

Implementation of Universal Microsatellite Instability and Immunohistochemistry Screening for Diagnosing Lynch Syndrome in a Large Academic Medical Center

Brandie Heald, Thomas Plesec, Xiuli Liu, Rish Pai, Deepa Patil, Jessica Moline, Richard R. Sharp, Carol A. Burke, Matthew F. Kalady, James Church, and Charis Eng

All authors: Cleveland Clinic; Richard R. Sharp and Charis Eng, Case Western Reserve University, Cleveland, OH.

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Corresponding author: Charis Eng, MD, PhD, Cleveland Clinic, 9500 Euclid Ave, NE50, Cleveland, OH 44195; e-mail: engc@ccf.org.

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A B S T R A C T

Purpose

In 2009, the Evaluation of Genomic Applications in Practice and Prevention recommended that all colorectal cancers (CRCs) be screened for Lynch syndrome (LS) through microsatellite instability (MSI) or immunohistochemistry (IHC). No studies report how this process is implemented on a health system-wide basis.

Methods

Since 2004, Cleveland Clinic has screened CRC specimens with MSI/IHC. Between January 2004 and July 2007, MSI/IHC results went only to the colorectal surgeon (approach 1). Between August 2007 and June 2008, colorectal surgeons and a genetic counselor received the MSI/IHC results, and the counselor e-mailed the colorectal surgeon regarding appropriate patients for genetic counseling (GC) referral (approach 2). After July 2008, the colorectal surgeon and counselor received MSI/IHC results, but the counselor contacted the patient to facilitate referral (approach 3). In approaches 2 and 3, patients were presumed to have sporadic CRC if the tumor lacked MLH1 expression and was also *BRAF* mutated or if the patient was diagnosed at age greater than 72 years and had no cancer family history.

Results

Abnormal MSI/IHC results occurred in 178 (16%) of 1,108 patients. In approach 1, 21 (55%) of 38 patients with abnormal MSI/IHC were referred for GC, 12 (32%) of 38 underwent GC, and 10 (26%) of 38 underwent genetic testing (GT). In approach 2, nine (82%) of 11 patients were referred for GC, seven (64%) of 11 underwent GC, and five (45%) of 11 underwent GT. In approach 3, 56 (100%) of 56 patients were referred for GC, 40 (71%) of 56 underwent GC, and 37 (66%) of 56 underwent GT. Time from referral to GC was 10-fold quicker in approach 3 than approach 1.

Conclusion

Implementation of universal MSI/IHC with GC/GT, along with effective multidisciplinary communication and plans of responsibility for patient contact, resulted in increased identification of patients with LS.

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INTRODUCTION

Lynch syndrome (LS) is the most common hereditary colorectal cancer (CRC) syndrome, affecting one in 35 patients with CRC.¹ It is an autosomal dominant condition caused by gene alterations in the mismatch repair pathway (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*). LS is associated with an increased risk of colorectal, endometrial, gastric, ovarian, small bowel, hepatobiliary, urothelial, and other cancers. Identification of these patients is critical to offer increased cancer surveillance and prophylactic surgeries to reduce the risk of cancer in the patients as well as their relatives. This has been un-

derscored as one of the agenda items in Healthy People 2020.²

Traditionally, patients at risk for LS were determined by clinical criteria such as the Amsterdam Criteria³ or the Bethesda Guidelines.⁴ The Amsterdam Criteria rely on clinicians to obtain a detailed family history and have been shown to have a sensitivity of less than 50%.^{1,5} Although the sensitivity of the Bethesda Guidelines is greater than 72%, these guidelines are burdensome to recall and have been shown to be poorly implemented in clinical practice.^{1,6}

In 2009, the Evaluation of Genomic Applications in Practice and Prevention recommended all

newly diagnosed patients with CRC be screened for LS through polymerase chain reaction–based microsatellite instability (MSI) testing or immunohistochemistry (IHC).⁷ Although universal screening of patients with CRC is conceptually possible, the development and implementation of systematic screening are complicated. These programs require cooperation and effective communication across multiple disciplines to ensure that patients at risk of LS are appropriately identified, notified of abnormal results, and referred for genetic counseling (GC) and genetic testing (GT). Here, we report our experience at a large academic medical center with a complex health system using three approaches to our institutional screening program with an aim to compare a more active approach to passive approaches to LS screening.

METHODS

Setting

The Cleveland Clinic is a large academic medical center with a complex health system comprising an academic practice on the main campus, two regional community hospitals, and multiple family health centers across northeast Ohio. Pathology, headquartered on the main campus, performs all histopathology, including polymerase chain reaction–based MSI analysis and IHC for mismatch repair proteins. Since September 2010, the western regional community hospital submitted all CRCs to Cleveland Clinic’s Department of Anatomic Pathology. The department only started performing MSI/IHC on some CRCs for the eastern regional community hospital in January 2009 and all CRCs from the western regional hospital in September 2010. Therefore, for purposes of this study, only CRCs surgically resected on the main campus were included for analysis.

MSI and IHC

Since 2004, the Cleveland Clinic screened CRCs with MSI and/or IHC. Results were kept in a registry approved by the Cleveland Clinic Institutional Review Board. Between January 2004 and March 2009, MSI testing was performed on all primary, surgically resected CRCs in patients diagnosed at age less than 50 years, that were right-sided or displayed any MSI-high (MSI-H) histology, as previously described.⁸ Any tumor that was MSI-low or MSI-H then underwent IHC. In April 2009, a universal screening approach was implemented, and all resected CRCs were screened either by MSI testing or IHC. Starting in June 2010, *BRAF* testing was automatically performed on any MSI-H tumor that showed lack of expression of MLH1.

Results Disclosure

Between January 2004 and July 2007, MSI/IHC results went only to the colorectal surgeon a few weeks after the initial pathology report was signed out via an addendum to the surgical pathology report in the electronic medical record. Disclosure of results and referral to GC occurred at the discretion of the colorectal surgeon (approach 1). Between August 2007 and June 2008, the colorectal surgeon received the results via the electronic medical record, but the Department of Anatomic Pathology also e-mailed a weekly report of all

MSI/IHC cases to the genetic counselor, as agreed on by the providers in pathology, colorectal surgery, and clinical cancer genetics. The genetic counselor then e-mailed the colorectal surgeon regarding which patients were appropriate for a GC referral; however, it was the surgeon’s responsibility to notify patients of their results and make the referral (approach 2). Between July 2008 and January 2012, the colorectal surgeon and genetic counselor received results as outlined in approach 2, but the counselor contacted the patient directly via telephone and/or letter on behalf of the surgeon to notify the patient of the results and facilitate a GC referral (approach 3).

In approaches 2 and 3, the genetic counselor reviewed all patients with lack of expression of MLH1 to determine which patients were most likely to have LS and, thus, were most appropriate for GC. Patients were presumed to have sporadic CRC and were not recommended for GC if the cancer was diagnosed at age ≥ 72 years (median age of CRC in the general population per 2008 Surveillance, Epidemiology, and End Results data) and there was no documented family history of cancer. After the addition of *BRAF* testing, none of the 24 patients with the V600E mutation were recommended for referral. All patients with lack of expression of MSH2, MSH6, or PMS2 were considered appropriate for GC referral.

Statistics

Descriptive statistics were used for each approach. Significant end points were GC referral, GC, and germline GT. Two-tailed *P* values were calculated using χ^2 with Yates correction for number of patients referred for GC, patients who underwent GC and germline GT, and patients identified to have a deleterious mutation between approaches 1 and 2, 2 and 3, and 1 and 3. Values for each approach were calculated based on the number of patients who should have been referred for GC. Mean, median, and standard deviation were calculated for the time from GC referral to GC appointment for each approach. Unpaired *t* tests were used to make comparisons between approaches 1 and 2, 2 and 3, and 1 and 3 for the time between GC referral and GC appointment.

RESULTS

Over an 8-year period, abnormal screening results occurred in 178 (16%) of 1,108 patients (Table 1, Fig 1). In approaches 2 and 3, 59 (33%) of 178 CRCs were presumed sporadic (Fig 1), by the operational definition noted earlier in Methods. Retrospective review of patients screened during approach 1 revealed that 38 patients should have been referred for GC, instead of the 21 (57%) who were actually referred (Fig 1). When compared with approach 1, a significantly greater proportion of patients were referred to GC in approaches 2 (*P* = .0232) and 3 (*P* < .001, Fig 1).

GC

When compared with approach 1, significantly more patients underwent GC in approach 3 (*P* < .001). Discrepancies were noted between the number of patients referred to GC and the number who pursued GC (Fig 1, Table 2). The primary reason for declined visits

Table 1. Summary of Abnormal MSI and IHC Results for Each Approach

Result	Approach 1		Approach 2		Approach 3	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
MSI-low/high, IHC NOS	6	11.5	0	0	1	0.1
MLH1/PMS2 loss	37	71.2	14	82.3	88	80.7
MSH2/MSH6 loss	7	13.5	2	11.8	11	10.0
MSH6 loss	2	3.8	1	5.9	6	5.5
PMS2 loss	0	0	0	0	3	2.8

Abbreviations: IHC, immunohistochemistry; MSI, microsatellite instability; NOS, not otherwise specified.

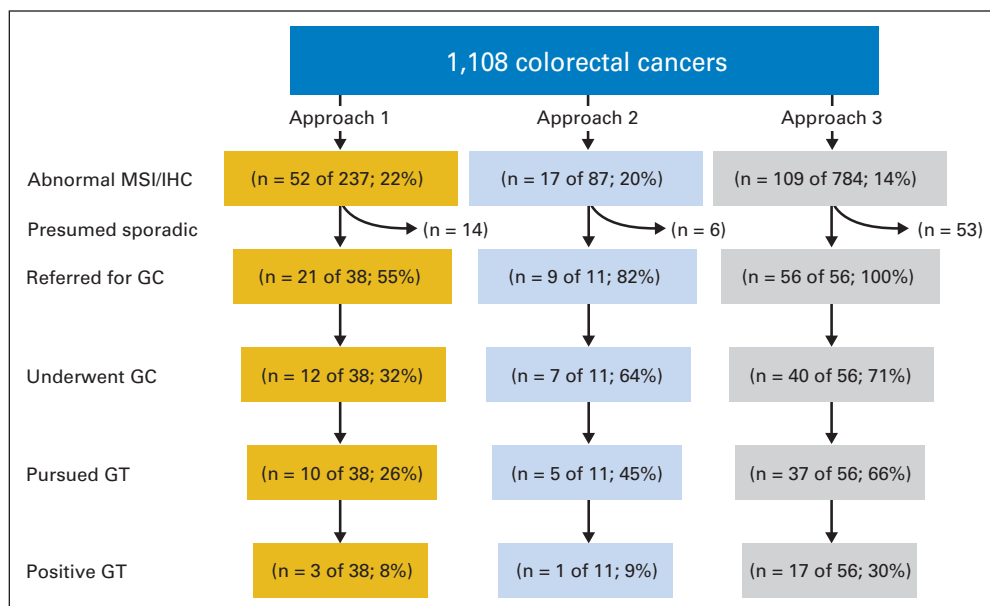


Fig 1. Schema summarizing the three approaches for microsatellite instability (MSI)/immunohistochemistry (IHC) screening for Lynch syndrome. A summary of screen-abnormal results for each approach is shown, as well as the number of patients who were referred, who pursued genetic counseling (GC) and genetic testing (GT), and who were found to have deleterious mutations.

was that patients felt GC would not benefit themselves or their family members.

Detailed, three- to four-generation pedigrees were obtained from all patients who pursued GC. Only 12 (20.3%) of 59 patients satisfied the Amsterdam Criteria. A higher percentage of patients met the Revised Bethesda Guidelines (39 of 59 patients, 66.1%), but these data are skewed because our initial testing criteria were loosely based on the Bethesda Guidelines.

Across all approaches, variation was observed in the time between referral and GC appointment (Table 3). Overall, the median number of days between referral and GC was 13 days. Six patients were seen more than 1 year after the referral was made. When compared with approach 1, patients referred during approach 3 were seen for GC significantly sooner ($P < .001$).

GT

Fifty-two (88%) of 59 patients who pursued GC proceeded with GT. Compared with approach 1, more patients had germline testing in approach 3 ($P < .001$) and more deleterious mutations were identified ($P = .0185$). Three patients declined testing, two patients never had blood drawn, one patient never received consent from the medical power of attorney, and one patient canceled because of lack of insurance coverage. Overall, we identified 21 deleterious mutations (*MLH1*, $n = 9$; *MSH2*, $n = 10$; *MSH6*, $n = 2$). Six patients with variants of uncertain significance were identified (*MLH1*, $n = 2$; *MSH2*, $n = 3$; *MSH6*, $n = 1$), two patients had sporadic CRC (one

BRAF and one *MLH1* promoter hypermethylation), and the remaining 23 patients had uninformative GT results.

DISCUSSION

There is strong support in the literature to develop universal screening for LS among all newly diagnosed patients with CRC. It has been shown that universal screening is feasible⁹ and also cost effective.^{10,11} Furthermore, chain-of-evidence methodology has shown this could lead to improved clinical outcomes for patients and their families.⁷ However, the success of universal screening is dependent on patients receiving the screening results with subsequent pursuit of GC and germline GT.

Our current study clearly showed a higher detection rate of LS by approach 3 ($P = .0185$; three patients in the period of 42 months from January 2004 to July 2007 by approach 1, one patient in the period of 10 months from August 2007 to June 2008 by approach 2, and 17 patients in the period of 42 months from July 2008 to January 2012 by approach 3) even as the monthly surgically resected CRC number remained reasonably stable. Of the patients for whom we had detailed pedigrees, we found that only 20.3% of patients met Amsterdam Criteria and 66.1% met Bethesda Guidelines. The increased LS diagnostic rate is likely a result of a combination of universal LS screening in all surgically resected CRCs and

Table 2. Reasons Why Genetic Counseling Was Not Pursued After Referral

Reason	No. of Patients	%
Lost to follow-up	12	44.4
Declined visit	11	40.7
Death	2	7.4
No show	2	7.4

Table 3. Average Length of Time Between Referral and Genetic Counseling for Each Approach

Time Between Referral and Counseling	No. of Days		
	Approach 1	Approach 2	Approach 3
Average time	457	293	44
Median time	156	30	9
Standard deviation	717	522	93
Range	0-1,945	6-1,218	0-365

the development of an active approach of reporting abnormal MSI/IHC screening results to patients.

The initial approach, approach 1, used what is standard in returning results from anatomic pathology practice (ie, with an addendum in the pathology report). In theory, this addendum should trigger the surgeon-of-record to act, by calling the patient in question and suggesting a GC referral. Unfortunately, this assumption, especially in a large academic medical center, may result in genetics professionals, gastroenterologists, colorectal surgeons, and pathologists operating in silos, which, at our center, yielded only half of appropriate patients being referred. Sanchez et al¹² previously published that when departments operate independently, an inappropriately low number of patients at risk of LS are referred for diagnostic testing. Recognizing the potential impact of this limited practice on our patients, changes were made to improve the process. A more collaborative approach evolved, resulting in interdisciplinary communication and clear roles for each subspecialist, which resulted in all patients being referred for counseling. As the data highlight, this evolution occurred over years and required tremendous commitment and buy-in from the numerous health care professionals. Unfortunately, barriers still remain to getting patients to undergo GC.

The challenge of capturing all patients in a screening program is not unique to the Cleveland Clinic Health System. Backes et al¹³ recently reported poor compliance with GC referral among patients with IHC results suggestive of LS. They found that only 27 (57%) of 47 patients expected to benefit from GC were referred and only 13 (28%) of 47 patients pursued GC. This group also surveyed patients about barriers to pursuing GC services and their risk perception. The most frequently quoted barrier was insurance coverage/cost, and they found that most patients underestimated their risk of LS and associated cancers.

Like Backes et al,¹³ we found that there were barriers to capturing patients for GC who were referred across all approaches. The most common reason for patients not pursuing GC at our center was that they were lost to follow-up. As with other large, tertiary-care hospitals, the Cleveland Clinic sees patients who undergo surgery but continue care at a referring (usually local) center. This complicates contacting patients to discuss results and facilitation of a GC referral. In all of these cases across all three approaches, we attempted to contact patients by telephone and/or letter to discuss the results and offered referral to a local genetic counselor, but we have yet to receive any follow-up.

In addition to the patients lost to follow-up, there were 11 patients who declined GC. The most common reason for not proceeding to GC was a perceived lack of benefit to the patient and/or his or her family, highlighting a clear educational need for this population. As suggested by Chubak et al,¹⁴ an informational fact sheet could be provided in the patient's preoperative materials to increase awareness about MSI/IHC testing and LS. Additionally, managing physicians have a key role in educating and encouraging patients who are initial decliners to using GC services.

Finally, two patients died before the completion of MSI/IHC results. Both patients' IHC results suggest that they had LS (one lacked MSH2/MSH6 and the other lacked MSH6). Given that there could be risk to other family members, it was important to communicate these results to the next of kin or medical power of attorney. Again, despite our attempts, we have had no success communicating with the deceased's family.

It is also important that patients undergo GC in a timely manner, so that, if indicated, patients can receive increased cancer surveillance. There was wide variability in the time between referral and GC (range, same day to 5 years). The shortest interval occurred in approach 3. This coincided with a genetic counselor providing care in colorectal surgery clinics. When possible, patients were offered a GC visit after their postoperative appointment to eliminate barriers associated with scheduling another appointment on a separate day. We believe that access to genetic care is a key factor in successful uptake of GC for those who screen positive.

The strength of this study is that it is the first of its kind to provide a framework for practical clinical implementation of universal MSI/IHC testing. The major limitation of this study is that it was performed at a single academic medical center, albeit large and complex. However, although a variety of approaches could be used for reporting abnormal results and referring patients for GC, all programs will face similar challenges.

It is possible to have a successful program with a high uptake of diagnostic, genetic services. Before initiating universal screening, a plan should be developed in accordance with institution-specific policies. To achieve the greatest success, the program minimally must have representation from colorectal surgery, gastroenterology, gynecologists, pathology, and genetics. Over the duration of our program, we have also sought input from our bioethicists and oncologists. Most importantly, a plan should be developed to assign roles and responsibility for screen results reporting to the patients and facilitating GC referral. At our institution, the screen results are reported to the patients by a genetic counselor, but this could be handled by a variety of disciplines as long as it is clearly detailed whose responsibility it is. The providers who follow these patients over time, such as the surgeons, oncologists, gynecologists, and gastroenterologists, play a critical role in educating and encouraging patients who were initial decliners to pursue GC. Thought should be given to how cases will be handled when patients are lost to follow-up or deceased. Finally, development of educational material based on the most updated information regarding LS screening and diagnosis is needed to increase GC compliance and GT rate in patients with newly diagnosed CRC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Brandie Heald, Matthew F. Kalady, Charis Eng
Financial support: Charis Eng
Administrative support: Brandie Heald, Richard R. Sharp, James Church, Charis Eng
Provision of study materials or patients: Brandie Heald, Jessica Moline, Carol A. Burke, Matthew F. Kalady, James Church, Charis Eng
Collection and assembly of data: Brandie Heald, Thomas Plesec, Xiuli Liu, Rish Pai, Deepa Patil, Jessica Moline, Richard R. Sharp, Carol A. Burke, Matthew F. Kalady, James Church
Data analysis and interpretation: Brandie Heald, Charis Eng
Manuscript writing: All authors
Final approval of manuscript: All authors

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