Examples of Funded Grants in Implementation Science

Overview

The National Cancer Institute (NCI) frequently receives requests for examples of funded grant applications. Several investigators and their organizations agreed to let Implementation Science (IS) post excerpts of their dissemination and implementation (D&I) grant applications online.

About

We are grateful to the investigators and their institutions for allowing us to provide this important resource to the community. To maintain confidentiality, we have redacted some information from these documents (e.g., budgets, social security numbers, home addresses, introduction to revised application), where applicable. In addition, we only include a copy of SF 424 R&R Face Page, Project Summary/Abstract (Description), Project Narrative, Specific Aims, and Research Strategy; we do not include other SF 424 (R&R) forms or requisite information found in the full grant application (e.g., performance sites, key personnel, biographical sketches).

Copyright Information

Accessibility

Individuals using assistive technology (e.g., screen reader, Braille reader, etc.) who experience difficulty accessing any information should send an email to the Implementation Science Team (NCIdccpsISteam@mail.nih.gov).

424 R&R and PHS-398 Specific

Table Of Contents

SF 424 R&R Face Page

PI: Rahm, Alanna K

Grant Number: 1 R01 CA211723-01A1

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

FOA: PAR16-238

FOA Title: DISSEMINATION AND IMPLEMENTATION RESEARCH IN HEALTH (R01)

Organization: GEISINGER CLINIC

Department: Genomic Medicine Institute

Senior/Key Personnel: Alanna Rahm Ph.D

Organization: GEISINGER CLINIC

Role Category: PD/PI

Project Summary

Lynch syndrome (LS) is the most common form of inherited colorectal cancer risk. People with Lynch syndrome are also at increased risk for endometrial, ovarian, gastric, small bowel, and renal cancers. Importantly, well-established clinical guidelines with strong evidence exist for cancer treatment, screening, and prevention in individuals with LS. Identification of individuals with LS is accomplished through a variety of techniques, including family and medical history evaluation, computational models, or tumor testing. The systematic screening of all colorectal tumors for LS was first recommended by the Evaluation of Genetic Application in Practice and Prevention (EGAPP) working group in 2009 and has been designated high priority by the National Academies of Science, Engineering, and Medicine working group and by the Blue Ribbon Panel. The potential public health impact to reduce cancer morbidity and mortality of this intervention supports this priority, as effective implementation of LS screening will help meet the goals of the Cancer Moonshot as well as demonstrate the promise of precision medicine. Currently, implementation of LS screening in healthcare systems remains suboptimal for a variety of reasons. LS screening involves the coordination of multiple departments and individuals across an organization, which is often difficult in large, complex, healthcare systems. Therefore, the overarching goal of this project is to utilize tools from implementation science to describe, explain, and compare decision making and other variations in LS screening implementation across multiple healthcare systems to create and evaluate in a real world setting an organizational toolkit to facilitate implementation of LS screening. Our specific aims are to (1) Describe variation in LS screening implementation across multiple healthcare systems; then (2) Explain practice variation and determine factors associated with optimal implementation; and (3) Determine the relative effectiveness, efficiency, and costs of different LS screening protocols by healthcare system; and finally to (4) Develop and test in a natural environment an organizational toolkit for LS screening. This toolkit will enable effective implementation of LS screening programs; ultimately preventing needless suffering of patients and their family members from preventable cancers, decreasing waste in healthcare system costs, and informing strategies to facilitate the promise of precision medicine.

Project Narrative

The overarching goal of this project is to create an organization-level toolkit for implementing, maintaining and improving Lynch syndrome (LS) screening by using tools from implementation science to describe, explain, and compare decision making and other variations in LS screening implementation across multiple healthcare systems. We will accomplish this through analyzing variation in LS screening implementation across diverse healthcare systems, estimating costs of different protocols by healthcare system, synthesizing this information into an organizational implementation toolkit, and testing the toolkit within the healthcare systems. This model will enable more effective and efficient implementation of LS screening; ultimately preventing needless suffering of patients and their family members from preventable cancers, decreasing waste in healthcare system costs, and informing strategies to facilitate the promise of precision medicine.

Specific Aims

The goal of precision medicine is to improve individual health outcomes by tailoring healthcare based on genomic and other relevant information[1]. One such example is the use of systematic tumor screening to identify all patients newly diagnosed with colorectal cancer whose cancer may be related to Lynch syndrome (LS)[2,3]. Estimates suggest about one million people in the US have LS, of which only about 2% are aware[4,5]; therefore, most are not receiving life-saving surveillance and treatment. LS screening includes evaluating tumors for mismatch repair gene deficiency and offering genetic counseling and confirmatory germline genetic testing to individuals who screen positive. LS screening is one of the first cost-effective[6,7] genomic medicine interventions with top-tier evidence[8] for reducing cancer morbidity and mortality and improving quality of life[9]. **In September, 2016 the Blue Ribbon Panel Report recommended LS screening as a high priority intervention with the potential to achieve the goals of the Cancer Moonshot**[4].

Implementation of new technologies into clinical practice, however, is challenging[10,11]. Contextual factors such as organization mission, organization structure, economic impact, providers, and patient population, all influence implementation decisions in healthcare systems[12-14]. Therefore, analysis of these contextual factors and their effects is critical to our understanding of variability in implementation[15-18]. The Consolidated Framework for Implementation Research (CFIR) is designed to guide multi-level evaluation of implementation, and has been used successfully to evaluate variation in program implementation[16,19]. The CFIR, along with Qualitative Comparative Analysis (QCA), can identify which implementation strategies are more likely to work under which circumstances; resulting in an organizational toolkit for implementing complex interventions in complex health care delivery systems[20-24].

Implementing LS screening involves multiple stakeholders and customization to local contextual factors such as individual organizational processes, patients, and costs. Because LS screening is infrequently and inconsistently implemented, there is poor understanding of how these contextual factors impede or facilitate implementation in healthcare systems and under what circumstances[15,22,25-27]. The goal of this proposal is to utilize the CFIR and other tools from implementation science to describe, compare, and explain variations in LS screening implementation across multiple healthcare systems and create a comprehensive, customizable organizational toolkit for implementing LS screening. Our specific aims are to:

Aim 1: Describe variations in LS screening implementation across multiple healthcare systems. Guided by the CFIR, we will conduct interviews with key stakeholders from multiple sites within members of the Healthcare Systems Research Network (HCSRN). We will describe variations in LS screening processes, organizational structure and resources, organizational decision making, and barriers and facilitators related to implementing LS screening as recommended by published guidelines.

Aim 2: Explain current practice variation and determine factors associated with optimal LS screening implementation. Through cross-case analysis and Qualitative Comparative Analysis (QCA) guided by the CFIR, examine associations between contextual factors and LS screening implementation to determine factors associated with implementation, maintenance, and improvement. We will conduct analyses to determine factors associated with implementing LS screening or not and analyses to determine factors associated with optimal and sub-optimal implementation across healthcare systems.

Aim 3: Determine the relative effectiveness, efficiency, and costs of different LS screening protocols. Using decision analysis models developed from previous work[28,29] and data specific to each healthcare system, we will demonstrate the relative effectiveness and efficiency of various LS screening protocols used by healthcare systems based on their local costs.

Aim 4: Develop and test in a natural environment an organizational toolkit to facilitate LS screening implementation and improvement. A draft toolkit will be disseminated to all sites. Additional interviews and analyses will assess utility for facilitating LS screening implementation or improvement.

Through systematic comparison and in-depth analyses of implementation across multiple healthcare systems, this study will create a comprehensive toolkit for organization-level decision-making to facilitate LS screening implementation and improvement and lead to testable hypotheses about associations between specific organizational contextual factors and implementation. This organizational toolkit will enable more effective and efficient implementation of LS screening; ultimately preventing needless suffering of patients and their family members from preventable cancers, decreasing waste in healthcare system costs, and informing strategies to facilitate the promise of other precision medicine initiatives.

Research Strategy

A. BACKGROUND AND SIGNIFICANCE

Colorectal cancer (CRC) is the third leading cause of cancer deaths in the US[30]. Importantly, colonoscopy is effective for both screening and primary prevention, particularly when those with hereditary risk can be identified and cared for appropriately[30,31]. Lynch Syndrome (LS) is the most common form of inherited CRC risk and includes significant risk for second primary cancer[31,32]. Cost-effective evidence-based systematic screening strategies to identify CRC patients with LS exist[6,7,28,29,33], yet this precision medicine approach for cancer prevention is inconsistently (if at all) applied within healthcare systems[15,22,27,34], resulting in unwarranted suffering and death from preventable cancers in cancer patients and their families[35].

Estimates indicate about one million people in the US have LS[4,5]. LS accounts for 3-5% of all newly diagnosed CRC[31]; yet only about 2% of individuals are diagnosed[5]. Individuals with LS have an increased risk of endometrial, ovarian, gastric, small bowel, and renal cancers, among others[31,32]. Diagnosis is confirmed when a germline genetic mutation is detected in any one of four DNA mismatch repair genes (*MLH1, MLH2, MLH6,* and *PMS2*). Importantly, well-established clinical guidelines with strong evidence exist for screening and prevention of cancers in individuals with LS[31]. Earlier (prior to population screening age) and more frequent colonoscopies in individuals with LS can reduce CRC risk by 62%[36] and CRC mortality by 70%[2,37-40]. Identification of individuals with LS can be accomplished through a variety of techniques, including family and medical history evaluation, computational models, or tumor testing[31,32]. However, clinical and family history-based methods alone, even if optimally applied, fail to identify at least one-third of LS patients[31,41].

Importance of LS screening is recognized by the Blue Ribbon Panel to save lives from cancer[4]. Systematic screening for LS has clear evidence supporting broad implementation in healthcare systems[9]. This "universal" approach was first recommended by the Evaluation of Genetic Application in Practice and Prevention (EGAPP) working group in 2009[2,42], has CDC-ranked top-tier evidence[8] for reducing cancer morbidity and mortality and improving quality of life[2,9], is currently recommended by multiple professional organizations[31,43-47], is endorsed by the National Comprehensive Cancer Network (NCCN)[48], is an objective of the Healthy People 2020 initiative[3], and was recently recommended by the Blue Ribbon Panel Precision Prevention and Early Detection Working Group to meet the goals of the Cancer Moonshot[4]. LS screening involves evaluating all CRC tumors for evidence of mismatch repair gene deficiency via immunohistochemistry testing or molecular testing for microsatellite instability. Individuals whose tumors screen positive are then offered confirmatory germline sequencing to diagnose LS[31,32,49]. For patients with cancer, diagnosis of LS changes surgical options, treatment and medical management, and additional screening and prevention requirements (especially for women). Emerging evidence suggests CRC patients with LS may benefit from treatment with certain immunotherapy options[50]. CRC patients with less than total colectomy have about a 20% risk for metachronous tumors in 10 years and therefore require more frequent screening[31,32]. Likewise, endometrial cancer occurs in 54% of women with LS, a risk that can be significantly reduced (90-100%) with prophylactic surgery[31,40,51].

Public health impact of LS screening cannot be realized without effective implementation. First degree relatives of patients with LS are at 50% risk to also have LS, and have an 85% lifetime risk of cancer[31,32,52]. Therefore, the cost effectiveness of LS screening is greatest when cascade testing identifies at-risk relatives[6,7,28,29,53]. When individuals with cancer are identified through LS screening, they are more likely to follow up with genetic counseling and diagnostic gene sequencing[54,55]. Likewise, evaluation and oversight of LS screening by genetic counselors results in higher patient follow through to gene sequencing[22,56]. However, unless the first individual is identified through effectively implemented LS screening, additional family members cannot be found and overall impact of this precision medicine intervention will be greatly reduced.

Implementation of LS screening in healthcare systems has been slow[4,8,27]. Only half of all genetic counselors report LS screening of some type at their institution[57] and more academic medical centers report implementing LS screening than other types of cancer centers[58]. This gap between evidence-based guidelines and their implementation into routine clinical practice is emblematic of one of the most critical issues in healthcare and public health today[25,59]. Therefore, this research proposal seeks to understand organizational factors impacting implementation and create an organizational toolkit to guide implementation, evaluation, maintenance, and improvement of LS screening - a recognized area of genomic medicine ready for national implementation with known variability and incomplete implementation across healthcare systems.

LS screening offers a prime opportunity to study and develop new models for implementation. Contextual factors such as organization mission, patient population, and economic impact of policies all influence decisions to implement genomic technologies in healthcare systems[12-14]. Factors specific to LS screening implementation may include: involvement of multiple key stakeholders and champions, availability of genetic counseling, and genetic testing costs. This complexity contributes to existing variability across healthcare systems, making it unlikely a single strategy or inflexible process will lead to successful LS screening implementation in all systems. In fact, there are multiple evidence-based protocols that are acceptable for use in LS screening[31,44]. Choosing the most appropriate protocol suited to the organization may determine the success or failure of implementation. Therefore, an organizational-level toolkit informed by the principles of implementation science can better facilitate LS screening implementation in healthcare systems by providing guidance on which protocol is best suited to specific organizational contexts and costs[25].

Evaluation of LS screening implementation and toolkit development will be guided by a framework from implementation science. The Consolidated Framework for Implementation Research (CFIR) uses constructs from multiple implementation science theories to guide multi-level evaluation of implementation. CFIR has been used successfully to evaluate variation in program implementation in the VA system[16,19] and variation in patient follow-through to confirmatory gene sequencing in LS screening[22]. The CFIR guides assessment of implementation barriers and facilitators at the individual, organizational, and external levels, and can also guide data gathering and structuring for Qualitative Comparative Analysis (QCA). QCA is useful for studying causal complexity in organizational implementation (LS screening implementation in this study)[20-23]. CFIR constructs also include cost, a critical component of implementation in healthcare systems. Business case analysis algorithms to understand local costs associated with LS screening were created by members of the study team and utilized by one healthcare system[28,29], but have not yet been widely disseminated.

The resulting organizational toolkit will provide guidance for the evaluation, maintenance, and improvement of LS screening in the face of organizational context and changes in scientific evidence. Most studies of implementation focus on barriers and facilitators in individual organizations, or across a few organizations, without providing guidance for other organizations. In addition, cost-effectiveness studies are usually performed from the societal perspective; which do not provide useful insights for local decision makers about the cost impact within a specific organization[60,61]. Finally, little attention is paid to the maintenance and improvement of programs in the face of changing organization contexts and scientific evidence. This point is critical, as the evidence base for new technologies, particularly genomic technologies, is likely to increase substantially due to the national precision medicine research initiative[62]. By creating an organizational toolkit that includes guidance for implementation, maintenance, and improvement, this project could accelerate optimal implementation of LS screening; benefitting patients, families, the healthcare system, and society; thus meeting a goal of the Cancer Moonshot and demonstrating the promise of precision medicine.

B. INNOVATION

This study will conduct an in-depth assessment of contextual factors impacting implementation across an unprecedented number of sites representing diverse healthcare systems, geographies, and patient populations served. This data will provide significant information for the Precision Prevention and Early

Detection Working Group of the Blue Ribbon Panel to successfully address the Cancer Moonshot[4], and for the working group of National Academies of Sciences, Engineering, and Medicine (NASEM) to successfully facilitate their goal of implementing LS screening[63]. The in-depth qualitative assessment of key stakeholders across this number of diverse sites is possible because of the collaborations and processes built within the Healthcare Systems Research Network (HCSRN), as well as the experience of this study team in researching LS and in conducting centralized qualitative studies of this magnitude. Finally, in creating an organizational toolkit guided by the CFIR, this study will also contribute to implementation science more generally.

This study combines multiple methods of exploring implementation in the complex environment of the healthcare system. Traditional case-based in-depth analyses of individual healthcare system barriers and facilitators will be conducted, followed by cross-case and Qualitative Comparative Analysis (QCA) to determine combinations of conditions necessary and/or sufficient for implementing LS screening in the presence of different organizational contextual factors, and cost-consequences modeling for local-level decision making. This process goes beyond a typical "lessons learned" approach to a comprehensive and critical analysis of implementation and non-implementation that is only possible because of the number of participating sites, a number of which (N=10) have not yet implemented LS screening and others with sub-optimal implementation at this time.

This study combines key stakeholder information with business case decision models populated with local data. Relevance of general societal cost to organizational decision-making has been questioned[60,61]; therefore, we will model site-specific costs of LS screening. Prior studies also indicate that organization-specific costs to screen and cost to detect LS cases for different protocols is critical information for health systems to make decisions about LS screening implementation[18,28,29]. To our knowledge, no studies have synthesized in-depth cross-site comparison of context, barriers and facilitators with local business case analyses into a comprehensive toolkit for organizations and that can be utilized beyond initial implementation.

This study will produce an innovative organizational toolkit to inform maintenance and improvement in addition to initial implementation. Because of the number of sites in various stages of implementation available for evaluation, this study will result in an organizational toolkit that informs initial LS screening implementation, ongoing evaluation and maintenance, improvement of sub-optimal implementation, and adaptation of optimal implementation to changing evidence. Traditional approaches to implementation lack flexibility to incorporate emerging evidence and are therefore less likely to be successful in the era of precision medicine. Likewise, most studies focus on strategies for initial implementation, rather than evaluation, maintenance, and improvement in the face of organizational context or evidence changes. For example, emerging evidence supports including evaluation of EC tumors when implementing LS screening[55,64,65]. Some early adopters of LS screening have adapted their LS screening to include EC tumors (Table 1, section C.1.2). How these sites adapted to new evidence will provide important information that has not been previously available in implementation science or in organizational implementation toolkits.

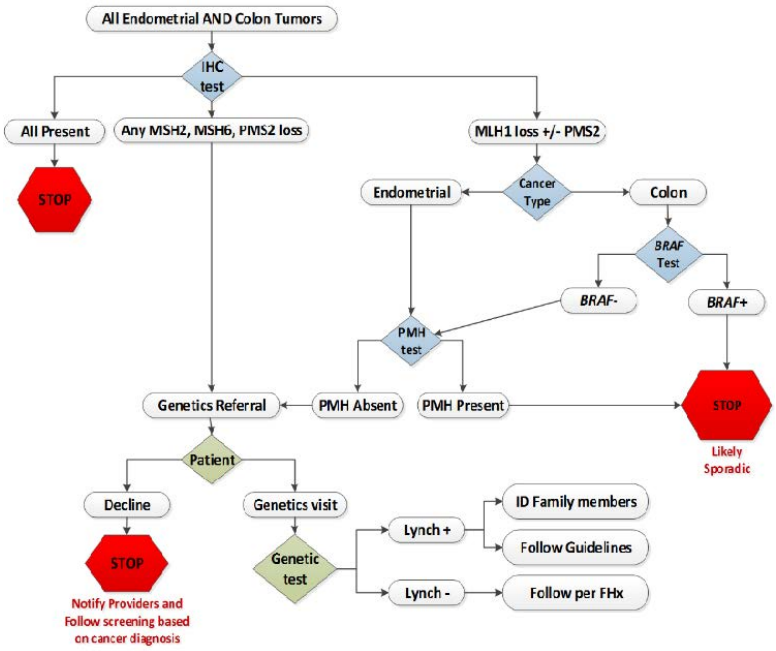
This study will demonstrate how an implementation toolkit can be used in organizational decision making to implement and improve LS screening. The greatest cost-effectiveness and cancer prevention benefit of LS screening will be realized only after effective cascade testing of at-risk relatives can be incorporated into optimally implemented programs. Providing a toolkit for organizational decision makers to guide implementation based on system-specific contextual factors and costs is a critical first step towards optimal implementation of LS screening through which familial cascade testing can be facilitated and studied. Additionally, this toolkit may be generalizable to implementing screening for other genomic conditions with top-tier evidence for effectiveness of familial cascade screening (e.g. Familial Hypercholesterolemia and Hereditary Breast and Ovarian Cancer).

C. APPROACH

C.1. Preliminary Studies

C.1.1 Universal LS screening. The most recent multi-society guidelines for CRC recommend systematic or "universal" LS screening programs test all CRCs, regardless of patient age, by IHC with reflex testing for *BRAF* V600E mutation and promoter hypermethylation (PHM) when there is MLH1 protein loss (Figure 1)[31,32]. Testing tumors with MLH1 protein loss for evidence of *BRAF* v600E point mutation or PHM identifies sporadic cancers not related to LS[31,32]. Confirmatory germline sequencing follows for screen positive individuals and medical management and additional cancer risk management for the patient as well as their at-risk family members is determined[31]. Figure 1 also includes screening EC, as some guidelines now recommend this[31,64,66,67] and some healthcare systems have already implemented EC screening into their LS screening protocols[68] (see Table 1, C.1.2). We will refer to this as "optimal implementation" in this application and study.

Figure 1. Suggested Optimal LS Screening Program Protocol



However, guidelines recognize the difficulty implementing LS screening in clinical practice and suggest that if all CRCs cannot be tested, then testing tumors under age 70 and using family history and other risk models to evaluate patients with CRC over age 70 is acceptable[31]; despite evidence demonstrating that age limits are not cost effective and that clinical assessments fail to result in genetic testing for LS[5,34]. Likewise, other guidelines advocate for maintaining age and tumor morphology limitations to EC screening[69]. These conflicting guidelines in the face of evolving evidence are therefore likely key contributors to variability in implementation[25].

C.1.2. Current LS screening across healthcare systems. Dr. Rahm recently surveyed leaders or delegates of sites in the HCSRN. Twelve sites responded (63% response rate) with information about their current LS screening protocols (Table 1). Two out of 12 systems reported no LS screening and only 4 sites included, or were in process of including, EC tumor screening

Table 1. Survey of LS Screening in the HSCRN

Site	LS Screening Implementation
1	CRC only - no age limits but no enforcement
2	No Implementation
3	No Implementation
4	CRC only - no age limits w/ reflex
5	CRC only <75 unless high risk
6	CRC only - no age limit, reflex ordered by oncologist
7	CRC and EC - no age limits with reflex
8	CRC only no age limits, EC under60, adding all EC
9	CRC only no age limits, with reflex, adding EC
11	CRC under research protocol, no clinical program
12	CRC and EC - no age limits with reflex

C.1.3. Pilot feasibility. To further develop our research approach, Dr. Rahm conducted exploratory interviews with one key stakeholder from each of 5 HCSRN sites with LS screening programs. These interviews were conducted to: a) determine feasibility of a CFIR-based interview guide to gather information about LS screening implementation, organizational context, barriers, and facilitators (see Appendix-Pilot Interview Guide), b) begin to understand the complexity of factors contributing to variability between sites, c) guide analysis plan development for the larger study, and d) determine the breadth of LS screening implementation processes available for analysis. While the survey (Table 1) provided a cross section of LS screening implementation and non-implementation across the HCSRN, interviews indicate that information from multiple stakeholders across a number of healthcare systems is necessary to fully understand the multi-level complexities of implementing LS screening.

Despite existing evidence supporting LS screening[2,27,42], recent calls to action by the NASEM and the Blue Ribbon Panel indicate a pressing need for increased efforts to improve implementation[4,63]. Our preliminary data indicate persistent variability in LS implementation across healthcare systems and demonstrates the need for additional data and organizational toolkits to facilitate implementation. The cross-site comparison and QCA proposed here will synthesize for organizational decision-makers the breadth of barriers to implementation, different solutions for those barriers, and which solutions are most likely to work under which conditions. This data will be the foundation of a toolkit that will more effectively guide future implementation efforts in these and other healthcare systems. One key example demonstrating this need is that one site recently implemented LS screening as a randomized trial[70,71]. However, rather than adopting protocols developed by researchers, clinical operations staff implemented by repeating work previously conducted by researchers. Stakeholders from this site will provide critical information on factors hindering direct adoption of research protocols (see Letters of Support KPNW). Without a toolkit to guide implementation based on strategies and contextual information from multiple systems, as proposed by this project, other healthcare systems will proceed with ad-hoc implementation, increasing risk of ineffective or unsustainable LS screening, or will simply continue to avoid implementation all together.

C.1.4. Guiding framework. All five pilot interviewees described LS screening implementation as an ongoing process; including improvement and adaptation over time as new evidence arises. LS screening implementation may be a continuum between no LS screening to the current optimal implementation of screening all CRC and EC tumors with reflexive *BRAF*/PHM testing[31,32] (Figure 1). Healthcare systems appear to utilize multiple approaches for starting, adapting, and optimizing LS screening, as some healthcare systems began with optimal implementation while others chose sub-optimal implementation (Table 1). Still others began with sub-optimal implementation and improved to optimal screening.

This preliminary indication that LS screening implementation is not a static endpoint is consistent with other reports of LS implementation[18,54,65], and is a critical concept for genomic medicine, as new evidence and technologies are constantly emerging. For example, the decreasing cost of gene sequencing could soon lead to sequencing of all CRC patients as the most cost-effective screening option[31]. The CFIR is therefore an ideal guiding framework for this study, as it describes implementation as an active process that changes and adapts over time[72]. We believe utilizing the CFIR to guide study design, data collection, and analyses, will result in the development of an organizational toolkit that will facilitate initial implementation, as well as maintenance and optimization of LS screening as evidence in genomic medicine changes over time.

C.1.5. Cost-consequences analysis. Value, determined by the relationship between a set of health outcomes and the costs associated with achieving those outcomes, is also critical to decision-making in healthcare systems[10], as each clinical site assesses value based on its individual mission and patient population[13]. Previous experience of members of this research team[18,28,29] in implementing LS screening identified that cost to the institution of the different testing protocols and of screening older cancer patients were key barriers[28,29]. The latter concern was based on provider perception that excluding older CRC patients from LS screening would substantially reduce total costs to the organization and increase efficiency with negligible impact on detection of LS[28]. This provider perception remains an oft cited barrier to screening all ages of CRC and EC patients in healthcare systems, despite evidence to the contrary[28,29,64,65]. Because local data including institutional testing costs, number of CRC patients diagnosed per year, and local prevalence of LS, have been reported as key inputs for creating budget impact and cost consequences models for organizational decision makers[21,28,29], we believe this information is a critical component of an implementation toolkit for LS screening.

C.1.5 Generalizability. The number and diversity of healthcare systems and clinical sites included in this study will enhance generalizability of the toolkit to guide LS screening implementation, maintenance, and improvement nationally and internationally. Evidence suggests issues and experiences of implementation are not unique to the HCSRN. To enhance generalizability, we have included one clinical site outside the HCSRN (Northwell Health). Other healthcare systems, as well as other countries are also seeking to implement LS

screening, yet these efforts continue similar inefficient ad-hoc implementation[56,73]. We have included collaborators from Cancer Care Ontario and the Lynch Syndrome Screening Network (LSSN) as part of an external project advisory panel to help ensure study results and implementation toolkit are broadly applicable to LS screening implementation.

C.2. Setting

We will study the contextual factors of 23 clinical sites across 8 healthcare systems; seven of which are members of the HCSRN. The HCSRN has standard data models and processes to facilitate IRB approval and data sharing to improve efficiency for conducting multi-site studies such as this. Some of the healthcare systems are also members of the Cancer Research Network (CRN), a subgroup of the HCSRN, which also includes a scientific working group specific to communication and dissemination research (C&D SWG); led by established experts in implementation science. The C&D SWG will serve as an additional venue for presenting preliminary study results to a multi-disciplinary group of scientists and for additional dissemination of study results (Letters of Support-C&D SWG).

C.3. Participants

Table 2. Lynch Syndrome Screening Implementation Across Healthcare Systems and Clinical Sites

Healthcare System	Clinical Site	NO SCREENING	CRC Screening	BRAF Reflex	PHM Reflex	EC Screening	PHM Reflex
Geisinger Health System	Geisinger		All Ages	x	x	All Ages	x
	Geisinger-Holy Spirit	x					
Palo Alto Medical Foundation	PAMF		All Ages				
Kaiser Permanente	KP-Colorado (KPCO)	x					
	KP-Northwest (KPNW)		All Ages	x	x		
Meyers Primary Care Institute	MCPI		All Ages				
Health Partners	Health Partners		All Ages	x	x	All Ages	x
Harvard Pilgrim	Harvard Pilgrim	x					
Northwell Health	Northwell Health		All Ages				
Catholic Health Initiatives (CHI)	CHI-Franciscan WA		All Ages	x	x	All Ages	x
	CHI- Tri-Health OH		All Ages	x	x	All Ages	x
	CHI-Mercy Des Moines IA		All Ages	x	x	All Ages	
	CHI-Kentucky One KY		All Ages				
	CHI-Chattanooga TN		All Ages	x	x	All Ages	x
	CHI-Good Samaratin NE	x					
	CHI-Lincoln NE		<70 years	x			
	CHI-St Francis NE	x					
	CHI-St Joes Bryan TX	x					
	CHI-St. Vincent AR	x					
	CHI-Centura CO		<70 years			<60	
	CHI-Alegent Creighton OH	x					
	CHI- St. Alexius ND	x					
	CHI- Mercy ND	x					

C.3.1. Healthcare systems. For this project, the unit of analysis is the clinical site through which LS screening is or can be implemented. Participating healthcare systems (N=8; Table 2) have been purposively selected to maximize the number of clinical sites (N=23) in various stages of implementing LS screening, as well as to maximize diversity of location, system structures, and patient populations. Sampling selection also includes one HCSRN system with LS screening recently acquired a smaller system that has not implemented LS screening (see Letter of Support - Geisinger Holy Spirit). Another HCSRN system, Catholic Health Initiatives (CHI) has a centralized research structure but the clinical sites (N=14) operate independently and have different clinical structures, patient populations, and LS screening implementation. CHI has the ability to influence clinical implementation in the organization both at the local site levels and from an overall policy level.

C.3.2. Patient and organizational stakeholders. In-depth qualitative interviews with key stakeholders will be utilized to elicit the information important to organizational decision making about LS screening implementation

and provide data for the site-level analysis. Key stakeholder opinions important to LS screening implementation include patient and organizational stakeholders. Patient opinion is important to organizational decision-making, as anticipation of patient reactions can be a barrier to implementation for some clinical sites. We will therefore interview newly diagnosed cancer patients (10 per site) and cancer patients who have received a positive LS screening result (N=25 total from sites with LS screening at the beginning of the study) in order to provide this information for organizational decision-making. Organizational stakeholders (N=10 per site) important to LS screening implementation include individuals from health plan leadership, pathology, genetics, surgery, oncology, and others[70,74] (Table 3 Section C.5.1). Patient and organizational stakeholder recruitment and data collection is described in detail in C.5.1.2 and C.5.1.3.

C.4. Study Design

Implementation, especially of complex interventions such as LS screening, is highly context dependent[15,18,74,75]. Therefore, we propose a multiple-case study design with a mixed-methods approach to analyses followed by a naturalistic observational evaluation. Study design and analyses are informed by the CFIR. The multiple case-study design utilizes purposive selection of cases (N=23 clinical sites; Table 2) with known variability in LS screening implementation, including cases (N=10 sites) without LS screening implementation at present. It is possible that any of these 10 sites may implement LS screening prior to the beginning of the study, however, given the significant barriers to implementation in healthcare systems, it is unlikely that all 10 sites would begin LS screening implementation prior to the beginning of the study. This study is specifically designed to evaluate cases (sites) based on their implementation status at the beginning of and throughout the study, and will thus provide information critical to LS screening specifically and implementation science in general.

Data for the multiple-case study design will be gathered via in-depth qualitative interviews with key stakeholders, including patients and organizational stakeholders (Table 3). Stakeholders will be identified through purposive and snowball sampling to provide the most in-depth information for describing variation in practice and factors influencing implementation, evaluation, maintenance, and improvement of LS screening at each site (Aim 1). The CFIR provides a process for analyzing qualitative data from a multiple case-study design to look for associations across cases (sites) in order to identify factors associated with where, when, and under which conditions different processes for implementing or improving LS screening might be successful (detail in C.7.2.1). Further in-depth Qualitative Comparative Analysis (QCA) will be utilized to develop a model of conditions necessary and/or sufficient for implementing and improving LS screening under different organizational conditions (detail in C.7.2.3). The large number of sites (N=23) increases the opportunity to measure outcomes common to multiple sites and compare with other sites (Aim 2).

Cost-consequence modeling[28,29] and other quantitative analyses will be utilized to address concerns of organizational decision-makers and the CFIR construct of intervention cost by modeling intermediate parameters in the LS screening pathway (e.g. results of different assays in a protocol). While Quality Adjusted Life Years (QALYs) are an accepted measure of cost-effectiveness on a population level, the relevance of this measure to healthcare decision-making has been questioned[60,61]. Testing costs for each clinical site, as well as tumor registry data for incident CRC and EC cases will be used to support economic model assumptions and values used to provide site-specific estimates of costs associated with the different LS screening protocols, the site-specific incremental costs of detecting LS cases, and the economic impact to the site of imposing of age cutoffs. Additional costs important to stakeholders that arise from Aim 1 interviews will be included as appropriate to provide the most locally relevant cost information for organizational decision-makers to compare implementation options and make informed decisions based on local clinical costs and impact. (Aim 3).

An organizational implementation toolkit will be developed from the data in Aims 1-3 and provided to all participating sites (Aim 4). We will utilize a naturalistic observational design with qualitative evaluation to assess utility of the tool for facilitating implementation at sites without LS screening and optimization in sites with screening. Additional organizational stakeholder interviews will be conducted to determine the utility of the

toolkit to facilitate organizational decision-making regarding LS screening implementation and improvement.

C.4.1. External Advisory Panel. A project-specific External Advisory Panel (EAP) has been created. The EAP has been involved in the development of this proposal and will continue to meet twice yearly via teleconference with study investigators for the duration of the project to provide guidance on data analysis and reporting, and assist in dissemination of study findings. This process will guide strategies for broader dissemination of the organizational toolkit to other healthcare systems. The EAP consists of individuals from the CRN C&D SWG, the Hereditary Colon Cancer Foundation, The Lynch Syndrome Screening Network (LSSN), and Cancer Care Ontario (See Letters of support and Budget Justification).

C.5. Procedures

C.5.1. Data collection - Aims 1 and 2:

Organizational and patient stakeholders will be recruited to participate in telephone interviews to provide data for Aims 1 and 2. Sample size, sampling plan, and other aspects of data collection are detailed in Table 3, while recruitment and interviewing is described in detail in the sections following. Interviews will be conducted centrally by experienced staff at either Geisinger or KPNW as detailed in Table 3.

Table 3. Data Collection Plan for Key Stakeholders

Key Stakeholder Type	Sample Size	Sampling Plan	Data Site	Interview Site
Organizational Stakeholders-Aim 1	10 per site	Purposive with snowball sampling	All sites	Geisinger
Newly Diagnosed CRC Patients	10 per site	Prospective	All sites	KPNW
CRC patients with Positive LS Screen	25 total	Retrospective	Sites with LS Screening ONLY	KPNW
Organizational Stakeholder-Aim 4	5 per site	Purposive with snowball sampling	All sites	Geisinger

C.5.1.2. Organizational stakeholder recruitment: Up to 10 organizational stakeholders per site will be recruited through purposive role-based recruitment and snowball sampling[70,76]. The actual number of and specific individual key stakeholders invited to be interviewed will depend on each site's organizational structure, however, based on previous research[19,22,70,76] it is anticipated that 10 organizational stakeholders per site will provide sufficient information about LS screening for analysis and that the stakeholder types will be relatively standard across sites. Standard role-based stakeholders relevant to LS screening include: pathology, genetic counselors, gastroenterology, gynecology, surgery, and health plan leaders (Table 4). Additional site-specific role-based stakeholders will be identified through snowball sampling. Research staff from each site will reach out to initial stakeholders from their organization via email or other methods, such as attending department meetings, to alert them to the study and invite them to participate in a telephone interview. At the end of each completed interview, the interviewee will be asked to identify any additional organizational stakeholders necessary for implementing new processes generally and LS screening specifically at the site. Additional stakeholders will be sent an email indicating that they were nominated to be invited into the study and offered the opportunity to participate in a telephone interview.

Table 4. Role-Based Key Stakeholder Types in LS Screening

Organizational Stakeholders
Pathology
Genetic counselors
Gastroenterology
Gynecology
Oncology
Surgery
Health Plan leadership
Other key stakeholders (as identified by each site)
Patient Stakeholders
Newly diagnosed CRC patients
LS screen positive patients

C.5.1.3. Patient stakeholder recruitment: Two different groups of patient stakeholders will be invited to participate in this study: (1) patients newly diagnosed with CRC (N=10 per site) and (2) patients who have been notified of a positive LS screen result and were recommended for additional genetic counseling and testing to confirm diagnosis (N=25 total across sites). For the patients with newly diagnosed CRC (group 1), study staff at each site will determine the best way to identify and contact patients up to one month post-diagnosis and offer the opportunity to participate in this one-time telephone interview. This group will illuminate for organizational decision-makers local patient attitudes and opinions about LS screening, while the diversity of these patients across all sites will provide insight into patient attitudes in general towards LS screening. Additionally, patients with CRC who have been notified of a positive LS screen result (group 2) will also be invited to participate in telephone interviews. A total of 25 patients will be recruited only from sites with LS screening at the start of the study (Table 3) to provide insight into patient experiences with a positive LS screen across different sites and different LS screening implementation protocols.

C.5.1.4. Qualitative data collection (patients and organizational stakeholders)*:* Semi-structured interviews will be conducted via telephone centrally by staff experienced in qualitative data collection. Centralized telephone interviewing and data analysis is an efficient and effective way for qualitative data collection from multiple stakeholders across multiple sites, and has been used successfully by this project team and others[75,77-79]. Utilizing the telephone allows interviews to be conducted at a time convenient to the key stakeholders and centralized processes reduces variability in interviewing. Finally, interviews conducted by personnel external to the interviewee's organization may facilitate more candid discussion regarding organizational facilitators and barriers[80]. The interview guide is described in more detail in section C.6.1.

A summary will be created immediately after each interview and reviewed with site investigators during regular study meetings. These summaries will be used to iterate the sampling procedure or interview guides, if necessary, and to create the initial coding schema and analytic framework. Summaries allow for high-level analysis during on-going data collection, facilitate initial codebook development, and reduce the number of de novo codes requiring re-review and re-coding of transcripts during data analysis[81,82].

Interviews with organizational stakeholders will be conducted centrally by staff at Geisinger led by Dr. Rahm. Patient interviews will be conducted centrally by staff at KPNW led by Dr. Hunter and Ms. Schneider. Interviewees will receive a $25 gift card upon completion of the interview.

C.5.2. Data collection - Aim 3: Addressing Aim 3 requires estimates of annual number of cancer cases, LS prevalence or the assumption of an equivalent rate for all populations, and cost of tests included in screening protocols from each site (collected in Aim 1) to populate decision analysis models. Data sources for Aim 3 are detailed in Table 5. All data will be summarized in aggregate for each site, creating de-identified data sets. In most instances, this data is available from electronic data stores and tumor registry.

Table 5. Data Sources for Aim 3

Input Variables	Definition	Data Source
# CRC cases per year	incidental CRC cases by year averaged over a 5 year period stratified by age at diagnosis	Site Electronic Data
# EC cases per year	incidental EC cases by year averaged over a 5 year period stratified by age at diagnosis	Site Electronic Data
Local testing costs	cost to institution of each test of the site-specific screening protocol	Billing or Contracts
Prevalence of LS in unselected CRC cases	number of LS cases detected through screening program if available	Site Electronic Data
Prevalence of LS in unselected EC cases	number of LS cases detected in screening protocol (if available)	Site Electronic Data
ite-specific LS screening protocol	site-specific LS screening protocol at the beginning of the study	Site Stakeholders -Aim 1 Interview

While letters of support detail commitment of clinical sites to obtain institutional cost data, we will use alternative methods when this data is not available due to proprietary reasons. Alternatives to local test cost may include using a test cost range based on the other participating clinical sites, or regional test cost figures if publicly available from testing companies, Medicare reimbursement, or other sources. We also recognize that reliable estimates of LS prevalence specific to each site may not be available; therefore, this model parameter may be estimated from sites with such data and/or the most current estimates for U.S. populations[33].

During year 1 initial exploration of site testing costs, cancer cases, and LS cases detected (if available) will be determined with preliminary data pulls and tested for accuracy. For sites with HCSRN VDW (virtual data warehouse) capability, we will use the standard distributed code process, where code is written and tested at one site and distributed to the other sites, where it is used within the new site's VDW. Because clinical sites, their LS screening protocols, and scientific evidence are dynamic, we do not expect testing costs or LS screening guidelines to be static. Therefore, this basic analytic framework will be updated to account for any evidence that may have emerged, and a final data pull will be conducted and aggregated data per site will be sent to Geisinger for economic analysis described in C.7.3 just prior to creating the draft organizational toolkit and distributing to participating sites.

C.5.3. Data collection - Aim 4: Data from Aims 1, 2, and 3 will be used to generate a working organizational toolkit to guide implementation, maintenance, and improvement of LS screening. Because healthcare systems are not static and guidelines are changing rapidly, additional observational data will be collected over the entire project period from monthly project meetings, communications from site investigators, pertinent data regarding site-specific screening changes, and external evidence or guideline changes for LS screening will be recorded in a project specific database created for tracking such information related to implementation[83]. Importantly, this tracking database of all other factors impacting implementation will provide additional information for the toolkit development should any sites begin to implement LS screening based on being interviewed for Aim 1, but prior to receiving the toolkit.

In year 5, additional qualitative interviews will be conducted with up to 5 organizational stakeholders at each site using the same processes described in section C.5.1.2 and analyzed as in C.5.1.4. Stakeholders will be contacted for interviews 6 months after distribution of the toolkit. Stakeholders from sites without LS screening and those with sub-optimal implementation will be interviewed about the utility of the tool to facilitate implementation and improvement. Stakeholders from sites with optimally implemented programs will be interviewed about the utility of the tool for improvement or adaptation to emerging evidence.

C.6. Measurement

C.6.1. Measurement - Aims 1 and 2: In years 2 and 3, we will conduct qualitative semi-structured interviews with patients and organizational stakeholders from each site to measure current LS screening protocols, attitudes towards LS screening, and specific implementation strategies employed (successfully and unsuccessfully). A draft semi-structured interview guide for organizational key stakeholders has been developed using the CFIR question bank[72] and pretested with 5 key stakeholders from different sites (Results presented in C.1.2). The patient interview guide will be adapted from a prior study which utilized similar constructs[71]. Interview guides (See Appendix for draft interview guides) will be reviewed at the start of the study with the site investigators and the project EAP. The CFIR-guided constructs to be assessed through the patient and organizational stakeholder interview guides are detailed according to CFIR domain in Table 6. For organizational stakeholders, interview guides will be further tailored to the position of the key stakeholder as necessary. For example, system leaders may be asked more questions about engagement of leadership, external influences such as pressure to be like other institutions, and reimbursement incentives. Tailoring questions to the position of the key stakeholder was found necessary in a similar study of organizational implementation[76,78].

Table 6. CFIR Constructs by Domain Specific to LS Screening to be Assessed in Stakeholder Interviews

CFIR Domain	CFIR Constructs Specific to LS Screening
Intervention Characteristics	Adaptability of LS screening to local context
	Perceived difficulty implementing LS screening
	Cost to the organization associated with screening
Outer Setting	Patient needs and resources
	Competitive pressure to implement screening
	Impact of external policies on organization
Inner Setting	Organization structure
	Perceived organizational priority to implement
	Implementation climate in organization
Characteristics of Individuals	LS knowledge and beliefs, perception of evidence
	Individual readiness to implement screening
	Self-efficacy to complete actions in screening
Implementation Process	Planning process to implement LS screening
	Champions, opinion leaders, and other stakeholders
	Tracking and feedback processes for LS screening

C.6.2. Measurement - Aim 3: Aim 3 will measure, via simulation modeling, 1) total testing costs and incremental testing costs by healthcare system for LS screening programs, 2) total costs to screen for site-specific protocol compared to all other possible protocols, and 3) site-specific costs to screen by age cutoff categories. The models previously developed by Dr. Williams and others[28,29] will be adjusted as necessary to appropriately reflect site-specific LS screening protocols as determined from data collected from site organizational stakeholder interviews in Aim 1.

C.6.3. Measurement - Aim 4: To measure facilitation of implementation and LS screening improvement in the natural environment after receiving the toolkit, data from sources listed in section C.5.3 will be coded for information regarding to whom the organizational toolkit was distributed at each site, questions that were asked by key stakeholders, and whether and how the toolkit was used by organizational decision makers to facilitate LS screening implementation and/or improvement. The interview guide for the additional post toolkit organizational stakeholder interviews will be adapted from the Aim 1 interview guide (C.6.1) and adjusted to gather information on ability of the toolkit to facilitate or improve implementation.

C.7. Analyses by Study Aim

C.7.1. Describe variation in LS screening implementation across multiple healthcare systems (Aim 1)

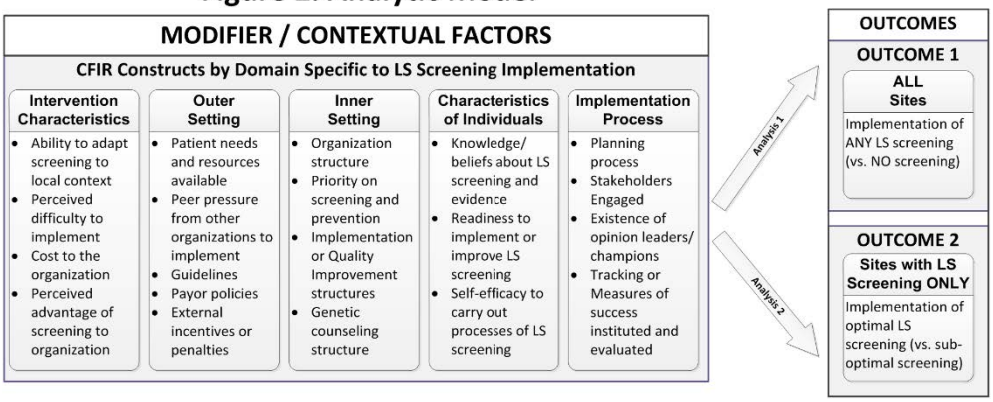
Qualitative analysis for Aim 1 will be led by Dr. Rahm and other study team members experienced in qualitative analysis. During the entire analytic process, progress, codebooks, and analytic framework will be reviewed and cross-checked with site investigators during monthly project meetings, with the C&D SWG leaders, and with the project EAP as part of their scheduled meetings.

C.7.1.1. Coding to describe LS screening implementation and contextual factor variation. All patient and organizational stakeholder interviews will be digitally recorded and transcribed verbatim. Transcripts will be uploaded into Atlas.ti (www.atlas.ti.com) for qualitative analysis. Interview transcripts will be initially coded using an *a priori* codebook developed from the semi-structured interview guides, interview summaries, and CFIR constructs. This first round of coding will look for description of LS screening, process of implementing LS screening, champions, and external factors important to the key stakeholders and other constructs described in Figure 2. Emergent (*de novo)* codes will be added to any other relevant sections of transcript text not fitting the *a priori* codes. This coding is an iterative process that will involve team members independently coding 2-3 transcripts at a time, then discussing their coding to adjust the codebook and to create a working analytic framework by grouping codes into categories or themes. This process will continue until the code list is static, all transcripts are coded, and the analytic framework is finalized. Geisinger team members experienced in qualitative analysis under direction of Dr. Rahm will analyze the organizational stakeholder interviews while Dr. Hunter and Ms. Schneider at KPNW will lead the coding and analysis of patient interviews. Both coding teams will coordinate to create the final analytic framework.

C.7.2. Explain current practice variation and determine factors associated with optimal implementation of LS screening. (Aim 2)

C.7.2.1. Coding for presence and impact of CFIR constructs. Transcripts from stakeholder interviews will be coded to capture selected CFIR constructs (Table 6 section C.6.1 and Figure 2) present and whether that construct was a barrier or facilitator of LS screening implementation, evaluation, maintenance, or improvement at each site.

Figure 2. Analytic Model



Transcript sections coded for the presence of specific CFIR constructs will be coded for whether the construct impacted implementation and/or choice of implementation strategy. If the construct was impactful, the study team will code for direction (positive or negative) and for magnitude of impact (small vs. large). This will allow analyses of which factors are important to implementation in different organizational contexts and provide initial information for the QCA. This coding for construct presence and impact will follow protocols detailed in the CFIR technical assistance website[72] and will be conducted by individuals described in C.7.1.1 and led by Drs. Cragun and Rahm with input from Dr. Mittman.

C.7.2.2. Framework matrix construction and cross-case analysis. A framework matrix will be created to summarize the completed coding of all interviews. This matrix will also facilitate comparison of the data across sites (the cross-case analysis) and will determine set membership for the QCA in Aim 2 (section C.7.2). Because this summary matrix maintains the link to the original coded data, the matrix and conclusions can be revised and restructured as needed based on feedback and insight from the larger project team, the individual site investigators, the CRN C&D SWG leaders, and the project EAP as part of a constant comparative process to minimize bias in qualitative data coding.

C.7.2.3. Qualitative Comparative Analysis (QCA). Conditions associated with LS screening implementation and conditions associated with optimal or sub-optimal implementation will be determined using QCA. QCA is a well-established methodology arising from political science research[21,23,24]. QCA uses set theory to identify combinations of conditions that are associated with an outcome and is particularly suitable when there is causal complexity (multiple conditions may lead to the same outcome)[24], as in LS screening implementation where a facilitator in the presence of one contextual factor may be a barrier to implementation in another. QCA is well-suited for case-oriented research and uses Boolean algebra instead of statistical correlation to determine which combinations of conditions (CFIR constructs) are consistently associated with an outcome (LS screening implementation)[23]. The QCA process is comprised of multiple steps[21] that can be summarized as follows: a) code the outcome (Figure 2), b) code the conditions (CFIR constructs; Figure 2) and calibrate if necessary, c) determine which conditions (CFIR constructs) are necessary and sufficient for the outcome and d) interpret solutions to create a model. Specific software (http://www.compasss.org/software.htm) designed for QCA is used to conduct this analysis.

C.7.2.4. QCA outcome definitions. Two different outcomes analyses will be conducted (Figure 2). Initial analysis will describe the outcome of no implementation of LS screening vs. any implementation of screening across sites. Secondary analysis will describe outcomes associated with optimal implementation (Figure 1; CRC and EC tumor screening with reflex testing) vs. sub-optimal implementation across sites with LS screening only. Additional analysis of this outcome will also examine conditions reported in previous studies to be more cost-effective, result in better patient ascertainment and completion of germline genetic testing, and show effective use of genetic services. Such conditions appear to include multidisciplinary involvement, effective tracking, and reflex testing for *BRAF* and PHM[22,28,29,54 68,84-86].

C.7.2.5. QCA analyses. In Aim 1 all CFIR constructs assessed are analyzed to ensure in-depth understanding of each site. In Aim 2, an iterative process will be used to evaluate and assign values to the CFIR constructs, which will serve as conditions in QCA[20,21,23]. For conditions (CFIR constructs) exhibited by more than 2 sites, QCA can be considered. Constructs relevant to each outcome are represented by a natural number (0,1,2, etc) based on the degree to which the construct falls within a particular set (i.e., whether or not screening is present, or degree to which screening has been optimized). Necessary and sufficiency analyses will be run using QCA software to determine conditions that are necessary or sufficient for each outcome. A resulting "truth table" is created in the sufficiency analysis, which is then analyzed for contradictions. In line with best QCA practices, the research team will resolve any contradictions by returning to the original data and using the in-depth knowledge of the cases (sites) from Aim 1 to determine if key conditions may be missing from the model. Once all contradictions are resolved, QCA software will make multiple comparisons of the data to create solutions, which will again be evaluated by the research team, with review and cross-checking of assumptions by the site investigators and the project EAP during scheduled meetings. Dr. Cragun has extensive experience in this analytic method and will direct these analyses in collaboration with Dr. Rahm. The resulting solutions will be the basis for the toolkit to help organizational decision makers determine what implementation strategies are more likely to work given their organizational context.

C.7.3. Determine the relative effectiveness, efficiency, and costs of different LS screening protocols. (Aim 3)

C.7.3.1. Efficiencies of different LS implementation strategies. Simulation modeling will be used to estimate multiple factors identified as important to stakeholders during Aim 1 and from previous modeling conducted for Intermountain Healthcare[28,29]. Table 7 details the parameters and data sources included in the models. The models will be populated with data described in C.5.2. The model used to address screening protocol efficiencies will estimate for each site: sensitivity of the different LS screening protocols (e.g. with or without reflex testing), average number of LS cases expected to be identified, total costs for each screening protocol for a defined cohort size (e.g. 500 cases per year), cost-per case-screened, cost-per-LS diagnosis, and incremental cost, case identification, and detection of an additional LS case between protocols. All analyses for this Aim will be conducted under the direction of Drs. Hao, Snyder, Williams, with input from other project team members experienced in economic analyses.

Table 7. Parameters and Data Source for Economic Modeling

Input Variable	Data Definition	Data Level	Data Source
#CRC cases per year	Incidental CRC cases	Local Site	Electronic Data
#EC cases per year	Incidental EC cases	Local Site	Electronic Data
% Appropriate tissue avialable	Eligible cases with tissue available for LS screening	Local Site	Pathology
Prevalence of LS in population	Number of LS cases in population (actual or estimate)	Local Site or Literature	Electronic Data Or Literature
Cost of IHC test	Institutional cost of test as available	Local Site	Billing Data
Sensitivity of IHC screen	From Laboratory or Local site as available	Local Site or Literature	Test information
Specificity of IHC screen	from Laboratory or Local site as available	Local Site or Literature	Test information
% IHC screens that are positive	Incidental CRC or EC cases with positive IHC screening tests	Lab or Local Site	Electronic Data
% IHC screens with MLH1 loss	IHC positive screens that demonstrate loss of MLH1 activity	Lab or Local Site	Electronic Data
% MLH1 positive Ruled out by BRAF	MLH1 loss cases due to BRAF mutation	Lab or Local Site	Electronic Data
%MLH1 positive ruled out by PHM	MLH1 loss cases due to PHM	Lab or Local Site	Electronic Data
Cost of BRAF test	Institutional cost of test as available	Local Site	Billing Data
Cost of PHM test	Institutional cost of test as available	Local Site	Billing Data
% Patients referred to genetics	Screen positive patients sent to genetics for follow up	Local Site	determined by site
% Patients offered germline testing	Screen positive patients offered confirmatory sequencing	Local Site	determined by site
% Patients with germline testing	Screen positive patients with an order for germline testing	Local Site	electronic data
Cost of sequencing test	Institutional cost of test as available	Local Site	Billing Data
Sensitivity of sequence test	From sequencing laboratory used	Literature	Literature
Specificity of sequence test	From sequencing laboratory used	Literature	Literature

C.7.3.2. Site-specific age cut-off modeling. Additional modeling of different LS screening age cut-off policies will also be conducted to estimate their impact on effectiveness, efficiency, and cost to each site using local-level data whenever practical (see C.5.2 for alternatives). Outcomes that will be simulated in this model include: total cost to screen age cutoff cohort vs. no age cutoff, LS cases expected in the age cutoff category, cost-per-LS case detected in each age category, and total number and percent of LS cases missed when age cutoff is applied[28]. This modeling will provide objective metrics, driven by local data, of the impacts of applying

age-cutoffs in LS screening implementation.

All modeling will be conducted using TreeAge (https://www.treeage.com/) or Microsoft Excel with the @Risk software add-on for Excel (Palisade) for sensitivity analyses. The purpose of these analyses is to provide information previously determined to be important to healthcare system stakeholders to inform initial LS screening implementation decisions or to improve existing LS screening. Acceptable variability associated with clinical/ business costs will also be illuminated by performing these analyses across multiple sites using local data. These results will provide site-specific cost information most relevant to organizational decision-makers, contribute to our overall understanding of variation in LS screening implementation, and highlight acceptable variation in LS screening related to different organizational costs. This process of reviewing local implementation costs of a complex intervention to illuminate acceptable variability may also be generalizable to other precision medicine programs and will contribute to the field of implementation science in general.

C.7.4. Develop and test in a natural environment an organizational toolkit to facilitate LS screening implementation and improvement. (Aim 4)

C.7.4.1. Toolkit Creation. An organizational toolkit will be created based on the CFIR conceptual framework, the in-depth knowledge of LS screening programs and contextual factors of healthcare systems from Aim 1, the cross-site comparison and QCA results from Aim 2, and economic modeling with local costs from Aim 3. This toolkit will be disseminated to all sites through site PIs and the tracking database will record to whom it is distributed, questions asked by those receiving the toolkit, and actions taken by the site.

C.7.4.2. Analyses of toolkit utility. Utility will be assessed in year 5 through additional post-toolkit stakeholder interviews. Interview coding and analyses will utilize the same methods described previously to identify conditions that changed within organizations to allow LS screening implementation, improvement, or adaptation of optimally implemented programs. The final organizational toolkit for LS screening implementation, maintenance, and improvement will be modified based on this information prior to broad dissemination.

C.8. Project timeline

Table 8. Project Timeline Overview

	Year 01				Year 02				Year 03				Year 04				Year 05			
General Project Tasks	Qtr 1	Qtr 2	Qtr 3	Qtr 4	Qtr 1	Qtr 2	Qtr 3	Qtr 4	Qtr 1	Qtr 2	Qtr 3	Qtr 4	Qtr 1	Qtr 2	Qtr 3	Qtr 4	Qtr 1	Qtr 2	Qtr 3	Qtr 4
IRB approval	x	x																		
Data Use Agreements	x	x																		
Exploratory data collection for Aim 3		x	x	x																
Finalize interview guides		x	x																	
key stakeholder recruitment and interviews* (Aim 1)				x	x	x	x	x	x	x	x									
CFIR guided cross-case and QCA (Aim2)						x	x	x	x	x	x	x	x	x						
Data pull and economic analysis (Aim 3)												x	x	x	x	x				
Collection and Tracking of data on change		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Develop and distribute toolkit (Aim 4)													x	x	x	x	x			
Natural Experiement with toolkit (aim 4)															x	x	x	x	x	x
Additional organizational stakeholder interviews																		x	x	x
Manuscript development and publication									x						x			x	x	x
External Advisory Panel meetings		x		x		x		x		x		x		x		x		x		x

C.9. Dissemination of study results.

The assembled study team will enable broad dissemination of study results and increase the significance of this work. Dr. Williams and Dr. Mittman are established national leaders in the area of translating genomics into clinical practice and will help identify opportunities for broad dissemination of study results. Through the HCSRN, CRN, and LSSN Dr. Rahm and her collaborators can reach additional healthcare systems to facilitate LS screening implementation. The organizational toolkit will be posted on the LSSN

website, making this model available to healthcare organizations nationally and internationally. Dr. Baxter of the External Advisory Group will be able to utilize the toolkit to further guide her work implementing LS screening in Ontario. Furthermore, collaborations have been initiated by Dr. Rahm and other study team members to disseminate results of this study through other networks, including CSER (Clinical Sequencing Exploratory Research), eMERGE (Electronic Medical Records and Genomics) and IGNITE (Implementing Genomics in Practice) networks. All three networks have prioritized LS screening for implementation.

Finally, through the new Precision Medicine Initiative more genomic applications with evidence for improving population will emerge. Now more than ever, a flexible organizational toolkit to guide efficient and effective implementation, evaluation, maintenance, and improvement of genomic applications is needed. **This research will create an organizational toolkit that addresses a major unmet need identified by the Blue Ribbon Panel to achieve the goals of the Cancer Moonshot; thus improving our understanding of clinical implementation of complex interventions and fulfilling the promise of precision medicine to improve health and prevent disease**.

References

1. Collins FS, Varmus H. A new initiative on precision medicine. The New England journal of medicine. Feb 26 2015;372(9):793-795.
2. Palomaki GE, McClain MR, Melillo S, Hampel HL, Thibodeau SN. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. Genetics in medicine : official journal of the American College of Medical Genetics. Jan 2009;11(1):42- 65.
3. Healthy People 2020. 2014; https://www.healthypeople.gov/2020/topics-objectives/topic/genomics/objectives. Accessed 1/22/2016.
4. Cancer Moonshot Blue Ribbon Panel Report 2016. National Cancer Institute 10/17/2016 2016.
5. Hampel H, de la Chapelle A. The search for unaffected individuals with Lynch syndrome: do the ends justify the means? Cancer prevention research (Philadelphia, Pa.). Jan 2011;4(1):1-5.
6. Mvundura M, Grosse SD, Hampel H, Palomaki GE. The cost-effectiveness of genetic testing strategies for Lynch syndrome among newly diagnosed patients with colorectal cancer. Genetics in medicine : official journal of the American College of Medical Genetics. Feb 2010;12(2):93-104.
7. Ladabaum U, Wang G, Terdiman J, et al. Strategies to identify the Lynch syndrome among patients with colorectal cancer: a cost-effectiveness analysis. Ann Intern Med. Jul 19 2011;155(2):69-79.
8. Khoury MJ, Coates RJ, Evans JP. Evidence-based classification of recommendations on use of genomic tests in clinical practice: dealing with insufficient evidence. Genetics in medicine : official journal of the American College of Medical Genetics. Nov 2010;12(11):680-683.
9. CDC. Genetic Testing: Genomic Tests and Family Health History by Levels of Evidence. 2105; http://www.cdc.gov/genomics/gtesting/tier.htm. Accessed 1/22/2016.
10. Williams MS. Genomic medicine implementation: learning by example. American journal of medical genetics. Part C, Seminars in medical genetics. Mar 2014;166c(1):8-14.
11. IOM. Crossing the Quality Chasm: A New Health System for the 21st Century. Washington, DC: National Academy Press: http://www.nap.edu/catalog/10027/crossing-the-quality-chasm-a-new-health-system-for-the. Accessed 1/22/2016.
12. Williams MS. Perspectives on what is needed to implement genomic medicine. Molecular genetics & genomic medicine. May 2015;3(3):155-159.
13. Wade JE, Ledbetter DH, Williams MS. Implementation of genomic medicine in a health care delivery system: a value proposition? American journal of medical genetics. Part C, Seminars in medical genetics. Mar 2014;166c(1):112-116.
14. Snyder SR, Mitropoulou C, Patrinos GP, Williams MS. Economic evaluation of pharmacogenomics: a value-based approach to pragmatic decision making in the face of complexity. Public Health Genomics. 2014;17(5-6):256-264.
15. Khoury MJ, Coates RJ, Fennell ML, et al. Multilevel research and the challenges of implementing genomic medicine. Journal of the National Cancer Institute. Monographs. May 2012;2012(44):112-120.
16. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implementation science : IS. 2009;4:50.
17. Eccles MP, Armstrong D, Baker R, et al. An implementation research agenda. Implementation science : IS. 2009;4:18.
18. Williams M. Delivery of Personalized Medicine in an Integrated Healthcare System. In: Ginsburg GS; Willard HF, ed. Genomic and Personalized Medicine. 2nd ed. New York: Elsevier Inc; 2013:340-352.
19. Damschroder LJ, Lowery JC. Evaluation of a large-scale weight management program using the consolidated framework for implementation research (CFIR). Implementation science : IS. 2013;8:51.
20. Kahwati LC, Lewis MA, Kane H, et al. Best practices in the Veterans Health Administration's MOVE! Weight management program. American journal of preventive medicine. Nov 2011;41(5):457-464.
21. Cragun D, Pal T, Vadaparampil ST, Baldwin J, Hampel H, DeBate RD. Qualitative Comparative Analysis: A Hybrid Method for Identifying Factors Associated With Program Effectiveness. Journal of Mixed Methods

Research. February 25, 2015 2015.
22. Cragun D, DeBate RD, Vadaparampil ST, Baldwin J, Hampel H, Pal T. Comparing universal Lynch syndrome tumor-screening programs to evaluate associations between implementation strategies and patient follow-through. Genetics in medicine : official journal of the American College of Medical Genetics. Oct 2014;16(10):773-782.
23. Devers KJL, Nicole Cafarella; Burton, Rachel A; Kahwati, Leila; McCall, Nancy; Zuckerman, Stephen. Using Qualitative Comparative Analysis (QCA) to Study Patient-Centered Medical Homes. 2013. https://innovation.cms.gov/Files/reports/QCA-Report.pdf. Accessed 1/22/2016.
24. Berg-Schlosser DDM, Gisele; Rihoux, Benoit; Ragin, Charles C;. Qualitative Comparative Analysis (QCA) as an Approach In: Ragin BRCC, ed. Configurational Comparative Methods: Qualitative Comparative Analysis (QCA) and Related Techniques Thousand Oaks, CA: Sage Publications, Inc; 2009.
25. Mittman B. Implementation Science in Health Care. In: Brownson RC CG, Proctor EK, ed. Dissemination and Implementation Research in Health. New York: Oxford University Press; 2012:400- 418.
26. Schully SD, Khoury MJ. What is translational genomics? An expanded research agenda for improving individual and population health. Applied & translational genomics. Dec 2014;3(4):82-83.
27. Bellcross CA, Bedrosian SR, Daniels E, et al. Implementing screening for Lynch syndrome among patients with newly diagnosed colorectal cancer: summary of a public health/clinical collaborative meeting. Genetics in medicine : official journal of the American College of Medical Genetics. Jan 2012;14(1):152-162.
28. Gudgeon JM, Belnap TW, Williams JL, Williams MS. Impact of Age Cutoffs on a Lynch Syndrome Screening Program. Journal of Oncology Practice. July 1, 2013 2013;9(4):175-179.
29. Gudgeon JM, Williams JL, Burt RW, Samowitz WS, Snow GL, Williams MS. Lynch syndrome screening implementation: business analysis by a healthcare system. The American journal of managed care. 2011;17(8):e288-300.
30. Colorectal Cancer Facts & Figures 2014-2016. 2014. http://www.cancer.org/acs/groups/content/documents/document/acspc-042280.pdf. Accessed 1/30/2016.
31. Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on Genetic Evaluation and Management of Lynch Syndrome: A Consensus Statement by the US Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol. 08//print 2014;109(8):1159-1179.
32. Lynch HT, Snyder CL, Shaw TG, Heinen CD, Hitchins MP. Milestones of Lynch syndrome: 1895-2015. Nature reviews. Cancer. Mar 2015;15(3):181-194.
33. Grosse SD, Palomaki GE, Mvundura M, Hampel H. The cost-effectiveness of routine testing for Lynch syndrome in newly diagnosed patients with colorectal cancer in the United States: corrected estimates. Genetics in medicine : official journal of the American College of Medical Genetics. Jun 2015;17(6):510-511.
34. Cross DS, Rahm AK, Kauffman TL, et al. Underutilization of Lynch syndrome screening in a multisite study of patients with colorectal cancer. Genetics in medicine : official journal of the American College of Medical Genetics. 12//print 2013;15(12):933-940.
35. Pasche B, Pennison MJ, DeYoung B. Lynch Syndrome Testing: A Missed Opportunity in the Era of Precision Medicine. Jama. Jul 5 2016;316(1):38-39.
36. Jarvinen HJ, Aarnio M, Mustonen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology. May 2000;118(5):829-834.
37. Jarvinen HJ, Renkonen-Sinisalo L, Aktan-Collan K, Peltomaki P, Aaltonen LA, Mecklin JP. Ten years after mutation testing for Lynch syndrome: cancer incidence and outcome in mutation-positive and mutation-negative family members. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Oct 1 2009;27(28):4793-4797.
38. de Jong AE, Hendriks YM, Kleibeuker JH, et al. Decrease in mortality in Lynch syndrome families because of surveillance. Gastroenterology. Mar 2006;130(3):665-671.
39. Stupart DA, Goldberg PA, Algar U, Ramesar R. Surveillance colonoscopy improves survival in a cohort of subjects with a single mismatch repair gene mutation. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. Feb 2009;11(2):126-130.
40. Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in

the Lynch syndrome. The New England journal of medicine. Jan 19 2006;354(3):261-269.
41. Moreira L, Balaguer F, Lindor N, et al. Identification of Lynch syndrome among patients with colorectal cancer. Jama. Oct 17 2012;308(15):1555-1565.
42. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. Genetics in medicine : official journal of the American College of Medical Genetics. Jan 2009;11(1):35-41.
43. Rubenstein JH, Enns R, Heidelbaugh J, Barkun A. American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Lynch Syndrome. Gastroenterology. Sep 2015;149(3):777-782; quiz e716-777.
44. Stoffel EM, Mangu PB, Gruber SB, et al. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology Clinical Practice Guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology Clinical Practice Guidelines. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Jan 10 2015;33(2):209-217.
45. Balmana J, Balaguer F, Cervantes A, Arnold D. Familial risk-colorectal cancer: ESMO Clinical Practice Guidelines. Annals of oncology : official journal of the European Society for Medical Oncology. Oct 2013;24 Suppl 6:vi73-80.
46. Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. Feb 2015;110(2):223-262; quiz 263.
47. Weissman SM, Burt R, Church J, et al. Identification of individuals at risk for Lynch syndrome using targeted evaluations and genetic testing: National Society of Genetic Counselors and the Collaborative Group of the Americas on Inherited Colorectal Cancer joint practice guideline. Journal of genetic counseling. Aug 2012;21(4):484-493.
48. NCCN. Clinical Practice Guidelines in Oncology - Genetic/Familial High-Risk Assessment: Colorectal. 2015; Version 2.2015. Available at: http://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf. Accessed 1/22/2016.
49. Pai RK, Pai RK. A Practical Approach to the Evaluation of Gastrointestinal Tract Carcinomas for Lynch Syndrome. The American journal of surgical pathology. Apr 2016;40(4):e17-34.
50. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. The New England journal of medicine. Jun 25 2015;372(26):2509-2520.
51. McCann GA, Eisenhauer EL. Hereditary cancer syndromes with high risk of endometrial and ovarian cancer: surgical options for personalized care. Journal of surgical oncology. Jan 2015;111(1):118-124.
52. Coates R, Williams M, Melillo S, Gudgeon J. Genetic testing for lynch syndrome in individuals newly diagnosed with colorectal cancer to reduce morbidity and mortality from colorectal cancer in their relatives. PLoS currents. 2011;3:Rrn1246.
53. Hampel H. Genetic counseling and cascade genetic testing in Lynch syndrome. Familial cancer. Jul 2016;15(3):423-427.
54. Heald B, Plesec T, Liu X, et al. Implementation of Universal Microsatellite Instability and Immunohistochemistry Screening for Diagnosing Lynch Syndrome in a Large Academic Medical Center. Journal of Clinical Oncology. April 1, 2013 2013;31(10):1336-1340.
55. Frolova AI, Babb SA, Zantow E, et al. Impact of an immunohistochemistry-based universal screening protocol for Lynch syndrome in endometrial cancer on genetic counseling and testing. Gynecol Oncol. Apr 2015;137(1):7-13.
56. Corinne Daly CR, Marcia Facey, Natalie A. Baker, Nancy N. Baxter. Reflex Lynch syndrome screening by example: A review of existing programs. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(suppl 3):abstr 543.
57. Cohen SA. Current Lynch syndrome tumor screening practices: a survey of genetic counselors. Journal of genetic counseling. Feb 2014;23(1):38-47.
58. Beamer LC, Grant ML, Espenschied CR, et al. Reflex immunohistochemistry and microsatellite instability testing of colorectal tumors for Lynch syndrome among US cancer programs and follow-up of abnormal

results. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Apr 1 2012;30(10):1058-1063.
59. Ellis P, Robinson P, Ciliska D, et al. A systematic review of studies evaluating diffusion and dissemination of selected cancer control interventions. Health psychology : official journal of the Division of Health Psychology, American Psychological Association. Sep 2005;24(5):488-500.
60. Sculpher MJ, Pang FS, Manca A, et al. Generalisability in economic evaluation studies in healthcare: a review and case studies. Health technology assessment (Winchester, England). Dec 2004;8(49):iii-iv, 1-192.
61. Schlander M. The use of cost-effectiveness by the National Institute for Health and Clinical Excellence (NICE): no(t yet an) exemplar of a deliberative process. J Med Ethics. Jul 2008;34(7):534-539.
62. The Precision Medicine Initiative. 2015; https://www.whitehouse.gov/precision-medicine. Accessed 1/30/2016.
63. National Academies of Sciences E, and Medicine. Applying an implementation science approach to genomic medicine: Workshop summary. Washington, DC: The National Academies Press; 2016.
64. Mills AM, Liou S, Ford JM, Berek JS, Pai RK, Longacre TA. Lynch syndrome screening should be considered for all patients with newly diagnosed endometrial cancer. The American journal of surgical pathology. Nov 2014;38(11):1501-1509.
65. Moline J, Mahdi H, Yang B, et al. Implementation of tumor testing for lynch syndrome in endometrial cancers at a large academic medical center. Gynecologic Oncology. 7// 2013;130(1):121-126.
66. Mange S, Bellcross C, Cragun D, et al. Creation of a network to promote universal screening for Lynch syndrome: the LynchSyndrome Screening Network. Journal of genetic counseling. Jun 2015;24(3):421-427.
67. Goodfellow PJ, Billingsley CC, Lankes HA, et al. Combined Microsatellite Instability, MLH1 Methylation Analysis, and Immunohistochemistry for Lynch Syndrome Screening in Endometrial Cancers From GOG210: An NRG Oncology and Gynecologic Oncology Group Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Dec 20 2015;33(36):4301-4308.
68. Rahm AK, Kip NS, Williams JL, et al. Coordinating Laboratory and Clinical Data to Include Endometrial Tumor Testing in the Universal Lynch Syndrome Screening Program at Geisinger Health System. National Society of Genetic Counselors Annual Education Conference; 2015; Pittsburgh, PA.
69. Meyer LA, Broaddus RR, Lu KH. Endometrial cancer and Lynch syndrome: clinical and pathologic considerations. Cancer control : journal of the Moffitt Cancer Center. Jan 2009;16(1):14-22.
70. Schneider JL, Davis J, Kauffman TL, et al. Stakeholder perspectives on implementing a universal Lynch syndrome screening program: a qualitative study of early barriers and facilitators. Genetics in medicine : official journal of the American College of Medical Genetics. 04/16/online 2015.
71. Hunter JE, Zepp JM, Gilmore MJ, et al. Universal tumor screening for lynch syndrome: Assessment of the perspectives of patients with colorectal cancer regarding benefits and barriers. Cancer. 2015:n/a- n/a.
72. CFIR Technical Assistance Website. http://cfirguide.org/. Accessed 1/30/2016.
73. Schofield L, Grieu F, Goldblatt J, Amanuel B, Iacopetta B. A state-wide population-based program for detection of lynch syndrome based upon immunohistochemical and molecular testing of colorectal tumours. Familial cancer. Mar 2012;11(1):1-6.
74. Yano EM, Green LW, Glanz K, et al. Implementation and spread of interventions into the multilevel context of routine practice and policy: implications for the cancer care continuum. Journal of the National Cancer Institute. Monographs. May 2012;2012(44):86-99.
75. Hamilton AB, Oishi S, Yano EM, Gammage CE, Marshall NJ, Scheuner MT. Factors influencing organizational adoption and implementation of clinical genetic services. Genetics in medicine : official journal of the American College of Medical Genetics. Mar 2014;16(3):238-245.
76. Rahm AK, Boggs JM, Martin C, et al. Facilitators and Barriers to Implementing SBIRT in Primary Care in Integrated Health Care Settings. Substance abuse : official publication of the Association for Medical Education and Research in Substance Abuse. Aug 15 2014:0.
77. Boggs JM RA, Martin CR, Beck A, Price DW, Backer TE, Gunter M, Ahmedani BK, Dearing JW. Feasibility of Implementing Screening Brief Intervention and Referral to Treatment (SBIRT) within Multiple Healthcare

Settings. 19th Annual HMO Research Network Conference; 2013; San Francisco, CA
78. Rahm AK BJ, Martin CR, Beck A, Pearson M, Backer TE, Ahmedani BK. Systematic Stakeholder Assessment to Determine Facilitators of and Barriers to SBIRT Implementation in Multiple Integrated Health Systems. 20th Annual HMO Research Network Conference; 2014; Pheonix, AZ.
79. Harris JN, Liljestrand P, Alexander GL, et al. Oncologists' attitudes toward KRAS testing: a multisite study. Cancer medicine. Dec 2013;2(6):881-888.
80. Frazier LM, Miller VA, Horbelt DV, Delmore JE, Miller BE, Paschal AM. Comparison of focus groups on cancer and employment conducted face to face or by telephone. Qualitative health research. May 2010;20(5):617-627.
81. Beebe J. Rapid Assessment Process: An Introduction. Walnut Creek, CA AltaMira Press 2001.
82. Padgett DK. Qualitative and Mixed Methods in Public Health. Thousand Oaks, CA: Sage; 2012.
83. Rahm A, Hawkins R, Dearing J, et al. Implementing an evidence-based breast cancer support and communication tool to newly diagnosed patients as standard care in two institutions. Translational behavioral medicine. 2015/06/01 2015;5(2):198-206.
84. Rahm AK, Kip NS, Williams JL, et al. Implementing Genomic Medicine in an Integrated Healthcare System: Evaluation and Improvement of a Universal Lynch Syndrome Screening Program. Dissemination and Implementation Conference; 2015; Washington, DC.
85. Rahm AK, Kip NS, Williams JL, et al. Evaluation and Optimization of a Universal Lynch Syndrome Screening Program at Geisinger Health System. American Society of Human Genetics Annual Meeting; 2015; Baltimore, MD.
86. Kip NS, Rahm AK, Williams JL, et al. Evaluation to Include Endometrial Carcinoma in Universal Lynch Syndrome Screening at Geisinger Health System. American Society for Clinical Pathology Annual Meeting 2015; Long Beach, CA.