International assessment of Lynch syndrome screening practices

by

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Abstract

Lynch syndrome (LS) is an inherited cancer syndrome that increases risk of developing certain cancers, most commonly colorectal and endometrial. It is important to distinguish between LS and sporadic cancers because it can help inform the risk of additional cancers as well as identify relatives who may also be at risk of developing LS-associated cancers. In the US, there has been considerable effort by organizations including the Lynch Syndrome Screening Network (LSSN) to promote universal tumor screening as part of routine diagnosis of colon and endometrial cancers to identify more cases of LS. However, it is unclear what LS screening practices currently exist internationally.

In order to characterize global LS screening practices with regards to screening of colorectal cancer tumors, this study implemented a survey to capture screening procedures and methods, cascade testing, and efficacy measures. The online survey was distributed to individuals at member organizations of LSSN, members of the International Society for Gastrointestinal Hereditary Tumors (InSiGHT), and the Collaborative Group of the Americas on Inherited Gastrointestinal Cancer (CGA-IGC). Additionally, two interview guides were developed depending on whether survey respondents’ organizations had a routine LS screening program or not. This was done by creating open-ended questions based on survey questions. This will support future work in elucidating how barriers and facilitators, such as insurance and social factors, may inform LS screening practices.
There were 27 survey respondents from seven countries: Canada, US, Denmark, Ireland, Netherlands, UK, and Japan. Some key findings from the survey showed that no institutions offer only direct-to-germline testing, 92.6% of responding institutions perform universal tumor screening, 81.5% of institutions use a patient-mediated method of informing relatives about cascade testing, and 48.1% of institutions systematically track LS detection rates. The public health significance of this project is that it identifies ways in which resources developed by LSSN could be leveraged to facilitate implementation of LS screening programs (especially universal tumor screening) world-wide and provide guidance on how population-specific improvements could be made to current screening programs. Ultimately, this will help to increase LS diagnoses and reduce the burden that LS can have in families globally.
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Preface

I would like to thank the Lynch Syndrome Screening Network for proposing this project idea and for bringing me on board. Of note, thanks to Dr. Jessica Ezzell Hunter, Dr. Alanna Kulchak Rahm, and Debra Duquette for your mentorship and ongoing support throughout this project. To Northwestern University, for your collaboration on this project. To Bianca Kun for being a wonderful research partner to work with. To Dr. Andrea Durst for your mentorship in the MPH Public Health Genetics program and for your support through this project, and to Dr. Jeanine Buchanich for your guidance on this essay.
1.0 Introduction

Lynch syndrome (LS) is a genetically inherited condition that increases the likelihood of developing certain cancers. It most greatly increases risk of colorectal and endometrial cancers, but also increases risk for stomach, brain, ovarian, and breast cancers, amongst others (Table 1). The condition arises due to autosomal dominant germline pathogenic variants in one or more genes that are responsible for repairing mismatches during DNA replication (\textit{MLH1}, \textit{MSH2}, \textit{MSH6}, \textit{PMS2}) or a gene known as \textit{EPCAM}, which if deleted, impacts the expression of \textit{MSH2} (Idos & Valle, 1993).

<table>
<thead>
<tr>
<th>Cancer Location</th>
<th>General Population Risk by Age 74</th>
<th>Cancer Risk by Age 70</th>
<th>MLH1</th>
<th>MSH2</th>
<th>MSH6</th>
<th>PMS2</th>
<th>EPCAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectum</td>
<td>2%</td>
<td>44% 53%</td>
<td>42%</td>
<td>46%</td>
<td>20%</td>
<td>12%</td>
<td>3%</td>
</tr>
<tr>
<td>Endometrium</td>
<td>1%</td>
<td>35% 46%</td>
<td>41%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>0.7%</td>
<td>11% 17%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>1%</td>
<td>8% 16%</td>
<td>10%</td>
<td>16%</td>
<td>2%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>&lt;1%</td>
<td>2% 1%</td>
<td>2%</td>
<td>4%</td>
<td>1%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>5%</td>
<td>11% 13%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

F = female; M = male
Adapted from: Idos & Valle, 1993 (updated in 2021)

In the US, 1 in every 279 individuals is estimated to have LS (Idos & Valle, 1993). An estimate from 2011 indicates that only approximately 1.2% of individuals with LS in the US have been diagnosed with the condition (Hampel & De La Chapelle, 2011). Thus, many patients with LS are not aware that they have the condition and are not receiving sufficient cancer surveillance, which presents a massive gap in healthcare (Kastrinos et al., 2016). One reason many individuals
with LS miss getting diagnosed is because of the numerous associated cancer types (Salikhanov et al., 2022). Given the high public health relevance of this condition, expert groups in the US, such as the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group, have recommended universal screening of all colorectal and endometrial tumors (without age or other limits) for identifying individuals most likely to have LS (“Recommendations from the EGAPP Working Group,” 2009). LS identification is typically a two-step process. First, the tumor is screened using immunohistochemistry (IHC) and/or microsatellite instability (MSI). Then, germline genetic testing of all patients with positive screens is done to confirm the diagnosis of LS.

The Lynch Syndrome Screening Network was established to help health care institutions implement universal screening for LS. The organization also partakes in research initiatives that help in translating research to clinical application (Lynch Syndrome Screening Network, n.d.). Research shows that worldwide prevalence of LS across various ethnic, geographical, and clinical groups are similar, which suggests that LS is of considerable public health relevance beyond the US (Abu-Ghazaleh et al., 2022). Information about LS screening practices in select countries exist, such as in Australia, Canada, and some European countries (Tognetto et al., 2017). However, it is unclear whether people are screened for LS in other countries and if there is even interest in LS screening given the associated barriers and facilitators involved with implementation. Furthermore, in cases where screening is available, it is not known how screening is done (i.e., whether screening is based on clinical criteria or done routinely on tumors of LS-associated cancers).

The goal of this essay is to report and interpret the findings of an international survey on current policies and practices surrounding LS screening both in and outside of the US, as well as
to present interview guides that can be used for future work in deepening our understanding of these screening practices. This research is innovative because it is the first time that global practices around screening for LS has been captured and characterized. An additional benefit of this work will be to share implementation experience regarding what works and what does not work and how it may vary based on factors such as context, health care system practices, and cultural norms.

Overall, this project relates to larger issues in the field of public health genetics, such as determining how access to screening and cascade testing are limited by factors like cost, insurance availability, and awareness. Additionally, a major goal within the field of public health genetics is to assess efficacy of screening programs. This project aligns with that goal by taking a snapshot of current practices in the US and around the world and identifying where improvements can be made to reduce the overall cancer burden associated with LS across the world.

1.1 Specific aims

The specific aims of this project are to:

- Use a mixed-methods approach to characterize policies (i.e., what is recommended to be done) and practices (i.e., what is being done) surrounding LS identification in the US and internationally (with a focus on colorectal cancer)

  - The survey will be implemented broadly and focus on questions regarding the following elements:
    - Screening approaches (two-step vs direct-to-germline testing)
    - Cascade testing (i.e., genetic testing of at-risk family members)
• Efficacy of existing screening programs
  
  o The interview guide will focus on obtaining detail on the following elements:

  • Determining what factors are involved in establishing universal tumor screening for LS in different countries, or reasons for not having established it

  • Understanding how health insurance (private or national) and cultural attitudes toward preventative care affect screening

• Provide a summary and analysis of survey results
2.0 Literature review/background

2.1 Introduction to Lynch syndrome

Among cancer-related deaths in the US, colorectal cancer (CRC) deaths are the second highest. Though most cases of CRC are sporadic, about 5-10% are hereditary, and the most common hereditary form is attributed to Lynch syndrome (LS) (Bhattacharya & McHugh, 2024). LS is the most common cause of CRC and endometrial cancers but is severely underdiagnosed. As of 2011, only about 1.2% of the total estimated individuals in the US with LS were aware that they had the condition (Hampel & De La Chapelle, 2011).

LS arises due to autosomal dominant germline pathogenic variants in one or more mismatch repair (MMR) genes (\textit{MLH1, MSH2, MSH6, PMS2}) or a gene known as \textit{EPCAM}, which if deleted, impacts the expression of \textit{MSH2} (Idos & Valle, 1993). The main function of MMR proteins in the context of LS is to remove insertions, deletions, and base pair mismatches that arise from DNA polymerase slippage during the DNA replication process (Graham V et al., 2018). When the MMR proteins are non-functional, it results in an increased mutation rate especially within repetitive regions of the DNA known as microsatellites. Repetitive DNA sequences exist in the coding region of many genes, and when inactivating variants are present in tumor suppressor or proto-oncogenes, they are not able to perform their roles of initiating cell death and keeping cells healthy, respectively. In effect, harmful variants within repetitive regions of tumor suppressor and proto-oncogenes lead to the development of cancer (Duraturo et al., 2019). \textit{MLH1, MSH2, MSH6, PMS2}, and \textit{EPCAM} are collectively referred to as the ‘Lynch syndrome genes’ and are what typically get screened and tested for during the LS identification process (Idos & Valle,
1993). Though LS can present with various cancer forms, this paper will primarily focus on CRC because it is the most common cancer associated with LS and is a way to assess screening practices across countries in a simplified manner.

The problem of underdiagnosis in the context of LS is particularly concerning, given that most patients are unaware of the high risk of having the condition and therefore are not receiving sufficient cancer surveillance, which presents a significant gap in healthcare (Kastrinos et al., 2016). With early identification of LS, there are several evidence-based measures that individuals can take to prevent and/or significantly improve negative outcomes associated with LS. Notably, individuals with a diagnosis of LS can begin frequent colonoscopies, which has both preventative and therapeutic functions – it can both prevent development of cancerous polyps and remove existing polyps that may or may not be cancerous (Stauffer & Pfeifer, 2024). For example, a colonoscopy every three years was shown to reduce the CRC incidence among individuals with LS by 65% and essentially eliminate CRC-related mortality among these individuals (Hampel & De La Chapelle, 2013). Additionally, screening for LS is important because the condition increases the risk that another primary cancer develops, the diagnosis may alter the course of treatment once the pathogenic variant is identified, and it helps prevent LS-related cancers in at-risk blood relatives through earlier screenings and/or genetic testing (Idos & Valle, 1993).

The two common tumor screening methodologies used to identify those at risk for LS are IHC, which screens tumor tissue for the four MMR proteins, and MSI, which looks for significant variation in microsatellite repeat lengths between normal and tumor tissue within the patient. These screening methods may be used individually or in tandem to detect an increased risk for LS (Idos & Valle, 1993). LS identification is typically a two-step process. First, the tumor is screened using IHC and/or MSI. Initial screening using either IHC or MSI (or both) can be followed up with
reflexive testing of two types when appropriate: testing the \textit{BRAF} gene for a V600E mutation (in CRC cases) or testing for hypermethylation in the \textit{MLH1} promoter region. These reflexive tests are helpful in distinguishing sporadic from inherited genetic changes (due to LS) causing CRC (Idos & Valle, 1993).

While all missing MMR proteins can result from sporadic changes due to biallelic somatic mutations, absent MLH1 and/or PMS2 proteins commonly arise from sporadic genetic changes and are typically not indicative of LS (Idos & Valle, 1993). Additionally, it has been shown that \textit{BRAF} V600E mutations are not present in LS-associated CRCs and that the \textit{MLH1} promoter region can be hypermethylated, which is typically a somatic event that shuts down the \textit{MLH1} gene. Thus, if hypermethylation exists at the \textit{MLH1} promoter or a V600E mutation exists in the \textit{BRAF} gene (in the case of CRCs only), the individual most likely does not have LS and should not undergo germline testing. Then, of the patients with MSI-positive screens or missing MMR proteins, germline genetic testing is done to verify a LS diagnosis (Idos & Valle, 1993). The two-step process is typically done as it more cost-effective than directly performing germline testing on everyone (Mvundura et al., 2010). Though currently more cost-effective, the two-step process also makes LS screening programs difficult to implement given the additional logistical and organizational efforts involved (\textit{Lynch Syndrome Screening Network}, n.d.). It is worth noting that as the cost of germline testing decreases, it may become more common to perform direct-to-germline testing rather than using the two-step process.
2.2 Traditional methods of LS detection

There are many approaches that have traditionally been used by medical professionals to identify individuals at risk of having LS and thus would be best suited for further screening and/or genetic evaluation. These approaches fall into two broad categories: clinical criteria-based guidelines and prediction models. Table 2 outlines some commonly used criteria-based guidelines and the three prediction models, along with the utility and sensitivity/specificity measures of each approach.

Despite having these criteria-based and computational screening modalities, none can pick up all individuals with LS even if used perfectly (i.e., each has its inherent limitations). In the case of clinical criteria, using criteria perfectly implies that family history is accurately reported, a health care provider verifies that the patient meets the clinical criteria, and that the patient gets referred to genetic counseling and testing. Moreover, the literature shows that clinical criteria-based screening has not been used perfectly in clinical practice. In a 2010 study done by Mukherjee and colleagues, it was shown that it is often difficult to obtain complete and accurate family history data, referral rates for cancer genetic counseling are not always as high as they should be, and patient compliance to follow through with counseling and testing can also be lower than ideal.

The Amsterdam criteria is based solely on personal and family history and has relatively low sensitivity and specificity measures. These low values explain why many people with LS do not meet the Amsterdam criteria and also why even if a person meets all these criteria, their chances of truly having LS is not as high as one would expect. (Colorectal Cancer Genetic Testing | Lynch Syndrome Testing | American Cancer Society, n.d.). The revised Bethesda guidelines help determine whether an individual with CRC should have their tumor tested for MSI changes associated with LS. The revised Bethesda guidelines take multiple factors into account, such as
the patient’s age at diagnosis, their tumor histology, and their personal and family history of LS-associated tumors (Umar et al., 2004). The sensitivity and specificity measures suggest that even if these criteria are perfectly applied – whereby family history is reported accurately and there is adequate collaboration between the pathologist (looking into tumor histology) and clinician (looking into clinical criteria) – there are still a significant number of patients with LS who do not meet these criteria. It is estimated that proper adherence to these criteria misses up to 30% of Lynch-associated tumors. The Jerusalem criteria, which has the highest sensitivity and specificity measures of the tools evaluated here, also has a limitation whereby it is estimated to miss just over 10% of LS cases (Boland & Shike, 2010).

The three computational models (MMRPro, MMRPredict, and PREMM) estimate the total probability that an individual carries a germline mutation in the *MLH1*, *MSH2*, and/or *MSH6* genes using personal and family history of cancer, and they can guide medical professionals in determining whether tumor screening or germline testing should be done thereafter. If the risk of carrying a mutation in any one of the three genes is 5% or higher, the individual typically undergoes further genetic evaluation using tumor screening and/or germline testing (Kastrinos et al., 2013). While the purpose of the three models is the same, the utility and sensitivity/specificity measures of each are slightly different (Table 2). Each model also has its own limitations, but the common limitation between the three is that it can only be used to predict pathogenic variant carriers based on three of the five LS genes, which excludes *PMS2* and *EPCAM* (Pouchet et al., 2009). Given the limitations of these clinical criteria-based approaches and prediction models, it suggests the need for a more robust screening method.
Table 2 Summary of criteria and sensitivity/specificity measures for six traditional methods of identifying potential Lynch syndrome cases

<table>
<thead>
<tr>
<th>Criteria/Utility</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amsterdam Criteria</strong></td>
<td>61 (Syngal et al., 2000)</td>
<td>67 (Syngal et al., 2000)</td>
</tr>
<tr>
<td>• “a minimum of three relatives with a Lynch-associated cancer (whereby one is a parent, brother, sister, or child of the other two relatives)”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• “at least two consecutive generations affected”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• “at least one relative who had their diagnosis of cancer when they were younger than age 50” (Vasen et al., 1991)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Revised Bethesda Guidelines</strong></td>
<td>82 – 95 (Trujillo-Rojas et al., 2023)</td>
<td>77 – 93 (Trujillo-Rojas et al., 2023)</td>
</tr>
<tr>
<td>• “colorectal or uterine cancer diagnosed in a patient less than 50 years of age”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• “presence of synchronous, metachronous colorectal, or other LS-associated tumors, regardless of age”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• “CRC with the MSI-H histology diagnosed in a patient that is under age 60”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• “CRC diagnosed in one or more first-degree relatives with a LS-related tumor, with one of the cancers being diagnosed under age 50”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• “CRC diagnosed in two or more first- or second-degree relatives with LS-associated tumors,”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jerusalem Criteria</td>
<td>“All CRC tumors in individuals under the age of 70 are screened” (Boland &amp; Shike, 2010)</td>
<td>85</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------------------------------------------------------</td>
<td>----</td>
</tr>
<tr>
<td>MMRPro</td>
<td>“Best for calculating risk of a mutation when both MSI and germline testing results are negative and strong suspicion of LS remains” (Pouchet et al., 2009)</td>
<td>31 - 86</td>
</tr>
<tr>
<td>MMRPredict</td>
<td>“Useful for individuals with early-onset CRC without any other LS-related cancers” (Pouchet et al., 2009)</td>
<td>75</td>
</tr>
<tr>
<td>PREMM</td>
<td>“Best for families that have LS-related cancers in addition to CRC and endometrial cancers” (Pouchet et al., 2009)</td>
<td>71-100</td>
</tr>
</tbody>
</table>

2.3 Universal screening

Until population screening (i.e., screening everyone in the population) for LS occurs, universal screening appears to be the next best solution to identify more individuals with LS that clinical criteria and/or computational models may miss out on. The term ‘universal screening’ was coined based on a 2009 evidence-based recommendation published by the EGAPP working group. Their recommendation was that in order to identify individuals at an increased risk for LS, every person with a new CRC diagnosis should undergo screening regardless of age, family history or...
ethnicity ("Recommendations from the EGAPP Working Group," 2009). The universal screening approach was developed to support an objective of Healthy People 2020, which is to "increase the proportion of persons with newly diagnosed colorectal cancer who receive genetic testing to identify Lynch syndrome (or familial colorectal cancer syndromes)" (Genomics | Healthy People 2020, n.d.).

Following the EGAPP recommendation, two other organizations updated their guidelines for universal screening as well. Since 2014, the US Multi-Society Taskforce on CRC recommends universal tumor screening of all CRCs to identify LS (Giardiello et al., 2014). Furthermore, in 2016, the National Comprehensive Cancer Network changed its screening recommendations to include universal screening of all colorectal and/or endometrial cancer tumors regardless of age or family history (NCCN Clinical Practice Guidelines in Oncology: Colon Cancer NCCN Evidence Blocks™ (version 4.2023), 2023; NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms NCCN Evidence Blocks™ (version 1.2024), 2024).

The reason universal screening has been recommended by several professional organizations is to overcome the limitations associated with testing based on clinical criteria or prediction models. Specifically, it helps to diagnose patients with LS at older ages than expected and overcome the barrier of not having the family history of LS-associated tumors or not having accurate information. Universal tumor screening also addresses an important equity issue, given that many individuals from minority populations are less likely to have their family history accurately captured or captured at all (Cross et al., 2013). An additional benefit of universal screening for LS in the context of CRC is that it can save the life of the primary patient by significantly reducing CRC-associated and overall mortality through frequent colonoscopy evaluations. It also helps family members catch LS-related cancers or prevent them early on
through increased surveillance (Kozak et al., 2022). In addition to identifying patients more likely to have LS, universal tumor screening can identify more patients with MSI-high tumors that may respond well to immunotherapy as a method of cancer treatment (Hampel et al., 2018).

While universal tumor screening has several merits, there have been many barriers encountered when implementing it. One of the challenges is that universal screening involves a sophisticated testing protocol that can be confusing to clinicians and patients given there are many steps involved and the protocol may differ between institutions. Additionally, the entire process occurs over a relatively long time period (up to several weeks), which increases the risk of not being able to follow-up with patients until the end (Khoury, 2018). In a 2016 qualitative study by Schneider and colleagues, more than half the interviewees expressed uncertainty on how best to transition from criteria-based models (like the Amsterdam or Bethesda guidelines) to a universal screening model. Internal barriers include the need for communication across multiple departments (e.g., pathology and genetic counseling) and debates about cost effectiveness. Some organizational factors that increase complexity include lack of clarity on who will lead such routine screening efforts and ambiguity about which department the screening program belongs to. Some cost-related apprehensions include providing these services and not generating adequate income in return, and difficulty in determining whether costs will truly be saved with a universal screening program given that some benefits may be for relatives that are on a different health plan. There are also uncertainties about the universal screening program would be funded and which departmental budgets would contribute towards this funding (Schneider et al., 2016).

On the other hand, there are environmental and organizational facilitators that promote the implementation of universal screening for LS. The main environmental facilitator that this paper reported was that ample literature on universal screening being the ‘gold-standard’ for identifying
LS is encouraging organizations to change their current practices. One organizational facilitator reported was the fact that universal screening for LS typically aligns with organizational goals to improve screening and treatment for CRC. Another reported facilitator is that in many organizations, departments that would need to collaborate and communicate closely with one another (e.g., pathology and genetics) for universal LS screening are already doing so for other universal genetic screens (Schneider et al., 2016). Many organizations have already developed and implemented protocols such as testing for Her-2 neu breast cancers, and all that would be needed is modifying such protocols for LS screening. Another facilitator that was brought up was that if an organization previously had experience with successfully implementing other genetic screening initiatives, they would be more likely to implement universal screening for LS. The potential to save costs was also a facilitator, and if the organization believed that the cost of treating cancer patients in advanced stages of disease was greater than the cost of implementing a universal LS screening program over a long period of time, implementation of universal screening would be worthwhile (Schneider et al., 2016).

2.4 Cascade testing

‘Cascade testing’ is used to describe the systematic process of genetically testing and counseling blood relatives of a person identified with a pathogenic variant. Testing of relatives closest to the index patient occurs first and then branches to more distant relatives to distinguish carriers of that pathogenic variant within the family (Samimi et al., 2017). In the context of LS, cascade testing can help identify family members who are more likely to get colorectal, endometrial, and other LS-associated cancers by testing for the same pathogenic variant as
identified in the index patient (i.e., the first individual in the family to be diagnosed with LS). Given that interventions for LS start only in adulthood, most guidelines in the US recommend testing for LS only on adults 18 years and above in most situations (Idos & Valle, 1993). In the US, depending on which company performed the genetic testing, testing at-risk family members may be available free of charge or at a discounted rate. In certain situations, free or discounted testing for at-risk family members is only available for a limited time after the patient’s initial genetic test. Many insurance companies cover genetic testing for families if a known pathogenic variant is identified (Cascade Testing for Lynch Syndrome | CDC, n.d.).

2.5 Lynch syndrome screening network

Having realized the importance and need to universally screen CRC tumors for LS, the Lynch Syndrome Screening Network (LSSN) was established by representatives from various cancer facilities, health departments and academic medical centers across the US. Their mission involves promoting universal screening for LS on all colorectal and endometrial tumors and helping institutions to implement universal screening by utilizing network collaboration to share data and resources. LSSN members are involved in several research projects that aim to achieve an evidence-based public health recommendation for universal screening (Lynch Syndrome Screening Network, n.d.).

One of the current projects, which is the focus of this essay, involves assessing how screening is carried out in different institutions outside the US. Since most of the work of the LSSN has been focused on programs in the US, the goal of the project is to determine whether screening protocols for LS exist in cancer institutions internationally, and if so, to identify whether patients
are screened based on traditional clinical criteria/prediction models or universal/routine tumor screening.

2.6 Screening practices at US and international institutions

2.6.1 US practices

Based on an online literature search for screening practices at institutions in the US, it is evident that practices have been variable across sites. These practices are summarized in Table 3. However, with several recommendations to adopt universal screening for LS in the US, it appears that many institutions are implementing it. Based on data collected in 2020, LSSN had 72 partner institutes and 82% of them had implemented universal screening. Nonetheless, this statistic must be interpreted with caution as institutions that perform universal screening are more likely to be a member of LSSN given their interest in screening (Fritzler et al., 2021).

2.6.2 International practices

Internationally, information regarding LS screening practices is even more scarce. Table 3 outlines the practices and outcomes at select institutions in Switzerland, Australia, Canada, and Brazil. Across these international institutions, it appears that the two-step process (IHC with genetic testing) for LS identification is most widely used, except for one institution in Brazil, where direct-to-germline testing is performed.
In Switzerland, the nation-wide practice is that universal screening is performed on all CRC tumors using the IHC method (Salikhanov et al., 2022). A reflexive \textit{BRAF} test is performed if there is no MLHI protein found through the IHC screen. Subsequently, germline testing is performed to confirm a LS diagnosis along with mandatory genetic counseling before and after testing (Salikhanov et al., 2022).

In Switzerland, germline testing to confirm a LS diagnosis is done in two steps. First, two of four MMR genes are sequenced using next-generation sequencing. Then, the sequencing results are confirmed by using Sanger sequencing to sequence specific exons and then performing a gene dosage analysis. Once a LS diagnosis is confirmed in a patient, they can invite four first- and/or second-degree relatives without CRC for cascade testing (Salikhanov et al., 2022). Switzerland has universal health care, and this system is paid for by individuals (as opposed to by taxpayers and/or employers) and is mandatory for anyone living in Switzerland for over three months. As part of this insurance plan, genetic testing is covered after genetic counseling takes place and informed consent is received. The Swiss healthcare system currently does not cover cascade testing, which may pose a barrier to getting additional blood relatives screened apart from the four that they invite (Stoll et al., 2021).

In Australia, there is a single-payer, universal healthcare program called Medicare. If the specific criteria are met, individuals across Australia are eligible to get genetic testing for high-risk variants through the Medicare program. These criteria include a previous cancer diagnosis and/or a family history of genetic disease (\textit{National DNA Screening Could Save Lives for People with High-Risk Hereditary Disease Gene Variants | Australian Government Department of Health and Aged Care}, 2022).
In the province of Manitoba, Canada, individuals who are diagnosed with LS are referred to the provincial hereditary gastrointestinal cancer clinic for coordinated care and cascade testing. The Manitoba universal health care plan is what funds genetic testing and cascade testing for relatives. A challenge for adopting the universal screening model in Canada, generally, is that there are long wait times to access genetic testing, which results in many patients not getting access to testing. Additionally, for those who do get tested, there are not enough genetic counseling resources to meet the demand (Stone et al., 2023).

At the two healthcare facilities analyzed in Brazil, clinical criteria are primarily used to refer patients for screening and/or testing for LS (Della Valle et al., 2019). Approximately 70% of the Brazilian population depends on the two main public health care systems – the Unified Health System or the SUS. SUS does not currently have any specifications on how to manage hereditary cancers. About 20-30% of Brazilians have private medical insurance; and since 2012, it has become mandatory to cover genetic testing under this insurance scheme. There are several barriers to implementing universal screening in Brazil. One is the overall low awareness about LS among the public and the importance of universal screening among clinicians. Another is the financial and logistical challenges associated with implementing such a program as is the case with implementing universal screening in the US. Lastly, access to genetic testing and counseling are limited in Brazil, which makes it difficult to follow through with a universal screening protocol (Kozak et al., 2022).

<table>
<thead>
<tr>
<th>Country</th>
<th>Criteria</th>
<th>Screening/Care Pathway</th>
<th>LS detection rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA – Ohio</td>
<td>Universal CRC tumor screening</td>
<td>1) IHC or MSI</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) If MLH1 loss, do <em>BRAF</em> test</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td>Methodology</td>
<td>Genetic Testing Steps</td>
<td>Number</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>(Heald et al., 2013)</td>
<td></td>
<td>3) Genetic counseling and testing</td>
<td></td>
</tr>
</tbody>
</table>
| USA – California          | CRC with:                                                                  | 1) IHC  
2) BRAF test if MLH1 loss  
3) Genetic counseling and testing                                                                                                                                                                                                                                                                                                                                                                         | 5.3    |
| (Kidambi et al., 2016)    |                                                                             | 1) IHC  
2) BRAF test if MLH1 loss  
3) Genetic counseling and testing                                                                                                                                                                                                                                                                                                                                                                         |        |
| USA – Washington          | Universal CRC tumor screening                                               | 1) IHC or MSI, or both (depending on case)  
2) BRAF test if MLH1 loss or MSI-high  
3) Genetic counseling and testing                                                                                                                                                                                                                                                                                                                                             | 0      |
| (Cohen et al., 2016)      |                                                                             | 1) IHC  
2) BRAF test if MLH1 loss  
3) Genetic counseling and testing                                                                                                                                                                                                                                                                                                                                                                         |        |
| Switzerland               | Universal CRC screening                                                    | 1) IHC  
2) BRAF test if MLH1 loss  
3) Genetic counseling and testing                                                                                                                                                                                                                                                                                                                                                                         | 0.8    |
| (Zumstein et al., 2016)   |                                                                             | 1) IHC  
2) BRAF test if MLH1 loss  
3) Genetic counseling and testing                                                                                                                                                                                                                                                                                                                                                                         |        |
| West Australia            | CRC with:                                                                  | 1) IHC  
2) Confirmatory MSI test  
3) BRAF test  
4) Genetic counseling and testing                                                                                                                                                                                                                                                                                                                                                                  | N/A    |
| (Schofield et al., 2014)  |                                                                             | 1) IHC  
2) Confirmatory MSI test  
3) BRAF test  
4) Genetic counseling and testing                                                                                                                                                                                                                                                                                                                                                                  |        |
| Canada – Manitoba         | CRC screening for patients 70 years or younger (Jerusalem criteria)         | 1) IHC  
2) Reflexive testing  
3) Genetic counseling and germline testing  
4) Referral to provincial hereditary GI                                                                                                                                                                                                                                                                                                                                            | N/A    |
<table>
<thead>
<tr>
<th>Cancer Clinic for Patients with LS</th>
<th>Amsterdam &amp; Bethesda</th>
<th>1) IHC 2) Genetic testing</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil – Salvador (Della Valle et al., 2019)</td>
<td>Bethesda</td>
<td>1) Genetic testing</td>
<td>N/A</td>
</tr>
<tr>
<td>Brazil – Sao Paulo (Della Valle et al., 2019)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 2.7 Cultural attitudes towards preventative care

Cultural and other attitudes are important to consider when determining reasons why some countries may not have a LS screening program established or may not have been successful in trying to establish one. One attitude that may impact the success of LS screening programs internationally is the prioritization of curative treatment over preventative care. For example, in Korea, preventative medicine is not commonly sought because it is engrained in the social culture to visit the doctor only for treating symptoms (OECD, 2020). This type of social culture may hinder the success of any implemented LS screening programs (especially the cascade testing component of the program). This is because even if a known LS pathogenic variant is identified in the family, relatives may not deem it necessary to get LS screening done until they start to show symptoms of CRC or another LS-related cancer.

Literature shows that in the context of cervical and endometrial cancer prevention in the US, there are general fears among several cultural groups that Pap smears and endometrial biopsies
take away one’s virginity (Johnson et al., 2008). This type of attitude may impact the uptake of LS screening programs based on endometrial cancer risk, as women may be reluctant to get endometrial tumors screened (Johnson et al., 2008). Additionally, in Islamic societies, the gender of medical professionals plays a big role in whether preventative care is sought. When health care professionals are mostly male, it presents a barrier for female patients as many women feel uncomfortable seeking care from a professional of the opposite sex. To increase breast cancer screening rates in Iran, a successful technique used was having religious ministries promote the message that “preventative health care is a divine imperative along the lines of ‘God helps those who help themselves’” (Babu et al., 2011). If LS screening programs were to be implemented in Iran or other Islamic countries, using this type of technique may be beneficial to nudge patients and at-risk relatives towards seeking and following through with LS screening.

2.8 Summary

Overall, LS remains an underdiagnosed condition. Diagnosing LS is not only important for the patient, but due to the hereditary nature of the disease, it is also highly relevant for blood relatives as they may be able to prevent the development of cancers that they may be genetically predisposed to using risk-mitigating interventions (e.g., colonoscopies in the case of CRC). Over the years, there has been increased awareness and efforts made by several US medical institutions to implement universal tumor screening for LS. However, it remains unclear whether similar efforts are being made in medical institutions globally, and if not, what factors are hindering the implementation or success of LS screening programs. This study aims to characterize LS screening procedures around the world and focus on different insurance schemes and societal/cultural
attitudes towards preventative care as factors that impact the implementation and/or success of LS screening programs.
3.0 Methods

3.1 Survey and interview guide development

The goal of the study was to better characterize global policies and experiences in implementing universal tumor screening for LS. To do this, a mixed methods approach was used. An online survey was conducted to capture quantitative data on tumor screening and germline genetic testing related to CRC, given that CRC is the most common cancer associated with LS. Then, interview guides were developed for a more focused qualitative analysis of programs. These could be used for future work by LSSN to enhance our understanding of why LS screening programs are set up the way they are in different countries. Through this mixed methodology, we hope to more specifically understand how factors such as insurance and social culture (among others) influence the success of screening programs.

3.1.1 Survey

The online survey was developed by Bianca Kun and Aparna Udiaver using the Research Electronic Data Capture (REDCap) tool hosted by Northwestern University and in collaboration with LSSN (Harris et al., 2009); (Harris et al., 2019). The survey comprised of questions regarding general demographics about the respondent, whether routine screening of colorectal tumors for LS is done at their institution, methods of screening/genetic testing, availability of cascade testing, efficacy of the screening program amongst others. At the end of the survey, respondents were asked if they would agree to be interviewed. They were directed to a separate Qualtrics page where
their contact information could be collected so that their personal information could be kept private and would not be linked to their survey responses (Qualtrics, 2005). If participants felt that someone else within their institution would be better suited to be interviewed, they had the option of providing the contact information of that individual through the Qualtrics page. Some questions included in the survey were adapted from a research article assessing global LS screening practices (Tognetto et al., 2017). A few questions were from a previous LSSN membership survey, which is a form that member institutions of LSSN are asked to complete to assess their use of universal tumor screening to identify LS. The remaining questions included in the survey were novel based on the specific aims of this study. Skip logic was embedded as part of the REDCap survey to ask relevant questions depending on whether the respondent had a routine LS screening program or not and whether they perform tumor screening only, direct-to-germline testing only, or both. See Appendix B.1 for survey questions.

3.1.2 Interview guides

Two interview guides were developed by Bianca Kun and Aparna Udiaver, in collaboration with Dr. Jessica Ezzell Hunter and Dr. Alanna Kulchak Rahm (members of the LSSN Board of Directors and mentors for this study). For feasibility, one interview guide was developed for interviewees that had an established routine LS screening program at their institution at the time of the interview, and the other interview guide was for interviewees that had either never implemented a LS screening program at their institution or tried but discontinued their routine LS screening program. The interview guides were designed to range from 30-60 minutes and included a verbal consent that explained the purpose of the study and details that may facilitate decision-making around interview participation.
3.2 Survey dissemination

The survey was disseminated with approval of Northwestern University’s Institutional Review Board (Appendix A). A link to the survey along with study information was disseminated via email to the LSSN and International Society for Gastrointestinal Tumors (InSiGHT) membership lists and was also posted on the Collaborative Group of the Americas on Inherited Gastrointestinal Cancer’s (CGA-IGC) e-news bulletin. These organizations were chosen because their members are involved in gastrointestinal cancer care and/or research, and InSiGHT was specifically chosen because it is the professional society related to gastrointestinal hereditary cancers that has the broadest membership in terms of countries. Members of these three organizations were given two weeks to complete the survey, and a reminder was sent out after the first week.

3.3 Analysis of preliminary survey results

All survey results were analyzed by Bianca Kun and Aparna Udiaver. The analysis presented here was based on responses collected within one week from initial survey dissemination. This was done by generating data on the demographics of survey respondents, counting data based on the specific aims of the study, and comparing these data across countries and continents. First, preliminary reports were generated using the REDCap report generation feature to compile all survey responses. Then, Microsoft Excel was used to generate the tables and graph based on information from the REDCap reports (Microsoft Excel, 2022). A full analysis of the data will be completed by the LSSN at a later date.
4.0 Results

4.1 Survey results

4.1.1 Demographics of survey respondents

In the first week of responses, there were 27 survey respondents representing seven countries. Distributed by continent, 17 (63%) responses came from North America, 8 (30%) were from Europe, and 2 (7.4%) were from Asia. 59.3% of responses were from the US, 74.1% were from academic-affiliated hospitals/clinics, and the most represented job title was genetic counselor. These demographic characteristics of the survey respondents are summarized in Table 4.

Table 4 Demographics of survey respondents (N= 27)

<table>
<thead>
<tr>
<th>Country</th>
<th>Counts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>Denmark</td>
<td>2 (7.4%)</td>
</tr>
<tr>
<td>Ireland</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>Japan</td>
<td>2 (7.4%)</td>
</tr>
<tr>
<td>Netherlands</td>
<td>2 (7.4%)</td>
</tr>
<tr>
<td>UK</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>USA</td>
<td>16 (59.3%)</td>
</tr>
</tbody>
</table>
### Type of facility

<table>
<thead>
<tr>
<th>Type of facility</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academic-affiliated hospital/clinic</td>
<td>20</td>
<td>74.1%</td>
</tr>
<tr>
<td>Publicly funded health care facility related to universal health care</td>
<td>2</td>
<td>7.4%</td>
</tr>
<tr>
<td>Non-academic hospital/clinic</td>
<td>5</td>
<td>18.5%</td>
</tr>
</tbody>
</table>

### Job Title

<table>
<thead>
<tr>
<th>Job Title</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic Counselor</td>
<td>13</td>
<td>48.1%</td>
</tr>
<tr>
<td>Professor</td>
<td>5</td>
<td>18.5%</td>
</tr>
<tr>
<td>Surgeon</td>
<td>1</td>
<td>3.7%</td>
</tr>
<tr>
<td>Physician</td>
<td>2</td>
<td>7.4%</td>
</tr>
<tr>
<td>Gastroenterologist</td>
<td>3</td>
<td>11%</td>
</tr>
<tr>
<td>Consultant</td>
<td>1</td>
<td>3.7%</td>
</tr>
<tr>
<td>Head of Department</td>
<td>1</td>
<td>3.7%</td>
</tr>
<tr>
<td>Nurse Practitioner</td>
<td>1</td>
<td>3.7%</td>
</tr>
</tbody>
</table>
4.1.2 Global and continent-specific survey results

All respondents had a routine LS screening program established at their institution that involved screening CRC tumors. All use tumor screening approaches with some indicating they also offer direct-to-germline genetic testing; none offers direct-to-germline genetic testing only. Of the 27 responses, 24 (88.9%) perform reflexive testing for the \textit{BRAF} gene and/or promoter hypermethylation in the case of MLH1 absent tumors. Additionally, 25 (92.6%) respondents reported screening all CRC tumors (i.e., without any age or other limits). The two respondents that reported having limits at their institutions indicated that they screen the CRC tumors of all patients less than 50 years of age and less than 70 years of age, respectively. Of the 13 institutions that indicated that they do direct-to-germline genetic testing, only three institutions (in Europe) sequence the five LS-associated genes, while three sequence genes as part of a colorectal cancer panel and seven sequence genes as part of a broader cancer panel. Figure 1 shows that 22 of 27 (81.5%) institutions reported patients being responsible for contacting their family members regarding testing for LS based on a diagnosis in the family. The overall survey results showed that 100% of respondents offered cascade testing for family members at their institution. The LS screening practices at each of the 27 institutions are outlined in Table 5.

4.1.2.1 North American institutions

When looking at LS screening practices by continent, from the 17 North American institutions, 10 (58.8%) respondents indicated their institute performs tumor screening only, while the other seven (41.2%) indicated their institute offers both tumor screening and direct-to-germline testing. With regards to tumor screening methods, 10 institutions use IHC only and seven use both
IHC and MSI (Table 5). Eight institutions track LS rates from the CRC tumors screened, and of this, one respondent knew the percentage of LS cases detected from the patients screened. Of the respondents that knew the approximate percentage of eligible people who get their tumors screened, all responses were in the 76-100% category. Furthermore, of the institutions that performed germline genetic testing and of which the testing rate of eligible patients was known, the testing rate was somewhere between the range of 26-75% (Table 6).

4.1.2.2 European institutions

Of the eight responses from European institutions, three (37.5%) do tumor screening only and five (62.5%) do both tumor screening and direct-to-germline genetic testing. In terms of tumor screening methods, five institutions do IHC only and three use both IHC and MSI (Table 5). Four institutions track LS rates from the CRC tumors screened. Of the four institutions that track this information, only the institutions from the UK had information on the approximate percentage of LS cases detected from the patients screened, which ranged between 2-5%. From the respondents that knew the approximate tumor screening rate from eligible individuals, the screening rate was between 76-100%. Additionally, of the institutions that performed germline genetic testing and of which the testing rate was known, the rate as a percentage was somewhere between 76-100% (Table 6).

4.1.2.3 Asian institutions

From the 2 responses that came from Asia (Japan), one does tumor screening only and the other offers both tumor screening and direct-to-germline genetic testing. Both institutions use MSI and IHC as their tumor screening methods (Table 5). One institution provided information on the screening efficacy metrics, whereby a LS detection rate of less than 2% was reported. 76-100% of
eligible individuals undergo tumor screening and germline testing, respectively, at this institution (Table 6).

<table>
<thead>
<tr>
<th>Table 5 Lynch syndrome screening practices in seven countries (N=27 responses)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>North America</strong></td>
</tr>
<tr>
<td><strong>N=17</strong></td>
</tr>
<tr>
<td>Canada</td>
</tr>
<tr>
<td>N=1</td>
</tr>
</tbody>
</table>

**Routine LS screening**

<table>
<thead>
<tr>
<th></th>
<th>Yes - tumor screening</th>
<th></th>
<th>Yes - DTG</th>
<th></th>
<th>Yes – both</th>
<th></th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>North America</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Canada</td>
<td>1 (100%)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>9 (56.3%)</td>
<td></td>
<td>1 (50%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td>1 (100%)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ireland</td>
<td>1 (50%)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Netherlands</td>
<td></td>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
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<td></td>
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**CRC screens**

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>North America</strong></td>
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</tr>
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<td>1 (100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
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</tr>
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</tr>
<tr>
<td>Ireland</td>
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<tr>
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<tr>
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**Tumor screening method**

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th>MSI</th>
<th></th>
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</tr>
<tr>
<td>US</td>
<td>9 (56.3%)</td>
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<tr>
<td>Denmark</td>
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<tr>
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<td>Japan</td>
<td></td>
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</table>

**Reflexive testing offered**

<table>
<thead>
<tr>
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</tr>
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<tbody>
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<td><strong>North America</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Canada</td>
<td>1 (100%)</td>
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<tr>
<td>US</td>
<td>13 (81.3%)</td>
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<tr>
<td>Denmark</td>
<td>2 (100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ireland</td>
<td>1 (100%)</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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**Tumor screening limits**
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<thead>
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<th>Count</th>
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<tr>
<td>Age/other limits</td>
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<td>0 (50%)</td>
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<tr>
<td>Genes sequenced</td>
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<td></td>
</tr>
<tr>
<td>LS-genes</td>
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<td>0 (50%)</td>
</tr>
<tr>
<td>Broader cancer panel</td>
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<td>0 (50%)</td>
</tr>
<tr>
<td>CRC panel</td>
<td>0</td>
<td>0 (50%)</td>
</tr>
<tr>
<td>Not available</td>
<td>1</td>
<td>0 (50%)</td>
</tr>
</tbody>
</table>

**Figure 1** Individual responsible for contacting at-risk family members about a Lynch syndrome diagnosis at different institutions
Table 6 Efficacy measures of global Lynch syndrome screening programs (N= 27)

<table>
<thead>
<tr>
<th></th>
<th>North America</th>
<th></th>
<th>Europe</th>
<th></th>
<th>Asia</th>
</tr>
</thead>
<tbody>
<tr>
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<td>N=16</td>
<td>N=2</td>
<td>N=1</td>
<td>N=2</td>
</tr>
<tr>
<td></td>
<td>Canada</td>
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<td>Denmark</td>
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**Tracking program**

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**% LS cases detected**

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**Data not tracked/available**

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**% people eligible for tumor screening that get screened**

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**Data not tracked/available**

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**% people eligible for germline testing that get tested**

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<tr>
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<td>0</td>
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<tr>
<td>Ireland</td>
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There were two interview guides developed to be used with institutions that had set up a routine LS screening program or had not (Appendix B.2). Both interview guides initially ask icebreaker questions to gather demographic information regarding the respondent, the institution they work at, whether they have a screening program or not, and information on national policies/registries with information about LS.

Most interview guide questions were an extension of survey questions but focused on reasons for why policies and practices are the way they are. For respondents that had a routine LS screening program, major domains we were looking to capture through the interviews included: overall program questions, tumor types other than those of CRC being screened, age/other limits for screening, direct-to-germline testing, LS tracking programs, influence of insurance on screening, healthcare follow-up, availability of cancer registries with information on LS, cascade testing, and cultural factors affecting screening. For respondents that did not have a routine LS screening program, questions were divided into two domains depending on whether they had a program in the past that was discontinued or if they never tried to implement a routine LS screening program. Major concepts we were looking to capture through these interview guides that were not covered on the survey included barriers and facilitators to implementing a screening program, especially as it related to organizational and societal/cultural factors.
Three online practice interviews were conducted using the interview guides in Appendix B. Two were conducted with Dr. Alanna Rahm, and one was conducted with a genetic counselor from Kaiser Permanente Center for Health Research. None of the practice interview responses contained factual data. The purpose of the practice interviews was to practice interviewing skills and obtain feedback on interview guide questions. There were four changes that were made to the interview guides upon completion of the three practice interviews. One was incorporating a question at the end about asking for additional information that was not discussed in the interview already. Another was being more specific about what is meant by coordinated care (i.e., specialized treatment and/or increased surveillance). For the interview guide designed for respondents without a routine LS screening program, a question about what might help with implementation was added as a final question. Lastly, for interviewees without a routine LS screening program, we added a comment to point the interviewee to the LSSN website for implementation tools. A caveat to this comment for international interviewees was that some of the LSSN implementation tools are specific to the US (e.g., the economic tool), but still may be beneficial for international audiences to adapt for their own use.
5.0 Discussion

The first aim of the survey was to identify the approaches used to screen for LS. The results show that 92.6% of institutions surveyed do not have age or other limits for screening CRC tumors. This suggests that most institutions with routine LS screening programs in the US and around the world have adopted universal screening for LS based on CRC diagnoses, and it also shows that universal screening has become a more common screening model than it was in the past in the US and Canada (Tognetto et al., 2017). The increase in universal screening presents a step in the right direction towards identifying more LS cases globally. Further, a respondent from Denmark indicated as an open-field response that since 2022, Denmark has expanded national, universal screening for LS from only CRC adenocarcinomas to all colorectal-, endometrial-, ovarian-, and small bowel adenocarcinomas, as well as upper urinary tract urothelial tumors and sebaceous skin tumors. This also shows that awareness of the importance of LS screening is increasing and is thus being incorporated as part of national guidelines outside the US. Of the 13 (48.1%) institutions that offer direct-to-germline testing, seven use a broader cancer gene panel to identify all hereditary cancers syndromes (i.e., not restricted to LS only). There were no institutions that only perform direct-to-germline testing, which may suggest that screening tumors for possible LS cases first and then doing genetic testing based on positive screens (i.e., the two-step process) is likely still the most cost-effective method. A study on the cost-effectiveness of systematically testing CRC patients for LS in Australia showed that universal direct-to-germline testing was not as cost-effective as universal tumor screening strategies (Kang et al., 2020).

The second aim for the survey was to gather information surrounding cascade testing of relatives once an index patient is identified. All respondents indicated that their institution offers
cascade testing, which suggests that the importance of cascade testing on LS identification is globally recognized and has been implemented. Additionally, 81.5% of respondents indicated that the patient is responsible for contacting at-risk family members. This is consistent with what has been reported in the literature, whereby the most common practice worldwide is patient-mediated dissemination of genetic information (Barnoy et al., 2023). Having the patient, as opposed to a medical provider, be responsible for contacting relatives has certain merits and risks associated with whether accurate genetic information gets disseminated to all relevant relatives.

In most countries, there are laws similar to the US regarding genetic information being considered as private information. An important merit of the patient-mediated method of information dissemination is that it provides index patients the autonomy to control who this information can be shared with. Additionally, it alleviates burden on providers from having to contact relatives. (Barnoy et al., 2023).

A major challenge associated with cascade testing for relatives of index patients with LS, in general, is that the uptake rate is low, at 52% or less (Sharaf et al., 2013). Some risks that come with the patient-mediated method are that accurate genetic information may not be disseminated and not all relevant relatives may be contacted. A survey conducted on individuals with LS as part of the Swiss CASCADE cohort shows that patients with LS are willing to contact first-degree relatives about cascade testing, but the willingness to contact relatives decreases as the degree of relatedness decreases (Sarki et al., 2022). This presents a risk whereby second- and third-degree relatives may miss out on an opportunity to be screened for LS. Furthermore, family dynamics play an important role in determining how likely an index patient is to inform their relatives and how likely the relatives are to follow through with testing (Sarki et al., 2022).
Based on the responses from Denmark on this survey, in addition to patient-mediated cascade testing, the national register mails unsolicited letters to at-risk family members to inform them about their risk for developing LS-associated cancers, options for genetic testing, and risk-reducing surveillance. This presents the possibility of a hybrid approach (patient-mediated with provider/national-level guidance) for disseminating genetic information as being an ideal method for informing relatives about cascade testing. This is where medical providers empower index patients with the right resources and guidance on contacting family members for patients to ultimately conduct this process independently (Barnoy et al., 2023).

Of the institutions surveyed, 25 (92.6%) offer cascade testing to family members that is covered by insurance of some form, whether that be through federal/national means or by private insurance. The two institutions that do not offer cascade testing are in Japan, which suggests that in Japan, and possibly other Asian countries, not having the costs covered for index patient genetic testing or cascade testing of family members presents a major barrier in identifying LS cases (Tomita et al., 2021). The literature shows that a major issue in Asian countries is the fact that genetic testing is not covered by federal means or by insurance companies, which means patients must pay out-of-pocket to get testing done (Kwong, 2016). For institutions that do offer genetic testing at a subsidized rate, they often rely on research grants and philanthropic means. Unlike the West, Asian countries are still in their infancy with regards to genetic testing and management of hereditary cancers, and thus working on covering the cost of testing could be an area where further advocacy and efforts could focus on (Kwong, 2016).

The third aim of the survey was to determine the efficacy of screening programs at each site to determine what inefficiencies may exist in their screening program. This was done by examining whether LS detection rates are tracked, what percentage of LS cases are identified from
the CRC tumors screened, and what the screening and genetic testing rates are. The results from Table 3 reveal that 13 respondents (48%) have a program to track LS detection rates at their institution. Furthermore, of the 13 respondents that reported having a LS tracking program, only 5 knew what the LS detection rates were. While LS detection rates depend on prevalence of LS in specific populations and on screening sensitivity and specificity, the fact that many institutions do not have tracking systems or do not know this information is of concern. This presents an opportunity for improvement, whereby the success of global screening programs gets tracked to increase optimization of the program. Additionally, tracking new LS cases is also important for establishing LS prevalence in other countries.

From the seven countries represented in these survey results, the European countries (UK, Netherlands, and Denmark) appear to be ahead in terms of their data collection methods with the establishment of national registries that track LS cases. Notably, the three UK institutions assessed here each had an institution-level LS tracking program and could report the percentage of new LS cases detected from patients screened. Furthermore, the UK respondents also commented on how regional registries are being developed as part of the NHS National Lynch syndrome transformation project. This project is a collaboration between Genomic Medicine Services in the UK, and it has three goals. They are to improve LS detection and management, bridge the gap between LS testing and diagnosis, and to support early cancer detection and personalized care access (National GMSA Transformation Project: Lynch Syndrome - North Thames GMS: North Thames GMS, n.d.). In Netherlands, registration of LS cases at the national level occurs only with informed consent by the index patient or family member. It is interesting to note that the US has established national level cancer registries and has many federal-level recommendations surrounding LS screening but does not have a national level registry that tracks LS cases.
Registering information on LS cases at least at the national level is crucial to collect accurate and complete data regarding LS, understand the disease better and how it affects the country’s population, and figure out how to allocate resources for addressing LS (Importance of Cancer Registry | SEER Training, n.d.).

Based on North American responses, of the respondents that knew the tumor screening rate at their institution as a percentage (number of people that get screened / number of people eligible for screening), the screening rate is generally high given that responses were in the 76-100% category. This finding suggests that tumor screening is being performed with a high degree of effectiveness. However, for the North American institutions that offer germline testing as well, the genetic testing rate as a percentage (number of people that get tested / number of people eligible for genetic testing) appears to be lower than tumor screening rates as the responses were between 26-75%. This may present an inefficiency in getting patients with positive screens to follow through with testing, which could be explained by several factors. A major factor pertinent to the US is that patients may not have adequate insurance coverage for testing, given the large variability in the types of coverage individuals typically have in the US. Other factors that may be of importance include lack of proper genetic counseling to explain the benefits of genetic testing and not wanting to know the result in case it may be positive (Mange et al., 2012). As well, some individuals may not have a family history of cancer (or are unaware of a family history) so they are incorrectly not concerned, or there could simply be cases of loss to follow up, whereby individuals never come back for genetic testing despite being contacted (Kanga-Parabia et al., 2018).

By contrast, among the European countries analyzed from this survey, there was both a high tumor screening germline testing rate (i.e., in the 76-100% category). While similar barriers
related to getting genetic testing done in US may hold true in European countries as well, an important reason for the increase in genetic testing rates in Europe relative to US institutions could be that genetic testing tends to be included as part of standard health care or insurance coverage without charge to patients in several European countries, which removes the cost barrier for patients. In the UK, if a patient is referred for genetic testing by a specialist, it is free of cost for the patient as part of the National Health System (Genetic and Genomic Testing - NHS, n.d.). Likewise, in Denmark, if genetic testing is deemed medically relevant, it is offered to patients free of charge through the department of Clinical Genetics as part of Denmark’s national health care system (Gerdes et al., 2021).

5.1 Strengths and limitations

There are several strengths and limitations to this study. One strength is that it provides information on the most recent LS screening practices happening across three continents – North America, Europe, and Asia. The survey explored a variety of factors, including screening methodologies, insurance coverage for genetic testing, cascade testing, and institution-level and nation-wide LS tracking systems, which help to explain why programs are set up the way they are and provides a basis to identify where improvements could be made to existing LS screening programs. Providing the option to explain ‘Other’ responses and to explain any other information not asked about on the survey helped to capture novel information that we may not have been able to capture otherwise through a purely multiple-choice survey format. Furthermore, the findings from this survey provide insights on LS screening programs that have not been and may never get
published in the literature, thereby adding to our knowledge about how LS programs are implemented in practice.

Some limitations of this study were that the number of responses were limited and most were from the US and/or from countries that we have some knowledge about with regards to their LS screening practices. The conclusions drawn from this analysis should be interpreted with caution (especially the continent-specific ones), given the bias towards US responses in the North American analysis and the fact that the two responses from Asia were from institutions in Japan. However, the survey was available for longer than what was analyzed for this study, and there was a higher response rate from more countries and in more continents, where information about their LS screening practices is less understood but could not be included in this essay due to time constraints on project completion. Another limitation was that some responses had missing data or were incomplete beyond the consent/demographics page and thus were excluded from analysis. Additionally, there is likely the voluntary response bias involved, whereby only individuals from an institution with a LS screening program are likely to respond, even though there was interest in hearing from institutions that do not routinely screen for LS as well. It is also important to note that the survey intended to assess the use of tumor screening approaches with follow-up germline testing compared to emerging use of direct-to-germline genetic testing. However, it is possible that respondents confused the use of direct-to-germline testing with follow-up germline testing, which may have conflated the use of direct-to-germline testing approaches. The potential confusion could be explored in interviews. Furthermore, based on the high rate of universal tumor screening identified from the survey, it could suggest that this sample may not be truly representative of all institutions doing routine LS screening. This is because those who are members of the organizations we used to recruit study participants might be more likely to be involved in universal
tumor screening. Lastly, the survey was only available in English, which presents a major limitation to receiving responses from other countries.

5.2 Future directions

To continue this project further, it would be beneficial to include more responses as part of the analysis to assess trends in different countries and continents with more confidence. Additionally, select respondents should be interviewed based on the interview guide to further understand what factors influence routine LS screening practices and why some institutions have not implemented a routine LS screening program. Specifically, interesting factors to explore would be the effect of insurance coverage and social culture in different countries on the success of LS screening programs. It could be beneficial to have translators for other languages, so that information on LS screening practices can more easily and accurately be captured from countries where English is not a primary language. Additionally, it would be interesting to interview institutions that perform tumor screening only to clarify whether confirmatory germline testing is done (perhaps outsourced) or not to confirm a LS diagnosis. As well, for institutions that offer both tumor screening and germline testing, it is assumed that the two-step process is being followed. It would be interesting to learn whether there are instances where direct-to-germline testing is performed (i.e., without doing tumor screening first). It would also generally be interesting to interview specific countries to gain a more in-depth understanding of how LS detection interventions can be tailored to different populations. For future work, given that all sites offer cascade testing and knowing the importance of cascade testing in helping detect LS-associated cancers earlier in relatives, it would be worthwhile to gather data on the cascade testing
up-take rate by family members to assess whether it remains low or has improved over the years. Lastly, future research could also focus on translating the survey, interview guides, and potentially other LSSN materials to other languages to make them more accessible internationally.
6.0 Conclusion

In summary, this essay reported on information regarding LS screening practices in the US and internationally by presenting the preliminary results of a survey and interview guides for future use by LSSN. The survey focused on three categories of questions: information on LS screening practices, cascade testing, and efficacy of screening programs. Interview guide questions were designed to gather more in-depth information on different parts of the survey and to specifically understand how insurance and social culture in different countries impact the success of LS screening programs globally. Key outcomes from the survey were that 92.6% of sites perform universal screening on all CRC tumors, 81.5% of institutions use a patient-mediated method for informing relatives about cascade testing, and 48.1% of respondents reported that either their institution does not have a formal system to track LS detection rates for newly diagnosed CRCs or that they are unaware if such a tracking system exists. Based on continent-specific analyses, it appears that European countries are advanced in terms of setting up national and regional level registries to track LS cases. Overall, the outcomes from the survey serve to increase our knowledge regarding current LS screening practices, provide insight on how LS screening has improved over the years, and identify how further improvements could be made to screening programs to ultimately increase LS diagnoses and reduce the burden that LS can have in families around the world.
Appendix A IRB exemption

Northwestern University
Institutional Review Board
Biomedical IRB  Social & Behavioral Sciences IRB
750 North Lake Shore Dr., 7th 600 Foster St., 2nd Floor
Fl.
Chicago, Illinois 60611  Evanston, Illinois 60208
irb@northwestern.edu  sbsirb@northwestern.edu
Office 312.503.5338  Office 847.467.1723

Notification of Exempt Determination

To:  Debra Duquette
Link:  STU00220556
P.I.:  Debra Duquette
Title:  Policies on LS screening
Description:  The committee reviewed this submission and assigned a determination of Exempt. For additional details, click on the link above to access the project workspace.
Appendix B Supplementary data

Appendix B.1 Routine Lynch syndrome screening practices survey questions

Page 1:

Thank you for your interest in our study! This survey should take approximately 5-15 minutes to complete.

Below is some general information about this study and on the next page is the study consent with more information about what will happen if you join the study. If you would like to join the study after reading this information and the study consent, please click "I Agree" and you will be taken to the survey.

We are collaborating with the Lynch Syndrome Screening Network (LSSN) to understand the policies and procedures surrounding the screening practices of Lynch Syndrome. We are particularly interested in gathering information on whether organizations perform routine screening for Lynch syndrome (either through tumor testing or direct to germline testing) in ALL cases of colorectal cancer or a defined subset (e.g., all cases under the age of 80 years). You will be asked a series of questions about whether your organization does or does not have a program for routine screening for Lynch Syndrome. We are also interested in learning why some organizations do not offer Lynch Syndrome screening while others do.
If you have any questions, please contact the principal investigator, Debra Duquette, MS, CGC, at debra.duquette@northwestern.edu.

Page 2: Waived Consent form & Participant agreement

Page 3: Survey Question Bank

Please fill in the information about your facility:

Institution and Site Name: __________________

Type of Facility:

a) Academic-affiliated hospital/clinic
b) Non-academic hospital/clinic
c) Publicly funded health care facility related to universal health care
d) Other
   a. Please specify: __________________
e) N/A
   Town: __________________
   City: __________________
   Country: __________________
   Job Title: __________________

The following questions ask about your institution’s policies and/or procedures for identifying Lynch syndrome. You do not have to answer all of the questions.

Do you have a program in place to routinely identify individuals with Lynch syndrome such as a tumor screening program or direct-to-germline testing?
Note: Tumor screening refers to screening cancerous tumor tissue to identify if the cancer was caused by Lynch syndrome.

Direct-to-germline testing refers to performing a genetic test to identify the presence of inherited mutations that typically cause Lynch syndrome.

a) Yes – tumor screening
b) Yes – direct-to-germline
c) Yes – tumor screening & direct-to-germline
d) Yes – other
e) No
f) Don’t know

If other, please explain the type of program: __________________

Are there national guidelines about screening and/or testing for Lynch syndrome that are separate from your institutional policies?

a) Yes
b) No

If yes, please explain the national guidelines: __________________

As part of your program, does your organization currently screen colorectal cancer tumors to identify Lynch syndrome?

c) Yes
d) No
e) Don’t know

Has your organization tried to implement colorectal cancer tumor screening for Lynch syndrome?

a) Yes
b) No
c) Don’t know
Has your organization tried to implement direct-to-germline testing for Lynch syndrome?

a) Yes  
b) No  
c) Don’t know

When is family history typically taken to identify individuals at-risk for hereditary cancer?

a) When screening for colon cancer (e.g., colonoscopy)  
b) When screening for another cancer  
c) During routine care  
d) Don’t know  
e) Other

If other, please specify: __________________

What criteria do you use to identify individuals at-risk for Lynch syndrome?

a) Bethesda criteria  
b) Amsterdam II criteria  
c) Combination / revised version of Bethesda and Amsterdam II criteria  
d) Computational model (MMRpredict model, MMRpro model, etc.)  
e) Other
   a. Please explain: __________________

Who is primarily responsible for diagnosing Lynch syndrome?

a) Ob-gyn  
b) Oncologist  
c) Pathologist  
d) Surgeon  
e) Clinical geneticist  
f) Gastroenterologist  
g) Genetic counselor  
h) Molecular geneticist  
i) Other
   a. Please specify: __________________
The following questions will ask about colorectal cancer tumor screenings.

What method do you use to screen tumors?

a) MSI only
b) IHC only
c) Both MSI and IHC
d) Other
   a. Please specify: __________________
e) Don’t know

For IHC screening, do you have a process for reflexive testing for BRAF and/or promoter hypermethylation in the case of MLH1 absent tumors?

a) Yes
b) No
c) Don’t know

Do you screen all tumors regardless of age or do you have limits on which tumors are screened?

a) Don’t know
b) All tumors screened
c) Age/other limits
   a. Please specify: __________________

The following questions will ask you about direct-to-germline testing.

What genes are sequenced during direct-to-germline testing?

a) All Lynch-associated genes (*MLH1, MSH2, MSH6, PMS2, EPCAM*)
b) A subset of Lynch genes
c) Genes as part of the colorectal cancer panel
d) Genes as part of the broader cancer panel

How is genetic testing for Lynch syndrome most accessed in your healthcare system/country?
The following questions will ask you about cascade testing at your facility. In this context, cascade testing refers to informing family members about a Lynch syndrome diagnosis and getting them genetically tested for the condition.

Do you offer genetic testing to at-risk family members of individuals identified with Lynch syndrome?

a) Yes
b) No
c) Don’t know

Who typically contacts the at-risk family members for testing?

a) Patient
b) Genetic counselor
c) General practitioner
d) Medical geneticist
e) Nurse
f) Other
   a. Please specify: __________________

Is genetic testing for at-risk family members covered by insurance?

a) Yes – Federal/national
b) Yes – Private insurance
c) Yes – Both federal/national and private insurance
d) Yes – Other
   a. Please specify: __________________
e) No
f) Don’t know
The following questions will ask you about the Lynch syndrome identification program at your facility.

Do you have a program in place to track Lynch syndrome detection rates for newly diagnosed colorectal cancers?

a) Yes
b) No
c) Don’t know

Over the period of your program, approximately what percentage of new Lynch syndrome cases were detected from the patients screened? **Note: If you aren’t sure about this information, select “Don’t know”.

a) < 2%
b) 2-5%
c) > 5%
d) Don’t know
e) We don’t track this

On average over the period of your program, of those eligible for Lynch syndrome tumor screening, what percentage are actually being screened? **Note: If you aren’t sure about this information, select “Don’t know”.

a) 0-25%
b) 26-50%
c) 51-75%
d) 76-100%
e) Don’t know
f) We don’t track this
On average over the period of your program of those eligible for Lynch syndrome direct-to-germline testing, what percentage are actually being tested? **Note: If you aren’t sure about this information, select “Don’t know”.

a) 0-25%
b) 26-50%
c) 51-75%
d) 76-100%
e) Don’t know
f) We don’t track this

Does your country record data on Lynch syndrome as part of a population-based cancer registry?

a) Yes – national registry
   a. Please specify: ________________
b) Yes – regional registry
   a. Please specify: ________________
c) Yes – both national and regional registries
   a. Please specify: ________________
d) No
e) Don’t know

Is there anything else we should know?

Would you agree to be interviewed?

a) Yes
b) No
Appendix B.2 Interview guides

Icebreaker questions

- Tell me about yourself
  - City and country
  - Facility you work at
  - Your role
  - How long you have been working there
- Does your facility have a Lynch syndrome screening program?
- Are there any national policies or guidelines regarding Lynch syndrome screening in your country?
- Does your country have a population-based cancer registry, and does it track Lynch syndrome?

Appendix B.2.1 Interview guide – no program

A) Tried to implement a program **BUT** did not continue

<table>
<thead>
<tr>
<th>Stem Question</th>
<th>Probes/Clarifying Question(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was a program set up and running?</td>
<td>- How far did you get?</td>
</tr>
</tbody>
</table>
| 2. When did the LS screening program run and how long did it run for? | - What were the approximate start and end dates of the program?  
- Did it last for 6 months, a year, longer?  
- Why did it not continue? |
| 3. What factors initially helped with the implementation process for screening for LS? | - Ex. Finances, adequate awareness about LS, etc. |
4. What barriers did you face while implementing a program to screen for LS?  
   • Barriers may include: financial problems, issues with other stakeholders (disagreements), infrastructure problems, etc.

5. In your opinion, what is one reason your organization decided to stop the program/stop screening for LS?  
   • General reasons: lack of funding, lack of interest or support, an organizational decision?

6. Do you think your facility would try implementing a LS program again in the future?  
   • What would be needed to be done differently to implement this program again?

7. Is there anything else you would like to tell me that I did not ask about?

B) Have NOT tried to implement a program

<table>
<thead>
<tr>
<th>Stem Question(s)</th>
<th>Probes/Clarifying question(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What are some reasons your institution decided not to establish a LS screening program?</td>
<td>• Potential reasons: expensive/financial cost, lack of knowledge in the general population on LS, etc.</td>
</tr>
<tr>
<td>2. What are some societal/cultural considerations that need to be taken into account when/if trying to implement screening for LS? What are some organizational considerations that need to be taken into account when/if trying to implement screening for LS?</td>
<td>• Cultural consideration → is your society more concerned with prevention or treating the symptoms? • What are some other factors to consider?</td>
</tr>
<tr>
<td>3. What are some barriers you believe are impeding implementation of a LS screening program? What are some factors that might help with implementation of a LS screening program?</td>
<td>• Not feasible? • Not implementable? • Not appropriate? • Are there too many competing interests? • Not enough time? • No leadership support?</td>
</tr>
<tr>
<td>4. Is there anything else you would like to tell me that I did not ask about?</td>
<td></td>
</tr>
</tbody>
</table>
Appendix B.2.2 Interview guide – program in place

## Topic: Overall program questions

<table>
<thead>
<tr>
<th>Stem question</th>
<th>Probe/clarifying statements or questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Tell us about your program</td>
<td>- What cancers are screened for?</td>
</tr>
<tr>
<td></td>
<td>- How long the program has been running for?</td>
</tr>
<tr>
<td></td>
<td>- Do you do tumor screening only, germline testing only, or both?</td>
</tr>
<tr>
<td></td>
<td>- What are some reasons for only having one or the other?</td>
</tr>
<tr>
<td></td>
<td>- What are some reasons you added endometrial cancer screens to the program?</td>
</tr>
<tr>
<td>2. What is going well with the program?</td>
<td>--</td>
</tr>
<tr>
<td>3. What factors helped with implementation of the LS screening program?</td>
<td>- Ex. Finances, adequate awareness about LS, etc.</td>
</tr>
<tr>
<td>4. What are some barriers that you faced when implementing your program?</td>
<td>- Examples of barriers: financial barriers, lack of communication between departments, etc.</td>
</tr>
<tr>
<td>a. Do you continue to face these barriers?</td>
<td></td>
</tr>
<tr>
<td>5. What are some areas where your program needs improvement?</td>
<td>- What are some difficulties you are continuing to face, if any?</td>
</tr>
</tbody>
</table>

## Topic: Tumor screening

<table>
<thead>
<tr>
<th>Stem question</th>
<th>Probe/clarifying statements or questions</th>
</tr>
</thead>
</table>
1. Are there any other tumors being screened at your institution other than colorectal cancer tumors? - For example, are you also screening endometrial tumors?

2. If yes, why are you also screening [insert tumor type] tumors? --

**Topic: Age/other limits for screening**

<table>
<thead>
<tr>
<th>Stem question</th>
<th>Probe/clarifying statements or questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What are some reasons why you have age/other limits for your LS screening program?</td>
<td>--</td>
</tr>
</tbody>
</table>

**Topic: Direct-to-germline testing (for respondents that only conduct DTG testing)**

<table>
<thead>
<tr>
<th>Stem question</th>
<th>Probe/clarifying statements or questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Why are you only conducting DTG testing?</td>
<td>Is there a reason you aren’t also conducting molecular testing, i.e., IHC or MSI?</td>
</tr>
<tr>
<td>2. If you are only testing a subset of the LS genes, why those genes?</td>
<td>--</td>
</tr>
</tbody>
</table>

**Topic: LS tracking program**
How do you know your program is going well?  

Do you have a tracking system/registry in place?  

If yes, do you know how many individuals eligible for screening are being screened?  

- Why do you think only a small percentage of eligible individuals are actually being screened?  

  - OR -  

- What’s leading to the success of everyone/almost everyone being screened?  

**Topic: Insurance**

<table>
<thead>
<tr>
<th>Stem question</th>
<th>Probe/clarifying statements or questions</th>
</tr>
</thead>
</table>
| 1. In your opinion, does insurance play a role in who undergoes screening? | - For example, in the US, the type of insurance you have dictates screening/testing available for a patient and whether the patient would need to pay out of pocket costs  
- What components of LS screening are covered by your universal/country wide health care and what components do they need additional coverage for?  
- Are there any out-of-pocket costs in your country/healthcare system? |
<table>
<thead>
<tr>
<th>Stem question</th>
<th>Probe/clarifying statements or questions</th>
</tr>
</thead>
</table>
| 1. Do you have dedicated healthcare pathways for coordinated care for individuals identified with LS? | - By coordinated care, we mean services such as specialized treatment and increased screening  
- If not: why?  
- If so: how often are these taken up by individuals from your experience?  
  - Very often  
  - Often  
  - Sometimes  
  - Hardly  
  - Never |

**Topic: Cancer registry**

<table>
<thead>
<tr>
<th>Stem question</th>
<th>Probe/clarifying questions or statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Does your country have a population-based cancer registry and does it track LS?</td>
<td>- If yes: are registries used to help with follow-up care?</td>
</tr>
</tbody>
</table>

**Topic: Cascade testing / At-risk family member testing**

<table>
<thead>
<tr>
<th>Stem question</th>
<th>Probe/clarifying statements or questions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1. Is cascade testing offered at your institution?
   - If yes: What are some barriers or issues you face when trying to perform cascade testing?
   - If not: why?

**Topic: Cultural factors affecting screening**

<table>
<thead>
<tr>
<th>Stem question</th>
<th>Probe/clarifying questions or statements</th>
</tr>
</thead>
</table>
| 1. Can you provide a brief explanation about the social culture in your country and how it can affect healthcare decisions? | - How does the social culture in your country affect how willing people are to take up preventive care such as screening?  
   - What other factors might be involved in people’s willingness to take up preventive care? |

**Topic: Other**

Is there anything else you would like to tell me that I did not ask about?


