Implementing Universal Lynch Syndrome Screening: A Qualitative Analysis of Organizational Stakeholder Interviews

by

Amber Mariah Stafford

B.S. Biology, George Mason University, 2017

Submitted to the Graduate Faculty of the

Department of Human Genetics

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Public Health

University of Pittsburgh

2022

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

This essay is submitted

by

Amber Mariah Stafford

on

April 29, 2022

and approved by

Essay Advisor: Andrea Durst, MS, DrPH, CGC, Assistant Professor of Human Genetics, Director of the MPH in Human Genetics Program, Graduate School of Public Health, University of Pittsburgh

Essay Reader: Alanna Kulchak Rahm, PhD, MS, CGC, Associate Professor, Genomic Medicine Institute, Geisinger

Essay Reader: Zachary Salvati, MS, CGC, Genomic Medicine Institute, Geisinger

Essay Reader: Phuong Mai, MD, Associate Professor, Department of Obstetrics, Gynecology and Reproductive Sciences, School of Medicine, University of Pittsburgh

Implementing Universal Lynch Syndrome Screening: A Qualitative Analysis of Organizational Stakeholder Interviews

Amber Mariah Stafford, MPH

University of Pittsburgh, 2022

Abstract

Lynch syndrome accounts for 3-5% of all newly diagnosed colorectal cancer cases. Numerous clinical guidelines recommend universal tumor screening of all newly diagnosed colorectal cancer patients for Lynch syndrome, and it has become the standard of care; however, some organizations have not yet implemented universal Lynch syndrome screening programs. Universal screening holds public health significance because it increases the detection of Lynch syndrome, allows for cascade testing of at-risk family members, and enables cancer surveillance and prevention which leads to reduced morbidity and mortality. The IMPULSS study aims to understand the variability in implementation, promote the implementation of Lynch syndrome screening at healthcare organizations, and encourage maintenance and evolution of existing screening programs through organizational toolkits based on the needs of organizational implementers and decision makers.

Team members of the IMPULSS study designed an economic modeling tool that allowed stakeholders from various healthcare organizations to understand the costs of LS screening protocols to their organization and to compare the costs of other protocols. Participants who used the tool were involved in the screening process and were interviewed by a study member to discuss their experience using the tool. Transcripts of the interviews were analyzed to help identify factors that affect the decision-making process of stakeholders involved with implementation.

Analysis of the transcripts showed that there are three thematic groups, which include "institutional characteristics", "personnel characteristics", and "informing decision-making." At the institutional level, costs, detection of cases, and adherence to clinical guidelines were prioritized when considering protocol implementation. Participants mentioned a common barrier to protocol implementation buy-in is the likelihood of increased testing volume, and participants identified organizational infrastructure as a common facilitator. At the personnel level, benefit to the patients was prioritized and participants shared that their networks and communication with other stakeholders were important to successful implementation. Within the decision-making process, participants considered costs, compared their current programs to ideal patient care scenarios, and checked other protocol options. Several participants expressed interest in direct-to-germline sequencing. The results from this paper will be used to inform the "deciding to implement" toolkit that will be created by the IMPULSS study.

Table of Contents

List of Tables

Preface

I would like to thank my supervisors on the project, Dr. Alanna Rahm and Zachary Salvati, a member of the IMPULSS project research support staff, Dina Hassen, and my mentor in the MPH program, Dr. Andrea Durst who helped every step of the way. Your guidance throughout my practicum and in writing this essay was a vital resource, and without it this process would not have been possible. I would also like to thank those who participated in the interviews on which this analysis was based. Lastly, I would like to thank Dan Waddell whose support and encouragement was unwavering.

1.0 Introduction

Lynch syndrome, also called hereditary non-polyposis colorectal cancer and abbreviated LS, is a hereditary cancer syndrome that is associated with an increased risk for several cancers, most commonly colorectal and endometrial cancers. The general population's risk of colorectal cancer is around 4% (Society, 2022), but someone with Lynch syndrome has a risk up to 80% (Bhattacharya P, 2021). Amsterdam and Bethesda Criteria were previously used to determine who would benefit from screening, after which germline genetic testing could be performed when appropriate (Syngal, Fox, Eng, Kolodner, & Garber, 2000). However, now universal tumor screening is considered the standard of care for all newly diagnosed patients with colorectal cancer (Hunter et al., 2015). A diagnosis of Lynch syndrome offers opportunity for cancer prevention and reduced morbidity, such that people can be more regularly screened for associated cancers, follow current recommendations for cancer prevention, and have tailored treatment options available to them if they already have cancer (Rahm et al., 2018).

It is estimated that roughly 1 in every 250 people (~1.3 million) have Lynch syndrome, which accounts for approximately 3-5% of all newly diagnosed colorectal cancers (Rahm et al., 2018). Of those with LS, only ~ 2% know that they have this condition (Hampel & de la Chapelle, 2011). One reason is the variable implementation of systematic screening; reducing the public health impact by resulting in fewer cases identified and fewer family members identified through cascade testing. Although many authoritative bodies on cancer screening guidelines, such as the Evaluation of Genetic Application in Practice and Prevention (EGAPP), the National Comprehensive Cancer Network (NCCN), and Healthy People 2020 all recommend universal

tumor screening, it is still poorly implemented in healthcare settings (Network, 2021; Prevention, 2011; Rahm et al., 2018; Services, 2010). Several factors may contribute to the lack of adherence to guidelines such as cost, knowledge of the guidelines, and healthcare organization complexity. If obstacles within organizations can be identified and overcome this would allow for more consistent application of the current guidelines, greatly improving the rate of diagnosis, promoting patient awareness, and providing them the knowledge to make informed life decisions.

Implementing Universal Lynch Syndrome Screening (IMPULSS) is a current study that is evaluating the implementation of universal tumor screening at various healthcare institutions. The overall purpose of the IMPULSS study is to understand the variations in existing tumor screening programs including their effectiveness, efficiency, and costs. This information will be used to develop a toolkit that will be distributed to help healthcare institutions implement new screening programs and to maintain and improve existing ones (Rahm et al., 2018). For the current analysis, fifteen stakeholders across seven different healthcare organizations were interviewed to gather opinions and experiences using an economic modeling tool designed as part of the IMPULSS project to aid organizational decision-makers in development and implementation of universal tumor screening programs as part of the IMPULSS toolkit.

The IMPULSS project is significant because there is currently a disconnect between universal tumor screening guidelines and real-world implementation. Data obtained from this project will be instrumental in bridging that gap because challenges for implementation will be understood and solutions provided based on mitigating factors, such as different organizational structures, costs, resources, and leadership sponsorship. IMPULSS has four aims which include describing variations in LS screening implementation, determining the factors associated with optimal LS screening programs, determining the effectiveness, efficiency, and costs of different

screening protocols, and developing and testing an organizational toolkit to aid in implementation and improvement of LS screening (Rahm et al., 2018). The focus of this paper is on participant perspectives of the economic modeling tool, which allows for exploration of program costs and expected outcomes for individuals identified with LS based on organization-specific data. The tool can be edited so that it will also be flexible to change with time as our understanding and knowledge surrounding genetics is always growing and shifting.

1.1 Specific Aims

Aim 1.) To conduct a qualitative analysis of responses obtained from user-testing interviews regarding stakeholder experience using the economic modeling tool created by the IMPULSS study.

Aim 2.) Provide specific information for how to use the cost modeling tool in the "deciding to implement" toolkit based on Aim 1 results.

2.0 Literature Review

2.1 Genetics

2.1.1 Mismatch Repair and Genes Involved

Lynch syndrome is a genetic condition with an autosomal dominant pattern of inheritance. The condition occurs because of pathogenic variants in the genes associated with the DNA mismatch repair system, which is responsible for detecting base pair mismatches (C. R. Boland & Goel, 2010). These variants can be observed in one of four mismatch repair genes: *MLH1*, *MSH2*, *MSH6*, and *PMS2* (Palomaki, McClain, Melillo, Hampel, & Thibodeau, 2009). Specific *EPCAM* deletions are also indicative of Lynch syndrome and should be included in Lynch syndrome genetic testing (Tutlewska, Lubinski, & Kurzawski, 2013). When pathogenic variants are present, DNA is unable to repair itself after errors occur during replication. As a result of the breakdown of the mismatch repair system, expansions and contractions are present in highly repetitive areas of DNA, and this instability can potentially result in various cancers (Tamura et al., 2019).

2.1.2 Associated Cancers

People with Lynch syndrome have a lifetime risk of up to 80% of developing colorectal cancer (Bhattacharya P, 2021). Although most of the current guidelines about screening for Lynch syndrome are focused on colorectal cancer, there are several other cancers associated with Lynch syndrome that can be caused by mutations in any of the five associated genes (Table 1).

Endometrial cancer is the second most commonly diagnosed cancer in people with Lynch syndrome. Women with Lynch syndrome have a lifetime risk of 30-45% for endometrial cancer, and about half of women with LS experience endometrial cancer as their first cancer. Aside from colorectal and endometrial cancers, people with Lynch syndrome are also at an increased risk for ovarian, stomach, small bowel, urothelial, brain, skin, and pancreatic cancers (Barrow, Hill, & Evans, 2013) (Table 2).

Table 1. Proportion of Lynch Syndrome Cases by Gene

Gene	Proportion of Lynch Syndrome Patients with Colorectal and Endometrial Cancers
MLHI	15-40%
MSH2	20-40%
MSH6	12-35%
PMS2	5-25%
EPCAM	<10%

Adapted from: (Idos & Valle, 1993)

Table 2. Cancer Risks in Individuals with Lynch Syndrome

Cancer Type	General Population Risk	Risk for Individuals with LS by Affected Gene and Sex							
		MLHI		*MSH2*		*MSH6*		*PMS2*	*EPCAM*
		F	M	F	M	F	M	F&M	F&M
Colorectal	2%	44%	53%	42%	46%	20%	12%	3%	75%
Endometrial	1%	35%		46%		41%		13% (F)	12%
Ovarian	0.7%	11%		17%		11%		3% (F)	
Stomach	1%	8%	16%	10%	16%	2%	4%	4%	
Small Bowel	<1%								
Ureter, Kidney	<1%	3%	4%	13%	16%	2%	4%	4%	
Urinary Bladder	<1%	3%	5%	7%	9%	1%	4%		
Prostate	4%		7%		16%		5%	5%	
Brain	<1%	2%	1%	2%	4%	1%	2%		
Breast	5%	11%		13%		11%		8%	

Adapted from: (Idos & Valle, 1993)

2.2 Diagnosis

2.2.1 Screening Criteria

Prior to 2009 when universal tumor screening was recommended, there were two sets of criteria used to identify people who may be at a high risk for Lynch syndrome. The sets of criteria

are Amsterdam II Criteria and Revised Bethesda Guidelines (Umar et al., 2004; Vasen, Watson, Mecklin, & Lynch, 1999) (Table 3). These two criteria placed an emphasis on family history and age of cancer onset, which was capable of capturing some people with Lynch syndrome but also missed many cases if they did not meet these criteria (Subramonian et al., 2020).

Table 3. Criteria Based Screening

Amsterdam II Criteria (Vasen et al., 1999)	**Revised Bethesda Guidelines** (Umar et al., 2004)
>3 relatives with a LS-related cancer and: • One should be a first degree relative • At least two successive generations are affected • At least one diagnosed before age 50 • Exclude Familial Adenomatous Polyposis (FAP)	• Colorectal cancer diagnosed before age 50 • Synchronous or metachronous colorectal or LS-related tumors, any age • Colorectal cancer with MSI-High histology • Colorectal cancer diagnosed in a person with at least one first-degree relative with LS-related cancer diagnosed before age 50 • Colorectal cancer diagnosis and at least two first- or second-degree relatives with LS-related tumor, any age

Adapted from: (Bhattacharya P, 2021)

2.2.2 Universal Tumor Screening

Since 2009, the recommendation by many organizations has been to conduct universal tumor screening of all patients newly diagnosed with colorectal cancer to identify as many cases of Lynch syndrome as possible. Screening is accomplished by testing tumors for deficient

mismatch repair genes and the screening tests often used in universal tumor screening are immunohistochemistry (IHC) or microsatellite instability screening (MSI), or a combination of the two (Rahm et al., 2018). Immunohistochemistry is used to examine the absence of mismatch repair protein(s), which indicates that one of the mismatch repair genes is not working. MSI screening is used to detect length discrepancies between normal tissue and tumor tissue of certain microsatellite regions of DNA, with the presence of discrepancies indicative of mismatch repair deficiency. A high level of instability can indicate Lynch syndrome but can also be caused by hypermethylation of the *MLH1* promoter region. Hypermethylation is a sporadic event, so it is important that either BRAF V600E testing or direct-to-germline sequencing be performed when abnormal results are returned from either screening method to confirm whether the patient has Lynch syndrome. IHC and MSI testing both have their own benefits, but IHC is typically less expensive, is more readily available, and identifies the particular gene affected (Shia, 2008).

2.2.3 Germline Genetic Testing

A Lynch syndrome diagnosis is made by performing germline genetic testing on a DNA sample obtained from a blood, saliva, or a cheek swab. Germline testing looks for pathogenic variants in the four mismatch repair genes and deletion in *EPCAM* and can be informative for ongoing patient care and at-risk family members of the person who screened positive. Some healthcare organizations jump straight to germline sequencing, but the more typical path is to first perform tumor screening with either MSI or IHC and to then follow up with germline sequencing for confirmation. Germline testing can be expensive and is not necessary with a negative screen and no other suspicions related to LS (Southey et al., 2005).

2.3 Prevention

2.3.1 Colonoscopies

Colonoscopies are imperative for those diagnosed with Lynch syndrome because not only can they detect colorectal cancer early, but they can also prevent it altogether. People with LS may develop precancerous polyps which can be removed if they are caught with regular colonoscopies. Excision of the polyps prevents them from becoming cancerous, but they must be caught early as polyps in people with LS progress from benign to malignant more quickly than normal (Bhattacharya P, 2021). Studies have found that regular colonoscopies can decrease incidence and mortality of colorectal cancer by up to 63%. People with Lynch syndrome have a lifetime risk for colon cancer of up to 80%, so it is recommended by current guidelines that people who are carriers of the mismatch repair gene mutations get annual to biannual colonoscopies (Niv et al., 2014). In those with LS, the recommended age for initiating surveillance with colonoscopies is 20-25 years, or two to five years younger than the age of the first diagnosis of a family member if that comes earlier (Network, 2021).

2.3.2 Other Preventative Measures

Prophylactic surgery is an option for women with Lynch syndrome as they can choose to have a hysterectomy and salpingoophorectomy to reduce their risk of endometrial and ovarian cancers. Research has shown these surgeries to be effective in preventing 90-100% of endometrial and ovarian cancers in women with LS (McCann & Eisenhauer, 2015). While these surgeries should be presented as options, they are not recommended for LS management due to their limited

benefits in risk reduction (Vasen et al., 2007). Aspirin has also been recommended for use in reducing colorectal cancers related to Lynch syndrome when taken for two or more years (Yurgelun & Hampel, 2018). A recent study found that taking 600 mg aspirin daily for two years significantly reduced the risk of future cancers when compared to a control group, but that the benefits were not apparent for at least four years (Burn et al., 2020).

2.3.3 Cascade Genetic Testing

One approach to improving Lynch syndrome screening and diagnosis is to perform cascade genetic testing in families once an index member of the family receives a positive diagnosis of LS. Cascade screening is defined as contacting the family members of those who have been diagnosed with a hereditary condition and offering genetic testing to those who are at risk. Family members who are at 50% risk, which includes all first-degree relatives, would be tested first, and if they test positive then it is recommended that their first-degree relatives are tested as well. A study by Hampel (2016) found that only 3.6 or fewer family members per positive diagnosis are tested for Lynch syndrome. Cascade genetic testing allows for earlier diagnosis of LS, but it also allows family members to have the opportunity to receive more regular surveillance screenings and preventive options. Genetic testing of family members maximizes the cost-effectiveness of universal tumor screening and improves morbidity and mortality rates for cancers associated with LS (Hampel, 2016).

2.4 Treatment

Treatment for cancers associated with Lynch syndrome takes many forms and depends on the stage of cancer. The surgical options include resection and colectomy. Resection, or a partial colectomy, removes a portion of the colon where the tumor exists, but there is an increased risk of recurrence for people with LS, so this is not always a permanent cure. A total colectomy would prevent future colorectal cancers since it removes all of the colon, but this is not a recommended treatment as there is no significant improvement in survival (Renkonen-Sinisalo, Seppälä, Järvinen, & Mecklin, 2017). Chemotherapy is also an option for cancer treatment with LS; however, some drugs have proven to be less effective for people with tumors that have high microsatellite instability (MSI-high) (Vasen et al., 2007).

Immunotherapies are the newest type of treatments and have been made possible from the genetic information gained by performing IHC and germline testing. Immune checkpoint inhibitors function by using the immune system to target immune checkpoints such as programmed death 1 (PD-1) receptors. Once these checkpoint blockades are inhibited, T cells can be reactivated and attack the cancerous cells to upregulate the process. (Yurgelun & Hampel, 2018). The success of this therapy has led to FDA approval of Keytruda, the first immunotherapy used as first-line treatment for people with Lynch syndrome (Therkildsen, Jensen, Rasmussen, & Bernstein, 2021). Studies conducted for FDA approval showed that of the study participants, there was a clinically meaningful measure of efficacy with an odds risk ratio of 39.6%. Of the 149 patients, 59 responded to treatment. The study also showed that response to the immunotherapy treatment lasted over 6 months in 78% of the 59 participants who responded (Marcus, Lemery, Keegan, & Pazdur, 2019).

2.5 Reasons for Universal Lynch Syndrome Screening

2.5.1 Benefits to the Patient

Universal tumor screening for Lynch syndrome is an important standard to uphold because approximately 3% of all patients newly diagnosed with colorectal cancer have Lynch syndrome, and with criteria-based screening alone nearly 25% of LS cases are missed (Li, Liu, & Wu, 2021). By decreasing the number of cases missed, morbidity and mortality are subsequently reduced. Once diagnosed with Lynch syndrome, another benefit of tumor screening is that the patients can receive informed treatment options. There has been an increased interest in immunotherapy, which is improving survival rates compared to chemotherapy, and is the standard of care for advanced colorectal cancer. Immunotherapy is typically well-tolerated and is initiated in patients who have MSI-High tumors with advanced colorectal cancer when chemotherapy has failed, but recent studies have experimented with initiating immunotherapy at earlier stages of cancer and even as a first-line treatment (Golshani & Zhang, 2020).

In addition to the direct benefits provided by universal tumor screening, patients with colorectal cancer are largely in favor of screening and intend to share the results of their genetic testing with family members (Hunter et al., 2017). An indirect benefit of universal tumor screening is that cascade testing can be performed on at-risk family members of those diagnosed with Lynch syndrome if the patient wishes to share their diagnosis. Surveillance can then be conducted by regular screenings for family members who also have Lynch syndrome and early diagnosis may prevent future cancers (Hampel, 2016).

2.5.2 Cost-Effectiveness

Universal tumor screening for all patients newly diagnosed with colorectal cancer is a costly process; however, it is cost-effective given its success for preventive medicine. Costs to the healthcare system are lowered with an earlier diagnosis of Lynch syndrome, as patients receive more frequent and earlier cancer screenings to detect existing cancers at earlier stages or prevent cancer onset altogether (Hampel, 2016). Some organizations such as the NCCN and the American College of Obstetricians and Gynecologists (ACOG) also recommend universal LS screening for all newly diagnosed endometrial cancer patients since this is the second most diagnosed cancer associated with Lynch syndrome (Network, 2021; Oncology, 2014).

A study by Mvundra et al. (2010) was conducted to estimate the cost-effectiveness of genetic testing for LS and compared universal tumor screening to age-targeted screening and no screening at all. When compared to no screening, universal tumor screening of all patients newly diagnosed with colorectal cancer has an incremental cost-effectiveness ratio of approximately $45,000 per life year saved if preliminary tests such as IHC are performed before germline testing. Cascade testing following the identification of LS in a proband can further improve the cost-effectiveness of universal tumor screening for the healthcare system. Lastly, universal tumor screening has proven to detect roughly twice as many LS cases as age-restricted screening in the United States (Mvundura, Grosse, Hampel, & Palomaki, 2010).

2.5.3 Guidelines

Universal tumor screening is recommended as the standard of care for all patients newly diagnosed with colorectal cancer, and some organizations also recommend screening for all

patients newly diagnosed with endometrial cancer (Table 4). Additionally, universal Lynch syndrome screening was an objective of Healthy People 2020, is an objective of Healthy People 2030, and is included in one of the research initiatives of the Cancer Moonshot (Institute, 2016; Services, 2010, 2020).

Table 4. Organization Guidelines

Organization	LS-Associated Cancers Recommended for Universal Screening	
	Colorectal Cancer	Endometrial Cancer
National Comprehensive Cancer Network (Network, 2021)	✓	✓
Evaluation of Genomic Applications in Practice and Prevention (Prevention, 2011)	✓	
American College of Medical Genetics and Genomics (Hegde et al., 2014)	✓	✓
American College of Obstetricians and Gynecologists (Oncology, 2014)	✓	✓
Society of Gynecologic Oncology (Oncology, 2014)	✓	✓
American Cancer Society (P. M. Boland, Yurgelun, & Boland, 2018)	✓	✓
American Society of Clinical Oncology (Yurgelun & Hampel, 2018)	✓	✓

US Multi-Society Task Force (Giardiello et al., 2014)	✓	

2.6 IMPULSS Study

The Implementing Universal Lynch Syndrome Screening (IMPULSS) study is being conducted to increase and improve implementation of universal tumor screening. The study is looking at variation in implementation across healthcare systems to understand what aspects of universal screening do or do not work well. Once those variables are identified, the study will be able to analyze the effectiveness, efficiency, and costs for each healthcare system. The final component of the study is to create a toolkit using the data obtained and to distribute the toolkit to health systems with the purpose of helping to implement new programs and maintain existing programs.

The toolkit includes an economic modeling tool which allows users to input data from their own institutions to estimate their current screening costs and compare them with other screening methods to find which approach works best. The economic tool was given to seven healthcare systems involved in the study so that various stakeholders could test it. After being given the tool for practice, interviews with the fifteen stakeholders were conducted to gather feedback for improvement, understand user experiences with the tool, and get an idea of how these sites used the tool. The stakeholders for the organizations included people from various roles such as genetic counselors, project managers, physicians, and pharmacists with the intention of gathering perspectives from varying positions within the implementation process. This study analyzes the feedback gained from the stakeholder interviews.

3.0 Materials and Methods

The specific aims of this project align with the third aim from the IMPULSS study, looking to understand the utility of the economic modeling tool as it was used by people with various educational backgrounds and positions within the healthcare system. The study also aimed to evaluate the experience of the users of the tool so that modifications could be made prior to creating a toolkit that will be distributed to all organizations involved in the study. Those who used the economic modeling tool were chosen by purposive sampling of healthcare professionals who are involved with helping to identify patients with LS at the various healthcare sites included in the study (Rahm et al., 2018). Interviewees were selected from healthcare sites that both did and did not have existing universal tumor screening programs. All sites included in the interviews for this portion of the study are members of the Healthcare Systems Research Network which is a network of health care systems that "serve as a research laboratory" to rapidly incorporate research findings into practice (Rahm et al., 2019). All participants who were willing to be interviewed participated in a Microsoft Teams meeting with the interviewer who is a genetic counselor and a member of the IMPULSS project's research staff. The interviews were conducted in 2021. There was a mixture of both individual and group semi-structured interviews. The interviews were recorded, and transcripts of the interviews were created and deidentified for analysis.

Following approval from the Geisinger Institutional Review Board (Appendix A), analysis of the transcripts was performed using the Rapid Data Analysis technique and was informed by the Consolidated Framework for Implementation Research (CFIR) guidelines (Rahm et al., 2018). Rapid Data Analysis is a technique used in qualitative data analysis that allows for quick interpretation of data and typically is best for semi-structured data collection methods (Hamilton

& Finley, 2019) similar to those that were used in the interviews for this portion of the IMPULSS study. The Framework Method was followed closely throughout the analysis. Transcripts from the interviews were thoroughly read through for familiarization and coded by the author with the goal of understanding what affects the decision to implement universal screening for Lynch syndrome. Relevant questions for each domain were established to aid in the process of coding. Data from coding were sorted into their corresponding domains (Table 5) on an Excel sheet and each bin on the Excel sheet was summarized. After summarization, transcripts were read through again to ensure a thorough collection of data. Data in the domains were then reviewed horizontally across all interviews to identify potential themes (Gale, Heath, Cameron, Rashid, & Redwood, 2013) (Appendix Table 1). Additionally, each of the domains was sorted into overarching categories that describe the nature of the domain to further organize the data that was collected from coding. The final categories were "institutional characteristics", "personnel characteristics", and "decision-making process."

Table 5. Domains and Associated Questions

Categories	Domain	Question
N/A	Sex(es)	N/A
	Position/Role	Please describe your background and current position/role in the organization.
	Degree(s)/Training	What is your degree/training?
	EMT Use	Have you used the economic modeling tool yourself?
	Institutional Priority	What is a priority to your institution?

Institutional Characteristics	Implementation Facilitator	What helped facilitate implementation at your institution?
	Readiness for Change	Is this organization/participant willing to change?
	Process Variation	What are the variations in processes at this organization, if any?
	Concerns/Barriers	What might be a concern or barrier surrounding implementation/change?
Personnel Characteristics	Personal Priority	What are your personal priorities?
	Knowledge of Current Protocol/Process	What is your knowledge of the current protocol/process at your organization?
	Networks and Communication	What are the relationships with the stakeholders?
	Champion	Who are the champions for implementation/change?
Decision-Making Process	Informing Decision-Making	What affects your decision to implement a new protocol/change your current protocol?
	Comparison to Current Program	How does your current program compare to other protocols?
	Check Options	Is there any interest in seeing other protocol options?
	Benefits to Direct Germline Sequencing	What are the benefits (or perceived benefits) to implementing direct germline sequencing (DGS)?

4.0 Results

4.1 Data Description

Data was obtained from fifteen stakeholders during the nine interviews that were conducted. The fifteen stakeholders who were interviewed held varying roles in their respective institution's LS identifying process, including genetic counselors, a cancer epidemiologist, a clinical genetics program manager, an oncologist, a pharmacist, a project manager, and a medical director. Stakeholders were sampled from seven different healthcare systems. Some stakeholders had used the tool before the interview, but some had not and used the tool for the first time during the interview. Each participant has been deidentified and will be referenced by participant number, "P#," and healthcare system number, "HS#," in this paper.

From the interviews conducted, participating organizations were categorized into three groups with varying levels of readiness for change: those that have an established screening program and are not looking to change, those that have an established screening program and are looking to change, and those that do not have an established screening program and are looking to implement one. Of the seven organizations interviewed, four organizations had a program established and were not interested in changing, one had an established program and was open to change, and two did not have an established program and were interested in implementation.

4.2 Themes

Themes were identified by looking horizontally across the feedback from participants for each domain. The themes and their corresponding domains can be found in Appendix Table 1. Each theme will be discussed further within the context of its domain.

4.3 Institutional Characteristics

4.3.1 Institutional Priority

Two participants from different organizations mentioned the Center for Disease Control's classification of Lynch syndrome as a tier one condition as a motivator to implement universal Lynch syndrome screening. Both organizations developed a precision medicine initiative and required that all their sites begin implementing universal Lynch syndrome programs if they had not already and were given until the end of 2021 to do so. Four participants from three organizations stated that cost is a priority to institutions considering implementation of screening programs and that it must be considered alongside protocol performance, with one of the four participants, P01 from HS01, noting that their organization "*wouldn't want something that's not as sensitive or specific if it's just the least costly option.*"

4.3.2 Implementation Facilitator

Interview participants brought up factors that they thought facilitated implementation at their organization. Five participants from three organizations contributed to this theme and all three of the organizations were those with established programs and were open to change. Lessening the workload for providers was cited as an implementation facilitator by four participants from two different organizations. The participants discussed the ways that the workload was decreased for providers and gave an example of simplifying processes for providers through their creation and automatic distribution of educational materials about testing that can be given to patients prior to meeting with a provider. Another perceived facilitator of implementation included genetic counselors taking on extra work, when possible, to prevent other departments from feeling overwhelmed by having additional LS cases.

Organization infrastructure was mentioned by five participants across three organizations as a facilitator for implementation of a screening program. Various examples of organization infrastructure included the establishment of a new cancer center at their organization potentially generating increased interest in screening, the use of existing screening programs such as microarray in pediatrics as a model for hereditary cancer and "*taking advantage of some of the tools* (P02, HS06)" they already have, and the small size of their organization being advantageous for the genetic counselor trying to take on extra work. Each example was specific to the organization of the participant.

4.3.3 Readiness for Change

Satisfaction with their current protocol(s) may prevent an organization from wanting to change or looking into other screening options. This theme was found from the comments of four participants, three of which were from organizations with established programs that were not looking to change, with one of those three participants stating that they thought they were "*in a good place where things are going the way they're supposed to* (P01, HS05)." The fourth participant, P01 from HS06, was from an organization that had an established program and was open to change and they mentioned that they "*implemented the model that [they] thought was best, but it was really maybe the only model [they] had at the time, but [they] knew… along the way [they] would probably be changing it.*" This participant said they like to "*quantify and prove*" to have concrete evidence such as the results provided from the economic modeling tool before making any changes.

As previously mentioned, the creation of precision medicine initiatives at organizations has been a driving factor for those organizations to implement a screening program if they do not already have one in place. This initiative came with a deadline for implementation from the participants' organizations and influenced their readiness for change. Of the two participants from different sites who mentioned this initiative, one participant's site had an established screening program, but the other did not and they used the initiative to "*leverage the necessity for moving forward with a project for Lynch syndrome* (P01, HS07)*."*

4.3.4 Process Variation

Variation in process was mentioned by seven participants from five different organizations when describing what is currently done at their organization and how that differed from the ideal scenario or when explaining how input values were informed during use of the economic modeling tool. There were numerous process variations mentioned that were often specific to the participant's organization and those variations included patient loss to follow up, patient death, human error with samples and test orders, apathy of patients in getting confirmatory testing due to old age, lab and genetic counseling services being performed externally, tests having wider use than LS only, and user difficulty in finding input values. Additionally, two participants from different organizations mentioned the complexity of processes/protocols at their organization and how their processes do not necessarily align with the diagrams provided in the tool because "*many of these algorithms tend to combine and so it was difficult to kind of parse out when it was asking specifically about this protocol to this protocol, how many patients came out, or things like that. It didn't quite fit* (P02, HS05)*."*

4.3.5 Concerns/Barriers

Throughout the interviews, some concerns with or barriers to universal Lynch syndrome screening were mentioned by participants. Two participants from separate organizations mentioned that by not having in-house pathology or having to send tests out, their organization's choice of which protocol(s) are used may be limited. Another concern surrounding universal tumor screening mentioned by five participants from three organizations was the case volume and workload for providers. One participant with an existing universal tumor screening program at

their organization stated that their organization experiences an annual increase in testing of 30-40% and that "*there are not enough providers for that* (P03, HS06)." Lastly, three participants, all from different organizations, said that it can be difficult to find the "*right people*" in the organization to be able to affect a change in regard to universal tumor screening implementation as there is often "*a lot of complexity and moving pieces and different parts that we have to consider* (P01, HS03)."

4.4 Personnel Characteristics

4.4.1 Personal Priority

Some personal priorities among participants regarding universal LS screening emerged as themes (Appendix Table 1). One common priority of the participants was acting in the interest of the patients to identify the most cases even if it costs more to do so. This was mentioned at both the organization level of incurring more costs to the institution to increase testing performance and at the personal level by providing the patients with information on testing options and encouraging them to choose the tests with the best performance even if it is at a greater cost to them. Three participants from different organizations stated this as their personal priority, with one of them mentioning the patient-specific costs as a consideration. Another personal priority was participant interest in the "ideal scenario" in which all patients would receive tumor screening and proper reflex testing. Four participants from two organizations discussed wanting to use the economic modeling tool to look at what is currently being done at their organization and know what changes could be made to improve the cost-effectiveness of their current protocol.

4.4.2 Knowledge of Current Protocol/Process

Nearly all participants shared some level of knowledge of their organization's current protocol/processes. Thirteen participants from the seven organizations with a program are included in this theme. The knowledge shared by participants varied from which protocols are offered at their organization and how their screening programs were established to the previously discussed variations that exist within their current processes.

4.4.3 Networks and Communication

Several participants mentioned the networks and communication that they shared with provider-stakeholders relevant to universal tumor screening. Six participants from five organizations discussed how involvement with the "*right people* (P01, HS03)" is essential for changes to protocols and program implementation because those are the people who make the decisions and/or have the information necessary to inform input values of the economic modeling tool. Examples of those relevant stakeholders included people in leadership positions, genetic counselors, oncologists, and pathologists, and various others involved in the screening process. Four participants from three organizations also expressed that finding the information for input values of the economic modeling tool was often a collaborative effort and was difficult without effective communication and strong relationships with other departments.

4.4.4 Champion

Throughout the interviews, five participants from four different organizations described genetic counselors as champions for universal Lynch syndrome screening. Participants stated that while genetic counselors are often not the decision-makers, they are helpful in making the case for implementation by providing the evidence for change to those in leadership positions who are responsible for making the decisions. One of the five participants, P03 from HS05, who is an oncologist and health services researcher, said that the genetic counselors at their organization "*[live] and [breathe] this [information] on a regular basis…I really wanted to talk to them because they are, without question, the experts*" on the topic of Lynch syndrome screening and understanding the information that was required for the economic modeling tool. Of the other four participants, all were genetic counselors.

4.5 Decision Making Process

4.5.1 Informing Decision Making

When considering implementation of a universal LS screening program or making changes to an existing program, there are many factors that go into the decision-making process and several that were noted by relevant stakeholders across multiple organizations. Eight participants across the seven organizations with a program stated that cost is a priority, especially to those in leadership positions who are making the decisions to implement a program. Given that cost is a priority, participants would present to leadership how much the program costs the organization

and break down cost per patient because "*everything comes down to cost benefit analysis* (P01, HS01)*."* Although cost is a priority, five participants from three organizations voiced interest in prioritizing the identification of more Lynch syndrome cases even if it means choosing a protocol that is more expensive to the institution. Another cost-related factor that contributes to the decision-making process is the use of outside labs. Six participants from five organizations mentioned how using outside labs is associated with higher costs and may affect which protocol an organization chooses to use.

Outside of costs, there were several other themes drawn from the interviews regarding benefits to the patient and benefits to the providers. Three participants from different organizations referred to national guidelines and standards of care such as those established by the CDC and the NCCN. They also mentioned checking with other healthcare organizations to see what they were offering. Three participants from different organizations said that turnaround time is a consideration because "*timelines for testing are important* (P02, HS01)" and this can affect which protocol is chosen by an organization. Six participants from five organizations mentioned direct-to-germline sequencing as an attractive option given its performance, and one organization found that it can even be cost-effective for them to go straight to germline sequencing since they did not have in-house pathology. Finally, a decision-making theme of easing the burden of more testing on providers was highlighted by four participants from two different organizations, with two of those participants noting that the decreased burden helps to allow for universal screening, specifically direct-to-germline sequencing.

4.5.2 Comparison to Current Program

During the interviews, five participants from four organizations used the economic modeling tool to compare their organization to the default values provided by the tool. The default, or "*base-case* (P02, HS06)" values allowed the participants to see what their program could look like in an ideal, or "*dream* (P03, HS01)," scenario and to compare their ideal scenario to the reality of what is currently being done. This comparison also allowed the participants to see if there were any areas that could be improved upon at their organization. One of the five participants, P02 from HS06, used the tool to demonstrate how an "*incremental cost*" increase compared to their current costs would make it so that they miss fewer cases and how the "*cost savings down the line to identify those folks and testing and screening other relatives would be good*."

4.5.3 Check Options

Several interview participants used the economic modeling tool to evaluate their options for universal LS screening. Eight participants from six organizations explained how the tool allowed organizations to "*go through the numbers*" from other protocols and see what "*[they] could have* (P01, HS02)" and if there are better options outside of what they currently offer. There was a specific interest in direct-to-germline sequencing from five participants, each from a different organization.

4.5.4 Benefits to Direct-to-Germline Sequencing

Direct-to-germline sequencing was brought up by six participants from five different organizations because it was said to be "*a lot better in terms of sensitivity and specificity* (P01, HS02)." Two participants, each from a different organization, also mentioned the potential utility of direct-to-germline sequencing in streamlining population health screening if it is done in the future. Two participants from different organizations discussed the decreased workload for pathology associated with direct-to-germline sequencing, which would benefit providers. The participants said this was beneficial because pathology would not have to work with tumor samples since germline samples are blood samples "*like any other cancer blood sample* (P01, HS07)."

5.0 Discussion

5.1 Summary

Focusing on what affects the decision to implement universal Lynch syndrome screening helped to guide the process of determining thematic codes. Upon analysis, several themes emerged within the various domains under three overarching categories: “institutional characteristics,” “personnel characteristics,” and “informing decision-making.” These categories and the domains within them help to illuminate the different levels at which implementation decisions are being made and the various factors that influence them. Understanding the levels of decision-making and who is involved in the process enables projects like IMPULSS to address stakeholder concerns and to inform the toolkit that will be created for distribution.

5.2 Interpretation

At the institutional level, priorities of adhering to national screening guidelines and weighing the institutional costs against detection were conveyed. This is consistent with another Lynch syndrome study which found that organizations were influenced by external policy and concerned about the costs of tumor screening (Cragun et al., 2014). Organizations wanted to know what costs they would incur for running a tumor screening program, but generally valued protocol performance above all else. Cost came up many times throughout the interviews, but since the participants were being interviewed to discuss an economic modeling tool it is possible that this

inflated the number of times institutional costs were mentioned by participants. A recent study evaluated the costs of each protocol for screening a newly diagnosed colorectal cancer patient which may be beneficial for the institutions that are open to change based on new data or looking to implement for the first time (Hao et al., 2021).

Only participants who were from organizations open to change or implementation brought up factors that they thought facilitated implementation at their organization, but the facilitators came up naturally in conversation with only one participant being directly asked about this by the interviewer. This could be due to the process of implementation being at the forefront of their minds when using the economic modeling tool as many were already seeking to implement changes. The workload for providers was discussed as a concern in that the participants acknowledged universal tumor screening increased the testing volume, but it was also brought up as a facilitator because they took actions to lessen the burden which made universal tumor screening a more appealing protocol. Other concerns or barriers mentioned by participants included the lack of in-house pathology limiting options and the difficulty communicating with relevant stakeholders to inform tool input values, which aligns with other literature (Cragun et al., 2014). Participants mentioned various ways that their organization's infrastructure impacted their ability to implement which also ties into their readiness for change as infrastructure was a facilitator for implementation.

At the personnel level, a priority emerged of acting in the patient's benefit, even if it costs more to do so, and all comments contributing to this theme came from genetic counselors which can likely be attributed to their role in the implementation process and direct interaction with the patients. Genetic counselors were considered to be the champions of universal screening, which again may be due to their role in implementation as it provides them with insight into the

parameters of the tool, so they may often have the information necessary to present to the decision-makers. Knowing who the "right people" are for those presentations and for gathering information was important to the participants and highlights the necessity of the networks and communication pathways that were mentioned because screening implementation is a collaborative process. Current literature on implementation strategies also found institutional champions to be helpful in universal tumor screening implementation (Cragun et al., 2014)

There were many factors mentioned by participants that inform the decision-making process and several of them involved costs, including program costs of different protocols, costs per patient, and costs of using outside labs. Again, the many considerations of cost may be due to participants being interviewed to discuss the use of an economic modeling tool. With the help of the tool, participants were able to compare what is currently being done at their organization to the ideal scenario of perfect protocol performance to see if they can make any improvements and check the costs and performance of other protocol options that their organization may not currently offer. Many participants expressed interest in direct-to-germline sequencing and noted its perceived benefits of greater performance, steps saved, and a decreased workload for providers. Although data shows that direct-to-germline sequencing is not currently the most cost-efficient model, it is conceivable that it can be soon as costs of genetic sequencing continue to decrease (Hao et al., 2021). The interest in direct-to-germline testing primarily came from participants at organizations that were open to change or implementation, whereas the other participants who mentioned the benefits of direct-to-germline sequencing were from organizations that were not open to change and spoke about interest in this protocol in a theoretical sense, but were hesitant due to the costs.

5.3 Limitations

There is potential researcher bias in this study given that the interviewer is a genetic counselor, and the data was collected purposively. Since the participants were mostly comprised of genetic counselors, it is possible that the interviewer's bias may have affected the results. This was also a limitation because that was the main perspective obtained and several of the genetic counselors mentioned that they are the end users of the tool but not the ones making the decisions. Future studies may benefit from including more participants from professions outside of genetic counseling, specifically those that were mentioned as decision-makers. Another limitation is the variation in tool use. Since some participants had used the tool prior to their interview, they were able to provide more informed feedback, but those who had not yet used the tool at the time of the interview were seeing it for the first time. This was helpful for capturing first impressions and procuring valuable data but did not help in understanding how the participant used the tool at their organization, or in fully understanding the relationships of those participants with other relevant stakeholders and barriers they may have faced.

5.4 Conclusions

Many papers exist on initial implementation of universal tumor screening and its importance, but none that compare decision-making that goes into implementation among organizations and address program maintenance. This paper illustrates the usefulness of implementation science and helps to bridge the gap between initial implementation of universal tumor screening and program maintenance. Interviews with stakeholders regarding the use of the

economic modeling tool created by the IMPULSS study were informative for implementation and maintenance of universal tumor screening programs as they delineated the factors that affect decision-making at different levels within healthcare organizations. This data is helpful for achieving the specific aims of performing a qualitative analysis of the interviews and providing information for how to use the cost modeling tool in the "deciding to implement" toolkit based on the results of the analysis. The analysis shows priorities from the institutional and personal levels of various healthcare organizations and some of the many factors that influence decision-making surrounding universal Lynch syndrome screening. Cost has a role in the decision-making process at all levels but does not overshadow the importance of choosing a protocol that performs well to detect cases of Lynch syndrome. The previously mentioned limitations could affect the results of the analysis.

5.4.1 Suggested Next Steps

The information obtained from this sub-analysis is helpful as part of a larger project, IMPULSS, to better understand what affects the decision-making process at organizations considering universal Lynch syndrome screening. Each transcript analyzed contained new information which is indicative that data saturation has not yet been reached and is encouraging for a larger study. A larger study with participants from a greater diversity of professions could provide decision-makers with well-rounded answers to questions they may have regarding implementation.

Appendix A IRB Approval

Geisinger Institutional Review Board (GIRB)
FWA # 00000063 IRB# 00008345

100 N. Academy Avenue
Danville, PA 17822-3069
570-271-8663
IRB@geisinger.edu

Geisinger

Approval Notice
KSP Modification

July 23, 2021

Alanna K Rahm, PhD, CGC
GMC - Genomic Medicine

IRB# 2017-0238 (IMPULSS Study), entitled ***Implementing Universal Lynch Syndrome Screening across Multiple Healthcare Systems: Identifying Strategies to Facilitate and Maintain Programs in Different Organizational Contexts***
RE: Key Study Personnel Amendment Form, 07/23/2021 08:34:57 AM EDT

Dear Alanna K Rahm, PhD, CGC:

Your Key Study Personnel Amendment Form was reviewed and approved administratively on 07/23/2021.

Submission Components		
Form Name	Version	Outcome
Key Study Personnel Amendment Form	Version 14.0	Approve

If you have any questions or need further help, please contact the Human Research Protection Program staff at (570) 271-8663.

Sincerely,

Geisinger Institutional Review Board

cc: Andrea Burnett-Hartman PhD MPH, Christine Lu PhD MSc, Ilene G Ladd, Jessica Hunter PhD MS, Mara Epstein ScD, Pamala Pawloski, PharmD, Ravi Sharaf, MD, Victoria M Schlieder

Key Study Personnel Amendment Form (Version 14.0)

1.0 Key Study Personnel (KSP) Modification Form

1.1 The Key Study Personnel Amendment (KSP) Form may only be used to submit modifications to Key Study Personnel - Adding or removing.

PLEASE NOTE: DO NOT use the Key Study Personnel Amendment Form when the amendment involves modifications to any study documents (protocol, consent form, letters, etc).

1.2 IRB Number

2017-0238

1.3 Study Title

Implementing Universal Lynch Syndrome Screening across Multiple Healthcare Systems: Identifying Strategies to Facilitate and Maintain Programs in Different Organizational Contexts

1.4 Principal Investigator

Alanna K Rahm, PhD, CGC

1.5 Name of Person (other than PI) to receive information from the IRB:

Alanna K Rahm, PhD, CGC, Ilene G Ladd, Christine Lu PhD MSc, Jessica Hunter PhD MS, Andrea Burnett-Hartman PhD MPH, Mara Epste

1.6 Protocol Summary

The purpose of this research study is to understand how some health care centers screen for Lynch Syndrome (LS). If health care centers do not screen for LS, we want to understand why. We will use this information to create a "toolkit" that will help helath care centers effectively implement programs to screen for this disease and prevent needless suffering in patients and thier families. In the first phase we want to understand LS screening through the eyes of the healthcare system, the providers, and patients. In this phase, we will talk to system leaders, medical providers, and patients with colon cacer and patients who have been identified through LS screening programs. In later phases we will use this information with other information about organizational costs and organizational structures to create and test the toolkit to help other healthcare systems implement LS screening.

1.7 Modification to research personnel, please check all that apply: REMINDER: An updated study application reflecting the KSP modification must be included with the submission. If PI change, upload a PDF of the completed and signed Principal Investigator Agreement. A current CV/biosketch must be uploaded into each new study personnel's iRIS account *(My Assistant -> My Account Information -> Biosketch, CV, Pubs)*. DO NOT attach CV/biosketches to this submission.

- [x] Collaborator
- [ ] Investigator - Sub-I/Co-I
- [ ] Principal Investigator (PI)
- [ ] Study Personnel

Geisinger defines **investigator** as the principal Investigator or program director and any other ***Senior/Key Personnel***, regardless of title or position, who is responsible for the design, conduct, or reporting of Research (which may include, for example, collaborators and consultants), regardless of Research funding source.

PLEASE NOTE: ***The following requirements must be met for the submission to proceed through the IRB review process.***

1. ***Current human research education training.***
2. ***Current copy of the biosketch included with the updated study application.***
3. ***The annual conflict of interest questionnaire and required training completed for new investigators (PI, sub-I, or Co-I) or collaborators.***
4. ***For PI change, a signed letter from the new PI accepting the role and responsibility of PI for the study.***

1.8 Please provide details on the KSP modification, such as, complete name, role on the study, and whether the modification is adding or removing the personnel:

Add Amber Stafford as a collaborator.

1.9 Please click on the link below to attach the revised study application.

Edit/ View	Version	Title
	1.27	Study Application (Version 1.27) - Attached

1.10 PLEASE NOTE: If the PI of the study is changing, please be sure to click on the link to upload a PDF of the signed Principal Investigator Agreement. The Principal Investigator Agreement can be found under the iRIS help, under Forms.

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
No Document(s) have been attached to this form.						

Subject: Fw: IRB Approval for Pitt
Date: Monday, November 29, 2021 at 1:16:54 PM Eastern Standard Time
From: Ivanusic, Carolyn
To: Stafford, Amber

Amber,

I consulted with the IRB director. Please see below.

Carolyn

****

Carolyn Ivanusic, MSW CIP
Research Review Coordinator
University of Pittsburgh
Institutional Review Board / Human Research Protection
Phone: 412-383-1789,ivanusic@pitt.edu

From: Barone, Jean Marie <baronej2@pitt.edu>
Sent: Monday, November 29, 2021 12:49 PM
To: Ivanusic, Carolyn <ivanusic@pitt.edu>
Subject: Re: IRB Approval for Pitt

She does not need an application here. Have her upload this email into the MyRA system where it asks for the IRB approval.

Jeannie

Appendix B Theme Table

Appendix Table 1. Domains and Corresponding Themes

	Domain	Theme(s)
Institutional Characteristics	Institutional Priority	• LS being a CDC Tier 1 condition has motivated organizations to implement universal screening programs (2 participants, 2 organizations) • Cost is a priority and must be considered alongside protocol performance (4 participants, 3 organizations)
	Implementation Facilitator	• Lessening the workload for providers through simplifying processes and genetic counselors taking on extra work facilitates implementation by preventing other departments from feeling overwhelmed with additional cases (4 participants, 2 organizations) • Organization infrastructure plays a role in whether implementation is feasible (5 participants, 3 organizations)
	Readiness for Change	• Satisfaction with current protocol may prevent an organization from wanting to change or checking

		other options until there is a need for change (4 participants, 3 organizations) • Precision medicine initiative has motivated organizations to implement a program if they do not have one (2 participants, 2 organizations) • Openness to change and desire to "move forward" impacts readiness for change (4 participants, 3 organizations)
	Process Variation	• Variation in protocols exists due to various reasons including: loss to follow up, death, human error with samples and orders, apathy of pts due to old age, services being performed externally, tests having wider use than LS only, and user difficulty in finding input values (7 participants, 5 organizations) • Two organizations mention the complexity of protocols at their organization and how their processes do not necessarily align with the diagrams provided in the tool (2 participants, 2 organizations)
	Concerns/Barriers	• Not having in-house pathology or having to send tests out may limit an organization's protocol choices (2 participants, 2 organizations)

		• It can be difficult to find the right people in the organization and there are often many "moving parts"(3 participants,3 organizations) • Case volume and workload for providers is a concern surrounding universal screening (5 participants, 3 organizations)
Personnel Characteristics	Personal Priority	• Acting in the interest of the patients to identify the most cases even if it costs more to do so (3 participants, 3 organizations) • Interest in the "ideal scenario" and knowing what changes can be made to improve cost-effectiveness (4 participants, 2 organizations)
	Knowledge of Current Protocol/Process	• Most interviewees shared some level of knowledge of their current protocol/processes from which protocols are offered and how they were established to the variations that exist within them (13 participants, 7 organizations)
	Networks and Communication	• Involvement with the right people is essential for changes/implementation because those are the people who make the decisions and/or have the information necessary to inform input values (6 participants, 5 organizations)

		• Finding the information for input values is often a collaborative effort and can be difficult without good communication and relationships with other departments (4 participants, 3 organizations)
	Champion	• While genetic counselors are often not the decision makers, they are helpful in making the case for implementation (5 participants, 4 organizations)
Decision-Making Process	Informing Decision-Making	• Cost is a priority, especially to those in leadership positions who are making the decisions to implement (8 participants, 7 organizations) • Interest in capturing more LS cases even if it means choosing a protocol that is more expensive to the institution (5 participants, 3 organizations) • Turnaround time is a factor in choosing which protocol is chosen by an organization (3 participants, 3 organizations) • Following guidelines and practicing standard of care are important (3 participants, 3 organizations) • Use of outside labs is associated with higher costs and may affect which protocol an organization chooses to use (6 participants, 5 organizations)

		• DGS is an attractive option for many organizations given its performance and can even be cost effective for some organizations (6 participants, 5 organizations) • Easing the burden on providers is mentioned often by genetic counselors who are trying to make universal screening a more "irresistible offer" (4 participants, 2 organizations)
	Comparison to Current Program	• Comparison of sites to default values allows organizations to see what their program could look like in an ideal scenario and if there are any areas that could be improved upon at their organization (5 participants, 4 organizations)
	Check Options	• Tool allows organizations to "go through the numbers" from other protocols and see what they could have if there are protocols that they do not currently offer (8 participants, 6 organizations) • Interest from several organizations to test the DGS protocol (5 participants, 5 organizations)
	Benefits to Direct Germline Sequencing	• DGS offers the best performance and captures the most patients (6 participants, 5 organizations)

		• DGS saves steps which will be helpful if population screening is done in the future (2 participants, 2 organizations) • DGS will decrease the workload in pathology since it is a blood sample "like any other cancer blood sample" (2 participants, 2 organizations)

Bibliography

Barrow, E., Hill, J., & Evans, D. G. (2013). Cancer risk in Lynch Syndrome. *Familial Cancer, 12*(2), 229-240. doi:10.1007/s10689-013-9615-1

Bhattacharya P, M. T. (2021). Lynch Syndrome. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK431096/. Retrieved 2021 Dec 18, from StatPearls Publishing https://www.ncbi.nlm.nih.gov/books/NBK431096/

Boland, C. R., & Goel, A. (2010). Microsatellite instability in colorectal cancer. *Gastroenterology, 138*(6), 2073-2087.e2073. doi:10.1053/j.gastro.2009.12.064

Boland, P. M., Yurgelun, M. B., & Boland, C. R. (2018). Recent progress in Lynch syndrome and other familial colorectal cancer syndromes. *CA: a cancer journal for clinicians, 68*(3), 217-231. doi:10.3322/caac.21448

Burn, J., Sheth, H., Elliott, F., Reed, L., Macrae, F., Jukka-Pekka, M., . . . Side, L. (2020). Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial. *The Lancet, 395*(10240), 1855-1863. doi:http://dx.doi.org/10.1016/S0140-6736(20)30366-4

Cragun, D., DeBate, R. D., Vadaparampil, S. T., Baldwin, J., Hampel, H., & Pal, T. (2014). Comparing universal Lynch syndrome tumor-screening programs to evaluate associations between implementation strategies and patient follow-through. *Genet Med, 16*(10), 773-782. doi:10.1038/gim.2014.31

Gale, N. K., Heath, G., Cameron, E., Rashid, S., & Redwood, S. (2013). Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Med Res Methodol, 13*, 117. doi:10.1186/1471-2288-13-117

Giardiello, F. M., Allen, J. I., Axilbund, J. E., Boland, C. R., Burke, C. A., Burt, R. W., . . . Rex, D. K. (2014). Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on Colorectal Cancer. *Dis Colon Rectum, 57*(8), 1025-1048. doi:10.1097/dcr.000000000000000

Golshani, G., & Zhang, Y. (2020). Advances in immunotherapy for colorectal cancer: a review. *Therap Adv Gastroenterol, 13*, 1756284820917527. doi:10.1177/1756284820917527

Hamilton, A. B., & Finley, E. P. (2019). Qualitative methods in implementation research: An introduction. *Psychiatry Res, 280*, 112516. doi:10.1016/j.psychres.2019.112516

Hampel, H. (2016). Genetic counseling and cascade genetic testing in Lynch syndrome. *Familial Cancer, 15*(3), 423-427. doi:10.1007/s10689-016-9893-5

Hampel, H., & de la Chapelle, A. (2011). The Search for Unaffected Individuals with Lynch Syndrome: Do the Ends Justify the Means? *Cancer Prevention Research, 4*(1), 1-5. doi:10.1158/1940-6207.Capr-10-0345

Hao, J., Hassen, D., Gudgeon, J. M., Snyder, S. R., Hampel, H., Williams, M. S., . . . Rahm, A. K. (2021). Economic Evaluation of Universal Lynch Syndrome Screening Protocols among Newly Diagnosed Patients with Colorectal Cancer. *J Pers Med, 11*(12). doi:10.3390/jpm11121284

Hegde, M., Ferber, M., Mao, R., Samowitz, W., Ganguly, A., a Working Group of the American College of Medical, G., & Genomics Laboratory Quality Assurance, C. (2014). ACMG

technical standards and guidelines for genetic testing for inherited colorectal cancer (Lynch syndrome, familial adenomatous polyposis, and MYH-associated polyposis). *Genetics in Medicine, 16*(1), 101-116. doi:10.1038/gim.2013.166

Hunter, J. E., Arnold, K. A., Cook, J. E., Zepp, J., Gilmore, M. J., Rope, A. F., . . . Goddard, K. A. B. (2017). Universal screening for Lynch syndrome among patients with colorectal cancer: patient perspectives on screening and sharing results with at-risk relatives. *Fam Cancer, 16*(3), 377-387. doi:10.1007/s10689-017-9972-2

Hunter, J. E., Zepp, J. M., Gilmore, M. J., Davis, J. V., Esterberg, E. J., Muessig, K. R., . . . Goddard, K. A. (2015). Universal tumor screening for Lynch syndrome: Assessment of the perspectives of patients with colorectal cancer regarding benefits and barriers. *Cancer, 121*(18), 3281-3289. doi:10.1002/cncr.29470

Idos, G., & Valle, L. (1993). Lynch Syndrome. In M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. H. Bean, G. Mirzaa, & A. Amemiya (Eds.), *GeneReviews(®)*. Seattle (WA): University of Washington, Seattle

Copyright © 1993-2021, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.

Institute, N. C. (2016). Cancer Moonshot. *Hereditary Cancers*. Retrieved from https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/implementation/hereditary-cancers

Li, X., Liu, G., & Wu, W. (2021). Recent advances in Lynch syndrome. *Experimental Hematology & Oncology, 10*(1), 37. doi:10.1186/s40164-021-00231-4

Marcus, L., Lemery, S. J., Keegan, P., & Pazdur, R. (2019). FDA Approval Summary: Pembrolizumab for the Treatment of Microsatellite Instability-High Solid Tumors. *Clin Cancer Res, 25*(13), 3753-3758. doi:10.1158/1078-0432.Ccr-18-4070

McCann, G. A., & Eisenhauer, E. L. (2015). Hereditary cancer syndromes with high risk of endometrial and ovarian cancer: surgical options for personalized care. *J Surg Oncol, 111*(1), 118-124. doi:10.1002/jso.23743

Mvundura, M., Grosse, S. D., Hampel, H., & Palomaki, G. E. (2010). The cost-effectiveness of genetic testing strategies for Lynch syndrome among newly diagnosed patients with colorectal cancer. *Genet Med, 12*(2), 93-104. doi:10.1097/GIM.0b013e3181cd666c

Network, N. C. C. (2021). Genetic/Familial High-Risk Assessment: Colorectal. (NCCN Guidelines Version 1.2021). Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf

Niv, Y., Moeslein, G., Vasen, H. F., Karner-Hanusch, J., Lubinsky, J., & Gasche, C. (2014). Quality of colonoscopy in Lynch syndrome. *Endosc Int Open, 2*(4), E252-255. doi:10.1055/s-0034-1377920

Oncology, T. A. C. o. O. a. G. S. o. G. (2014). *Lynch Syndrome*. Retrieved from https://www.sgo.org/wp-content/uploads/2012/09/2014-ACOG-bulletin.pdf

Palomaki, G. E., McClain, M. R., Melillo, S., Hampel, H. L., & Thibodeau, S. N. (2009). EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. *Genetics in Medicine, 11*(1), 42-65. doi:10.1097/GIM.0b013e31818fa2db

Prevention, C. f. D. C. a. (2011, 10/21/2011). Lynch Syndrome EGAPP Recommendation. Retrieved from https://www.cdc.gov/genomics/gtesting/egapp/recommend/lynch.htm

Rahm, A. K., Cragun, D., Hunter, J. E., Epstein, M. M., Lowery, J., Lu, C. Y., . . . Williams, M. S. (2018). Implementing universal Lynch syndrome screening (IMPULSS): protocol for a

multi-site study to identify strategies to implement, adapt, and sustain genomic medicine programs in different organizational contexts. *BMC Health Serv Res, 18*(1), 824. doi:10.1186/s12913-018-3636-2

Rahm, A. K., Ladd, I., Burnett-Hartman, A. N., Epstein, M. M., Lowery, J. T., Lu, C. Y., . . . Hunter, J. E. (2019). The Healthcare Systems Research Network (HCSRN) as an Environment for Dissemination and Implementation Research: A Case Study of Developing a Multi-Site Research Study in Precision Medicine. *EGEMS (Wash DC), 7*(1), 16. doi:10.5334/egems.283

Renkonen-Sinisalo, L., Seppälä, T. T., Järvinen, H. J., & Mecklin, J.-P. (2017). Subtotal Colectomy for Colon Cancer Reduces the Need for Subsequent Surgery in Lynch Syndrome. *Diseases of the Colon & Rectum, 60*(8), 792-799. doi:10.1097/dcr.0000000000000802

Services, U. S. D. o. H. a. H. (2010). Healthy People 2020. *Genomics.* Retrieved from https://www.healthypeople.gov/2020/topics-objectives/topic/genomics

Services, U. S. D. o. H. a. H. (2020). Healthy People 2030. *Cancer.* Retrieved from https://health.gov/healthypeople/objectives-and-data/browse-objectives/cancer/increase-proportion-people-colorectal-cancer-who-get-tested-lynch-syndrome-c-r03

Shia, J. (2008). Immunohistochemistry versus microsatellite instability testing for screening colorectal cancer patients at risk for hereditary nonpolyposis colorectal cancer syndrome. Part I. The utility of immunohistochemistry. *J Mol Diagn, 10*(4), 293-300. doi:10.2353/jmoldx.2008.080031

Society, A. C. (2022). Key Statistics for Colorectal Cancer. Retrieved from https://www.cancer.org/cancer/colon-rectal-cancer/about/key-statistics.html#:~:text=Lifetime%20risk%20of%20colorectal%20cancer,25%20(4.0%25)%20for%20women

Southey, M. C., Jenkins, M. A., Mead, L., Whitty, J., Trivett, M., Tesoriero, A. A., . . . Hopper, J. L. (2005). Use of molecular tumor characteristics to prioritize mismatch repair gene testing in early-onset colorectal cancer. *J Clin Oncol, 23*(27), 6524-6532. doi:10.1200/jco.2005.04.671

Subramonian, A., Smith, D., Dicks, E., Dawson, L., Borgaonkar, M., & Etchegary, H. (2020). Universal tumor screening for lynch syndrome: perspectives of patients regarding willingness and informed consent. *Personalized Medicine, 17*(5), 373-387. doi:10.2217/pme-2020-0026

Syngal, S., Fox, E. A., Eng, C., Kolodner, R. D., & Garber, J. E. (2000). Sensitivity and specificity of clinical criteria for hereditary non-polyposis colorectal cancer associated mutations in MSH2 and MLH1. *J Med Genet, 37*(9), 641-645. doi:10.1136/jmg.37.9.641

Tamura, K., Kaneda, M., Futagawa, M., Takeshita, M., Kim, S., Nakama, M., . . . Tatsumi-Miyajima, J. (2019). Genetic and genomic basis of the mismatch repair system involved in Lynch syndrome. *Int J Clin Oncol, 24*(9), 999-1011. doi:10.1007/s10147-019-01494-y

Therkildsen, C., Jensen, L. H., Rasmussen, M., & Bernstein, I. (2021). An Update on Immune Checkpoint Therapy for the Treatment of Lynch Syndrome. *Clin Exp Gastroenterol, 14*, 181-197. doi:10.2147/ceg.S278054

Tutlewska, K., Lubinski, J., & Kurzawski, G. (2013). Germline deletions in the EPCAM gene as a cause of Lynch syndrome - literature review. *Hered Cancer Clin Pract, 11*(1), 9. doi:10.1186/1897-4287-11-9

Umar, A., Boland, C. R., Terdiman, J. P., Syngal, S., de la Chapelle, A., Rüschoff, J., . . . Srivastava, S. (2004). Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst, 96*(4), 261-268. doi:10.1093/jnci/djh034

Vasen, H. F., Möslein, G., Alonso, A., Bernstein, I., Bertario, L., Blanco, I., . . . Wijnen, J. (2007). Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). *J Med Genet, 44*(6), 353-362. doi:10.1136/jmg.2007.048991

Vasen, H. F., Watson, P., Mecklin, J. P., & Lynch, H. T. (1999). New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology, 116*(6), 1453-1456. doi:10.1016/s0016-5085(99)70510-x

Yurgelun, M. B., & Hampel, H. (2018). Recent Advances in Lynch Syndrome: Diagnosis, Treatment, and Cancer Prevention. *American Society of Clinical Oncology Educational Book*(38), 101-109. doi:10.1200/edbk_208341