Prospective Multicenter Study of the Impact of Oncotype DX Colon Cancer Assay Results on Treatment Recommendations in Stage II Colon Cancer Patients

GEETIKA SRIVASTAVA,^a LINDSAY A. RENFRO,^a ROBERT J. BEHRENS,^b MARGARITA LOPATIN,^c CALVIN CHAO,^c GAMINI S. SOORI,^d SHAKER R. DAKHIL,^e REX B. MOWAT,^f J. PHILIP KUEBLER,^g GEORGE KIM,^h MIROSLAW MAZURCZAK,ⁱ MARK LEE,^c STEVEN R. ALBERTS^a

^aMayo Clinic, Rochester, Minnesota, USA; ^bMedical Oncology and Hematology Associates, Des Moines, Iowa, USA; ^cGenomic Health, Inc., Redwood City, California, USA; ^dAlegent Bergan Mercy Cancer Center, Omaha, Nebraska, USA; ^eCancer Center of Kansas, Wichita, Kansas, USA; ^fToledo Clinic, Toledo, Ohio, USA; ^gColumbus Oncology Associates, Columbus, Ohio, USA; ^hMayo Clinic, Jacksonville, Florida, USA; ⁱSanford Hospital, Sioux Falls, South Dakota, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Colon cancer • Chemotherapy • Adjuvant • Risk assessment • Decision analysis

ABSTRACT

Purpose. The Oncotype DX colon cancer assay is a clinically validated predictor of recurrence risk in stage II colon cancer patients. This prospective study evaluated the impact of recurrence score (RS) results on physician recommendations regarding adjuvant chemotherapy in T3, mismatch repair-proficient (MMR-P) stage II colon cancer patients.

Patients and Methods. Stage IIA colon cancer patients were enrolled in 17 centers. Patient tumor specimens were assessed by the RS test (quantitative reverse transcription-polymerase chain reaction) and mismatch repair (immunohistochemistry). 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 RS and mismatch repair results were provided.

Results. Of 221 enrolled patients, 141 patients had T3 MMR-P tumors and were eligible for the primary analysis.

Treatment recommendations changed for 63 (45%; 95% confidence interval: 36%–53%) of these 141 T3 MMR-P patients, with intensity decreasing for 47 (33%) and increasing for 16 (11%). Recommendations for chemotherapy decreased from 73 patients (52%) to 42 (30%), following review of RS results by physician and patient. Increased treatment intensity was more often observed at higher RS values, and decreased intensity was observed at lower values ($p = .011$).

Conclusion. Compared with traditional clinicopathological assessment, incorporation of the RS result into clinical decision making was associated with treatment recommendation changes for 45% of T3 MMR-P stage II colon cancer patients in this prospective multicenter study. Use of the RS assay may lead to overall reduction in adjuvant chemotherapy use in this subgroup of stage II colon cancer patients. *The Oncologist* 2014;19:492–497

Implications for Practice: The use of adjuvant therapy for resected stage II colon cancer remains of uncertain benefit. Patients with high-risk features appear to gain benefit, whereas patients with a deficiency in mismatch repair enzymes have a low risk of recurrence and should not receive adjuvant chemotherapy. For all other stage II patients, defining recurrence risk has been challenging. Using the Oncotype DX colon cancer assay with a recurrence score in this patient group, we observed a change in the initial treatment recommendation in 45% of patients, indicating that the assay can provide meaningful information with regard to adjuvant therapy decisions.

INTRODUCTION

For patients with resected colon cancer, individualized approaches to adjuvant therapy decision making offer the promise of an improved, patient-specific balance between toxicity and treatment benefit. With the advent of new tools for risk assessment to individualize these decisions, an important consideration will be the level and the quality of evidence supporting not only the clinical validity of the tools

but also whether these tools affect treatment decisions in practice in a clinically meaningful way.

Although adjuvant therapy for patients with resected stage III colon cancer is routinely recommended, decision making regarding adjuvant treatment in stage II patients has remained a challenge. Overall, 75%–80% of patients with stage II colon cancers are cured with surgery alone, and

Correspondence: Steven R. Alberts, M.D., Mayo Clinic, Division of Medical Oncology, G0-10, 200 First Street SW, Rochester, Minnesota 55905, USA. Telephone: 507-284-8432; E-Mail: alberts.steven@mayo.edu Received October 16, 2013; accepted for publication January 6, 2014; first published online in *The Oncologist Express* on April 7, 2014. ©AlphaMed Press 1083-7159/2014/\$20.00/0 <http://dx.doi.org/10.1634/theoncologist.2013-0401>

adjuvant 5-fluorouracil (5-FU) chemotherapy has been shown to provide a relatively small absolute benefit (3%–4% absolute risk reduction for overall survival in the QUASAR trial and in meta-analysis of multiple trials) [1–4]. The use of oxaliplatin, together with 5-FU and leucovorin, has been advocated for high-risk stage II patients but remains of uncertain benefit in stage II patients lacking high-risk features [1]. The National Comprehensive Cancer Network recommends consideration of either observation or a fluoropyrimidine but not oxaliplatin for low-risk patients [5]. As such, it is critical to balance the side effects of chemotherapy with the expected benefit of treatment for these patients. The challenge has been in reliably identifying stage II patients, who lack traditional pathological high-risk features but who may still have an increased risk of recurrence and for whom adjuvant therapy should be considered, and low-risk patients, who can more appropriately be observed.

Until recently, the risk of recurrence for stage II colon cancer patients following curative surgery was largely determined by traditional clinicopathological factors, including bowel obstruction or perforation, number of lymph nodes assessed, T stage, lymphovascular invasion, perineural invasion, and tumor grade [5, 6]. With the exception of T stage and nodal assessment, these markers have been significantly limited by lack of standardization, variable reproducibility, and inconsistent results in the literature [7, 8]. These limitations have prompted the development of biomarkers to better discriminate recurrence risk for stage II patients and thus to enable more informed treatment decisions. Two markers that have been well validated in prospectively designed studies are mismatch repair (MMR) status of the tumor tissue, in which MMR deficiency has been associated with lower recurrence risk [9], and the 12-gene recurrence score (RS; Oncotype DX colon cancer assay; Genomic Health, Inc., Redwood City, CA, <http://www.oncotypedx.com>). The Oncotype DX assay determines recurrence risk using a gene expression profile derived from 1,851 patients with stage II and III colon cancers enrolled in three National Surgical Adjuvant Breast and Bowel Project (NSABP) studies and an observational cohort from the Cleveland Clinic [10]. In these studies, 761 candidate genes identified from the colon cancer literature were evaluated to produce a final set of 12 genes (7 recurrence genes and 5 reference genes) and an algorithm that yields an RS result scaled from 0 to 100.

In the prospectively designed QUASAR validation study [4], the RS was found to be significantly associated with risk of recurrence (hazard ratio per interquartile range: 1.38; 95% confidence interval [CI]: 1.11–1.74; $p = .004$) in stage II colon cancer patients treated with surgery alone. The prespecified low-risk group (RS values <30) had a 12% risk of recurrence, and the high-risk group (RS values ≥ 41) had a 22% risk of recurrence. The RS result remained a significant predictor of recurrence-free interval (RFI) in multivariable analyses controlling for T stage, MMR, number of nodes examined, lymphovascular invasion, and grade. In addition to the RS result, T stage and MMR were also found to be strong predictors of recurrence (both $p < .001$). Evaluation of patients randomized in QUASAR to observation versus adjuvant 5-FU revealed that proportional benefit of 5-FU was similar across the range of RS results such that patients with high-RS disease

derived larger absolute treatment benefits than those with low-RS disease. The greatest value of the RS result resides in the ~70% of patients for whom T stage and MMR status are not informative, that is, in patients with T3 stage and MMR-proficient (MMR-P) tumors. These results have now been confirmed in two independent, prospectively designed studies, including a study of stage II colon cancer patients from the Cancer and Leukemia Group B (CALGB) 9581 trial and a study of patients with stage II and III colon cancer from the NSABP C-07 trial [11].

To further the understanding of how physicians and patients use individualized, quantitative recurrence-risk information in clinical practice, we conducted a prospective multicenter study to evaluate how the clinically validated recurrence score assay affects adjuvant treatment decision making for patients with T3 MMR-P stage II colon cancer.

METHODS

Patients

Consecutive patients with resected stage II colon cancer were identified at the participating institutions for participation in this study. Based on annual estimates, sites seeing at least 60 new colon cancer cases (inclusive of all stages but exclusive of rectal cancers) or roughly 20 stage II cases per year were eligible to participate. Patients eligible to participate were required to have completely resected stage II colon cancer with T3 tumors. Other inclusion criteria included age ≥ 18 years, the ability to give consent and answer written questions in English, and candidacy for treatment with adjuvant chemotherapy. Major exclusion criteria included rectal tumors, T4 stage, perforations or obstructions, synchronous tumors, or contraindications for adjuvant chemotherapy according to a physician's judgment.

A signed, written informed consent was obtained from all patients prior to their participation. This study was approved by the Mayo Clinic institutional review board and by the institutional review boards of the participating institutions within the Mayo Clinic Cancer Research Consortium. Unrestricted funding was provided by Genomic Health, Inc.

Physician and Patient Assessments

For consented patients, information was collected on patient demographics, performance status, comorbidities, and other clinical and pathological tumor characteristics. At the time of patient registration, the medical oncologist independently completed a baseline pre-Oncotype DX questionnaire, recording the planned treatments as observation, fluoropyrimidine monotherapy (5-FU [infusional or bolus] or capecitabine), or combination chemotherapy with oxaliplatin. Treatment recommendations were captured in the context of MMR status, if known, or with hypothetical MMR results. The patient's tumor specimen was then submitted for testing at Genomic Health with the commercially available MMR immunohistochemistry assay and the Oncotype DX colon cancer assay. After results of the Oncotype DX colon cancer assay became known and were thoroughly discussed with the patient, the medical oncologist completed a post-Oncotype DX questionnaire (supplemental online Appendix).

Statistical Methods

The primary objective was assessment of the impact of the Oncotype DX colon cancer assay (the RS result) on treatment recommendations by medical oncologists regarding adjuvant chemotherapy for T3 MMR-P stage II colon cancer patients. Changes in treatment recommendation included changes from chemotherapy to observation, changes from observation to chemotherapy, or changes in the chemotherapy regimen to exclude or include oxaliplatin. Changes in intensity of treatment recommendations from baseline to follow-up were defined as follows: changes from observation to any chemotherapy or from fluoropyrimidine monotherapy to combination chemotherapy with oxaliplatin constituted increased treatment intensity, whereas changes from combination chemotherapy with oxaliplatin to fluoropyrimidine monotherapy or from any chemotherapy to observation constituted decreased treatment intensity. Further exploratory analyses were performed to evaluate other clinical and pathological factors potentially related to changes in treatment plan.

A target sample size of 170 patients with T3 MMR-P tumors was based on the desire for a 95% two-sided confidence interval of 12% for an anticipated overall treatment decision change rate of 20%. Because patients with MMR-P and MMR-deficient (MMR-D) tumors were eligible for the study and approximately 15% of subjects were anticipated to be MMR-D, the study targeted accrual of approximately 220 patients.

The primary analysis was conducted in patients with resected T3 MMR-P stage II colon cancer; secondary analyses included both MMR-P and MMR-D patients. For the primary endpoint, the proportion of T3 MMR-P patients for whom the physicians' treatment recommendation changed from baseline to follow-up was calculated along with the 95% confidence interval. The distribution of treatment recommendations at baseline and follow-up were separately examined for MMR-P and MMR-D patients. Changes in treatment recommendations were evaluated according to Oncotype DX recurrence score risk groups (as previously defined in QUASAR) [4] in MMR-P and MMR-D patients separately. Ordinal logistic regression was used in overall (MMR-P and MMR-D) and MMR-P-only populations to model association between the continuous RS and change in recommended treatment intensity, defined as "decreased intensity," "increased intensity," or "no change." The appropriateness of the proportional odds assumption was confirmed. Potential nonlinearity of the effect of RS on the log-odds of treatment-recommendation change was examined via restricted cubic splines but was not detected. In additional secondary analyses for each population, prior knowledge of MMR status at baseline and MMR status (in the overall population only) were further examined for association with change in treatment recommendation using chi-square tests. An ordinal logistic regression model including RS and adjustment for knowledge of MMR at baseline was fitted for the primary evaluable (MMR-P) population. All analyses were carried out using SAS version 9.2 (SAS Institute, Inc., Cary, NC, <http://www.sas.com>).

RESULTS

From May 21, 2010, through May 15, 2012, 221 patients were enrolled at 17 participating centers, with 2 patients deemed

ineligible per protocol. Thirty-two patients were not evaluable, mostly because of incomplete data or loss to follow-up. The final evaluable population included 141 patients with T3 MMR-P tumors (the primary analysis population) and 46 patients with T3 MMR-D tumors.

In the overall protocol-eligible population, patients had a median age of 66 years, were predominantly white, and had an Eastern Cooperative Oncology Group performance status of 0. Distribution of tumor characteristics (e.g., tumor grade, lymphovascular invasion) were generally as expected, including a high number of examined nodes (median: 18) reflecting contemporary standards for staging. More than 90% of patients had 12 or more lymph nodes assessed. A somewhat higher proportion of MMR-D tumors (46 of 187, 25%) was observed in this study compared with other large trials (14% in QUASAR, 21% in CALGB 9581) [4, 12]. Patient and tumor characteristics of all protocol-eligible patients ($n = 219$) and the subset of MMR-P patients evaluable for the primary endpoint ($n = 141$) were similar (Table 1).

In the primary analysis, treatment recommendations changed for 45% (95% CI: 36%–53%) of T3 MMR-P patients. At baseline, 48% of T3 MMR-P patients were recommended to receive observation, 24% to receive fluoropyrimidine monotherapy, and 28% to receive combination chemotherapy with oxaliplatin. At postassay follow-up, most changes in treatment recommendation led to decreases in intensity of therapy (i.e., changes to observation or to remove oxaliplatin from the adjuvant therapy) (Table 2). Recurrence score values ranged from 2 to 57, with a median of 25. Most RS values (71%) were in the low-risk group, as defined in the QUASAR validation study (i.e., <30). The rate of change was fairly consistent across RS groups (46.0%, 39.4%, and 42.8% for low-, intermediate-, and high-RS groups, respectively) (Table 3). Among patients with changed treatment recommendations, as expected, the highest rate of recommendations for decreased treatment intensity (39.0%) occurred in the low-RS group. For the seven patients in the high-RS group, three patients (42.8%) had changes in treatment recommendation, all to increased treatment intensity. Among evaluable MMR-D patients (not shown), most treatment recommendations at both baseline and follow-up were for observation, with only three changes in each direction (increasing and decreasing intensity).

In ordinal logistic regression, the RS result was significantly associated with changes in treatment recommendation in both the overall evaluable (MMR-P and MMR-D) population ($p = .001$) and the primary MMR-P population ($p = .011$). Lower RS values were associated with changes in the direction of lower intensity, and higher RS values were associated with changes to increased treatment intensity (Table 4). MMR status was significantly associated with change in recommendation ($p < .001$), with physicians of MMR-P patients significantly more likely to change treatment recommendations than those of MMR-D patients (45% vs. 15% change in recommendations for MMR-P vs. MMR-D patients, respectively) (Table 5). Knowledge of MMR status at baseline was not significantly associated with a change in recommendation in this population ($p = .109$). In the primary evaluable population (MMR-P), however, knowledge of MMR at baseline was moderately associated with treatment recommendation change ($p = .040$), with change more likely to occur among

Table 1. Patient and tumor characteristics

Characteristic	Protocol eligible (n = 219)	Evaluable for primary endpoint (n = 141)
Age		
Mean (range)	64.7 (27–87)	63.2 (27–87)
Gender, n (%)		
Female	108 (49.3)	58 (41.1)
Male	111 (50.7)	83 (58.9)
Race, n (%)		
White	206 (94.1)	130 (92.2)
Black	8 (3.7)	6 (4.3)
Other, unknown	5 (2.2)	5 (3.5)
Performance status, n (%)		
ECOG 0	145 (66.2)	92 (65.2)
ECOG 1	74 (33.8)	49 (34.8)
Tumor size		
Mean (range)	5.1 (1.0–25.0)	4.9 (1.0–25.0)
WHO tumor grade, n (%)		
High grade	32 (14.6)	16 (11.3)
Low grade	187 (85.4)	125 (88.7)
Tumor type, n (%)		
Adenocarcinoma NOS	200 (91.3)	132 (93.6)
Mucinous carcinoma	12 (5.5)	5 (3.5)
Other	7 (3.2)	4 (2.8)
Lymphatic invasion, n (%)		
Absent	201 (91.8)	133 (94.3)
Present	18 (8.2)	8 (5.7)
Vascular invasion, n (%)		
Absent	204 (93.2)	132 (93.6)
Present	15 (6.8)	9 (6.4)
Tumor location, n (%)		
L-sided	67 (30.6)	52 (36.9)
R-sided	132 (60.3)	74 (52.5)
Transverse colon	20 (9.1)	15 (10.6)
Number of lymph nodes examined		
Mean (range)	21.9 (3–134)	22.3 (3–134)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified; WHO, World Health Organization.

patients with unknown MMR status at baseline. Of note, in a multivariable ordinal regression analysis, RS remained a significant predictor of change in treatment intensity ($p = .010$) after adjusting for knowledge of MMR at baseline.

DISCUSSION

The use of molecular markers of risk recurrence is becoming increasingly important in oncology to guide the use of expensive and often toxic therapies. For resected stage II colon cancer, traditional pathological or clinical findings (i.e., bowel obstruction or perforation, inadequate number of lymph nodes assessed, T4 stage, lymphovascular invasion, perineural invasion, high tumor grade) have been used to

define a group of patients felt to be at high risk of recurrence and therefore more likely to benefit from chemotherapy. For the remaining group of patients with resected stage II colon cancer, no method of risk stratification existed until the recent introduction of molecular-based risk-scoring systems. In this prospective multicenter study, information provided by the recurrence score assay resulted in treatment recommendation changes for 45% of patients with T3 MMR-P (not high risk) stage II colon cancer. Changes in treatment recommendations were associated with RS results in the expected direction. The majority of changes in treatment recommendations led to decreases in the intensity of therapy. Given these findings, this study demonstrates the real-world clinical utility of the Oncotype DX colon cancer assay in standard-risk stage II colon cancer patients with T3 MMR-P tumors, a clinical setting in which conventional clinical and pathological measures are not informative.

The high rate of treatment decision change observed in this study is, in part, likely to be a reflection of limited physician confidence in the conventional paradigm of qualitative risk assessment, based on conventional clinicopathological factors such as T stage, number of nodes examined, tumor grade, lymphovascular invasion, and bowel perforation or obstruction. Although T4 stage and MMR deficiency are now well established as predictors of recurrence risk in stage II colon cancer [9], relatively few stage II patients have either T4 or MMR-D tumors, and for the majority of patients who have T3 MMR-P tumors, clinicopathological factors have only limited utility in discriminating recurrence risk [6, 13]. The recurrence score assay has now been shown to provide more accurate, quantitative recurrence-risk information for these patients, and strong clinical validation data across three large, independent, prospectively designed studies (QUASAR, CALGB 9581, and NSABP C-07) [1, 11, 12] have demonstrated the ability of this standardized, quantitative assay to predict recurrence risk in stage II colon cancer beyond conventional clinicopathological factors. The availability of quantitative recurrence-risk information provided by the recurrence score assay, as contrasted with qualitative risk assessment with conventional factors, is likely to have been an important driver of changes in treatment recommendations in this study. Similar findings have been reported in multiple studies of node-negative, hormone receptor-positive breast cancer patients provided with quantitative recurrence-risk information with the Oncotype DX breast cancer assay, after which treatment decisions were changed in more than one third of cases [14, 15].

Some limitations of this study should be acknowledged. Compared with the validation studies, a higher proportion of patients were observed in the low-risk RS group (71%) and a lower percentage of patients were observed in the high-RS group (5%), potentially reflecting some degree of patient selection by the enrolling physicians and/or differences in patient populations observed in contemporary clinical practice compared with clinical trials. In addition, the study enrolled a larger proportion of patients with MMR-D tumors (~25%) than the expected rate of 15% [9]. Consequently, the primary analysis population was limited to 141 T3 MMR-P patients, below the anticipated sample size of 170 patients. This is the first large, prospective, multicenter study to evaluate the impact of a gene expression-based recurrence-risk assessment

Table 2. Pre- and postassay treatment recommendations, mismatch repair-proficiency patients

Preassay	Postassay			Total, n (%)
	Observation, n (%)	5-FU monotherapy, n (%)	5-FU + oxaliplatin, n (%)	
Observation	54 (38.3)	8 (5.7)	6 (4.3)	68 (48.2)
5-FU monotherapy	24 (17.0)	8 (5.7)	2 (1.4)	34 (24.1)
5-FU + oxaliplatin	21 (14.9)	2 (1.4)	16 (11.3)	39 (27.7)
Total	99 (70.2)	18 (12.7)	24 (17.0)	141 (100)

Abbreviations: 5-FU, 5-fluorouracil; RS, recurrence score.

Table 3. Treatment recommendation change by RS groups, mismatch repair-proficiency patients

Treatment change intensity	Low RS group, n (%)	Intermediate RS group, n (%)	High RS group, n (%)	Total, n (%)
Total	100 (71.4)	33 (23.6)	7 (5.0)	140 (100.0)
Change	46 (46.0)	13 (39.4)	3 (42.8)	62 (44.3)
Decreased intensity	39 (39.0)	7 (21.2)	0 (0.0)	46 (32.9)
Increased intensity	7 (7.0)	6 (18.2)	3 (42.8)	16 (11.4)
No change	54 (54.0)	20 (60.1)	4 (57.1)	78 (55.7)
Increased intensity				
From observation	6 (85.7)	5 (83.3)	3 (100.0)	14 (87.5)
From 5-FU monotherapy	1 (14.3)	1 (16.7)	0 (0.0)	2 (12.5)
Total	7 (43.8)	6 (37.5)	3 (18.8)	16 (100.0)
Decreased intensity				
From 5-FU + oxaliplatin	21 (53.8)	1 (14.3)	0 (0.0)	22 (47.8)
From 5-FU monotherapy	18 (46.2)	6 (85.7)	0 (0.0)	24 (52.2)
Total	39 (84.8)	7 (15.2)	0 (0.0)	46 (100.0)

RS groups: low, <30; intermediate, 30–40; high ≥41.

For one patient, the RS value was recorded inconsistently on a follow-up questionnaire and a laboratory report, and this patient was excluded from the analysis by RS range.

Abbreviations: 5-FU, 5-fluorouracil; RS, recurrence score.

Table 4. Association of recurrence score with change in treatment recommendation intensity, relevant to the median score (median score 25)

Patient subset	OR	95% CI ^a	p value ^b
Overall evaluable-patient subset			
Recurrence score / 25	0.274	(0.12–0.61)	.001
Primary evaluable-patient subset			
Recurrence score / 25	0.342	(0.15–0.78)	.011

^aProfile-likelihood confidence intervals.

^bLikelihood-ratio test.

The validity of the parallel lines assumption was confirmed.

Abbreviations: CI, confidence interval; OR, odds ratio.

tool on stage II colon cancer adjuvant treatment decision making in real-world clinical practice. An important strength of this study is its prospective design, conducted at 17 centers within an experienced community-based research network of medical oncology practices and led by an academic center (Mayo Clinic) with expertise in colon cancer. More than 90% of patients in the study had at least 12 lymph nodes examined, which is indicative of the quality of surgery and pathology within these centers and the representativeness of the stage II patient population studied. The study was designed to mirror conventional patient workflow and thus was able to document

treatment decision making in real time as medical oncologists advised their patients with and without the results of the recurrence score assay. The high level of association observed in this study between RS results and changes in the intensity of recommended treatment demonstrates the value of the assay for clinical decision making across a wide variety of clinical practice settings.

CONCLUSION

Prospective evaluation of new clinical tools for treatment decision making will be critically important for assessing and validating their value and utility in real-world practice. The findings of this prospective multicenter study demonstrate that the quantitative recurrence-risk information provided by the recurrence score test is meaningful and important to practicing physicians and can guide treatment planning for T3 MMR-P stage II colon cancer patients in clinical practice. Moving forward, it will also be important to evaluate how the RS results affect the decision-making process for patients, including assessment of patient confidence in the treatment decision and the corresponding effects on patient quality of life. In this regard, a health economic analysis, performed as a substudy in this trial and reported separately, demonstrates that treatment decisions based on incorporation of the recurrence score assay, as observed in this study, would be

Table 5. Association of MMR with change in treatment recommendation intensity

Patient subset	Change in intensity, n (%)	No change in intensity, n (%)	p value ^a
Eligible subset			
MMR status			<.001
MMR-P	63 (44.7)	78 (55.3)	
MMR-D	7 (15.2)	39 (84.8)	
MMR knowledge at baseline			.103
Yes	6 (23.1)	20 (76.9)	
No	64 (39.8)	97 (60.2)	
Evaluable for primary subset			
MMR knowledge at baseline			.037
Yes	5 (23.8)	16 (76.2)	
No	58 (48.3)	62 (51.7)	

^aChi-square test.

Abbreviations: MMR, mismatch repair; MMR-D, mismatch repair-deficiency; MMR-P, mismatch repair-proficiency.

expected to result in both significant increases in patient quality-adjusted life-years as well as cost savings for the health care system [16]. Incorporation of the RS into adjuvant treatment planning in stage II colon cancer patients with T3

MMR-P tumors informs clinical decision making for a large proportion of patients, with attendant expected positive impacts on patient care and health care resource utilization.

AUTHOR CONTRIBUTIONS

Conception/Design: Geetika Srivastava, Lindsay A. Renfro, Margarita Lopatin, Calvin Chao, Mark Lee, Steven R. Alberts

Provision of study material or patients: Robert J. Behrens, Gamini S. Soori, Shaker R. Dakhil, Rex B. Mowat, J. Philip Kuebler, George Kim, Miroslaw Mazurczak, Steven R. Alberts

Collection and/or assembly of data: Lindsay A. Renfro, Robert J. Behrens, Shaker R. Dakhil, Rex B. Mowat, J. Philip Kuebler, George Kim, Miroslaw Mazurczak, Steven R. Alberts

Data analysis and interpretation: Geetika Srivastava, Lindsay A. Renfro, Margarita Lopatin, Calvin Chao, Mark Lee, Steven R. Alberts

Manuscript writing: Geetika Srivastava, Robert J. Behrens, Margarita Lopatin, Calvin Chao, J. Philip Kuebler, Mark Lee, Steven R. Alberts

Final approval of manuscript: Geetika Srivastava, Lindsay A. Renfro, Robert J. Behrens, Margarita Lopatin, Calvin Chao, Gamini S. Soori, Shaker R. Dakhil, Rex B. Mowat, J. Philip Kuebler, George Kim, Miroslaw Mazurczak, Mark Lee, Steven R. Alberts

DISCLOSURES

Mark Lee: Genomic Health, Inc. (E, OI); **Calvin Chao:** Genomic Health, Inc. (E, OI); **Margarita Lopatin:** Genomic Health, Inc. (E, OI). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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