Findings of UTS for LS in an Integrated Healthcare System

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Abstract

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Introduction: Lynch syndrome (LS) is associated with an increased risk of colorectal (CRC) and endometrial (EC) cancers. Universal tumor screening (UTS) of all patients diagnosed with CRC and EC is recommended to increase identification of LS. Kaiser Permanente Northwest (KPNW) implemented a UTS program for LS among individuals newly diagnosed with CRC in January 2016 and EC in November 2016. Screening includes immunohistochemistry (IHC) of mismatch repair proteins associated with LS, followed by reflex testing, if indicated, to rule out likely sporadic cases.

Materials and methods: Individuals newly diagnosed with CRC and EC were identified between the start of the respective screening programs and July 2018. Electronic medical records were reviewed to extract patient data related to tumor screening, including IHC and reflex testing results, date of referrals to the genetics department, and genetic testing results.

Results: 344 out of 400 CRC patients and 66 out of 69 EC patients who were eligible were screened for LS. Most (53/59 or 90%, including 52/56 CRC and 1/3 EC) individuals that were not screened only had a biopsy sample available. Fifteen individuals (3.6% overall, including 14/344 CRC and 1/66 EC) received an abnormal screen result after reflex testing and were referred for genetic counseling. Of these, 11 individuals (82% overall, including 10/14 CRC and 1/1 EC) underwent genetic testing. Six CRC patients were found to have pathogenic variants.

Conclusion: The UTS programs assist in identifying LS in KPNW patients. Timing of screening (i.e., soon after surgery for CRC) was not a significant barrier for follow-up. There are opportunities for improvement, such as consistent use of biopsy samples for screening.

Key Words: Lynch syndrome; HNPCC; colorectal cancer; genetic screening; genetic testing; microsatellite instability

INTRODUCTION

Lynch syndrome (LS) is a hereditary cancer syndrome which notably leads to an increased risk of colorectal cancer (CRC) and endometrial cancer (EC), among many other cancer types. Males diagnosed with LS have a lifetime risk of 30-75% for CRC, while females diagnosed with LS face a lifetime risk of 25-50% for CRC and 30-40% for EC.[1] LS accounts for 3% of all cases of CRC and 2% of all cases of EC.[2-4] This autosomal dominant condition is caused by pathogenic variants in DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*)[5,6] and deletions in *EPCAM* which result in inactivation of *MSH2*.[7,8] Despite a prevalence estimate of 1 in 279 for LS in the United States general population, less than 2% of people affected by LS have been diagnosed.[9] Undiagnosed individuals represent a missed opportunity to implement medical interventions to reduce cancer-related morbidity and mortality, including increased surveillance and risk-reducing surgery or medication.[1,10,11]

Historically, methods to screen for Lynch syndrome focused on the presence of high-risk criteria, such as a personal and family history or early age at onset of LS-associated cancers.[12] The Revised Amsterdam and Bethesda criteria[13-16] and risk assessment algorithms, such as $PREMM_5$, MMRpro, and MMRpredict,[17-19] are examples of methods developed for selective screening of LS. However, these methods may miss LS in patients who have limited or unreliable family history, do not meet the high-risk criteria,[20,21] or meet the high-risk criteria but do not undergo evaluation for LS.[22-27] Universal tumor screening (UTS) for LS is one proposed method for increasing the identification of LS. This approach systematically screens all individuals newly diagnosed with CRC and EC, regardless of family history or age. Screening based upon cancer diagnosis as opposed to other risk criteria may lead to LS diagnoses in individuals who would otherwise be missed and may be a complimentary approach to increasing

LS identification. Such UTS approaches are recommended by multiple expert guidelines to increase the identification of LS.[12, 28-33] Though the exact approach for UTS may vary across health care systems, the first step is to typically screen the tumor tissue (via microsatellite instability (MSI) or immunohistochemistry (IHC) testing) to detect the absence of one or more of the MMR proteins. Reflex testing follows if MLH1 loss is reported to detect the presence of *BRAF* V600E or *MLH1* hypermethylation, two indicators of sporadic *MLH1* loss unrelated to LS. Individuals that screen positive for LS after these steps are then referred for genetic counseling and germline testing to confirm an LS diagnosis.[4]

UTS has been implemented into many healthcare systems, but its uptake is still limited. Many barriers exist for healthcare systems to implement effective UTS programs.[34-36] Additionally, there are limited data on the outcomes of such screening programs in community healthcare settings, including measures of uptake of genetic counseling and testing. While there is substantial evidence to support UTS as a valuable method for diagnosing LS, mixed results have been reported even in healthcare systems and regions similar to Kaiser Permanente Northwest (KPNW).[37,38]

The goal of this study was to assess the effectiveness of UTS programs implemented by an integrated healthcare system by systematically determining whether all individuals with CRC and EC that should be screened were screened and to assess the rate of appropriate follow-up with the genetics department. This study adds to the evidence for UTS by detailing the flow of patients through the screening process to identify points in the process that could be improved to maximize the effectiveness of UTS programs in identifying individuals with LS. These findings and lessons learned during the implementation of a universal screening program can inform other healthcare systems looking to design or improve their own screening programs.

MATERIALS AND METHODS

Study Population

KPNW is an integrated health care system that serves more than 625,000 members in northwest Oregon and southwest Washington. KPNW began to perform tumor screening among all individuals newly diagnosed with colorectal cancer (CRC) in January 2016 and all individuals newly diagnosed with endometrial cancer (EC) in November 2016.

Universal Screening Protocol

According to the UTS protocol at KPNW, each CRC and EC case undergoes tumor screening with immunohistochemistry (IHC) to detect the presence or absence of the 4 MMR proteins: MLH1, MSH2, MSH6, or PMS2. If loss of MLH1 is detected, reflex testing is performed to assess presence of *BRAF* V600E (in CRC patients only) and *MLH1* hypermethylation (in CRC and EC patients) which are likely non-inherited (sporadic) causes of MLH1 loss. Individuals with MMR loss detected through IHC, and absence of *BRAF* V600E and/or *MLH1* hypermethylation for individuals with detected MLH1 loss, are referred to the genetics department for follow-up. Patients meet with a genetic counselor to discuss LS, their risk, and order diagnostic testing, if indicated. Test results are disclosed by the genetic counselor.

EMR Review

The KPNW Tumor Registry was searched for all diagnoses of CRC (ICD-10 diagnosis codes: C18.0, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8, C18.9, C19.9, C20.9, and C21.8) and EC (ICD-10 diagnosis code: C54.1) between the start of the respective screening programs and July 2018. We excluded individuals who opted to have their medical data excluded

from all types of research and individuals who opted to be excluded from genetics research. Electronic medical record (EMR) review of each case was performed by a study genetic counselor to extract patient data related to tumor screening: date of birth, date of biopsy and/or surgery, results of IHC performed on tumor tissue, results of reflex testing, date of referrals to genetics department, date of encounters with genetics department, date genetic testing ordered, and results of genetic testing. All protocols were approved by the Institutional Review Board at KPNW.

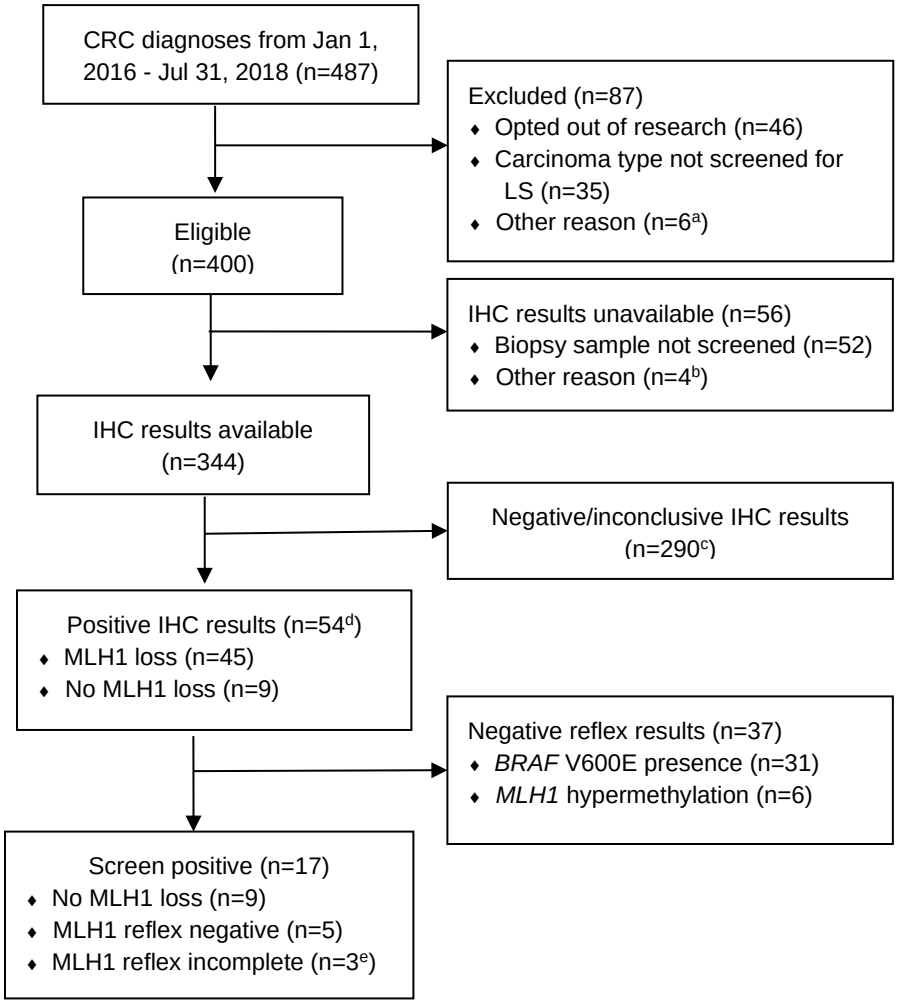
Statistical Analysis

Detection rates for LS in CRC samples were calculated along with the associated 95% Wilson score confidence intervals.

RESULTS

Universal Tumor Screening in CRC Patients

Figure 1. Overview of UTS Results in Patients Newly Diagnosed with CRC.



a. 3 individuals had an absence of malignancy (dysplasia only). 3 individuals had a lack of tissue to screen (no biopsy or tumor tissue available).

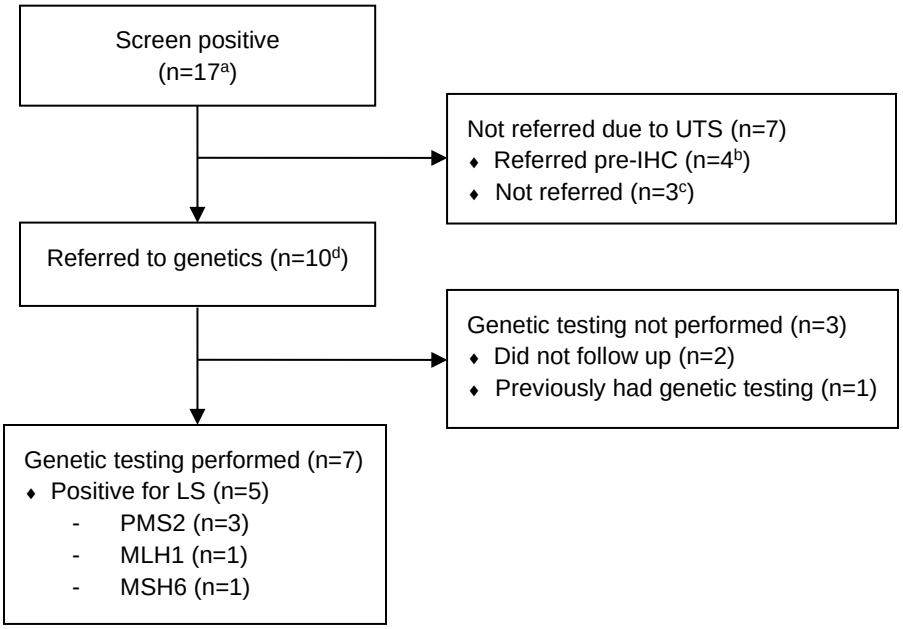
b. 3 individuals had tumor tissue available after surgery that was not screened. 1 individual had IHC results pending.

c. 1 individual was missing IHC results for PMS2, though the other MMR proteins were screened for and present.

d. 1 individual had MLH1 loss only and needed reflex testing. 44 individuals had MLH1 & PMS2 loss and needed reflex testing. 2 individuals had MSH2 & MSH6 loss. 2 individuals had MSH6 loss only. 5 individuals had PMS2 loss only.

e. 1 individual was negative for the *BRAF* V600E variant, but *MLH1* hypermethylation was not tested. 2 individuals did not receive any reflex testing. These individuals were classified as positive and in need of genetics referrals.

Figure 2. Overview of Genetic Counseling Among Patients with a Positive Tumor Screen



a. 5 individuals had PMS2 loss, 8 individuals had MLH1 & PMS2 loss, 2 individuals had MSH2 & MSH6 loss, and 2 individuals had MSH6 loss.

b. 3 individuals with MLH1 & PMS2 loss and 1 individual with MSH2 & MSH6 loss were referred to genetics before IHC results were available, meaning these referrals were not due to UTS. 3 of these individuals had genetic testing and 1 was positive for LS (*MSH2*). 1 individual did not follow up with genetics.

c. 3 individuals were eligible for referral but were not referred, which included 2 individuals with MLH1 & PMS2 loss and 1 individual with PMS2 loss who died shortly after tumor testing.

d. 4 individuals had PMS2 loss, 3 individuals had MLH1 & PMS2 loss (including the individual missing MLH1 hypermethylation reflex testing results), 2 individuals had MSH6 loss, 1 individual had MSH2 & MSH6 loss, and 2 individuals had incomplete IHC results.

An overview of the screening and referral process of patients diagnosed with CRC are summarized in Figures 1 and 2.

Of the 400 cases eligible for screening, 56 were not screened. Most of the cases not screened (52/56 or 93%) only had biopsy samples available. However, 86 of the 344 who were screened also only had a biopsy sample available, indicating inconsistent use of biopsy samples for screening when tumor resections were not available.

Overall, among the 10 individuals who were referred to genetics after screening positive for LS, eight (80%) followed up with genetics. Of the eight individuals that followed up with genetics after a referral based on IHC results, seven had genetic testing, and one individual who was found to have undergone genetic testing previously was not retested. Five (63%) of the seven individuals who had genetic testing had a subsequent diagnosis of LS. One additional individual was diagnosed with LS from the four individuals who screened positive but were referred prior to IHC results. These four individuals would have been eligible for referral due to UTS results had they not already been referred. Of those with a diagnosis of LS, age at onset of cancer ranged from 32 to 81 years.

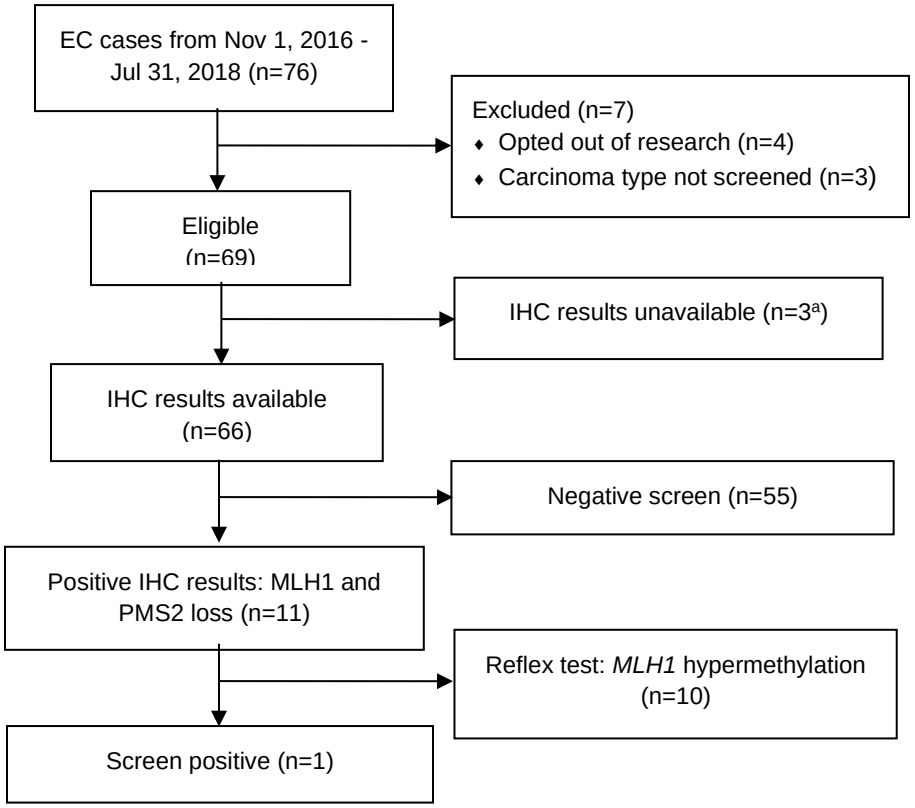
Of the 289 individuals that had a negative UTS result (i.e., all 4 MMR proteins were present on IHC), 47 were referred for genetic evaluation (21 prior to UTS and 26 after UTS results were available). In addition, of the 37 who had a positive screen on IHC but had *BRAF* V600E or *MLH1* hypermethylation present, 10 were referred for genetic evaluation (four prior to UTS and six after UTS results were available). Of these 57 referred for genetic evaluation, 32 (56%) had a visit with genetics and 24 (42%) underwent genetic testing. Only one of the individuals who underwent genetic testing (4%) was diagnosed with LS (a pathogenic variant in *MSH6* in a case with MLH1 loss and *BRAF* V600E present). Because of the inconsistencies in this individual's LS diagnosis, IHC, and reflex results, it is suspected that there was an error in IHC results. Laboratory services declined a request for repeat testing to follow up on this inconsistency. A VUS in *MLH1* was detected in a second case (no MMR protein loss on IHC).

From the 344 individuals who underwent screening with IHC results, there was a detection rate of 1.45% (95% CI: 0.62% - 3.36%). If we include the individuals referred before IHC results were available, the detection rate increases to 1.74% (95% CI: 0.80% - 3.75%). The detection

rate is greater than the proportion of LS expected in the general population (1/279 or 0.7%) but less than the expected proportion among CRC patients (3%). The detection rate is an underestimate of the sample LS prevalence.

Universal Tumor Screening of EC Cases

Figure 3. Overview of UTS and Genetic Counseling for Patients Newly Diagnosed with EC



a. 1 individual had a biopsy sample available that was not screened. 1 individual had tumor tissue available after surgery but was not screened. 1 individual had surgery performed just prior to chart review and IHC results were not available.

An overview of the screening and referral process of patients diagnosed with EC is summarized in Figure 1.

Overall, one individual was eligible for referral for genetic evaluation based on a positive screen for LS. This individual was referred for genetic evaluation after screening results were available. The patient underwent genetic testing which was negative for LS.

One individual was not screened although a biopsy sample was available. Of the 55 individuals that had a negative result for IHC (i.e., all four MMR proteins were present), eight were referred for genetic evaluation (four prior to UTS results and four after UTS results were available). In addition, of the 10 who had a positive screen on IHC but had *MLH1* hypermethylation present, five were referred for genetic evaluation (all after UTS results were available). Of these 13 referred for genetic evaluation, nine had a visit with genetics and four underwent genetic testing. None of these individuals were diagnosed with LS. One individual who had a visit with genetics was already known to have a genetic variant associated with hereditary CRC and was not retested.

DISCUSSION

This study assesses the effectiveness of UTS programs for LS implemented in an integrated healthcare system. The UTS programs contributed to the identification of 5 cases of LS out of the 469 individuals assessed in this study who were eligible for screening. These represent individuals who may not have received a referral for genetic counseling and services without receiving a positive tumor screen. In addition, there was a high frequency of follow-up for individuals (82%) that screened positive and were referred to genetics, which has been reported as a considerable barrier to screening success in other systems.[39,40]

However, opportunities for improvement were identified through this analysis. The use of biopsy samples for screening is being explored by KPNW. Currently, tumor tissue resections are used for screening, while biopsy samples are inconsistently used. In 86 of the 344 CRC patients

screened, biopsy or polypectomy samples were used. In 3 of the 66 EC patients screened, biopsy samples were used. Consistent use of biopsy samples could have reduced the number of individuals who had tissue available but were not screened from 59 to as few as 6 individuals. Several studies have found comparable results for MMR screening when comparing biopsy samples to tissue resections in both EC and CRC patients.[41-45] There is also evidence to support the use of biopsy samples for *BRAF* V600E testing, a part of the reflex for CRC patients showing a loss of MLH1.[46-48] Biopsy sample use would also allow for LS diagnosis before surgical treatment. Knowledge of LS status could alter decision making for surgical treatment of tumors. The US Multi-Society Task Force on Colorectal Cancer published a set of guidelines on LS management which recommends the use of biopsy samples for this reason.[32] Extended, subtotal, or total colectomies, for example, may be recommended for patients with LS.[49,50] Preoperative LS diagnosis would allow patients to be fully informed about their own risks and recommended surgical treatment options.

Other missed opportunities included individuals who had tumor tissue available did not undergo tumor testing, and individuals who screened positive did not end up being referred to genetics. It was also found that some CRC and EC patients were under the age of 50 but had a normal screening result and were not referred to genetics. The screening methodology does not have 100% sensitivity[51] and individuals meeting other high-risk criteria, such as individuals diagnosed below age 50, may still benefit from genetic evaluation for hereditary colorectal cancers. The benefit of genetic testing in this group should be further explored.

Lessons learned:

- Biopsy sample use should be considered. Use of biopsy samples can significantly reduce the number of unscreened individuals.
- Follow-up with patients is needed to ensure eligible patients undergo screening and receive referrals as needed. This includes referrals for both patients who screen positive, and patients who meet other high-risk criteria.
- Universal screening for Lynch Syndrome can identify individuals in high-risk populations. Other health systems should explore implementing universal screening if they have not already.

Limitations to this study include small sample sizes. We expect universal screening for LS in the individuals diagnosed with EC to be effective at identifying LS. However, in part due to the limited number of individuals included in our analysis, the UTS program did not identify any cases of LS in this group. Similar integrated health care systems have reported LS UTS to be ineffective at increasing LS detection in EC patients.[52] More work should be done to explore this area. Other limitations include challenges with generalizability: KPNW is a single, integrated health care system with patients who have health insurance and reside in/around Oregon and southwest Washington.

Diagnosing LS through UTS at KPNW was one step in addressing the low proportion of individuals who are aware of their increased cancer risk. This program directly led to diagnoses for 5 individuals. There is also potential to indirectly lead to further diagnoses through cascade screening and testing, the identification and genetic testing of at-risk family members. Other health systems looking to improve LS identification in their patient population will likely

encounter similar challenges to those described in this paper. It is our hope that sharing the experiences and lessons learned at KPNW may assist others during implementation or quality improvement of UTS for LS.

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