant therapy. The test appeared to distinguish patients at high versus low risk or recurrence (HR = 1.63; p = 0.031). Sensitivity and specificity of OncoDefender-CRC were compared with NCCN guidelines and showed similar sensitivity (69% versus 73%) with improved specificity (48% versus 26%). However, the isolated performance of the test in patients with stage II colon cancer was not reported, and several NCCN high-risk findings (bowel obstruction or perforation and lymphovascular invasion) demonstrated higher HRs than observed with the molecular signature. The study alluded to but did not directly address clinical utility.

OncotypeDX Colon Recurrence Score

In 2021, Oki et. al. conducted a prospective study to evaluate whether the 12-gene recurrence score (12-RS, Oncotypte DX Colon) assay affected physicians' recommendations on adjuvant treatment selection. Patients with stage IIIA/IIIB or stage II colon cancer were enrolled. After the patients discussed adjuvant treatment with their treating physicians, the physicians filled in the questionnaire before assay indicating the treatment recommendation. When the 12-RS assay results were available, the physicians again filled in the questionnaire after assay. The primary endpoint was the rate of change in treatment recommendations from before to after the assay, with a threshold rate of change being 20%. Patients with stage IIIA/B to II were enrolled in a ratio of 2: 1. Overall, the treatment recommendations changed in 40% of cases after obtaining 12-RS assay results. Recommendations were changed in 45% (80/178; 95% confidence interval, 37% to 53%; P < 0.001) and 30% (29/ 97; 95% confidence interval, 21% to 40%; P < 0.001) of patients with stage IIIA/B and II colon cancer, respectively. Patients with stage IIIA/B cancer had significantly more change than those with stage II cancer (P ¼ 0.0148). From before to after the 12-RS assay, the percentage of patients whose physicians reported being confident in their treatment recommendations significantly increased from 54% to 81% in stage IIIA/B (P < 0.001) and from 65% to 83% in stage II (P < 0.001). There are several limitations in this study. Despite those limitations, the SUNRISE-DI study confirmed the usefulness of the 12-RS assay in aiding the physician patient decision-making process and physicians' acceptance of the 12-RS in patients with stage IIIA/B colon cancer after availability of the results of IDEA collaboration. The 12-RS also provided valuable support to physicians in treating patients with stage II. However, further long-term follow-up is needed in order to confirm the clinical utility of the 12-RS assay.

In 2016, Yamanaka et. al. evaluated the 12-gene Recurrence Score assay for stage II and III colon cancer without chemotherapy to reveal the natural course of recurrence risk in stage III disease in the SUNRISE Study. A cohort-sampling design was used. From 1,487 consecutive patients with stage II to III disease who had surgery alone, 630 patients were sampled for inclusion with a 1:2 ratio of recurrence and nonrecurrence. Sampling was stratified by stage (II versus III). The assay was performed on formalin-fixed, paraffin-embedded primary cancer tissue. Association of the Recurrence Score result with recurrence-free interval (RFI) was assessed by using weighted Cox proportional hazards regression. Overall, 597 of 630 patients were analyzable 247 patients had stage II, and 350 had stage III colon cancer. The continuous Recurrence Score was significantly

associated with RFI after adjustment for disease stage (hazard ratio for a 25 unit increase in Recurrence Score, 2.05; 95% CI, 1.47 to 2.86; P < .001). With respect to prespecified subgroups, as defined by low (< 30), intermediate (30 to 40), and high (≥ 41) Recurrence Score risk groups, patients with stage II disease in the high-risk group had a 5-year risk of recurrence similar to patients with stage IIIA to IIIB disease in the low-risk group (19% versus 20%), whereas patients with stage IIIA to IIIB disease in the high-risk group had a recurrence risk similar to that of patients with stage IIIC disease in the low-risk group (approximately 38%).

Reimers et. al. (2014) conducted a prospectively designed study to validate this assay for prediction of recurrence risk in stage II and III rectal cancer patients from the Dutch Total Mesorectal Excision (TME) trial. RNA was extracted from fixed paraffin-embedded primary rectal tumor tissue from stage II and III patients randomized to TME surgery alone, without (neo) adjuvant treatment. Recurrence Score was assessed by quantitative real time-polymerase chain reaction using previously validated colon cancer genes and algorithm. Data were analyzed by Cox proportional hazards regression, adjusting for stage and resection margin status. All statistical tests were two-sided. Recurrence Score predicted risk of recurrence (hazard ratio [HR] = 1.57, 95% confidence interval [CI] = 1.11 to 2.21, P = .01), risk of distant recurrence (HR = 1.50, 95% CI = 1.04 to 2.17, P = .03), and rectal cancer-specific survival (HR = 1.64, 95% CI = 1.15 to 2.34, P = .007). The effect of Recurrence Score was most prominent in stage II patients and attenuated with more advanced stage (P(interaction) ≤ .007 for each endpoint). In stage II, five-year cumulative incidence of recurrence ranged from 11.1% in the predefined low Recurrence Score group (48.5% of patients) to 43.3% in the high Recurrence Score group (23.1% of patients). Risk classification with Recurrence Score and estimated recurrence risks for patients with stage III rectal cancer were not reported

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

Immunoscore
In 2020, Mlecnik et. al. evaluated the prognostic value of Immunoscore in patients with stage III colon cancer (CC) and to analyze it association with the effect of chemotherapy on time to recurrence (TTR). An international study led by the Society for Immunotherapy of Cancer evaluated the predefined consensus Immunoscore in 763 patients with American Joint Committee on Cancer/Union for International Cancer Control TNM stage III CC from cohort 1 (Canada/United States) and cohort 2

(Europe/Asia). CD31 and cytotoxic CD81 T lymphocyte densities were quantified in the tumor and invasive margin by digital pathology. The primary end point was TTR. Secondary end points were overall survival (OS), disease-free survival (DFS), prognosis in microsatellite stable (MSS) status, and predictive value of efficacy of chemotherapy. Patients with a high Immunoscore presented with the lowest risk of recurrence, in both cohorts. Recurrence-free rates at 3 years were 56.9% (95% CI, 50.3% to 64.4%), 65.9% (95% CI, 60.8% to 71.4%), and 76.4% (95% CI, 69.3% to 84.3%) in patients with low, intermediate, and high Immunoscores, respectively (hazard ratio [HR; high v low], 0.48; 95% CI, 0.32 to 0.71; P 5 .0003). Patients with high Immunoscore showed significant association with prolonged TTR, OS, and DFS (all P < .001). In Cox multivariable analysis stratified by participating center, Immunoscore association with TTR was independent (HR [high v low], 0.41; 95% CI, 0.25 to 0.67; P 5 .0003) of patient's sex, T stage, N stage, sidedness, and microsatellite instability status. Significant association of a high Immunoscore with prolonged TTR was also found among MSS patients (HR [high v low], 0.36; 95% CI, 0.21 to 0.62; P 5 .0003). Immunoscore had the strongest contribution x2 proportion for influencing survival (TTR and OS). Chemotherapy was significantly associated with survival in the high Immunoscore group for both low-risk (HR [chemotherapy v no chemotherapy], 0.42; 95% CI, 0.25 to 0.71; P 5 .0011) and high-risk (HR [chemotherapy v no chemotherapy], 0.5; 95% CI, 0.33 to 0.77; P 5 .0015) patients, in contrast to the low-Immunoscore group (P > .12). Limitations of the study might be due to the heterogeneity of the patient population in real-life clinical practice with standard-of-care treatments from 13 different countries, with 65% and 16% of the patients having MSI and mutational status, respectively; this nonrandomized approach was aimed at demonstrating the robustness of the consensus Immunoscore across multiple ethnicities and patient-care practices. Both Immunoscore and genetic biomarkers should be investigated in larger prospective studies to determine whether mutations occurring at different disease stages have a differential effect on the intertumoral immune infiltrates and on patients' prognosis. It will now be important to further validate the Immunoscore in randomized clinical trials for prognostic purpose and prediction of chemotherapy response.

Pages et. al. (2020) evaluated the prognostic and predictive value of Immunoscore for disease free survival (DFS) in stage III colon cancer patients treated with oxaliplatin in the prospective IDEA France PRODIGE-GERCOR cohort study. IDEA France4 was a multicenter, two-arm, open-label, randomized phase III trial with an accrual goal of 2000 stage III CC patients within the IDEA international collaboration (N ¼ 12834)3 comparing 3 versus 6 months of adjuvant fluoropyrimidine and oxaliplatin-based chemotherapy after surgery. Densities of CD3þ and CD8þ T cells in the tumor and invasive margin were determined by immunohistochemistry, quantified by digital pathology, and converted to IS. Mismatch repair status was determined by immunohistochemistry or by pentaplex PCR. Prediction of disease-free survival (DFS) by IS was analyzed by a multivariable Cox regression model in each study arm. Harrell's C-statistics were used to investigate the IS performance. Samples of 1322 patients were available. IS Low, Intermediate (Int), and High were observed in 43.6%, 47.0%, and 9.4% of patients, respectively. IS Low identified patients at higher risk of relapse or death

compared with Int þ High [hazard ratio (HR) = 1.54; 95% confidence interval (CI) 1.24-1.93, P = 0.0001]. The 3-year DFS was 66.80% (95% CI 62.23-70.94) for IS Low and 77.14% (95% CI 73.50e80.35) for IS Int + High. In multivariable analysis, IS remained significantly independently associated with DFS (P = 0.003) when adjusted for sex, histological grade, T/N stage, and microsatellite instability. For mFOLFOX6-treated patients (91.6% of the cohort), a statistically significant interaction was observed for the predictive value of IS for treatment duration (3 versus 6 months) in terms of DFS (P = 0.057). IS Int þ High significantly predicted benefit of 6 months of treatment (HR = 0.53; 95% CI 0.37-0.75; P = 0.0004), including clinically low- and high-risk stage III CC (all P < 0.001). Conversely, patients with IS Low (46.4%) did not significantly benefit from the 6-month mFOLFOX6 versus the 3-month mFOLFOX6. A limitation of this study is that 90% of patients in the IDEA France study were treated with the mFOLFOX6 regimen, which precludes any robust conclusion for patients receiving CAPOX. In addition, the median follow-up of the overall mITT population was 4.3 years and therefore it is still impossible to analyze the Immunoscore impact on long-term treatment benefit. The predictive value of Immunoscore needs to be confirmed in FOLFOX- and/or CAPOX-treated patients in another cohort of the IDEA collaboration to validate the potential use of the Immunoscore test in guiding the choice of duration of adjuvant therapy.

In 2019, Galon et. al. reported on the clinical utility of Immunoscore for patients with colon cancer stage II with high risk clinicopathologic features for whom adjuvant treatment may be avoided. A subgroup analysis was performed on the St II untreated patients (n = 1130) from the Immunoscore international validation study (Pagès The Lancet 2018 below). The high-risk patients (with at least 1 clinicopathological high-risk feature) were classified in 2 categories using pre-defined cutoffs: Low Immunoscore versus High Immunoscore and their five-year time to recurrence (5Y TTR) was compared to the TTR of the low-risk patients (without any clinicopathological high-risk feature). Among the patients with high-risk features (n = 630), 438 (69.5%) had a High Immunoscore with a corresponding 5Y TTR of 87.4 (95% CI 83.9-91.0), statistically similar (log rank pv not stratified p > 0.42, wald pv stratified by center p > 0.20) to the TTR 89.1 (95% CI 86.1-92.1) observed for the 500 low-risk patients (with no clinicopathological feature). Furthermore, 5Y TTR for these patients were statistically similar to those of St II patients with high-risk features and a High Immunoscore (n = 438), who received adj. CT (n = 162) (5Y TTR of 83.4 (95% CI 77.6-89.9). These data show that despite the presence of high-risk features that usually trigger adjuvant treatment, when not treated with CT, a significant part of these patients (69.5%) have a recurrence risk similar to the low-risk patients.

In 2018, Pages et. al. assessed the prognostic value of total tumor-infiltrating T-cell counts and cytotoxic tumor infiltrating T-cells counts with the consensus Immunoscore assay in patients with stage I-III colon cancer. An international consortium of 14 centers in 13 countries, led by the Society for Immunotherapy of Cancer, assessed the Immunoscore assay in patients with TNM stage I–III colon cancer. Patients were randomly assigned to a training set, an internal validation set, or an external validation mset. Paraffin sections of the colon tumor and invasive margin from each patient were

processed by immunohistochemistry, and the densities of CD3+ and cytotoxic CD8+ T cells in the tumor and in the invasive margin were quantified by digital pathology. An Immunoscore for each patient was derived from the mean of four density percentiles. The primary endpoint was to evaluate the prognostic value of the Immunoscore for time to recurrence, defined as time from surgery to disease recurrence. Stratified multivariable Cox models were used to assess the associations between Immunoscore and outcomes, adjusting for potential confounders. Harrell's C-statistics was used to assess model performance. Tissue samples from 3539 patients were processed, and samples from 2681 patients were included in the analyses after quality controls (700 patients in the training set, 636 patients in the internal validation set, and 1345 patients in the external validation set). The Immunoscore assay showed a high level of reproducibility between observers and centers (r=0·97 for colon tumor; r=0·97 for invasive margin; p<0·0001). In the training set, patients with a high Immunoscore had the lowest risk of recurrence at 5 years (14 [8%] patients with a high Immunoscore *vs* 65 (19%) patients with an intermediate Immunoscore *vs* 51 (32%) patients with a low Immunoscore; hazard ratio [HR] for high *vs* low Immunoscore 0·20, 95% CI 0·10–0·38; p<0·0001). The findings were confirmed in the two validation sets (n=1981). In the stratified Cox multivariable analysis, the Immunoscore association with time to recurrence was independent of patient age, sex, T stage, N stage, microsatellite instability, and existing prognostic factors (p<0·0001). Of 1434 patients with stage II cancer, the difference in risk of recurrence at 5 years was significant (HR for high *vs* low Immunoscore 0·33, 95% CI 0·21–0·52; p<0·0001), including in Cox multivariable analysis (p<0·0001).

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 in patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

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 in December 2012, reviewed the clinical evidence for gene expression profiling (GEP) assays for predicting outcomes, including benefit from adjuvant chemotherapy, in patients with stage II colon cancer. The 4 commercially available assays reviewed were included in the brief. No prospective studies were identified that assessed change in net health outcome with the use of a GEP assay, and no studies were identified that used a net reclassification analysis and subsequently evaluated the impact of reclassification on net health outcome. Additionally, evidence was limited on the reproducibility of test findings, indications for GEP testing in stage II patients, and whether results of GEP assays can stratify patients into groups with clinically meaningful differences in recurrence risk. No studies have been identified in subsequent literature updates that

evaluated the impact of GEP testing on recurrence in patients with stage II or III colon cancer.

In the absence of direct evidence, an indirect chain of evidence could demonstrate clinical utility if all links in the chain are intact. An indirect chain of evidence for clinical utility of GEP testing involves the following series of questions:

- Does GEP testing provide prognostic information? Yes. Patients with a low recurrence score have a decreased risk of recurrence and patients with a high-risk score have a higher risk of recurrence. However, the degree of difference in risk conferred by the test is not large.
- Does GEP testing provide incremental prognostic information compared to the standard clinical workup for prognosis? Uncertain. No well-done studies have compared the prognostic information from GEP testing to standard prognostic information provided by clinical and pathologic workup.
- Does the incremental prognostic information lead to classifying patients into different groups for which management differs? No. There are no well-defined treatment protocols that differ according to risk of recurrence. The intensity of surveillance and management may be impacted by results of GEP testing, but the evidence to demonstrate this is weak and not definitive.
- Do the changes in management resulting from GEP testing lead to improvements in health outcomes? No. There is no evidence that different treatment protocols for patients with different risks of recurrence improve outcomes.

The findings of this technical brief state: Published studies have not provided information related to clinical utility, the effect that using the GEP result in patient care has on net health outcome. Limited information was found for analytic validity. The current evidence does not provide the type of information needed to answer major questions about use of GEP assays in these patients.

The technical brief concluded although information is emerging about the use of GEP assays to inform the decision about use of adjuvant chemotherapy in patients with stage II colon cancer, studies to date have not provided the type of information needed to address major uncertainties.

An 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 and III colon cancer. The researchers identified no clinical utility studies with mortality, morbidity, or harms outcomes.

Summary

Some studies have reported management changes following gene expression profiling (GEP) testing. However, these studies did not report clinical outcomes, and there is no direct evidence to determine whether GEP testing improves net health outcomes. A chain of evidence might be constructed if there was evidence that changes in the management for patients with stage II colon cancer improve 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 improve health outcomes is weak and not definitive. Therefore, the evidence does not demonstrate clinical utility.

Summary of Evidence

For individuals who have stage II or III colon cancer who receive gene expression profiling (GEP) testing or Immunoscore biomarker testing, the evidence includes development and validation studies, and decision-impact studies. The available evidence has shown that gene expression profiling (GEP) testing and Immunoscore biomarker testing for colon cancer can improve risk prediction, particularly the risk of recurrence in patients with stage II or III colon cancer, however, the degree of difference in risk conferred by the test is small. Evidence to date does not permit conclusions on whether this testing is sufficient to modify treatment decisions in stage II or III colon cancer patients. Studies showing management changes as a consequence of testing have not demonstrated whether such changes improve outcomes. The current NCCN guideline Colon Cancer Version 2.2022 states the following: "The 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 to estimate risk of recurrence or determine adjuvant therapy. The NCCN Panel encourages enrollment in clinical trials to help with the generation of additional data on these assays." Per the European Society of Medical Oncology (ESMO) Immunoscore was a strong predictor for time to recurrence, overall survival (OS) and disease-free survival (DFS), however, its role in predicting chemotherapy benefit is uncertain and firm evidence of its prognostic role in a stage II-only dataset is currently lacking. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Practice Guidelines and Position Statements

European Society for Medical Oncology (ESMO)

In 2020, the European Society for Medical Oncology (ESMO) issued clinical practice guideline for diagnosis, treatment and follow-up which included the following:

Use of personalized medicine in localized colon cancer/biomarkers for risk assessment

Use of personalized medicine in localized colon cancer/ biomarkers for risk assessment Besides MSI status, other genetic markers, e.g. RAS and BRAF mutations are not recommended for the routine assessment of risk of recurrence in non-metastatic patients, based on their lack of utility in the adjuvant decision-making process.67 However, other biomarkers such as gene signatures, Immunoscore and postoperative circulating tumor DNA (ctDNA) have demonstrated some benefit in determining the risk of recurrence and can be considered in addition to pathological features and MSI status to further tailor the adjuvant decision making in difficult cases.

Gene signatures have emerged as potential candidates for prognostic stratification in locoregional disease. At the time of writing, only Oncotype DX68 and GeneFx Colon69 have been validated in multivariate analysis of independent prospective randomized cohorts of stage II colon cancer with formalin-fixed paraffin-embedded (FFPE) tumor samples. Although routine clinical utility is not warranted due to lack of predictive value for chemotherapy benefit and the small prognostic differentiation margins between high, intermediate and low scores, their use might be considered in complementing clinicopathological information on intermediate-risk stage II scenarios: i.e., to treat T3 N0 classified as high risk by the signature, or for avoiding chemotherapy in T4 N0 classified as low risk by the signature [II, C].

Immunoscore has been recently validated in a large prospective cohort of >2500 patients TNM stage IeIII.70 Immunoscore was a strong predictor for time to recurrence, OS and disease-free survival (DFS) (all $P < 0.0001$), independently of patient age, sex, MSI and other existing prognostic factors. Immunoscore had the highest relative contribution to the risk of all clinical parameters, including the UICC TNM classification system. Therefore, Immunoscore could help refine the prognosis of early colon cancer patients in conjunction with the TNM scoring [III, C]. However, its role in predicting chemotherapy benefit is uncertain and firm evidence of its prognostic role in a stage II-only dataset is currently lacking.

Finally, ctDNA monitoring, also known as liquid biopsy, is a promising tool under investigation to identify patients with high risk of recurrence after primary tumor resection. Indeed, ctDNA detection after stage II colon cancer resection has been demonstrated to provide direct evidence of residual disease and to identify patients at very high risk of recurrence.71 The results of ongoing trials investigating the role of ctDNA as a tool to stratify patient's risk of relapse and to determine allocation to different adjuvant therapeutic strategies must be awaited before this is accepted in routine practice. The CIRCULATE-IDEA and de Circulatie-Europa collaborations seek to pool the data coming from the main national trials exploring ctDNA follow-up in the adjuvant setting. The results of this initiative will probably set the final role of ctDNA in the adjuvant decision-making process.

Recommendations

- Adjuvant therapy options should be fully discussed with the patient, taking into consideration tumor risk of recurrence, expected benefit from chemotherapy and risk of complications.
- The risk of relapse after a colon cancer resection should be assessed by integrating the TNM staging, MMR/MSI status and number of lymph nodes sampled (12) [III, A].
- Other additional clinicopathological features such as the histological subtype and grading, lymphatic or venous or perineural invasion, lymphoid inflammatory response, involvement of resection margins and serum CEA should be taken into consideration for refining the risk assessment on stage II tumors [III, A].

- Patient age alone has no predictive value for or against the indication to an adjuvant treatment and must be considered in the context of (potential) benefit, underlying risk for relapse, life expectancy in relation to (biological) age and comorbidities. However, it can be generalized that benefits of treatment with both, fluoropyrimidines alone and plus/minus oxaliplatin, seem to be more limited with a higher likelihood for toxicity in older patients. MSI/MMR status is the only validated molecular marker used in adjuvant decision making and should be determined in stage II CRC. In stage III, usage of MMR status is limited to detect and identify Lynch syndrome [IV, A].
- DPD genotyping or phenotyping is strongly recommended before initiating fluoropyrimidine-based adjuvant therapy according to regulatory bodies [III, A].
- Gene expression signatures are not recommended for routine practice due to lack of predictive value for chemotherapy benefit; however, clinicians and patients may consider their use to complement clinicopathological information in intermediate-risk stage II scenarios although their role in predicting chemotherapy benefit is uncertain [II, C].
- Immunoscore could be considered to refine the prognosis of early colon cancer patients used in conjunction with the TNM scoring and thus adjust the chemotherapy decision-making process in stage II and even in low-risk stage III patients [III, C], although its role in predicting chemotherapy benefit is uncertain.

National Comprehensive Cancer Network (NCCN)
Colon Cancer, Version 2.2022

Principles of Risk Assessment for Stage II Disease

- Patient/physician discussion regarding the potential risks of therapy compared to potential benefits, including prognosis. This should include discussion of evidence supporting treatment, assumptions of benefit from indirect evidence, morbidity associated with treatment, high-risk characteristics, and patient preferences.
- When determining if adjuvant therapy should be administered, the following should be taken into consideration:
    - Number of lymph nodes analyzed after surgery (<12)
    - Poor prognostic features (e.g., poorly differentiated histology [exclusive of those that are MSI-H]; lymphatic/vascular invasion; bowel obstruction; PNI; localized perforation; close, indeterminate, or positive margins)
    - Assessment of other comorbidities and anticipated life expectancy
- The benefit of adjuvant chemotherapy does not improve survival by more than 5%
- MSI or MMR testing

Decision making regarding the use of adjuvant therapy for patients with stage II disease should incorporate patient/physician discussions individualized for the patient and should include explanations of the specific characteristics of the disease and its prognosis and the evidence related to the efficacy and possible toxicities associated with treatment

centering on patient choice. Observation and participation in a clinical trial are options that should be considered. Patients with average risk stage II colon cancer have a very good prognosis, so the possible benefit of adjuvant therapy is small. Patients with high-risk features on the other hand traditionally have been considered more likely to benefit from adjuvant chemotherapy. However, the current definition of high-risk stage II colon cancer is clearly inadequate because many patients with high-risk features do not have a recurrence while some patients deemed to be average risk do. Furthermore, no data point to features that are predictive of benefit from adjuvant chemotherapy, and no data correlate risk features and selection of chemotherapy in patients with high-risk stage II disease.

Overall, the NCCN Panel supports the conclusion of a 2004 ASCO Panel and believes that it is reasonable to accept the relative benefit of adjuvant therapy in stage III disease as indirect evidence of benefit for stage II disease, especially for those with high-risk features. Additional information that may influence adjuvant therapy decision for stage II and/or stage III disease (MSI, multigene assays, and the influence of patient age is discussed below. Research into additional possible predictive markers may allow for more informed decision-making in the future.

Multigene Assays, Immunoscore, and Circulating Tumor DNA (ctDNA)
Several assays have been developed in hopes of providing prognostic and predictive information to aid in decisions regarding adjuvant therapy in patients with stage II or III colon cancer.

- Oncotype DX colon cancer assay quantifies the expression of 7 recurrence risk genes and 5 reference genes as prognostic classifier of low, intermediate, or high likelihood of recurrence.
- ColoPrint quantifies the expression of 18 genes as a prognostic classifier of low versus high recurrence risk. This assay is being further validated for its ability to predict 3-year relapse rates in patients with stage II colon cancer in a prospective trial (NCT00903565).
- ColDx is a microarray based multigene assay that uses 634 probes to identify patients with stage II colon cancer at high risk of recurrence. Similar to the other assays described here, the recurrence risk determined by ColDx is independent of other risk factors.
- Immunoscore, a scoring system reported as percentiles of CD3+ and CD8+ immune cell densities in prespecified regions of the tumor sample by dedicated software, for patients with stage III colon cancer.

In summary, the 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. ESMO has released similar recommendations regarding these assays, stating 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.

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

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

- **ColoPrint 18 – Gene Colon Cancer Recurrence Risk Assay (Agendia)** – ColoPrint is a microarray-based 18 gene expression signature for predicting the risk of distant recurrence for stage II colon cancer who have undergone surgery.
- **GeneFx Colon (Helomics Therapeutics; also known as ColDx, Almac Diagnostics)** – Is a proprietary gene signature test (634 probe set signature) utilizing an individual patient's RNA expression and a complex proprietary algorithm. GeneFx Colon is performed on a small amount of tumor tissue that categorizes patients as being at either high or low risk of having a tumor recurrence within 5 years of surgery. GeneFx Colon provides a clear result for risk recurrence that can help guide physicians regarding the use of adjuvant therapy in patients with colon cancer.
- **OncoDefender-CRC (Everist Genomics)** – Is a prognostic gene-based laboratory assay (5 gene test) intended to help guide treatment decisions following tumor resection in patients with pathologically confirmed stage I or II colorectal cancer diagnosis. The OncoDefender-CRC assay evaluates the expression levels of a specific panel of genes from colorectal cancer tissue samples with a proprietary computation rule. The OncoDefender – CRC results report includes an indication of risk for cancer recurrence within 3 years of surgery (resection).
- **Oncotype DX Colon Recurrence Score (Genomic Health)** – Oncotype DX Colon Cancer Assay uses an algorithm to generate a recurrence score result that is based on 12 genes: seven genes associated with recurrence and 5 genes used to normalize gene expression. This uses a technique called reverse transcriptase-polymerase chain reaction (RT-PCR) to determine the expression of a panel of 12 genes in the tumor tissue. The recurrence score result is calculated from the gene expression results, and ranges from 0-100. This GEP assay is utilized in stage II patients with adenocarcinoma or mucinous carcinoma limited to the colon. It is unknown whether the findings apply to other patients outside this criteria.

Immunoscore biomarker (immunohistochemical staining of colon cancer tissue) that measures the response of a patient's immune system to a tumor. Immunoscore allows the

quantification of two T-cell subsets (CD3 and CD8) in two tumor regions (core and invasive margin tumors and measures how well the body's immune system, including lymphocytes, surround and enter a tumor. When used with TNM scoring which is the method clinicians use to assign staging to a disease and appears to be a promising way to predict an individual's risk of recurrence, which may help develop a personalized treatment plan.

PRIOR APPROVAL

Not applicable.

POLICY

Gene expression profile (GEP) testing using tumor tissue, including but not limited to the following, for the management of colon cancer is considered **investigational** for all indications, including but not limited to its use in estimating risk of disease recurrence or determining adjuvant therapy in individuals with stage II or III colon cancer following surgery, because the evidence is insufficient to determine the effects of the technology on net health outcomes:

- OncotypeDX colon cancer assay
- OncoDefender – CRC assay
- GeneFx colon (also known as ColDx)
- ColoPrint

The use of Immunoscore biomarker testing using tumor tissue for the management of colon cancer is considered **investigational** for all indications, including but not limited to its use in estimating risk of disease recurrence or determining adjuvant therapy in individuals with stage II or III colon cancer following surgery, because the evidence is insufficient to determine the effects of the technology on net health outcomes:

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 81525 Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 21 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin embedded tissue, algorithm reported as a recurrence score (OncotypeDX colon cancer assay)
- 84999 Unlisted chemistry procedure (may be used for OncoDefender CRC assay; GeneFx colon (also known as ColDx); ColoPrint)

- 88299 Unlisted cytogenetic study (may be used for OncoDefender CRC assay; GeneFx colon (also known as ColDx); ColoPrint)
- 81599 Unlisted multi-analyt assay with algorithmic analysis (may be used for OncoDefender CRC assay; GeneFx colon (also known as ColDx); ColoPrint)
- 81479 Unlisted molecular pathology procedure (may be used for OncoDefender CRC assay; GeneFx colon (also known as ColDx); ColoPrint)
- 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.

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POLICY HISTORY

Date	Reason	Action
March 2022	Annual Review	Policy Revised
March 2021	Annul Review	Policy Revised
March 2020	Annual Review	Policy Renewed
March 2019	Annual Review	Policy Revised
March 2018	Annual Review	Policy Revised
March 2017	Annual Review	Policy Revised
March 2016	Annual Review	Policy Revised
April 2015	Annual Review	Policy Revised
October 2014	Interim Review	Policy Revised
May 2014	Annual Review	Policy Revised
July 2013	Annual Review	Policy Renewed
August 2012	Annual Review	Policy Revised
August 2011	Annual Review	Policy Renewed

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

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