Prospective Screening for Lynch Syndrome in a Cohort of Colorectal Cancer Surgical Patients in the Presbyterian Health Care System in Albuquerque, New Mexico 2008 -2013

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SCREENING LYNCH SYNDROME COMMUNITY

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ABSTRACT

Background:

Lynch syndrome, the most common hereditary colorectal cancer syndrome, is responsible for approximately 3% of newly diagnosed colorectal cancer patients. Tumor mismatch repair screening for Lynch syndrome is uncommon in community hospital cancer programs accredited by the American College of Surgeons Commission on Cancer in the United States. This study describes a prospective molecular screening program for Lynch syndrome identification utilizing a community hospital colorectal cancer surgical cohort ≤ 60 years of age.

Study Design:

From January 2008 through December 2013, 815 patients with newly diagnosed colorectal cancer underwent colorectal surgery. The study group consisted of the 218 patients who were ≤ 60 years of age. This group had their surgical specimens analyzed for a mismatch repair defect, the hallmark of Lynch syndrome, either by immunohistochemistry or microsatellite instability. In the last 2.5 years of the study, specimens exhibiting microsatellite instability were further screened with a MLH1 promoter methylation assay.

Results:

Twenty-five patients of the study group (11%) had pathology specimens with evidence of a mismatch repair defect. Of the 25 with a mismatch repair defect, 1 patient had a BRAF mutation and 5 patients showed MLH1 promoter methylation. Among the 19 remaining, 14 (74%) underwent genetic cancer risk assessment. Twelve mutation positive Lynch syndrome patients were identified, which represents 5.5% (95% CI, 3.0%-9.7%) of the screened cohort.

Conclusions:

A prospective Lynch syndrome tumor-screening program can successfully identify Lynch syndrome patients in a community hospital healthcare system. Other community hospital cancer programs could use our strategy.

Keywords: Hereditary cancer; Lynch syndrome tumor molecular screening; Microsatellite instability; MLH1 Methylation; Community hospital

INTRODUCTION:

Lynch syndrome (LS) refers to individuals with a hereditary predisposition to colorectal cancer (CRC), endometrial cancer (EC) and certain other malignancies who have a deleterious (disease causing) germ line mutation in a mismatch repair (MMR) gene.[1,2] LS includes patients who have cancer and those who have not had cancer. Individuals with LS have a colon cancer risk between 22% and 58% by age 70.[2,3] Surveillance in patients with LS can delay the appearance of new CRC and reduce mortality from CRC in both men and women.[4-6] Each identified LS patient has on average 3 family members carrying the same mutation, multiplying the benefit of identifying an individual patient with a LS mutation at the first diagnosis of cancer when at-risk family members can be offered genetic testing.[1,6,7] The molecular marker for the presence of a MMR defect in tumor tissue is the presence of microsatellite instability (MSI).

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (EWG) found sufficient evidence to recommend routine pathologic screening (reflex testing) of all newly diagnosed colorectal cancer tumor specimens for either MSI or immunohistochemistry (IHC) expression of the MMR proteins. For those patients with positive screening results genetic testing should be offered.[3]

Establishing a LS screening program is labor and resource intense and requires a leader who has dedicated time to coordinate appropriate action on positive screening tests between the patient and multiple

caregivers. There are no LS screening program templates that can be applied to all clinical practice situations. Most importantly, communities must have the appropriate providers with genetic cancer and risk assessment (GCRA) expertise and must include third party payers in the planning process. Recent publications from academic centers emphasize the complexities and pitfalls in establishing LS screening programs.[7-10]

A 2012 survey found that MMR-tumor testing for LS in community hospital cancer programs accredited by the American College of Surgeons Commission on Cancer (ACOS-CoC) are uncommon.[11] In the United States (US) 70% of cancer patients are cared for in ACOS-CoC accredited cancer programs.[12] They identified that 71% of NCI comprehensive cancer centers (NCI-CCC), 36% of community hospital comprehensive cancer programs (COMP) and 15% of community hospital cancer programs (CHOP) had molecular LS screening programs in place. From the survey data presented, one surmises the majority of newly diagnosed CRC patients in the US are not screened for LS.

We report the experience of designing and implementing a screening program for LS in a community hospital comprehensive cancer program (COMP) accredited by the ACS-CoC. The results of the first 6 years of screening (2008 through 2013) are presented here and an abstract of the 2008-09 results were presented in 2010.[14]

PATIENTS AND METHODS:

Study Setting, Design and Patient Selection

Presbyterian Health Services (PHS) is a private not-for-profit health care system and health insurance provider in the state of New Mexico. PHS has partnered with the University of New Mexico in TriCore Reference Laboratories, a not-for-profit lab services corporation. The PHS cancer program in Albuquerque is certified by the ACS-CoC as a COMP.

Beginning January 1, 2008 reflex IHC for MMR proteins was performed in all patients who were ≤ 60 years of age undergoing a surgical resection for colorectal cancer. Our analysis of the age distribution of LS in newly diagnosed CRC patients in published data showed that nearly 80% of LS diagnosis occurs in patients ≤

60 years of age.[7-8] We anticipated CRC patients ≤60 years of age at diagnosis would comprise approximately 35% of the total newly diagnosed CRC cohort.[8] In addition, the pathologists could reflex test any patient >60 years of age in the PHS pathology database who had a prior colorectal or other LS associated tumor. These cases would be analyzed separately. The Cancer Committee and Medical Executive Committee of the Presbyterian Medical Staff along with the PHS health plan approved as a standard of care change. An essential element was to obtain insurance coverage for the screening protocol from Presbyterian Health Plan. Specific patient consent for routine pathology testing (reflex testing) done on all patients with CRC undergoing surgery was not required, as "no consent" was the norm among North American sites with similar screening programs.[14] Patient consent would be required for any germ line genetic testing. All patients screened were diagnosed in the Presbyterian Health system in Albuquerque and were attended by physicians on the PHS medical staff. Anonymity of all patients was a priority among the participating health care providers.

Pathology, Molecular Studies and Results Disclosure

Initially, IHC for the 4 MMR proteins were performed.[3,7-8] If the tumor failed to express MLH1, a BRAF V600E gene assay or a MLH1 promoter methylation assay was done. If BRAF is mutated, LS is very unlikely. However, an absence of the MLH1 MMR protein or a MSI H assay can also be caused by an acquired defect secondary to inactivation of the MLH1 promoter region by methylation. An assay for the presence of MLH1 promoter methylation can be performed by Polymerase chain reaction (PCR) to identify patients with an acquired and not inherited defect.[15] In July 2011 the protocol was modified and MSI by PCR became the initial test with reflex to a MLH1 promoter methylation assay also by PCR if MSI present (figure 1). MSI is more specific than IHC and MLH1 promoter methylation assay is more specific and has a higher positive predictive value than BRAF to identify an acquired defect.[3,15] IHC for MMR, MSI and MLH1 methylation by PCR, and BRAFV600E gene assays are currently performed at TriCore. One staff pathologist and author (RMF) is responsible for maintaining a comprehensive spread sheet of results and he reviews the pathology and laboratory logs regularly to ensure inclusion of all eligible patients.

Results of the reflex assays are sent to the attending surgeon as an addendum to the pathology report and if the testing suggests LS, the pathologist calls the surgeon and the patient is referred for GCRA by either the surgeon or medical oncologist.

Genetic Cancer Risk Assessment (GCRA) and genetic testing

A community healthcare system that sponsors a LS screening program must have professionals trained in GCRA within their network. In Albuquerque there are physicians, primarily medical oncologists, nurse practitioners and physician assistants who have completed the City of Hope cancer genetics program and are members of the Clinical Cancer Genetics Community Research Network (CCGCRN).[16] Many medical oncologists have participated in the American Society of Clinical Oncology cancer genetics workshops and offer GCRA to their patients.[17] Lynch syndrome education in the Albuquerque community has been ongoing for 15 years with the leadership of 2 physicians and authors (PRD, JTL) who established a familial cancer clinic within their private oncology practice.[18] Masters level genetic counselors staff the University of New Mexico Cancer Center, a designated NCI-CCC and constitute a referral source when needed.

A nurse practitioner (KJS), a member of CCGCRN, joined the medical oncology clinic staff in year 3 of the study and coordinates GCRA during treatment. A similar process is recommended in a recent publication.[9] LS patients are strongly encouraged to contact their immediate family members about their LS diagnosis. She also is a resource for family members who will need GCRA and has been able to meet with some of them directly.

If the patient undergoes germ line genetic testing, the presence of a deleterious mutation in EPCAM or 1 of the 4 mismatch repair (MMR) genes MLH1, MSH2, MSH6 and PMS2[2,7-8,19] identifies Lynch syndrome.

Lynch-like syndrome (LLS) is a recently identified group of patients who have all the molecular characteristics of LS except that no deleterious MMR mutation can be identified.[20] Patients with LLS have an intermediate risk of cancer between LS and the risk of families with sporadic CRC and need special tailored cancer surveillance protocols.

Statistical Methods

Confidence intervals were calculated using the Wilson score method with continuity correction described in Newcombe.[21]

RESULTS:

In the 6-year period of this study, 815 patients were diagnosed with CRC, of which 221 (27%) were ≤ 60 years of age. All 221 specimens were obtained and analysis was completed in 218 (98.6%). In one patient there was insufficient tissue for reflex testing. The attending surgeon requested no reflex testing in two patients. Twenty-five patients (11%) had evidence of a MMR defect. In this group, 5 patients had the presence of MLH1 promoter methylation and 1 had a mutation in BRAF V600E. The remaining 19 patients were candidates for GCRA and 14 (74%) completed their evaluation. This data is presented in Table 1. Five of the 19 patients did not undergo GCRA: 2 declined, 2 were lost to follow-up, and 1 patient is delaying GCRA while undergoing LS surveillance by gastroenterology. Out of 14 patients who received GCRA, 12 patients received GCRA from community providers: oncologists, nurse practitioners and physician assistants who are members of CCGCRN. Two were evaluated by genetic counselors at the University of New Mexico Cancer Center (UNM). Twelve LS mutations were identified representing 5.5% (95% CI 3.0%-9.7%) of the 218 patients screened.[21] The median age at the first cancer diagnosis in the mutation positive group ≤ 60 years of age is 46 years. In the first 2 years of the program 56% of LS candidate patients completed GCRA. In the last 4 years, 91% of patients completed GCRA in a median time of 6 weeks after the introduction of a nurse practitioner with GCRA expertise. LS patients are followed according to accepted practice guidelines.[6,22-23]

Two patients were diagnosed synchronously with endometrial cancer and colon cancer. In 1 of these patients there was discordance in the results of tissue testing with the initial endometrial tissue showing MLH1 promoter methylation and the colon tissue did not. The gynecologic oncology community in Albuquerque has pursued a LS screening program in women ≤ 60 years of age. Another patient with a prior rectal cancer showed MSI high on the archival tissue whereas the current renal pelvis tumor was MSI low. This is consistent with

results observed by others and emphasizes the importance of considering the colon cancer tissue as the tissue of choice for the molecular studies when the patient has multiple Lynch tumors.[24] Two patients after the initial biopsy showing CRC were referred for GCRA prior to definitive resection because of family history.

The pathology database did enhance our ability to identify LS in those >60 and four patients with clinical LS were identified and 3 were identified with a LS mutation. All developed upper tract urothelial cancer (UTUC). The lifetime risk of UTUC in LS patients is reported to be 8.4% to age 70, is most common in patients with a mutation in MSH2 and in males with a MSH2 mutation a lifetime risk of 27.7%.[24]

Overall, including the 3 patients >60 years of age and the 2 patients with LLS we identified 17 patients who along with their family members need increased CRC surveillance.

DISCUSSION:

The overall rate of LS identification in our study is 5.5%(95%CI 3.0-9.7%) in the screened population ≤60 years of age. This is consistent with the Ohio State LS screening data, reported in their published Appendix (Table A-2)[8] Their data shows 5.7% LS in 593 patients < 60 years of age. Two recent screening studies of CRC patients ≤50 years of age, one from the US and one from New Zealand, reported similar rates of LS identification of 5.1%[26] and 5%,[27] respectively. We identified 12 new LS patients and 2 LLS during the study period. Only 2 of these patients were identified as possible LS prior to their surgical resection. Our screening program identified the remaining 13. The surgeon knowing that a patient has LS preoperatively may recommend an extended resection as a surgical option based on current recommendations.[22]

Five patients with abnormal screening studies did not receive GCRA in a timely manner. We now maximize capture of patients needing GCRA by providing for that service in the oncology clinic and >90% of eligible patients complete GCRA and genetic testing. The patient's failure to complete CGRA and genetic testing is the most common reason citied in previous reports of LS screening for suboptimal screening results.[9-10,26-28]

Identification and recruitment of community based professionals skilled in GCRA will be increasingly important for the successful implementation of LS screening strategies in the community health care systems in the US. Our success with GCRA using physicians, nurse practitioners, and physician's assistants who are members of the City of Hope CCGCRN demonstrates a strategy that works for us.[16-18] We have identified a higher success rate in obtaining GCRA when the professional providing the GCRA is available in the follow-up clinic. This is observed by others.[9] We are able to refer patients needing more in depth counseling to masters level genetic counselors at UNM.

Medical oncologists throughout the United States are guiding their patients in the area of GCRA and the new area of genomics.[17-18,23] Following the recent simultaneous publication of consensus guidelines for the diagnosis and management of LS in 4 major gastroenterology journals, more gastroenterologists and surgeons may develop an interest and expertise in genetic gastrointestinal cancer evaluation and diagnosis.[22] This will add to the potential pool of providers who can participate in or lead LS screening programs in the community.

We were able to capture 98.6% of the eligible CRC specimens by implementing a system in pathology to confirm on a regular basis that all specimens were included and all appropriate reflex studies were ordered and tabulated. In a screening program one needs to maximize the yield of each step.

Current screening is performed with MSI by PCR with reflex of MSI-H specimens to MLH1 promoter methylation by PCR and the algorithm is displayed in Figure 1. This strategy identifies a cohort of candidate LS patients who need GCRA and who are all at increased risk for new colon cancers. This strategy may miss a small proportion of patients who have LS but also have secondary methylation of the MLH1 promoter.[29]

When this LS screening protocol started, there was no consensus on an upper age-cutoff for screening. A screening protocol is not designed to find all cases but to detect most cases by testing a high-risk population. The high-risk population for LS identification is those CRC patients ≤ 60 years where 5.7% are expected to have LS.[8] By limiting screening to ≤60 years of age we only screened 27% of our incident CRC patients and realized significant cost savings in reflex testing costs.

The NCCN guidelines call for screening for LS every newly diagnosed patient with CRC or at a minimum all ≤ 70 years of age and for those >70 years who meet the Revised Bethesda Guidelines.[30] The results of a LS screening program in patients ≤ 50 years of age from Memorial Sloan-Kettering Cancer Center are published.[26] They found LS in 5.1% of patients screened and they found no reason to justify screening patients >50 years of age routinely in their center.

The buy-in of all stakeholders is important when one initiates a Lynch screening program[31] and the program needs to be customized based on an individual institution's capabilities, the capabilities of the medical community and available resources.[22,32]

CONCLUSIONS:

We have demonstrated a successful strategy for the prospective identification of LS in a cohort of newly diagnosed CRC patients ≤ 60 years of age undergoing surgery by reflexing the surgical tissue for MSI followed by a second reflex of the MSI H specimens to a MLH1 promoter methylation assay. This identifies those patients with potential LS that need GCRA. We believe this strategy is appropriate for community hospital programs contemplating the establishment of a LS screening program.

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Table 1 Results ≤ 60 years of age in Colorectal Cancer Cohort	
Number	**Notes**
218	**Patients** in the screened cohort ≤ 60 years of age; average age 51 at time of initial surgery; 51% female
25	**Mismatch repair defect** identified in 11% of the cohort
6	**Methylation** of MLH1 promoter or BRAF mutated in the MMR defect cohort
19	**Patients who potentially have Lynch syndrome and need GCRA** • Fourteen patients (74%) completed GCRA and genetic testing
12	**Deleterious mutations** found in one MMR protein gene; median age 46 years; 50% female Rate of LS identification is 5.5% (95% CI 3.0%-9.7%) of screened cohort • Mutations: MLH1 5; MSH2 4; EPCAM 1; MSH6 2 • Median age at first cancer diagnosis 46 years • Two patients had synchronous CRC and endometrial cancers • GCRA completed median time of 6 weeks (range 3-40 weeks)
2	**Lynch-Like Syndrome patients**: MSI H and mutation analysis negative for deleterious mutation directed by IHC • Patient age 46 years died of metastatic disease • Patient age 51 years undergoing active cancer surveillance
5	**Patients with Mismatch Repair Defect identified who failed to complete GCRA** • Patient age 51 years; regular surveillance colonoscopy; GCRA postponed • Patient age 54 years; family history suggestive of LS; declined GCRA • Patient age 38 years; MSI H; MLH1 methylation negative; lost to follow-up • Patient age 47 years; declined GCRA in 2008 • Patient age 59 years; referred to outside institution and lost to follow-up in 2009
14	**Patients completing GCRA** • Twelve patients received GCRA from members of the CCGCRN • Two patients seen by genetic counselor at University of New Mexico

FIGURE 1
SCREENING LYNCH SYNDROME COMMUNITY

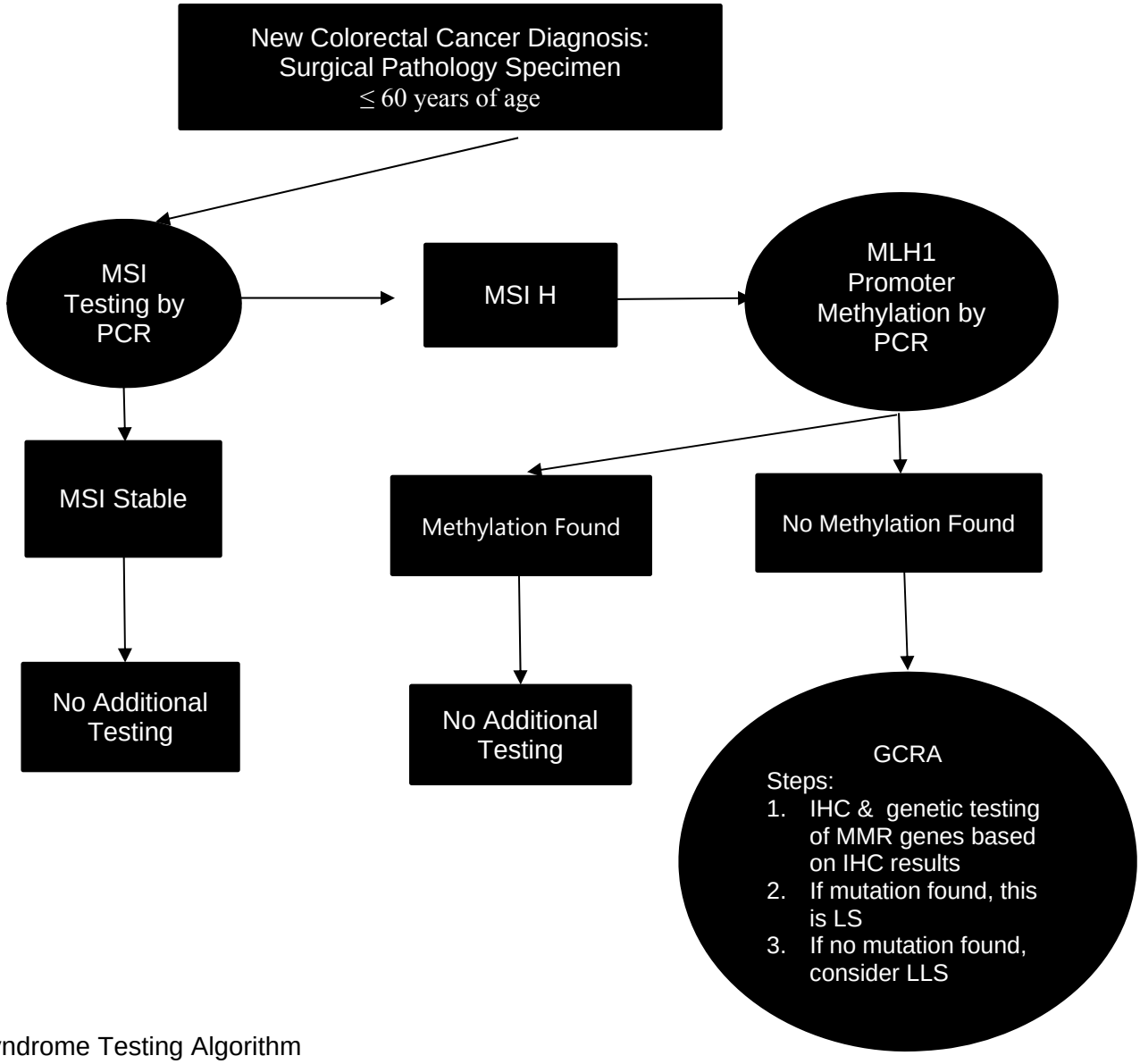

Figure 1
Lynch syndrome Testing Algorithm Utilized in the Final 2 ½ Years of the Protocol Period.