Facilitating Informed Decisions Regarding Microsatellite Instability Testing Among High-Risk Individuals Diagnosed With Colorectal Cancer

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Submitted July 9, 2009; accepted October 13, 2009; published online ahead of print at www.jco.org on February 8, 2010.

Supported by Grant No. CA109332 from the National Cancer Institute and Grant No. P30 CA006927 to Fox Chase Cancer Center.

Trial registration clinicaltrials.gov identifier NCT00450424.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

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0732-183X/10/2808-1366/\$20.00

DOI: 10.1200/JCO.2009.25.0399

ABSTRACT

Purpose

To evaluate the impact of a CD-ROM intervention in the education of patients with suspected Lynch syndrome (LS) about microsatellite instability (MSI) and immunohistochemistry (IHC) testing.

Patients and Methods

Two hundred thirteen patients meeting Bethesda criteria were randomly assigned to receive either a brief educational session with a health educator ($n = 105$) or a brief educational session plus a CD-ROM ($n = 108$). Assessments were administered at baseline and 2 weeks post-treatment. Primary outcomes included MSI and IHC knowledge and level of satisfaction with and completeness of the preparation to make the decision for MSI testing. Secondary outcomes included decisional conflict, difficulty making the decision, cancer-specific and global anxiety, and level of discussion about MSI testing with family and friends.

Results

Participants in the education plus CD-ROM condition reported significant increases in knowledge about the MSI and IHC tests, greater satisfaction with the preparation to make a decision for testing, lower decisional conflict, and greater decisional self-efficacy. The effects of the education plus CD-ROM on most outcomes were not moderated by preintervention levels of exposure to MSI testing, family support for MSI testing, or the family history of cancer.

Conclusion

Incorporation of new media education strategies for individuals at risk for LS may be a valuable component of the informed consent process. As clinical criteria for MSI and IHC testing continue to expand, the need for alternative educational approaches to meet this increased demand could be met by the self-administered computer-based strategy that we described.

J Clin Oncol 28:1366-1372. © 2010 by American Society of Clinical Oncology

INTRODUCTION

The increased sophistication and use of genetic susceptibility testing creates unique challenges. Patients grapple with the purpose and implications of tests that may provide uncertain results. The use of microsatellite instability (MSI) testing in suspected Lynch syndrome (LS) highlights issues in educating patients to make a well-informed decision. LS is the most common cause of hereditary colorectal cancer (CRC)¹ accounting for 3% to 5% of CRCs.² It carries a high lifetime risk of multiple cancers with clinical implications for proband and family.^{3,4} Lacking an easily recognizable phenotype, LS can be difficult to diagnose. Amsterdam and Bethesda criteria are most commonly used. The former requires that families have three or more affected members,

that cancers span two generations, and that at least one patient is younger than 50 years of age.⁵ Patients meeting Amsterdam Criteria often proceed directly to genetic counseling and germline testing.³ The less stringent Bethesda criteria were established to select patients whose tumor should be screened for MSI (Manne et al, unpublished data, 2004) a phenotype present in nearly all LS tumors.⁶ Testing has high sensitivity, but low specificity, because MSI occurs in approximately 15% of sporadic colorectal tumors. Recently, in selected centers, methylation and/or *B-raf* testing has become available to identify this subgroup of patients. However, this more sophisticated testing is not widely available. Therefore, an MSI high (MSI-H) result remains associated with a fair degree of uncertainty. Patients with MSI-positive tumors are referred for further genetic evaluation.

Expert panels recommend informed consent for MSI testing;⁷ however, current clinical practice is inconsistent. Evidence suggests that patients know very little about the MSI test and perceive they are inadequately informed about its purpose and implications.⁸ Helping patients understand why a screening test is being offered, the possible results, and the associated uncertainty can facilitate more well-informed decisions and greater satisfaction with preparation.

Most research on facilitating informed consent for cancer mutation testing has surrounded *BRCA*.^{9,10} Generally, interventions have increased knowledge, enhanced perception of the importance of the risks of testing, decreased perceived advantages of testing, and reduced interest in obtaining a *BRCA* test. However, no studies have evaluated the adequacy of the consent process for genetic susceptibility screening tests. Genetic counselors are the gold standard for education about risks and benefits of mutation testing. The large number of colon cancer diagnoses in the population makes MSI-related genetic counseling impractical. To aid informed decision making about MSI testing, there is a need for an alternative, easy-to-disseminate approach to education.¹¹

To better facilitate a well-informed decision, we developed and tested a CD-based educational aid. A CD-based approach allows patients to view the material without a genetic counselor and if effective, could be easily disseminated into medical and surgical oncology practices. The CD was evaluated as an adjunct to a brief educational session versus the educational session alone in a randomized trial of patients at risk for LS. The primary aim was to evaluate the impact on knowledge about MSI and immunohistochemistry (IHC) tests, satisfaction with the preparation to make a decision about testing, and perceived completeness of the preparation for making the decision to have testing. Satisfaction with and completeness of the preparation were considered key outcomes because they are important components of a well-informed medical decision.¹² Additional aims were to assess the impact on attitudinal, affective, and behavioral outcomes, and evaluate possible moderators of the intervention effects.

PATIENTS AND METHODS

Participants

The 213 study participants met one of the revised Bethesda criteria for LS,⁶ but were excluded if they met the more stringent Amsterdam criteria. Patients meeting Amsterdam criteria were referred directly for genetic counseling.³

Procedure

Participants were enrolled from the medical or surgical clinics of two National Cancer Institute (NCI)-designated comprehensive cancer centers, the Fox Chase Cancer Center (FCCC) and Massachusetts General Hospital, (MGH) and one NCI-designated community cancer center, the Helen F. Graham Cancer Center of the Christiana Care Health System (CCHS). Details about the settings and recruitment methods are in Appendix (online only).

After signing an informed consent, participants completed the baseline survey and were randomly assigned, stratified by enrollment center, to one of the two study conditions, education only (Ed) or education plus CD-ROM (Ed plus CD-ROM). Two weeks later, the follow-up assessment was completed by telephone. Data were collected between June 13, 2005, and December 2, 2008.

Study Arms

Ed. The health educator provided a brief, standardized description of reasons for the test (ie, relevant Bethesda criteria), a description of the MSI and

IHC tests and what they evaluate, possible test results, and what might occur next should the test result prove abnormal. This description required approximately 3 minutes (standard deviation, 0.82 minutes).

Ed + CD-ROM. After the education session, participants viewed the study CD-ROM. Details about the CD development are in Appendix (online only).

The CD has four sections: "Why Test?," "Consent Concerns," "Issues to Consider," and "What Happens Next." The "Why Test" section provided navigation instructions and introduced the major questions and issues related to the MSI test. "Consent Concerns" focused on participant understanding of the MSI testing procedure and the implications of abnormal and normal results. The "Issues to Consider" section discussed issues regarding the decision to have the MSI test. The final section allowed the user to return to any previous sections for review or clarification. Throughout, there were optional "Learn More" screens if participants wanted more information on a certain topic. All sections had graphics and pictures to illustrate content and was professionally narrated. If a testing decision had been made, the participant was instructed to complete the medical consent form and return it.

Treatment fidelity. Twenty percent of the education sessions were audiotaped and rated for fidelity to the key points in the session. Fidelity was excellent, with more than 76% achieving a 100% rating and an average fidelity of 97.7%.

Outcome Variables

There were five primary outcomes which assessed three key constructs: knowledge (two measures): MSI and IHC knowledge; satisfaction with the preparation (two measures)—a face valid measure adapted by the investigators from the satisfaction with the decision-making process questionnaire,¹³ a well-validated measure of satisfaction with the communication with the health care team about the MSI test and information about the test (patient experience questionnaire [PEQ]¹⁴); and completeness of preparation (one measure)—a measure of the perceived completeness of decision preparation for MSI testing.

There were six secondary outcomes. Secondary decisional outcomes included decisional conflict¹⁵ (follow-up only), difficulty making the decision to have MSI/IHC testing (follow-up only), and decisional self-efficacy.¹⁶ Secondary emotional distress outcomes included cancer-specific emotional distress,¹⁷ cancer worry,¹⁸ and global anxiety.¹⁹ The behavioral outcome was the level of discussion with family about MSI testing.

Moderators, Medical Correlates, CD-ROM Usability and Evaluation

Baseline levels of exposure to information about MSI testing, family support for MSI testing, and family history of cancer (the number of first- and

Fig 1. Consort diagram.

second-degree relatives with cancer and total number of relatives who died from CRC) were study moderators.

Date and stage of original CRC diagnosis, Eastern Cooperative Oncology Group (ECOG) status, and metastatic status at study entry were collected from patients' medical records.

Participants enrolled in the CD-ROM condition were asked whether they viewed the CD, asked about the ease of its use, whether they saved the CD, and if they shared the CD, or discussed the CD with their family and friends.

Statistical Approach

Complete data on 92 participants per arm (184 total) would provide 80% power to detect differences of 0.69 for knowledge, 3.99 for satisfaction, and 4.98 for completeness. These sample size estimates were based on two-sided, two-sample *t*-tests ($\alpha = .05$) and standard deviations of 1.65, 9.6, and 12.0 for knowledge, satisfaction, and completeness scales, respectively.

Between group comparisons of baseline sociodemographic and medical data were conducted by χ^2 , Mann-Whitney, or *t*-tests depending on whether

the variable under consideration was nominal (eg, sex), ordinal (eg, education, stage of disease), or continuous (eg, age). Comparisons of intervention effects on the outcomes were done using two-sample *t*-tests and analysis of covariance when baseline values of the outcome were available. Univariate regression analyses were performed to identify covariates significantly associated with individual outcome variables. Finally, multivariable linear regressions were conducted for each outcome variable with the baseline value of the outcome variable (if a baseline value was assessed), factors identified as being significantly imbalanced across arms, factors significantly associated with the outcome and study condition included as covariates. Each outcome variable was modeled separately.

Additional models were evaluated to determine whether prior exposure to MSI testing, family support for MSI testing, and family cancer history moderated the effect of the intervention. In these analyses, the potential moderator and a treatment arm by moderator interaction were added to the final models previously identified for each outcome variable. Each potential moderator was assessed separately for each outcome variable. All tests were two

Table 1. Characteristics of the Study Sample

Characteristic	Full Sample				Education Only				Education + CD			
	No.	%	Mean	SD	No.	%	Mean	SD	No.	%	Mean	SD
No. of patients	213				105				108			
Sex												
Male	118	55.4			55	52.4			63	58.3		
Female	95	44.6			50	47.6			45	41.7		
Age, years			46.3	8.8			44.9	8.6			47.6	8.8
Race/ethnicity												
White	192	90.1			92	87.6			100	92.6		
Nonwhites	21	9.9			13	12.4			8	7.4		
Education												
≤ High school	51	24			22	20.9			29	26.9		
Some college	41	19.2			26	24.8			15	13.9		
4-year degree	71	33.3			36	34.3			35	32.4		
Some graduate education	8	3.8			3	2.9			5	4.6		
Graduate degree	42	19.7			18	17.1			24	22.2		
Mean annual income, \$		60,000-99,999				60,000-99,999				60,000-99,999		
Marital status												
Married	146	68.5			69	65.7			77	71.3		
Single/divorced/widowed	67	31.5			36	34.3			31	28.7		
Insurance status												
Has insurance	204	95.8			98	93.3			106	98.1		
Hospital recruited from												
FCCC	85	39.9			45	42.9			40	37		
MGH	91	42.7			46	43.8			45	41.7		
CCHS	37	17.4			14	13.3			23	21.3		
Year recruited into study												
2005	50	23.5			27	25.7			23	21.3		
2006	60	28.2			28	26.7			32	29.6		
2007	57	26.8			26	24.8			31	28.7		
2008	46	21.6			24	22.9			22	20.4		
Months since diagnosis			23.2	35.2			20.8	32			25.6	38.1
Metastatic disease (yes)	106	49.8			50	47.6			56	51.9		
ECOG performance status												
0	169	79.3			82	78.1			87	80.6		
1	40	18.8			20	19.0			20	18.5		
2	4	1.9			3	2.9			1	0.9		
No. of relatives with cancer			2.0	1.6			1.9	1.7			2.1	1.7
No. of relatives died of cancer			0.94	1.2			0.83	1.1			1.0	1.4
Time between baseline and follow-up			22.9	19.1			21.8	17.5			23.9	20.6

Abbreviations: SD, standard deviation; CCHS, Christiana Care Health System; FCCC, Fox Chase Cancer Center; MGH, Massachusetts General Hospital; ECOG, Eastern Cooperative Oncology Group.

sided with a 5% type I error. Analyses were conducted using SAS version 9 (SAS Institute, Cary, NC) software.

RESULTS

Participants

Two hundred eighty-nine patients were approached, with 213 patients consenting and completing the baseline survey (73.7%). Sixty three refused the study (21.8%), and 13 signed a consent form but did not complete a baseline survey (4.5%; Fig 1). "Too busy" was the most common reason for refusal (11.1%). One hundred eighty-seven participants (87.8%) completed the follow-up assessment. Comparisons between participants and refusers indicated that more participants reported poorer ECOG functional status ratings ($\chi^2(1) = 7.8$; $N = 289$; $\text{ECOG} \geq 1_{\text{participants}} = 8.7\%$, $\text{ECOG} \geq 1_{\text{refusers}} = 1.9\%$; $P < .01$). There were no differences with regard to age, time since diagnosis, or ethnicity.

Descriptive Information and Preintervention Differences

Information regarding the sample is contained in Table 1. Analyses revealed only one significant baseline difference in demographic and medical variables. Participants in the Ed + CD-ROM condition were (marginally) older than participants in the Ed condition ($t = 211$) = 1.97; $P = .05$).

Univariate Analysis Results

Descriptive information on study outcomes and univariate between-arm comparisons are presented in Table 2. The role of socio-demographic and medical covariates (including study site) were evaluated. For primary outcomes, study site was significantly associated with MSI and IHC knowledge ($P < .01$). Both MSI and IHC knowledge were higher at the Christiana Care Health System site than FCCC or MGH. Better ECOG performance status was associated with higher satisfaction with preparation ($P < .01$). ECOG status ($P < .01$) and the

Table 2. Means and SDs for Study Outcomes by Treatment Group

Outcome	Ed		Ed + CD-ROM		<i>P</i>	Baseline Adjusted <i>P</i>	Coefficient α
	Mean	SD	Mean	SD			
Primary	0.16	0.21					
MSI knowledge	0.35	0.27	0.19	0.22			
Baseline			0.64	0.24	.31		.89
Follow-up					< .0001	< .0001	.90
IHC knowledge							
Baseline	0.08	0.13	0.10	0.14	.27		.64
Follow-up	0.19	0.18	0.39	0.20	< .0001	< .0001	.63
Satisfaction with preparation							
Follow-up	2.96	0.93	3.72	0.57	< .0001		.95
PEQ*							
Follow-up	2.53	0.63	2.23	0.39	< .0001		0.85
Completeness of preparation							
Follow-up	2.79	0.61	3.18	0.37	< .0001		.90
Secondary							
Decisional variable							
Conflict†							
Follow-up	1.96	0.66	1.75	0.50	.01		.95
Difficulty†							
Follow-up	2.15	0.56	2.19	0.47	.63		.86
Self-efficacy							
Baseline	1.87	0.83	2.05	0.79	.11		.85
Follow-up	2.43	0.83	3.10	0.76	< .0001	< .0001	.85
Attitudes and behaviors							
Cancer-specific distress							
Baseline	30.84	20.9	28.9	20.6	.50		.93
Follow-up	27.1	21.8	24.7	18.2	.41	0.96	.93
Cancer-related worry							
Baseline	7.23	3.0	6.73	2.7	.19		.83
Follow-up	6.73	2.6	6.12	2.3	.09	0.43	.80
Global anxiety							
Baseline	55.3	12.3	54.8	10.9	.59		.95
Follow-up	53.5	11.9	53.5	11.4	.98	0.78	.95
Discussion with family							
Baseline	1.91	0.72	2.12	0.70	.04		.51
Follow-up	2.36	0.75	2.60	0.78	.03	0.11	.68

Abbreviations: Ed, education; SD, standard deviation; MSI, microsatellite instability; IHC, immunohistochemistry; PEQ, patient experiences questionnaire.

*Higher scores indicate lower satisfaction.

†Higher scores indicate greater conflict or difficulty.

Table 3. Multivariable Regression Results for Primary Study Outcomes

Variable	Parameter Estimate	t Value	P
MSI knowledge			
Baseline value	0.44	4.77	< .0001
Study condition	0.27	7.75	< .0001
IHC knowledge			
Baseline value	0.35	3.33	.001
Study condition	0.19	7.10	< .0001
Age	−0.004	−2.50	.01
PEQ			
Study condition	−0.28	−3.68	.0003
ECOG (≥ 1 v 0)	0.28	2.93	.004
Satisfaction with preparation			
Study condition	0.73	6.40	< .0001
Completeness of preparation			
Ethnicity (white v other)	0.26	2.0	.04
Study condition	0.36	4.84	< .0001

NOTE. The treatment effect and any significant sociodemographic or medical factors are included.

Abbreviations: MSI, microsatellite instability; IHC, immunohistochemistry; ECOG, Eastern Cooperative Oncology Group; PEQ, patient experiences questionnaire.

number of relatives with cancer ($P = .02$) were associated with the PEQ. Better physician-rated functional status and fewer relatives with cancer were associated with higher PEQ satisfaction. Ethnicity ($P < .05$) was associated with completeness of preparation, with white participants reporting a more complete preparation than nonwhites.

For the secondary outcomes, there were no significant correlates for decisional conflict, difficulty making the decision, and decisional self-efficacy. Women ($P < .01$) and married participants ($P < .05$)

reported significantly greater cancer-related emotional distress, and women reported significantly greater cancer-specific worry ($P < .01$). Women ($P = .01$), participants with a greater number of family members with cancer ($P < .05$), participants with a greater number of family members who died of cancer ($P < .01$), and participants reporting a longer time between the baseline and follow-up assessment ($P < .05$) reported greater global anxiety. Female participants ($P = .0006$), participants for whom the time between the baseline and follow-up assessment was longer ($P < .05$), participants from FCCC and CCHS as compared with MGH ($P < .01$), and participants recruited in 2006 ($P < .01$) reported significantly greater frequency of discussions about MSI testing with family members. Based on these analyses, each significant variable was included as a covariate in the final model for each outcome.

Final Intervention Effect Model

Results are presented in Table 3. Significant intervention effects in favor of the CD were found for all primary outcomes. CD-ROM participants reported significantly greater improvements in MSI and IHC knowledge, significantly higher satisfaction with preparation for making the decision regarding the MSI test, significantly lower PEQ scores (indicating greater satisfaction), and significantly greater perceived completeness of preparation. Several demographic and medical covariates continued to be significant in the final model. Older participants had lower gains in MSI knowledge. Participants with greater ECOG status reported less satisfaction with preparation, and participants with more relatives with cancer reported greater satisfaction with preparation. White participants reported greater completeness of preparation than nonwhites.

Table 4. Multivariable Regression Results for Secondary Study Outcomes

Variable	Parameter Estimate	t Value	P
Decisional conflict			
MSI, study condition	−0.22	−2.47	.01
Decisional difficulty			
Study condition	0.04	0.52	.61
Decisional self-efficacy			
Baseline value	0.22	3.20	.002
Study condition	0.62	5.34	< .0001
Discussion with family			
Baseline value	−0.35	4.76	< .0001
Study condition	0.17	1.73	.08
Sex (female v male)	0.26	2.62	.01
Time between baseline and follow-up	0.01	2.61	.01
Baseline year	−0.10	−2.11	.04
Cancer-related distress			
Baseline value	0.72	13.45	< .0001
Study condition	0.46	0.22	.83
Cancer worry			
Baseline value	0.6	12.47	< .0001
Study condition	−0.18	−.67	.50
Global anxiety			
Baseline value	0.73	15.16	< .0001
Time between baseline and follow-up	0.08	2.90	.004
Study condition	−0.19	−0.16	.87

NOTE. The treatment effect and any significant sociodemographic or medical factors are included.

Abbreviation: MSI, microsatellite instability.

With regard to secondary decisional outcomes (Table 4), results indicated significant intervention effects in favor of the CD intervention for two of the three decisional outcomes. Decisional conflict scores were significantly lower (indicating lower conflict) and self-efficacy scores were significantly higher among participants in the Ed + CD-ROM condition. There were no significant differences with regard to difficulty making the decision to have MSI testing.

No significant group effects were found for cancer-related distress, cancer worry, global anxiety, or discussions with family about MSI at follow-up, although the intervention effect for discussions with family was marginally significant ($P = .08$). The treatment effect was in favor of the CD intervention group.

Moderator Analyses

Baseline levels of family support for MSI testing, prior exposure to information about the MSI test, and family history of cancer and cancer death were evaluated as possible moderators of intervention effects for outcomes where a significant effect for the intervention group was found. These analyses entailed entering significant covariates, baseline values of the outcome variable if appropriate, study condition, and finally the interaction between study condition and the moderator.

There were no significant effects for the four moderators for MSI and IHC knowledge, satisfaction with preparation, completeness of preparation, decisional conflict, and decisional self-efficacy. For PEQ satisfaction, there were no significant moderating effects noted for family support, prior exposure to information about MSI testing, and the number of family members who died from cancer. However, there was a moderating effect noted for the number of relatives with cancer and study condition ($t = 2.2$; $P < .05$). Among CD-ROM participants, there was no difference between PEQ satisfaction with preparation between participants with a stronger family cancer history ($M = 2.2$) than those with a less strong family history ($M = 2.3$). Among education only participants, there was a lower level of satisfaction with preparation among those with a stronger family history ($M = 2.7$) than among those participants with a less strong family history ($M = 2.4$).

DISCUSSION

CRC patients who meet the revised Bethesda criteria were asked to pursue MSI testing with little information about this test or the ultimate implications of its results. We tested a computer-based educational aid to help patients make a well-informed decision about testing. The CD-ROM was a highly effective method of increasing knowledge about the test and its implications, as well as enhancing the level of confidence patients had in understanding the genetic basis of CRC and the meaning of the test result for their own and their families' health. The CD-ROM lowered decisional conflict and increased satisfaction with the level of preparedness for making the decision to have the MSI test. There were no significant effects on affective outcomes, including global and cancer-specific anxiety, and cancer worry, and the CD-ROM did not increase the likelihood that participants had difficulty making the decision to pursue testing or they would discuss the MSI test with their family.

These findings add to the literature suggesting that educational and decision aids can assist patients at high risk for cancer in making the decision whether to pursue genetic testing¹⁰ and other risk-reduction and risk management options.^{20,21} Our findings extend previous stud-

ies by demonstrating that educational aids can be utilized early in the screening process, even before formal genetic testing is considered.

It is important to note that the CD-ROM did not increase either global or cancer-related anxiety, a concern in some genetic testing settings.²² Our findings are consistent with previous studies suggesting that educational aids about genetic testing do not increase distress levels²³ or adversely effect emotional outcomes.²⁴

It is interesting to note that the CD-ROM intervention reduced decisional conflict but did not increase decisional difficulty, suggesting this educational aid improved the quality of the decision-making process (eg, feeling unclear about values) without an impact on other aspects of decision making (eg, decisional regret or distress). Because the majority of participants consented to the test (91%, with no group differences), it is possible that the decision to pursue testing was neither a difficult nor distressing choice. Indeed, approximately 86% of the sample reported having little to no difficulty making the decision, 90% of the sample reported little to no distress while making the decision, and 88% anticipated little to no concern that they would ultimately feel they made the wrong decision.

With one exception, our proposed moderators had little impact on the effectiveness of the CD-ROM. The level of satisfaction with the preparation for the MSI test was lower among those with a stronger family history of cancer in the education only group, whereas family history of cancer did not moderate the effects of the CD-ROM on satisfaction with preparation for MSI testing. A possible explanation is that the CD-ROM attenuated any differences in preparation that might have been present among those with a stronger family history of cancer.

There are two key limitations. The population was primarily white, well-educated, and possessed health insurance. Whether the CD-ROM would prove as effective for a more diverse, less well-educated, and uninsured population with less medical access is not known. Second, MSI and IHC knowledge were higher at CCHS. These patients may have received different levels of information by health care providers before enrollment. Nevertheless, all sites had comparable improvements in knowledge.

Despite these limitations, this study demonstrates that high-risk patients with CRC can benefit from a computer-based multimedia intervention. With some groups now recommending expanded MSI testing for all CRC patients^{25,26} and women diagnosed with endometrial cancer,²⁷ effective and easy-to-use methods of education about the purpose and utility of this test are necessary. Furthermore, the current CD could be easily adapted should MSI testing become routine before adjuvant chemotherapy.²⁸ With broader use of MSI testing, the utility of patient-centered interventions in general oncology practice may grow. We have developed one possible method to accomplish this goal.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Neal J. Meropol, Saladax (C); Daniel C. Chung, Myriad Labs (C) **Stock Ownership:** Neal J. Meropol, Saladax **Honoraria:** None **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

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