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Prevalence and Predictors of Appropriate Colorectal Cancer Surveillance in Lynch Syndrome

Elena M. Stoffel, MD, MPH[1,2,3], **Rowena C. Mercado, MD, MPH**[2], **Wendy Kohlmann, MS**[4], **Beth Ford, MPH**[2], **Shilpa Grover, MD**[1], **Peggy Conrad, MS**[5], **Amie Blanco, MS**[5], **Kristen M. Shannon, MS**[6], **Mark Powell, MA, MEd**[7], **Daniel C. Chung, MD**[3,6,8], **Jonathan Terdiman, MD**[5], **Stephen B. Gruber, MD, PhD, MPH**[4], and **Sapna Syngal, MD, MPH**[1,2,3]

[1] Division of Gastroenterology, Brigham and Women's Hospital, Boston, MA

[2] Division of Population Sciences, Dana-Farber Cancer Institute, Boston, MA

[3] Harvard Medical School, Boston, MA

[4] Division of Molecular Medicine and Genetics, University of Michigan Medical Center, Ann Arbor, MI

[5] University of California San Francisco Cancer Center, San Francisco, CA

[6] Center for Cancer Risk Analysis, Massachusetts General Hospital, Boston, MA

[7] Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA

[8] Gastroenterology Unit, Massachusetts General Hospital, Boston, MA

Abstract

Background—Lynch Syndrome (LS) is a hereditary cancer syndrome which conveys a high risk of colorectal cancer (CRC). Guidelines recommend colonoscopy every 1–2 years. There is limited information about screening compliance in this high risk group.

Corresponding Author: Elena M. Stoffel, MD, MPH, Division of Gastroenterology, Brigham and Women's Hospital, 75 Francis St Boston, MA 02115, 617-632-5335, Fax 617-632-4088, estoffel@partners.org.

Guarantor of the Article: Elena M. Stoffel, MD, MPH

Specific Author Contributions:
Dr. Stoffel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have approved the final manuscript.
Study concept and design: Stoffel, Grover, Syngal
Acquisition of data: Stoffel, Gruber, Chung, Terdiman, Syngal, Kohlmann, Conrad, Blanco, Shannon, Ford.
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Methods—Data about cancer screening behaviors were obtained from subjects recruited through 4 U.S. cancer genetics clinics. The main outcome was prevalence of appropriate CRC surveillance for LS.

Results—181 individuals had a family history that met Amsterdam Criteria for LS (n=154) and/or had an identified mutation in a mismatch repair (MMR) gene (n=105). 132/181 (73%) had appropriate LS surveillance with colonoscopies at least every 2 years for individuals age ≥25. Of those with inadequate surveillance, 26/49 (53%) had colonoscopies at 3–5 year intervals. There were no significant differences in health care setting, perceived risk of CRC, or compliance with screening for other cancers. Rates of appropriate surveillance were higher among individuals who had been referred for genetic evaluation for LS compared to those who had not (109/136 (80%) vs 23/45 (51%), respectively p=0.0004). In multivariate analysis, personal history of CRC (OR 2.81), having a first degree relative with CRC at age<50 (OR 2.61), and having undergone a genetic evaluation (OR 4.62) were associated with appropriate CRC surveillance for LS.

Conclusions—The time between colonoscopic exams in patients with LS is often longer than recommended by current guidelines and may place them at risk for interval cancers. Recognizing clinical features of LS and providing genetic counseling, evaluation, and intensive surveillance may improve cancer prevention for those at highest risk for CRC.

INTRODUCTION

Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer (HNPCC), is the most common inherited colorectal cancer syndrome and accounts for 2–5% of cases of colorectal cancer (CRC) [1]. LS is caused by germline mutations in mismatch repair (MMR) genes and mutation carriers have increased risk for developing CRC, endometrial, ovarian, small intestinal and urinary tract cancers [2]. The lifetime risk of CRC is 70–80% in the absence of colonoscopic screening, and many of these cancers develop in individuals before age 50. Most Lynch-associated CRCs exhibit a phenotype of defective MMR gene function, which is associated with accelerated progression of colorectal adenomas to carcinomas. Clinical genetic testing for germline mutations in the MMR genes *hMLH1*, *hMSH2*, *hMSH6*, and most recently *hPMS2* is available through commercial laboratories. Evaluating patients with CRC for family history of cancer and evidence of defective mismatch repair in tumors (through tests for microsatellite instability (MSI) and immunohistochemistry (IHC) staining for MMR proteins) has been determined to be cost-effective [3] and published guidelines recommend genetic evaluation for individuals who meet Revised Bethesda guidelines [4–6].

Colonoscopies provide an opportunity for early intervention in Lynch-associated colorectal neoplasia. In a Finnish cohort of individuals with LS who were offered endoscopic surveillance, CRC-related mortality was reduced by more than 60% among those who underwent colonoscopies every 3 years [7]. However, there are frequent reports of Lynch-associated CRCs arising within 3-year surveillance intervals [8, 9] and guidelines for management of LS have recommended colonoscopy every 1–2 years beginning at age 20–25 for those at-risk [6, 10, 11]. Furthermore, due to the elevated risk of endometrial cancer, guidelines recommend that women undergo endometrial screening or prophylactic hysterectomy [6, 11].

Small, single institution studies have suggested that many individuals at risk for LS do not have CRC surveillance as frequently as guidelines specify [12–16]. It is unclear whether inadequate CRC surveillance is the result of patient noncompliance or incorrect recommendations from physicians.

The objective of this multicenter study was to examine the prevalence of appropriate CRC surveillance among individuals at risk for LS and to identify clinical and demographic factors associated with appropriate CRC surveillance.

METHODS

We conducted a cross-sectional questionnaire study among individuals with a personal or family history of CRC that fulfilled Bethesda guidelines for evaluation for LS [17]. Eligible individuals were identified through one of 4 cancer genetics clinics (Dana-Farber Cancer Institute (DFCI) (Boston, MA), Massachusetts General Hospital (MGH) (Boston, MA), University of Michigan (UMich) (Ann Arbor, MI) and University of California San Francisco (UCSF) (San Francisco, CA). Subjects had either visited one of these clinics themselves or were referred to the study by a family member who had been evaluated at one of these clinics. All participants were age 18 years or older, and were able to read and write in English.

Potential subjects were invited to enroll in the study either at a clinical visit or by mail. Subjects who had visited a high risk clinic and/or undergone genetic testing were enrolled at least 3 months after the date of the clinic visit or disclosure of their genetic test result, whichever occurred later. Individuals approached by mail received an initial study packet with an introduction letter and questionnaire, as well as a decline to participate form. Those who did not return study materials after two follow-up telephone calls and two mailings were considered non-responders. Questionnaire data were scanned and entered into a computerized database. The study was approved by the institutional review board of each participating study site.

Family history of cancer was obtained through a detailed family history questionnaire completed by subjects. In evaluating prevalence of appropriate colorectal cancer surveillance among individuals with LS, we limited the study population to include only those subjects who met strict clinical criteria for LS screening defined as 1) a family history that fulfilled Amsterdam I or II criteria and/or 2) the presence of a known pathogenic MMR gene mutation in the family. Subjects who had previously had genetic testing which revealed that they were not carriers of the family MMR mutation and those who had molecular testing of their colorectal cancers which demonstrated no evidence of defective mismatch repair (microsatellite stable, normal immunohistochemistry staining for MMR proteins) were not considered to be at risk for LS and therefore were excluded from this analysis.

Measures

The study questionnaires collected standard demographic information and data in the following domains:

Cancer risk perception—Perceived lifetime risk for developing various cancers (CRC, endometrial, breast, prostate) was assessed using a 5-point Likert scale (very high, high, average, low, very low) and a 0–100% likelihood scale.

Health and cancer surveillance—Personal history of cancer (type, age at diagnosis) and history of previous surgical resection(s) of the colon were elicited. Participants estimated how many doctor's visits they had in the previous 12 months and indicated the type of medical setting where they received the majority of their cancer prevention care (private office, HMO, community hospital, academic/teaching hospital, specialized cancer center, other). Subjects were asked whether their physician had ever discussed their risk of developing cancer and whether he/she had recommended specific cancer screening tests. Subjects were asked how often they should undergo specific tests for cancer prevention.

Frequency of tests including colonoscopy, mammography, and digital rectal exam of the prostate was elicited (choices included: more frequently than every year, every 1 year, every 2 years, every 3 years, every 4–5 years, every 6–10 years, less frequently than every 10 years, other.)

Screening compliance—Participants rated whether they had "all," "some," or "none" of the cancer screening tests recommended by their doctor and ranked the importance (on a 5-point Likert scale 1=not important to 5=extremely important) of possible reasons why they did not have a specific cancer screening test (choices included: my doctor did not recommend it, I don't think I'm at high risk, I think it will be uncomfortable, my insurance will not cover the cost, I find the test embarrassing, if I had cancer I would rather not know, I have not had the time, and other). Self-reported history of physician visits and age-appropriate health screenings were used to create a measure of compliance with standard preventive health maintenance. Subjects were classified as being fully compliant with age-appropriate screening if they reported 1)visiting a health professional at least once in the previous 12 months and 2) having yearly mammograms (women over age 40 only) or digital rectal exams of the prostate (men over age 50 only). Those who had not visited a physician in the past 12 months or who had not had age-appropriate breast or prostate screening were classified as being partially compliant with their age-appropriate health maintenance.

Family history—Detailed family history was obtained including diagnoses of various types of cancer among first, second and third degree relatives.

Genetic testing—Participants were asked whether they or a member of their family had ever had genetic testing for mutations in a MMR gene and whether a genetic mutation had been identified in their family. Responses were correlated with medical records to confirm the clinical genetic test result as: positive for a pathogenic MMR gene mutation (positive result), negative for a MMR mutation previously identified in the individual's family (true negative result), or indeterminate/uninformative (negative with no known family mutation or variant of uncertain significance).

Insurance—Respondents were asked whether insurance issues had ever influenced the frequency of cancer screening tests, caused them to miss or delay cancer screening, or affected their decision to undergo genetic testing.

Our primary outcome measure of appropriate CRC surveillance for LS was defined as endoscopic examination of the colon at least every 2 years. Individuals over age 25 who did not report having a complete endoscopic exam of the colon at least every 2 years were classified as having had inadequate CRC surveillance for Lynch Syndrome. For those who had previously undergone an extensive colonic resection or subtotal colectomy, flexible sigmoidoscopy every 2 years was considered appropriate.

Statistical Analysis

The potential relationships between clinical and demographic factors and appropriate cancer surveillance were explored using univariate tests of association (Fisher's Exact and *t*-tests). Age was examined as both a continuous and categorical variable (<40 years, 40–49 years, 50 years and older) using age thresholds based on published guidelines for CRC screening[18, 19]. Perceived risk of CRC was examined as continuous (0–100%) and dichotomous (*higher than average risk vs average/lower than average risk*) variables. Factors which were found to be statistically significantly associated with appropriate cancer surveillance on univariate analysis or which were believed to have empiric clinical relevance were included in multivariable logistic regression models to identify those with a strong

independent association with appropriate CRC surveillance. Generalized estimating equations were used to account for potential clustering of results among members of the same family. Analyses were performed using SAS Version 9.1 (Cary, NC) software. All *p*-values are two-sided and a *p*-value of <0.05 was considered statistically significant.

Results

Four hundred sixty-two eligible individuals with personal or family history of CRC which met Bethesda guidelines for LS were invited to participate in the study. Of these, 270 (58%) completed the study questionnaire, 34 (7%) declined to participate, and 158 (34%) were non-responders. Women and college graduates were more likely to complete the study questionnaires. There were no significant differences in other demographic characteristics between study subjects and non-responders.

Two hundred and six of 270 (76%) individuals who completed study questionnaires had a family history that either fulfilled Amsterdam I or II Criteria for LS or included an identified pathogenic MMR gene mutation in one or more relatives. Of these, 25 had undergone genetic testing which confirmed they were not carriers of a known family mutation (true negative result); thereby leaving 181 individuals at high risk for developing CRC associated with LS. The mean age of subjects was 46 years and 100 participants (55.3%) had a prior diagnosis of cancer. Only eight (4.4%) did not have health insurance. 136/181 (76%) had visited a high risk clinic for genetic evaluation, 131(72.4%) had undergone genetic testing for LS and 105 (58%) were known to be carriers of an identified pathogenic mutation in a MMR gene. 35/181 (19%) subjects were enrolled in the study by mail, of these subjects, 29 were referred to the study by family members. Additional participant characteristics are presented in Table 1.

170/181 (94%) respondents reported they had undergone a colonoscopy at least once. 130(72%) had endoscopic screening of the colon every 2 years or more frequently and 2 individuals age<25 had not yet undergone screening for CRC; thus 132/181 (73%) subjects were classified as having appropriate CRC surveillance in accordance with LS guidelines. The univariate comparison of characteristics between those with appropriate vs. inadequate CRC surveillance is presented in Table 1. There were no significant differences in age, gender, level of education, or prior history of colorectal adenomas between those who did and did not have appropriate CRC surveillance for LS.

Personal and Family History of CRC

Prevalence of appropriate CRC surveillance was significantly higher among individuals with a prior diagnosis of CRC, with 64/75 (85%) reporting colonoscopies at the appropriate 1–2 year interval, compared with only 68/106 (64%) of those without a CRC diagnosis (p=0.002). In examining family history of cancer, having greater numbers of relatives with CRC and/or a first-degree relative with CRC diagnosed at age<50 were not significantly associated with appropriate CRC surveillance on univariate analysis. However, subjects who reported having a family member with an identified MMR gene mutation were significantly more likely to have appropriate CRC surveillance (85/103 (83%) vs 47/78 (60%), p=0.001).

Cancer Risk Perception and Health Practices

Overall, perception of lifetime risk for developing CRC was very high and 81% of subjects reported knowing they were at increased risk for CRC for 2 years or more. Mean cancer risk estimates did not differ significantly between those with appropriate *vs*. inadequate CRC surveillance (66.5% vs 62.7% lifetime risk for CRC, respectively). 96% of subjects reported making one or more visits to a doctor in the preceding 12 months and 85% were fully

compliant with age appropriate breast or prostate cancer screening. While having more doctor visits in the preceding 12 months was associated with appropriate CRC surveillance, there were no significant differences in rates of age-appropriate breast and prostate cancer screening between those who had appropriate vs. inadequate CRC surveillance for LS (p=0.35).

Risk Assessment and Genetic Evaluation

144 (80%) respondents said their physician had discussed their cancer risk with them and 136 (76%) had been referred to a specialized “high risk” or genetics clinic for further evaluation. 109/136 (80%) individuals referred for genetic evaluation reported having endoscopic screening of the colon at least every 2 years, as compared with only 23/45 (51%) of subjects who had not visited a specialty clinic or undergone genetic counseling (p=0.0004). 131 (72%) subjects had undergone genetic testing for MMR gene mutations associated with LS (13 subjects had genetic testing without visiting a specialized high risk/ genetics clinic). The prevalence of appropriate CRC surveillance among those who underwent genetic testing was high and did not differ between subgroups whose DNA test results revealed a pathogenic MMR mutation compared to those with indeterminate/ uninformative test results (89/105 (85%) vs. 21/26 (81%), p=0.6). History of a visit to a high risk clinic for genetic counseling and personal history of genetic testing were each significantly associated with appropriate CRC surveillance on univariate analysis (p<0.001).

Eighty-two (63%) subjects who had been referred for genetic evaluation said they subsequently increased the frequency of their cancer screening. Prevalence of appropriate CRC surveillance was no different between individuals who had their cancer prevention care at an academic medical center/cancer center *vs*. other health care settings (p=0.5); however those whose cancer prevention care was coordinated by a specialist (gastroenterologist, oncologist, surgeon) were more likely to have endoscopic screening of the colon at appropriate intervals than those whose screening was coordinated by their primary care provider (24/24 (100%) vs 100/145 (69%), respectively, p<0.01).

Multivariable Analysis

We used multivariable logistic regression to examine the relative impact of clinical and demographic factors on appropriate CRC surveillance. As there were only 49 participants who had inadequate CRC surveillance, the final model was limited to 5 variables to avoid overfitting. The variable personal history of CRC (yes/no) was included based on the significant association with appropriate CRC surveillance on univariate analysis. The variables “first degree relative with CRC age<50” and subject age (in 3 categories <40 years, 40–49, and ≥50), although not significant on univariate analysis, were added because they are used for risk stratification in published CRC screening algorithms [18, 19]. The variable “compliance with age-appropriate screening (full vs. partial)” was added to the model to control for potential associations between non-adherence with other cancer screening tests and CRC surveillance practices.

The variables “genetic testing status” (OR 6.84 [95% CI 3.13–14.12]), “visit to a high risk clinic” (OR 4.04 [95% CI 1.95–8.37]), and “MMR mutation in the family” (OR 2.74 [95%CI 1.41–5.33]) were each significantly associated with appropriate CRC surveillance in univariate analysis. However because these variables were clinically and statistically correlated with each other (p<0.0001), and the vast majority (90%) of individuals who underwent genetic testing for MMR gene mutations had also visited a high risk clinic, including 2 or more of these in the same multivariable model resulted in model instability. Placing each of these variables in the model individually yielded comparable parameter estimates and we chose the variable “genetic testing status” as the surrogate for genetic

evaluation for the final multivariable model. The results of the multivariable model are presented in Table 2. Genetic evaluation (OR 4.62 [95% CI 1.66–12.87]), personal history of CRC (OR 2.81 [95% CI 1.12–7.04]), and having a first degree relative with CRC at age<50 (OR 2.61 [95%CI 1.23–5.53]) were each independent predictors of appropriate CRC surveillance for LS. We performed supplemental analyses in order to explore which component(s) of genetic evaluation were most important in influencing compliance with surveillance. Modifying the analysis to examine genetic evaluation in 4 categories (1) high-risk clinic visit and DNA testing, 2) high-risk clinic visit without DNA testing, 3) DNA testing without a high-risk clinic visit and 4) Neither high-risk clinic visit nor DNA testing) demonstrated that genetic evaluation which included both a visit to a high risk clinic and DNA testing remained the strongest predictor of appropriate CRC surveillance for LS (OR 6.16 [95% CI 1.76–21.55]). In this expanded model, undergoing a genetic counseling visit without genetic testing or having genetic testing alone without counseling were not significant predictors; however the numbers of individuals in these categories were small and our power to evaluate these associations was limited.

Inadequate CRC Surveillance

Of the 49 respondents who had inadequate CRC surveillance, 26 (53%) reported undergoing endoscopic screening of the colon every 3–5 years and 13 (27%) had endoscopic exams less frequently than every 5 years. Only 10 (20%) individuals had never had a colonoscopy. Twenty seven (55%) subjects thought their own interval for colonoscopy screening should be “every 2 years or more frequently,” and 23 (47%) reported that they had been compliant with every test that their physician had recommended and had not missed any exams. Reasons rated as moderately or extremely important for missing endoscopy exams included 1) worry that the test would be uncomfortable (n=10) and/or embarrassing (n=6), 2) insurance would not cover the cost of colonoscopy (n=9), 3) their doctor had not recommended the test (n=8), and 4) they had not had time to schedule the test (n=7). Only 2 individuals said they had avoided a endoscopy exams because they would rather not know if they had cancer. Surprisingly, only 12/49 (24%) of those with inadequate CRC surveillance reported that their physician had recommended an endoscopic screening interval of every 1–2 years.

Discussion

As a potentially preventable cancer, CRC has been the target of recent public health campaigns and uptake of CRC screening tests is increasing. Individuals with a personal or family history of CRC or adenomatous polyps stand to benefit most from screening and current guidelines recommend different tests and surveillance intervals based on whether an individual’s cancer risk is estimated as average, moderately increased, or very high [18]. In a recent survey, 69% of Maryland residents aged ≥50 years were “up to date” with CRC screening, and 59% had undergone a colonoscopy in the last 10 years[20]. In our study, 73% of individuals who met clinical criteria for LS had appropriate surveillance with colonoscopies every 1–2 years, which suggests there is room for improvement in cancer prevention among patients at highest risk for CRC.

Studies of CRC screening in U.S. populations have identified various factors associated with test uptake, such as level of education, income, having health insurance, participating in other cancer screening tests, and receiving a recommendation from their physician for CRC screening [21]. In this sense, the sociodemographic characteristics of the highly motivated subjects in our study cohort would predict they would be ideal participants in CRC screening and, indeed, 94% reported having had at least one colonoscopy. However, only 2 in 3 “cancer unaffected” individuals at highest risk for CRC had colonoscopies at intervals necessary to prevent Lynch-associated neoplasms.

These findings differ dramatically from reports from Finland and the Netherlands, where centralized cancer registries coordinate genetic testing and cancer screening for individuals with hereditary cancer syndromes and compliance with CRC surveillance among individuals with LS approaches 98% [22, 23]. In contrast, in the U.S. the responsibility for identifying and managing patients with hereditary cancer syndromes resides with individual primary care physicians, oncologists, surgeons, and gastroenterologists. Surveys have shown that a minority of clinicians are familiar with diagnosis and management of hereditary CRC [2412] and simply referring patients for CRC screening because of "family history" may not be sufficient to ensure appropriate care of individuals at risk for hereditary CRC syndromes. In our cohort, half of subjects who had inadequate cancer surveillance reported having colonoscopies every 3–5 years, as recommended by their physicians. While this interval would be appropriate for patients categorized as at "increased familial risk" in CRC screening guidelines [18], it is not frequent enough to prevent a significant number of Lynch-associated CRCs [7, 8].

While it is not a surprise that individuals who had been diagnosed with CRC or who had a close relative with young-onset CRC were more likely to have appropriate surveillance, the finding that genetic evaluation is strongly associated with appropriate surveillance deserves attention. Current guidelines recommend genetic evaluation for individuals with personal or family histories that meet criteria for LS [10] and cost effectiveness analyses support MSI/IHC testing of selected CRC tumors [3] on the assumption that identifying high risk individuals will improve outcomes. To date, evidence that genetic evaluation for LS improves compliance with CRC surveillance has come from a few small studies: a Dutch study of 94 MMR gene mutation carriers found that the prevalence of colonoscopic screening increased from 31–88% following genetic testing [16] and two U.S. studies of 22 and 32 MMR gene mutation carriers each found that subjects increased their uptake of colonoscopy after receiving a positive genetic test result [14, 15]. Our large multicenter study of 181 individuals at risk for LS (including 105 MMR gene mutation carriers) found a strong association between genetic evaluation and appropriate CRC surveillance. Of those who underwent genetic evaluation, 63% reported that they subsequently increased cancer screening. CRC surveillance was appropriate in 80% of subjects who had undergone genetic evaluation compared with 51% in those who had not. The benefit of genetic evaluation was the same, regardless of the outcome of the genetic test (prevalence of appropriate CRC surveillance was 84% for subjects found to carry MMR gene mutations and 81% for those with indeterminate genetic test results). This suggests that the process of genetic evaluation (which at our centers includes genetic counseling, DNA testing, and a clinical visit with physicians with expertise in managing hereditary CRC), rather than just the result of the DNA test, may be an important intervention in educating patients and physicians about the need for specialized CRC surveillance and screening for other extracolonic cancers.

How can we improve CRC surveillance among those at highest risk? Our findings suggest that physician recommendations, rather than patient noncompliance, may be an important target for intervention. CRC screening should not be considered "one size fits all;" discussions about CRC screening should include a detailed review of the patient's family history. Current CRC screening algorithms are stratified by cancer risk and include specific recommendations for individuals at high risk for genetic syndromes [18]. Although clinical diagnostic criteria for LS remain complex, a number of web-based models allow clinicians to enter a patient's personal and family history and obtain a predicted probability that he/she carries an MMR gene mutation [25–27]. When individuals are referred for genetic evaluation, it is crucial that results of testing and recommendations for cancer surveillance be discussed with patients and communicated back to the referring physicians to ensure successful follow up.

We recognize that our study has certain limitations. Our study was conducted in a selected population of individuals who had direct or indirect contact with a cancer genetics clinic and agreed to spend 30-minutes completing a questionnaire. Consequently, these were highly motivated individuals who were aware of their family history of CRC. The primary outcome of appropriate cancer surveillance was assessed based on subjects' self reports of colonoscopy frequency and we were unable to obtain medical record confirmation for many of these reports. However, previous investigations have validated the reliability of patient self reports of endoscopic exams [28–30] and a number of studies, including the U.S. National Health Interview Surveys (NHIS), collect information about CRC screening practices using subject interviews. In this cohort we expected that the frequency of colonoscopic exams was more likely to be over-reported, rather than under-reported. Consequently, we believe our finding that 73% of individuals had colonoscopies every 1–2 years is probably an overestimation of the true prevalence of appropriate CRC surveillance among individuals at risk for LS. We acknowledge that our finding of a strong association between genetic evaluation and appropriate CRC surveillance does not permit us to differentiate whether the effect is attributable to the DNA test itself or to the clinical consultation with specialists in management of hereditary CRC. The clinical genetic evaluations performed at our centers included pre and post test genetic counseling, as is recommended by multiple organizations [31, 5,32]. Because 90% of subjects in this study who had DNA testing for MMR gene mutations had also had genetic counseling, we cannot determine whether genetic testing in the absence of specialist consultation and genetic counseling would afford the same benefit.

Despite these limitations, our data from this large multicenter U.S. study demonstrate that many patients at highest risk for CRC are not screened at intervals necessary for cancer prevention. Among our highly motivated subjects, those who already had a CRC diagnosis, had a first degree relative with CRC diagnosed at age<50, and/or had undergone genetic evaluation were significantly more likely to have colonoscopies at intervals necessary to prevent Lynch-associated CRC. Physician recommendations for less frequent colonoscopies, rather than patient noncompliance, appeared to be an important reason why subjects had colonoscopies less frequently than every 1–2 years. With CRC screening strategies moving toward less-invasive testing at less frequent intervals, our findings reinforce the need for physician-patient discussions about CRC risk which incorporate a detailed family history. As more patients at risk for LS are identified through clinical and molecular testing, it is important to ensure that they and their physicians are aware of the specialized surveillance required for cancer prevention in hereditary CRC syndromes.

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Abbreviations

LS	Lynch Syndrome
HNPCC	Hereditary nonpolyposis colorectal cancer
MMR	Mismatch repair

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Table 1

Factors Associated with Appropriate CRC Surveillance for LS (N=181) [1]

Categories	All High-Risk Subjects (N=181)	Appropriate Surveillance (N = 132)	Inappropriate Surveillance (N = 49)	
	Frequency Row %	Frequency Row %	Frequency Row%	p-value [2]
Demographics				
Mean Age	46.52 [18–79]	45.73 (+11.8)	48.65 (+13.8)	0.16
Less than 40 years old	51(28)	38(75)	13(25)	0.07
40–49 years old	49(27)	41(84)	8(16)	
50 years old and above	80(44)	52(65)	28(35)	
Unknown/Missing	1(--)	1--		
Gender				
Male	59(33)	42(71)	17(29)	0.72
Female	122(67)	90(74)	32(26)	
Educational Level				
Less than college	55(31)	41(75)	14(25)	0.86
At least college graduate	124(69)	90(73)	34(27)	
Unknown/Missing	2(--)	1--	1--	
Income				
Less than $50,000	39(23)	29(74)	10(26)	1.00
$50,000 or greater	129(77)	96(74)	33(26)	
Unknown/Missing	13(--)	7--	6--	
Health Insurance				
Yes	173(96)	125(72)	48(28)	0.69
No	8(4)	7(88)	1(12)	
Personal History				
Cancer Status				0.003
Have had cancer	100(55)	82(82)	18(18)	
Have not had cancer	81(45)	50(62)	31(38)	
Colorectal Cancer				
Have had CRC	75(41)	64(85)	11(15)	0.002
Have not had CRC	106(59)	68(64)	38(36)	
Adenomas				
Have had adenomas	33(18)	28(85)	5(15)	0.13
Have not had adenomas	148(82)	104(70)	44(30)	
Perceived Colon Cancer Risk				0.06
Higher than average risk	145(81)	111(77)	34(23)	
Average or low risk	35(19)	21(60)	14(40)	
Unknown/Missing	1(--)	-- --	1(--)	
Perceived Lifetime Colon Cancer Risk				
Mean (+/− SD)	65.48 (+/− 28.0)	66.54 (+28.6)	62.71 (+26.7)	0.42
Family History				

Categories	All High-Risk Subjects (N=181)	Appropriate Surveillance (N = 132)	Inappropriate Surveillance (N = 49)	
	Frequency Row %	Frequency Row %	Frequency Row%	p-value [2]
Amsterdam Criteria				
Yes	154(85)	111(72)	43(28)	0.64
No	27(15)	21(78)	6(22)	
First Degree Relative (FDR) with CRC at <50 years old				
Yes	101(56)	79(78)	22(22)	0.09
No	80(44)	53(66)	27(34)	
Mean No. of FDR with CRC	1.21 (+/− 0.96)	1.23 (+0.9)	1.16 (+1.1)	0.66
MMR Mutation in the Family				
Yes	103(57)	85(83)	18(17)	0.001
No	78(43)	47(60)	31(40)	
Health Practices				
Physician Visits (in 12 months)				
Never	7(4)	5(71)	2(29)	0.01
1–6 visits	129(71)	87(67)	42(33)	
7 or more visits	45(25)	40(89)	5(11)	
Provider Primarily Responsible for Health Care				
Primary Care Provider	145(82)	100(69)	45(31)	<0.01
Specialist Provider	24(13)	24(100)	0(0)	
Other or None	9(5)	6(67)	3(33)	
Unknown/Missing	3(--)	2--	1--	
Cancer prevention setting				
Private doctor’s office	62(35)	44(71)	18(29)	0.99
HMO	19(11)	14(74)	5(26)	
Community hospital	20(11)	15(75)	5(25)	
Academic hospital	48(27)	36(75)	12(25)	
Cancer center	23(13)	18(78)	5(22)	
Other	4(2)	3(75)	1(25)	
Unknown/Missing	5(--)	2--	3--	
Academic or cancer center	71(39)	54(76)	17(24)	0.50
Other	110(61)	78(71)	32(29)	
Participation with Cancer Screening Tests				
Fully compliant with age-appropriate health screening	153(85)	109(71)	44(29)	0.35
Partially compliant with age-appropriate screening recommendations	28(15)	23(82)	5(18)	
Genetic Risk Assessment				
Physician Discussed Cancer Risk				
Yes	144(80)	110(76)	34(24)	0.06
No	37(20)	22(60)	15(40)	

Categories	All High-Risk Subjects (N=181)	Appropriate Surveillance (N = 132)	Inappropriate Surveillance (N = 49)	
	Frequency Row %	Frequency Row %	Frequency Row%	p-value [2]
Visited High-Risk Clinic				
Yes	136(76)	109(80)	27(20)	<0.001
No	43(24)	22(51)	21(49)	
Unknown/Missing	2(--)	1--	1--	
Genetic Testing Status				
Had genetic testing	131(72)	110(84)	21(16)	<0.001
No genetic testing	50(28)	22(44)	28(56)	
Genetic Test Result				
Positive	105(80)	89(85)	16(15)	0.57
Indeterminate	26(20)	21(81)	5(19)	
True Negative	----	----	----	
Unknown	----	----	----	
Study Site				0.34
DFCI	76(42)	50(66)	26(34)	
UM	35(19)	27(77)	8(23)	
UCSF	62(34)	49(79)	13(21)	
MGH	8(4)	6(75)	2(25)	

[1] Includes study subjects who have part or all of their colon intact, and fullfilled at least one of the following:

[a] positive personal genetic result

[b] Amsterdam criteria and indeterminate genetic test result

[c] Amsterdam criteria and no genetic testing done

[d] No personal genetic testing, but with an identified mutation in the family

[2] Fisher's exact test was used for categorical variables, and T-test was used for continuous variables

Table 2

Multivariate analysis [1] of factors predicting appropriate CRC surveillance for LS (N=180) [2]

Characteristic	Odds Ratio[95% CI]	p-value
Age		0.05
less than 40 years old	1.00--	
40–49 years old	0.92[0.28–2.96]	
50 years old and above	2.45[0.86–7.03]	
Colorectal Cancer		**0.03**
Have had CRC	2.81[1.12–7.04]	
Have not had CRC	----	
Genetic Evaluation		**0.02**
Had genetic evaluation	4.62[1.66–12.87]	
Did not have genetic evaluation	----	
First Degree Relative (FDR) with CRC at <50 years old		**0.01**
Yes	2.61[1.23–5.53]	
No	----	
Compliant with Age-Appropriate Screening Recommendations		0.10
Yes	0.46[0.16–1.28]	
No	----	

[1] using Generalized Estimating Equation to control for family effects, with exchangeable working correlation = 0.18

[2] Includes high-risk individuals who had complete data on all variables