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ORIGINAL REPORT

Reflex Immunohistochemistry and Microsatellite Instability Testing of Colorectal Tumors for Lynch Syndrome Among US Cancer Programs and Follow-Up of Abnormal Results

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ABSTRACT

Purpose
Immunohistochemistry (IHC) for MLH1, MSH2, MSH6, and PMS2 protein expression and microsatellite instability (MSI) are well-established tools to screen for Lynch syndrome (LS). Although many cancer centers have adopted these tools as reflex LS screening after a colorectal cancer diagnosis, the standard of care has not been established, and no formal studies have described this practice in the United States. The purpose of this study was to describe prevalent practices regarding IHC/MSI reflex testing for LS in the United States and the subsequent follow-up of abnormal results.

Materials and Methods
A 12-item survey was developed after interdisciplinary expert input. A letter of invitation, survey, and online-survey option were sent to a contact at each cancer program. A modified Dillman strategy was used to maximize the response rate. The sample included 39 National Cancer Institute–designated Comprehensive Cancer Centers (NCI-CCCs), 50 randomly selected American College of Surgeons–accredited Community Hospital Comprehensive Cancer Programs (COMPs), and 50 Community Hospital Cancer Programs (CHCPs).

Results
The overall response rate was 50%. Seventy-one percent of NCI-CCCs, 36% of COMPs, and 15% of CHCPs were conducting reflex IHC/MSI for LS; 48% of the programs used IHC, 14% of the programs used MSI, and 38% of the programs used both IHC and MSI. One program used a presurgical information packet, four programs offered an opt-out option, and none of the programs required written consent.

Conclusion
Although most NCI-CCCs use reflex IHC/MSI to screen for LS, this practice is not well-adopted by community hospitals. These findings may indicate an emerging standard of care and diffusion from NCI-CCC to community cancer programs. Our findings also described an important trend away from requiring written patient consent for screening.

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INTRODUCTION

Colorectal cancers (CRCs) are the third most frequently occurring cancers in the United States.[1] The most common form of hereditary CRC is Lynch syndrome (LS), which accounts for 2% to 4% of all CRCs.[2] Approximately one in 35 individuals diagnosed with CRC has LS.[3] The importance of LS identification has been well-established as a result of the associated high risk for colorectal (70% to 80% lifetime) and endometrial (40% to 60% lifetime) cancers and the smaller increased risk for gastric, ovarian, hepatobiliary tract, urinary tract, small bowel, brain, and nervous system cancer risks, the early age of onset (often before age 50 years), the available screening and risk-reduction options[4-8], the potential influence on treatment decisions, and cancer screening and prevention for patients and their families.

LS is caused by inherited defects in the mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*.[9-11] The absence of one or more of the proteins by immunohistochemistry (IHC) staining of fresh or archival (formalin-fixed, paraffin-embedded) tumor tissue and/or the presence of microsatellite instability (MSI) in the tumor

suggest an MMR defect. MMR deficiency can be caused by an inherited MMR gene mutation, but may also be due to somatic hypermethylation of the *MLH1* promoter, which is often associated with a *BRAF* c.1799T>A (p.V600E) mutation.[12] These somatic mutations are typically associated with sporadic CRC. The reported sensitivity of IHC for the MMR proteins is 77% to 83%. The reported sensitivity of MSI is 89% for *MLH1/MSH2* and 77% for *MSH6*.[2] Although abnormal IHC or MSI may be detected in any LS-associated tumor, the greatest experience is with CRC, whether a biopsy specimen or resected tumor.[13]

National guidelines were created to help direct IHC and MSI testing of CRC tumors to screen for potential cases of LS. The main rationale for screening is the opportunity for timely initiation of risk-appropriate screening and prevention interventions for at-risk patients and their families. Historically, the revised Bethesda criteria have been the most frequently used guidelines, with the major indication for tumor testing being CRC diagnosis before age 50 years.[8] The National Comprehensive Cancer Network (NCCN) guidelines also support the use of IHC and MSI testing for LS in individuals with CRC diagnosed before age 50 years.[6] However, more recent data have shown that the use of only the Bethesda guidelines misses many individuals with LS.[3] The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group[14] described MSI and IHC testing as an effective approach for Lynch syndrome screening in all new colorectal diagnoses. The American College of Surgeons Commission on Cancer (ACS-CoC) recently added a requirement for cancer registry abstraction of MSI test results on tumors from the colon, rectum, small intestine, and appendix.[15] None of these guidelines address the practical issues of LS reflex testing, patient education, and whether written informed consent is necessary.

Whether or not written informed consent should be required before tumor testing for LS is a topic of debate in the medical community. Some have argued that informed consent is required for tumor testing because it suggests the presence of LS,[2,16] whereas others have argued that tumor testing is not a genetic test.[17] It has also been argued that MSI testing does not require informed consent because it does not suggest the presence of a mutation in a specific gene[16] or because it may portend tumor response to fluorouracil therapy.[18-21] Throughout this article, MSI and IHC reflex testing refers only to LS screening.

Cost-effective LS screening is the subject of many studies. According to the EGAPP working group, the most cost effective strategy is preliminary tumor testing followed by germline testing guided by abnormal tumor testing.[2] Furthermore, several elegant studies have suggested a population-based approach, with IHC and/or MSI testing of all analytic cases of CRCs in hospitals (cases diagnosed and/or initially treated at the hospital).[12,22,23]

Little is known about the use of reflex IHC and/or MSI screening after diagnosis of CRC in the United States. Although reflex testing has potential benefits and may diminish potential liability for failing to identify LS,[24-26] the standard of care has not been established, and no formal studies have described this practice. Therefore, we aimed to explore the practice of reflex MMR-tumor testing for LS in the United States by type of cancer program and number of analytic CRC cases and to identify the process and factors associated with follow-up of abnormal results. The use of reflex IHC and/or MSI testing predicted by the level of cancer program accreditation and number of analytic cases accessioned during the 2009 calendar year were the primary study outcomes. Secondary outcomes included the use of teaching materials, written informed consent, an opt-out option, age threshold, referral process for genetics consultation, and issues with uptake of genetics consultation.

MATERIALS AND METHODS

Study Design

A cross-sectional, mixed-mode survey method was used.

Survey Development

The survey was developed by a team of City of Hope researchers with input from external experts, including three certified cancer registrars and a pathologist, and followed by pilot testing in a diverse group of 22 health care providers. The final revised survey included 12 check-off questions and six questions with an option of other and space to provide a narrative response. The same survey was created online by using SelectSurvey.NET software (SelectSurvey.NET 2.2.5; ClassApps.com, Overland Park, KS).

The study was approved by the City of Hope institutional review board. The invitation letter described the study and confidentiality. Survey response implied consent to participate. A unique identifier was assigned to each cancer program. Only the principal investigator had access to the primary, identifiable, secured data sources.

Participants

The unit of analysis was cancer programs. The following three strata of cancer programs were used: ACS-CoC–accredited Community Hospital Cancer Programs (CHCPs) as the basic level, ACS-CoC–accredited Community Hospital Comprehensive Cancer Programs (COMPs) as the intermediate level, and National Cancer Institute–designated Comprehensive Cancer Centers (NCI-CCCs) as the most complex level. CHCPs and COMPs were identified from the ACS-CoC Web site. NCI-CCCs were identified from the National Cancer Institute Web site. The one NCI-CCC that specializes in pediatric oncology was not included because LS typically presents in adulthood.

Sample Selection

All 39 NCI-CCCs that provide adult oncology care were invited to participate. We randomly selected a sample of 50 COMPs and 50 CHCPs for participation by using a blinded digital technique from a computer-generated table of 568 random numbers for COMPs and a table of 522 random numbers for CHCPs. Each cancer program was represented by the number corresponding to its line in the original contact-information spreadsheet. The same method was used to select five CHCPs and COMPs to serve as alternates if a cancer program did not participate.

Recruitment

Individuals for recruitment were identified from the pathology, genetics, and/or tumor registry Web sites of each cancer program or membership directories from the National Cancer Registrars Association, the American Society of Clinical Oncology, and the National Cancer Institute Cancer Genetics Service Directory. The study packet (ie, invitation letter, program description form, and survey) was then sent concurrently via e-mail, fax, or US Postal Service to the directors of pathology and tumor registry at the cancer programs asking these individuals to collaborate on submitting a single response or to pass the information on to the most appropriate person. If there was no response after three attempts, each 2 weeks apart, the packet was sent to the primary genetics counselor/nurse of the cancer program; if there was no primary genetics counselor/nurse, the packet was sent to the director of the program. In the few cases in which the director was not identified, all medical oncologists in the American Society of Clinical Oncology directory that were noted to be affiliated with the cancer program were copied on a single e-mail with the study packet attached. These physicians were asked to choose who could best respond.

A modified Dillman strategy was used to maximize the response rate.[27] During the final attempt to recruit cancer programs via e-mail, the body of the

Table 1. Analytic Cases of Colon, Rectosigmoid, and Rectal Cancer Accessioned During 2009 by Type of Cancer Program

Cancer Program	Median Cases	Range of Cases
NCI-CCC	170	25 to 539
COMP	89	30 to 181
CHCP	60	26 to 200

Abbreviations: CHCP, Community Hospital Cancer Program; COMP, Community Hospital Comprehensive Cancer Program; NCI-CCC, National Cancer Institute–designated Comprehensive Cancer Center.

message was shortened to include only key points and the online-survey link. An attachment allowed an e-mailed message friendly to smartphone users. Survey responses could be submitted via SelectSurvey, e-mail, fax, or mail.

Analyses

All survey data were coded and entered into a database by using standard statistical software (Predictive Analysis SoftWare version 18; SPSS, Chicago, IL). Descriptive statistics included frequencies and proportions. A 2×3 χ^2 test of independence was used to measure the association between cancer program type and current reflex-testing practice. The hypotheses that the cancer program type and number of analytic CRC cases predicts cancer program use of reflex tumor testing were examined by using logistic regression models.

RESULTS

The overall response rate was 50% and included a 63% response rate for NCI-CCCs, 50% response rate for COMPs, and 40% response rate for CHCPs. The median number of analytic cases of colon, rectosigmoid, and rectal cancers accessioned during 2009 were 170, 89, and 60 cases for NCI-CCCs, COMPs, and CHCPs, respectively (Table 1). At least 84% of survey respondents (two respondents did not specify their occupations) were pathology and/or tumor registry directors, genetic counselors, or nurses. The remaining 15% were other physicians. Data from the only duplicate set of survey responses received were compared for validity, and responses were concordant.

Reflex-Testing Practices

Overall, 42% of responding cancer programs were currently using LS reflex IHC and/or MSI testing on CRC tumors and another 16% of programs planned to do so (Table 2). Specifically, this testing was being conducted in 71% of NCI-CCCs, 36% of COMPs, and 15% of CHCPs. Among programs conducting LS reflex testing, 48% of programs used IHC, 14% of programs used MSI, and 38% of programs used both IHC and MSI. Individuals who championed the reflex-testing process included pathologists (35%), genetic providers (17%), other providers (38%), and no one specific champion (7%).

Convention Used to Select Cases for Reflex Tumor Testing

Of the programs that currently use reflex LS IHC and/or MSI, 38% of programs tested all new cases of CRC, 27% of programs tested cases diagnosed before age 50 years, 14% of programs tested cases diagnosed before age 60 years, and 21% of programs used another convention to select CRC cases for this testing (Table 3). NCI-CCCs and COMPs most frequently used an LS reflex test for all new CRC cases, whereas CHCPs only used this testing for CRC cases diagnosed before age 50 years.

Table 2. Reflex Testing Practices for Lynch Syndrome by Level of Cancer Program

	NCI-CCC		COMP		CHCP		Total	
Type of Reflex Test	No.	%	No.	%	No.	%	No.	%
IHC only	7	29.2	6	24.0	1	5.0	14	20.3
MSI only	4	16.7	0	0.0	0	0.0	4	5.8
IHC and MSI	6	25.0	3	12.0	2	10.0	11	15.9
Plan future IHC	0	0.0	5	20.0	0	0.0	5	7.3
Plan future MSI	0	0.0	0	0.0	0	0.0	0	0.0
Plan future IHC and MSI	4	16.7	1	4.0	1	5.9	6	8.7
Not IHC or MSI and no future plans	3	12.5	10	40.0	16	80.0	29	42.0
Total	20	100.0	25	100.0	24	100.0	69	100.0

Abbreviations: CHCP, Community Hospital Cancer Program; COMP, Community Hospital Comprehensive Cancer Program; IHC, immunohistochemistry; MSI, microsatellite instability; NCI-CCC, National Cancer Institute–designated Comprehensive Cancer Center.

Preoperative Practices

Of the cancer programs that currently use reflex testing, 79% of programs did not routinely use additional preoperative processes such as brochures or offer testing options (Table 3). Only 14% of programs offered an option to opt out of reflex testing, 3.5% of programs provided a presurgical packet that included information on reflex testing, and 3.5% of programs did not specify the preoperative materials used. None of the responding cancer programs required written consent for reflex tumor testing.

Table 3. Convention Used to Select Cases for Reflex MSI and/or IHC Testing and Preoperative Practices (among cancer programs that currently use reflex testing for Lynch syndrome)

	NCI-CCC (n = 17)		COMP (n = 9)		CHCP (n = 3)		Total (n = 29)	
Cancer Program Practice	No.	%	No.	%	No.	%	No.	%
Convention to select cases								
All new cases	7	41.0	4	44.0	0	0.0	11	38.0
Diagnosed before age 60 years	1	6.0	3	33.0	0	0.0	4	14.0
Diagnosed before age 50 years	5	29.0	0	0.0	3	100.0	8	27.0
Other selection process used	4	24.0	2	22.0	0	0.0	6	21.0
Preoperative practices								
Presurgical packet includes reflex information	1	6.0	0	0.0	0	0.0	1	3.5
Signed consent for reflex is required	0	0.0	0	0.0	0	0.0	0	0.0
An opt-out option is offered	1	6.0	1	11.0	2	67.0	4	14.0
Other preoperative practice (NOS) is used	1	6.0	0	0.0	0	0.0	1	3.5
No preoperative practices are routinely provided	14	82.0	8	89.0	1	33.0	23	79.0

Abbreviations: CHCP, Community Hospital Cancer Program; COMP, Community Hospital Comprehensive Cancer Program; IHC, immunohistochemistry; MSI, microsatellite instability; NCI-CCC, National Cancer Institute–designated Comprehensive Cancer Center; NOS, not otherwise specified.

Table 4. Process of Referral to Genetic Services and Problems With Patient Follow-Up (among cancer programs currently using reflex testing for Lynch syndrome)

	NCI-CCC		COMP		CHCP		Total	
Mechanism for Referral	No.	%	No.	%	No.	%	No.	%
Referral automatic and electronic	3	17.65	0	0.0	0	0.0	3	
Referral initiated by specialist	3	17.65	0	0.0	0	0.0	3	
Referral initiated by result recipient	11	64.7	9	100.0	3	100.0	23	
Total	17	100.0	9	100.0	3	100.0	29	
Referrals to genetic services are tracked, yes	10	58.8	4	44.4	2	66.7	16	55.2
Aware of problem with patient follow-up of genetics referral, yes	9	52.9	3	33.3	2	66.7	16	55.2

Abbreviations: CHCP, Community Hospital Cancer Program; COMP, Community Hospital Comprehensive Cancer Program; NCI-CCC, National Cancer Institute–designated Comprehensive Cancer Center.

Genetics Referral Process, Patient-Tracking, and Identified Problems

Among COMPs and CHCPs, referrals to genetics services were expected to be initiated by the individual who received the reflex-test results (Table 4). The process used by NCI-CCCs showed greater diversity with 65% of referrals initiated by the results receiver, 18% of referrals initiated by an automatic electronic mechanism, and 17% of referrals initiated by a specialist.

Regarding monitoring of the referral process, 58.8% of NCI-CCCs, 44.4% of COMPs, and 66.7% of CHCPs implemented a tracking mechanism (Table 4). Among these programs, 53% of NCI-CCCs, 33% of COMPs, and 67% of CHCPs reported problems with patient follow-up of genetics referrals (Table 4).

Of the cancer programs that currently use LS reflex testing, the automatic recipient of the test results included the surgeon alone (27.6%), the surgeon and another health care provider (55.2%), a genetic health care provider alone (6.9%), a nonsurgeon and nongenetic health care provider (6.9%), or no one (3.4%; Table 5).

Association Between Cancer Program Type and Reflex Testing

There was a significant association between the type of cancer program and current reflex-testing practice ($\chi 2\,[2, n = 69], = 14.543$; $P = .001$). NCI-designated CCCs were significantly more likely to currently engage in reflex testing than were COMPs and CHCPs.

Multinomial logistic regression indicated that the number of CRC cases accessioned during 2009 predicted the current practice of reflex IHC/MSI testing ($P = .049$). Similarly, being an NCI-CCC predicted the current reflex IHC/MSI testing use ($P = .013$), whereas being a COMP did not (Table 6).

Table 5. Who Automatically Receives IHC/MSI Reflex Test Results (among cancer programs currently using reflex testing for Lynch syndrome)?

	NCI-CCC		COMP		CHCP		Combined	
Result Recipient	No.	%	No.	%	No.	%	No.	%
Surgeon alone or with other	12	70.6	9	100.0	3	100.0	24	82.8
Genetic health care provider	2	11.8	0	0.0	0	0.0	2	6.9
Nonsurgeon, nongenetic provider	2	11.8	0	0.0	0	0.0	2	6.9
No one	1	5.9	0	0.0	0	0.0	1	3.4
Total	17	100.0	9	100.0	3	100.0	29	100.0

Abbreviations: CHCP, Community Hospital Cancer Program; COMP, Community Hospital Comprehensive Cancer Program; IHC, immunohistochemistry; MSI, microsatellite instability; NCI-CCC, National Cancer Institute–designated Comprehensive Cancer Center.

Comments From Cancer-Program Respondents

Several cancer-program respondents described their concerns and challenges about adopting a program of reflex tumor testing. These comments included feelings of frustration. An NCI-CCC respondent replied, "It's very messy. This has been a battle.… Pathologists think they can tell by their review if it needs MSI/IHC. Genetics has been pushing for universal screening—with no luck."

Several respondents at COMP settings requested help with their deliberations as follows:

COMP1: "Do you have any recommendations on what criteria should be applied to justify MSI or IHC testing be performed?… although the NCCN is now acknowledging the EGAPP recommendation that all patients receive the testing, we fear that insurers are not yet ready to cover automatic testing for patients. Your toolkit should indeed prove valuable."

COMP2: "Interestingly, just this week I am investigating such a case of a patient who I think this testing is indicated on, however, I would like to receive from you any reference information available on the which/when/who we should be doing this screening on one of our colorectal carcinoma cases. I have some sense of this but we have not instituted any formal protocol to do so."

COMP3: "My institution is trying to decide what to do in regards to routine MSI/IHC screening on colon/endometrial tumors. I am frequently asked, 'What is everyone else doing?'"; "Finding a way to pay for IHC and MSI tests that are not covered by insurance is harder for small institutions than comprehensive cancer centers." Similarly, NCI-CCC2 responded, "Our pathologist/molecular diagnostics do not feel they will get reimbursed for all MSI studies, which is why we have limited it to under [age] 50 [years]."

DISCUSSION

To our knowledge, this was the first study to formally examine the implementation of reflex tumor testing by cancer programs in the United States. Findings suggested that reflex testing with MSI and/or IHC is an emerging standard of care. We identified heterogeneity in

Table 6. Multinomial Logistic Regression Predicting Reflex Testing Using Three Levels for the Dependent Variable (eg, now, future, or never)

Predictor	*B*	SE *B*	*P*	OR	95% CI
No. of CRC cases	0.012	0.006	.049	1.012	1.000 to 1.023
NCI-CCC	2.418	0.969	.013	11.221	1.681 to 74.898
COMP	1.388	0.801	.083	4.006	0.834 to 19.249

Abbreviations: COMP, Community Hospital Comprehensive Cancer Program; CRC, colorectal cancer; OR, odds ratio; NCI-CCC, National Cancer Institute–designated Comprehensive Cancer Center.

the practice of reflex tumor testing to screen for LS. However, NCI-CCCs are leading the way, with the majority having already implemented this testing.

Reflex testing of CRC tumors by IHC and/or MSI is a relatively recent innovation. The theory of diffusion of innovations purports that the rate of adoption for an innovation is primarily influenced by the following five attributes: relative advantage, compatibility, complexity, trialability, and observability.[28] Prestige (eg, using the innovation) or shame (eg, not using the innovation) may serve as motivators to engage in the innovation. Opinion leaders and change agents function to influence others to adopt innovations.[29] Opinion leaders (eg, The Ohio State University) are early adopters of the innovation and try to urge their peers to adopt the innovation. These early adopters allow middle and late adopters of an innovation the opportunity to view benefits, risks, and costs of the innovation before implementation in their own programs. Change agents (eg, the EGAPP and NCCN) work to expedite uptake and, thus, increase the expansion of the innovation. From comments of participants, it is clear that many of the programs that are contemplating the initiation of LS reflex tumor testing need information about implementation procedures such as patient-selection criteria and a literature base that documents benefits, limitations, and prevalent practices to help overcome institutional barriers. There may also be a need for education regarding this testing among health care professionals who provide care to patients with CRCs so that these professionals may serve as local champions to promote the practice.

Although the diffusion of LS reflex tumor testing practices is encouraging from the perspective of enhanced cancer prevention and control, the fact that approximately one-half of all respondents noted problems with patient participation in recommended follow-up consultations suggested a potential patient-side barrier to effectiveness. Thus, there is a need for companion behavioral research and monitoring of patient uptake for programs that implement reflex tumor testing.[30]

Manne et al[31] explored the use of a patient education CD-ROM intervention that focused on MSI tumor testing among individuals with CRC. A self-administered education tool may be an effective means to help prepare patients for the results of their testing and promote compliance with subsequent recommended follow-up consultations.

One important finding of our study related to the practical implications for implementation of a program of LS tumor testing. That is, none of the cancer programs that currently use this reflex testing required a specific informed consent for it.

The cross-sectional design did not allow for the capturing of prevalence over time; however, the design did capture programs that planned to do so in the immediate or more distant future.

The study was also limited by the modest sample size, although the NCI-CCCs were well represented, and there was a relatively good response rate overall. Although it is possible that programs with or who had explored reflex testing may have been more likely to respond, the relatively high response rate (63%) suggested that the practices are reflective of NCI-CCCs at the least. Furthermore, if programs that were not using reflex testing were less likely to respond, the key finding regarding no requirement for written informed consent is still valid. Random selection was used to select COMPs and CHCPs, and respondents represented a broad sample of every geographic region of the continental United States and Alaska.

These findings may indicate an emerging standard of care and reflect a diffusion from NCI-CCC to the community cancer programs. Professional resources to guide the implementation of LS reflex tumor testing are needed and may help individual centers overcome barriers to adoption. Behavioral research is needed to realize the potential benefits and patient-side barriers of identifying LS cases and families.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

Conception and design: All authors
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Administrative support: Jeffrey N. Weitzel
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Manuscript writing: All authors
Final approval of manuscript: All authors

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