

Original article

Effect of the 12-gene colon cancer assay results on adjuvant treatment recommendations in patients with stage II colon cancer

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Abstract**Introduction:**

The 12-gene colon cancer Recurrence Score assay is a clinically validated predictor of recurrence risk in stage II colon cancer patients. A survey was performed characterizing the assay's impact on treatment recommendations for these patients.

Methods:

US medical oncologists ($n = 346$) who ordered the assay for ≥ 3 stage II colon cancer patients were asked to complete a web-based survey regarding their most recent such patient. Physicians surveyed represented users of the assay within the first 2 years of commercial availability which may include 'early adopters'.

Results:

Most of 116 eligible physicians were in community practice (86%), with median 14.5 years' experience (range = 2–40). Mean patient age was 61 years (range = 32–85); 81% had T3 disease, and 38% had comorbidities. Of 76 patients tested for mismatch-repair/microsatellite-instability (MMR/MSI), 13 (17%) were MMR-deficient/MSI-high; 46 (61%) MMR-proficient/MSI-low; and 17 (22%) unknown. Most patients (84%) had ≥ 12 nodes examined. Median Recurrence Score result was 20 (range = 1–77). Before assay, treatment recommendations were specified for 92 (79%) patients, with no recommendation for 24 (21%). Of the 92 with pre-assay recommendations, chemotherapy was planned for 52 (57%) and observation for 40 (43%); the assay changed recommendations for 27 (29%). Treatment intensity decreased for 18 (67%) and increased for nine (33%) patients; it was more likely to decrease for lower Recurrence Score values and increase for higher values ($p < 0.001$).

Conclusion:

For stage II colon cancer patients receiving Recurrence Score testing, 29% of treatment recommendations were changed. Use of the assay may lead to reductions in treatment intensity. Study limitations include retrospective design, data gathering during the first 2 years of assay availability only, and potential non-representativeness of respondents.

Introduction

Each year, more than 103,000 Americans are diagnosed with colon cancer and nearly 50,000 die of colon and rectal cancers combined¹. Early diagnosis often leads to a complete cure, and treatment for patients with stage II or III disease includes surgery that may be followed by adjuvant chemotherapy. The benefit of adjuvant chemotherapy has been convincingly demonstrated in stage III disease, where the standard of care is to offer adjuvant fluoropyrimidine-based chemotherapy².

In contrast, the benefit of adjuvant chemotherapy in stage II colon cancer has been controversial, with mixed results in individual studies and meta-analyses. The National Surgical Adjuvant Breast and Bowel Project (NSABP C-07)³ and the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC)⁴ found mixed OS and DFS benefit with the addition of oxaliplatin to fluorouracil (5-FU)/leucovorin in stage II colon cancer. A retrospective cohort study of the SEER-Medicare database found no survival benefit with adjuvant chemotherapy for older patients with stage II disease^{5,6}. On the other hand, the QUick And Simple And Reliable (QUASAR) trial of 5-FU-based chemotherapy vs observation following surgery demonstrated a 3.6% absolute survival benefit at 5 years for adjuvant chemotherapy in stage II colorectal cancer patients⁷. A subsequent systematic review of 12 randomized controlled trials, including the QUASAR trial, also found improved survival in stage II patients using a variety of post-operative chemotherapy regimens, consistent with analyses of the large Adjuvant Colon Cancer Endpoints (ACCENT) database⁸.

Given the small magnitude of benefit with adjuvant therapy in stage II colon cancer, chemotherapy is often selected for patients based on their physicians' subjective assessment of clinical factors such as patient age, comorbidities, and patient preference, as well as pathologic factors such as tumor grade, lymphovascular invasion, T stage, bowel obstruction, number of lymph nodes examined, perineural invasion, tumor perforation, and margin status². T stage and mismatch repair (MMR) status are recognized as important predictors of risk⁹⁻¹³. In multiple studies, stage II patients with MMR-D (deficient)/microsatellite instability (MSI)-high tumors have been found to have significantly lower recurrence risk and may derive little benefit from fluorouracil-based adjuvant chemotherapy¹¹⁻¹³. However, T4 and MMR-D are observed in only a relatively small proportion of stage II colon cancer patients, and additional information is needed to guide treatment for most patients who have T3 MMR-P (proficient) tumors.

Other pathologic markers such as tumor grade and lymphovascular invasion may not adequately predict recurrence risk for stage II colon cancer patients. The use of tumor grade as a prognostic factor for colorectal cancer is based primarily on historical retrospective observational studies¹⁴⁻²² that often combined different stages of the disease (I-IV). In more-recent studies, high tumor grade has not been found to predict high recurrence risk for stage II colon cancer²³⁻²⁷. The utility of lymphovascular invasion as a prognostic factor is limited because of substantial inter-observer variability among pathologists in assessing its presence or absence²⁸.

The 12-gene colon cancer Oncotype DX[®] Recurrence Score[®] Assay (Genomic Health, Inc., Redwood City, CA) was developed using data from 1851 stage II/III colon cancer patients in four large independent studies conducted with the National Surgical Adjuvant Breast and Bowel Project and the Cleveland Clinic²⁹. The continuous Recurrence Score result was clinically validated as an independent predictor of recurrence risk in stage II colon cancer patients in two prospectively designed studies using 1436 stage II colon cancer patients from the QUASAR clinical trial²⁴ and 690 stage II colon cancer patients from the Cancer and Leukemia Group B 9581 clinical trial^{26,30}. In both validation studies, the Recurrence Score result provided additional discrimination of recurrence risk beyond conventional clinical and pathologic risk factors, including T-stage, MMR status, number of nodes examined, lymphovascular invasion, and tumor grade. In particular, for patients with T3 and MMR-P tumors who would otherwise be considered at standard risk for recurrence, a high Recurrence Score result reveals a more-aggressive underlying tumor biology that is associated with higher risks of recurrence and, therefore, larger expected absolute benefits from 5-FU-based chemotherapy. Accordingly, oncologists may use the Recurrence Score assay to help guide their adjuvant treatment recommendations for these standard risk patients where other existing markers are not informative.

Physicians began using Oncotype DX for stage II colon cancer patients in January 2010. This study is one of the first to evaluate the relationship between Oncotype DX results and adjuvant treatment recommendations for stage II colon cancer patients through a survey of medical oncologists in the US who ordered the assay in their practices.

Methods

Survey development and administration

To develop the survey, we conducted cognitive interviews with four medical oncologists who had ordered Oncotype DX for stage II colon cancer patients. These physicians were from single-specialty and academic medical groups, had been in practice for 3-19 years, and typically treated 25-50 stage II colon cancer patients per year. We interviewed the physicians using a semi-structured format to better delineate factors such as usual diagnostic work-up and treatment decision-making processes, relevant patient characteristics, reasons for ordering the assay, perceived clinical usefulness of the assay, and their interpretation and use of the assay results in treatment decision-making processes. The survey was developed using information from these interviews, reviewed by the investigators and a practicing medical oncologist for clarity and content,

and pilot tested by three medical oncologists. The final survey was implemented on a secure web-based platform (password-protected, 128-bit Secure Sockets Layer encryption, and redundant firewalls) and made accessible to respondents by a secure link. The study protocol was approved by an independent institutional review board.

We used a database maintained by Genomic Health, Inc. to create a list of US medical oncologists who had ordered the *Oncotype DX* assay for three or more stage II colon cancer patients starting in January 2010, when the assay became commercially available. No patient information was included in this list. The list was continually updated as more physicians became eligible by ordering the assay for at least three patients during the study period (December 15, 2010, to December 10, 2011). Identified physicians ($n = 346$) were contacted by two of the authors (T.B. and M.B.) through email or postal mail (if email address was unavailable) and offered \$150 to complete a web-based survey regarding the single most recent stage II colon cancer patient for whom the assay was ordered. Weekly follow-up invitations were emailed or mailed to physicians who did not respond. A pre-specified goal of enrolling at least 100 physicians was set as adequate for analysis in this study.

Respondents were instructed to refer to the chart of the most recent stage II colon cancer patient for whom they ordered the *Oncotype DX* assay when answering specific survey questions about that patient. The 34-item survey recorded the patient's characteristics, pre- and post-assay treatment recommendations, and the oncologist's general practice patterns. In addition, the survey asked about physician practice characteristics such as their practice setting (academic, community, other), number of years in practice, and number of newly diagnosed colon cancer patients they saw in a typical year. With regard to their stage II colon cancer practice, physicians were asked to report on typical diagnostic tests ordered and rates and types of adjuvant chemotherapy treatments typically provided.

Study outcomes

Our primary outcome measure was the proportion of patients for whom the oncologist changed his/her treatment recommendation after receipt of the *Oncotype DX* results. Change in recommendation was defined as a change between any of the following categories: oxaliplatin-containing chemotherapy, non-oxaliplatin-containing chemotherapy, or observation. Changes in treatment recommendations were characterized according to treatment intensity. A decrease in treatment intensity was defined as a change from any chemotherapy to observation or from oxaliplatin-containing chemotherapy to non-oxaliplatin-containing chemotherapy. An increase in treatment intensity was defined as the addition of any

chemotherapy to observation or a change from non-oxaliplatin-containing chemotherapy to oxaliplatin-containing chemotherapy.

Statistical analysis

We included surveys from physicians who confirmed that they were US medical oncologists and had ordered *Oncotype DX* for three or more stage II colon cancer patients. If multiple surveys were completed by the same physician, only the first survey was used in the analysis. The characteristics and practice patterns were described for all physicians who completed the survey. The primary analysis population included physicians who provided a treatment recommendation before ordering the assay.

Data were extracted from the web-based survey application, and statistical analyses were performed using SAS[®] version 9.2 (SAS Institute, Cary, NC). Distributions of survey responses were summarized using descriptive statistics. Pre- and post-assay recommendations and changes in recommended treatment intensity were summarized by Recurrence Score tertiles and by previously defined Recurrence Score groups (<30 , $30-40$, ≥ 41). An ordinal logistic regression analysis was performed to determine if change in treatment intensity (decrease, no change, or increase) was associated with the continuous Recurrence Score. Missing data were not imputed, and counts of missing responses for each variable were reported. The survey was closed after 12 months, shortly after reaching the pre-specified minimum of 100 respondents. All authors of this article had full access to the data.

Results

We invited 346 physicians to participate, and the online survey was accessed 139 times. Four survey responses were ineligible (physicians indicated they were not medical oncologists or had not ordered three or more assays, or the response was provided by a physician who had already completed a survey), and 19 responses were incomplete, leaving 116 completed surveys (34% response rate). Most physicians (86%) came from a community setting, and 12% were from academic settings (Table 1). Physicians had a median of 14.5 years in practice. Half of the oncologists saw more than 40 newly diagnosed colon cancer patients in a typical year, and on average 24% of such patients had stage II disease. The oncologists reported performing MMR/MSI testing for approximately half of the stage II patients and treating on average 36% of stage II patients with adjuvant chemotherapy. Among patients treated with adjuvant chemotherapy, approximately two-thirds (on average) were reported to receive an oxaliplatin-containing regimen.

Table 1. Population characteristics.

Variable	All (n = 116)
Characteristics of 116 medical oncologists who ordered <i>Oncotype</i> DX for ≥ 3 stage II colon cancer patients	
Practice setting	
Academic	14 (12.1%)
Community	100 (86.2%)
Other	2 (1.7%)
No. of years in practice, median (range)	14.5 (2–40)
No. of newly diagnosed colon cancer patients seen in a typical year, median (range)	42.5 (10–250)
Characteristics of 116 patients with stage II colon cancer ^a	
Median age, years (range)	62 (32–85)
Tumor classification (T stage)	No. of responses (%)
T3	94 (81.0)
T4a	22 (19.0)
T4b	0 (0)
No. of lymph nodes examined to establish the N0 stage	
≤ 8	4 (3.4)
9–11	15 (12.9)
12	11 (9.5)
≥ 13	86 (74.1)
MMR tested (n = 76)	
MMR-D/MSI-H	13 (17.1)
MMR-P/MSI-L	46 (60.5)
Unknown	17 (22.4)
Comorbidities ^b	
Any of the following comorbidities	44 (37.9)
Diabetes mellitus	24 (20.7)
Uncontrolled hypertension	5 (4.3)
History of stroke or other cerebrovascular disease	4 (3.4)
Congestive heart failure or other chronic heart disease	4 (3.4)
Pulmonary fibrosis or other chronic lung disease	4 (3.4)
Chronic renal insufficiency	7 (6.0)
Peripheral neuropathy	7 (6.0)
Cytopenias	2 (1.7)
Other comorbidity	10 (8.6)

MMR-D, mismatch repair deficient; MMR-P, mismatch repair proficient; MSI-H, high-degree microsatellite instability; MSI-L, low-degree microsatellite instability; SD, standard deviation.

^aMost-recent patients for whom physician respondents ordered an *Oncotype* DX assay.

^b'Yes' response only.

Respondents ordered the *Oncotype* DX assay for a median of five stage II colon cancer patients (range = 3–30; mean = 6). The primary reasons for ordering the assay were to obtain additional data to help predict patients' recurrence risk (89%), to confirm initial assessment of a patient's recurrence risk (77%), or to assess a patient's expected absolute benefit from chemotherapy (66%), and to provide 'peace of mind' for the physician and/or patient regarding adjuvant treatment decisions (63%).

Table 1 describes the characteristics of the 116 most-recent stage II colon cancer patients for whom the *Oncotype* DX assay was ordered. The median age was 62 years (range = 32–85; mean = 61), and 38% had at least one co-morbidity, with diabetes being the most common (21%). Most patients had T3 disease (81%). At least 12 or more lymph nodes had been examined for 84% of patients. Recurrence Score values ranged from 1–77 (out of a possible range from 0–100), with an average of 23 and standard deviation of 12 (median = 20; interquartile range = 14–28). Most Recurrence Score values (80%)

were in the pre-defined low group (<30), and 10% were in the high group (≥ 41).

Of 116 evaluable physicians, 92 (79%) specified a treatment recommendation before ordering the *Oncotype* DX assay. Information provided by the Recurrence Score assay resulted in changes for 27 (29%) of 92 treatment recommendations (Table 2). Of the 27 treatment recommendations that changed, treatment intensity decreased for 18 (67%) and increased for nine (33%). Overall, 52 (57%) of the 92 pre-assay treatment recommendations included chemotherapy compared with 47 (51%) post-assay recommendations. In a sub-set of patients excluding those with T4 and/or MMR-deficient tumors, 18 (26%) of 68 pre-assay treatment recommendations were changed with most changes (13 (72%) of 18) in the direction of decreased treatment intensity.

In the low Recurrence Score group, 21 (28%) of 74 treatment recommendations changed, with treatment intensity decreased for 17 patients and increased for four patients (Table 3). In the high Recurrence Score group, four (44%) of nine treatment recommendations changed,

Table 2. Pre- vs post-assay treatment recommendations of medical oncologists who were surveyed about their most-recently tested stage II colon cancer patient ($n = 92$)*.

Pre-assay	Post-assay (No.)			Total	Change	
	Observation (no chemotherapy)	Non-oxaliplatin-containing chemotherapy	Oxaliplatin-containing chemotherapy		<i>n</i>	%
Observation (no chemotherapy)	31	4	5	40	9	22.5
Non-oxaliplatin-containing chemotherapy	6	13	0	19	6	31.6
Oxaliplatin-containing chemotherapy	8	4	21	33	12	36.4
Total	45	21	26	92	27	29.3

*Patients whose physicians had 'no recommendation' ($n = 24$) were excluded from the analyses of primary and secondary outcome measures.

Table 3. Change in treatment intensity as a function of Recurrence Score results ($n = 92$)*.

Category	Changed	Decreased	Increased	No change	Total
Recurrence Score Tertile					
Low (<16)	12 (38.7)	10 (32.3)	2 (6.5)	19 (61.3)	31 (100.0)
Mid (16–24)	9 (31.0)	7 (24.1)	2 (6.9)	20 (69.0)	29 (100.0)
High (≥ 25)	6 (18.8)	1 (3.1)	5 (15.6)	26 (81.3)	32 (100.0)
Recurrence Score Group					
Low (<30)	21 (28.4)	17 (23.0)	4 (5.4)	53 (71.6)	74 (100.0)
Intermediate (30–40)	2 (22.2)	1 (11.1)	1 (11.1)	7 (77.8)	9 (100.0)
High (≥ 41)	4 (44.4)	0 (0)	4 (44.4)	5 (55.6)	9 (100.0)
Overall	27 (29.3)	18 (19.6)	9 (9.8)	65 (70.7)	92 (100.0)

Italic values represent totals.

*Patients whose physicians had 'no recommendation' ($n = 24$) were excluded from the analyses of primary and secondary outcome measures.

with treatment intensity increased in all four cases. In the low Recurrence Score group, 41 (55%) of 74 pre-assay recommendations included chemotherapy compared with 32 (43%) post-assay, whereas, in the high Recurrence Score group, five (56%) of nine pre-assay recommendations included chemotherapy compared with nine (100%) post-assay recommendations. Changes in recommended treatment intensity across the range of Recurrence Score values were also examined by Recurrence Score tertiles (Table 3), revealing consistent patterns. Evaluation of the association between changes in treatment intensity and the continuous Recurrence Score demonstrated that decreases in treatment intensity were more likely for lower Recurrence Score values and increases were more likely for higher Recurrence Score values ($p < 0.001$).

Discussion

This online survey assessed the relationship between the 12-gene Recurrence Score assay and treatment recommendations for stage II colon cancer patients who received Recurrence Score testing as part of their treatment planning process. Treatment recommendations were changed

29% of the time, suggesting that assay results impacted physicians' adjuvant treatment decisions for stage II colon cancer patients. Treatment intensity changed in both directions, with two-thirds of recommendations resulting in decreased treatment intensity, one-third in increased treatment intensity, and a net result of reduced treatment intensity overall. As expected, a trend of decreasing treatment intensity with lower Recurrence Score values was observed. These results are consistent with a recent prospective multi-center study of the impact of the Oncotype Dx assay on treatment recommendations in T3 MMR-P patients with stage II colon cancer where most of the changes represented a reduction in treatment intensity³¹.

Our survey included over 100 medical oncologists and their most recent stage II colon cancer patients for whom the assay was ordered. To ensure familiarity with the assay, only physicians who had used the test for three or more patients were included in the study. To minimize recall bias, physicians were instructed when answering survey questions to retrieve patient charts of their most recent stage II colon cancer patient to receive the Oncotype DX assay. Most physicians were from community practices, with more than 15 years of experience on average, and a history of using adjuvant chemotherapy for approximately

one-third of their stage II colon cancer patients. These physician characteristics and practice patterns are representative of contemporary colon cancer medical practices in the US^{32,33}.

Patients described in this survey were representative of contemporary stage II colon cancer patients in the US, with most having T3 tumors and 12 or more lymph nodes examined^{34,35}. One-fifth of patients had T4 tumors, suggesting that some physicians anticipated that the assay may help guide decisions for certain patients with stage II colon cancer and T4 stage; implications for decision-making in this patient population are uncertain, however, because of the relatively small number of T4 patients in this study.

The distribution of the Recurrence Score results among the patients in our study was shifted towards lower values compared with those observed in the QUASAR validation study, with a median score of 20 compared with 32 in QUASAR²⁴. The tendency towards lower Recurrence Score values in the current study may reflect sampling, including an inclination for practicing oncologists to order assays more often for patients lacking high-risk clinical and pathologic features. This observation is consistent with lower scores reported for the *Oncotype DX Breast Cancer Assay* in commercial data-sets compared with clinical studies³⁶. We found that lower Recurrence Score values were associated with overall decreases in treatment intensity, and thus use of the assay could lead to an overall decrease in treatment intensity, either through decreased use of oxaliplatin or more patients opting not to receive adjuvant chemotherapy. It is important to note that the *Oncotype DX Colon Cancer Assay* does not predict the magnitude of relative benefit from adjuvant chemotherapy in stage II colon cancer and, as with the conventionally used clinical and pathologic risk factors, cannot be used to identify patients who derive no benefit from adjuvant therapy. In the absence of predictive markers, prognostic markers (such as T4 stage) are regularly used in clinical practice to guide treatment decisions by estimating absolute benefit as a function of recurrence risk. Accordingly, in managing stage II colon cancer following surgery, the optimal treatment decision requires an accurate understanding of recurrence risk following surgery. With similar relative risk reduction due to chemotherapy across the range of Recurrence Score results (observed in QUASAR), patients with high Recurrence Score results would be expected to derive larger absolute benefit than patients with low Recurrence Score results.

Our results suggest that the *Oncotype DX* assay may allow physicians to better assess and personalize treatment planning by helping to identify patients more or less likely to need chemotherapy. This may correct both over- and under-treatment of stage II colon cancer, by directing life-prolonging benefits of chemotherapy to patients who would be expected to derive the largest absolute benefits

and avoiding unnecessary toxicities among those with smaller expected absolute benefits. Such enhanced patient care would improve not only health but also quality-of-life and economic outcomes.

For example, among patients with lower recurrence risk, less-aggressive treatment may help individuals avoid potentially unnecessary treatments and associated adverse effects, translating into improved quality-of-life, greater productivity, and reduced chemotherapy-related costs. On the other hand, for patients with higher Recurrence Score values, and thus higher recurrence risks, more-aggressive treatment might be appropriate, in light of the larger expected absolute treatment benefits with adjuvant therapy³⁷. Although formal economic analyses are needed to determine the assay's cost effectiveness in this patient population, each course of 5-FU/oxaliplatin combination chemotherapy that can be avoided could potentially save \$50,000^{38,39}. Since two-thirds of the assay-directed treatment changes resulted in reduced treatment intensity, our results suggest that use of the assay may decrease overall chemotherapy utilization for the healthcare system. Results of ongoing prospective decision impact and health economic studies will help further evaluate the assay's benefit in patients' health and quality-of-life as well as in the healthcare system overall.

Our results should be considered in light of the study limitations. This was a retrospective survey that did not permit a real-time assessment of the impact of Recurrence Score results on treatment recommendations. Because the survey focused on patients who had already been selected for Recurrence Score testing, these results should be taken to apply specifically to those patients for whom treatment decision-making was felt to require additional risk discrimination provided by Recurrence Score results. We used a voluntary, web-based survey of medical oncologists in the US who had ordered the assay for an average of six stage II colon cancer patients, and respondents were compensated for completing the survey. One-third of all physicians invited to participate responded to the survey, a response rate at or above those reported in the literature^{40,41}. The community-based nature of these physicians' practices may render it difficult for them to take time away from their patients, regardless of the survey's simplicity and the compensation offered. Despite this, the physician and patient characteristics were similar to those of stage II colon cancer practices in the US.

The survey focused on physicians who used the *Oncotype DX* assay within the first 2 years of commercial availability, and responses from these 'early adopters' may not be representative of all physicians who treat colon cancer. In addition, the pre-assay rate of chemotherapy recommendations in this study (57%), which is substantially higher than that seen in large unselected population studies^{6,42}, is likely reflective of physician selection of patients for Recurrence Score testing; a higher rate

might be anticipated in the sub-population of patients for whom the assay is ordered, as they are presumably already under consideration for treatment. Physicians are unlikely to order the Oncotype DX assay if they consider the patient not to be a candidate for adjuvant chemotherapy due to reasons such as comorbidities, patient preference, or very advanced age. In this regard, the median age of this survey population is ~7 years younger than the reported median age for all colon cancer patients in the US. A recent independent, prospective study of the Oncotype DX assay found a similar proportion (52%) of patients with a pre-assay recommendation for chemotherapy³¹.

The association between assay results and treatment recommendations could not be assessed for the 21% of patients without documented pre-assay recommendations. Although physicians were prompted to complete the survey with these patients' charts open in front of them to decrease recall bias, we also could not confirm that this was done nor attempt to evaluate the accuracy or completeness of the medical record itself. Nevertheless, by sampling nearly 100 practicing oncologists, this survey provides valuable insight into the impact of the Recurrence Score assay in real-world settings where the test has been applied. As such, the survey results are representative of the magnitude and direction of changes in chemotherapy treatment recommendations resulting from use of the assay in oncology practices.

Conclusion

The results of this study suggest that use of the Oncotype DX assay is associated with an overall change of nearly one in three treatment recommendations for stage II colon cancer patients receiving this test. With changes in treatment intensity occurring in both directions, assay use may lead to more-appropriate use of adjuvant treatment and address both over- and under-treatment in stage II colon cancer patients. Studies are ongoing to prospectively investigate the impact of the Oncotype DX assay on clinical decisions and to evaluate its cost-effectiveness in clinical practice.

Transparency

Declaration of funding

The work described in this manuscript was funded by Genomic Health, Inc. The sponsor did not alter or influence the results of the study, which was conducted using clearly delineated analytic methods.

Declaration of financial/other relationships

MLee, ML, and CC are employees of Genomic Health, Inc. TC has no conflict of interest related to the conduct of the research described in this manuscript. TB, MB, and EC are employees of

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