Title

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Journal

JCO Oncology Practice, 12(3)

ISSN

2688-1527

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Publication Date

2016-03-01

DOI

10.1200/jop.2015.007062

Peer reviewed

The full version of this article may be viewed online at
DOI: 10.1200/JOP.2015.007062

Oncologists' Selection of Genetic and Molecular Testing in the Evolving Landscape of Stage II Colorectal Cancer

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CONTEXT AND QUESTION ASKED: Genetic testing can be used in the diagnosis of Lynch syndrome, formerly known as hereditary nonpolyposis colorectal cancer (CRC), the most common inherited disorder that increases the risk for CRC; however, test results related to Lynch syndrome screening may also be used for predictive and prognostic purposes in patients with stage II CRC. Although national guidelines recommend the use of several genetic and molecular tests for patients with CRC, little is known about how guidelines, particularly the complex testing recommendations for Lynch syndrome, are translated into clinical practice. In this study, we asked: how does the family history of patients with stage II CRC influence medical oncologists' selection of genetic and molecular testing, both related and unrelated to Lynch syndrome?

SUMMARY ANSWER: We found that oncologists' self-reported ordering of Lynch syndrome–related tests was strongly associated with the strength of CRC family history, but even so, not all oncologists would order germline testing for mismatch repair (MMR) genes, much less screen for Lynch syndrome by ordering microsatellite instability and/or immunohistochemistry for MMR proteins, in a patient scenario with the strongest family history of CRC (Table 2). We also found overtesting of *KRAS* and Onco*type* DX for stage II CRC associated with certain practice and provider characteristics, with graduates of non-US or non-Canadian medical schools and physicians compensated under fee-for-service or by productivity-based salaries being more likely to choose *KRAS* testing. Fee-for-service and productivity-based salaries were also associated with increased Onco*type* DX testing.

METHODS: In 2012 and 2013, we surveyed medical oncologists in the Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) and evaluated their selection of microsatellite instability and/or immunohistorchemistry for MMR proteins, germline testing for MMR genes, *BRAF* and *KRAS* mutation analysis, and Onco*type* DX in stage II CRC. Physicians were randomly assigned to receive one of three vignettes, varying by strength of CRC family history. We compared differences in testing by family history and provider and practice characteristics, and we used multivariate logistic regression to identify provider and practice characteristics associated with testing.

BIAS, CONFOUNDING FACTOR(S), DRAWBACKS: Although we surveyed a large cohort of oncologists from diverse geographic and practice settings, there were several limitations to this study. Whereas CanCORS patients are representative of the national patient population, participants were mostly oncologists who care for patients enrolled in CanCORS and who may be slightly older than US oncologists as a whole. Furthermore, our measures of testing relied on physician self-reporting rather than direct measures of use. In addition, we did not ask oncologists to report on the sequence in which they would order the various tests, and we were unable to determine whether such respondents would have

DOI: 10.1200/JOP.2015.007062

ordered simultaneous or sequential testing. Finally, our study focused on patients with stage II CRC and may not be further generalizable.

REAL-LIFE IMPLICATIONS: The high lifetime risk of CRC and other cancers among affected individuals and family members and low detection rates led the Centers for Disease Control and Prevention to recommend universal Lynch syndrome screening of all patients newly diagnosed with CRC. Previous efforts to increase the identification of patients and family members with Lynch syndrome have unfortunately achieved limited success. It remains to be seen whether the recapitulation by the National Comprehensive Cancer Network of the Centers for Disease Control and Prevention recommendation to screen all incident CRC specimens for Lynch syndrome can increase diagnoses. Undertesting related to Lynch syndrome screening and overtesting involving molecular tests among surveyed oncologists highlight the need for improved implementation, targeted education, and evaluation of organizational and financial arrangements to promote the appropriate use of genetic and molecular tests. JOP

Table 2. Percentages of Oncologists Who Reported They Would Order Genetic and Molecular Testing for a Patient Newly Diagnosed With Stage II CRC, Unadjusted

Test	Overall, No. (%)	Clinical Scenario*			
		No Family History, % (n = 109)	Weak Family History, % (n = 103)	Strong Family History, % (n = 109)	*P*
Individual					
Germline	143 (45)	16	32	87	< .001
MSI and/or IHC for MMR proteins	205 (64)	53	58	82	< .001
BRAF	44 (14)	8	10	24	.001
Onco*type* DX	120 (38)	37	38	39	.97
KRAS	75 (24)	20	24	27	.51
Combinations					
BRAF and MSI and/or IHC for MMR proteins	32 (10)	4	7	20	< .001
Germline and MSI and/or IHC for MMR proteins	124 (39)	15	26	77	< .001
Germline and *BRAF*	30 (10)	1	5	24	< .001
Onco*type* DX and MSI and/or IHC for MMR proteins	87 (28)	22	26	35	.11
KRAS and *BRAF*	35 (11)	7	9	18	.04

Abbreviations: IHC, immunohistochemistry; MMR, mismatch repair; MSI, microsatellite instability.
*Maximum number of respondents for each scenario.

Oncologists' Selection of Genetic and Molecular Testing in the Evolving Landscape of Stage II Colorectal Cancer

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Abstract

Purpose

Little is known about the roles of genetic and molecular testing and Lynch syndrome screening in the formulation of predictive and prognostic assessments for patients with stage II colorectal cancer (CRC).

Methods

From 2012 to 2013, we surveyed medical oncologists in the Cancer Care Outcomes Research and Surveillance Consortium and evaluated oncologists' selection of microsatellite instability (MSI) and/or immunohistochemistry (IHC) for mismatch repair (MMR) proteins, germline testing for MMR genes, *BRAF* and *KRAS* mutation analysis, and Onco*type* DX in stage II CRC. Physicians were randomly assigned to receive one of three vignettes that varied by strength of CRC family history. We used multivariable logistic regression to identify physician and practice characteristics associated with test selection.

Results

Among 327 oncologists, MSI and/or IHC for MMR proteins were most frequently selected (n = 205; 64%), with 82% versus 53% choosing MSI/IHC testing in patients with strong versus no CRC family history, respectively (adjusted odds ratio [OR], 3.87; 95% CI, 2.07 to 7.22). *KRAS* and Onco*type* DX testing were chosen by 24% and 38% of oncologists, respectively. Graduates of non-US and Canadian medical schools and physicians compensated by fee-for-service or on the basis of productivity were more likely to choose *KRAS* testing versus those receiving salaries not on the basis of productivity (OR, 2.16; 95% CI, 1.17 to 3.99; and OR, 1.94; 95% CI, 1.02 to 3.66, respectively). Fee-for-service or productivity-based salaries were also associated with increased odds of Onco*type* DX testing (OR, 2.04; 95% CI, 1.17 to 3.55).

Conclusion

Among surveyed oncologists, we found undertesting and overtesting related to genetic and molecular testing and Lynch syndrome screening for patients with stage II CRC, highlighting the need for improved implementation, targeted education, and evaluation of organizational and financial arrangements to promote the appropriate use of such tests.

ASSOCIATED CONTENT

Appendices DOI: 10.1200/JOP.2015.007062

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INTRODUCTION

Colorectal cancer (CRC) is increasingly viewed as a heterogeneous disease with various germline and somatic mutations that lead to the development of tumors that differ in both natural history and response to treatment.[1,2] In recognition of this, there are a growing number of available tests to identify mutations, guide diagnostic assessments, and/or tailor therapeutic approaches to individual patients with CRC.[3] However, the ways in which oncologists use these different genetic and molecular tests for patients with CRC and how test results inform treatment recommendations are poorly understood. This evidentiary gap may be particularly challenging when considering patients with stage II CRC, for whom decisions regarding adjuvant chemotherapy are multifactorial. Genetic testing can be used in the diagnosis of Lynch syndrome (formerly known as hereditary nonpolyposis CRC), the most common inherited disorder that increases the risk of developing CRC; however, test results related to Lynch syndrome screening may also be used for predictive and prognostic purposes in patients with stage II CRC.[4-6] Although national guidelines recommend the use of several genetic and molecular tests for patients with CRC, little is known about how guidelines, particularly the complex testing recommendations for Lynch syndrome, are translated into clinical practice. In this study, we sought to assess how the family history of patients with stage II CRC influences medical oncologists' selection of genetic and molecular testing, both related and unrelated to Lynch syndrome (Table 1).

METHODS

Study Design and Cohort

We surveyed medical oncologists caring for patients with lung or CRC and who were enrolled in the Cancer Care Outcomes Research and Surveillance (CanCORS) Consortium study.[22] The population-based CanCORS patient cohort is comprised of individuals diagnosed with lung or CRC from 2003 to 2005 at participating sites (eight counties in Northern California, Los Angeles County, the states of Iowa and Alabama, 22 counties in central and eastern North Carolina, five integrated delivery systems, and 15 Veterans Affairs [VA] Medical Centers). Surveys were conducted 4 to 6 months after diagnosis, 12 months after diagnosis, and 6 to 8 years after diagnosis. CanCORS participants are similar to patients diagnosed with cancer in the United States as a whole.[23]

We surveyed physicians who were reported by patients in at least one CanCORS survey to have provided or discussed chemotherapy, or physicians identified by medical record abstraction or self-identified as a medical oncologist in an earlier physician survey conducted from 2006 to 2008.[24] Physicians were ineligible if they were deceased, no longer practicing, or not medical oncologists.

Survey Development

The survey included three patient vignettes, of which oncologists received only one by random assignment and varying by strength of CRC family history. The vignettes presented a 55-year-old woman with newly diagnosed stage II CRC who had just undergone hemicolectomy, with pathology revealing 15 negative lymph nodes. The three versions (and strengths) of the patient's family history were: no family history of CRC (no); one uncle diagnosed with CRC at age 62 (weak); and three relatives with CRC, including her father, who was diagnosed at age 48 (strong). The strong CRC history scenario follows the Amsterdam guidelines for Lynch syndrome screening, whereas the no CRC and weak CRC scenarios address recommendations that suggest that all individuals less than 60 years of age should be screened for Lynch syndrome.[25,26] We asked oncologists how likely they were to order germline mutation analysis for Lynch syndrome, microsatellite instability (MSI) and/or immunohistochemistry (IHC) for mismatch repair (MMR) proteins, *KRAS* mutation analysis, *BRAF* mutation analysis, and/or Onco*type* DX testing (Genomic Health, Redwood City, CA). Response options for each test were: very unlikely, somewhat unlikely, somewhat likely, very likely, or I have limited experience with the test. The survey also obtained information about physicians' age, graduation year, medical school, teaching, number of new and total patients with CRC seen per month, practice setting, and financial arrangements (clinical compensation by nonproductivity-based salary, productivity-based salary, fee-for-service or capitation). The institutional review boards of all participating institutions approved the study.

Survey Administration Procedures

Survey procedures have been described in detail elsewhere.[24] In brief, in the summer of 2012, physicians were mailed a self-administered questionnaire with a $50 incentive check. Three weeks after the initial mailing, the survey was mailed again to all nonrespondents. Approximately 2 weeks later, a research assistant called the offices of nonresponding physicians to

Table 1. Evidence Supporting Genetic and Molecular Tests in Stage II CRC

Test	Recommended for All Patients	Equivocal and/or Applicable in Selected Contexts	Lack of Clinical Applicability	Guideline Recommendations
Individual				
Germline		X		Gold standard for Lynch syndrome testing is to perform germline testing of MMR genes—*MSH2*, *MLH1*, *PMS2*, and *MSH6* and *EPCAM*—but mutation testing is labor intensive and costly.[7]
MSI and/or IHC for MMR proteins	X			Alternative method to screen for Lynch syndrome using polymerase chain reaction to detect microsatellites via MSI testing.[4,8,9] If sample exhibits abnormalities in less than 30% of the microsatellites tested or has at least instability of microsatellites in at least two or more markers, the tumor is classified as MSI-H.[10]
BRAF		X		As not all MSI-H tumors are caused by Lynch syndrome and those that are not have a *BRAF* mutation, MSI combined with *BRAF* mutation testing is another way to screen. In addition, decreased MMR protein expression in tumor samples via IHC staining, also combined with *BRAF* mutation testing, is another way to screen for Lynch syndrome,[11,12] as data have shown that IHC analysis of known MMR proteins yields comparable results to MSI testing.[4,13]
Onco*type* DX		X		The Onco*type* DX assay has been shown to be predictive of recurrence risk for selected patients with stage II CRC but not predictive of benefit with adjuvant chemotherapy.
KRAS			X	Recently, testing for other *RAS* mutations has become recommended given that additional mutations identified in previously wild-type patients may also predict lack of benefit with anti-EGFR therapy, but only in patients with stage IV CRC.[14]
Combinations*				
BRAF and MSI and/or IHC for MMR proteins		X		*BRAF* can be done for Lynch syndrome screening if loss of *MLH* or MSI is seen. *BRAF* can also be done for prognostic information, with mutations portending a worse prognosis.[4,15,16]
Germline and MSI and/or IHC for MMR proteins		X		It can be redundant to do germline testing in combination with MSI and/or IHC for MMR proteins, but there are selective cases in which germline testing is negative in patients with suspected Lynch syndrome. For such patients, further MSI testing may be required to help interpret the results.[17]
Germline and *BRAF*		X		This is not a standard combination of testing but can be used in select cases of suspected Lynch syndrome when interpreting negative germline testing in the context of MSI testing and *BRAF*.[17]
Onco*type* DX and MSI and/or IHC for MMR proteins		X		Onco*type* DX should not be done in patients who are MSI-H.[18-21]
KRAS and *BRAF*			X	As above, *KRAS* testing is recommended for patients with stage IV CRC only.

Abbreviations: CRC, colorectal cancer; EGFR epidermal growth factor receptor; IHC, immunohistochemistry; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability high.
*Other combinations of tests were considered but were not deemed to be relevant.

verify that the survey had been received, encourage physicians to complete and return it, and offer to mail or fax a replacement questionnaire. Research assistants also verified the specialty of nonresponding physicians. Up to four attempts were made to reach each nonresponding physician. From April 2013 to May 2013, a third mailing of the survey and cover letter were sent to nonresponding physicians with an additional $50 check. Physicians were also given the option to complete a Web-based version of the survey.

The American Association for Public Opinion Research response rate (ie, response rate among all physicians not known to be ineligible) was 46.4%, and the refusal rate was 9.8%.[27] The participation rate among eligible physicians for whom we had valid contact information was 52.9%. Respondents and nonrespondents did not differ by sex, United States or Canadian graduation status, or year of graduation from medical school (all $P > .70$).[24] Item nonresponses were infrequent ($\leq 4\%$ for all variables); we used multiple imputation to impute missing data for all variables except physician responses regarding genetic testing (the key dependent variables). Among 357 respondents, we excluded 30 doctors who reported that they did not provide care for patients with CRC during the previous 12 months, which resulted in a final study cohort of 327 oncologists.

Statistical Analysis

We used χ^2 analyses to compare selection of testing by provider and practice characteristics, including physician age (continuous), United States or Canadian medical school graduation, time spent teaching (< 6 *v* ≥ 6 d/mo), number of CRC patients seen (five or fewer *v* six or more per month), proportion of CRC patients in their practice ($< 25\%$ *v* $\geq 25\%$), practice setting (health maintenance organization [HMO], VA or government-based, office-based, or hospital-based), compensation (nonproductivity-based salary *v* fee-for-service [FFS] or productivity-based salary, which has incentives for volume of patient visits similar to FFS). The FFS group included a small number of physicians who reported being paid via capitation for some patients; however, no oncologists were paid exclusively by capitation. Using sensitivity analyses, we assessed for potential collinearity between practice setting and physician compensation by eliminating practice setting alone, eliminating compensation alone, and including both practice setting and compensation. We also examined compensation categorized as FFS versus productivity-based salary versus nonproductivity-based salary. In addition, we used χ^2 tests to assess the association of selection of individual genetic and molecular tests with the strength of family history. Multivariate logistic regression analysis was performed to assess the association of CRC family history strength and physician and practice characteristics with selection of individual genetic and molecular tests. All analyses were performed using SAS 9.3 (SAS Institute; Cary, NC).

RESULTS

Characteristics of the 327 medical oncologists who cared for patients with CRC and who completed the survey are presented in Appendix Table A1 (online only). The mean age was 54.3 years (standard deviation, 9.2 years). Most respondents did not teach regularly (81%), saw five or fewer new patients with CRC per month (79%), had patient panels with less than 25% patients with CRC (79%), were office- or hospital-based (69%), and were compensated by FFS or productivity-based salary (61%).

Physician selection of genetic and molecular testing overall and across family history scenarios is summarized in Table 2. Overall, MSI and/or IHC analyses for MMR proteins were the most frequently chosen tests (64%), with high rates for the patient scenarios of no family history (53%), weak family history (58%) and strong family history (82%). For the scenario of a strong family history of CRC, germline mutation testing was frequently selected (87%). In addition, the frequency of reported germline mutation testing increased with stronger CRC family history (no, 16%; weak, 32%; and strong, 87%; $P < .001$). In contrast, the rates of Oncotype DX testing (no, 37%; weak, 38%; and strong, 39%; $P = .97$) and *KRAS* (no, 20%; weak, 24%; and strong, 27%; $P = .51$) did not differ by strength of family history.

Table 2 shows oncologists' selection of test combinations. Of physicians surveyed, 39% and 10% reported that, in addition to germline mutation testing, which is the gold standard for diagnosing Lynch syndrome, they would also separately order MSI and/or IHC for MMR proteins and *BRAF* as screening tests, respectively. Only 10% of oncologists selected both MSI and/or IHC for MMR proteins and *BRAF*, another appropriate diagnostic strategy. Oncologists who received the vignette featuring the strong family history of CRC reported that they would order all test combinations, including *KRAS* with *BRAF* (18% *v* 7% and 9%), more frequently than oncologists who received the no and weak family history vignettes, respectively ($P < .05$). Overall, 28% of physicians chose the combination of MSI and/or IHC for MMR proteins with Oncotype DX testing.

Table 2. Percentages of Oncologists Who Reported They Would Order Genetic and Molecular Testing for a Patient Newly Diagnosed With Stage II CRC, Unadjusted

Test	Overall, No. (%)	Clinical Scenario*			
		No Family History, % (n = 109)	Weak Family History, % (n = 103)	Strong Family History, % (n = 109)	*P*
Individual					
Germline	143 (45)	16	32	87	< .001
MSI and/or IHC for MMR proteins	205 (64)	53	58	82	< .001
BRAF	44 (14)	8	10	24	.001
Onco*type* DX	120 (38)	37	38	39	.97
KRAS	75 (24)	20	24	27	.51
Combinations					
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Germline and MSI and/or IHC for MMR proteins	124 (39)	15	26	77	< .001
Germline and *BRAF*	30 (10)	1	5	24	< .001
Onco*type* DX and MSI and/or IHC for MMR proteins	87 (28)	22	26	35	.11
KRAS and *BRAF*	35 (11)	7	9	18	.04

Abbreviations: IHC, immunohistochemistry; MMR, mismatch repair; MSI, microsatellite instability.
*Maximum number of respondents for each scenario.

Bivariate analyses were performed to evaluate the association between physician selection of genetic tests and provider and practice characteristics (Tables 3 and 4). Graduation from a non-US or non-Canadian medical school ($P < .03$) and FFS or productivity-based salary ($P < .02$) were associated with an increased selection of *KRAS*. Stronger CRC family history ($P < .001$) and non-US or non-Canadian medical school graduation were associated with an increased selection of *BRAF* ($P < .001$). However, for Lynch syndrome screening (ie, MSI/IHC and germline mutation testing), only stronger family history of CRC was associated with increased selection ($P < .001$ for both). In addition, HMO and VA or government-based providers were less likely to choose Onco*type* DX testing ($P < .001$), whereas physicians with a productivity-based or FFS salary structure were more likely to select it ($P < .001$).

Multivariate logistic regressions that assessed the association between the strength of CRC family history and physician selection of testing revealed that stronger CRC family history was associated with increased odds of *BRAF* testing (odds ratio [OR], 4.22; 95% CI, 1.77 to 10.06 for strong family history *v* no family history), MSI/IHC (OR, 3.87; 95% CI, 2.07 to 7.22 for strong family history *v* no family history), and germline mutation testing (OR, 40.82; 95% CI, 18.27 to 91.21 for strong family history *v* no family history; Tables 3 and 4). Factors associated with increased odds of *KRAS* testing included being a graduate of a non-US or non-Canadian medical school (OR, 2.16; 95% CI, 1.17 to 3.99) and under an FFS and/or productivity-based compensation plan (OR, 1.93; 95% CI, 1.02 to 3.66). Factors associated with increased odds of *BRAF* testing included being a graduate of a non-US or non-Canadian medical school (OR, 3.12; 95% CI, 1.51 to 6.47) and having patients with CRC comprise ≥ 25% of the physician's practice (OR, 2.39; 95% CI, 1.08 to 5.29). Factors associated with increased odds of Onco*type* DX testing included compensation by FFS or productivity-based salary (OR, 2.04; 95% CI, 1.17 to 3.55). Practicing in an integrated delivery system or a VA or government setting was associated with decreased odds of reporting such testing (OR, 0.35; 95% CI, 0.19 to 0.64). Results of sensitivity analyses did not suggest collinearity between practice setting and physician compensation and showed that physicians compensated by FFS were similar to physicians compensated on the basis of productivity. No factors other than patient family history were associated with MSI/IHC and germline mutation testing.

DISCUSSION

Genetic and molecular testing in oncology is a rapidly evolving and complex area. Although some guidelines for test selection exist, understanding the appropriateness of specific genetic and molecular tests under differing clinical circumstances is challenging.[28,29] We focused our evaluation on physicians' selection of five tests for patients with newly diagnosed stage II CRC, including three tests that screen for Lynch syndrome.

Table 3. Bivariate Analyses of the Likelihood of Ordering Five Genetic Tests, by Provider and Practice Characteristics

Variables	*KRAS*, %	*P*	*BRAF*, %	*P*	MSI/IHC, %	*P*	Germline, %	*P*	Oncotype DX, %	*P*
Family history										
None	20.2	.51	8.3	.001	52.8	< .001	15.9	< .001	37.0	.97
Weak	24.3		9.7		58.4		32.4		37.9	
Strong	26.9		24.3		81.7		86.9		38.7	
Age of physician, years										
36-45	21.4	.09	13.0	.99	67.1	.41	50.7	.32	32.9	.61
46-55	22.2		14.1		67.4		49.5		37.0	
56-62	18.8		15.0		66.3		37.5		37.0	
≥ 63	35.4		14.0		55.9		43.9		43.9	
Sex of physician										
Male	23.2	.66	13.6	.70	61.8	.09	44.5	.71	38.7	.52
Female	25.6		15.4		72.2		46.8		34.6	
Country of medical school graduation										
United States or Canada	21.0	.03	10.8	.002	66.3	.25	44.4	.46	36.4	.35
Non–United States or non-Canada	33.8		25.4		58.9		49.3		42.5	
Teaching frequency										
≤ 5 d/mo	23.6	.89	14.9	.37	64.0	.83	46.3	.38	37.7	.94
≥ 6 d/mo	24.6		10.3		65.6		40.0		37.3	
No. of new patients with CRC per month										
1-5	23.0	.45	14.2	.33	63.8	.78	44.8	.85	38.4	.41
≥ 6	19.0		9.5		65.6		46.1		32.8	
Patients with CRC in physician's practice, %										
< 25	23.1	.33	12.4	.06	63.8	.56	44.7	.51	38.9	.40
≥ 25	28.8		21.5		67.7		49.2		33.3	
Practice setting										
Office or hospital	26.1	.16	16.0	.14	65.3	.65	48.4	.10	46.3	< .001
HMO, VA, or government	18.8		9.8		62.8		38.6		19.8	
Clinical compensation										
Nonproductivity-based	16.7	.02	11.6	.34	69.4	.25	44.3	.69	24.2	< .001
Fee-for-service or productivity-based	27.8		15.4		63.0		46.6		46.9	

Abbreviations: CRC, colorectal cancer; HMO, health maintenance organization; MSI/IHC, microsatellite instability and/or immunohistochemistry for mismatch repair proteins; VA, Veterans Affairs.

There are various analytic approaches to diagnosing Lynch syndrome, which is a disease characterized by an increased susceptibility to multiple cancers as a result of defects in the repair of mismatched DNA base pairs due to germline mutations in MMR genes.[13,30] MMR gene mutations result in increased variability in the length of repeated DNA sequences or microsatellites, a phenomenon known as MSI. Tumors high in MSI comprise approximately 15% of all CRCs; however, only 3% result from Lynch syndrome. The remaining 12% are sporadic because of acquired hypermethylation of the *MLH1* promoter, resulting in reduced expression of MLH1 mRNA and its protein.[8,13,31] Sporadic cases can be distinguished from those associated with Lynch syndrome by the detection of *BRAF* mutations in the former.

Clinically based Lynch syndrome screening recommendations, such as the Amsterdam criteria, have been used by physicians for many years to identify those patients most likely to have Lynch syndrome and to determine who should undergo screening[11,25,26,32]; however, evidence suggests that implementation of clinically based guidelines is suboptimal.[33] In one study, only 3% of patients with CRC and a strong family history suggestive of Lynch syndrome were tested.[34] Although only 3% of all CRCs are attributable to Lynch syndrome, the high lifetime risk of CRC and other cancers among affected

Table 4. Multivariate Analyses of the Likelihood of Ordering Five Genetic Tests, by Provider and Practice Characteristics

Variables	*KRAS*	*BRAF*	MSI/IHC	Germline	Oncotype DX
Family history					
None	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Weak	1.48 (0.75 to 2.92)	1.39 (0.52 to 3.72)	1.27 (0.72 to 2.22)	2.69 (1.36 to 5.34)	1.18 (0.65 to 2.14)
Strong	1.69 (0.87 to 3.30)	4.22 (1.77 to 10.06)	3.87 (2.07 to 7.22)	40.82 (18.27 to 91.21)	1.11 (0.62 to 1.99)
Age of physician (for each year)	1.03 (1.00 to 1.06)	1.02 (0.98 to 1.06)	0.98 (0.96 to 1.01)	0.98 (0.95 to 1.01)	1.00 (0.98 to 1.03)
Sex of physician					
Male	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Female	1.65 (0.86 to 3.17)	1.58 (0.69 to 3.59)	1.44 (0.78 to 2.65)	1.05 (0.52 to 2.12)	1.13 (0.62 to 2.05)
Country of medical school graduation					
United States or Canada	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Non–United States or non-Canada	2.16 (1.17 to 3.99)	3.12 (1.51 to 6.47)	0.74 (0.42 to 1.31)	1.41 (0.72 to 2.79)	1.44 (0.81 to 2.55)
Teaching frequency					
≤ 5 d/mo	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥ 6 d/mo	1.20 (0.59 to 2.43)	0.69 (0.26 to 1.85)	1.02 (0.54 to 1.93)	0.60 (0.27 to 1.31)	1.24 (0.66 to 2.34)
No. of new patients with CRC per month					
1-5	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥ 6	0.87 (0.42 to 1.76)	0.69 (0.27 to 1.80)	1.14 (0.61 to 2.16)	1.30 (0.64 to 2.66)	0.91 (0.48 to 1.75)
Patients with CRC in physician's practice, %					
< 25	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥ 25	1.44 (0.74 to 2.78)	2.39 (1.08 to 5.29)	1.16 (0.61 to 2.19)	1.42 (0.70 to 2.88)	0.77 (0.41 to 1.45)
Practice setting					
Office or hospital	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
HMO, VA, or government	0.86 (0.44 to 1.65)	0.60 (0.25 to 1.42)	0.77 (0.44 to 1.36)	0.59 (0.30 to 1.15)	0.35 (0.19 to 0.63)
Clinical compensation					
Nonproductivity-based	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Fee-for-service or productivity-based	1.93 (1.02 to 3.66)	1.31 (0.61 to 2.85)	0.82 (0.46 to 1.45)	1.20 (0.63 to 2.30)	2.04 (1.17 to 3.55)

NOTE. All data are given as odds ratio (95% CI) unless otherwise noted.

Abbreviations: CRC, colorectal cancer; HMO, health maintenance organization; MSI/IHC, microsatellite instability and/or immunohistochemistry for mismatch repair proteins; VA, Veterans Affairs.

individuals and family members, as well as the low detection rates, led the Centers for Disease Control and Prevention (CDC) to recommend in 2009 the universal screening for Lynch syndrome of all newly diagnosed patients with CRC.[35,36] In our study, we found that oncologists' self-reported ordering of Lynch syndrome–related tests strongly correlated with the strength of CRC family history. Even so, not all oncologists would order germline testing for MMR genes, much less screen for Lynch syndrome by ordering MSI and/or IHC for MMR proteins, in the patient scenario with the strongest family history of CRC. Previous efforts to increase identification of patients and family members with Lynch syndrome have unfortunately achieved limited success.[5,34,37] It remains to be seen if the recapitulation in 2014 by the National Comprehensive Cancer Network (NCCN) of the CDC recommendation to screen all incident CRC specimens for Lynch syndrome can result in increased diagnoses.[2,17,38]

In addition to multiple guidelines and testing approaches, determining the optimal care for patients with CRC is further complicated by the fact that MMR deficiency and high MSI are considered biomarkers for decreased recurrence risk in patients with stage II CRC.[10] There is controversy regarding whether patients with stage II CRC who have MMR-deficient and MSI-high tumors derive clinical benefit from single-agent fluorouracil chemotherapy.[39] NCCN guidelines also recommend that, to aid in the decision of whether or not to prescribe chemotherapy, MMR testing should be performed in patients with stage II CRC for whom adjuvant therapy with fluorouracil is being considered.[2,19] MMR results should

therefore also be considered in the context of potentially providing prognostic and pharmacogenetic information in the formulation of treatment recommendations.

In contrast to testing for Lynch syndrome, the adoption of testing for *KRAS* mutation in patients with stage IV CRC has been widespread and has now expanded to other *RAS* mutations.[14] In our study, 23% of oncologists chose *KRAS* mutation testing in the stage II setting despite the lack of clinical utility of *KRAS* results for patients with stage II CRC. *KRAS* testing did not vary with family history, which is consistent with the use of this test.[15,40] Physician characteristics associated with an increased likelihood of *KRAS* selection included graduation from a non-US or non-Canadian medical school and clinical income that was FFS or productivity-based. Non-US and non-Canadian medical school graduates, however, represented a small segment of the study cohort, and caution should be taken in making broader conclusions on the basis of our small sample. Nevertheless, our overall results suggest a need for more education about appropriate testing and opportunities for reduction in unnecessary testing.

The ordering of Onco*type* DX, a proprietary and heavily marketed assay, was largely influenced by oncologists' practice settings and payment structures, unlike that of the other, more widely available tests. Onco*type* DX testing also did not vary with family history, as expected. Onco*type* DX testing yields a 12-gene recurrence score that has been shown to predict recurrence risk for patients with stage II CRC and T3 tumors that are MMR-proficient, which is not the case for approximately 26% of patients with stage II CRC. The Onco*type* DX recurrence score is not relevant in patients who have MMR-deficient or MSI-high tumors because these patients have better prognoses and do not benefit from adjuvant chemotherapy.[18-21,41] Moreover, a higher recurrence score does not correlate with benefit from adjuvant chemotherapy for patients with stage II CRC. Of note, only 28% of oncologists selected both MSI and/or IHC for MMR proteins in combination with Onco*type* DX testing. Practicing in settings where cost containment measures exist (eg, the VA or an HMO) was associated with decreased odds of selecting Onco*type* DX, whereas oncologists receiving compensation on the basis of FFS or productivity were more likely to choose it than those receiving non–productivity-based compensation. Marketing campaigns may be more influential in promoting the ordering of testing among such physicians than those working in large organizations and who are often salaried.[42,43] Value-based approaches to purchasing oncology care may provide incentives to providers and health care systems to reduce potential overuse of tests such as *KRAS* and Onco*type* DX. Further efforts are needed to develop strategies that prevent the unnecessary ordering of tests, as some physicians may not feel adequately prepared to implement genetic testing in practice. Targeted education of provider groups may be useful.[44,45]

Although we surveyed a large cohort of oncologists from diverse geographic and practice settings, there were several limitations to this study. Although CanCORS patients are representative of the national patient population, participants were mostly oncologists who cared for patients enrolled in CanCORS from 2003 to 2005 and who may be slightly older than US oncologists as a whole. Furthermore, our measures of testing relied upon physician self-reporting rather than direct measures of testing use, although prior research has indicated that self-reporting is a good proxy for physician practice patterns.[46] In addition, we did not ask oncologists to report on the sequence in which they order the various tests. For example, some providers chose MSI and/or IHC and germline testing, although, typically, MSI and/or IHC testing is done as the screen and germline testing follows if high MSI is found. Physicians may have chosen MMR germline testing but may not have chosen the test if initial IHC results showed protein expression. We were unable to determine if such respondents would have ordered testing simultaneously or sequentially, and, thus, we could not comment on whether inappropriate overuse of germline testing occurred. Finally, our study focused on patients with stage II CRC and our findings may not be generalizable to other patients.

In conclusion, despite existing guidelines, we found substantial variability in oncologists' selection of genetic and molecular testing, including both undertesting and overtesting. Our findings highlight the need for improved implementation, targeted education, and evaluation of organizational and financial arrangements to promote the appropriate use of genetic testing in the complex environment of stage II CRC. This study provides compelling data to support further prospective studies on genetic and molecular testing in this setting. Further research is needed to assess the effectiveness of quality improvement efforts, better characterize physician understanding of genetic testing in CRC, and evaluate outcomes associated with care delivery models and the ordering patterns of different genetic and molecular tests. JOP

Acknowledgment

This work was supported by Grant No. 5U01CA093344-08 from the National Cancer Institute to the Cancer Care Outcomes Research and Surveillance Consortium Statistical Coordinating Center; by Grant No. K24CA181510 from the National Cancer Institute (N.L.K.); and by Grant No. K24113433 from the National Cancer Institute (S.S.).

Authors' Disclosures of Potential Conflicts of Interest

Disclosures provided by the authors are available with this article at jop.ascopubs.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Oncologists' Selection of Genetic and Molecular Testing in the Evolving Landscape of Stage II Colorectal Cancer

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Appendix

Table A1. Characteristics of Responding Oncologists (N = 327)

Characteristic	
Sex	
Male	75
Female	25
Mean age, years (SD)	54.3 (9.2)
United States or Canadian graduate	
Yes	76
No	24
Involvement in resident or student teaching	
< 6 d/mo	81
≥ 6 d/mo	19
No. of new patients with CRC seen per month	
1-5	79
≥ 6	21
Patients with CRC in practice, %	
< 25	79
≥ 25	21
Practice type	
HMO, VA, or government	31
Office or hospital based	69
Clinical compensation	
Fee-for-service or productivity based	61
Nonproductivity based	39

NOTE. All data given as percent unless otherwise noted.
Abbreviations: CRC, colorectal cancer; HMO, health maintenance organization; SD, standard deviation; VA, Veterans Affairs.