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Creation of a Network to Promote Universal Screening for Lynch Syndrome: The Lynch Syndrome Screening Network

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Abstract

The Evaluation of Genomic Applications in Practice and Prevention Working Group published an evidence-based recommendation stating that every newly diagnosed colorectal cancer (CRC) should undergo tumor screening for Lynch syndrome (LS). In 2011, leading cancer institutions and public health agencies created the Lynch Syndrome Screening Network (LSSN) in order to promote routine LS screening on all newly diagnosed CRCs and endometrial cancers (EC). The LSSN facilitates implementation of appropriate screening via shared resources, protocols and data through network collaboration. The LSSN website contains resources for institutions interested in initiating screening, including materials for program development, implementation and sustainability. The LSSN listserv gives providers access to experts in LS screening and implementation. The LSSN database will allow exploration of key gaps in implementation as a consortia-wide endeavor. To date, the LSSN's membership includes 85 institutions involved in the

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Conflict of Interest

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care of CRC patients and nine official partners such as national and state public health entities and other non-profit institutions. Nearly 80 % of the LSSN's members have already implemented routine or universal CRC and/or EC screening. LSSN serves to further the population health potential of universal LS screening through collaborative efforts and resources.

Keywords

Lynch syndrome; Universal screening; Colon cancer; Endometrial cancer; Genetic testing; Genetic counseling

Introduction

Over 140,000 new colorectal cancers (CRCs) and over 49,000 new endometrial cancers (ECs) are projected in the United States (US) in 2013 (Howlader et al. 2013). Lynch syndrome (LS) is an autosomal dominant hereditary cancer syndrom that is responsible for the majority of hereditary colorectal and endometrial cancers (Hampel et al. 2005a, b). One out of every 35 CRC cases and one out of every 40 EC cases have LS (Hampel et al. 2008).

For individuals with LS, the average lifetime risk for CRC is 54–74 % for men and 30–52 % for women (Barrow et al. 2008; Hampel et al. 2005a, b; Stoffel et al. 2009). Women with LS also have a 31–66 % lifetime risk for endometrial cancer (Hampel et al. 2005a, b; Stoffel et al. 2009). LS is associated with slightly increased risks for a variety of other cancers including gastric, ovarian, upper urinary tract, small bowel, biliary tract, central nervous system and rare types of skin cancer (Watson et al. 2008; Weissman et al. 2011). These increased cancer risks are due to mutations in the DNA mismatch repair (MMR) genes MLH1 (32 % of LS cases), MSH2 (38 % of LS cases), MSH6 (14 % of LS cases), or PMS2 (15 % of LS cases) (Palomaki et al. 2009). Deletions in EPCAM, a gene responsible for cell adhesion, have been implicated in approximately 1 % of LS cases because these deletions can disrupt the MMR pathway by causing methylation of the MSH2 gene (Kempers et al. 2011).

A diagnosis of LS allows individuals and their family members to engage in screening and preventive measures to reduce morbidity and mortality. Clinical criteria such as Amsterdam I (Vasen et al. 1991), Amsterdam II (Vasen et al. 1999) and the revised Bethesda guidelines (Umar et al. 2004) use personal and family history information to determine those at high risk of LS. However, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group of the Centers for Disease Control and Prevention (CDC) determined that using tumor-based screening protocols to identify CRC patients with LS produced more consistent results and identified a higher percentage of patients than using personal and family history criteria (Bonis et al. 2007; Coates et al. 2011; Evaluation of Genetic Applications in Practice and Prevention [EGAPP] 2009; Palomaki et al. 2009).

In 2009, the EGAPP Working Group published an evidence-based recommendation that every person with newly diagnosed CRC should be offered screening for LS to reduce morbidity and mortality in their relatives (Evaluation of Genetic Applications in Practice and Prevention [EGAPP] 2009). This paper delineates the factors necessary for successful

implementation of the EGAPP recommendation. In addition, we describe the creation of the Lynch Syndrome Screening Network (LSSN), a collaborative group committed to furthering the adoption of universal LS screening. The LSSN's formation, mission and vision, products, future direction and intended public health impact are presented. To explore issues surrounding implementation of the EGAPP recommendation, the CDC convened a multidisciplinary working group meeting in 2010. The meeting sought to address the context of the environment in which the EGAPP recommendation could be implemented, and concluded that an evaluation of implementation barriers and pilot implementation projects is needed to demonstrate effectiveness and provide additional evidence of feasibility (Bellcross et al. 2012).

Offering screening to all newly diagnosed CRC patients – regardless of personal or family history—is termed "universal screening." This approach supports an objective of Healthy People 2020, which is to increase the number of newly diagnosed CRC patients who are screened for LS (healthypeople.gov 2013). Although the EGAPP recommendation promoting universal screening was published in 2009, a 2011–2012 survey of hospitals assessing current LS screening practices revealed that 70 % of National Cancer Institute (NCI)-designated Comprehensive Cancer Centers, 36 % of Community Hospital Comprehensive Cancer Programs and only 15 % of Community Hospital Cancer Programs were performing routine screening for LS among their newly diagnosed CRC patients (Beamer et al. 2012).

The EGAPP Working Group did not recommend use of a particular screening method, and there is currently no standard of care regarding the process of LS screening and follow-up that has been endorsed by another independent body or professional organization. Tumor-based studies used for routine screening include microsatellite instability (MSI) testing and immunohistochemical (IHC) analysis. MSI and IHC are not diagnostic, but provide information regarding characteristic features of LS-associated tumors. In many cases, reflex testing is required to differentiate germline from somatic changes. The purpose of tumor screening is to identify individuals who should be referred for genetic services to pursue diagnostic genetic testing for LS.

Patient follow-through with genetic counseling and germline testing is critical to: 1) improve the cost-efficacy of universal screening programs, 2) assure accurate diagnosis of LS, 3) communicate genetic risk to patients and their relatives, and 4) offer increased cancer surveillance and prophylactic surgeries to reduce the risk of cancer. Cancer surveillance, consisting of early initiation (between ages 20 and 25) of colonoscopy and frequent follow-up (every 1–2 years), has been shown to reduce CRC incidence and related mortality (Järvinen et al. 2000, 2009). With long-term follow-up and high compliance, patients with LS have shown no increase in cancer-related mortality when compared with mutation-negative family members (Järvinen et al. 2009). There is also evidence that women with LS who undergo risk-reducing hysterectomy and bilateral salpingo-oophorectomy significantly reduce their risk for both endometrial and ovarian cancers, although a very small residual risk for primary peritoneal cancer remains (Schmeler et al. 2006, 2010).

Creation of the LSSN

To address needs and reduce the cancer burden associated with LS, the Michigan Department of Community Health (MDCH) convened a LS universal screening network planning meeting with one-time funding from the CDC Office of Public Health Genomics in 2011. This national meeting expanded the work from a MDCH-CDC cooperative agreement that included Michigan-specific surveillance and education on the EGAPP LS recommendation. At the first meeting, 35 participants from multiple institutions in the United States who were currently performing or considering universal LS screening on newly diagnosed CRCs met to discuss developing a collaborative network. Representatives from the National Institutes of Health, CDC, academic medical centers, cancer facilities and health departments were in attendance, and these representatives included genetic counselors, physicians, researchers, epidemiologists, administrators and others. The group unanimously agreed that a network focused on universal LS screening did not exist and was greatly needed; the Lynch Syndrome Screening Network (LSSN) was formed to enable ongoing cooperative efforts. With support, in part, from the NCI's Epidemiology and Genomics Research Program, the LSSN has held three in-person meetings open to all interested institutions and one in-person planning meeting for the LSSN's Board of Directors and other key LSSN institutions.

The LSSN's vision and mission were developed through a consensus process involving the general membership. The mission of the LSSN is to promote universal LS screening on all newly diagnosed colorectal and endometrial cancers; to facilitate the ability of institutions to implement appropriate screening by sharing resources, protocols, and data through network collaboration; and to investigate universal screening for other LS related malignancies. This mission will enable the LSSN to realize its vision of reducing the cancer burden associated with LS.

Membership

Membership in the LSSN is at the institutional level, not the individual level, since implementation of LS screening requires an institutional commitment. Participating LSSN institutions have access to LSSN resources, meetings, networking opportunities and database projects. Institutions work together to create new resources and share existing protocols and educational materials to facilitate routine screening for LS on newly diagnosed CRC and EC. There are currently no membership fees for LSSN institutions. Institutions such as hospitals, clinics or academic medical centers involved in the clinical care of patients are eligible for membership as either full or affiliate members. Of note, institutions electing to conduct routine, systematic screening on a subset of CRCs as determined by age of diagnosis or other criteria are eligible for full membership. Full and affiliate membership criteria are summarized below:

Full Member

1. Institutions currently performing routine tumor screening on CRCs and/or ECs
2. Commitment to enter tumor screening and follow-up data into the LSSN database for surveillance and/or research purposes

3. Institutional review board (IRB) approval (either obtained or in process) to enter data into the LSSN database
4. A genetic counselor or other qualified healthcare provider trained in providing cancer genetic services is required by the institution
5. A genetic counselor or other qualified healthcare provider must have access (either through clinical responsibilities and/or IRB approval) to both normal and abnormal routine tumor testing results

Affiliate Member

1. Institutions performing routine tumor screening, but not meeting all criteria for full membership; OR
2. Institutions interested in starting routine screening

Other organizations that have an interest in promoting routine tumor testing to identify individuals with LS and/or are performing related research may be eligible to be official partners of the LSSN. For-profit laboratories are not eligible for partner status. Official LSSN partners include the following categories:

Official Partners

1. Federal and state agencies
2. Professional societies
3. Patient support and advocacy groups
4. Non-profit laboratories and companies

Governance

The founding Board of Directors and the governance working group have developed bylaws and an organizational structure for the LSSN. The by-laws detail the application process and the criteria for membership and official partnership status. The by-laws also outline the terms, qualifications, responsibilities and election of directors, in addition to the scheduling and establishment of meetings, committees and dues.

Application

Institutions have been invited to participate in the LSSN via select professional organizations involved in cancer genetics; membership/partnership is open to any organization that meets specified criteria and fills out an application. Application data collected from members includes existing screening and follow-up protocols, plans for future implementation of routine screening, current number of various cancer types screened for LS, changes in number of cancers screened over time and willingness to contribute routine tumor screening data to a shared online database.

To date, the LSSN includes 94 members and official partners. Nine of these institutions are official partners, 18 member institutions are planning to implement routine tumor testing, and 67 member institutions currently perform routine tumor testing for LS; all 67 are

screening CRCs and 34 are also screening ECs. Of the members with complete application data, 53 of 66 (80 %) and 17 of 34 (50 %) have implemented universal screening on CRCs and ECs, respectively. Member institutions screen colorectal tumors using IHC (78 %), MSI (11 %), or MSI and IHC concurrently (11 %); ECs are screened using IHC (88 %), MSI (3 %), or MSI and IHC concurrently (9 %). In 2012 and 2013, 25 and 17 LSSN members began routinely screening CRCs and EC, respectively. In total, the LSSN member institutions have reportedly screened over 20,000 estimated cancers, including 16,300 CRCs and 4,051 ECs, for LS.

Resources

Website

The LSSN website, located at http://www.lynchscreening.net, has been developed by members with donated time and resources and is publically accessible. Goals and content outlines for the educational resources contained in the website were established by the education working group. Materials currently contained on the website are intended as resources for institutions interested in implementing universal LS screening; many were developed by LSSN institutions. The web resources include LS screening literature and guidelines, materials for screening program development, implementation, and resources for providers and patients. Additional evidence-based resources on effective implementation practices are in development.

Listserv

Beginning in 2012, a listserv has been available to LSSN institutions. This listserv is active and has served as a discussion forum for troubleshooting issues that impede the implementation of universal screening at various institutions. In addition, the listserv is effectively a resource of LS screening experts. Most discussion involves questions on difficult and rare case situations, with multiple genetics professionals weighing in with their expert opinions. All discussion is conducted in a HIPAA-compliant manner. The LSSN is developing resources based on these compiled questions and responses for future reference.

Database

The LSSN database was established with funding from the CDC’s Office of Public Health Genomics, and has received additional funding from the NCI’s Epidemiology and Genomics Research Program. The LSSN has created a secure online database capable of housing limited protected health information, including patient demographic information, proband cancer history and pathology, tumor screening results, genetic counseling, genetic test results, family history and cascade testing of family members. Patient information includes an anonymous patient code rather than identifiable data. These data will be entered by participating LSSN institutions, and will be coupled with information on each institution’s screening protocols over time. Institutions will have full access to their own data for internal clinical and quality control purposes.

The database was designed through a consensus process with the following purposes: Surveillance of routine LS screening on newly diagnosed CRCs in support of the US Healthy People 2020 Developmental Objective

- Measure the identification of LS over time, in terms of both the number and proportion of cases identified through routine screening
- Answer questions regarding the effectiveness of various screening and follow-up protocols
- Provide statistics on LS screening, genetic counseling and genetic testing to insurers to better inform coverage policies
- Evaluate screening outcomes for non-CRC LS cancers to assess the need for additional recommendations
- Determine uptake of testing by proband and relatives in real-world settings
- Continue evaluation of universal screening recommendations by assessing clinical and family history associated with LS

Table 1 provides a list of elements included in the database. The database contains several optional fields that will allow institutions to conduct special research projects related to LS, in addition to analyses related to screening. The data elements selected for the LSSN database were developed through an iterative process involving the LSSN Board and members (medical, genetic and public health professionals with expertise in LS), further refined by the database working group, and beta-tested by eight centers performing routine screening. The database has a web-based data entry form that is accessible globally via the Internet and is secure and encrypted. The LSSN database will allow questions related to universal LS screening efficacy, efficiency and real-world utility to be addressed. Over 55 institutions nationwide have expressed a commitment to enter data into the database, and that number is expected to increase with the official launch of the database in 2014. The LSSN plans to develop key research publications as a consortia-wide endeavor, but the data generated by LSSN institutions will also be available to LSSN members and their partners for additional research studies. In order to obtain de-identified multi-institution data for research, members will be required to submit an application that will be reviewed by the LSSN research committee.

Public Health Impact

To maximize the public health impact of LS screening, universal screening must be widely adopted by hospitals and cancer centers across the nation. Universal tumor screening has great potential to improve the identification of LS in underserved and minority populations. However, disparities in identification and access could widen without widespread adoption by non-academic institutions and centers that serve rural or minority populations. The LSSN website and listserv promote widespread adoption by disseminating information to help institutions overcome barriers and successfully implement tumor screening.

The role of the LSSN in bridging the gap between the practices of public health and medicine is particularly important because, unlike other conditions of public health concern,

LS tumor screening lacks statewide public health systems to implement screening and track results. The LSSN and its products are well suited to help fulfill core public health functions, which include assessment, policy development and assurance. Assessing the implementation and outcomes of screening will provide critical information to inform implementation policies or recommendations.

The US Healthy People 2020 goal of increasing the proportion of persons with newly diagnosed CRC who receive genetic testing to identify LS is developmental, which means that it requires baseline data and longitudinal measurements to remain in place. The LSSN institutions are at the forefront of commitment to and implementation of routine LS screening. Establishing baseline numbers and screening outcomes over time will provide needed data from leading institutions across the US. The variability of institutions and protocols will also enable a comparison of strategies to maximize screening potential.

The LSSN database will fill an assessment need among a number of institutions that currently have no tracking system in place. Institutions that enter data into the centralized data- base will have access to their own data in order to track outcomes at their institution and assure that patients are being notified of results and are given the opportunity to receive genetic counseling and germline testing. Institutions will then be able to compare themselves to other de-identified institutions in terms of their expected and actual proportion of positive tumor screens and the percentage of patients who follow through with genetic counseling and germline testing after a screening result that suggests possible LS. This type of assessment is needed because tumor screening is only effective when patients receive the services necessary to confirm a diagnosis and learn about ways to reduce future cancer risks for themselves and their at-risk family members.

The LSSN data will also contribute to policy development and assurance through the identification of best tumor screening practices, which was not addressed by EGAPP due to insufficient evidence. Tumor screening practices vary across institutions (Beamer et al. 2012; Cohen 2013), yet little is known about which laboratory and follow-up procedures work best in various settings.

Some institutions elect to conduct routine screening on a subset of CRCs as determined by age of diagnosis or other criteria. The LSSN data will provide information regarding the extent of differences with respect to detection and follow-up for truly universal vs. criteria-defined routine screening. The database will also allow for investigation of the application and effectiveness of screening and follow-up protocols for endometrial and other LS-related malignancies, potentially paving the way for additional screening recommendations.

As the most effective screening strategies and follow-up protocols have not yet been defined, the LSSN database will allow for examination of these factors. Such information is essential to clarify remaining questions regarding clinical validity and utility of LS screening and thereby address research gaps identified by EGAPP.

Challenges and Future Directions

Infrastructure

The LSSN membership application is useful as a tool for measuring changes in LS screening over time, especially at leading institutions in the US. As more institutions apply for LSSN membership, this information will be increasingly useful as a means of measuring national progress towards the US Healthy People 2020 Genomics Goal for LS.

While the expansion of LSSN will increase the likelihood of national impact, this growth will also increase the need to sustain a centralized and neutral site for coordination, health information technology, data management and technical assistance. LSSN partners continue to look for opportunities to sustain this infrastructure, and provide support and technical assistance to the growing number of member institutions implementing universal tumor screening.

Patient Follow-through

Several procedural differences exist across institutions, including how screening is coordinated with multiple disciplines (pathology, surgery, oncology, and genetics), methods of disclosure and follow-up with screen-positive patients. Preliminary evidence suggests these procedures may influence patient follow-through (Cragun et al. 2013). Comparing outcomes across institutions will help to identify solutions to the challenges of patient and family follow-through in a variety of patient populations and settings. Changes implemented as a result will be monitored by the database to determine impact on effectiveness.

Patient and Family Engagement

Patient and family engagement is necessary to increase the effectiveness of tumor screening in terms of both patient follow-through and cascade testing among family members. A premise regarding the population health benefit of LS screening is uptake of cascade testing. Cascade testing can reduce morbidity and mortality in relatives of individuals identified with LS through cancer screening, and yet challenges in facilitating cascade testing and the impact of testing on relatives are largely unknown. The LSSN is poised to provide information on the number of family members receiving LS testing after identification of a mutation in their relative as well as the number of family members who are found to have LS. The impact of routine screening on family members will be necessary for cost-effectiveness calculations, which should no longer rely on assumptions about cascade testing in relatives. The LSSN impact could be further enhanced by 1) assessment of baseline information on family reach among the LSSN member institutions; 2) determination of barriers and facilitators to cascade testing; and 3) identification of patient-centered approaches to sharing LS diagnosis, genetic results, and implications for relatives.

Summary

Despite potential challenges, the LSSN facilitates the ability of institutions to implement universal screening as recommended by EGAPP. The LSSN has successfully convened representatives from the NIH, CDC, academic medical centers, cancer facilities, and health

departments in ongoing collaborative work. These efforts have resulted in a multitude of resources related to universal tumor screening, including a website and educational materials, listserv, membership application and database. Continued collaboration will allow the LSSN to meet its threefold mission:

1. Promote universal LS screening on all newly diagnosed colorectal and endometrial cancers.
2. Facilitate the ability of institutions to implement appropriate screening by sharing resources, protocols and data through network collaboration.
3. Investigate universal screening for other LS related malignancies.

By assisting institutions in overcoming screening barriers, answering questions surrounding universal screening, and tracking implementation and results, the LSSN serves to further the population health potential of universal LS screening through public health functions.

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Table 1

Lynch syndrome screening network database contents

De-identified patient code
Demographics
Age in years
Sex
Race/ethnicity
Insurance status
Previous LS-related cancer history
Cancer type
Age at diagnosis
Index cancer
Date of diagnosis
Cancer and specimen type
Stage
Pathological features
Tumor screening
Type (MSI, IHC, BRAF V600E, MLH1 promoter methylation)
Results
Genetic counseling
Completion status
Reasons for non-completion
Family cancer history
Amsterdam I, II or Bethesda criteria met
First and second degree relative cancer history
Genetic testing
Germline testing completed
Test results (gene and identified mutation)
Mutation testing in relatives of proband with LS
Number and degree of relationship
Test results