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Universal Tumor Screening for Lynch Syndrome: Identification of system-level implementation factors influencing patient reach

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Universal Tumor Screening for Lynch Syndrome: Identification of system-level implementation factors influencing patient reach

by

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DEDICATION

I dedicate this dissertation to my family members, friends, and mentors who have helped me in my long and winding journey to forge a career path. I would also like to dedicate this work to the many families with Lynch syndrome who have lost loved ones to cancer. My hope is that in the near future all individuals with Lynch syndrome will be identified early and have access to appropriate screening so as to reduce associated morbidity and mortality.

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ABSTRACT

Lynch syndrome (LS) is the most prevalent cause of hereditary colorectal cancer (CRC) and confers high risks for several other types of cancer. Universal tumor screening (UTS) of all newly diagnosed patients with CRC can improve LS identification and decrease associated morbidity and mortality among patients and family members. However, for UTS to be effective, patients who screen positive must pursue genetic counseling and confirmatory germline testing (i.e., high patient reach). The purposes of this study were to characterize UTS programs, identify barriers and facilitators to implementation, document whether there have been negative outcomes, and determine institutional and implementation conditions that are associated with high and low patient reach.

Using two conceptual frameworks, RE-AIM and Consolidated Framework for Implementation Research, a baseline survey was conducted of 25 representatives from different institutions performing UTS. Descriptive statistics were used to illustrate similarities and differences among programs. A multiple-case study was then conducted by extracting data from surveys and interviews of representatives from 15 different institutions where UTS programs had been operational for over 6 months and where aggregated patient outcome data were available. Qualitative comparative analysis was performed to make systematic cross-case comparisons and identify conditions uniquely associated with high or low patient reach. Data were triangulated to create models explaining how UTS

implementation and system-level factors influence patient reach.

Few patient concerns or negative outcomes were reported. UTS procedures and patient reach were highly variable. All 5 high-reach (H-R) centers have genetics professionals disclose positive screening results and either do not require a referral from another health care provider or have streamlined the referral process. Although 2 of the 5 mid-reach (M-R) centers also share these conditions, they have a less automated follow-up procedure and report difficulty contacting patients as a barrier. Both of the academic institutions with low patient reach (L-R) did not receive patient information that would allow them to follow-up on positive screening results. The three non-academic L-R institutions reported a high proportion of challenges to facilitators during implementation and did not have genetic professionals disclose positive screening results to patients.

Implementing a combination of procedures to streamline UTS protocols and procedures, eliminate barriers to patient follow-through after a positive tumor screen, and incorporate a high level of involvement of genetic professionals in contacting patients and disclosing screening results are expected to lead to improvement in patient reach.

SECTION I: INTRODUCTION

Background and Significance

Colorectal cancer (CRC) is the third most common type of cancer and third leading cause of cancer-related death in the United States (U.S.) ("Colorectal Cancer Facts & Figures 2011-2013,"). Lynch syndrome (LS) is the most prevalent cause of hereditary CRC, occurring in 1 out of every 35 CRC patients (Hampel et al., 2008). Several retrospective studies have found that LS confers a 50-70% lifetime risk of CRC (Barrow et al., 2008; Hampel et al., 2005; Stoffel et al., 2009), a 40-60% chance of endometrial cancer in females (Barrow et al., 2009; Hampel et al., 2005; Stoffel et al., 2009), and increased risks for several other malignancies including cancers of the ovary, stomach, small intestine, hepatobiliary tract, urinary tract, brain, and skin (Barrow et al., 2009; Watson et al., 2008). The first prospective study confirmed prior retrospective study findings and also found pancreatic cancer and female breast cancer risks are increased among LS carriers (Win et al., 2012).

Diagnosing LS alters cancer surveillance recommendations for patients with CRC (due to high risks for secondary cancers) and provides the opportunity to prevent cancer among patients' at-risk relatives through increased cancer screening and/or surgical prevention options (Järvinen et al., 2009; Schmeler et al., 2006; Stupart, Goldberg, Algar, & Ramesar, 2009; Vasen et al., 2010). The public health significance of diagnosing LS is acknowledged in the following

provisional Healthy People (HP) 2020 Genomics Objective: *"Increase the proportion of persons with newly diagnosed colorectal cancer [CRC] who receive genetic testing to identify Lynch syndrome (or familial CRC* syndromes)" ("Genomics - Healthy People,").

Despite the public health significance of diagnosing LS, 28% to 70% of CRC patients who have LS remain unidentified when screening is limited to tumors from patients who meet certain age or family history criteria (Hampel et al., 2008; Morrison et al., 2011; Tranø, Sjursen, Wasmuth, Hofsli, & Vatten, 2010; van Lier et al., 2011). Universal screening of tumors from all newly diagnosed patients with CRC has the potential to improve the identification of LS. Several studies have demonstrated the feasibility, efficacy, and theoretical cost-effectiveness of universal tumor screening (UTS) for LS (Gudgeon et al., 2011; Hampel et al., 2008; Ladabaum et al., 2011; Morrison et al., 2011; Mvundura, Grosse, Hampel, & Palomaki, 2010; Tranø et al., 2010). Nevertheless, the impact that universal genetic screening policies will have on institutions or individuals is largely uncertain as UTS for LS is the first universal screening to be implemented for the purpose of detecting hereditary disease in adults.

Currently, in the United States, at least 35 cancer centers or hospitals are performing UTS for LS, with wide institutional variability in terms of the following: a) tumor screening methodology (i.e., IHC, MSI, with or without automatic reflex testing via hypermethylation or BRAF); b) whether explicit informed consent is obtained or an option to "opt out" is presented; c) what types of information are provided to the patients; d) who is responsible for follow-up with positive

(abnormal) screens; and e) how patients are given results (Beamer et al., 2012; Cohen, 2013). In addition, the percentage of patients with a positive screen who follow-through with genetic counseling and testing (i.e., patient reach) is highly variable, differing by more than 50% across cancer centers for which data has been published (Heald et al., 2013; Lynch, 2011; South et al., 2009).

Potential risks of UTS for LS are believed to be minimal (Hampel, 2010). However, in several studies that occurred prior to UTS implementation, patients with CRC expressed concern that genetic testing for hereditary CRC may lead to adverse psychological outcomes for themselves or their family members (Kinney et al., 2000; Kinney, DeVellis, Skrzynia, & Millikan, 2001; Lerman, Marshall, Audrain, & Gomez-Caminero, 1996; Ramsey, Wilson, Spencer, Geidzinska, & Newcomb, 2003). Patients with CRC have also expressed concerns about costs associated with genetic testing (Cragun, Malo, Pal, Shibata, & Vadaparampil, 2012; Kinney et al., 2001; Ramsey et al., 2003).

Recognizing the need to pool Lynch syndrome tumor screening resources and to track outcomes, several institutions came together in September of 2011 to form the Lynch Syndrome Screening Network (LSSN). Since the initial meeting, the LSSN has grown to include approximately 91 institutions across the United States; however, as of June 2012, only 35 of these institutional members were known to be performing routine screening for LS on tumors from all newly diagnosed CRC patients. To meet the needs of the many centers that are still trying to implement UTS, the LSSN has already created a website that houses tumor screening resources (www.lynchscreening.net). However, information

about keys to successful implementation, “best practices”, and ways to overcome barriers is lacking from the website.

Three centers have previously reported aggregated patient data showing the percentage of patients who follow through with genetic counseling and germline genetic testing after a positive screen (i.e., patient reach) varies by over 50% (Lynch, 2011; South et al., 2009; Heald et. al, 2013). Two of these centers have also published or presented prospective data suggesting that changes in their protocol and follow-up procedures have improved patient reach (Hampel et. al, 2012; Heald et. al, 2013). However, further research into 'real-world' implementation is needed to assess cost effectiveness as well as unanticipated consequences or negative patient outcomes. Furthermore, determining how implementation and system-level factors influence patient reach can help identify 'best practices' that can be used to maximize the effectiveness of UTS programs in order to justify the development of infrastructure and cost required for UTS implementation on a national level.

This research is significant to public health because programs that automatically screen tumors from all newly diagnosed CRC patients have the potential to identify the 28% to 70% of CRC patients with LS who are missed using common practices of limiting screening to those who fulfill certain age (<50 years) or medical/family history criteria (Hampel et al., 2008; Morrison et al., 2011; Tranø et al., 2010; van Lier et al., 2011). This allows for the prevention or early detection of secondary cancers among patients and provides an opportunity to diagnose family members who have LS in order to prevent

associated morbidity and mortality. UTS also has the potential to improve the identification of LS among ethnic minorities who are currently less likely to be identified and/or referred for genetic counseling and testing for hereditary cancer (Hall & Olopade, 2006; Kupfer, McCaffrey, & Kim, 2006; Shields, Burke, & Levy, 2008).

Study Purpose and Objectives

The long-term goal of this ongoing line of research is to improve the ability of universal tumor screening programs (UTS) programs to achieve the Healthy People 2020 provisional objective: “Increase the proportion of persons with newly diagnosed CRC who receive genetic testing to identify Lynch syndrome” (“Genomics - Healthy People”.) and thereby reduce the morbidity and mortality associated with hereditary cancer. The objectives of the current study were: 1) to compare current UTS screening programs at U.S. institutions (i.e., hospitals and cancer centers); 2) compile a list of “lessons learned” during implementation; 3) document any negative outcomes; and 4) determine “best UTS practices”.

Theoretical Frameworks, Research Questions, and Hypothesis

The RE-AIM evaluation framework ("DCCPS: Cancer Control Research: Implementation Science: RE-AIM," ; Glasgow, Klesges, Dzewaltowski, Estabrooks, & Vogt, 2006; Glasgow, Nelson, Strycker, & King, 2006; Glasgow, Vogt, & Boles, 1999) and constructs from the Consolidated Framework for Implementation Research (CFIR) (Damschroder et al., 2009; Damschroder & Hagedorn, 2011) were used to meet the aforementioned objectives and answer research questions listed in Table I-1. The goal of RE-AIM is to enhance the

quality, speed, and impact of efforts to translate research into practice in a manner that considers both internal and external validity ("DCCPS: Cancer Control Research: Implementation Science: RE-AIM," n.d.; Glasgow et al., 1999). RE-AIM aids in evaluating programs by assessing the following dimensions that may impact generalizability of findings: *Reach, Effectiveness, Adoption, Implementation*, and *Maintenance* (see Table I-1 for dimension descriptions). In the current study, RE-AIM was used to identify patient *Reach* (i.e., the proportion of patients with an abnormal screen who follow-through with genetic counseling and germline testing), real-world *Effectiveness* (i.e., unanticipated consequences / negative outcomes of UTS), reasons for UTS program *Adoption*, differences in program *Implementation*, and the extent to which programs have changed (i.e., *Maintenance*).

The Consolidated Framework for Implementation Research (CFIR) aided in identifying key system-level and implementation factors related to UTS. The CFIR was developed in 2009 to open the black box of the *Implementation* dimension in RE-AIM and aids in research planning by consolidating constructs from various implementation theories and an established evidence base spanning multiple scientific disciplines (Damschroder et al., 2009). These constructs are organized into five domains described in Table I-2. Various constructs were selected for inclusion in the CFIR based on their perceived relevance in a variety of health care contexts and research demonstrating that they are related to the adoption, implementation, and/or effectiveness of

evidence-based recommendations (Damschroder et al., 2009). Table I-2 lists constructs from the CFIR and provides a brief description of each.

A number of CFIR constructs come from *Diffusion of Innovations,* which is a theoretical framework explaining how and why new ideas, practices, or technologies (i.e., innovations) are communicated through channels over time (Rogers, 2003). *Diffusion of Innovations* is primarily used to explain factors associated with decisions to adopt, implement, maintain, and sustain innovations (Glanz, 2008; Rogers, 2003). Research guided by *Diffusion of Innovations* has provided a number of valuable insights, including a recognition regarding "...the importance of achieving a good fit between the attributes of an innovation, the adopting individual or organization, and the environment or context where the process takes place" (Glanz et al., 2008; p. 330).

Ironically, this insight also highlights some acknowledged criticisms of diffusion research, including a "tendency to hold individuals responsible for their problems, rather than the system of which the individual is a part" (Glanz et al., 2008; p.329) and limitations in the ability of *Diffusion of Innovations* to contribute to an understanding of the complex organizations where innovation adoption decisions often take place (Glanz et al., 2008). The CFIR addresses these concerns through its focus on institutions as important units of analysis and its inclusion of a number of constructs specific to organizations. These additional constructs can be used to explore how organizational characteristics or system-level factors may influence adoption, implementation processes, and

effectiveness of innovations. Additionally, the CFIR includes constructs specific to the implementation process itself, and thereby allows exploration into how aspects of this process may increase or reduce the chance for successful outcomes that result from innovation implementation. CFIR developers never intended for all constructs to be utilized in any single study (Damschroder et al., 2009; Damschroder & Hagedorn, 2011). As such, a subset of constructs (i.e., contextual factors) from the CFIR that were hypothesized to play a role in implementation and effectiveness of LS UTS programs were used to develop questions for the surveys and interview guides. Table I-3 lists outcomes used to define successful UTS programs as well as conditions that might influence these outcomes.

Subsequently, the central hypothesis for the current study was that high patient *Reach* and few unanticipated or negative outcomes occur among UTS programs that possess one or more combinations of the following contextual factors: 1) streamlined UTS procedures (i.e., fewer steps need to be taken by patients in order to follow-up with genetic counseling and germline testing or patients can have genetic counseling at the same time or in the same location as other follow-up appointments); 2) direct involvement of genetic professionals in patient follow-up; 3) high quality communication among specialists (based on self-reported ratings by the primary contact and others involved with UTS at each institution); 4) consideration of patient needs and resources; 5) positive implementation climate (i.e., ratings of the extent to which UTS is rewarded,

supported, and expected within the institution) (Klein & Sorra, 1996); 6) high level of implementation readiness (based on ratings of how open the institution is to new initiatives and how much planning was done prior to implementation); and 7) positive attitudes toward LS UTS among key personnel who serve in administrative positions or are directly involved with UTS. The central study hypothesis was tested by employing a multiple-case study and qualitative comparative analysis (QCA) of data from several UTS programs.

Dissertation Organization

This dissertation includes two manuscripts that will eventually be submitted to peer-reviewed journals. The first manuscript presents the main findings of the current study within the RE-AIM framework (Section II). The purpose of the second manuscript (Section III) is to disseminate information on the utility of Qualitative Comparative Analysis in mixed methods research. To this end, the second manuscript includes: 1) findings from systematic reviews in Pub Med and the *Journal of Mixed Methods Research* illustrating the slow rate of diffusion of Qualitative Comparative Analysis (QCA) into health research and limited adoption among mixed-methods researchers; 2) a practical illustration of how to apply this hybrid technique using data from the multiple-case study; and 3) advantages and limitations to QCA. Section IV of this dissertation concludes with an overall summary, study implications, future directions, and a description of additional manuscripts that are planned after the submission of this dissertation.

Table I-1. Applying the RE-AIM Framework and Consolidated Framework for Implementation Research (CFIR) to Evaluate Lynch Syndrome Universal Tumor Screening (LS UTS) Programs

RE-AIM Dimension	Research Questions	Relevant CFIR Domains (see Table I-2)
Reach Absolute number, proportion, and representativeness of individuals who participate.	• What proportion of patients who screen positive follow-through with genetic counseling and germline testing at each respective institution?	• NA
Efficacy / effectiveness The impact of an intervention on outcomes (including potential negative effects).	• Have there been any unexpected outcomes or negative effects associated with UTS implementation?	• NA
Adoption Absolute number, proportion, and representativeness of settings and staff who currently offer a program. Characteristics of the intervention may increase the likelihood of adoption.	• What led to the adoption of UTS? • Who was involved in making the decision to adopt UTS? • What characteristics of the centers/institutions may increase the likelihood of adopting UTS? • What characteristics of UTS (e.g., compatibility, complexity) relate to the decision to adopt it?	• Individuals involved • Inner setting, Outer setting • Intervention characteristics
Implementation Consistency of delivery, time and cost of the program, and what adaptations to the program are made in various settings.	• Describe those involved in implementation. Were they the same as those who decided to adopt UTS? • What impact did key individuals have on implementation? • How was screening implemented (what was involved in planning & initiation)? • What challenges had to be overcome when implementing screening? • What is the institution's screening protocol? • Does implementation vary based on characteristics of the protocol chosen, institution, or individuals?	• Individuals involved • Implementation Process • Intervention (protocol) characteristics, Inner setting, Outer setting, Individuals involved
Maintenance How the intervention and its effects change over time.	What changes have been made to UTS programs over time?	• Individuals • Inner & Outer setting • Intervention characteristics

Table I-2. Domains and Constructs of the Consolidated Framework for Implementation Research (CFIR)

CFIR *Domains* and Constructs	Description
Intervention -- Characteristics of the intervention such as complexity, cost, and relative advantage that influence adoption, implementation, etc.	
Intervention source	Perception of key stakeholders about whether the intervention is externally or internally developed to solve a local problem and the legitimacy of the source (Greenhalgh, Robert, Macfarlane, Bate, & Kyriakidou, 2004). Externally developed interventions and lack of user input can lead to ineffective implementation (Helfrich, Weiner, McKinney, & Minasian, 2007; Kitson et al., 2008; Klein, Conn, & Sorra, 2001).
Evidence strength and quality	Stakeholder's perceptions of the quality and validity of evidence that the intervention will have desired outcomes (Fitzgerald, Ferlie, & Hawkins, 2003). Although evidence to support the intervention is important and can increase the likelihood that it will be adopted (Kitson et al., 2008), evidence is typically not sufficient to ensure adoption, nor is it always a primary consideration when deciding whether to adopt an innovation (Denis, Hébert, Langley, Lozeau, & Trottier, 2002; Fitzgerald et al., 2003).
Relative advantage	Stakeholder beliefs about the benefits of UTS compared with the status quo or an alternative (Rogers, 2003). Relative advantage and observability are constructs from Diffusion of Innovations (Rogers, 2003). They are combined because benefits, if visible to the stakeholders, aid adoption and implementation (Denis et al., 2002; Feldstein & Glasgow, 2008; Greenhalgh et al., 2004; Grol & Grimshaw, 2003; Grol, Bosch, Hulscher, Eccles, & Wensing, 2007).
Adaptability	Perceptions about whether and how an intervention can be tailored to meet specific needs or characteristics of an institution (Rogers, 2003). There are generally 'core components' that are necessary elements of the intervention and an 'adaptable periphery' (Greenhalgh et al., 2004). According to Diffusion of Innovations, programs that can easily be modified to are more likely to be adopted (Rogers, 2003).
Trialability	Ability to test an intervention on a small scale and reverse implementation if warranted (Rogers, 2003). According to Diffusion of Innovations, trialability has a strong positive association with adoption (Greenhalgh et al., 2004; Rogers, 2003). It also increases the likelihood of effective implementation because piloting provides experience that can be used to improve full scale implementation (Kitson et al., 2008)
Complexity	Perceived difficulty of implementation (duration, scope, radicalness, disruptiveness, centrality and number of steps required) (Rogers, 2003). According to Diffusion of Innovations complexity plays a critical role in the decision to adopt an innovation. In addition, simple interventions are more likely to be effective (Greenhalgh et al., 2004). Assessing complexity can also help in understanding and avoiding unintended consequences (Kochevar & Yano, 2006).
Design quality and packaging	Perceived excellence in how the intervention is presented/assembled (Grol et al., 2007). When the quality of the intervention is perceived to be poor, it can evoke negative attitudes among users and decrease intervention use and effectiveness (Grol et al., 2007; Helfrich et al., 2007; K J Klein, Conn, & Sorra, 2001).

Table I-2 (continued).

Costs	Costs of the intervention as well as implementation costs (Rogers, 2003). Cost is a characteristic from Diffusion of Innovations and is negatively associated with adoption (Rogers, 2003; Teplensky, Pauly, Kimberly, Hillman, & Schwartz, 1995). Cost is also likely to influence how the intervention is implemented and its overall effectiveness.
Outer setting - Economic, political, and social context in which an organization resides.	
Patient needs and resources	The extent to which patient needs, barriers, and facilitators are accurately known and prioritized. (Feldstein & Glasgow, 2008; Graham & Logan, 2004). A number of implementation theories postulate that taking these issues into account will increase the chance that the intervention will be effective (Ferlie & Shortell, 2001; Kitson et al., 2008). Quality improvement initiatives have proven more successful if there has been a strong focus on the patients' needs (Ferlie & Shortell, 2001).
Cosmo-politanism	Degree to which the organization is networked with other external institutions (i.e., social capital of the organization) (Greenhalgh et al., 2004). The degree of external networking increases the likelihood of implementing new practices quickly once advantages become apparent (Greenhalgh et al., 2004).
Peer pressure	Competitive pressure to implement an intervention (to either obtain a competitive edge or because other organizations already have implemented it) (Greenhalgh et al., 2004). There is strong evidence that peer pressure influences organizational adoption or programs / interventions / technologies (Greenhalgh et al., 2004).
External policies and incentives	External strategies to spread interventions (e.g., mandates, pay-for-performance, political directives, recommendations, collaboratives) (Greenhalgh et al., 2004; Mendel, Meredith, Schoenbaum, Sherbourne, & Wells, 2008). Many times these strategies lead to adoption and increase effective implementation, but there are some exceptions (Greenhalgh et al., 2004; Grol et al., 2007; Klein & Sorra, 1996).
Inner setting - Structural, political, and cultural contexts through which implementation proceeds.	
Structural characteristics	Social architecture (i.e., how people are clustered into smaller groups and how actions are coordinated), age, maturity, and size of an organization (Damanpour, 1991; Greenhalgh et al., 2004). Several structural characteristics have been found to be significantly associated with implementation effectiveness, often with mixed results (Frambach & Schillewaert, 2002). A greater number of departments involved in decision making may slow down the process, but generally increases successful implementation (Damanpour, 1991; Greenhalgh et al., 2004).
Networks and communication	Nature, quality, and extent of social networks (social capital). Formal and informal communications within an organization (Greenhalgh et al., 2004; Helfrich et al., 2007). Coordination and teamwork across departments and specialties is typically important for effective implementation of programs or initiatives (Feldstein & Glasgow, 2008; Ferlie & Shortell, 2001). Clear role definitions and high quality communication increase the likelihood of success (Simpson & Dansereau, 2007).

Table I-2 (continued).

Organizational Culture	Norms, values and basic assumptions of a given organization (these are relatively stable, socially constructed, subconscious) (Gershon, Stone, Bakken, & Larson, 2004; Scott, Mannion, Davies, & Marshall, 2003). The ways in which culture is defined vary, but it has been shown to influence implementation effectiveness in complex ways (Helfrich et al., 2007; Scott et al., 2003). Organizations that emphasize or value flexibility over centralized control and those that value human relations and a supportive climate are expected to be more successful with implementation.
Implementation climate	Absorptive capacity for change, shared receptivity of those involved, extent to which involvement with the intervention is rewarded, supported, or expected within the organization. (Gershon et al., 2004; Greenhalgh et al., 2004; Klein & Sorra, 1996). Climate includes the following 6 sub-constructs: Tension for change – degree to which stakeholders perceive current situation as needing change. Compatibility – degree of fit between the meaning and values of the intervention and individual's and institution's values as well as fit with work flow and systems. Greater perceived fit = greater likelihood of adoption according to Diffusion of Innovations and empirical research (Greenhalgh et al., 2004; Klein & Sorra, 1996; Rogers, 2003). Relative priority – shared perception of how important implementation is. The higher the priority the more likely it is to be successful (Helfrich et al., 2007). Organizational incentives/rewards – include but are not limited to goal-sharing awards, performance reviews, raises in salary, increased stature or respect. Strong incentives increase the likelihood of implementation success (Helfrich et al., 2007; Klein et al., 2001). The number of different types of incentives has been positively related to use of best practices by healthcare organizations (Shortell et al., 2001). Goals and feedback – Goals that are specific, incremental, and attainable increase effective implementation. Feedback has been shown to have small to moderate effects (Jamtvedt, Young, Kristoffersen, O'Brien, & Oxman, 2006). Learning climate – climate where leaders recognize they are fallible and need input, and team members feel their input is valued. This is hypothesized to influence the ability of an organization to fully assimilate an intervention (Greenhalgh et al., 2004).

Table I-2 (continued).

Readiness for implementation	Tangible and immediate indicators of organizational commitment to its decision (Greenhalgh et al., 2004; Kitson et al., 2008). This includes 3 sub-constructs. Leadership engagement – commitment, involvement, and accountability of managers. This is critical to successful implementation (Meyer & Goes, 1988). It leads to a stronger implementation climate (Helfrich et al., 2007; Klein, et al., 2001). Available resources – level of resources implemented (i.e., money, time, space). The level of resources is positively associated with implementation, but does not guarantee success (Klein et al., 2001). Access to information and knowledge – Access to easy to use information about UTS and how to incorporate it is essential for successful implementation (Greenhalgh et al., 2004; Helfrich et al., 2007; K J Klein et al., 2001). Timely, on the job training (particularly if provided at a team level) contributes to success (Greenhalgh et al., 2004). This is also critical to get key stakeholders engaged (Grol et al., 2007).
Individuals - Individuals in the inner or outer setting can promote or hinder the implementation process and alter program effectiveness.	
Knowledge and beliefs about the intervention	Familiarity with principles related to the intervention and how-to knowledge as well as positive and negative attitudes about the intervention and value placed on the intervention (Klein & Sorra, 1996; Rogers, 2003). Principles and how-to knowledge are constructs from Diffusion of Innovations (Rogers, 2003). Attitudes are key constructs in some theories that explain individual behavior change.
Self-efficacy	Individual belief in capability to execute behavior needed to achieve implementation goals. Perceived ability to perform a specific action within a specific context (Bandura, 1997). This construct is included in multiple theories of behavior change (Glanz, Rimer, & Viswanath, 2008) However, self-efficacy is originally attributed to Bandura.
Individual stage of change	Progression toward use of the intervention. Stage depends on the specific model used (i.e., Prochaska's Transtheoretical model, Roger's Diffusion of Innovations, etc) (Levesque, Cummins, Prochaska, & Prochaska, 2006; Prochaska & DiClemente, 1983; Rogers, 2003).
Individual identification with the organization	How individuals perceive the organization and their relationship and commitment to the organization ("AHRQ Innovations Exchange | Will It Work Here? A Decisionmaker's Guide to Adopting Innovations," ; Cropanzano, Rupp, & Byrne, 2003). This can affect the willingness of individuals to fully engage in implementation efforts, but this construct has not been widely studied in health care settings.

Table I-2 (continued).

Process - Include actions that lead to implementation, protocol and procedures, and ongoing reflection.	
Planning	Degree to which the methods and tasks for implementation and evaluation are developed (Damanpour, 1991; Greenhalgh et al., 2004; Rogers, 2003). Although planning is generally necessary for implementing institutional programs (Greenhalgh et al., 2004), additional research is needed into how planning influences implementation effectiveness.
Engaging	Attracting and involving appropriate people in implementation using social marketing, education, role modeling, training, and other activities ("AHRQ Innovations Exchange | Will It Work Here? A Decisionmaker's Guide to Adopting Innovations," n.d.; Greenhalgh et al., 2004; Kitson et al., 2008). If implementation leaders are similar to intended users they are more likely to adopt the intervention (Greenhalgh et al., 2004). Chances of success are greater if all stakeholders are engaged early on in the process (Greenhalgh et al., 2004).
Executing	Carrying out the implementation according to plan (Carroll et al., 2007; Damanpour, 1991; Edmondson, Bohmer, & Pisano, 2001; Helfrich et al., 2007). In cases where there is not a plan, assessing execution is difficult. Execution quality may be related to the following: level of fidelity to the plan, intensity of implementation, timeliness of task completion, and degree of engagement of key stakeholders (Carroll et al., 2007; Edmondson et al., 2001).
Reflecting and evaluating	Quantitative and qualitative feedback about the progress and quality of implementation. Team debriefing and reflection ("AHRQ Innovations Exchange | Will It Work Here? A Decisionmaker's Guide to Adopting Innovations,").

Table I-3. Study Outcomes and Contextual Factors for Qualitative Comparative Analysis (QCA)

Outcomes of Lynch Syndrome Universal Tumor Screening (LS UTS)
1. The proportion of patients who screen positive and follow-through with genetic counseling and germline testing 2. Unexpected problems, patient concerns, negative outcomes 3. Problems with reimbursement for tumor screening
Conditions[a] that May Influence LS UTS Outcomes

• Intervention Characteristics
  ○ Complexity
  ○ Costs
• Outer Setting
  ○ Knowledge of patient needs and resources
  ○ Extent to which patient needs are considered
• Inner Setting
  ○ Quality of communication within the organization, coordination across departments, and clearly defined roles
  ○ Degree to which implementation was supported
• Process
  ○ Ability to attract and motivate the appropriate people necessary for implementation
  ○ How UTS was implemented (procedures/protocol) including:
  • screening method (IHC, MSI, both)
  • when and how positive results are given to patients
  • how results are tracked
  • whether a referral is necessary for patient to receive genetic counseling
• Individuals involved
  ○ Attitudes, knowledge, and experiences regarding UTS
  ○ Who discloses positive tumor screening results and follows-up with patients
  ○ Who tracks results
  ○ Who discusses germline testing

Note: [a]Conditions are derived from the 5 domains of the Consolidated Framework for Implementation Research

SECTION II: IMPLEMENTATION EFFECTIVENESS OF UNIVERSAL TUMOR SCREENING FOR LYNCH SYNDROME

Abstract

Background: Universal tumor screening (UTS) of all newly diagnosed colorectal cancer (CRC) patients improves the identification of Lynch syndrome, the most common cause of hereditary CRC, and provides an opportunity for prevention and early detection of cancers. However, for UTS to be effective, a high proportion of patients who screen positive must pursue genetic counseling and germline testing (i.e., high patient reach).

Objective: This study uses the RE-AIM framework to characterize UTS programs, identify barriers and facilitators to UTS implementation, document any negative outcomes, and identify implementation factors associated with different levels of patient reach.

Methods: A web-based survey was conducted of 25 key contacts from institutions in the U.S. that were actively implementing UTS. Frequencies were used to identify similarities and differences among programs. Qualitative comparative analysis (QCA) of all 15 institutions where patient outcome data were available was performed to identify conditions uniquely associated with levels of patient reach.

Results: All 5 high-reach (H-R) centers have genetics professionals disclose positive screening results and either do not require a referral from another health care provider or have streamlined the referral process. Although 2

of the 5 mid-reach (M-R) centers also share these conditions, they have a less automated UTS protocol and report difficulty contacting patients as a barrier. The 3 remaining M-R centers and all 5 low-reach centers lacked all of the key conditions associated with H-R centers.

Conclusions: Streamlining UTS procedures, eliminating key barriers, and incorporating a high level of involvement of genetics professionals is expected to improve patient reach.

Introduction

Colorectal cancer (CRC) is the third most common type of cancer and third leading cause of cancer-related death in the United States ("Colorectal Cancer Facts & Figures 2011-2013,"). Occurring in approximately 1 out of every 35 patients with CRC, Lynch syndrome is the most common cause of hereditary CRC (Hampel et al., 2008). Lynch syndrome confers a 50-70% lifetime risk of CRC (Barrow et al., 2008; Hampel et al., 2005; Stoffel et al., 2009) , a 40-60% chance of endometrial cancer (Barrow et al., 2009; Hampel et al., 2005; Stoffel et al., 2009), and increased risks for several other malignancies (Barrow et al., 2009; Watson et al., 2008).

The significance of diagnosing Lynch syndrome for preventing cancers and improving health outcomes has been acknowledged in the following provisional Healthy People (HP) 2020 Genomics Objective: “Increase the proportion of persons with newly diagnosed colorectal cancer [CRC] who receive genetic testing to identify Lynch syndrome (or familial CRC syndromes)” (“Genomics - Healthy People”). Screening tumors from all newly diagnosed

patients with CRC has the potential to substantially improve the identification of Lynch syndrome; and reduce cancer incidence among at-risk family members ("Recommendations from the EGAPP Working Group," 2009). Furthermore, several studies have demonstrated universal tumor screening (UTS) feasibility, efficacy, and theoretical cost-effectiveness (Gudgeon et al., 2011; Hampel et al., 2008; Ladabaum et al., 2011; Morrison et al., 2011; Mvundura et al., 2010; Tranø et al., 2010).

At least 35 institutions (i.e., cancer centers, hospitals) in the U.S. perform UTS, but screening methods vary across institutions (Beamer et al., 2012; Cohen, 2013). For example, microsatellite instability (MSI) testing and/or immunohistochemical (IHC) testing can be used as the initial screening method. Secondary screening tests using BRAF or hypermethylation can be performed on a sub-set of screen-positive tumors in order to reduce the need to follow-up with a proportion of screen-positive patients who do not likely have Lynch syndrome (Bellcross et al., 2012; Palomaki, McClain, Melillo, Hampel, & Thibodeau, 2009; "Recommendations from the EGAPP Working Group," 2009).

Regardless of the screening protocol, UTS will only be successful if patients who screen positive subsequently undergo genetic counseling and germline testing. Genetic counseling is critical to help the patient understand the following: 1) Lynch syndrome substantially increases lifetime risks for several types of cancer; 2) family members could also have Lynch syndrome; and 3) successful prevention or early detection of cancers among patients with Lynch syndrome is possible through increased surveillance and surgical options.

Germline testing to identify the underlying gene mutation in a family allows other unaffected relatives to be tested for Lynch syndrome. The percentage of patients with a positive screen who follow-through with genetic counseling and germline testing (i.e., patient reach) is highly variable, differing by more than 50% across the few cancer centers for which data has been published (Heald et al., 2013; Lynch, 2011; South et al., 2009).

Recognizing the need for additional research into the public health impact of UTS and desire to enhance the effectiveness of these efforts, the RE-AIM evaluation framework (Glasgow et al., 1999) was employed to conduct a multiple-case study of UTS programs. The RE-AIM framework aids in multi-level, comprehensive program evaluation through the identification of factors within five dimensions defined in the current study as follows:

1) *Reach* - percentage of patients at an institution with a positive tumor screen who follow-through with genetic counseling and germline testing

2) *Efficacy* - potential negative effects and unanticipated outcomes

3) *Adoption* - reasons for performing UTS and characteristics of participating institutions that have adopted UTS

4) *Implementation* - consistency of UTS delivery as well as adaptations made in various settings

5) *Maintenance* - changes in the intervention and its effects over time.

Subsequently, the objectives of this study were to: 1) quantify patient *Reach* at multiple different institutions that have implemented UTS; 2) identify negative or unanticipated outcomes of UTS (i.e., *Effectiveness*); 3) determine

reasons for UTS *Adoption*; 4) characterize similarities and differences in *Implementation* across institutions; 5) identify barriers and facilitators to *Implementation*; and 6) determine what conditions are associated with high and low patient *Reach* in order to characterize “best UTS practices.

With regard to the sixth objective, the researchers hypothesized that high patient *Reach* would occur among programs that possess one or more combinations of the following conditions: 1) streamlined UTS procedures (i.e., implementation of automatic reflex testing, fewer steps need to be taken by patients in order to follow-up with genetic counseling and germline testing, and/or referrals from other health care providers are not a barrier); 2) direct involvement of genetic professionals in results disclosure and patient follow-up; and 3) support for implementation (i.e., facilitators outweigh barriers or challenges that were faced during implementation). Conversely, low patient reach was hypothesized to occur when one or more of these factors were not present.

Methods

Study Design

After obtaining approval from the University's Institutional Review Board a multiple-case study was initiated in the fall of 2012. Data for the multiple-case study were obtained primarily from initial surveys of primary institutional representatives. In addition, data from follow-up surveys and interviews performed approximately six-months after the initial surveys were used to illustrate the RE-AIM dimension *Maintenance* and inform the interpretation of the findings.

Participant Recruitment and Procedures

Initial surveys of primary institutional representatives. Using the LSSN listserv, an e-mail invitation containing information about the study was directed to all primary representatives of the 35 institutional members of the Lynch Syndrome Screening Network (LSSN) that were performing universal tumor screening (UTS), and to approximately 27 institutional representatives that were in the process of actively planning or implementing UTS. Institutions that limit screening based on age or other criteria were not included in the study. Interested representatives who contacted the principal investigator (PI) and qualified for the study were asked to review the consent form, complete an online survey, and indicate whether they would be willing to be contacted in the future.

Follow-up survey and interview with institutional representatives. Nearly six months after the baseline survey, all 15 participants from institutions that had been screening for more than six-months at the time of the initial survey and had access to patient reach data were sent a personal e-mail invitation and link to complete a follow-up survey designed to obtain patient reach updates, UTS protocol/procedural details or changes, and interest in participating in a follow-up interview.

Interviews lasting an average of 50 minutes were conducted by the PI with10 of the 15 institutional representatives. Interview data was used to fill in missing details and to clarify discrepant information from the two surveys. During the interviews notes were taken by the PI and interviews were audio recorded in order for the PI to verify details as needed. At the end of the interviews

participants were asked to forward an invitation to participate in a brief interview or survey to other individuals at their institution who had been involved with UTS.

Interviews with additional key personnel. Eight primary representatives agreed to forward an e-mail invitation to one or two individuals at their center. Brief 15-30 minute interviews were completed with three pathologists and one program director from four institutions and 45-60 minute interviews were completed with two individuals who could fill in missing details about implementation at a fifth institution.

Measures

Initial survey. The baseline survey was developed to collect information regarding: a) institutional characteristics; b) factors influencing UTS adoption; c) UTS protocol (including follow-up procedures); d) barriers and facilitators to UTS implementation; e) percentage of patients who follow-through with genetic counseling and germline testing after a positive screen; and f) barriers or facilitators to patient follow-through. The survey was reviewed for face and content validity by a medical geneticist, two genetic counselors, an epidemiologist, and a behavioral cancer scientist, all of whom were familiar with Lynch syndrome tumor screening. The revised survey included five open-ended questions and approximately 20 multi-part, closed-ended questions that also allowed participants to write in additional responses or details. The online survey was piloted by two genetic counselors and a nurse practitioner, all of whom were involved in setting up a UTS program for Lynch syndrome at their respective institutions.

Patient reach was operationalized using two survey questions that assessed the percentage of screen positive patients under the current institutional screening protocol who 1) pursue germline genetic testing and 2) receive genetic counseling. Response options were the same for both questions: 1 = ≤10%; 2 = 11-25%; 3 = 26-40%; 4 = 41-55%; 5 = 56-70%; 6 = 71-85%; and 7 =>85%. Ordinal response categories for the two questions were averaged to create patient reach scores with a possible range from 1-7. After arranging cases in descending order by patient reach, the researchers identified two natural breaks and used these to categorize cases into the following three groups; “high-reach” (H-R); “mid-reach” (M-R); and “low-reach” (L-R).

Follow-up survey. The follow-up survey was developed by the PI to help clarify responses from the initial survey, obtain additional details, and identify changes that may have occurred in patient reach and UTS protocol or procedures. The follow-up survey was reviewed for face and content validity by a medical geneticist, three genetic counselors, and a behavioral cancer scientist, all of whom were familiar with Lynch syndrome tumor screening.

Interview guides. Semi-structured interview guides used for follow-up interviews included several open-ended questions about UTS implementation and experiences as well as several institution-specific questions designed to clarify and expand upon information collected from the surveys. The guides were tailored for each participating institution by the PI with input from a medical geneticist and experts in behavioral health research. A subset of relevant questions was selected by the PI for inclusion in interviews of other key

personnel based on their expertise and role in UTS implementation.

Data Analysis

Frequencies and percentages for responses to closed-ended survey questions were generated using an Excel spreadsheet. After grouping together eight centers where patient reach data were not available and stratifying the other fifteen centers according to patient reach, frequencies of responses to closed-ended questions were generated for each of the four groups. Open-ended survey and interview responses were categorized according to patient reach and then reviewed by the PI to identify commonalities and diversity in themes across centers for each of the RE-AIM dimensions.

Qualitative comparative analysis (QCA) was used to test the study hypothesis and determine which combinations of factors were uniquely associated with high and low patient reach among the 15 centers where patient reach data were available. QCA is an analytic technique for performing cross-case comparative analyses in order to systematically identify and simplify key factors (i.e., conditions) that are “sufficient” for an outcome of interest to occur (Ragin, 1989; Rihoux & Ragin, 2009). Although QCA is different from inferential statistics, conditions are analogous to independent variables that are hypothesized to influence the outcome of interest (i.e., patient reach).

Conditions were coded for use in QCA as follows: 1=condition present; and 0=condition absent. Patient reach was coded into two variables as follows: 1) H-R=1 for all institutions with a patient reach score of 5 or above and H-R=0 for all other institutions; 2) L-R=1 for all institutions with a patient reach score of 2 or

below and L-R=0 for all other institutions. Specialized software (fsQCA 2.0) was used to perform a *sufficiency analysis* using the *truth table* approach ("Citing fs/QCA 2.0,") in order to determine whether one or more combination of conditions are unique to centers that reported high patient reach (H-R). A separate sufficiency analysis was performed to determine combinations of conditions that are unique to centers reporting low patient reach (L-R). Steps used to perform QCA are included in Table II.1.

Results

Institutions and Participants

Of the 35 health care providers who were serving as institutional representatives for the Lynch Syndrome Screening Network (LSSN) and worked at institutions that had implemented UTS, 20 (57%) responded to an e-mail invitation and provided baseline data via the online survey. An additional 3 representatives from centers that were in the process of implementing UTS also completed relevant portions of the survey. Based on survey responses, 15 institutions met the following a priori inclusion criteria for use in hypothesis testing: 1) UTS had been fully implemented for 6 months or longer at the time of the initial survey; and 2) data needed to determine patient reach were provided.

All primary contact persons were genetic counselors, except for one physician who responded from an institution that was still in the process of implementing UTS. Table II-2 provides demographic characteristics of all participating institutions and lists these same characteristics after stratifying centers into four groups according to the availability of patient reach data. Four of

the five H-R institutions were academic/research centers that were designated by the National Cancer Institute (NCI) as either a comprehensive cancer center (CCC) or cancer center (CC). In contrast, three of the five M-R and three of the five L-R institutions were classified as non-academic institutions with only one classified as a NCI-CCC. Most institutions had been performing UTS for over one year as of October 2012. The total number of colorectal cancer patients screened and number of positive screens over a six month time period were highly variable across institutions (Table II-2).

Patient Reach

Frequencies showing the percentages of patients who followed through with genetic counseling and with germline testing after a positive tumor screen are reported in Table II-3. There is wide variability on these two measures across centers, with no overlap between H-R and L-R institutions.

Effectiveness

Patient concerns, unanticipated outcomes, or problems with reimbursement related to UTS rarely or sometimes occurred (Table II-3). Institutional representatives provided descriptions of these events in open-ended responses or follow-up interviews. For instance, one representative described how a couple of patients expressed surprise because they were unaware that tumor screening was part of the surgical informed consent they signed; and two representatives indicated that a few patients expressed concerns about their inability to pay for genetic counseling and/or germline testing. One representative also indicated that one patient did not really want the results but felt obliged to

follow-up on them and undergo germline testing. Unanticipated outcomes that were described included the need to plan for how to handle results from prison inmates or from patients who are deceased. Other challenges included how to follow-up when results are equivocal (i.e., partial loss of protein expression on IHC) or when results are atypical (i.e., absence of MLH1 and MSH6).

A fair number of institutional representatives were uncertain whether reimbursement for tumor screening was an issue. However, in follow-up interviews, individuals at four centers where screening is performed on tumor resections indicated that there is usually no additional fee recovered for tumor screening because it is included as part of the overall costs that insurers reimburse as part of the inpatient surgery. At another institution where the protocol was changed so that tumor biopsies rather than tumor resections are screened, the pathologist indicated that because biopsies are performed as outpatient procedures, fees could be recovered.

Reasons for UTS Adoption

The most commonly identified reason for adopting UTS was to “improve the identification of individuals with Lynch syndrome”, followed by “to benefit relatives of patients with Lynch syndrome”. Several other reasons were also selected and are listed in Table II-4. None of the centers checked “to increase revenue” as a reason for adoption. The number of reasons checked by representatives varied, but there did not appear to be any consistent patterns or associations between reasons for adoption and patient reach.

Barriers and Facilitators to Implementation

Only three institutional representatives checked “no real barriers or challenges” when asked about barriers to implementing UTS at their institution (Table II-5). Interestingly, all three representatives reporting no barriers represented academic institutions, including two H-R centers and 1 L-R center. Concerns about informed consent and about screening costs or reimbursement were the most commonly cited barriers or challenges to implementation. Difficulty convincing key stakeholders why UTS is important, general lack of knowledge by key stakeholders, and communication barriers between stakeholders were reported by institutional representatives from several M-R and L-R centers as well as centers where outcomes data were not reported; in contrast, these were selected as barriers to implementation at the non-academic H-R center, but none of the other H-R centers.

The most commonly cited facilitators to implementation were collaborative relationships that existed across departments, obtaining useful information from other centers that had implemented UTS, and having an institutional champion who worked hard to implement UTS (Table II-5). None of the institutional representatives reported having protected time for planning UTS. There were no apparent trends between implementation facilitators and patient reach. However, all institutions except three L-R centers and the 1 non-academic H-R center reported a greater number of implementation facilitators than barriers/challenges.

Heterogeneity in Implementation

UTS protocols were found to be heterogeneous among the different

institutions (Table II-6). In reviewing the type of screening performed by each institution (IHC versus MSI), who orders the screening, where the screening is performed, or whether patients are consented or receive information prior to screening, no clear patterns seemed to distinguish centers with high or low patient reach. Most centers use immunohistochemical (IHC) testing in conjunction with automatic reflex testing (i.e. BRAF or hypermethylation) to help rule out Lynch syndrome in patients who screen positive on IHC (due to absence of the MLH1 protein), but do not need to follow-up with genetic counseling or germline testing unless their personal or family history would indicate otherwise.

In contrast to screening protocols, follow-up procedures when patients have a positive tumor screen appeared to systematically differ by patient reach (Table II-7). With the exception of two L-R centers, a Master's trained genetic counselor routinely receives information on patients who screen positive. In addition, all H-R centers routinely have genetic counselors disclose positive screening results to patients; two of the five M-R centers also have genetic counselors routinely disclose positive screening results to patients. In contrast, all L-R centers have various and even multiple types of non-genetics professionals disclose screening results. Additionally, all L-R centers and three M-R centers indicated that the primary mechanism by which germline testing is ordered required that the patient's physician refer the patient for genetic counseling. Although none of the H-R centers indicated that referral was the primary mechanism by which germline testing is ordered, two H-R centers do have genetic counselors obtain referrals or enter referrals into the system on behalf of

the physicians.

Differences in procedures for handling negative tumor screening results were also identified (Table II-8). Most centers include negative results as an addendum in the pathology report, but do not report these results to patients. Two centers send letters with results of negative screening to the patients. In their letters they include a list of clinical characteristics that may indicate a hereditary predisposition to cancer and recommend that patients see a genetic counselor if any of these pertain to the patient or their family. A few primary contact persons indicated that they will review negative screening results and contact physicians if patients are young (i.e., under age 40 or 50) or if medical records document any personal or family history features that might indicate a hereditary predisposition.

System-level and Implementation Influences on Patient Reach

Potential barriers to high patient reach. Barriers to patient follow-through with genetic counseling or germline testing on closed-ended survey items are summarized in Table II-9. Lack of insurance or financial means to pay for genetic counseling or germline testing and patients are dealing with too many concerns at the time of diagnosis were the most commonly checked barriers by the institutional representatives. Only one H-R institution cited lack of referral as a barrier; and at this center other health professionals occasionally disclose positive screening results. Lack of patient referral was reported as a problem for all M-R and L-R centers except the 2 M-R centers where genetic counselors routinely disclose positive screening results. All L-R centers and over half of the

M-R centers reported lack of understanding about the importance of germline testing among health care providers as a barrier, but this was not cited as a barrier by any of the H-R centers. Difficulty contacting patients was cited as a barrier at three M-R centers including the two where a genetic counselor usually discloses positive screening results and a third where the genetic counselor contacts physicians to solicit referrals before following up with patients to arrange genetic counseling and germline testing.

Potential facilitators for high patient reach. Due to the researchers' uncertainty about potential facilitators to genetic counseling and germline testing, facilitators were assessed using two open-ended questions asking participants what they have found to help or what they think might help to increase patient follow-through with genetic counseling and germline testing. The majority of participants completed these open-ended questions; and their answers primarily consisted of ways to reduce key barriers.

Two of the four H-R centers whose representative completed the question about genetic counseling facilitators identified that meeting the patients at another follow-up appointment (i.e. post-operative visit) was helpful; and the other two indicated that having the genetic counselor contact patients facilitates genetic counseling follow-through. The other H-R representative did not provide a comment. Two representatives from M-R centers commented that increasing the likelihood that physicians make referrals or that continuing education of physicians regarding the importance of genetic counseling and germline testing for patients with a positive screen would facilitate higher rates of patient follow-

through with genetic counseling. All but one L-R center representative provided a comment; and their responses all indicated that genetic counselors need to contact patients directly and/or that physicians need more education on the importance of genetic counseling and germline testing.

The only two H-R centers that commented on how to facilitate germline testing indicated that improved insurance would facilitate testing. One of the M-R centers again commented that physicians need more education. Another M-R center suggested that physicians need to stress to the patient why it is important that the patient follow-through when they make a referral. This respondent also mentioned the need for better insurance coverage to facilitate testing. All four L-R centers that responded to this question reiterated the need to get patients in for genetic counseling or have the genetic counselor contact patients directly.

Implementation factors associated with high and low patient reach. The presence and absence of conditions hypothesized to be associated with high and/or low patient reach based on data from the initial survey are shown in Table II-10. Although patterns of configurations are discernible based on this table, QCA was used to systematically formulate concise solutions that show which conditions are uniquely and consistently associated with high patient reach as well as those associated with low patient reach. QCA solutions are listed as part of a results summary table (Table II-11).

Maintenance at Six-month Follow-up

Although results from the initial and follow-up surveys were largely consistent, several centers reported changes in patient reach at the six-month

follow-up. By far the most striking case was one L-R institution where *Reach* changed from 1.5 on the initial survey to 5 at six-month follow-up. This change in patient reach coincided with the initiation of automatic reflex testing to rule out some patients who did not need to be referred for genetic counseling because they were unlikely to have Lynch syndrome. Another explanation postulated by the primary representative for the increase in patient *Reach* included additional physician education that occurred over time and a subsequent increase in referrals. Although genetic counselors at this institution do not disclose screen-positive results to patients, a genetic counselor routinely attends a bi-weekly case conference where each of the patients is discussed. At that time the counselor reminds physicians of the need for and importance of referral for patients with a positive tumor screen. Additionally, after the case conference, the genetic counselor mails and faxes letters to one or more of the patients' treating physicians in order to reiterate what was discussed during the case conference and provide directions on how to complete the patient referral. Once a referral is received, the genetic counselor contacts the patients. Thus the genetic counselor is highly involved in follow-up with the physicians and patients, despite not disclosing positive screening results.

No other institutions reported changes in their protocols since the initial survey. However three other institutions moved into or out of the M-R set due to relatively small changes in patient reach. The institution with the second highest patient reach score of the five original M-R centers shifted into the bottom of the H-R set at six-month follow-up. Interviews with the primary contact and two other

individuals involved with UTS at this institution suggested that their success may be due to the extensive efforts of the genetic counselor who requests referrals from one or more of the treating physicians for each patient with a positive screen. Although she does not disclose screening results directly to patients she reports typically being successful at obtaining a referral; she then calls the patient to arrange follow-up and explain the importance of counseling and germline testing. Additionally, it was clear from interviews that the genetic counselor, a key administrator, the pathologist, and many (if not most) physicians at this institution are supportive of UTS and have received a substantial amount of education about hereditary colorectal cancer from various sources including the genetic counselor, presentations at a regularly held multidisciplinary tumor board, and two representatives from a laboratory that offers germline testing for Lynch syndrome.

This institution, along with the aforementioned L-R institution where patient reach improved after ensuring that BRAF reflex testing is automatic, both demonstrate that if the environment is supportive, physicians are well educated, and the genetic counselor takes on an extensive role to follow-up on all positive tumor screening results, then patient reach can be relatively high even when various different referring physicians disclose results of tumor screening to patients. Nevertheless, despite improvements, patient reach scores at these two centers remained lower than the six-month follow-up scores at the four academic H-R centers where genetic counselors routinely disclose positive results.

The only H-R institution that is not an academic center reported a small

decrease in patient reach, changing from 5 to 4.5 at six-month follow-up. Upon interviewing the counselor at this institution, she indicated that her initial report of the percentage of patients with a positive screen who had genetic counseling was more reflective of the proportion of patients she talks to and offers genetic counseling, but some patients who are concerned about costs of genetic counseling, who have Medicaid (which does not cover the cost of genetic counseling in that state), or who lack insurance do not actually come in for genetic counseling even though she talks with them by phone. Furthermore, she reported that a couple of physicians do not always let her disclose positive tumor screening results to their patients.

The last institution to be reclassified was originally at the very bottom of the M-R set in terms of patient reach. At six-month follow-up this institution would have been reclassified into the L-R group due to a small decrease in patient reach from 2.5 to 2. Notably, this institution did not share any of the characteristics associated with H-R centers.

Results Summary and Proposed Model of High and Low Patient Reach

Table II-11 provides a summary of study results within the RE-AIM framework. Consistent with the methodology employed in the multiple-case study (Ragin, 1989), QCA solutions in conjunction with substantive knowledge obtained at six-month follow-up were used to formulate a causal model to explain high and low patient reach.

High patient reach. Institutions with high patient reach (H-R) have instituted a combination of procedures to streamline UTS protocols and

procedures, eliminate barriers to patient follow-through after a positive tumor screen, and incorporate a high level of involvement of genetic professionals in contacting physicians and/or patients. More specifically, H-R centers either do not require patients who have a positive screen to be referred by another health care provider for genetic counseling and germline testing or obtaining a referral is not reported as a barrier because genetic counselors contact physicians to request referrals as part of a standardized process that is agreed upon and/or supported by the physicians. The need for referrals presumably adds complexity to the procedures and causes patient reach to be highly contingent upon multiple different health care providers' knowledge about the importance of genetic counseling and germline testing as well as health care providers' actions to both convey this importance to the patient and to make a referral.

In the current study, elimination of the need for referral altogether only occurred at centers where genetic professionals receive and disclose positive screening results to patients. This latter condition could be contributing to higher patient follow-through because direct patient contact allows the genetics professional to build rapport with the patients early on in the process and to convey to patients the importance of genetic counseling and germline testing. At four of the original H-R centers, disclosure of positive screening results was almost always performed by a master’s trained genetic counselor. However, at one H-R center, it has become increasingly common for patients to receive positive results disclosure by a nurse who is knowledgeable about Lynch syndrome, had years of experience working with and observing cancer genetic

counseling sessions, and was considered highly qualified by the genetic counselor.

Even if a genetic counselor or someone knowledgeable and well-trained in cancer genetic counseling discloses positive screening results, patient reach is logically contingent upon successfully contacting the patients. In the current study, difficulties contacting patients were reported as a barrier to patient reach by the two M-R centers where genetic counselors usually disclosed positive tumor screening results to patients, but not at any H-R centers. Nevertheless, at six-month follow-up, representatives from H-R centers admitted that patient contact was occasionally a barrier or that patient contact used to pose a barrier; however, three of these centers helped to overcome this barrier by having a genetic counselor or nurse meet the patient at a follow-up appointment (i.e., surgical post-op appointment). Unfortunately this approach is not always feasible due to limited genetics personnel or at centers where follow-up appointments occur at several different locations that are not in close proximity to the counselors (i.e., private practices). Interestingly, physical distance between the locations of genetic counselors and post-op appointments was the impetus for having a nurse, rather than master's trained genetic counselor, disclose positive screening results during post-op appointments at one of the original H-R centers.

Additional reasons why certain institutions may experience difficulty with patient follow-through were elucidated during a follow-up interview with a genetic counselor who personally discloses positive screening results to patients by phone at one of the M-R institutions. Her institution is located in a

socioeconomically disadvantaged city where several patients do not even attend their post-operative appointments. Therefore, even if genetic counselors were available to meet patients at the post-op appointments, patient reach may continue to be problematic.

Finally, automatic reflex testing streamlines the tumor screening process by eliminating the need to follow-up with a proportion of patients who do not likely have Lynch syndrome and by eliminating additional steps required to order reflex testing. The absence of automatic reflex testing may also partially explain why the two M-R centers where genetic counselors disclose results reported lower patient reach than H-R centers.

Low patient reach. Conditions associated with low patient reach (L-R) provide additional insights into the potential relationships between implementation and patient reach. One of the two conditional configurations unique to L-R centers included the absence of having a genetics professional disclose the results of positive tumor screening to patients in combination with the presence of a higher ratio of implementation challenges compared to implementation facilitators. The latter condition may be indicative of several different types of organizational challenges or communication barriers that could inhibit high patient reach.

Nevertheless, challenges during implementation are insufficient to prevent relatively high patient reach from eventually being achieved. Evidence for this comes from two participating institutions. The first is the non-academic center that was originally classified in the H-R set, but dropped into the M-R set at six-

month follow-up. Despite facing a number of implementation challenges, UTS planning occurred during a period of over two years, several people worked very hard to implement UTS, and patient reach was relatively low when first implemented. Notably, two individuals from this institution commented that it takes time for physicians to really see the benefits of UTS and/or to agree to have the counselor disclose screening results to patients. Indeed a key difference between this center and the L-R centers is that the genetic counselor usually discloses screening results to patients. The other center that proves a high ratio of implementation challenges to facilitators does not prevent improvement in patient reach is the L-R center that was able to achieve relatively high patient reach at six-month follow-up after streamlining their protocol.

As for the two academic L-R centers, neither of the representatives at these institutions reported experiencing more challenges than facilitators during the implementation process. However, these centers presumably have low patient reach because the genetic counselors do not routinely receive a list of patients who screen positive and they are subsequently unable to follow-up with physicians or patients. Interestingly, the representative at one of these two centers indicated in open-ended responses that patient follow-through was higher under her old protocol when she used to receive a list of patients who screened positive and could contact physicians to help ensure patients were referred. Unfortunately the protocol was changed due to concerns that were raised about patient privacy under the Health Insurance Portability and Accountability Act (i.e., HIPAA).

With the exception of these two L-R centers, all other institutional representatives reported receiving key information on patients who had a positive screen. A few of the representatives volunteered that they were given access to this information by making the argument that genetics was part of the healthcare team and/or that having one person review all results is critical for quality assurance or to reduce legal liability for the institution. Recognizing the legal liability issue, the L-R academic center that never provided patient results to the genetics program began doing so just prior to the six-month follow-up. At that time, the institutional representative confirmed that a number of patients had not been referred. Furthermore, in at least one case, the screening result had not been followed up on appropriately because BRAF testing had not been completed. Subsequently automatic BRAF testing was initiated along with changes that would allow the genetic counselor to disclose positive screening results and directly follow-up with patients.

Discussion

To our knowledge this is the first study to quantify and compare outcomes at multiple institutions that have implemented universal tumor screening (UTS) programs, whereby tumors from all newly diagnosed patients with colorectal cancer (CRC) are screened for Lynch syndrome. Two prior national surveys revealed heterogeneity in the implementation of Lynch syndrome tumor screening protocols across the U.S. and documented that a high proportion of centers reported problems with patients not following through with genetic counseling and germline testing after a positive screen (Beamer et al., 2012;

Cohen, 2013). Additionally, two centers have now independently reported data on their institutional experiences with UTS which revealed how patient reach increased following changes to their institutional follow-up procedures so that genetic counselors receive and disclose positive screening results to patients and take an active role to initiate genetic counseling and germline testing (Heald et al., 2013; Hampel, 2012).

Despite the longitudinal experiences at these two institutions, whether or not genetic counselors received and disclosed the results of screen positive tumors was not correlated with whether or not problems with patient follow-through were reported according to results from a recently published national survey of cancer genetic counselors (Cohen, 2013). Importantly, differences in patient follow-through were not quantified as part of that national survey and the bivariate statistical approach did not allow for the possibility that having genetic counselors disclose positive screening results was alone insufficient to prevent difficulties with patient follow-through.

The current study expands upon these earlier studies and contributes uniquely to the literature by documenting wide institutional variation in patient reach and providing additional evidence for several key leverage points that are likely to improve patient reach. The current study also provides potential insights as to why a finding from the national survey by Cohen (2013) initially seemed contradictory to the longitudinal experiences that have been reported. More specifically, in the current study, genetic counselor disclosure of screen-positive results was indeed insufficient to ensure high patient reach. However, this did not

mean that the involvement of genetic counselors was unimportant. On the contrary, results from the current study suggest that the involvement of genetic counselors is part of a more complex recipe for achieving high patient reach; a recipe in which difficulties with patient contact and other barriers such as the need for a physician referral must be overcome.

There are several strengths to the current multiple-case study that support data credibility, reliability and validity (Baxter & Jack, 2008; Yin, 2008) Baxter. First, information gathered six months after the initial survey from institutional representatives at 13 of the 15 institutions enabled confirmation of initial survey results. In addition, member checks were initiated in which summaries of the institutional data were shared with institutional representatives and reviewed for accuracy during an interview or e-mail correspondence with 11 of the15 institutional representatives. Almost all institutional representatives reported having good tracking systems in place and they were quite confident in the accuracy of the patient reach numbers they reported. However, there were a couple of centers where the representatives were not as confident in their numbers because they admitted that germline testing could be performed by a surgeon or oncologist without their knowledge. However, these representatives did not believe this was occurring regularly.

One limitation of the study was the inability to verify or collect patient reach data in a systematic fashion and necessitated the reliance on numbers reported by each institutional representative. Other study limitations stemmed from an imperfect system of categorizing institutions into three patient reach groups as

well as fluctuations in patient reach that occurred over time. Nevertheless, with the exception of the center where the protocol changed, institutions remained in their classification group or there was limited movement of institutions into or out of the M-R group. Furthermore, evidence for the proposed model is supported by findings that M-R institutions with the highest patient reach shared more key characteristics of H-R centers, whereas M-R centers with the lowest patient reach tended to share features of L-R institutions.

Additional limitations related to the measures used in the current study include the use of: data collected from a single individual at all but five of the institutions; conditions that were measured as either absent or present; and measures that failed to capture a number of nuances that distinguish between institutions. Additional data from open-ended survey responses and at six-month follow-up helped to elucidate some of these nuances. Thus, despite measurement limitations, general patterns of conditions associated with high and low patient reach among these cases remained evident in support of the proposed models.

Although models generated from multiple case studies can serve as a "vehicle for generalizing results" (Yin, 2008; p. 40), the ability to generalize findings from this study may also be limited because the primary institutional representatives were all genetic counselors and a fair number of centers that participated in the current study are believed to be innovators and early adopters (Rogers, 2004). Thus, the conditions identified as being important for high patient reach in this study may not be feasible at all institutions and additional paths to

success may need to be identified or forged. Therefore other institutions that have achieved high patient reach should continue to be identified in order to confirm, revise, or add to the institution-level mechanisms identified to be associated with high patient reach in the current model.

Although the study design limits the ability to assert causality, the “causal” model is strengthened given that two institutions have meticulously documented improvements in patient reach after implementing some of the same follow-up procedures identified to be important in the current study (Hampel, 2012, Leach et al, 2013). Furthermore, one representative from a L-R institution in the current study reported that patient follow-through was higher under her institution’s former protocol where she received results of positive screens and could follow-up with physicians to help ensure a referral was made. Lastly, the L-R institution that improved patient reach substantially at six-month follow-up streamlined their procedures by instituting automatic reflex testing, thereby providing additional support for this component of the complex causal model associated with high patient reach. Together these experiences increase confidence that if institutions model their UTS program after the H-R institutions in this study they have greater odds of experiencing higher patient reach. However, simply modeling UTS procedures after H-R institutions would not necessarily guarantee high patient reach, especially if the patient population is difficult to contact or has a high rate of uninsured or underinsured patients.

Finally, data available for the current study did not allow us to account for the influence that differences in patient populations may have on patient reach.

Nevertheless, patient-level factors were identified in the current study as barriers to patient follow-through by institutional representatives, particularly those at centers with streamlined procedures, a high level of involvement in follow-up by genetic counselors, and removal of other system-level barriers. In order to determine the relative influence of patient-level versus system-level effects on patient outcomes, a large, multi-site effectiveness study that employs multilevel modeling should be undertaken.

Utilization of the RE-AIM framework in planning, evaluating, and presenting findings from future studies are needed to provide a more complete assessment of the public health impact of UTS programs. Although RE-AIM aided in planning and summarizing results, the current study was not designed to fully characterize each RE-AIM dimension. For instance, practical considerations necessitated limiting the definition of patient reach even though the true public health impact of UTS lies in its ability to have broader reach through the identification of family members with Lynch syndrome. Additionally, the current study was not designed to assess the overall proportion or representativeness of all U.S. institutions that have adopted UTS. Subsequently, data on adoption using more representative sampling techniques is needed to determine the overall public health impact of UTS, confirm that a disproportionately high number of academic/ research institutions across the U.S. have adopted UTS as suggested by findings from two national surveys (Beamer, et al 2012; Cohen, 2013), and determine whether those institutions that employ a master's trained genetic counselor are also more likely to adopt UTS compared to other

institutions. This additional information on adoption would be useful because adoption patterns have the potential to increase disparities in the identification of hereditary cancer among certain geographic regions or minority populations.

Conclusion

Universal screening of tumors from all newly diagnosed patients with colorectal cancer is a promising method to achieve the Healthy People 2020 provisional objective: *"Increase the proportion of persons with newly diagnosed colorectal cancer [CRC] who receive genetic testing to identify Lynch syndrome"*. Current results provide evidence that universal tumor screening programs can be successful. In addition, the study provides a model based on empirical data from 15 institutions that helps to further explain how implementation and system-level factors can influence patient reach. This information could be used to inform decision-making by stakeholders and potentially improve patient reach so that the long-term goal of reducing high levels of morbidity and mortality associated with hereditary cancer can be achieved.

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Table II-1. Summary of Steps Used to Perform Crisp-set QCA

csQCA steps	Application of QCA steps in the current study
Step 1: **(a)** Determine, define, and operationalize the outcome of interest	**(a)** Outcome =patient reach Defined as the percentage of patients who follow-through with genetic counseling and germline testing following an abnormal tumor screen at each institution. Operationalized based on two survey questions as described in the manuscript.
(b) Assign dichotomous set membership scores for the outcome	**(b)** Cases naturally fell into three groups or sets: high-reach (H-R); mid-reach (M-R); and low-reach (L-R). Cases with a patient reach score $\geq$5 were included in the H-R set (coded as H-R=1). All other cases were coded H-R=0 and are referred to with a tilde to indicate they are not in the high-reach set (i.e., ~H-R). For the second analysis, cases with a patient reach score $\leq$2 were coded as L-R=1 and all others as L-R=0.
Step 2: Select Cases	Several high-reach and several low-reach institutions were needed. However, to maximize both sample size and diversity in contextual variables, all available cases that met the minimum a priori inclusion criteria were used in the analysis.
Step 3: **(a)** Identify key conditions **(b)** Assign dichotomous set membership scores for each condition **(c)** Create a data matrix of scores for conditions	**(a)** Based on theory and knowledge of the cases, the following conditions were hypothesized to be associated with H-R when either present (+) or absent (-): 1) reflex testing on a subset of tumors is performed automatically to rule out patients with an initial positive screen who do not need genetic counseling and germline testing (+); 2) genetics professional discloses positive screening results to patients (+); 3) difficulty contacting patients was reported as a barrier (-); 4) referral from another health care provider was reported as the primary mechanism by which germline testing is conducted (-). Similarly, the following conditions hypothesized to be associated with L-R when either present (+) or absent (-) were selected based on theory and knowledge of the cases: 1) number of barriers to implementation were $\geq$ to number of facilitators (+); 2) genetics receives a copy of all positive screens (-); 3) genetics professional discloses positive screening results to patients (-); 4) referral is needed as a primary mechanism by which germline testing is ordered (+) **(b)** All of the conditions were already dichotomized as either present=1 or absent=0 based on how they were asked as part of the survey. **(c)** A data matrix was created by listing membership scores for the outcome and key conditions for each case.
Step 4: Determine whether conditions are necessary for the outcome	None of the conditions were originally hypothesized to be necessary for either high patient reach or low patient reach. Thus, a necessary analysis was not conducted.
Step 5: Determine whether certain conditions are sufficient for the outcome using the “truth table” approach	Although not necessary for the presence of high or low patient reach, conditions may still be sufficient for the respective outcome either when occurring alone or in combination with other conditions. Using fsQCA 2.0, two truth tables were created showing all possible configurations of conditions for each of the two selected outcomes (i.e., H-R and L-R).

Table II-1 (continued).

Step 6: Examine the truth table and resolve contradictions	No contradictions were identified.
Step 7: Use computer software to generate solutions through multiple comparisons of case configurations in the truth table	Using fsQCA 2.0 software, a "Standard Analysis" was performed to identify conditions associated with H-R and a second analysis was performed to identify conditions associated with L-R. This software uses the Quine-McCluskey algorithm (which is based on Boolean simplification) to make multiple comparisons of case configurations represented in the truth table and logically simplify the data. The idea behind this minimization procedure is that if two configurations differ in only one condition, yet produce the same outcome, then the condition that distinguishes the two configurations can be considered irrelevant to the outcome and removed to create a simpler expression. During this process, input from the researchers was required to select prime implicants and determine which simplifying assumptions were tenable. The software then used this information to generate three solutions (complex, parsimonious, and intermediate) with H-R as the outcome; and in a separate analysis three solutions were generated with L-R as the outcome. Only the intermediate or parsimonious solutions are shown in Table II-11. The other solutions are available from the primary author.
Step 8: Determine if the influence of conditions is symmetrical	To determine if conditions associated with H-R are the same as those associated with the absence of the outcome (~H-R), steps 4-6 were repeated using ~H-R as the outcome. Similarly, these steps were repeated using ~L-R as the outcome.
Step 9: Evaluate the consistency and coverage of the solutions	For each of the analyses for the four outcomes (H-R, L-R, ~H-R, and ~L-R) the overall solution consistencies were 1; indicating that the respective combination of conditions were consistently associated with the respective outcome. For each analysis the overall coverage was 1; indicating that all of the cases with the presence of the outcome fit the solution.
Step 10: Interpret the resulting solutions and create causal models	Even when conditions are uniquely and consistently associated with an outcome, it does not necessarily mean they cause the outcome. However, these solutions in conjunction with theories, frameworks, and details about the cases can be used to develop a causal theoretical model that describes how the conditions might lead to the outcome.

Table II-2. Demographic Characteristics of Institutions and their Respective Universal Tumor Screening (UTS) Programs

Characteristics	All institutions (N=23)	H-R (n=5)	M-R (n=5)	L-R (n=5)	Outcome not reported (n=8)
	n (%)	n (%)	n (%)	n (%)	n (%)
Institution type					
Academic / research institution	10 (44)	4 (80)	2 (40)	2 (40)	2 (25)
Non-academic institution	13 (56)	1 (20)	3 (60)	3 (60)	6 (75)
Designations[a]					
National Comprehensive Cancer Network Member	4 (17)	2 (40)	1 (20)	1 (20)	0 (0)
NCI designated comprehensive cancer center	6 (26)	3 (60)	2 (40)	1 (20)	0 (0)
NCI designated cancer center	2 (9)	1 (20)	0 (0)	0 (0)	1 (12.5)
How long ago screening was initiated					
Currently in the process	3 (13)	0 (0)	0 (0)	0 (0)	3 (37.5)
<3 months	1 (4)	0 (0)	0 (0)	0 (0)	1 (12.5)
3-5 months	1 (4)	0 (0)	0 (0)	0 (0)	1 (12.5)
6-12 months	5 (22)	0 (0)	2 (40)	2 (40)	1 (12.5)
>1 year	13 (54)	5 (100)	3 (60)	3 (60)	2 (25)
# patients that have been screened in last 6 months or less if recently implemented UTS					
<10	1 (4)	0 (0)	0 (0)	0 (0)	1 (12.5)
10-29	3 (13)	1 (20)	0 (0)	0 (0)	2 (25)
30-49	5 (22)	0 (0)	3 (60)	1 (20)	1 (12.5)
50-69	2 (9)	1 (20)	0 (0)	1 (20)	0 (0)
70-89	3 (13)	0 (0)	1 (20)	2 (40)	0 (0)
90-109	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
≥110	5 (22)	3 (60)	0 (0)	1 (20)	1 (12.5)
Uncertain/ not applicable	4 (17)	0 (0)	1 (20)	0 (0)	3 (37.5)
# patients with a positive screen in last 6 months or less if recently implemented UTS					
0	2 (9)	0 (0)	0 (0)	0 (0)	2 (25)
1-2	1 (4)	0 (0)	1 (20)	0 (0)	0 (0)
3-5	5 (22)	1 (20)	1 (20)	2 (40)	1 (12.5)
6-10	6 (26)	1 (20)	2 (40)	2 (40)	1 (12.5)
11-15	3 (13)	2 (40)	0 (0)	1 (20)	0 (0)
16-20	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
over 20	2 (9)	1 (20)	1 (20)	0 (0)	0 (0)
Uncertain / not applicable	4 (17)	0 (0)	0 (0)	0 (0)	4 (50)

Notes: [a]NCCN and NCI designations are independent, but there is overlap and thus column percentages

Table II-3. Patient Reach[a] and Effectiveness [b]

Questions and response options	All institutions (N=23)	H-R (n=5)	M-R (n=5)	L-R (n=5)	Outcome not reported* (n=8)
% patients with positive screen that receive genetic counseling					
≤10%	5 (22)	0 (0)	1 (20)	4 (80)	0 (0)
11-25%	2 (9)	0 (0)	0 (0)	1 (20)	1 (12.5)
26-40%	1 (4)	0 (0)	1 (20)	0 (0)	0 (0)
41-55%	3 (13)	1 (20)	2 (40)	0 (0)	0 (0)
56-70%	2 (9)	1 (20)	1 (20)	0 (0)	0 (0)
71-85%	3 (13)	2 (40)	0 (0)	0 (0)	1 (12.5)
>85%	1 (4)	1 (20)	0 (0)	0 (0)	0 (0)
Uncertain / not applicable	6 (26)	0 (0)	0 (0)	0 (0)	6 (75)
% patients with a positive screen that pursue germline testing					
≤10%	5 (22)	0 (0)	0 (0)	5 (100)	0 (0)
11-25%	1 (4)	0 (0)	1 (20)	0 (0)	0 (0)
26-40%	4 (17)	0 (0)	3 (60)	0 (0)	1 (12.5)
41-55%	3 (13)	2 (20)	1 (20)	0 (0)	0 (0)
56-70%	1 (4)	1 (20)	0 (0)	0 (0)	0 (0)
71-85%	1 (4)	1 (20)	0 (0)	0 (0)	0 (0)
>85%	1 (4)	1 (20)	0 (0)	0 (0)	0 (0)
Uncertain / not applicable	7 (30)	0 (0)	0 (0)	0 (0)	7 (87.5)
Patients express concerns about UTS					
Never	9 (39)	2 (40)	5 (100)	1 (20)	1 (12.5)
Rarely	3 (13)	3 (60)	0 (0)	0 (0)	0 (0)
Sometimes	1 (4)	0 (0)	0 (0)	0 (0)	1 (12.5)
Uncertain / not applicable	10 (43)	0 (0)	0 (0)	4 (60)	6 (75)
Problems or unanticipated outcomes					
Never	9 (39)	2 (40)	3 (60)	2 (40)	2 (25)
Rarely	6 (26)	2 (40)	1 (20)	2 (40)	1 (12.5)
Uncertain / not applicable	8 (35)	1 (20)	1 (20)	1 (20)	5 (62.5)
Problems with reimbursement for tumor screening					
Never	5 (22)	1 (20)	2 (40)	0 (0)	2 (25)
Rarely	2 (9)	1 (20)	0 (0)	1 (20)	0 (0)
Uncertain / not applicable	16 (70)	3 (60)	3 (60)	4 (80)	6 (75)

Notes: [a]Percentage of patients receiving genetic counseling and germline testing after a positive tumor screen.
[b]Negative or unanticipated outcomes or problems related to universal tumor screening (UTS).

Table II-4. Reasons for Universal Tumor Screening (UTS) Adoption

Survey question	n (%)[a]				
	All Institutions (N=22)[b]	H-R (n=5)	M-R (n=4)	L-R (n=5)	Outome not reported (n=8)
Recommended by EGAPP	15 (68)	3 (60)	4 (100)	3 (60)	5 (62.5)
Improve identification of patients with LS	21 (91)	5 (100)	4 (100)	5 (100)	7 (87.5)
Reduce cancer mortality	12 (55)	4 (80)	1 (25)	2 (40)	5 (62.5)
"Keep up" with other institutions	10 (45)	1 (25)	3 (75)	2 (40)	4 (50)
Generate increased revenue	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Benefit relatives of patients with LS	17 (77)	5 (100)	3 (75)	4 (80)	5 (62.5)
Other[c]	2 (9)		1 (25)		1 (12.5)

Notes: [a]Column percentages do not add to 100 because multiple options could be chosen.
[b]One primary contact person representing a M-R institution did not answer these questions because she was not involved in the program when UTS was first implemented.
[c] Other included: *"We felt it was becoming standard of care"; "Our umbrella organization recommended"*

Table II-5. Implementation Barriers and Facilitators

Survey question	n (%)[a]				
	All Institutions (N=22)	H-R (n=5)	M-R (n=4)	L-R (n=5)	Outcome not reported (n=8)
Implementation Barriers					
No real barriers or challenges	3 (14)	2 (40)	0 (0)	1 (20)	0 (0)
Lack of stakeholder knowledge about LS	6 (27)	0 (0)	2 (50)	2 (40)	2 (25)
Concerns about reimbursement / costs	14 (64)	2 (40)	2 (50)	3 (60)	7 (87.5)
Difficulty deciding on screening method	4 (18)	0 (0)	0 (0)	2 (40)	2 (25)
Disagreement on how to handle results	3 (14)	0 (0)	1 (25)	2 (40)	0 (0)
Difficulty convincing key stakeholders why UTS is important	9 (41)	0 (0)	1 (25)	1 (20)	7 (87.5)
Challenge to arrange time for stakeholders to meet	12 (55)	2 (40)	2 (50)	2 (40)	6 (75)
Concerns about need for informed consent	16 (73)	3 (60)	2 (50)	4 (80)	7 (87.5)
One or more individuals tried to prevent UTS	1 (4.5)	1 (1)	0 (0)	0 (0)	0 (0)
Communication barriers existed between stakeholders	7 (32)	0 (0)	1 (25)	2 (40)	4 (50)
Whether to include option to 'opt out' was debated	6 (27)	1 (20)	1 (25)	2 (40)	2 (25)
Lack of laboratory expertise/resources	2 (9)	0 (0)	0 (0)	0 (0)	2 (25)
Perception that other screening method was better or more cost effective	1 (4.5)	1 (20)	0 (0)	0 (0)	0 (0)
Other[c]					1 (12.5)
Implementation Facilitators					
High risk multidisciplinary colorectal cancer clinicclnic	5 (23)	2 (40)	0 (0)	1 (20)	2 (25)
Prior to UTS, already routinely screening a subset of tumors	9 (41)	2 (40)	2 (50)	3 (60)	2 (25)
“Institutional champion” worked to implement	13 (59)	4 (80)	4 (100)	3 (60)	2 (25)
Collaborative relationships across departments	16 (73)	5 (100)	4 (100)	3 (60)	4 (50)
Support from high-level administrator or supervisor	12 (55)	2 (40)	3 (75)	3 (60)	4 (50)
Protected time provided for planning	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Useful information obtained from other institution	14 (64)	3 (60)	3 (75)	4 (80)	4 (50)
Multiple planning meetings helped facilitate	10 (45)	2 (40)	2 (50)	3 (60)	3 (37.5)
Institution willing to try something new to improve patient care	9 (41)	3 (60)	1 (25)	3 (60)	2 (25)
Total # Barriers $\geq$ Total # Facilitators	12 (55)	1 (20)	0 (0)	3 (60)	8 (100)

Notes: [a]Column percentages do not add to 100 because multiple options could be chosen.
[b]One primary contact person representing a M-R institution did not answer these questions because she was not involved in the program when UTS was first implemented.
[c]“Physicians did not realize that this had become a national and community care standard; our pathologists were under a spending freeze and not allowed to bring on new tests; concern about Medicare fraud and reimbursement in general; misunderstanding the cost of testing (physicians thought it was much higher than it is)”

Table II-6. Variability in Tumor Screening Protocols

	All institutions ([a]N=22)	H-R (n=5)	M-R (n=5)	L-R (n=5)	Outcomes not reported (n=7)
Type of tumors screened					
Colorectal tumor biopsies	3 (14)	0 (0)	2 (40)	1 (20)	0 (0)
Colorectal tumor resections	12 (55)	5	2 (40)	2 (40)	3 (43)
Colorectal tumor biopsies and resections	7 (32)	0 (0)	1 (20)	2 (40)	4 (57)
Endometrial tumors	14 (64)	5	2 (40)	3 (60)	4 (57)
Method of screening colorectal tumors					
Immunohistochemical (IHC) testing	4 (18)	0 (0)	2 (40)	2 (40)	1 (14)
IHC with automatic reflex testing	14 (64)	4(80)	3 (60)	1 (20)	5 (71)
Microsatellite Instability (MSI) testing	1 (4.5)	0 (0)	0 (0)	0 (0)	1 (14)
MSI with automatic reflex testing	2 (9)	0 (0)	0 (0)	2 (40)	0 (0)
MSI then IHC with automatic reflex testing	1 (4.5)	1 (20)	0 (0)	0 (0)	0 (0)
Who orders screening					
Nobody, automatic	8 (36)	1 (20)	5 (100)	0 (0)	2 (29)
Pathologist	6 (27)	2 (40)	0 (0)	4 (80)	0 (0)
Surgeon	2 (9)	0 (0)	0 (0)	0 (0)	2 (29)
Genetic professional	1 (4.5)	1 (20)	0 (0)	0 (0)	0 (0)
Other / unknown	5 (23)	1 (20)	0 (0)	1 (20)	3 (43)
Where screening is performed					
Internal lab	15 (68)	3 (60)	4 (80)	4 (80)	4 (57)
External lab (send out)	6 (27)	2 (40)	1 (20)	0 (0)	3 (43)
Part internal and part external	1 (4.5)	0 (0)	0 (0)	1 (20)	0 (0)
Prescreening information, consent, “opt out”					
Information on screening provided to patient before results given (usually or always)	6 (27)	2 (40)	2 (40)	0 (0)	2 (29)
Patient informed consent obtained before screening (verbal or written)	5 (23)	1 (20)	1 (20)	0 (0)	3 (43)
Option to “opt out” provided	1 (4.5)	0 (0)	1 (20)	0 (0)	0 (0)

Notes: [a]One institution with no outcomes reported was still in the process of implementing UTS and had not determined their protocol or procedures.

Table II-7. Variability in Follow-up Procedures when Patients Screen Positive for Lynch Syndrome

	All institutions ([a]N=22)	H-R (n=5)	M-R (n=5)	L-R (n=5)	Outcome not reported (n=7)
Who discloses positive screen					
Genetics professional only	9 (41)	4 (80)	1 (20)	0 (0)	4 (57)
Both genetics and non-genetics Professionals	3 (14)	1 (20)	1 (20)	0 (0)	1 (14)
Non-genetics professional(s) only	10 (45)	0 (0)	3 (60)	5 (100)	2 (29)
How positive results are usually disclosed					
Telephone call	8 (36)	3 (60)	1 (20)	0 (0)	4 (57)
At patient visit	6 (28)	2 (40)	2 (40)	1 (20)	1 (14)
Unknown / up to non-genetics Professional	8 (36)	0 (0)	2 (40)	4 (80)	2 (29)
Primary mechanism germline testing is ordered					
Patient contacted directly by GC	8 (36)	3 (60)	1 (20)	0 (0)	4 (57)
Physician refers patient	10 (45)	0 (0)	3 (60)	5 (100)	2 (29)
Genetic counselor calls physician to get referral or permission and then contacts patient directly	3 (14)	2 (40)	1 (20)	0 (0)	0 (0)
Unknown	1 (4.5)	0 (0)	0 (0)	0 (0)	1 (14)
Who provides pretest discussion of germline testing					
Genetics professional	18 (82)	5 (100)	4 (80)	5 (100)	5 (71)
Both genetics and non-genetics Professionals	3 (14)	0 (0)	1 (20)	0 (0)	2 (29)
Uncertain / not reported	1 (4.5)	0 (0)	0 (0)	0 (0)	0 (0)

Notes: [a]One institution with no outcomes reported was still in the process of implementing UTS and had not determined their protocol or procedures.

Table II-8. Variability in Follow-up Procedures when Patients Screen Negative

	All institutions ([a]N=22)	H-R (n=5)	M-R (n=5)	L-R (n=5)	Outcome not reported (n=7)
How negative screening results are handled					
Patients informed in a letter or follow-up visit	3 (14)	1 (20)	1 (20)	0 (0)	1 (14)
Non-genetics professional informs patient	1 (4.5)	0 (0)	1 (20)	0 (0)	0 (0)
Up to ordering physician	1 (4.5)	0 (0)	0 (0)	1 (20)	0 (0)
Results included in pathology report or chart but patient is not informed	15 (68)	4 (80)	3 (60)	4 (80)	4 (50)
Uncertain	2 (9)	0 (0)	0 (0)	0 (0)	2 (25)
Protocol for high risk patients with negative screen[b]					
Uncertain	3 (14)	0 (0)	1 (20)	0 (0)	2 (25)
Some patients are NOT identified as high risk	6 (27)	1 (20)	2 (40)	3 (60)	0 (0)
No formal protocol exists	5 (23)	0 (0)	1 (20)	1 (20)	3 (43)
Protocol varies					
According to physician	7 (32)	1 (20)	2 (40)	2 (40)	2 (25)
Depending on patient scenario	4 (18)	2 (40)	2 (40	0 (0)	0 (0)
Referred to genetics					
Usually	6 (27)	1 (20)	1 (20)	0 (0)	4 (57)
Sometimes	11 (50)	4 (80)	3 (60)	3 (60)	1 (12.5)
Rarely	1 (4.5)	0 (0)	0 (0)	0 (0)	1 (12.5)
Additional genetic screening or testing is considered					
Often	4 (18)	1 (20)	1 (20)	0 (0)	2 (29)
Sometimes	9 (41)	4 (80)	2 (40)	3 (60)	0 (0)
Rarely	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other[c]	3 (14)	0 (0)	2 (40)	0 (0)	1 (12.5)

Notes: [a]One institution with no outcomes reported was still in the process of implementing UTS and had not determined their protocol or procedures.
[b]High risk patients typically have one or more of the following characteristics: cancer under age 40, multiple colon polyps, previous history of colorectal cancer or other cancers, multiple family members with colorectal or other cancers.
[c]Other included the following: GC reviews pathology reports looking for other risk factors; The patient is encouraged to contact genetics if they have other red flags that are listed in the patient letter that is generated; addendum on path report re: IHC states to still refer pt to genetics if they are high risk.

Table II-9. Barriers to Genetic Counseling or Germline Testing Following a Positive Screen for Lynch Syndrome

	All institutions ([a]N=19)	H-R (n=5)	M-R (n=5)	L-R (n=5)	Outcome not reported (n=4)
Patient lacks insurance / financial difficulties[b]	15 (79)	5 (100)	3 (60)	4 (80)	2 (50)
Patient never referred[b]	12 (63)	1 (20)	3 (60)	5 (100)	3 (75)
Healthcare provider fails to see importance of counseling/testing[b]	11 (58)	0 (0)	3 (60)	5 (100)	3 (75)
Patients fail to see importance of counseling/testing[b]	13 (68)	4 (80)	3 (60)	2 (40)	4 (100)
Inconvenient for patients to arrange a separate counseling appointment	6 (32)	2 (40)	3 (60)	1 (20)	0 (0)
Inconvenient for patients to provide blood or saliva sample for testing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Difficulty contacting patients[b]	4 (21)	0 (0)	3 (60)	0 (0)	1 (25)
Patients dealing with too many issues at initial diagnosis[b]	15 (79)	4 (80)	4 (80)	3 (60)	4 (100)
Patients don't want to face possibility of risks to family[b]	8 (42)	0 (0)	3 (60)	3 (60)	2 (50)
Patients are concerned about genetic discrimination[b]	2 (10.5)	1 (20)	0 (0)	0 (0)	1 (25)

Notes: [a]Three institutions have not started screening and one institution has had no positive screens.
[b]Two questions were combined so that centers are counted as yes if the representative indicated that the item was a barrier to germline testing OR was a barrier to genetic counseling.

Table II-10. Data Matrix Depicting Patient Reach Scores and Conditions

Institution	Patient reach score[a]	# of barriers ≥ # of facilitators[b]	Automatic reflex testing[b]	Genetics usually receives copy of all positive screening results[b]	Genetics professional usually discloses positive screen result[b]	Difficulty contacting patients to arrange GC or germline testing[b]	Physician refers patient for germline testing[b]
High reach centers (H-R)							
H1	6		X	X	X		
H2	5.5		X	X	X		
H3	5		X	X	X		
H4	5		X	X	X		
H5	5	X	X	X	X		
Mid reach centers (M-R)							
M1	4			X	X	X	
M2	3.5		X	X		X	X
M3	3			X	X	X	
M4	3		X	X			X
M5	2.5		X	X			X
Low reach centers (L-R)							
L1	1.5	X		X			X
L2	1		X				X
L3	1						X
L4	1	X		X			X
L5	1	X	X	X			X

Notes: [a]Patient reach was calculated by averaging the ordinal response options from two questions estimating the percentage of patients who follow-through with genetic counseling and percentage who follow-though with germline testing after a positive screen.
[b]The presence of each condition is indicated with a "X".

Table II-11. Overall Findings from Applying the RE-AIM Framework

RE-AIM Dimension Description	**General Findings**	**Findings specific to High-Reach (H-R) Institutions**	**Findings specific to Low-Reach (L-R) Institutions**
Reach Percentage of screen positive patients who follow-through with germline testing and genetic counseling	• Patient Reach was highly variable across centers (ranging from <10% to >85%) • *High* and *Low Patient Reach* were consistently associated with specific combinations of conditions related to *Implementation*	• Patient reach (>56-70%) • H-R centers have all of the following unique conditions based on results from QCA: 1) Automatic reflex testing is performed on subset of screen positive tumors 2) *genetic counselor (GC)* discloses positive results 3) contacting patients is NOT a major barrier 4) obtaining a referral from physician is NOT a barrier	• Patient reach (< 25%) • L-R centers have either of the following unique conditions based on QCA results: GC does NOT disclose results AND implementation barriers ≥ facilitators OR GC does NOT receive screening results
Effectiveness The impact of an intervention on outcomes (including potential negative effects)	• Institutional representatives report patients rarely or never have expressed concerns related to UTS • Challenges have been encountered at both H-R and L-R institutions • Only two centers reported rarely experiencing difficulties with reimbursement for tumor screening; others did not know or reported no reimbursement issues	• H-R centers adapted to compensate when faced with challenges • Early on or prior to UTS, two H-R centers recognized that pathologists were doing screening on subset of patients, but physicians were neither reporting out the result to patients nor referring patients for genetic counseling	• L-R centers reported difficulties with patient reach, and many reported challenges to making changes • **Potential negative outcomes included:** • Concern that failure to disclose results, refer to genetic counseling, or order germline testing is a liability for institutions and/or physicians • Concerns raised by one L-R center that reflex tests are interpreted incorrectly or not seen on pathology addendum

Table II-11 (continued).

Adoption The absolute number, proportion, and representativeness of institutions and staff who currently offer a program Characteristics of intervention may increase the likelihood of adoption	• Academic centers have previously been found to be more likely to adopt UTS (Beamer et al., 2012) • At most centers genetic counselors were the source of the idea for UTS, but multiple stakeholders were often involved in making the decision to adopt UTS. • Common reason for UTS adoption are to improve identification of Lynch syndrome patients and benefit family members • Cost was a key characteristic in the decision to adopt UTS	• All but one of the five H-R institutions are academic /research institutions	• Two of the five L-R centers are academic institutions
Implementation Consistency of delivery, time and cost of the program, and what adaptations to the program are made in various settings.	• Successful implementation required buy in from others besides genetic counselors. • Substantial heterogeneity in UTS implementation exists across institutions • Several of the differences are NOT consistently associated with *patient reach* including method of screening IHC versus MSI, and whether results are disclosed by phone or in person. • Common barriers and facilitators to implementation were identified (Table II-5)	Several adaptations have been made to streamline the process and overcome barriers: • Automate reflex testing to reduce the number of patients needing counseling and germline testing • GCs disclose results • Eliminate the need for a referral from another health care provider entirely • Lack of referral overcome at a couple of H-R centers by GC actively contacting physicians to obtain permission to contact patient directly and log in the referral if needed • At least 3 H-R centers found that meeting the patient at a follow-up appointment was successful because it removes additional barriers.	• The number of implementation barriers was greater than or equal to the number of facilitators for three of the L-R centers • L-R center representatives want the ability to contact patients directly, but physicians are resistant. • L-R centers where GC actively solicits a referral from physicians are reliant on physician believing and expressing the importance of genetic counseling and germline testing to the patient. • Not logistically feasible for GCs to meet patients at follow-up appointments at some institutions.

Table II-11 (continued).

Maintenance How the intervention and its effects changed over time.	• Some centers have modified their protocol over time such as making BRAF or hypermethylation testing automatic in a subset of tumors. • Centers have also changed their follow-up procedures over time.	• At least 3 H-R centers report having changed their procedures over time to streamline the process and increase involvement of GCs, which resulted in higher patient reach	• Several L-R centers have run into barriers in trying to change their protocols or procedures • At least one L-R center has since changed their procedures as a result of the current study

SECTION III: QUALITATIVE COMPARATIVE ANALYSIS (QCA): A HYBRID METHOD FOR IDENTIFYING KEYS TO SUCCESSFUL PROGRAM IMPLEMENTATION

Abstract

Qualitative comparative analysis (QCA) is a hybrid analytic technique that combines elements of quantitative and qualitative research. Despite several relative advantages of QCA, this article illustrates that it has not been widely adopted by mixed methods researchers and has been slow to diffuse through health research channels. Applying the Diffusion of Innovations Theory, potential reasons for limited diffusion and adoption of QCA are explored. Finally, to reduce perceived complexity of QCA, data obtained as part of a multiple-case study is used to demonstrate how to perform QCA and illustrate several associated limitations and benefits.

Introduction

Use of what is still sometimes dichotomized into qualitative and quantitative research methods in complimentary or comparative ways has become widely accepted in several social science disciplines (Bazeley, 2009). In contrast, analytic techniques that fuse or blend qualitative and quantitative methods are not routinely utilized (Ragin, 1999). Qualitative comparative analysis (QCA) is a method developed by Charles Ragin over 25 years ago (Ragin, 1989) to bridge the qualitative and quantitative research gap. Although rooted within a qualitative research paradigm (Ragin, 1989), QCA takes a practical approach to

understanding complex, real-world situations and therefore may more accurately fall within what Morgan (2007) promotes as a pragmatic paradigm. QCA is a hybrid technique that cannot easily be dichotomized as either “qualitative” or “quantitative”, yet many criticisms that researchers have leveled at QCA originate from what researchers have referred to as the “paradigm wars” (Morgan, 2007).Other criticisms are based on the perceived complexity or lack of relative advantage of QCA over other methods (Hawley, 2007).

Despite criticisms QCA is extremely versatile. For example, researchers have used QCA to analyze both unstructured data (e.g., interview transcripts) and structured data (e.g., responses to closed-ended survey questions) (Kahwati et al., 2011; Shanahan, Vaisey, Erickson, & Smolen, 2008; Weiner, Jacobs, Minasian, & Good, 2012). In addition, QCA can be used to analyze small, medium, and large sample sizes. Furthermore, QCA has been used in conjunction with various types of research designs.

Although QCA has many applications, it was initially developed for case study research in order to derive solutions that contain a list of one or more factors that when present or absent are uniquely associated with the presence or absence of an outcome. Other methods of performing multiple cross-case comparisons exist, but as the number of cases increases, systematic comparisons across multiple cases may not be logistically feasible without using QCA software. Additionally, journals that publish primarily “quantitative” research may look more favorably on QCA due to its mathematical approach and ability to quantitatively assess the overall merit of the solutions.

QCA may also be particularly useful in theory development and model building by determining which combinations of conditions are likely to be 'necessary' and/or 'sufficient' for a particular outcome of interest to occur. For example, knowledge about a positive health behavior may be necessary, but it is rarely sufficient to ensure that individuals will perform the health behavior. According to the Health Belief Model (Janz & Becker, 1984), individuals often require a combination of the following factors in order to perform a positive health behavior: 1) knowledge about the behavior; 2) high level of perceived threat to their health if they fail to perform the behavior; 3) high-level of perceived benefits to performing the behavior; and 4) low-level of perceived barriers to performing the behavior. The ability to identify this type of “causal complexity” is one reason why QCA can be useful when generating or testing theoretical models (Ragin, 1989).

Structural equation modeling (SEM) is a more commonly used analytic technique that also allows researchers to incorporate multiple variables and test theoretical models. Although Hawley (2007) has argued that SEM would be easier to use than QCA, SEM requires large samples and the results are interpreted in a reductionist manner by considering the influence that one variable has on the outcome while holding all other variables in the model constant. Furthermore, unlike QCA, SEM and other inferential statistical analyses typically fail to consider the possibility of equifinality, whereby different combinations of factors can lead to the same outcome (Ragin, 1989; Rihoux & Ragin, 2009). For example, the combination of knowledge about how to perform

a behavior and a high level of perceived benefits may be sufficient to elicit a positive health behavior among a subset of women who do not face a particular barrier; however, additional or different factors may be needed to elicit the behavior among other individuals. If a key factor is relevant to the outcome for only a subset of individuals, the correlation between the factor and outcome is weakened, potentially causing what may be a key factor to be deemed insignificant if inferential statistics are used. Additionally, inferential statistics assume that the influence of variables is symmetrical even though factors that lead to the consistent performance of a health behavior may be different from factors that cause poor adherence to the behavior.

Despite several relative advantages to QCA it remains unclear why this hybrid analytic technique has not diffused more widely across academic disciplines. In addition, the extent to which QCA has been adopted among various populations is not well documented. Thus, the first objective of this article is to describe QCA's lack of both widespread diffusion through health research channels and adoption among mixed methods researchers. To achieve this objective, results are presented from a literature search of articles indexed by *PubMed* and articles published in the *Journal of Mixed Methods Research*. The second objective is to discuss several potential reasons for the slow diffusion and adoption rates of QCA. Subsequently, to promote the broader goal of active QCA dissemination, the final objective is to increase knowledge of QCA. To achieve the final objective we demonstrate how to perform QCA and illustrate several limitations and benefits of QCA using data obtained as part of a multiple-case

study.

Diffusion and Adoption of QCA

The index term “qualitative comparative analysis” was used for online searches of articles indexed by both PubMed and the Journal of Mixed Methods Research (JMMR). The abstracts of all articles that were retrieved after typing in the search term were reviewed. Several of the complete articles identified in PubMed and all of the articles identified in JMMR were reviewed. Articles were initially counted if the authors employed QCA in an original research study or illustrated the use of QCA using hypothetical data. However, to be more inclusive the literature search was extended to include any articles where the author(s) described or mentioned QCA.

Only 25 articles meeting the original criteria had been indexed by PubMed as of March 2013. Of these, all but one reported data from an original study. After extending the criteria, an additional PubMed article was included. This article described QCA and other methods of synthesizing qualitative and quantitative evidence. No articles published in the Journal of Mixed Methods Research (JMMR) met the initial search criteria, but 7 met the expanded criteria. The single article in JMMR to focus solely on QCA was a book review by Hawley (2007). An additional six articles mentioned QCA during discussions on various topics including: integration in mixed methods research (Bazeley, 2009; Bazeley & Kemp, 2012); mixed research synthesis (Sandelowski, Voils, Leeman, & Crandell, 2012); triangulation strategies in Comparative Public Policy Research (Wolf, 2010); qualitative data analysis tools (Onwuegbuzie, Bustamante, &

Nelson, 2010); or data analysis as a process of interpretation (Van Ness, Fried, & Gill, 2011).

Although limited in scope, this literature search substantiates the assertion that QCA has been slow to diffuse into health research. The findings also suggest that the rate at which QCA is being used in health research may be increasing over time. Support for this latter assertion comes from the finding that half of the QCA articles identified in PubMed were published between the years 2010 through 2012; and nine of these articles were published after 2011.

Diffusion of Innovations Theory (Rogers, 2003) provides several possible explanations for these findings. First, an innovation takes time to diffuse within and across social groups and the rate of diffusion is dependent on communication channels. QCA was developed in the late 1980's by Charles Ragin, a Sociologist who studies politics (Ragin, 1989). QCA therefore had to spread across members of those disciplines through a limited number of communication channels into other disciplines. Second, QCA is viewed by some researchers as being incompatible with the methodological paradigm to which they may still subscribe (Barbour, 1998). “Qualitative” researchers might view QCA as incompatible because it is based on Boolean algebra and a computer program is typically used to aid the researcher in identifying solutions which are then evaluated using quantitative measures of solution consistency and coverage. Whereas “quantitative” researchers may view QCA as incompatible because it entails an iterative process of evaluating data, typically from a non-random sample, and requires researchers to use their substantive knowledge of

the cases to make several 'subjective or interpretive' decisions at multiple points during the analysis (Rihoux & Ragin, 2009). Third, knowledge about how QCA works may be limited as there appear to be a relatively small number of researchers who have been trained to conduct QCA. Fourth, performing QCA was complex until computer software became widely available and automated much of the process. Nevertheless, Hawley (2007) has pointed out that the unique terminology used in QCA also makes learning this technique inherently difficult. Furthermore, additional complexities have arisen as researchers have developed several different types of QCA or other related configurational comparative techniques since QCA was first introduced (Rihoux & Ragin, 2009).

Given that mixed methods researchers generally take a pragmatic approach that transcends the positivist/constructivist or quantitative/qualitative “paradigm wars” (Morgan, 2007), findings which suggested that few mixed methods researchers have adopted QCA were somewhat surprising. Hawley’s (2007) description of QCA in the book review published in JMMR suggests that high perceived complexity and lack of relative advantage over other techniques may explain the slow diffusion and low adoption rates. Therefore, to reduce complexity, the following section provides a stepwise account of how QCA was instrumental as an initial step in a multiple-case study designed to evaluate the implementation processes and effectiveness of universal tumor screening programs at several hospitals and cancer centers.

Background on Universal Tumor Screening (UTS) for Lynch syndrome

Occurring in approximately 1 out of every 35 patients with colorectal cancer

(Hampel et. al., 2008), Lynch syndrome is the most common cause of hereditary colorectal cancer (CRC). The identification of Lynch syndrome among CRC patients and subsequently their family members is critical as Lynch syndrome confers a 50-70% lifetime risk of colorectal cancer (CRC) (Barrow et al., 2008; Hampel, Stephens, et al., 2005; E. Stoffel et al., 2009) as well as increased risks for secondary cancers and several other types of malignancies (Barrow et al., 2009; Hampel, Stephens, et al., 2005; Stoffel et al., 2009; Watson et al., 2008).

Universal tumor screening (UTS) is the process whereby tumors from all newly diagnosed CRC patients are screened to identify those patients who may have Lynch syndrome. Details about UTS have been described elsewhere (Bellcross et al., 2011). Over 35 cancer centers and hospitals across the U.S have implemented UTS, but substantial variability in protocols and procedures exist across institutions (Beamer et al., 2012; Cohen, 2013). Outcomes also vary across institutions as noted by large differences in patient reach, which is defined here as the percentage of patients with a positive screen who follow-through with genetic counseling and germline testing (Beamer et al., 2012; Lynch, 2011; South et al., 2009). In view of the fact that patient reach is critical to the successful identification of family members with Lynch syndrome and the prevention or early detection of cancers, a multiple-case study was initiated to identify institution-level factors that might contribute to the wide variability in patient reach.

Methods

Study Design

A multiple-case study was initiated during the fall of 2012. The rationale

for employing a multiple-case study design was based on the following (adapted from Yin, 2008): (a) the key objective was to provide a detailed understanding of a complex phenomenon (i.e. UTS program implementation and patient reach) for which there is limited data; (b) the purpose was to answer how and why questions; (c) the behavior of those involved could not be manipulated; and, (d) it was hypothesized that contextual conditions would be relevant to variations in patient outcome .

Conceptual Framework

The conceptual framework for the multiple-case study was based on the RE-AIM evaluation framework and the Consolidated Framework for Implementation Research (CFIR) (Damschroder et al., 2009; Glasgow et al., 1999). The RE-AIM evaluation framework is comprised of five evaluation dimensions (*Reach, Effectiveness, Adoption, Implementation, and Maintenance)* that assist with identifying factors for multi-level comprehensive evaluations (Glasgow, Klesges, et al., 2006). In the current study the RE-AIM evaluation dimensions were defined as follows:

- *Reach*: the percentage of patients with a positive tumor screen who follow-through with genetic counseling and germline genetic testing.
- *Effectiveness*: the impact of UTS on outcomes (including potential negative effects).
- *Adoption*: the absolute number, proportion, and representativeness of institutions and staff who implement UTS.

- *Implementation*: the consistency of delivery, time and cost of the UTS program and what adaptations are made in various settings
- *Maintenance*: the effects of UTS over time with regard to both the institution and patients.

RE-AIM was selected based on the expectation that it would increase the quality, speed, and impact of stakeholder efforts to more effectively translate universal tumor screening for Lynch syndrome into practice. The CFIR provided a framework for exploring factors within the *Implementation* dimension of RE-AIM in order to gain a detailed understanding of UTS implementation and identify factors that might influence patient reach. Table III-1 lists the five CFIR dimensions and several constructs within each (Damschroder et al., 2009).

Study Participants

Fifteen representatives for the Lynch Syndrome Screening Network (LSSN) who worked at institutions that perform UTS were recruited through the LSSN listserv. These participants completed an initial survey and met the minimum a priori inclusion criteria as follows: 1) institutions must have been performing Lynch syndrome screening on tumors from all newly diagnosed colorectal cancer (CRC) patients for at least six months; and 2) institutional data on patient follow-through with genetic counseling and genetic testing was shared by the institutional representative.

Measures

The initial online survey was developed using the RE-AIM and CFIR frameworks as well as the researchers' knowledge of institutional variations in

UTS protocols. Information collected included: a) length of time UTS had been performed at the institution; b) details on the implementation process, protocol, and procedures (e.g., facilitators and barriers to implementation; method of screening; who receives and/or discloses positive screening results; who discusses germline testing with the patient; and when, where and how screening results are disclosed and germline testing is discussed); c) percentage of patients who undergo genetic counseling and percentage who undergo germline testing that were used to calculate the outcome (i.e., patient reach); and, d) additional factors within CFIR domains that may have helped facilitate or impede implementation or patient reach.

Crisp-Set Qualitative Comparative Analysis (csQCA)

In the current study QCA was used to identify facilitators, barriers or other institution-level conditions that were unique to centers with high patient reach and those that were unique to centers that did not report high patient reach. Crisp-set QCA (csQCA) was chosen for two main reasons: 1) the conditions assessed as part of the survey were dichotomous; and 2) csQCA is simpler to perform and interpret than other QCA methods. Steps used to perform csQCA are summarized in Table III-2. These steps are somewhat fluid because QCA is an iterative process that allows for modifications as researchers gain additional information and insights into the cases. Briefly, steps 1-3 are needed to prepare data for use in QCA. Step 4 involves deciding which type of analyses to perform (i.e., necessary and/or sufficiency analyses). Steps 5-9 describe how to determine which conditions are sufficient for the outcome. Step 10 is the step in

which solutions are interpreted to propose “causal models”.

Step 1: Outcome operationalization and set membership scoring. Patient reach was operationalized using two questions assessing the percentage of patients who follow-through with genetic counseling and percentage who follow-through with genetic testing. Response options were the same for both questions: 1 = <10%; 2 = 11-25%; 3 = 26-40%; 4 = 41-55%; 5 = 56-70%; 6 = 71-85%; and 7 =>85%. The ordered categorical response options for the two questions were averaged to create a “patient reach” score ranging from 1-7. After arranging cases in descending order by patient reach, two natural breaks in patient reach scores were identified (Table III-3, column 1). The first 5 cases were grouped into a “high-reach” set (H-R), the second 5 cases into a “mid-reach” set (M-R) and the last 5 into a “low-reach” set (L-R). Natural breaks were chosen to ensure that cases with very similar values were grouped together in the H-R and L-R groups, as has been recommended (Rihoux & De Meur, 2009)

One key limitation of cs-QCA is that all variables, including the outcome, need to be dichotomized so that the case either belongs to the set (dummy code=1) or does not belong to the set (dummy code=0). In the current study the threshold for inclusion in the H-R set was a patient reach score $\geq$5. All other cases did not belong in the H-R set. In QCA cases not in a set are referred to by placing a tilde before the abbreviation (i.e., ~H-R).

Step 2: Case selection. Although QCA has been used to analyze data from random samples, it was developed to compare cases that are carefully selected using one of a number of different selection procedures (Gerring, 2007). In the

current study at least a few institutions with high patient reach and a few institutions with low patient reach were needed to determine why large discrepancies in patient reach might exist across institutions. To maximize both sample size and diversity in contextual variables, all cases that met minimal inclusion criteria were included and dichotomized according to membership in the H-R set.

Step 3: Selection of key conditions. Although many CFIR constructs were measured to assist in gaining an in-depth understanding of each case, only a relatively small number of key factors could be used in QCA for two main reasons. First, the number of possible configurations increases exponentially according to an increase in the number of contextual variables; and this increases the likelihood that there will be a number of configurations for which there are no cases (i.e.,remainders). Second, when the ratio of conditions to cases is high, the probability of getting a solution that just by chance appears sound even when the model is misspecified increases (Marx & Dusa, 2011). Guidelines from a simulation study by Marx and Dusa (2011) were therefore followed by limiting analyses to no more than 4 conditions so that misspecification of the model would most likely lead to contradictory cases (i.e., cases with the same configuration of conditions, but different outcomes).

In the current study, processes related to results disclosure and discussion of germline testing as well as the individuals involved with these processes were hypothesized to have the most direct influence on patient reach. As a first step in narrowing down the number of conditions to consider for QCA, a computer

spreadsheet of responses from each institutional representative was created by the researchers with cases organized from highest to lowest patient reach. Frequencies of responses were then generated for each *reach* category (i.e., H-R, M-R, L-R). Each contextual factor was evaluated by the researchers in terms of how it might relate to patient reach independently or in combination with other factors. During the selection process the researchers created a data matrix (Table III-3) of membership scores for the factors considered for inclusion in QCA. The data matrix was then reviewed by the researchers to narrow down the list of conditions. This process consisted of a series of decisions described in more detail below whereby similar pairs of conditions were combined to create composite conditions (presented in Table III-3); and several conditions were then deleted from Table III-3.

General differences between patient reach groups were found with regard to who discloses abnormal (positive) screening results to patients. All representatives of the H-R institutions reported that a genetics professional discloses abnormal screening results to patients. There were also two M-R institutions where a genetics professional discloses positive results. This condition was included in QCA and is referred to as (gen_prof_disclose_screen). How positive results were disclosed (i.e., by phone or at a follow-up visit) was mixed across the patient reach groups; and was subsequently deleted from the data matrix.

Several conditions that could act as barriers to follow-through with genetic counseling and germline testing were also considered (Table III-3). Obtaining a

referral from a healthcare provider as the primary mechanism for the patient to receive germline testing was reported by most ~H-R institutions and was coded as (referral_barrier) for use in QCA. Similarities were noted in the pattern of responses for other barriers to genetic counseling and barriers to germline testing. Therefore analogous pairs of barriers were combined using the Boolean operator “OR”, which indicates Boolean addition. As an example, the new composite condition (difficulty_contact_pt) was “present” if (1) the institutional representatives indicated that difficulty contacting patients to set up genetic counseling was a barrier “OR” (2) that difficulty contacting patients to set up germline testing was a barrier. Whereas if neither of these barriers were reported, then the new composite condition was considered absent. Conditions used to create the composite barriers were maintained in the data matrix for possible inclusion in QCA.

Nearly all institutions have genetics professionals provide pretest counseling prior to germline testing. Consequently, this condition was deleted from the data matrix because unless a condition varies, it cannot be associated with the outcome (Rioux ch 3). The revised data matrix contained three conditions selected for inclusion in QCA (gen_prof_disclose_screen, referral_barrier, and gen_directly_contacts_pt) as well as several additional barriers to consider including. Once complete, the principal investigator saved the data matrix (which was in an Excel spreadsheet) as a .csv file because this type of file can be opened and read by fsQCA2.0 software using the point and click FILE menu (“Citing fs/QCA,” n.d.).

Step 4: Decide which analyses to run. While the focus of QCA is often on identifying conditions that are sufficient for the presence of an outcome, researchers have suggested that sufficiency analysis be preceded by identifying potential necessary conditions (Schneider & Wagemann, 2010). A necessary condition is one that occurs in all cases that demonstrate the presence of the outcome. There are many instances where a theory or previous empirical observations would lead researchers to hypothesize that certain conditions may be either 1) necessary and sufficient for an outcome or 2) necessary but insufficient for an outcome. However, in the current study, none of the conditions were originally hypothesized to be necessary in all cases. Therefore, only analyses to determine sufficiency were performed.

FsQCA 2.0 software developed by Charles Ragin was chosen to run the sufficiency analyses as it is freely available for download online at http://www.u.arizona.edu/~cragin/fsQCA. A manual detailing how to use this software is also available at the same website. However, to help decrease perceived complexity, basic steps performed in the current study are described below. Also, to reduce complexity, key terms are defined and illustrated throughout the step-by-step description, but QCA jargon is used sparingly.

Step 5: Determine if conditions are sufficient. Using fsQCA software, "Truth Table Algorithm" was selected under the ANALYSE > Crisp sets menu. The outcome and conditions were chosen as prompted in the pop-up window before clicking the "run" button. The software then created a truth table similar to the replica in Table III-4. Each row of the truth table shows a configuration of

conditions and lists the number of cases that share that configuration. As is often the case, several configurations had no case examples (rows E-H); and these are called remainders (Rihoux & Ragin, 2009).

Step 6: Examine the truth table and resolve contradictions. The objective when creating a truth table is to ensure that all cases that share a configuration also share the same outcome. The consistency score for each row indicates the proportion of cases in the respective configuration that belong to the H-R set (i.e., outcome is present). When the consistency is above .9 it indicates that the configuration of conditions is almost always associated with the presence of the outcome (Rihoux & Ragin, 2009). In the initial truth table (Table III-4) generated for the current study, rows A and B have consistency scores of 0.8 and 0.5, respectively. This suggests that these rows represent configurations where the outcome is inconsistent. Specifically, row A represents a configuration that is shared by 4 H-R cases and 1 M-R case; and row B represents a configuration that is shared by 1 H-R case and 1 M-R case. The need to resolve such contradictions often occurs in QCA (Marx & Dusa, 2011). Contradictions provide researchers an opportunity to gain additional understanding of the cases and serves as a mechanism for building models (Ragin, 2004). For example, contradictions could indicate that a key condition is missing from the model.

To resolve the contradictions, the research team went back to the reduced data matrix to examine the cases and select another key barrier. Logic dictated that difficulty contacting patients after a positive screen (difficulty_contact_pt) would directly lower patient reach. Once this condition was added, the new truth

table contained no contradictions (Table III-5). The consistency scores for the first two configurations (rows A-B) were 1 and the consistency scores for the other configurations (rows C-F) were 0. Thus, the outcomes of the first two configurations (rows A-B) were coded 1 by the researchers and the outcomes of all the other configurations for which there were cases (rows C-F) were coded 0. Table III-5 does not show configurations (rows) for which there were no cases (i.e., remainders), as these configurations were deleted before running a standard analysis.

Step 7: Use software to generate solutions. Although the final truth table (Table III-5) is quite revealing in terms of which contextual conditions are associated with high patient reach, it can be helpful to have the computer software generate three solutions (complex, parsimonious, and intermediate), particularly when truth tables are large, multiple different configurations are associated with the same outcome, or fuzzy-set QCA (in which outcomes and/or conditions are not dichotomized) is used instead of crisp-set QCA. As part of the current study, the researchers ran a “Standard Analysis” by clicking this option in the menu at the bottom of the window. The computer software used the Quine-McCluskey algorithm (which is based on Boolean simplification) to make multiple comparisons of case configurations and logically simplify the data ("Citing fs/QCA 2.0," ; Rihoux & Ragin, 2009). The idea behind this minimization procedure is that if two configurations differ in only one condition, yet produce the same outcome, then the condition that distinguishes the two configurations can be considered irrelevant to the outcome and removed to create a simpler

expression.

The fsQCA2.0 software determines three solutions with input from the researchers. The first is the complex solution, which is determined by the computer through minimizing only those configurations for which cases are available (i.e., remainders are not used to make simplifying assumptions). When there are multiple conditions or multiple configurations leading to the presence of the outcome, this solution may be so complex that it is not very useful. This is why the software generates a parsimonious and intermediate solution with input from the researchers.

To determine the parsimonious solution, the software makes assumptions about what the outcome might be for the configurations that do not have cases (i.e., remainders) and uses these remainders to further simplify the expression. During the minimization process in the current study, a “prime implicant chart” appeared on the screen. A prime implicant chart appears when there are multiple ways of simplifying a solution. In order to obtain the most parsimonious solution, researchers must choose one prime implicant to cover each configuration in the chart. In the notation for prime implicants, the tilde (~) indicates the condition is absent. An asterisk (*) indicates Boolean “AND” (meaning that the conditions joined by * must both be present). The prime implicant chart in the current study showed that the configurations for the H-R cases could be simplified in two different ways: (a) ~referral_barrier * ~difficulty_contact_pt; or (b) gen_prof_disclose_screen * ~difficulty_contact_pt. Despite an inability to make a compelling argument for choosing one prime implicant over the other, in the

current study the researchers chose the first prime implicant so that the software would continue the analysis. In some instances (such as the current study) the prime implicant chosen to create the parsimonious solution does not influence the researchers' final interpretation because they will reject the parsimonious solution if they cannot use logic and knowledge of the topic to substantiate all of the simplifying assumptions upon which the parsimonious solution is based.

Even though it is often the case that assumptions underlying the parsimonious solution cannot all be reasonably justified by the researchers, certain assumptions might be easy for the researchers to substantiate to create an intermediate solution; these are referred to as "easy counterfactuals"(Ragin, 2004). As part of the analytic process, the computer software automatically opens another window so that researchers can decide which simplifying assumptions are reasonable. In order for the software to generate the intermediate solution in the current study, the following logic-based assumptions were selected:

1. Absence of each barrier (i.e., ~difficulty_contact_pt and ~referral_barrier) will contribute to high patient reach (H-R), but the presence of each barrier will not contribute to H-R.
2. Involvement of a genetic professional in the disclosure of screening results (gen_prof_disclose_screen) and in directly contacting the patient to arrange genetic counseling and testing (gen_directly_contacts_pt) will contribute to high patient reach, while lack of involvement by genetics professionals will not be associated with H-R.

Step 8: Determine if the influence of conditions is symmetrical. The combinations of factors that are associated with high patient reach may differ from those associated with less successful outcomes. In the real world there are often more pathways that lead to the failure of a health program than there are leading to successful programs. Because QCA is not based on correlations, it does not assume that conditions will have a symmetrical influence. To illustrate this point, QCA steps 4-6 were repeated using the absence of high patient reach (~HR) as the outcome. During this analytic process the latter of the following two prime implicants was chosen to be consistent with the initial analysis: (a) ~gen_prof_disclose_screen or (b) referral_barrier. Assumptions made to generate the intermediate solution were the inverse of the assumptions chosen for the first analysis (i.e., presence of barriers would contribute to ~H-R, and absence of involvement by genetics professionals would contribute to ~H-R).

Step 9: Evaluate consistency and coverage scores for the solutions. Consistency and coverage are interpreted differently when determining whether conditions are necessary versus when determining if they are sufficient. When performing sufficiency analyses, solution consistency should be close to 1 in order for researchers to conclude that the combination(s) of conditions in the solution is(are) almost always associated with the outcome of interest (Ragin, 2004). A solution coverage of 1 indicates that all cases with the outcome of interest are represented or covered by at least one of the combinations of conditions in the solution. When there are multiple combinations of conditions within a solution, raw and unique coverage can be used by the researcher to

assess the importance of each combination of conditions and the extent to which a case is covered by more than one combination of conditions.

Step 10: Interpret the resulting solutions and create causal models. Even if conditions are consistently associated with an outcome, it does not mean they cause the outcome. However, researchers can use solutions in conjunction with theory, conceptual frameworks, and detailed knowledge about the cases to develop causal models that help unpack potential mechanisms leading to the outcome (Ragin, 2004). In the current study the researchers used their substantive knowledge of UTS and theoretical framework (CFIR) to interpret the solutions and piece together key conditions to create tentative models that were intended to be modified as additional details about the cases were obtained.

Results

Table III-6 lists the complex, parsimonious, and intermediate solutions from the first csQCA analysis performed to determine institutional and implementation conditions associated with high patient reach (H-R). The parsimonious solution was rejected because all of the simplifying assumptions could not be substantiated. The model was based on the intermediate solution, which in this case, happened to be the same as the complex solution. This intermediate solution is interpreted as meaning that all of the following three conditions are together sufficient for high patient reach: 1) a genetics professional discloses the results of positive tumor screening to patients; AND 2) a referral from another health care provider is not the primary mechanism for the patient to receive testing; AND 3) difficulty contacting patients is not a barrier.

This combination of three conditions is unique only to the H-R cases, which is why the consistency score is 1. The coverage score of 1 verifies that that this combination of three conditions characterizes (covers) all 5 cases that belong to the H-R set.

The bottom of Table III-7 presents all three solutions for the absence of the outcome (i.e.,~H-R). The three solutions were all different; thus, the causal model was based on the intermediate solution because it was not too simple, but made more logical sense than the complex solution. The intermediate solution for absence of high reach (~H-R) revealed two distinct sets of conditions that were both associated with the absence of the outcome (Table III-6). The intermediate solution can be interpreted as meaning that difficulty contacting patients who screen positive is sufficient but not necessary to prevent high patient reach. Alternatively the following three conditions are together sufficient to prevent high patient reach: genetic professionals do not disclose positive screening results, AND genetic counselors do not contact patients directly to arrange genetic counseling and testing, AND health care provider referral is the key mechanism for patients to receive genetic testing. The consistency of the intermediate solution was 1, indicating there were no contradictory cases. The coverage score of 1 indicates that all cases without high-reach (~H-R) fit one or both of the combinations in the solution. The raw coverage for the first configuration (i.e., difficulty contacting patients) was 0.3, indicating that the presence of this barrier distinguished 3 of the 10 ~H-R cases from the H-R cases. The unique coverage for this configuration was lower (0.2) because 1 of the 3 institutions with difficulty

contacting patients also shared the second combination of conditions that uniquely covered the other ~H-R cases (Table III-6).

Discussion

QCA was used as part of a multiple-case study to formulate tentative causal models explaining high variability in patient reach across institutions that have implemented a universal tumor screening program. Nevertheless, models may be overly simplistic; and findings do not preclude the possibility that other combinations of factors could lead to high patient reach at institutions that were not part of the current study. Indeed one advantage of QCA is that it can identify multiple different “recipes” for success. Subsequently, as more information about each institution is obtained and additional cases are identified it is likely that the model will be expanded and modified.

QCA was also useful in identifying additional research questions to be explored as part of the ongoing multiple-case study. For example, why did representatives from the five high-reach centers report no difficulty contacting patients or obtaining a referral from a health care provider? In addition, what may prevent stakeholders at low or mid-reach centers from: (a) altering the UTS procedures so that genetics professionals contact patients to disclose positive screening results; and (b) eliminating the need for a referral? Insights gained from QCA have informed the creation of semi-structured interview guides and follow-up surveys to answer further questions that were identified during the process of QCA, obtain information on the nuanced differences between UTS programs at different institutions, and possibly reveal other key conditions that

may contribute to patient reach as part of a continuing iterative process to better understand how implementation factors influence patient reach.

Many criticisms that researchers have leveled at QCA originate from what Morgan (2007) referred to as the “paradigm wars”. For instance, researchers who view QCA using a “quantitative” lens might consider performing multiple analyses on the same data to be problematic. However, multiple analyses are consistent with the iterative nature of QCA. Furthermore, determining which factors are associated with both the presence and absence of the outcome is considered good practice by QCA researchers (Schneider & Wagemann, 2010) as it can provide broader or more in depth insights into the underlying mechanisms and can add to the credibility of the proposed models. Several other concerns that critics raise such as the use of purposive sampling and the iterative nature of QCA are also unproductive from a pragmatic perspective. Nevertheless, several more practical limitations are worth mentioning.

One limitation of QCA is the potential for measurement error and case misclassification. The current study was based on data that were self-reported by a single individual from each institution and may contain inaccuracies or bias. Furthermore, the use of natural breaks for set membership scoring does not prevent the possibility of misclassification. For example, an open-ended survey response from the institutional representative of a mid-reach (M-R) center revealed that this institution may instead belong in the high-reach (H-R) set due to a unique difference in this institution’s protocol that may have led to an underestimation of patient reach. This institution had the highest patient reach

among the M-R set and was similar to H-R institutions in several ways. However, the representative reported difficulty contacting patients as a barrier. Given that difficulty contacting patients was sufficient to prevent H-R under the current model, reclassification of this institution into the H-R set would unveil a contradiction that would need to be resolved through modifications to the model based on additional information. For instance, it is possible that the genetic professional at this M-R institution has relatively few difficulties contacting patients. Unfortunately, the extent to which patient contact is difficult was not captured in the survey measure.

The measurement issue described above illustrates a limitation of crisp-set QCA, whereby conditions and outcomes must be dichotomized. In contrast, fuzzy-set QCA overcomes this limitation by allowing the researcher to code the outcome and/or conditions on a calibrated scale from 0 to 1. This fuzzy-score represents the extent to which a case falls within the set rather than being fully in or fully out of a set (Rihoux & Ragin, 2009). The resulting advantages of fsQCA over csQCA include the ability to maintain variation and to more accurately represent social reality when outcomes and/or conditions are not truly dichotomous. Although bias and measurement error may remain a concern, using fsQCA may lead the researcher to assign a set membership score that is off by only a small degree rather than misclassifying it into the opposing set; and this is expected to have a smaller impact on the results. Unfortunately, the advantages of fsQCA also make it more complicated than csQCA.

Conclusion

Although rooted in a qualitative paradigm, QCA may appeal to researchers or journal editors that prefer “quantitative” methods because QCA: (a) takes a logical and mathematical approach; (b) can be used to analyze small, medium, and large data sets; (c) provides a tool for identifying causal complexity and equifinality; (d) allows the researcher to generate solutions (with the aid of a computer program); and (e) calculates measures to evaluate the merit of the solutions (i.e., solution consistency and coverage). Given that QCA confers several advantages over other techniques, one of the purposes of this article is to encourage its active diffusion across mixed methods research channels. This article has attempted to reduce perceived complexity of QCA by illustrating how to perform the simplest type of QCA (i.e., crisp-set QCA). The example presented here demonstrated how QCA aids in systematically identifying and simplifying key factors (i.e., conditions) that are uniquely associated with an outcome of interest. Although the use of cross-sectional data inhibits the ability to demonstrate causation, QCA provides solutions that researchers can use to propose logical mechanisms by which key factors may act together to facilitate or impede outcomes. The iterative nature of QCA allows the researcher to gain an in-depth understanding of multiple cases and alter “causal” models as additional information is discovered.

QCA and other techniques that fuse qualitative and quantitative methods (Bazeley, 1999) provide an opportunity to help in bridging the gap that “paradigm wars” have created. Ultimately, we believe researchers should first consider how

resources or other factors may limit the type of data they can feasibly obtain to answer their research questions and then choose one or more of a wide variety of analytic tools based on how well-suited the tools are for answering their specific research questions. To that end, QCA is another tool that mixed methods researchers may find useful.

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Table III-1. Five Domains of the Consolidated Framework for Implementation Research (CFIR)

CFIR Domain	Description and Examples of Associated Constructs
Intervention	Characteristics of the intervention such as complexity, cost, and relative advantage.
Inner setting	Structural, political, and cultural contexts through which implementation proceeds. Includes organizational structure, social architecture, communication/networks, and implementation climate & readiness.
Outer Setting	Economic, political, and social context in which an organization resides. Includes the extent to which the organization has an accurate knowledge of patient needs, billing & reimbursement, funding constraints, and ties to external organizations.
Individuals involved	Individuals in the inner or outer setting can promote the implementation process and alter program effectiveness via their actions which are influenced by motivations, attitudes, etc.
Implementation Process	Processes include actions that lead to implementation, protocol and procedures, and ongoing reflection.

Table III-2. Summary of Steps Used to Perform Crisp-set Qualitative Comparative Analysis (csQCA)

csQCA steps	Application of QCA steps in the current study
Step 1: **(a)** Determine, define, and operationalize the outcome of interest **(b)** Assign dichotomous set membership scores for the outcome	**(a)** Outcome =patient reach Defined as the percentage of patients who follow-through with genetic counseling and germline testing following an abnormal tumor screen at each institution. Operationalized based on two survey questions as described in the manuscript text. **(b)** Cases naturally fell into three groups or sets: high-reach (H-R); mid-reach (M-R); and low-reach (L-R). Cases with a patient reach score $\geq$5 were included in the H-R set (coded as H-R=1). All other cases were coded H-R=0 and are referred to with a tilde to indicate they are not in the high-reach set (i.e., ~H-R).
Step 2: Select Cases	Several high-reach and several low-reach institutions were needed. However, to maximize both sample size and diversity in contextual variables, all available cases that met the minimum a priori inclusion criteria were used in the analysis.
Step 3: **(a)** Identify key conditions **(b)** Assign dichotomous set membership scores for each condition **(c)** Create a data matrix of scores for conditions	**(a)** As part of the multiple-case study data on many contextual factors were collected to gain an in-depth understanding of the cases. Based on theory and careful review of the cases, factors (i.e., conditions) for possible inclusion in QCA were selected as detailed in the manuscript text. **(b)** Although this is often not the case, all of the conditions were already dichotomized as either present=1 or absent=0 based on how they were asked as part of the survey. **(c)** A data matrix (Table III-3) was created by listing membership scores for the outcome and key conditions for each case.
Step 4: Determine which analyses to run	To determine whether conditions are necessary for the presence of an outcome, a separate analysis is recommended. However, none of our conditions were hypothesized to be necessary in all cases of high or low patient reach. Thus, only sufficiency analyses were conducted.
Step 5: Determine if certain conditions are sufficient for the outcome using the "truth table" approach	Although not necessary for the presence of high patient reach, conditions may be sufficient for the outcome (i.e. H-R) either when occurring alone or in combination with other conditions. Using freely available software (fsQCA 2.0), a truth table was created showing all possible configurations of conditions (Table III-4).
Step 6: Examine the truth table and resolve contradictions	The first row of the truth table (Table III-4) shows the configuration that contains 4 H-R cases as well as 1 M-R case (consistency =.8). The second row contains 1 H-R and 1 M-R case (consistency = .5) To resolve these contradictions, an additional condition (diff_contact_pt) was added to create a revised the truth table (shown in abridged form in Table III-5).

Table III-2 (continued).

Step 7: Use computer software to generate solutions through multiple comparisons of case configurations in the truth table	Using fsQCA 2.0 software, a "Standard Analysis" was performed to identify conditions associated with H-R. This software uses the Quine-McCluskey algorithm (which is based on Boolean simplification) to make multiple comparisons of case configurations represented in the truth table and logically simplify the data. During this process input from the researchers was required to select prime implicants and determine which simplifying assumptions were tenable. The software then used this information to generate three solutions (complex, parsimonious, and intermediate) for H-R.
Step 8: Determine if the influence of conditions is symmetrical	To determine if conditions associated with H-R are the same as those associated with the absence of the outcome (~H-R), steps 4-6 were repeated using ~H-R as the outcome.
Step 9: Evaluate the consistency and coverage of the solutions	The overall solution consistencies were 1 for each of the two outcomes evaluated (H-R and ~H-R), indicating that the respective combination of conditions were consistently associated with the respective outcome. The overall coverage for each solution was 1; indicating that all of the cases with the presence (or absence) of the outcome were explained (covered) by the respective solution.
Step 10: Interpret the resulting solutions and create causal models	Even when conditions are uniquely and consistently associated with an outcome, it does not necessarily mean they cause the outcome. However, these solutions in conjunction with theories, frameworks, and details about the cases can be used to develop a causal theoretical model that describes how the conditions might lead to the outcome.

Table III-3. Data Matrix of Conditions Considered for Inclusion in QCA

Patient reach score[a]	Set member-ship[b]	Out-come	Conditions											
		(H-R)[c]	d	e	F	G	h	i	j	k	l	m	n	o
6	H-R	1	1	0	1	0	0	0	0	0	0	0	1	1
5.5	H-R	1	1	0	1	0	0	0	0	0	0	0	1	0
5	H-R	1	1	1	0	0	0	0	0	0	0	0	1	1
5	H-R	1	1	1	0	0	0	0	0	0	0	0	1	1
5	H-R	1	1	1	0	0	0	0	0	0	0	0	1	1
4	M-R	0	1	0	1	0	0	0	0	1	1	1	1	0
3.5	M-R	0	0	-	-	1	1	0	1	1	1	1	1	0
3	M-R	0	1	1	0	0	0	0	0	1	1	1	1	1
3	M-R	0	0	-	-	1	1	0	0	0	0	0	1	0
2.5	M-R	0	0	0	1	1	1	0	1	0	0	0	1	0
1.5	L-R	0	0	0	1	1	1	1	1	0	0	0	1	0
1	L-R	0	0	-	0	1	0	1	1	0	0	0	1	0
1	L-R	0	0	1	0	1	1	1	1	0	0	0	1	0
1	L-R	0	0	-	-	1	0	1	1	0	0	0	0	0
1	L-R	0	0	-	-	1	1	1	1	0	0	0	1	0

Notes: [a]Patient reach was calculated by averaging the ordinal response options from two questions estimating the percentage of patients who follow-through with genetic counseling and percentage who follow-though with germline testing after a positive screen.
[b]Natural break points were used to initially categorize institutions into three sets based on patient reach score (H-R=high reach; M-R=medium reach; L-R=low reach).
[c]The outcome for the initial QCA was high patient reach (presence=1, absence=0).
[d]Genetic professional discloses positive screening results (presence=1, absence=0,).
[e]Positive screening results disclosed by telephone (presence=1, absence=0, don't know = "-").
[f]Positive screening results disclosed at follow-up visit (presence=1, absence=0, don't know = "-").
[g]Obtaining/receiving a referral from a non-genetics health care provider is primary mechanism for genetic testing (presence=1, absence=0)
[h]Health care providers often fail to see the importance of genetic counseling after a positive screen (presence=1, absence=0).
[i]Health care providers often fail to see the importance of germline testing after a positive screen (presence=1, absence=0).
[j]Combined condition based on Boolean addition "OR" (presence of condition "h" OR condition "i"=1, absence of both conditions=0).
[k]Difficulty contacting patients to set up genetic counseling after a positive tumor screen (presence=1, absence=0).
[l]Difficulty contacting patients to arrange germline genetic testing after a positive screen (presence=1, absence=0).
[m]Combined condition based on Boolean addition (presence of condition "k" OR condition "l"=1, absence of both=0).
[n]Genetic professional is responsible for pre-test discussion of germline testing with the patient (presence=1, absence=0).
[o]Genetic professional contacts patient directly to set up pre-test counseling and germline testing (presence=1, absence=0).

Table III-4. Initial Truth Table of All Potential Conditional Configurations

Row[a]	gen_prof_ disclose_ screen [b]	referral_ barrier [c]	gen_directly_ contacts_pt [d]	# cases fitting configuration	H-R [e] (outcome)	Raw consistency
A	1	0	1	5		0.8[f]
B	1	0	0	2		0.5[f]
C	0	1	0	8		0[g]
D	0	1	1			(remainder)[h]
E	0	0	0			(remainder)[h]
F	0	0	1			(remainder)[h]
G	1	1	0			(remainder)[h]
H	1	1	1			(remainder)[h]

Notes: This is a replica of the initial truth table generated using fsQCA 2.0 software. However, the first column was added to label configurations and several descriptors were added in parentheses.

[a]Each potential configuration of conditions is represented by a row. Since there are 3 conditions there are 2^3 (8) possible configurations.

[b]Genetics professional discloses positive screening results (presence=1, absence=0)

[c]Referral is primary mechanism for patient to receive genetic testing (presence=1, absence=0)

[d]Genetic professional contacts patient to set up counseling and testing (presence=1, absence=0)

[e]The outcome column is blank because the software requires the researchers to fill in a 0 or 1 for each configuration (row) based on whether or not the cases that share that configuration have the outcome of interest (i.e., high patient reach; H-R).

[f]These configurations contain contradictions (as indicated by consistency scores). Consistency for row A is 0.8 because 4 of the 5 cases with this configuration have high patient reach (H-R=1). Consistency for row B is 0.5 because only one of the two cases in this configuration belongs to the H-R set. Contradictions must be resolved before assigning outcome scores.

[g]The consistency score for row C is 0 because none of the cases with this configuration have high patient reach.

[h]There are no consistency scores for rows D-H because there are no cases in this sample that fit these configurations. These are called remainders.

Table III-5. Revised Truth Table

Row[a]	gen_prof_ disclose_ screen [b]	referral_ barrier [c]	gen_directly_ contacts_pt [d]	difficulty_ contact_pt [e]	# cases fitting configuration	H-R (outcome)	Raw consis-tency
A	1	0	1	0	4	1	1[f]
B	1	0	0	0	1	1	1[f]
C	0	1	0	0	7	0	0[g]
D	0	1	0	1	1	0	0[g]
E	1	0	1	1	1	0	0[g]
F	1	0	0	1	1	0	0[g]

Notes: The revised truth table was created using fsQCA 2.0 software by adding a fourth condition to the original truth table, assigning outcome scores for each configuration, and deleting configurations with no cases (remainders).

[a]Each row represents a configuration of conditions. Although there are 2^4 (16) possible configurations, but only those configurations for which there are cases are shown.

[b]Genetics professional discloses positive screening results (presence=1, absence=0)

[c]Referral is primary mechanism for patient to receive genetic testing (presence=1, absence=0)

[d]Genetic professional contacts patient directly to set up counseling and testing (presence=1, absence=0)

[e]Difficulty contacting patients after a positive tumor screen (presence=1, absence=0)

[f]The consistency scores for rows A-B are 1 because all cases with these configurations have high patient reach (H-R=1).

[g]The consistency scores for rows C-F are 0 because none of the cases in those configurations have high patient reach (H-R=0)

Table III-6. QCA Solutions, Consistency and Coverage

Outcome		Solutions	Consistency	Raw Coverage	Unique Coverage
High Patient Reach (H-R)	Complex:	gen_prof_disclose_screen * ~referral_barrier * ~difficulty_contact_pt	1.0	1.0	1.0
	Parsimonious:	~referral_barrier * ~difficulty_contact_pt	1.0	1.0	1.0
	Intermediate:[a]	**gen_prof_disclose_screen * ~referral_barrier * ~difficulty_contact_pt**	**1.0**	**1.0**	**1.0**
				Overall consistency = 1.0	
				Overall coverage = 1.0	
Absence of High Patient Reach (~H-R)	Complex:	gen_prof_disclose_screen * ~referral_barrier* difficulty_contact_pt	1.0	0.2	0.2
		+			
		~gen_prof_disclose_screen * referral_barrier * ~gen_directly_contacts_pt	1.0	0.8	0.8
	Parsimonious:	difficulty_contact_pt	1.0	0.3	0.2
		+			
		referral_barrier	1.0	0.8	0.7
	Intermediate:[b]	**difficulty_contact_pt**	**1.0**	**0.3**	**0.2**
		+			
		~gen_prof_disclose_screen * referral_barrier * ~gen_directly_contacts_pt	**1.0**	**0.8**	**0.7**
				Overall consistency = 1.0	
				Overall coverage = 1.0	

Notes: A tilde (~) indicates the absence of the outcome or condition.
The intermediate solutions are bolded because they were determined to be the most theoretically sound and not overly simple or complex.
* The asterisk indicates Boolean multiplication (i.e. logical “AND”)
+The plus sign indicates Boolean addition (i.e. logical “OR”)
[a] The following three conditions are sufficient for high patient reach: 1) a genetics professional discloses the results of positive tumor screening; AND 2) obtaining a referral from another health care provider for the patient to receive genetic counseling and testing is not a barrier; AND 3) difficulty contacting patients is not a barrier.
[b] Two distinct sets of conditions could both explain the absence of the outcome (Table III-6). Difficulty contacting patients who screen positive is sufficient but not necessary to prevent high patient reach. Alternatively, the following three conditions are together sufficient but not necessary to prevent high patient reach: 1) genetic professionals do not disclose positive screening; AND 2) genetic counselors do not contact patients directly to arrange genetic counseling and testing ; AND 3) the need for a health care provider to refer the patient for genetic counseling and testing is a barrier.

SECTION IV: CONCLUSIONS AND RECOMMENDATIONS

Public Health Significance and Practical Implications

Screening tumors from all newly diagnosed colorectal cancer patients (i.e., universal tumor screening; UTS) is a promising method to achieve the Healthy People 2020 provisional objective: *"Increase the proportion of persons with newly diagnosed colorectal cancer [CRC] who receive genetic testing to identify Lynch syndrome (LS)"*. ("Genomics - Healthy People"). Diagnosing LS allows for the prevention or early detection of colorectal and other types of cancer among patients and their relatives; thereby reducing associated morbidity and mortality. However, the health benefits of tumor screening will only be realized if patient reach is high (i.e., a large percentage of patients who screen positive follow through with germline testing and genetic counseling.)

Given that the RE-AIM evaluation framework was designed to increase the public health impact of evidence-based programs (Glasgow et al., 1999), this framework was used in the current study. Results add to the current literature by confirming that centers vary substantially in terms of patient reach. Even more importantly the current study identified several key implementation factors that characterized institutions with high and low patient reach. These factors included: 1) streamlining UTS procedures by making BRAF or hypermethylation testing automatic in order to rule out a subset of individuals who screen positive but do not need to follow-up with genetic counseling and germline testing and by eliminating the requirement for referral or systematizing the process of obtaining

a referral so that the need for referral is not a barrier); 2) incorporating a high level of involvement of genetics professionals in receiving screening results, disclosing positive tumor screening results to patients, and initiating genetic counseling and germline testing; 3) reducing barriers to patient contact and follow-up (i.e., meet patients at post-op appointments, arrange appointments at convenient times to coincide with other follow-up appointments, etc).

Study findings can serve as key leverage points to inform policy decisions among stakeholders. Implementing UTS practices and procedures that consistently led to high patient reach in this multiple-case study is expected to ultimately contribute to the long-term goal of reducing high levels of morbidity and mortality associated with hereditary cancer. Indeed the results of this study have already prompted one L-R institution to change their follow-up procedures. Unfortunately, some centers may be unable to alter their practices; and ways to work around barriers may be necessary. Interviews conducted as part of the current study for member checks identified additional information that may help centers that are implementing UTS and it is expected that much of this information will be consolidated and shared on the Lynch Syndrome Tumor Screening (LSSN) website. Nevertheless, additional implementation and dissemination efforts in conjunction with research studies will be required before the provisional Healthy People 2020 objective can be achieved and before UTS will have a substantive public health impact.

Implications for Future Research

Given that the current study did not comprehensively evaluate all

dimensions of RE-AIM, several unanswered research questions remain and are listed in Table IV-1. For example, future studies should extend the definition of *Reach* to include the number of family members that are diagnosed as a result of UTS programs, particularly because prevention of cancers in family members determine a large portion of the public health benefit of UTS programs. Interviews with a few institutional representatives suggest that some centers have diagnosed several family members as the result of UTS, but systematic methods of tracking family members over time will be necessary to more thoroughly answer questions pertaining to patient *Reach* and *Maintenance*.

Additionally, widespread *Adoption* of UTS screening by hospitals and cancer centers is critical for UTS to have a large public health impact. Given that academic/research institutions appear to have been quicker to adopt UTS (Beamer et al., 2012; Cohen et al., 2013), health disparities could increase in rural areas or among minority populations that may be less likely to be treated at academic/research centers. Smaller, non-academic centers may have fewer resources or expertise needed for implementation and may face a greater number of barriers. Therefore to help actively disseminate UTS, summaries of the current study findings related to overcoming barriers and strategies for successful UTS implementation are expected to be posted on the Lynch Syndrome Screening Network (LSSN) website (www.lynchscreening.net) where several other useful documents and information on UTS are currently housed.

Additional research is needed to evaluate other UTS programs, particularly those implemented in non-academic centers or institutions that do not

employ genetics professionals. Evaluating programs that have been able to achieve high patient reach but do not conform to the key conditions identified in the current study may help to better understand other implementation strategies that fit better within certain institutions and are therefore more feasible. Although the current study found only a single model leading to successful UTS implementation, different recipes to achieve high patient reach are possible. Therefore future research is expected to confirm, add to, or refine the institution-level mechanisms that appeared to consistently lead to effective program implementation in the current study.

By demonstrating the importance of institution-level factors for patient outcomes, the current study data has already informed further evaluations of UTS. Specifically, LSSN now plans to include institution-level data in addition to individual-level patient data in the database that is being developed. Given the clustered nature of the data, with patients nested within institutions, multilevel modeling (MLM) is necessary when analyzing individual-level data (as opposed to aggregated data used in the current study) in order to reduce the type I error rate (Kreft, 1996) and prevent any unanalyzed institution-level effects from obscuring or exaggerating pooled findings (Seltzer, 1994). A major advantage of MLM is that it allows both random (institution-level) effects and fixed (patient-level) effects to be examined (Seltzer, 1994). In other words, MLM could be used to determine the extent to which differences in patient reach across sites are the result of institution-level effects versus patient-level characteristics (such as stage of cancer, age, gender, or insurance status). MLM will also ensure that individual-

level factors do not confound institution-level findings and thereby overcome a key limitation of the current study.

Implications for Theory

Integrating the RE-AIM and CFIR Frameworks

Given that relatively few implementation studies have employed theoretical models (Damschroder & Hagedorn, 2011), results from the current research could contribute more broadly to the theoretical underpinnings of implementation science. Since its development in 1999 by Glasgow, RE-AIM has been used to evaluate the public health impact of many different evidence-based programs and is a useful conceptual model. However, RE-AIM does not provide enough detail to comprehensively characterize the *Implementation* dimension or define key constructs that are important for *Implementation*. The Consolidated Framework for Implementation Research (CFIR) was developed in 2009 to open the "black box of the RE-AIM framework" (Damschroder et al., 2009). Employing the RE-AIM evaluation framework together with the CFIR can help to better determine how *Reach*, *Effectiveness*, *Adoption*, *Implementation*, and *Maintenance* interact. In particular, the current study results lend support for the critical influence implementation processes have on outcomes, specifically patient reach. Using qualitative comparative analysis (QCA), several *Implementation* processes were determined to be key conditions associated with patient *Reach* in the current study. Additionally, interviews performed as part of the current study revealed the importance of several other CFIR constructs in the decision making process to *Adopt* UTS and in determining how to *Implement*

UTS. Themes from interviews are now being categorized according to various CFIR constructs as shown in Table IV-2 and then will be integrated within the broader RE-AIM framework to further illustrate the interactions between RE-AIM dimensions.

Quantitative Measures of CFIR Constructs

Lack of validated tools is currently a weakness identified in implementation and dissemination research (Damschroder et al., 2009). Despite the small sample size, the current study provides pilot data to help evaluate the new survey tools that were designed to include measures of several CFIR constructs that are not specific to the processes of UTS. Further analysis of the current data can aid in the refinement of these survey instruments for use in evaluating the adoption and implementation of other evidence-based programs or practices.

Additional Manuscripts

Development of Quantitative Measures for CFIR Constructs

A manuscript describing the development and pilot testing of quantitative CFIR measures is planned. This will include a discussion of the many problems or challenges inherent in developing this type of measure, particularly those related to measuring institutional constructs using survey data from individuals. The paper will also triangulate findings from interviews with findings from the survey measures to determine whether qualitative and quantitative methods of identifying key CFIR constructs are consistent. The article will conclude with lessons learned during the development and pilot of the instruments as well as recommendations going forward that may help improve upon the newly

developed measures.

Policy Implications for Lynch Syndrome Universal Tumor Screening

Another manuscript will focus on several policy and practical implications of the research findings. This will include a more detailed discussion of the barriers to implementation and possible challenges to effective implementation and dissemination of UTS on a broader scale. For example, during interviews with a few individuals who are not genetic counselors, they reported that their institution would not have implemented UTS without a genetic counselor on site (and many hospitals do not have genetic counselors). Furthermore, disparities in at least four cities or large geographical regions became apparent during the interviews. Lastly, follow-up on positive tumor screens is not being performed in any systematic fashion at some centers; and patients are definitely falling through the cracks, whereas other institutions have even begun implementing methods to check or ensure that all patients are screened and either follow-through or provide informed refusal of follow-up counseling and testing.

Implementation of Genomic Technologies: Practical & Ethical Considerations

Another potential manuscript could describe ethical considerations and practical issues of widespread implementation of genomic technologies and illustrate how UTS can be used as a model for implementation of these other technologies. Specifically, sequencing the genome of tumors to help determine treatment options is expected to become a common practice in the future. Similar to UTS where an abnormal screen must be verified with germline testing, there

are likely to be cases where tumor sequencing suggests the potential of a germline mutation. These individuals will require genetic counseling so they can be informed of the implications that identifying a germline mutation may have for themselves and for their family members. Although a couple of key differences exist between tumor sequencing and UTS, lessons learned from UTS implementation may be useful in preparing for and identifying best methods for implementing future genomic technologies.

Table IV-1. Future Directions for Applying RE-AIM and Consolidated Framework for Implementation Research (CFIR)

RE-AIM Dimension Description	**Relevant Study Result**	**Future Research**
Reach Absolute number, proportion, and representativeness of individuals who participate.	• Patient Reach (i.e., proportion of screen positive patients who receive information on germline testing and follow-through with germline testing and genetic counseling) is highly variable across centers (ranging from <10% to >85%).	• Determine characteristics of patients who follow-through • Identify the number of family members who are diagnosed with LS as a result of patient diagnosis
Effectiveness The impact of an intervention on outcomes (including potential negative effects).	• Institutional representatives report few negative effects associated with screening. • Potential liability was identified by a few centers where patient reach is low and several expressed concerns that patients may not always be referred after a positive screen.	• Do patients perceive UTS to have a positive or negative impact? In what ways?
Adoption The absolute number, proportion, and representativeness of settings and staff who currently offer a program. Characteristics of intervention may increase the likelihood of adoption.	• Centers report a variety of reasons for adopting UTS, but most common reasons are the EGAPP recommendation and to benefit patients and their families. • Multiple stakeholders are typically involved in making the decision to adopt UTS and changes to the procedures. • Projected cost was a common factor in weighing the decision to adopt UTS at most participating institutions.	• Overall in the U.S. what centers/institutions have adopted UTS and how do they compare to others that have not adopted UTS?
Implementation Consistency of delivery, time and cost of the program, and what adaptations to the program are made in various settings.	• Centers with direct and high level of involvement of genetic counselors in disclosing results and follow-up procedures is sufficient for high patient reach in the absence of two barriers including lack of referral from another healthcare provider for patient to undergo genetic counseling and difficulty contacting patients. • The number of implementation barriers was greater than or equal to the number of facilitators for most low-reach centers, but only 1 H-R center. • Recurring themes and a few unique responses were identified regarding how centers can facilitate implementation and overcome barriers/challenges.	• Are there other procedures that can lead to high patient reach particularly at centers that do not have genetics professionals?

Table IV-1 (continued).

Maintenance Extent to which the program is institutionalized and maintained or altered over time. At the individual level, maintenance is the long-term effects of a program on outcomes after 6 or more months.	A few centers have changed their screening protocol so that genetic professionals disclose positive screening results and meet patients at a follow-up appointment to discuss germline testing. These centers saw improvement in patient follow-through and under their current protocol they were achieving high patient reach. A few other centers are now in the process of changing their procedures. One low-reach center used to let the genetic counselor see all positive screening results and follow-up to ensure she received a referral for all of these patients. She reported that since she could no longer do this it reduced the percentages who followed through.	Do other centers that alter their procedures to resemble those of high-reach centers in our study see improved patient reach? What prevents programs from changing to try and improve patient reach? Are patients who have been diagnosed with Lynch syndrome through UTS or as a result of cascade testing of at-risk relatives undergoing recommended cancer screening?

Table IV-2. Study Themes Consistent with the Consolidated Framework for Implementation Research (CFIR)

CFIR Construct	Description	Relevant Findings from Current Study
Intervention Characteristics		
Intervention source	Perception of key stakeholders about whether the intervention is externally or internally developed to solve a local problem and the legitimacy of the source (Greenhalgh, Robert, Macfarlane, Bate, & Kyriakidou, 2004). Externally developed interventions and lack of user input can lead to ineffective implementation (Helfrich, Weiner, McKinney, & Minasian, 2007; Kitson et al., 2008; Katherine J. Klein, Conn, & Sorra, 2001).	A few GCs cite that if it is simply coming from them other physicians won't listen. So need to get a pathologist and a surgeon on board early on in the process.
Relative advantage	Stakeholder beliefs about the benefits of UTS compared with the status quo or an alternative (Rogers & Rogers, 2003). Relative advantage and observability are constructs from Diffusion of Innovations (Rogers & Rogers, 2003). They are combined because benefits, if visible to the stakeholders, aid adoption and implementation (Denis et al., 2002; Feldstein & Glasgow, 2008; Greenhalgh et al., 2004; Grol, Bosch, Hulscher, Eccles, & Wensing, 2007).	One GC indicated that once the physicians started seeing how family members were diagnosed and that they were using the information to be proactive in screening they would get on board. Observing how patients were being missed without UTS helped some centers get it implemented.
Adaptability	Perceptions about whether and how an intervention can be tailored to meet specific needs or characteristics of an institution (Rogers & Rogers, 2003). There are generally 'core components' that are necessary elements of the intervention and an 'adaptable periphery' (Greenhalgh et al., 2004). According to Diffusion of Innovations, programs that can easily be modified to are more likely to be adopted (Rogers & Rogers, 2003).	Whether or not they do IHC or MSI does not appear to be necessary for success. Some centers only do IHC in house and that was one reason for selecting IHC.
Trialability	Ability to test an intervention on a small scale and reverse implementation if warranted (Rogers & Rogers, 2003). According to Diffusion of Innovations, trialability has a strong positive association with adoption (Greenhalgh et al., 2004; Rogers & Rogers, 2003). It also increases the likelihood of effective implementation because piloting provides experience that can be used to improve full scale implementation (Kitson et al., 2008; Rycroft-Malone et al., 2002).	Some centers were already screening a sub-set of tumors before going to universal screening and they reported that this helped because systems were already in place.

Table IV-2 (continued).

Complexity	Perceived difficulty of implementation (duration, scope, radicalness, disruptiveness, centrality and number of steps required) (Rogers & Rogers, 2003). According to Diffusion of Innovations complexity plays a critical role in the decision to adopt an innovation. In addition, simple interventions are more likely to be effective (Greenhalgh et al., 2004). Assessing complexity can also help in understanding and avoiding unintended consequences (Kochevar & Yano, 2006).	Perceived difficulty of implementation did not appear to be consistently associated with patient reach but those with low-reach reported more barriers than facilitators. GCs expressed how complex it is to implement in a hospital or hospital system where the physicians are private and NOT employed by the hospital. Reduction in complexity of follow-up procedures following a positive screen appears to be a key to success of high reach institutions.
Costs	Costs of the intervention as well as implementation costs (Rogers & Rogers, 2003). Cost is a characteristic from Diffusion of Innovations and is negatively associated with adoption (Rogers & Rogers, 2003; Teplensky, Pauly, Kimberly, Hillman, & Schwartz, 1995). Cost is also likely to influence how the intervention is implemented and its overall effectiveness.	Costs are a common concern in deciding whether to adopt universal tumor screening. Because it is part of DRG when performed on resections the hospital is essentially adding on the screen without recouping additional money. Some centers are going to biopsies in part because they are outpatient procedures and more likely to be reimbursed.
Outer setting		
Patient needs and resources	The extent to which patient needs, barriers, and facilitators are accurately known and prioritized. (Feldstein & Glasgow, 2008; Graham & Logan, 2004; Rycroft-Malone et al., 2002). A number of implementation theories postulate that taking these issues into account will increase the chance that the intervention will be effective (Ferlie & Shortell, 2001; Kitson et al., 2008; Rycroft-Malone et al., 2002). Quality improvement initiatives have proven more successful if there has been a strong focus on the patients' needs (Ferlie & Shortell, 2001).	Several programs changed their protocol to better meet patient needs by simplifying follow-up procedures and removing barriers. Several centers considered patient needs in their discussion of whether or not informed consent was necessary and what information patients should be provided.

Table IV-2 (continued).

Cosmo-politanism	Degree to which the organization is networked with other external institutions (i.e., social capital of the organization) (Greenhalgh et al., 2004). The degree of external networking increases the likelihood of implementing new practices quickly once advantages become apparent (Greenhalgh et al., 2004).	*"You need to keep up to date with the literature and use other centers that have been doing UTS as a resource!" quote* Some centers indicated that they modeled their program after another one, such as Ohio State. This was even one reason why they chose IHC. One GC recommended that people should join LSSN if they want to implement UTS.
Peer pressure	Competitive pressure to implement an intervention (to either obtain a competitive edge or because other organizations already have implemented it) (Greenhalgh et al., 2004). There is strong evidence that peer pressure influences organizational adoption or programs / interventions / technologies (Greenhalgh et al., 2004).	Several centers reported this as a reason for implementation as follows: Seeing competitor hospitals doing it was a motivation. Also, one center reported that the fact they would be the first to implement in their area was helpful because administration liked the idea of being ahead of others.
External policies and incentives	External strategies to spread interventions (e.g., mandates, pay-for-performance, political directives, recommendations, collaboratives) (Greenhalgh et al., 2004; Mendel, Meredith, Schoenbaum, Sherbourne, & Wells, 2008). Many times these strategies lead to adoption and increase effective implementation, but there are some exceptions (Greenhalgh et al., 2004; Grol et al., 2007; Katherine J. Klein & Sorra, 1996).	One M-R center indicated that they implemented UTS because they believed it was "becoming standard of care" Some implemented because of EGAPP, but more often EGAPP was used to support it and they wanted to implement to improve identification of patients.

Table IV-2 (continued).

Inner setting		
Structural characteristic	Social architecture (i.e., how people are clustered into smaller groups and how actions are coordinated), age, maturity, and size of an organization (Damanpour, 1991a; Greenhalgh et al., 2004). Several structural characteristics have been found to be significantly associated with implementation effectiveness, often with mixed results (Frambach & Schillewaert, 2002). A greater number of departments involved in decision making may slow down the process, but generally increases successful implementation (Damanpour, 1991b; Greenhalgh et al., 2004).	Many of high reach centers are NCCN designated academic research focused. If the physicians are not actually employed by the hospital this made it more challenging for some to implement. Also, this prevents GCs from being able to follow-up at post op appointments. Even one center where GCs could follow-up the physical structure of having genetics so far away required them to rely on a nurse who is knowledgeable about genetics to meet patient at follow-up appts. The more physicians or hospitals reported to be part of the system the longer it seems to have taken to get UTS implemented one hospital system took 3 years and even after that not all came on board. Also seen with the affiliate hospitals of one center that implemented UTS with no problem, but affiliate has not yet.
Networks and communi-cation	Nature, quality, and extent of social networks (social capital). Formal and informal communications within an organization (Greenhalgh et al., 2004; Helfrich et al., 2007). Coordination and teamwork across departments and specialties is typically important for effective implementation of programs or initiatives (Feldstein & Glasgow, 2008; Ferlie & Shortell, 2001). Clear role definitions and high quality communication increase the likelihood of success (Simpson & Dansereau, 2007).	Role definitions and quality communication are cited as critical to implementation. Those centers where physicians sometimes disclose and GCs sometimes disclose tend to have lower patient reach. Teamwork among genetics, pathology, and surgeons was cited as a key to successful implementation by many H-R centers. Lack of communication cited among many L-R centers.

Table IV-2 (continued).

Implementation climate	Absorptive capacity for change, shared receptivity of those involved, extent to which involvement with the intervention is rewarded, supported, or expected within the organization. (Gershon et al., 2004; Greenhalgh et al., 2004; Katherine J. Klein & Sorra, 1996).Climate includes the following 6 sub-constructs: Tension for change – degree to which stakeholders perceive current situation as needing change. Compatibility – degree of fit between the meaning and values of the intervention and individual's and institution's values as well as fit with work flow and systems. Greater perceived fit = greater likelihood of adoption according to Diffusion of Innovations and empirical research (Greenhalgh et al., 2004; Katherine J. Klein & Sorra, 1996; Rogers & Rogers, 2003). Relative priority – shared perception of how important implementation is. The higher the priority the more likely it is to be successful (Helfrich et al., 2007; Katherine J. Klein, Conn, et al., 2001). Organizational incentives/rewards – include but are not limited to goal-sharing awards, performance reviews, raises in salary, increased stature or respect. Strong incentives increase the likelihood of implementation success (Helfrich et al., 2007; Katherine J. Klein, Conn, et al., 2001). The number of different types of incentives has been positively related to use of best practices by healthcare organizations (Shortell et al., 2001). Goals and feedback – Goals that are specific, incremental, and attainable increase effective implementation. Feedback has been shown to have small to moderate effects (Jamtvedt, Young, Kristoffersen, O'Brien, & Oxman, 2006). Learning climate – climate where leaders recognize they are fallible and need input, and team members feel their input is valued. This is hypothesized to influence the ability of an organization to fully assimilate an intervention (Greenhalgh et al., 2004).	Having gastroenterologists and surgeons who were receptive was necessary. Preliminary analysis using scale measure of implementation climate those with higher scores are the H-R centers. H-R centers have set goals for UTS and keeping track of outcomes carefully

Table IV-2 (continued).

Readiness for implementation	Tangible and immediate indicators of organizational commitment to its decision (Greenhalgh et al., 2004; Kitson et al., 2008). This includes 3 sub-constructs. Leadership engagement – commitment, involvement, and accountability of managers. This is critical to successful implementation (Meyer & Goes, 1988; Repenning, March). It leads to a stronger implementation climate (Helfrich et al., 2007; K J Klein, Conn, et al., 2001). Available resources – level of resources implemented (i.e., money, time, space). The level of resources is positively associated with implementation, but does not guarantee success (K J Klein, Conn, et al., 2001). Access to information and knowledge – Access to easy to use information about UTS and how to incorporate it is essential for successful implementation (Greenhalgh et al., 2004; Helfrich et al., 2007; K J Klein, Conn, et al., 2001). Timely, on the job training (particularly if provided at a team level) contributes to success (Greenhalgh et al., 2004). This is also critical to get key stakeholders engaged (Grol et al., 2007).	Not all centers had to have the administration on board (tended to be academic centers). Community hospitals reported the need for administration on board for implementation. Community hospitals may have fewer resources and more difficult to implement. One hospital indicated if they did not have a GC on site they probably would not have implemented it.
Characteristics of individuals		
Knowledge and beliefs about the intervention	Familiarity with principles related to the intervention and how-to knowledge as well as positive and negative attitudes about the intervention and value placed on the intervention (Katherine J. Klein & Sorra, 1996; Rogers & Rogers, 2003). Principles and how-to knowledge are constructs from Diffusion of Innovations (Rogers & Rogers, 2003). Attitudes are key constructs in some theories that explain individual behavior change, specifically the Theory of Reasoned Action (Fishbein & Ajzen, 2009).	Genetic professionals may be more knowledgeable. Lack of knowledge among physicians more often cited as barrier by L-R centers.
Self-efficacy	Individual belief in capability to execute behavior needed to achieve implementation goals. Perceived ability to perform a specific action within a specific context (Bandura, 1977). This construct is included in multiple theories of behavior change (Glanz, Rimer, & Viswanath, 2008) However, self-efficacy is originally attributed to Bandura and is a key construct in Social Cognitive Theory (Bandura, 1977).	Not measured here

Table IV-2 (continued).

Individual stage of change	Progression toward use of the intervention. Stage depends on the specific model used (i.e., Prochaska's Transtheoretical model, Roger's Diffusion of Innovations, etc) (Levesque, Cummins, Prochaska, & Prochaska, 2006; Prochaska & Velicer, 1997; Rogers & Rogers, 2003).	NA
Individual identification with the organization	How individuals perceive the organization and their relationship and commitment to the organization ("AHRQ Innovations Exchange | Will It Work Here? A Decisionmaker's Guide to Adopting Innovations," n.d.; Cropanzano, Rupp, & Byrne, 2003). This can affect the willingness of individuals to fully engage in implementation efforts, but this construct has not been widely studied in health care settings .	Not assessed, except for the finding that those centers where the physicians are not actually hospital employees reported more difficulty implementing. Though actual commitment to organization was not assessed.
Process		
Planning	Degree to which the methods and tasks for implementation and evaluation are developed (Damanpour, 1991b; Greenhalgh et al., 2004; Rogers & Rogers, 2003). Although planning is generally necessary for implementing institutional programs (Greenhalgh et al., 2004), additional research is needed into how planning influences implementation effectiveness.	Level of planning may be important in outcomes. One hospital system worked on implementation and planning for 3 years and are a H-R institution.
Engaging	Attracting and involving appropriate people in implementation using social marketing, education, role modeling, training, and other activities ("AHRQ Innovations Exchange | Will It Work Here? A Decisionmaker's Guide to Adopting Innovations," n.d.; Greenhalgh et al., 2004; Kitson et al., 2008; Lukas et al., 2007; Pronovost, Berenholtz, & Needham, 2008). If implementation leaders are similar to intended users they are more likely to adopt the intervention (Greenhalgh et al., 2004). Chances of success are greater if all stakeholders are engaged early on in the process (Greenhalgh et al., 2004).	Multiple stakeholders need to be in agreement, upfront, to implementing this screening. More people "on board" from the beginning means less problems that arise after the screening begins. (/Tia) Having a champions that are pathologists and GI / surgeons, etc was helpful in getting others on board.

Table IV-2 (continued).

Executing	Carrying out the implementation according to plan (Carroll et al., 2007; Damanpour, 1991b; Edmondson, Bohmer, & Pisano, 2001; Helfrich et al., 2007). In cases where there is not a plan, assessing execution is difficult. Execution quality may be related to the following: level of fidelity to the plan, intensity of implementation, timeliness of task completion, and degree of engagement of key stakeholders (Carroll et al., 2007; Edmondson et al., 2001).	*my institution used to allow me to review all MSI/IHC results so I could make sure a referral was made. Because of HIPAA concerns this was stopped. IF we institute this again I believe genetic counseling would increase.* *I also had a problem with receiving the results for reflex tests when I was screening, specifically BRAF, so that I couldn't determine if a patient needed genetic counseling as almost all of our abnormal results were loss of expression of MLH1 and PMS2. If the reflex process and reporting process were cleaned up this would also assist in increaseing genetic counseling referrals.* *Have genetic counselors review all pathology reports and follow up with patients on their own* *Need to get them in the door to discuss testing*
Reflecting and evaluating	Quantitative and qualitative feedback about the progress and quality of implementation. Team debriefing and reflection ("AHRQ Innovations Exchange | Will It Work Here? A Decisionmaker's Guide to Adopting Innovations," n.d.).	Actually getting the data has helped some centers make changes. After talking to a pathologist he said it got him thinking of ways to better streamline the process

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APPENDICES

Appendix A: Literature Review

Public Health and Hereditary Colorectal Cancer

Healthy People genomics objectives. According to the Healthy People (HP) 2020 website, the addition of genomics as a topic area reflects "the increasing scientific evidence supporting the health benefits of using genetic tests and family health history in clinical and public health interventions" ("Genomics - Healthy People," n.d.). Two objectives have been included in the HP 2020 genomics topic area. My focus will be on the following provisional objective: "Increase the proportion of persons with newly diagnosed colorectal cancer (CRC) who receive genetic testing to identify Lynch syndrome (or familial CRC syndromes)."

Prevention of disease and death. Colorectal cancer (CRC) is the third most common type of cancer and third leading cause of cancer-related deaths in the United States (U.S.) ("Colorectal Cancer Facts & Figures 2011-2013," n.d.). In 2011, an estimated 141,210 people will be diagnosed with CRC and 49,380 people in the U.S. will die of the disease ("Colorectal Cancer Facts & Figures 2011-2013," n.d.) Occurring in approximately 1 out of every 35 patients with CRC (Hampel et al., 2008), Lynch syndrome (LS) is the most common cause of hereditary CRC. LS confers a lifetime risk for CRC as high as 78%-80% (Aarnio, Mecklin, Aaltonen, Nyström-Lahti, & Järvinen, 1995; H. F. Vasen et al., 1996). However, due to probable ascertainment bias, more accurate CRC risks likely fall in the range of 54-69% for men with LS and 43-52% for women with LS (Barrow et al., 2008; Hampel, Stephens, et al., 2005; E. Stoffel et al., 2009). The average

age of onset of CRC among individuals with LS ranges from 44-62 years (Hampel, Stephens, et al., 2005). It is also important to note that risks of CRC and age of onset appear to vary based on which gene is implicated as the cause of LS (Bonadona et al., 2011; E. Stoffel et al., 2009).

LS is also referrred to as hereditary nonpolyposis colorectal cancer (HNPCC) despite being associated with substantial increases in risk for several other types of cancer including: endometrial, ovarian, gastric, small bowel, pancreatic, hepatobiliary, brain, and urothelial cancers (Barrow et al., 2009; Kastrinos et al., 2009; Watson et al., 2008). Notably, the second most common malignancy associated with LS is endometrial cancer. Risks for women with LS to develop endometrial cancer range from 32-54% (Barrow et al., 2009; Hampel, Stephens, et al., 2005; E. Stoffel et al., 2009). Studies have found that approximately 2% of patients with endometrial cancer have LS (Hampel et al., 2006). In 2011, an estimated 46,470 women will be diagnosed with endometrial cancer in the United States and approximatelyt 8,120 women will die of the disease (“Cancer Facts & Figures 2011,” n.d.).

The greatest public health benefit of identifying LS among newly diagnosed patients with CRC is the opportunity it provides to prevent cancer among patients' at-risk relatives. Given the autosomal dominant inheritance pattern of LS, first degree relatives of patients with LS have a 50% chance of having inherited the same cancer-predisposing gene mutation. Furthermore, depending on which side of the family the gene was inherited, second degree relatives may have a 25% chance of having LS.

Fortunately for at-risk relatives, early identification of LS has been proven to reduce cancer incidence, morbidity, and mortality through both primary and secondary cancer prevention (Heikki J Järvinen et al., 2009; H J Järvinen et al., 2000; “Recommendations from the EGAPP Working Group,” 2009; Schmeler et al., 2006; Stupart, Goldberg, Algar, & Ramesar, 2009; H. F. A. Vasen et al., 2010). With early and intensive surveillance, such as colonoscopy every one to two years (beginning at age 20-25 years) (“NCCN Clinical Practice Guidelines in Oncology,” n.d.), the incidence of CRC can be reduced by approximately 59-62% (Heikki J Järvinen et al., 2009; H J Järvinen et al., 2000; Stupart et al., 2009) and overall mortality can be decreased by at least 65% (H J Järvinen et al., 2000). Furthermore, evidence suggests that genetic testing improves compliance with screening procedures (“Hereditary Nonpolyposis Colorectal Cancer: Diagnostic Strategies and Their Implications: Structured Abstract,” n.d.). Chemoprevention may also become a routine prevention strategy in the future in light of recently published results from a randomized trial demonstrating that among individuals with LS, long-term use of aspirin reduces the risk of CRC by around 60% compared to no aspirin use (Chan & Lippman, 2011). Evidence has also demonstrated the efficacy of surgical options (i.e., hysterectomy and salpingoophorectomy) for reducing risks of ovarian and endometrial cancers (Auranen & Joutsiniemi, 2011; Koornstra et al., 2009; H. T. Lynch & Casey, 2007; “NCCN Clinical Practice Guidelines in Oncology,” n.d.; Schmeler et al., 2006). Although annual transvaginal ultrasound and endometrial sampling (biopsy) are often recommended beginning at age 30-35, published evidence that these

screening methods reduce mortality is insufficient (“NCCN Clinical Practice Guidelines in Oncology,” n.d.; Auranen & Joutsiniemi, 2011; Koornstra et al., 2009; Barrow et al., 2009). The utility of screening for other cancers among patients with LS has not been established, but surveillance for gastric cancer has been recommended for patients born before 1935 (Barrow et al., 2009) or for families with more than one member affected by this type of cancer (Koornstra et al., 2009). Additional surveillance measures have also been recommended for individuals with more than one urinary tract cancer in the family (Koornstra et al., 2009; “NCCN Clinical Practice Guidelines in Oncology,” n.d.).

The HP genomics objective clearly has the potential “to prevent disease, disability, and premature death”, which is an overarching HP goal (“About Healthy People - Healthy People 2020,” n.d.). This potential is greatest for family members of patients with LS. Nevertheless, identifying LS in patients with CRC may help to prevent secondary cancers and improve clinical treatment. More specifically, a diagnosis of LS alters future cancer surveillance recommendations and cancer prevention options due to increased risks for developing additional cancers (Balmaña, Castells, & Cervantes, 2010; Rex et al., 2006). Given that one in four women with CRC related to LS will go on to develop endometrial cancer within 10 years (Obermair et al., 2010), diagnosing LS can be particularly beneficial if these women choose to pursue hysterectomy and salpingoophorectomy (Ladabaum et al., 2011). If LS is suspected based on screening performed on a tumor biopsy, the diagnosis may help inform surgical treatment options (i.e., subtotal colectomy versus segmental colectomy)

(Natarajan, Watson, Silva-Lopez, & Lynch, 2010). There is also preliminary (yet highly controversial) evidence to suggest that patients with LS respond differently to adjuvant chemotherapy with 5-fluorouracil than other patients whose tumors demonstrate microsattelite instability as a result of somatic mutations (Tejpar, Saridaki, Delorenzi, Bosman, & Roth, 2011).

Screening and/or germline testing for LS has historically been offered to certain patients who are at high risk for the syndrome based on their personal and/or family medical histories (Park et al., 1999; Umar et al., 2004), yet many cases remain unrecognized due, in part, to limitations in the collection and interpretation of family history (De Bruin et al., 2006; Singh, Schiesser, Anand, Richardson, & El-Serag, 2010; Sjursen et al., 2010). Screening all tumors from newly diagnosed patients with CRC, a process referred to as universal tumor screening (UTS) (Bellcross et al., 2011), has been shown to substantially improve the identification of LS (Hampel, Frankel, et al., 2005; Hampel et al., 2008; Ladabaum et al., 2011; Mvundura, Grosse, Hampel, & Palomaki, 2010; “Recommendations from the EGAPP Working Group,” 2009; Tranø, Sjursen, Wasmuth, Hofsli, & Vatten, 2010). UTS presents an opportunity to identify most of the estimated 28% to 50% of individuals with LS who would not otherwise be identified with the common practices of limiting tumor screening to patients who fulfill family history or age criteria (Hampel et al., 2008; Mvundura et al., 2010).

Although not specifically stated in the provisional HP genomics objective, UTS is a promising method of achieving this objective. Furthermore, if UTS is successful, it could serve as a model for implementing other evidence-based

public health genomic applications. The potential population health impact if screening were to be performed on all tumors from both newly diagnosed patients with CRC and newly diagnosed patients with endometrial cancer (EC) in the U.S. is detailed in a paper by Bellcross et al. (Bellcross et al., 2011).

Despite substantial clinical evidence demonstrating the feasibility and efficacy of UTS for LS (Bellcross et al., 2011; Hampel et al., 2008; Palomaki, McClain, Melillo, Hampel, & Thibodeau, 2009; "Recommendations from the EGAPP Working Group," 2009; Sjursen et al., 2010; Tranø et al., 2010), evidence to support the real-life effectiveness of screening programs is limited (Hall, 2010) and consensus or best practice measures for UTS have not been established ("Recommendations from the EGAPP Working Group," 2009).

Health care costs. Given limited health care resources, public health genomic applications should not be implemented without first considering the fiscal impact. Simulation and modeling of various different CRC tumor screening protocols have demonstrated that the incremental cost-effectiveness ratio of screening CRC tumors for LS is comparable to other preventive cancer screening services provided in the U.S. (Gudgeon et al., 2011; Ladabaum et al., 2011; Mvundura et al., 2010; S D Ramsey et al., 2001). More specifically, costs associated with screening tumors of patients < 50 years have been estimated in three separate studies with the following results: $7,556 per life year saved (S D Ramsey et al., 2001); $7,832 per life year saved (Mvundura et al., 2010), and $27,900 per life year saved (Ladabaum et al., 2011). Despite the lower costs associated with limiting screening to individuals under age 50, this approach

would miss approximately 50% of LS cases (Mvundura et al., 2010). As such, additional estimates have been calculated. A U.S. wide system of universal voluntary screening with 2/3 uptake after counseling was determined to have an incremental cost effectiveness ratio relative to age-targeted testing of $22,552 per life year saved (Mvundura et al., 2010). Two additional cost effectiveness studies that have been published also concluded that costs associated with UTS may be acceptable (Gudgeon et al., 2011; Ladabaum et al., 2011). More specifically, Gudgeon et al. estimated that screening tumors of all patients who are newly diagnosed with CRC within their single managed health care system will cost a minimum of $10,369 per case detected (Gudgeon et al., 2011) Taking a broader U.S. health system perspective, Ladabaum et al. calculated the increased cost effectiveness ratio for UTS to be $88,700 per life year gained, as compared to $44,200 per life-year gained when limiting screening to individuals < 70 years (Ladabaum et al., 2011). Differences in these cost-effectiveness models presumably result from differences in their underlying assumptions as well as differences in the number and types of factors that were taken into account. An important limitation, pertinent to all of these models, is that assumptions may not be consistent with real-world practice.

Cost-effectiveness of tumor screening is highly dependent on the behavior of those who screen positive and their family members (Gudgeon et al., 2011; Ladabaum et al., 2011; Mvundura et al., 2010). Although systematic reviews have found adequate test uptake among individuals with CRC and their relatives (Palomaki et al., 2009; “Recommendations from the EGAPP Working Group,”

2009), centers that have already begun UTS for LS have found varying success rates in terms of the percentage of patients with an abnormal screen who follow-through with genetic counseling/testing (Bellcross et al., 2011; South et al., 2009). Without high compliance from patients, these types of large-scale public health screening programs will fail to be effective in terms of both cost and ability to decrease morbidity and mortality. Therefore UTS programs should be evaluated to determine real-world effectiveness.

Educational Needs

With respect to UTS, Bellcross et al., eloquently and succinctly point out that "multi-level education" will be needed to ensure the following:

> "...that entities at all layers—patients, family members, health care providers, public and private health systems, policy makers—are operating from the same understanding of the rationale for universal LS screening, the importance of genetic counseling and diagnostic testing for individuals whose tumor screens are positive, and the need to follow through with identification of at-risk family members and ensure appropriate surveillance of mutation-positive individuals" (Bellcross et al., 2011, p. 7).

Education of the general public. At the most fundamental level, educational efforts are needed to increase awareness of the existence of genetic tests for hereditary cancer. According to the 2000 National Health Interview Survey (NHIS), only 44.4% of the U.S. adult population had even heard of genetic testing for inherited susceptibility to cancer (Wideroff, Thomas Vadaparampil, Breen, Croyle, & Freedman, 2003). Awareness varied substantially by race/ethnicity, with approximately 50% of whites having heard of testing versus 33% of African Americans, 32% of American Indians/Alaskan Natives, 28% of Asian/Pacific Islanders, and 21% of Hispanics (Wideroff et al.,

2003). Data from the 2005 NHIS showed similar trends in racial/ethnic disparities as well as an overall 2.9% decrease in awareness of genetic testing since 2000 (Vadaparampil, 2009). Results from the 2010 NHIS survey are not yet published, but it is likely that the need to increase awareness still exists, particularly among non-white racial/ethnic groups.

Additional genetics information is necessary for patients to understand what genetic screening/testing will mean for them in order to make informed decisions. Condit points out that determining which information is "decision-relevant" is challenging (Condit, 2010); and she describes steps needed to address the general lack of genetics education among the public as follows:

> "If prescriptions for the contents of public education are not merely to expand to the unrealistic desire to convey the entire universe of existing expert knowledge of genetics, there remains a pressing need for carefully designed empirical examinations of what information people actually can and will use and benefit from most in their decision making processes (Condit, 2010, p. 7).

Although I strongly agree that additional research involving patients is needed, there are some specific knowledge gaps, already identified among the public, which may be particularly relevant. More specifically, the general public is largely lacking in an understanding of molecular genetics (Condit, 2010). Without basic knowledge about molecular genetics, it may be difficult to understand various aspects regarding tumor screening for LS. However, the amount and type of information that CRC patients need or desire in order to make informed decisions about UTS is unknown. I suspect that many people view genetics a lot like I view computers. I wouldn't really care to nor would I need to know details about a computer virus. I would simply need to recognize that my computer got a

virus, know who can fix it, determine whether my laptop could also be affected, and find out what I can do to prevent getting a computer virus again. My husband, on the other hand, loves computers. If I were to get a computer virus he would probably start telling me all of the technical details about the virus and what he needs to do to determine the extent of the damage. In turn, I would tune him out and may even miss important information that I really need to know. Similarly, patients may not care about the technical details of tumor screening, which protein(s) is/are missing, or what additional reflex testing may be performed. Genetics health professionals therefore run the risk that critical information will be missed unless they engage patients in the process of determining how much molecular genetic information to include in educational materials.

Compared to molecular genetics, heredity is viewed as a much more salient aspect of genetics by the general public (Condit, 2010). It is easier for people to see the direct impact of heredity in their lives, which probably explains why family history has a substantial influence on an individuals' perceptions of whether cancer is likely to be hereditary (Lucke, Hall, Ryan, & Owen, 2008). Individuals' understandings of inheritance may, however, conflict with the medical perspective due to the complex ways in which people perceive vulnerability and personalize risk (Walter, Emery, Braithwaite, & Marteau, 2004) UTS for LS may be particularly challenging because human beings generally have difficulty understanding probabilities (Visschers, Meertens, Passchier, & de Vries, 2009) and individuals who lack a strong family history of cancer or who hold

misconceptions may fail to see how screening and genetic counseling are applicable to them.

There are several additional examples of how perceptions about heredity could act as barriers to the achievement of the HP genomics objectives. One example is the finding that variable penetrance alleles, including genes associated with LS, can result in the perception that hereditary cancer “skips generations” and lead to misconceptions regarding the probability that an individual or their offspring inherited the disease causing allele (Henderson & Maguire, 2000). Misconceptions about hereditary breast/ovarian cancer may be even more prevalent or concerning because a fair number of individuals, including health care providers, fail to take paternal family history into consideration when assessing risks due to the mistaken belief that males cannot inherit or cannot pass on the cancer causing allele to their offspring (Miesfeldt, Cohn, Ropka, & Jones, 2001; Yong, Zhou, & Lee, 2003).

Education to address common misconceptions pertaining to heredity and risk is important, but it will not address the many other attitudes, fears, or misconceptions that may influence decisions related to genetic testing (Balmaña, Stoffel, Emmons, Garber, & Syngal, 2004; Cragun, Malo, Pal, Shibata, & Vadaparampil, 2012; Esplen et al., 2001, 2007; L. A. Keogh et al., 2009; Kinney, DeVellis, Skrzynia, & Millikan, 2001; Scott D Ramsey, Wilson, Spencer, Geidzinska, & Newcomb, 2003; Rose, Peters, Shea, & Armstrong, 2005; Sally W. Vernon et al., 1999). For example, patients who take a fatalistic viewpoint or are unaware of advantages and medical benefits of identifying hereditary cancer for

themselves and/or their family members may be less likely to demonstrate interest in or pursue genetic testing (Balmaña et al., 2004; Cragun et al., 2012; Sally W. Vernon et al., 1999). Educating the public about the benefits of genomic information is essential. Education about state and federal laws designed to protect against genetic discrimination in the contexts of employment and health insurance are also needed, as fears of genetic discrimination have been negatively related to interest in or uptake of genetic counseling and/or genetic testing (Balmaña et al., 2004; L. A. Keogh et al., 2009; Kinney et al., 2001; Scott D Ramsey et al., 2003; Sally W. Vernon et al., 1999). Although it is possible that fear of discrimination may have declined in recent years with the implementation of the federal Genetic Information Nondiscrimination Act (GINA) in 2009, data from a representative sample of Michigan residents in 2010 revealed that only 13% were aware of GINA ("Genetic Testing and Genetic Non-Discrimination Laws," 2011).

Education for health professionals and health educators. Health Care Professionals also need to be educated about GINA. Results from a national survey of family physicians approximately 17 months after GINA was signed revealed fewer than half of respondents were aware of this federal law (Laedtke, O'Neill, Rubinstein, & Vogel, 2011). Even more concerning, however, was that no significant correlation was found between concerns about discrimination and knowledge of GINA among these physicians (Laedtke et al., 2011). Additional evidence for why this is a critical issue comes from another study which found that physician's concern about genetic discrimination was a reason for non-

referral among a minority of Californian physicians surveyed (Lowstuter et al., 2008).

In addition to knowledge about GINA, health care professionals and members of the public health workforce who may be involved with UTS or the related HP genomics objective should, at a minimum, possess the following genomics competencies: 1) a basic understanding of the rationale behind UTS; 2) the ability to identify the limits of his/her genomic expertise; and 3) knowledge regarding where to go for information, resources, and referrals (Bellcross et al., 2011; “Genomics|Training|Competencies,” n.d.). Additional genomics competencies will be necessary for health care professionals who will be interpreting tumor screening results and/or discussing them with patients. Given that screening tests are not conclusive, health professionals must be educated about best practices for discussing a positive screen and about the need to emphasize the importance of follow-up genetic counseling and genetic testing to their patients, even in the absence of a strong family history of cancer.

As part of the public health workforce, public health educators have been identified as having the potential to play a unique role by helping health professionals communicate with community groups and individuals regarding genomic information and related technologies, relaying or reflecting communities' concerns to health care professionals or policy makers, and providing educational and health promotion services in the context of a multidisciplinary team to facilitate informed decision-making related to genomics and health (L.-S. Chen & Goodson, 2007). Even though over 88% of U.S. public health educators

who responded to a survey strongly agreed or agreed with genomics competencies that have been proposed by the CDC for the public health education workforce (L.-S. Chen & Goodson, 2007; "Genomics|Training|Competencies," n.d.), they perceived many barriers to incorporating genomics into health promotion (L.-S. Chen & Goodson, 2009). Barriers included lack of genomics knowledge, limited training in genomics, having to deal with lay public member's reaction, and lack of priority, time and resources (L.-S. Chen & Goodson, 2009). Possible ways to remedy the ambivalent attitudes and knowledge gap would be to incorporate more genomics into the curriculum of public health education programs.

The inability to utilize the talents and skills of public health educators due to their current lack of training and knowledge regarding genomics would be unfortunate, but even more concerning is the potential that their lack of knowledge will lead to misrepresentation of genomic information to the public and the possibility that public health educators could hinder progress toward the HP genomics objectives.

Educational resources for institutional implementation of UTS. As more centers consider implementing UTS, there is a need for accessible educational resources such as tumor screening protocol algorithms, samples of laboratory reports, guidelines for interpreting results, fact sheets, ways to deal with procedural concerns or issues that may arise, samples of patient letters/brochures, information regarding insurance and reimbursement, and lessons learned from other centers. Collecting and dissemination educational

resources is one of the primary goals of the Lynch Syndrome Screening Network (LSSN), which is a group of representatives from approximately 35-40 institutions who have formed a collaborative group to improve Lynch syndrome screening and increase the capacity for institutions to implement UTS.

Evolution of Genomic Research and Practice

> "Scientific and technological advances in genomics are revolutionizing our approach to genetic counseling and testing, targeted therapy, and cancer screening and prevention, fulfilling the promise of personalized medicine (Weitzel et al., p. 1) (Weitzel, Blazer, MacDonald, Culver, & Offit, 2011)."

In oncology, the use of presymptomatic testing for germline mutations and the use of "targeted therapies" tailored to the molecular genetic characteristics of tumors are often part of routine evaluation and care (Robson, Storm, Weitzel, Wollins, & Offit, 2010; J. N. Weitzel et al., 2011). Despite a number of successes, translating research into practice is often complex and there is always the risk that promising genomic discoveries may never successfully be translated into practice or that tests may be implemented widely before there is sufficient evidence of clinical validity (i.e., accuracy with which the test predicts a particular outcome (Burke et al., 2002) and/or clinical utility (i.e., capacity for the test result to inform clinical decision making and facilitate the prevention of adverse health outcomes) (Burke et al., 2010; Grosse & Khoury, 2006).

Since the completion of the human genome project a substantial amount of research and resources have focused on identifying the contribution of genetic variants to the pathology of common diseases such as cancer (S D Schully, Benedicto, Gillanders, Wang, & Khoury, 2011). Many single nucleotide polymorphisms (SNPs) associated with increased risks for cancer have been

identified via genome wide association studies (Jostins & Barrett, 2011; Wacholder et al., 2010). GWAS studies may be providing valuable information about biological pathways involved in cancer and other diseases (Tuma, 2009). However, these studies have generally found SNPs that confer only small relative risks; and/or the clinical validity and clinical utility of testing for these SNPs remain somewhat uncertain (Jostins & Barrett, 2011; Robson et al., 2010; Wacholder et al., 2010).

To address the growing concern about potential limitations regarding the practical relevance of genomic research to the primary causes and remedies of diseases, an international, multidisciplinary meeting was held in May 2010 in Ickworth, United Kingdom (Burke et al., 2010). Key themes from this meeting centered around a need to reconfigure the focus of genomic research so that greater attention is given to areas with greatest potential health impact and so that a greater emphasis is placed on the translation of basic science to practical applications (Burke et al., 2010). Although translational research appears to be increasing in recent years (Muin J Khoury, Gwinn, & Ioannidis, 2010), nearly all (98.2%) genetics-related grant funding by the National Cancer Institute from Fiscal Year 2007 was dedicated to discovery research (S D Schully et al., 2011), whereas translational research that evaluates a candidate genetic application to develop evidence based recommendations, assesses how to integrate an evidence-based recommendation into cancer care and prevention, or that evaluates health outcomes and population impact has been extremely under-represented in both funding and similarly in the published literature (S D Schully

et al., 2011).

The new challenge for epidemiology is to work with allied disciplines to integrate knowledge and effective interventions into various societal settings to ensure that interventions have their intended effects on individual and public health (Hiatt, 2010). The HP 2020 provisional genomics objective takes on this challenge by focusing efforts on improving the identification of individuals who have Lynch syndrome (LS) and other hereditary colorectal cancer (CRC) syndromes so that effective prevention and treatment options can be implemented to reduce associated morbidity and mortality.

Evidence in Favor of Lynch Syndrome (LS) Tumor Screening

Utilizing the ACCE (analytical validity; clinical validity; clinical utility; and ethical, legal, and social issues) framework, the Evaluation of Genomics Applications in Practice and Prevention (EGAPP) working group found sufficient clinical validity and clinical utility evidence in favor of offering tumor screening to all newly diagnosed patients with CRC for purposes of identifying family members at increased risk for Lynch syndrome (LS) (“Recommendations from the EGAPP Working Group,” 2009). EGAPP did not recommend a specific protocol or screening methodology for universal tumor screening (UTS), but possible screening methods have a number of different benefits and limitations (Mvundura et al., 2010; Shia, 2008). Notably, immunohistochemistry (IHC) for the presence or absence of DNA mismatch repair (MMR) proteins in tumor samples is more cost effective than microsattelite instability (MSI) testing, particularly when V500E mutation testing in the BRAF gene is added as an additional reflex

test in cases where the MLH1 stain is absent on IHC (Ladabaum et al., 2011; Mvundura et al., 2010).

Regardless of the screening protocol that is chosen, abnormal results are not considered diagnostic of LS. Therefore patients with an abnormal tumor screen require subsequent germline testing of one or more of the genes that can cause LS (i.e., MLH1, MSH2, MSH6, PMS2, and EPCAM) as well as genetic counseling to discuss associated implications and recommendations for cancer prevention or early detection.

Germline genetic testing has been distinguished from genetic screening performed on tumors, in that the former involves DNA analysis from blood or saliva to identify inherited mutations that increase risks for cancer, whereas the latter is typically used to predict cancer prognosis or treatment response (Robson et al., 2010). MSI and IHC are performed on tumor tissue and can provide prognostic information (A. J. Clark, Barnetson, Farrington, & Dunlop, 2004; Gologan & Sepulveda, 2005). Preliminary evidence also suggests that MSI and IHC could possibly provide information about treatment response (de la Chapelle & Hampel, 2010; Tejpar et al., 2011). However, these screening tests are unique in that they have generally been employed for the purpose of determining whether an individual is at increased risk for LS, thereby leading to debate about whether or not explicit informed consent is necessary. On one hand, Chubak et al. argue that informed consent for IHC may be required because unlike MSI, IHC can reveal information about a patient's germline (Chubak, Heald, & Sharp, 2011). In contrast, others argue that because neither IHC nor MSI are definitive

genetic tests, explicit informed consent is not required (Ladabaum et al., 2011). Valid concerns have been raised that a lack of explicit informed consent may infringe upon an individuals' autonomy or “right not to know”(Peres, 2010). However, requiring explicit informed consent is concerning from a logistical standpoint due to the time and effort it requires. Furthermore, suggesting to patients that their cancer might be hereditary before screening is completed could lead to unnecessary increases in anxiety and additional decisional burdens among newly diagnosed CRC patients, the vast majority of whom do not have LS (Peres, 2010).

Implications of Universal Genetic Testing Policies for Adult Populations

The impact that universal genetic testing policies will have on adult populations is largely uncertain as UTS for LS is truly the first universal genetic screening to be implemented for the purpose of detecting hereditary disease in adults. Other genetic screening programs that have been widely implemented are aimed at identifying genetic conditions in fetuses and infants or determining carrier status among healthy couples to assess genetic risks for offspring. Although not specific to adults, lessons learned from universal newborn screening (NBS) may offer several insights into potential implications of universal tumor screening (UTS). This is explored in more depth in the ethical implications paper that is included as part of the dissertation.

One of the key ethical considerations involves informed consent. Programs that automatically screen all tumors from newly diagnosed CRC patients have the potential to identify the greatest number of patients with LS.

This approach also raises ethical concerns related to autonomy (M. J. Hall, 2010). On the other hand, if screening requires explicit informed consent, this will make implementation much more challenging and could reduce the number of individuals with CRC who are screened for LS. Genetic testing of adults up until this point has mainly been performed on individuals who actively sought out genetic counseling and testing. With UTS programs, particularly those that do not require explicit informed consent, the patient is being confronted with the possibility of a genetic risk factor that he or she is not expecting, did not seek out, and may not even want.

Assessing potential harms of UTS will be important. There have been no published studies designed to identify risks or unintended outcomes associated with UTS. Although risks are believed to be minimal (H. Hampel, 2010), a couple of anecdotal reports from my own personal correspondence with genetic counselors suggest that UTS can result in substantial psychological distress for at least a few patients with who are erroneously led to believe they have LS. Furthermore, in several studies that occurred prior to UTS implementation, patients with CRC expressed concern that genetic testing for hereditary CRC may lead to adverse psychological outcomes for themselves or their family members (Kinney et al., 2000, 2001; Lerman, Marshall, Audrain, & Gomez-Caminero, 1996; Scott D Ramsey et al., 2003). Patients with CRC have also expressed concerns about costs associated with genetic testing (Kinney et al., 2001; Scott D Ramsey et al., 2003). Confirmatory genetic testing for LS is approximately $1,000 to $3,000 and it is not always covered by insurance (J. N.

Weitzel et al., 2011). Having a positive screen, but not being able to follow-through with genetic counseling and/or testing may invoke anxiety and worry. UTS, if enacted widely throughout the U.S., therefore has the potential of adding to the financial and/or psychological burdens of over 190,000 patients who are diagnosed with CRC in the U.S. each year ("Colorectal Cancer Facts & Figures 2011-2013," n.d.). Prior to wide-spread implementation, studies should be conducted to identify whether there are any unanticipated harms associated with UTS so that risks can be minimized.

Despite the possibility of negative outcomes, the potential benefits of UTS are substantial and anecdotal reports have indicated that patients are often appreciative of the additional information they obtain from UTS (Peres, 2010). Nevertheless, it is possible that the estimates of benefit in terms of reducing morbidity and mortality may be overstated. If penetrance in certain families identified through UTS is lower than current estimates and age of cancer onset is later, a higher cost-benefit ratio may result from applying existing cancer screening protocols (Bellcross et al., 2011). As such, if studies continue to show varying penetrance with consistent genotype/phenotype correlations, recommendations may need to change to ensure that individuals do not undergo unnecessary procedures that would be of little clinical benefit and could cause harm (Kempers et al., 2011; Henry T Lynch, Lynch, Snyder, & Riegert-Johnson, 2011).

Comparisons between NBS and UTS are useful when considering the potential impact of UTS. In addition, applying standardized state-wide laboratory

and follow-up processes similar to those that have been implemented for NBS has been proposed as a potential way to reduce cost and improve standardization, quality of care, and access to genetic counseling by trained health care providers (Bellcross et al., 2011). Thus NBS may serve as a model to help decrease the likelihood of negative UTS outcomes.

Institutional Lynch Syndrome Screening Policies and Procedures

Published data on policies and procedures related to tumor screening for Lynch syndrome (LS) are limited (Bellcross et al., 2011), and most of what is known comes from the results of two surveys that were shared during the first Lynch Syndrome Screening Network (LSSN) meeting in September of 2011. Based on these surveys, at least 30 centers are performing routine screening for LS on tumors from all newly diagnosed CRC patients and several others are screening based on specific criteria. Some centers are also screening endometrial tumors to identify additional patients at increased risk for LS (Bellcross et al., 2011; Peres, 2010).

UTS protocols vary widely across institutions. Several specific details come from a 2010 survey of institutions across the U.S. including 39 NCI-designated Comprehensive Cancer Centers (NCI-CCCs) (63% response rate), 50 randomly selected ACS-accredited Community Hospital Comprehensive Cancer Programs (COMPs) (50% response rate), and 50 randomly selected Community Hospital Cancer Programs (CHCPs) (40% response rate) (Beamer et al., 2012). Of the respondents, IHC and/or MSI is being conducted on at least some tumors at 71% of NCI-CCCs, 36% of COMPs, and 15% of CHCPs. Most

(48%) use IHC, 14% use MSI, and 38% use both. Of the institutions performing screening, 38% test all CRC patients, 27% test those diagnosed under the age of 50, 14% test those diagnosed under the age of 60, and 21% use other selection criteria. Only 14% offer an option to opt-out of screening for LS and only 3.5% offer pre-operative information on LS tumor screening. Centers reported that results go to the surgeon alone (27.6%), to the surgeon and another provider (55.2%), to a genetic health provider alone (6.9%), or to a non-surgeon and non-genetic health provider (6.9%); whereas 3.4% indicated that results go to no one. Most of the centers expect the person receiving the results to initiate a referral to genetics. However, among the NCI-CCCs 18% indicated that referrals were initiated using an automatic electronic mechanism and 17% were initiated by a specialist. The majority of centers have implemented a genetics referral tracking mechanism and problems with patient follow-through with genetic counseling were reported by 53% of the NCI-CCCs, 33% of COMPs, and 67% of CHCPs that track this information.

Universal Tumor Screening (UTS) Evaluation

Data evaluating the real-world effectiveness of UTS programs is extremely limited. As such, several studies that are not specific to UTS will also be included in the following literature review in order to provide a better understanding of three of the key steps that patients and/or at-risk family members must take in order for UTS to be successful once it has been implemented. These key steps include: 1) Patient Reach – patients must accept tumor screening (if consent is required) and patients must follow-through with genetic counseling and testing in

cases where screening is abnormal; 2) Cascade testing of family members (Bellcross et al., 2011) – patients who are found to have LS need to communicate with their at-risk family members who must then follow-through with genetic counseling and testing; 3) Adherence to cancer screening recommendations and/or cancer risk reduction through uptake of surgical options by patients and family members who are diagnosed with LS. Although literature pertaining to all of these steps will be reviewed below, the focus will be primarily on patient reach, as this is most pertinent to my dissertation research.

UTS Evaluation: Patient Reach (i.e., follow-through with genetic counseling & testing)

Factors related to genetic counseling and germline genetic testing uptake may be similar; however, differences may also exist. Based on unpublished survey results, it is clear that variability in patient follow-through with genetic counseling exists across centers that are performing UTS. Differences in patient reach could be the result of individual-level differences in patient populations. However, it is also likely that variations in screening protocol or institutional factors may help facilitate or hinder compliance with genetic counseling and testing (P. M. Lynch, 2011).

The experience at Ohio State University, one of the first centers to implement universal screening, found that uptake of genetic counseling dropped substantially once their research protocol ended and clinical implementation of UTS was begun. Under the research protocol, counseling and testing were free and travel was not required because counseling could be provided by phone (H.

Hampel et al., 2008). Once screening was initiated on a clinical basis, only 27% of those who screened positive followed up with genetic counseling (South et al., 2009).

In an editorial published in the journal Diseases of the Colon and Rectum, Dr. Patrick Lynch reports that follow-through with genetic counseling at his institution, M.D. Anderson, is about 80% (P. M. Lynch, 2011). This is an important contrast to the experience reported at Ohio State where patient follow-through is substantially lower (27%). Differences between these centers may contribute to this wide variability (P. M. Lynch, 2011). For example, instead of having to make an appointment in a separate genetics department, as is the case at Ohio State, genetic counselors are present within the GI centers at M.D. Anderson, potentially making referrals “more seamless” (P. M. Lynch, 2011). Additional insights into possible reasons for variability in patient follow-through come from a variety of studies discussed in more detail below that are not directly related to UTS.

Genetic counseling interest and uptake. Only a couple of studies have explored issues related to interest or uptake of genetic counseling for hereditary CRC. Secondary data analysis of surveys from patients with CRC who were at various levels of risk for hereditary CRC reveal offers several insights. Compared to those with no intention of making an appointment (n=70) to discuss genetic testing for hereditary CRC, those with positive intention (n=18) perceived there to be greater medical benefits from genetic testing (p=.02) and were less fearful of insurance and/or employment discrimination (p=.04). They were also more likely

to perceive themselves to be appropriate candidates for genetic testing regardless of their personal and family history of cancer ($p<.001$) (Cragun et al., 2012). A German study compared individuals at high risk for CRC based on whether they attended a genetic information session (Monika Keller et al., 2004). Those who attended the session reported more distress about the possibility of CRC being hereditary. No group differences were found in terms of awareness of potential hereditary predisposition or clinical criteria suggestive of LS.

Uptake of genetic counseling for hereditary breast cancer may also provide relevant insights (Chin et al., 2005; O'Neill, Peters, Vogel, Feingold, & Rubinstein, 2006; Thompson et al., 2002; Vadaparampil et al., 2009). Factors shown to positively influence or correlate with genetic counseling uptake for patients with breast cancer include increased awareness of genetic counseling and/or hereditary breast cancer, perceived benefits of counseling, and a perception that genetic counseling is personally relevant to them. Factors that were negatively associated with pursuit of counseling include confusion about a referral in the absence of a strong family history of cancer, financial concerns about the cost of genetic counseling, and concerns about the potential for negative outcomes as a result of having genetic testing.

In a recent study of endometrial cancer patients, 26 of 47 patients who had an abnormal tumor screen for LS responded to a survey (Backes, Mitchell, Hampel, & Cohn, 2011). Of these, 20 (77%) reported that they were referred by their physician for genetic counseling, but only nine saw a genetic counselor. The most common reason for not seeing a genetic counselor was lack of adequate

insurance coverage or concern about the cost of the visit followed by anxiety about the results. Nine patients also stated that they or their family members did not want to know information regarding hereditary cancer risk.

Genetic testing interest and uptake. Interest or uptake of genetic testing among patients with CRC has varied widely across studies (ranging from 17-100%) (Balmaña et al., 2004; Esplen et al., 2007, 2001; Hadley et al., 2003; M Keller et al., 2002; Monika Keller et al., 2004; L. A. Keogh et al., 2009; Kinney et al., 2000, 2001; Loader, Shields, Levenkron, Fishel, & Rowley, 2002; Metcalfe, Werrett, Burgess, Chapman, & Clifford, 2009; Scott D Ramsey et al., 2003; Ramsoekh et al., 2007; S W Vernon et al., 1997). This wide variability may be due to differences in recruitment of study participants and/or inconsistencies between studies in terms of the patient population sampled, information provided to participants, and ways in which cost and other contextual factors were addressed. Two studies, which each analyzed responses from nearly 100 surveys of CRC patients, found that the respective percentages of CRC survivors interested in genetic testing for hereditary CRC were 67% (Cragun et al., 2012) and 72% (Kinney et al., 2000). These two studies provide the only published estimates that could be identified regarding interest in genetic testing among CRC patients who were not all at high risk for hereditary cancer or were not already pursuing genetic counseling. Nevertheless, the level of interest in genetic testing reported in these two studies may not be representative of CRC patients in general due to sampling issues and potential participation bias. Nonparticipants would in all likelihood be less inclined to pursue genetic testing

for many of the same reasons they chose not to participate in the respective surveys (e.g., medical complications from cancer treatment). As such, it is possible that a substantial proportion of CRC patients (at least 28-33%) are not interested in or are uncertain whether they would undergo genetic testing for hereditary CRC if it were made available to them.

Among patients with CRC, statistically significant associations between various demographic variables (i.e., gender, number of family members with cancer, age) and interest in or uptake of genetic testing for hereditary CRC have been inconsistent across studies (Cragun et al., 2012; Monika Keller et al., 2004; Kinney et al., 2000; Loader et al., 2002; Sally W. Vernon et al., 1999). Some studies have found that interest in or uptake of genetic testing for hereditary CRC is associated with the following demographic factors: being a parent (Loader et al., 2002); having more cancer in the family (Loader et al., 2002); having a larger social network (Loader et al., 2002); younger age (Kinney et al., 2000); and less advanced disease stage (Kinney et al., 2000); however, the magnitude of these associations was relatively small. Furthermore, other studies of CRC patients have either failed to find similar relationships or demographic variables do not remain statistically significant after controlling for attitudinal variables (Cragun et al., 2012; Monika Keller et al., 2004; Sally W. Vernon et al., 1999). Given that demographic variables generally cannot be altered, attitudinal factors that strongly correlate with interest in or uptake of genetic testing may serve as better leverage points or targets for improving the reach of UTS for LS.

Among patients with CRC, interest in and uptake of genetic testing has

consistently been associated with and/or attributed to perceptions of positive outcomes of genetic testing, including: helping other family members; determining cancer risks for offspring; improving the ability to make more informed decisions about cancer treatment/screening; and/or increasing one's ability to plan for the future (Balmaña et al., 2004; Cragun et al., 2012; Esplen et al., 2001, 2007; Hadley et al., 2003; Kinney et al., 2001; Metcalfe et al., 2009; Scott D Ramsey et al., 2003; Sally W. Vernon et al., 1999). More frequent thoughts, worry, or distress about CRC being hereditary may also have a significant positive correlation with interest in genetic testing (Kinney et al., 2000) and intention to learn genetic test results (Sally W. Vernon et al., 1999). Although few studies appear to have asked CRC patients about the influence of health care providers on their decision, one study reported that CRC patients' decisions to undergo genetic testing was influenced by a recommendation from a physician or genetic counselor (Esplen et al., 2007).

Studies suggest that negative attitudes regarding testing (e.g., concerns about negative psychological consequences and insurance discrimination) may also influence genetic testing decisions (Balmaña et al., 2004; L. A. Keogh et al., 2009; Kinney et al., 2000, 2001; Sally W. Vernon et al., 1999). However, in two studies that have performed multivariable analyses, the relationship between negative attitudes and either interest in testing or intention to receive test results were no longer statistically significant after controlling for positive attitudes about genetic testing (Cragun et al., 2012; Sally W. Vernon et al., 1999).

After controlling for attitudes toward testing, a belief that personal and/or

family history makes individuals appropriate candidates for testing remained significantly associated with interest in testing (Cragun et al., 2012). An implication of this finding is that requiring explicit informed consent for tumor screening may result in relatively low rates of uptake unless patients are convinced that they are appropriate candidates for screening. Automatic screening of all tumors may therefore be more successful as long as patients who screen positive can be convinced that genetic counseling is appropriate for them.

Although interest in genetic testing may be a necessary precursor for action, uptake of testing is generally lower than interest (Monika Keller et al., 2004). One potential reason for the discrepancy between interest and uptake may be financial barriers. Based on the collective experience of members of the Lynch Syndrome Screening Network, insurance typically covers the cost of screening which generally ranges between $250-$500, depending on the laboratory and screening strategy. The costs of germline testing are higher, generally between $900 to $3,000 depending on the number of genes tested. Lack of insurance or insufficient insurance coverage for genetic counseling and germline testing has been shown to be an important barrier to interest in or uptake of hereditary cancer counseling and genetic testing (Backes et al., 2011; Chin et al., 2005; Cragun et al., 2012; Kinney et al., 2001; Scott D Ramsey et al., 2003; Weitzel et al., 2011). In one study, the percentage of CRC patients who indicated they would be willing to pay $2,000 for genetic testing (13.6%) was substantially lower than the 67% who indicated being interested in having genetic

testing before cost was mentioned (Cragun et al., 2012). Assessing the maximum amount that individuals would be able or willing to pay and determining the likelihood that insurance would cover costs associated with germline testing may be helpful before implementing UTS, as this will likely affect overall effectiveness. Although insurance and financial issues are individual barriers, changes to the health care system and insurance plans will likely be needed so that cost barriers do not prevent patients from choosing to undergo genetic counseling, confirmatory germline testing, colonoscopy, and other cancer surveillance or prevention measures.

Cascade testing of family members. High levels of patient follow-through with genetic counseling and genetic testing is essential to ensure that UTS programs are effective. However, it is the patients' unaffected family members who stand to gain the most benefit from UTS, and the prevention of cancer in unaffected relatives is critical in UTS cost-benefit sensitivity analyses (Gudgeon et al., 2011; Ladabaum et al., 2011; Mvundura et al., 2010). In order for testing of family members to occur, patients must understand the potential implications for family members, recognize the benefits of diagnosing LS in other family members, and communicate this information effectively with at-risk family members. Although genetic health professionals can play an important role in this process (Mesters, Ausems, Eichhorn, & Vasen, 2005; Pentz et al., 2005), the responsibility of informing family members often resides with the patients due to confidentiality issues (“Genetics of Colorectal Cancer (PDQ®) - National Cancer Institute,” n.d.).

Several studies have explored genetic risk communication patterns among patients with LS and their families (K. I. Aktan-Collan et al., 2011; Ersig, Hadley, & Koehly, 2011; C. L. Gaff, Collins, Symes, & Halliday, 2005; Mesters et al., 2005; Susan K Peterson et al., 2003; Elena M Stoffel et al., 2008). Individuals are generally willing to share genetic test results with family members, but tend to favor a cascade approach whereby they inform first-degree relatives and then those family members inform other immediate family members (Gaff et al., 2005; Mesters et al., 2005; Susan K Peterson et al., 2003; Elena M Stoffel et al., 2008). Family role and gender differences have been reported in communication patterns (Gaff et al., 2005; Koehly et al., 2003; Susan K Peterson et al., 2003). Although communication is generally viewed as an open process ("Genetics of Colorectal Cancer (PDQ®) - National Cancer Institute," n.d.), several barriers have been identified including: lack of close relationship, desire not to worry relatives, presence of familial conflict, and perceptions that relatives were either too young, would not understand, or would not be interested (Gaff et al., 2005; Mesters et al., 2005; Elena M Stoffel et al., 2008).

Once informed about the potential hereditary risk, family members must seek genetic counseling and genetic testing. A review of several studies revealed that about half of family members pursued genetic counseling and most who underwent counseling pursued germline testing ("Recommendations from the EGAPP Working Group," 2009). However, uptake of genetic testing for LS among at-risk individuals can be highly variable and may depend on the context in which testing is offered ("Genetics of Colorectal Cancer (PDQ®) - National Cancer

Institute," n.d.). Many factors influence whether family members pursue genetic counseling/testing for LS, such as: perceived benefits to self and family members; higher perceived risk of or worry about developing CRC; and concerns about genetic discrimination, ability to cope with results, or cost (K. Aktan-Collan et al., 2000; Claes, Denayer, Evers-Kiebooms, Boogaerts, & Legius, 2004; Codori et al., 1999; K Glanz, Grove, Lerman, Gotay, & Le Marchand, 1999; Hadley et al., 2003; L. Keogh et al., 2011; Kinney et al., 2001; Lerman et al., 1999, 1996; J. T. Lowery, Marcus, Horick, Finkelstein, & Ahnen, 2011; Petersen et al., 1999; Ramsoekh et al., 2007; Sally W. Vernon et al., 1999; Warner, Curnow, Polglase, & Debinski, 2005).

Cancer screening adherence. In order for individuals with LS to decrease associated morbidity and mortality it is important that they follow appropriate cancer screening guidelines and/or pursue surgical options to reduce cancer risks. In a review article, adherence to colonoscopy recommendations among individuals with LS was found to range from 53% to 100% ("Recommendations from the EGAPP Working Group," 2009). Adherence to gynecologic surveillance ranged from 69% to 97% in three studies of women who either have LS or are at 50% risk for LS (V. R. Collins et al., 2007; Heikki J Järvinen et al., 2009; Anja Wagner et al., 2005) Little is known about uptake of prophylactic surgeries to reduce risks for endometrial and ovarian cancer.

Colon cancer screening adherence among individuals with LS or individuals who are at high risk for hereditary CRC has been associated with reminder letters, strong family history of cancer, having a medical

recommendation to screen, having been referred for a genetic evaluation, and encouragement to screen from family members (Bleiker et al., 2005; Ersig, Hadley, & Koehly, 2009; Murff, Peterson, Greevy, Shrubsole, & Zheng, 2007; Rees, Martin, & Macrae, 2008; Elena M Stoffel et al., 2010). Many of the barriers to colonoscopy in high risk individuals are similar to those in the general population (e.g., discomfort, cost, embarrassment) (Bleiker et al., 2005).

Additional steps for successful UTS implementation. There are several additional steps involving health care professionals that are likely to be necessary to the success of UTS. These include effective communication of screening results, patient referrals, and coordination between various specialists and primary care providers to facilitate the process by which patients and their family members receive genetic counseling, genetic testing, and appropriate screening. Detailed information regarding these steps has not been reported and research and additional research in this area is needed.

Summary

The Healthy People (HP) 2020 provisional genomics objective is intended to help translate genomic medicine into individual and public health benefits through improving the identification of individuals with hereditary colorectal cancer (CRC). Achievement of the HP 2020 provisional genomics objective has the potential to substantially reduce morbidity and mortality among unaffected relatives of CRC patients who are identified with Lynch syndrome (LS). Making a diagnosis of LS in patients who already have CRC may also benefit the patients directly, given that having LS may influence clinical treatment and will certainly

alter future screening recommendations due to high risks for additional cancers.

Universal tumor screening (UTS), whereby tumors from all newly diagnosed patients with CRC are screened for Lynch Syndrome (LS), has the potential to help achieve this HP objective and result in population health benefits at a reasonable cost. However, in order for this approach to be successful, education will be needed at many levels. At a minimum, all individuals involved with UTS and patients who are found to have an abnormal screen should be aware of the rationale for UTS, the importance of genetic counseling and diagnostic testing for individuals with abnormal tumor screens (regardless of family history or age at diagnosis), the need for follow-through with identifying at-risk family members, and the importance of increased cancer surveillance for all individuals identified with LS. Additional education will be needed to dispel misconceptions about inheritance, to increase awareness of state and federal laws that are designed to protect against genetic discrimination, and to improve awareness of the positive health benefits associated with making a diagnosis of LS if appropriate cancer screening recommendations are followed. Educational resources that are being compiled by the Lynch Syndrome Screening Network (LSSN) will be extremely valuable in the dissemination of UTS, but systematic evaluation of existing UTS programs will also be needed to fully inform centers that are considering how to best implement UTS at their institution. Additional research and collaborative efforts are needed to help prioritize or determine additional educational efforts that may be necessary in order to help practitioners, health educators, patients, and other stakeholders achieve the HP

2020 genomics objective.

The feasibility of UTS has been demonstrated in research and clinical settings. However, prior to widespread implementation of UTS, lessons from universal newborn screening and potential ethical, legal and social implications of universal genetic screening for adults should be considered. Further research into “real-world” implementation is needed to determine whether there are any risks or unintended consequences associated with UTS and to collect additional data that is necessary to justify the development of infrastructure and cost that would be required for implementation of UTS on a national level (Bellcross et al., 2011). To assess “real-world” effectiveness the following data will be critical: patient reach (i.e., follow-through with genetic counseling and testing after an abnormal screen); initiation of cascade testing of at-risk family members; adherence to recommended cancer surveillance for individuals identified with LS; and uptake of surgical prevention options.

Among centers already performing UTS, there is evidence of wide institutional variability in terms of UTS screening protocols and patient reach. Reasons for this institutional variability have not been explored. Research has established that patient factors may influence interest in and uptake of genetic counseling and testing outside the context of UTS, but data is needed to confirm that similar patient factors contribute to follow-through with genetic counseling and testing among patients who receive an abnormal tumor screen. There is also some evidence to suggest that contextual factors (e.g., patient-provider communication and policies or practices of health insurance providers and health

care institutions) may be influential in patient follow-through with genetic counseling and testing, either directly by creating barriers/facilitators or indirectly by altering patients' attitudes, knowledge, and perceptions. Comparing existing UTS programs can determine the extent to which different protocols/procedures are effective or ineffective in specific contexts in order to help identify best practices. This type of research is a critical step toward reaching the longer-term goals of optimizing current UTS programs and wide-spread diffusion of effective UTS practices.

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Appendix B: IRB approval

USF
UNIVERSITY OF SOUTH FLORIDA

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Institutional Review Boards, FWA No. 00001669
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August 24, 2012

Deborah Cragun
Community and Family Health
1738 W. Ferris Ave
Tampa, FL 33603

RE: **Expedited Approval** for Initial Review
IRB#: Pro00004918
Title: Implementation Effectiveness of Universal Tumor Screening (UTS) for Lynch Syndrome (LS)

Dear Ms. Cragun:

On 8/23/2012 the Institutional Review Board (IRB) reviewed and **APPROVED** the above referenced protocol. Please note that your approval for this study will expire on 8/23/2013.

Approved Items:
Protocol Document(s):
UTS study protocol

It was the determination of the IRB that your study qualified for expedited review which includes activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the categories outlined below. The IRB may review research through the expedited review procedure authorized by 45CFR46.110 and 21 CFR 56.110. The research proposed in this study is categorized under the following expedited review categories:

(6) Collection of data from voice, video, digital, or image recordings made for research purposes.

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

Your study qualifies for a waiver of the requirements for the documentation of informed consent as outlined in the federal regulations at 45CFR46.117 (c) which states that an IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either: (1) that the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of

confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or (2) that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

As the principal investigator of this study, it is your responsibility to conduct this study in accordance with IRB policies and procedures and as approved by the IRB. Any changes to the approved research must be submitted to the IRB for review and approval by an amendment.

We appreciate your dedication to the ethical conduct of human subject research at the University of South Florida and your continued commitment to human research protections. If you have any questions regarding this matter, please call 813-974-5638.

Sincerely,

John Schinka, Ph.D., Chairperson
USF Institutional Review Board

ABOUT THE AUTHOR

Deborah Cragun is a Master's trained genetic counselor with several research interests including: implementation and dissemination of genomic technologies in medicine; evaluation of methods to achieve the Healthy People genomics objectives; application of family health history in medical care to aid in the prevention and early diagnosis of chronic diseases; and genetics education for health care professionals. Prior to pursuing her Ph.D. she spent two years as a visiting instructor of Genetics and Biology at the University of Tampa. Her prior clinical experience includes four years working as a full-time genetic counselor at Cincinnati Children's Hospital and two-years working part-time as a genetic counselor and research coordinator at Moffitt Cancer Center. Upon graduation she will begin a post-doctoral fellowship in Epidemiology at Moffitt Cancer Center where she will focus on translational epidemiology in cancer genomics. Ms. Cragun has pursued advanced training in mixed methods, data analysis, and measurement