

The Return of Genetic Research Results in the Context of an
International Colon Cancer Family Registry

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Abstract

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The overall aim of this dissertation study was to describe the experience of the Colon Cancer Family Registry (C-CFR) with return of results (ROR) from genetic research and to document site-specific ROR outcomes. The C-CFR is comprised of six registry sites: the University of Hawaii, Honolulu, HI (HI); the Mayo Clinic, Rochester, MN (MA); the Fred Hutchinson Cancer Research Center, Seattle, WA (SE); the University of Southern

California, Consortium, Los Angeles, CA (USC); the Cancer Care Ontario, Canada (ON); and the University of Melbourne, Melbourne, Australia (AU).

Registry site-specific experiences with ROR and ROR-related outcomes were explored using a mixed-methods study design. For Specific Aim 1, qualitative interviews with 14 registry investigators and staff from the six C-CFR sites demonstrated the complexity of ROR protocol development and implementation in practice. Thematic analysis from the interviews identified three main factors underlying site-specific ROR protocol and implementation differences: 1) the training and prior experience of C-CFR staff, 2) access to a robust public health infrastructure, and 3) the influence of local regulatory norms and/or informed consent. For Specific Aim 2, multivariable logistic regression model analysis of the association between acceptance of Lynch Syndrome (LS) genetic research results and participant demographic characteristics had identified the participant's age, marital status, and race/ethnicity as significantly associated with the likelihood of LS genetic research result acceptance. Overall, the proportion of participants accepting LS genetic research results among the SE, HI, MA and AU C-CFR sites was 63% (481/763). For Specific Aim 3, a sequential mixed-methods investigation of Seattle C-CFR participants approached for LS-related ROR explored post-disclosure result clinical validation and sharing of results with family members and health care providers. Twenty-six of 34 SE C-CFR participants (76.5%) who accepted non-CLIA genetic research results completed a survey 12 months post disclosure. Of these, 4 (15.4%) reported having clinically verified their non-CLIA genetic research results, 22 (84.6%) reported having shared the results with family members, and 15 (57.7%) participants shared with their health care providers. Follow-up qualitative

interviews with a subset of these participants found that acting on the recommendation of the research team and informing future clinical care were the main reasons given for pursuing clinical verification. Participants who did not verify their results cited lack of insurance coverage and limited perceived personal and/or clinical benefits as relevant reasons to their decision.

From the experience of a multi-site international research cancer registry, results from this dissertation study provide valuable insights into the complexity of ROR protocol development and implementation, as well as the potential impact of genetic research result return on participants and their families. As such, these study findings should help guide future policy development regarding the return of individual results from genetic research in related settings.

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DEDICATION

For the future yet to be created

CHAPTER 1: INTRODUCTION

In the mid 1990s, the United States National Cancer Institute (NCI) offered funding for an effort to address the increasing worldwide colorectal cancer (CRC) burden [1]. Numerous research proposals were submitted and six research groups were chosen to establish the Colon Cancer Family Registry (C-CFR) [2] as an international CRC consortium. The original six collaborating cancer registries included the University of Hawaii, Honolulu, HI (HI); the Mayo Clinic, Rochester, MN (MA); the Fred Hutchinson Cancer Research Center, Seattle, WA (SE); the University of Southern California, Consortium, Los Angeles, CA (USC); Cancer Care Ontario (1997–2012), Toronto, Ontario, Canada (ON); and the University of Melbourne, Melbourne, Australia (AU) [2, 3]. The overall aim of the C-CFR was to provide an infrastructure that will allow researchers to collect and access registry participant data and biospecimen samples for studying the genetic and environmental factors contributing to CRC incidence.

CRC is the third most common cancer diagnosed in men and second in women worldwide [4]. Risk factors associated with CRC include certain types of diet, physical inactivity, obesity, smoking, alcohol consumption, increasing age, and personal history of colon polyps, as well as having a family history of CRC [5-7]. Although the majority of CRC cases are considered sporadic, up to 5% of all new cases are estimated to be attributable to an underlying hereditary cancer syndrome [8]. Over the years, researchers using C-CFR data and biospecimens have found cases (i.e., participants diagnosed with CRC) and some of their enrolled family members have genotypes consistent with Lynch syndrome (LS) or *MUTYH*-associated polyposis (MAP) syndrome [9-11]. Specifically for LS, some registry participants were found to have pathogenic variants in the mismatched repair (MMR) genes. Researchers

have also identified families who met the clinical criteria for Familial Colorectal Type X [9-11]. In the face of on-going controversy regarding whether researchers are obligated to return individual research results (ROR) to participants [12-17], and recognizing the accepted clinical utility of LS and related findings, individual C-CFR sites developed policies and incrementally implemented site-specific ROR protocols between 1998 and 2011.

Return of Research Results Debate

The traditional goal of research is to provide generalizable knowledge for broad societal benefit [12] and some researchers have expressed concern that offering individual results from genetic research to participants actually contradicts this goal. However, ethical consensus has shifted and most recent ethical recommendations suggest that researchers should consider the return of certain types of individual genetic research results [18-20]. As such, genetic researchers now share similar ROR endeavors with other kinds of medical researchers. Arguments for and against the return of individual results from genetic research should be considered with respect to the ethical principles of respect for autonomy, beneficence, nonmaleficence, and justice.

Respect for Autonomy

The bioethical principle respect for autonomy pertains to the capacity of individuals to make informed decisions about themselves, free from coercion [21]. Several scholars have argued that honoring the participant's "right to know" justifies returning individual research results [22, 23]. In addition, several authors have argued in support of ROR as a sign of respect for participants [24]. Other researchers, however, suggest that respect can be demonstrated with the return of aggregate study results instead of individual findings [25]. Nevertheless, many

participants, when asked, express a preference for individual results, citing reasons such as disease prevention, an opportunity to change their lifestyle behaviors, or engagement in cancer screening [22, 26-29], as well as wanting to know results relevant for family members. For example, Facio et al. asked 311 participants enrolled in the NIH ClinSeq study about their preferences regarding ROR [28]. The majority of participants (94.5%, 294 of 311) wanted to know the results of genome sequencing, stating their intention to use the information to change their lifestyle behaviors in order to prevent disease occurrence [26]. In the research context, respect for participants' autonomy is most often operationalized during the informed consent process [16], and until recently it was uncommon for genetic researchers to address the potential for result return in their informed consent documentation [30]. Accordingly, current recommendations have emphasized that participants should be informed at the time of their recruitment about the possibility of receiving research results [18, 19, 31], and that they should have the right to decline the offered information [13, 18].

Beneficence

The principle of beneficence describes actions that benefit others [21]. In the ROR context, supporters of result return suggest that researchers have an ethical obligation to return research results when the results have clinical utility, i.e., hold potential clinical benefit, for participants [18, 19, 32-34]. In essence, researchers have a "duty to rescue," that arises when "an investigator discovers genetic information that clearly indicates a high probability of a serious condition for which an effective intervention is readily available" [12]. Prior research suggests that many researchers find beneficence a compelling rationale for pursuing ROR endeavors [23, 35, 36]. Further, using beneficence in its reasoning, at least one group has proposed a method of determining which genetic variants should be returned and which

should not [37]. A research result is usually deemed clinically useful when the information would allow participants to take distinct clinical actions, while some ethicists suggest that it is also appropriate to offer research results that could be used for reproductive decision making, hence be of personal and not clinical utility [38].

Nonmaleficence

Nonmaleficence is an “obligation not to inflict harm on others”[21]. Ravitsky and Wilfond argued that not returning individual results with clinical significance puts participants at risk [13]. In addition, despite broad ethical consensus regarding the appropriateness of return in many cases, a number of questions have been raised that focus on potential harms of result return. These concerns involve the potential for therapeutic misconception [39-41] and returning results not generated in laboratories compliant with the Clinical Laboratory Improvement Amendments of 1988 (CLIA) [42]. For example, Dressler has argued that result return to research participants compromises the informed consent process [35] because participants may mistakenly believe that the main purpose of their study participation is to provide medical benefit rather than to advance human knowledge. To mitigate this concern, Fernandez et al. [15] suggested that results should be communicated to participants by a team member other than the principal investigator and that the research results should be shared with the participant’s primary care provider. Regarding the CLIA issue, Evans recently argued that a researcher’s First Amendment right is violated if he or she is prevented from communicating non-CLIA laboratory findings [43]. A CLIA research exception does exist, which provides for the return of results of tests performed in non-CLIA compliant laboratories with the caveat that such results are for informational and not clinical purposes [43, 44].

Justice

The ethical principle of justice in the ROR context primarily involves the distribution of resources to enable result return [13, 15], as well as equal participant access to the information. As an ethical principle, justice focuses on the “fair, equitable, and appropriate distribution” of benefits and burdens [21]. To illustrate, if researchers are obligated to return individual results to participants, research funds may need to be reallocated, which may negatively affect overall research progress [16]. In addition, supporters of returning results have argued that the duration and the nature of the researcher–participant relationship must be taken into account in terms of the obligation of returning results [12, 13]. However, this perspective may be unfair for a participant who joined a study for a year but does not have the same right of access to research results as a participant does who has been in the study much longer.

As outlined above, current ethical consensus suggests that researchers (and managers of larger data collections, such as biobank managers) have an obligation to offer identified individual results from genetic research when such return has a significant clinical benefit that outweighs any harm to participants [45-48]. However, genetic researchers are not obligated to search for and return incidental findings in the course of such research. To our knowledge, nothing has been specifically written about the responsibilities of investigators associated with cancer registries such as the C-CFR consortium.

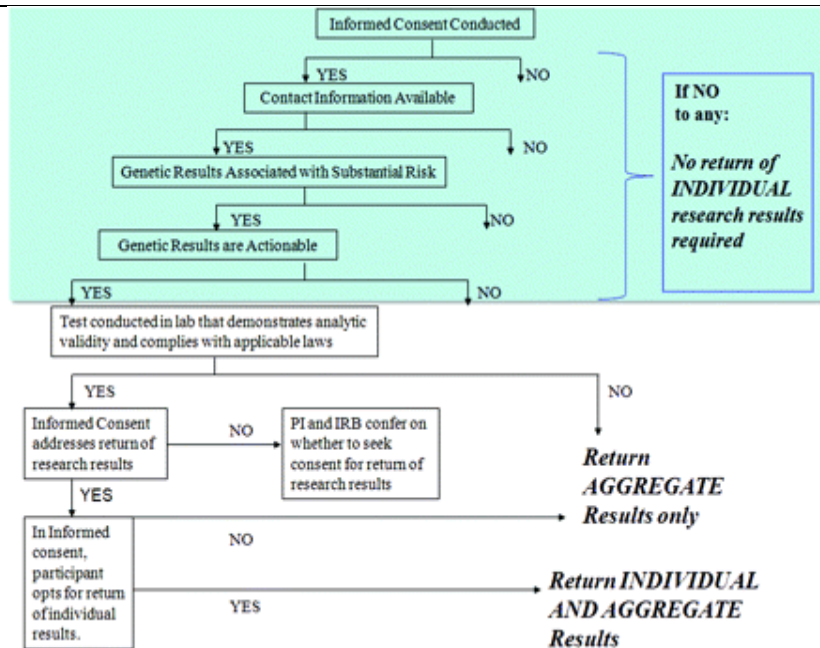
Existing Guidelines Regarding the Return of Results from Genetic Research

Several international and national guidelines have been published to guide research policy surrounding return of individual genetic research results. In the United States, the National

Bioethics Advisory Commission [49] stated that genetic results can be returned if (a) the findings are scientifically valid and confirmed; (b) the findings have significant implications for the subjects' health concerns; and (c) a course of action to ameliorate or treat these concerns is readily available. In 2010, the US National Heart, Blood, and Lung Institute (NHLBI) working group provided a decision flow chart for researchers to use in their ROR decision-making (Figure 1). The NHLBI working group emphasized the importance of informed consent and recommended that principal investigators consult with their IRBs if the possibility of result return was not addressed in the informed consent process at the time of participant recruitment.

In 2014, the ROR committees of the Clinical Sequencing Exploratory Research (CSER) Consortium and the Electronic Medical Records and Genomics (eMERGE) acknowledged that controversy remained about returning results from non-CLIA-compliant laboratories, as well as the best way to return results to participants [18]. However, committee members upheld the recommendation that “researchers should offer individual genomic research results that are valid, medically important, and actionable”. Such an offer is especially important if the results identified are related to study aims and not merely incidentally identified. All of the above-mentioned guidelines agree on the importance of incorporating plans for result return in the study design. Moreover, Jarvik et al. emphasized that funding agencies should strongly consider allocating funds specifically for this endeavor [18].

Figure 1: Decision Flow Diagram Regarding the Return of Individual Research Results



Source: National Heart, L., et al., Ethical and practical guidelines for reporting genetic research results to study participants: updated guidelines from a National Heart, Lung, and Blood Institute working group. *Circ Cardiovasc Genet*, 2010. 3(6): p. 574-80.

As mentioned, there is limited information or consensus on how best to return genetic research results to participants. Dressler [35], in her review of guidelines written from 1999 to 2006, noted that most recommended the involvement of a genetic counselor or medical geneticist during the ROR process. Specifically, pre- and post-genetic counseling was highly recommended. In addition, these guidelines also noted that the responsibility of deciding whether to disclose research findings lies with the IRB and the researcher [35]. Other guidelines, however, have recommended the involvement of a Central Advisory Board (i.e., not the IRB) to serve as an oversight committee for an institution’s ROR decision making and standardization of procedural processes [54].

As ROR national and international guidelines were being drafted and bioethicists continued to debate the appropriateness of returning research results, investigators at the C-CFR sites began offering results from genetic research to their participants [27, 30, 55-58].

Dissertation Roadmap

Five of the six C-CFR sites decided to return individual results from genetic research to registry participants, and each return occurred at slightly different times and using varying ROR protocols. Thus, the overall aim of the dissertation was to describe the ROR experience at each C-CFR site and to document site-specific outcomes of result return.

The specific aims, hypothesis and approaches of this dissertation study were:

1. **To explore, via key informant interviews of C-CFR staff, the decision-making processes when developing site-specific ROR policy and experiences with ROR protocol implementation.** Semi-structured qualitative interviews were conducted with C-CFR staff representing each of the six registry sites. *Hypothesis:* Among sites participating in result return, expectations with respect to clinical benefit were expected to drive decision-making. Logistical and/or financial barriers were expected to be the primary reasons why some sites chose not to return or took some time to implement their ROR policy.
2. **To determine the proportion of participants who accepted research results and investigate which participant characteristics influenced the likelihood of result acceptance.** Previously collected demographic information from participants approached for ROR was obtained from the central C-CFR database. By logistic regression model analysis, participant characteristics of those who accepted results

were compared to those who declined using data from four of six C-CFR sites.

Hypothesis: An association between acceptance of genetic research result and age, reproductive history, education level, and personal and family history of cancers was expected. Sex, status of either being a case or relative, and whether a family member had pursued clinical genetic testing, were not expected to influence acceptance of individual research results within and across C-CFR sites.

- 3. To determine whether Seattle C-CFR participants pursued follow-up recommendations after accepting non-CLIA genetic research results pertaining to Lynch syndrome.** A sequential mixed-method study design was conducted using Seattle C-CFR participants' post-genetic counseling survey data and qualitative interview data. Participants surveyed shared whether they verified their non-CLIA genetic research results in a clinical laboratory and if they discussed their results with family members and health care providers. *Hypothesis:* Individuals who tested positive for their familial pathogenic variant for LS were expected to report a significant impact of knowing their status on themselves and close family members. Participants who tested positive for a pathogenic LS variant were expected to contact their health care providers and to seek to clinically confirm their non-CLIA genetic research findings more often than participants who tested negative.

Dissertation study results from each of these Specific Aims are presented in Chapters 2-4. Together, the study findings illustrate the complexities of addressing research ethics recommendations for individual result return from genetic research in an international collaborative research cancer registry consortium.

**CHAPTER 2: “*I feel a responsibility and an obligation to the people who helped us*”:
Experience of a Population-based Cancer Family Registry with Return of Results**

Abstract

Purpose: The Colon Cancer Family Registry (C-CFR), an international population-based and clinic-based cancer consortium established in 1997, adopted protocols for the return of results (ROR) relevant to hereditary cancer predisposition syndromes in a staggered fashion. The first C-CFR site implemented result return in 1998 and the most recent site opted to return results beginning in 2011. Our study aimed to identify the views of the C-CFR staff on ROR implementation experience and the factors that contributed to site-specific differences in ROR protocols.

Method: We conducted semi-structured key informant interviews with 14 C-CFR affiliated investigators, including principal investigators, genetic counselors and program managers/study coordinators. Each C-CFR site had at least one investigator and/or staff interviewed and questions focused on experiences with result return, ethical considerations relevant to return, and other factors that influenced the adoption of the site’s ROR protocol. Each interview was audio-recorded, transcribed, and coded to identify relevant themes.

Results: Thematic analysis from the interviews identified three main factors underlying site-specific ROR implementation differences: 1) the training and prior experience of C-CFR staff, 2) access to a robust public health infrastructure, and 3) the influence of local regulatory norms and/or informed consent.

Conclusion: The ROR protocol development and implementation experience of the C-CFR illustrates the numerous challenges posed by choosing to return clinically actionable research findings in an international cancer registry consortium.

Introduction

The Colon Cancer Family Registry (C-CFR) was formed in 1997 with support from the National Cancer Institute (NCI) [2]. The primary aim of the C-CFR was to determine the genetic and environmental factors contributing to colorectal cancer (CRC) incidence. The C-CFR is an international multisite collaboration composed of six cancer registries including the University of Hawaii, Honolulu, HI (HI); the Mayo Clinic, Rochester, MN (MA); the Fred Hutchinson Cancer Research Center, Seattle, WA (SE); the University of Southern California, Consortium, Los Angeles, CA (USC); the Cancer Care Ontario (1997-2012), Toronto, Ontario, Canada (ON); and the University of Melbourne, Melbourne, Australia (AU) [2, 3]. Genetic research using samples from C-CFR participants identified some cases (i.e., participants diagnosed with CRC), and their enrolled family members with pathogenic variants in the mismatch repair (MMR) genes (i.e., *MLH1*, *MSH2*, *MSH6* and *PMS2*) consistent with the diagnosis of Lynch syndrome (LS), a hereditary cancer syndrome [59, 60]. In addition, genetic research also identified participants with bi-allelic pathogenic variants in the *MUTYH* gene consistent with *MUTYH*-Associated Polyposis (MAP) [61]. Lastly, some C-CFR participants met clinical criteria for Familial Colorectal Type X syndrome [62, 63]. Given that such genetic findings are returned to patients in the context of clinical care, and in the wake of considerable ethical and legal debate surrounding the return of results (ROR) to research participants [14, 35, 36, 44, 47, 64, 65], C-CFR investigators

had to decide whether and how to re-contact participants for whom such results had been identified.

The AU and ON C-CFR sites began returning research results in 1998 and 1999 respectively, whereas the four C-CFR sites based in the United States (MA, HI, SE, USC) returned in 2008 or later [34]. For the five C-CFR sites that have actively returned results to date, there was consensus only on returning pathogenic variants in the MMR genes for LS [34]. The C-CFR sites differed with regard to the return of MAP-related and Familial Colorectal Type X syndrome (Figure 2). Moreover, registry- or government-funded genetic counselors were involved during ROR protocol implementation across all C-CFR sites.

Figure 2: Genetic Test Results Offered and Protocols for Returning Genetic Results

	HI	ON	MA	AU	SE
Which genetic results were offered, and to whom?					
<i>MMR mutations</i>					
To cases	Y	Y	Y	Y	Y
To their relatives	Y	Y	Y	Y	Y
<i>Biallelic MUTYH mutations</i>					
To cases	Y	Y	Starting	Y	Y
To their relatives	Y	Y	Starting	Y	Y
<i>VUS</i>					
To cases	Y	Y	N	N	Y
To their relatives	N	N	N	N	N
<i>Familial Colorectal Cancer Type X</i>					
To cases	Y	Y	N	N	Y
To their relatives	N	Y	N	N	N
Protocols for returning genetic results					
Who provides counseling? (genetic counselor [GC])	Study GC	GC shared by study and hospital	Study MD or GC	Government-funded GC service	Study GC
Mode of delivery of genetic counseling	In-person/telephone	In-person/telephone	Telephone	In-person	In-person/telephone
Participant encouraged to seek CLIA-approved testing	Yes	NA ^a	Yes	NA ^a	Yes
CLIA Clinical Laboratory Improvement Amendments					
^a Testing offered through clinical services					

Source: Keogh, L.A., et al., *How do researchers manage genetic results in practice? The experience of the international Colon Cancer Family Registry*. J Community Genet, 2013.

Although several ROR consensus recommendations have been published [18, 19, 53, 66, 67], these guidelines do not provide specific recommendations for cancer research registries or address the complexities of negotiating ROR policy in the context of an international cancer registry consortium. Furthermore, previously published papers describing C-CFR ROR efforts [34, 55] have focused more on the outcome of result return but have not fully identified factors contributing to the reported differences in ROR protocols across sites. To address this gap, our study aimed to identify registry investigators' views of the C-CFR ROR implementation experience and their impressions of the factors that contributed to site-specific differences in ROR protocols. This work highlights the complexity of ROR protocol implementation and the factors that may influence similar implementation in other cancer consortia.

Methods

The University of Washington Institutional Review Board (IRB # 45998) approved this dissertation research protocol and informed consent procedures. This study was also conducted with approval from the C-CFR consortium (C-CFR Project ID: C-EX-0412-04).

Study Design

We conducted semi-structured key informant qualitative interviews with C-CFR affiliated investigators (principal investigators, genetic counselors and program managers/study coordinators) who were purposely selected to encompass those with responsibility for the development of the return of result policy and/or implementation at each registry site.

Interview Guide

A semi-structured interview guide (Appendix A) was designed to explore C-CFR staff experiences with respect to (1) deciding whether to offer genetic results to registry participants, and (2) if applicable, distinguishing which types of genetic results to return.

Open-ended questions included:

- 1) “What was your experience when your registry decided to return genetic test results to your participants?”
- 2) “What ethical considerations influenced registry decision making?”
- 3) “What main legal and broader policy considerations impacted registry policy about result return?”

In addition, key informants were asked to recall barriers to returning results and to describe what aspects of the ROR protocol were implemented to address the perceived barriers. In particular, the interview focused on the following factors: 1) logistical issues; 2) availability of genetic counselors; and 3) involvement of the IRB. Interview questions also explored decision-making surrounding the return of results. Figure 3 illustrates the interview questions specifically addressing C-CFR ROR policies.

Figure 3: Interview Questions Concerning C-CFR site-specific ROR policies

Prompt: Though it continues to be a much-debated issue, offering the return of results identified to have important research results, directly to registry participants, has been initiated within the Colon CFR consortia.

Does your registry site have a policy with regard to the return of individual genetic findings? If so, what is that policy exactly?

Was this policy already in place at the inception of your registry site? If this has not always been the policy, what was the initial policy that this current return of results policy replaced? How long has this been the policy of the registry?

What were the factors going on at the time that established the need for an ROR policy? Possible Prompts: What do you think influenced this request for a policy change?

Key Informant Recruitment and Data Collection

Recruitment of C-CFR investigators targeted those involved in ROR decision-making process and/or implementation. Following IRB approval, the Seattle C-CFR PI (PN) sent an e-mail to the principal investigators (PIs) at each C-CFR site to invite participation in the interview study. Using snowball sampling, C-CFR PIs nominated C-CFR staff members, either current or previous employees, for recruitment. ML then contacted each potential key informant to gauge their interest in participating and, if interested, to schedule the interview. Each key informant received a copy via e-mail of the informed consent form to review prior to interview. Following verbal informed consent, interviews were conducted over the phone or via SKYPE. In total, 14 key informant interviews were conducted from January to July 2014. At least one key informant represented each C-CFR site. All key informant interviews were audio-recorded and transcribed verbatim.

Thematic Analysis

Interview transcripts were proofed against the audio-recordings, redacted to remove identifying information, and stored on a secure, password-protected computer at the Fred Hutchinson Cancer Research Center (FHRC). Transcripts were uploaded in Atlas.ti [68], computer-assisted qualitative software, for directed content thematic analysis [69]. A code list was created based on the topics covered in the interview guide, and additional codes were added based on the themes identified from the interview responses. Two research team members [ML, AT] independently coded the transcripts for validity and investigators [ML and SMF] reviewed and modified the codes in an iterative process. By constant comparison [70] of the generated codes between the gathered interview data, directed content thematic concepts were then organized hierarchically under specific categories [Supplemental Figure S1] as the key informants described their ROR experiences and discussed the influential factors contributing to their site-specific ROR protocol development and its implementation.

Results

Key Informants

Interviews were conducted with three male and eleven female key informants, including four principal investigators (PI), four genetic counselors (GC), and six program managers (PM)/study coordinators (SC). At least one key informant from each of the six C-CFR sites was interviewed. All of the PIs had worked in their respective registries since inception. They were trained in epidemiology, clinical genetics, or statistics, and their responsibilities included securing and seeking additional grant funding, providing staff oversight, conducting genetic research, and playing a major role in ROR implementation decision-making at their

respective sites. The genetic counselors were all involved in ROR implementation. Their main roles were to provide genetic counseling services for participants who chose to receive research results. One of the four had assisted with the development of their site's ROR protocol and IRB submission. For the program manager/study coordinators, all but one were hired at C-CFR inception and they were all tasked with providing coordination regarding the daily operations of the registry (e.g., participant recruitment, biospecimen handling and staff training). They all played a major role during the ROR protocol development, its implementation, and communicated quite often with participants to assist them with the referral process (i.e., making an appointment with their doctors or a genetic counselor and eventually receiving their research results).

Key Factors Relevant to Site-Specific Implementation

The ON and AU C-CFR sites began returning research results in 1998 and 1999, respectively [30]. The MA and HI C-CFR sites implemented their ROR protocols in 2008, while the SE C-CFR site began returning results in 2011. The USC site, a cancer consortium within the C-CFR consortium, had not adopted a standardized ROR protocol at the time that informants were interviewed. Key informants identified three broad sets of factors contributing to site-specific ROR protocol development and implementation (Table 1): 1) clinical and/or research experience of the C-CFR staff; 2) public and health care system infrastructure; and 3) existing regulations at local institutions and informed consent.

Clinical and/or research experience of the C-CFR staff

Key informants described how the expertise and background of registry staff at each site was important to ROR protocol development and implementation (Table 1). For example, the PIs

at the two early implementation sites (AU and ON) shared their experience participating in other cancer registries where results had been offered to be a factor in their ROR decision-making. For example, one of the PIs at the AU C-CFR described his prior involvement in the Victorian Colon Cancer Family Registry (1992-1997). As part of that registry's work, participants were identified who tested positive for pathogenic variants associated with Lynch syndrome. In that instance, the original informed consent form was silent on the matter of result return and the research group had to work closely with its ethics review board to develop a ROR policy *post hoc*. At the inception of the C-CFR, the same ROR policy was rapidly implemented in the AU site. For the ON C-CFR site, their staff also learned from the prior decisions of the Ontario Breast registry when they had to develop a ROR protocol (Table 1).

In contrast, the SE and HI C-CFR sites were unable to implement a ROR protocol rapidly in part because of the time required to receive approval from their institution's respective IRBs. In both cases, the ROR protocol implementation was the first such request made to their respective IRBs (Table 1). As such, additional time was needed to consult their local institution's legal department as well as the general council before they were able to grant approval. The key informants from these sites did not have the opportunity to learn from experiences of other researchers at their local institutions that dealt with the ROR issue since, to the best of their knowledge, there were none.

Public and health care system infrastructure

Another factor identified as relevant to both the timing of implementation, and to the nature of the specific ROR protocol adopted, was the health care infrastructure available for support and follow-up. In particular, the AU and ON C-CFR sites were able to utilize government-

and/or provincial-funded genetic counselors as part of their ROR endeavors (Table 1). At the AU C-CFR, investigators released registry research results to a government-funded genetic counselor upon receiving verification (via separate informed consent) that a registry participant was interested in receiving their research results. In some cases, the participant was referred to counseling for clinical validation in a blinded fashion (i.e., the counselor did not have the research result in hand) and in other situations the counselors received the result and acted to validate the information prior to result return. For the ON C-CFR, registry-funded genetic counselors provided research results to interested participants over the phone or referred a participant to a provincial-funded genetic counselor from whom they might choose to receive their research result during the clinic visit.

ROR implementation at the MA, HI and SE C-CFR sites began nearly a decade later, in part because of the need to secure funding to support the hire of genetic counselors to assist with ROR. These sites, located in the United States, did not have a public health infrastructure to draw on in the same way as the AU and ON C-CFR sites. At one site, a principal investigator with clinical genetics training first returned results until they were able to obtain the funding required to hire their own genetic counselor. At another site, it was cheaper to establish a contractual agreement with the genetic counselors at their hospital rather than hiring their own registry-based genetic counselor (Table 1). All four genetic counselors interviewed for the study indicated that they would have not been involved with the C-CFR if the consortium had not decided to return research results.

In addition to counseling, another major infrastructure issue was the support available for clinical validation of the research findings. At the ON and AU C-CFR sites, the clinical verification of the research results was paid for by funds from the provincial or government-

funded national health care system. For the C-CFR sites based in the United States, no such support was available. Participants who were advised that they should verify their non-CLIA genetic research results in a CLIA-compliant laboratory had to rely on personal health insurance or pay out of pocket. In certain cases, this meant that registry participants did not validate the non-CLIA genetic research results they received in a CLIA-compliant laboratory (described in more detail in Chapter 4).

Existing regulations at local institutions and/or informed consent

Finally, key informants noted the role of local institutional norms and research regulations in ROR implementation. In the United States, return of research results was largely discouraged until the mid-2000s. Accordingly, for two C-CFR sites (SE and USC), the original site-specific registry informed consent form had stated that no individual results would be returned (Supplemental Table S1). As a consequence, the SE C-CFR was required by their IRB to re-contact their registry participants to obtain informed consent for the potential offer of research results, if available, and this contributed to the delay. In contrast, other C-CFR sites (ON, AU, MA and HI) addressed the possibility of result return in their informed consent documentation. As such, a second consent process was not required. Except for some sub-sites belonging in the USC consortium, all C-CFR sites now have ROR language in their current informed consent forms (Table 2 for AU, MA, HI, ON, SE C-CFR sites and Table 3 for USC C-CFR sites).

Table 1: *Colon Cancer Family Registry Consortium Protocol on the Implementation of the Return of Results from Genetic Research (1998-2013)*

	1998/1999 Implementation	2008 or later Implementation
Influential Factors	Representative Quote	Representative Quote
Clinical and/or research experience of the C-CFR staff	<p>“We also have some experience from the BCR which was the Ontario Breast registry, which is sort of our sister registry for colon cancer. They had started about a year or two before us. We also had been sitting in on with them as they plan how they were going to give results.” [P12, GC]</p>	<p>“I think the initial biggest challenge was that it hadn’t been done at our center before. And so we are always the trailblazers.” [P3, PM]</p>
Public and health care system infrastructure	<p>“We then explain to people [registry participants] that if they wanted to avail themselves of that information, they could do so and we would direct them to the family cancer clinics in Australia. There were state cancer services across country, but very few only at the time and that they could go to get the results.” [P7, PI]</p>	<p>“Seriously, we actually budgeted for genetic counseling. The last genetic counseling was, I think, the end of 2013. We had them continuously from 2008 to 2013. It was a cost per session. And it was a flat rate cost per session. That was a negotiated cost and I personally appealed to the Vice President of this hospital and explained a win-win situation.” [P14, SC]</p>
Existing regulations at local institutions and informed consent	<p>“We had established our clinic registry in 1980s, so for years and years that we’re doing research looking at Lynch syndrome and we’re giving the results back. So we had already gone to Ethics committee to show them that we’d never had complaints from the patients. We thought that we were doing something that was beneficial to the patients.” [P12, PM]</p>	<p>“We would meet with IRB and they’d say, “Gosh, I don’t know, we should talk to legal about this.” Just -- because it always starts with a telephone call and then the meetings. Legal went through our consent forms and with us, we had dialogues about what did we tell the participants and things we’re going to do. That was always the first question. And then, it was “Huh? Well, let’s think about this.” [P3, SC]</p>

*GC – genetic counselor; PI – principal investigator; PM – program/project manager; SC-study coordinator

Table 2: *Verbatim Excerpts from the Updated Informed Consent Forms Given to Participants at Each Site**

Ontario (ON)

Genetic counseling will be offered to all interested participants and family members. Genetic counseling will include a discussion of individual cancer risks, an explanation of the causes of cancer and the availability of screening and preventive strategies. If individual results are available, the Ontario Familial Colon Cancer Registry, consisting of a group of health-care professionals will review the quality of research results and decide when, and if, they should be available to the study participants.

Australia (AU)

It is possible during our research that we may find genetic information relevant to you or your family. If you choose to be informed: We will only write to you if we find genetic information relevant to you or your family. We will offer to give you this information through a clinical counseling service...If you decide to proceed to genetic testing it will be carried out *free of charge*...

Mayo Clinic (MA)

No results will be given to you unless researchers at Mayo Clinic find something important that could be useful for you to know. If this occurs, you will be notified in writing of the option of learning of this research result and would be given an opportunity to learn more about the risks and benefits of learning about a test result before actually getting a result. Before any results of this type of testing would be shared with you or your family members, you will be contacted and given the chance to have further counseling to help you choose if you would like to get this information or not.

Hawaii (HI)

The Research Monitoring and Ethics Review Panel will look at the results of all research projects that use the Registry. If they determine that the research done using my samples and others samples gives information that is of any possible medical benefit, I will get that information from a newsletter which will be sent to me by the Registry staff. If I then want to know how these research findings would make a difference for me personally, especially about genetic factors, I can have counseling and possible testing outside this research study. These services would have to be at my own cost.

University of Southern California (USC)

Please see Table 3

Fred Hutchinson Cancer Research Center (SE)

We are currently conducting genetic and other testing on many of the samples donated by our participants. Since test results can be important for health care decisions, we will contact you if the study finds genetic information, which may be useful to you and your family. Please note that because we are working within the constraints of resources intended for research results, we may not test everyone's sample. If we notify you, it will simply be an opportunity to discuss the option of discussing your genetic information with a genetic counselor.

*initially compiled by Allyson Templeton, project coordinator of the C-CFR consortium

Table 3: *Verbatim Excerpts from the Updated Informed Consent Forms Given to Participants at USC Consortium Sites**

University of Arizona (AZ)

In the future, blood samples will be tested for genes that may affect the risk of [CRC]. You will not be informed of the results of this gene testing. No one but study investigators will know the results.

Cleveland Clinic (CC)

Although individual test results will not be distributed, we will update you on the overall progress of the research through a newsletter containing new discoveries in cancer research that have resulted from use of the registry. You will potentially benefit from a free genetic counseling session in the Personalized Genetic Health care Clinic at the Cleveland Clinic, which is offered to each participating family in the study

University of Colorado Denver (UC Denver)

Results of gene studies will not be made available to you or any other individual participants.

University of Minnesota (UM)

Your family history will be reviewed by a medical geneticist for indications of your family's risk of cancer. You will be informed of these results and, if you family is found to be at high risk, you will be contacted by telephone as well. The blood sample will be used in possible future studies of genetic factors that may cause [CRC]. These tests will be performed in research laboratories for research purposes only, and therefore, the results will not be available to you or your family.

University of Northern Carolina (UNC)

In the future, your blood or mouthwash sample will be tested for genes that may or may not affect the risk of Colon cancer. We do not yet know which genes or how many genes will be studied, and we do not yet know the medical or other meaning of these tests. Because of this, you will not be given the results of genetic tests.

University of New Hampshire (Dartmouth)

Individual results from genetic testing or other research are not available as part of this study. If you wanted to determine your personal genetic makeup, it would be necessary to get a referral for testing outside the research study... From samples provided to the registry, we may discover information about the role of genes in [CRC]. Individual test results from genetic testing or other research are not available as part of this study and therefore will not be distributed.

University of Southern California (USC)

This is a research study and was not originally intended to provide information that is currently known to affect your medical care. However, as the research progresses, if we uncover a specific genetic finding that could be relevant to your medical care, you will be offered the opportunity to review those preliminary research results with a genetic counselor.

* initially compiled by Allyson Templeton, project coordinator of the C-CFR consortium

The USC C-CFR faced additional challenges in having to standardize policies across seven institutions encompassed by that site: University of Arizona, Cleveland Clinic, University of Colorado Denver, University of New Hampshire (Dartmouth College), University of Minnesota, University of North Carolina-Chapel Hill, and the University of Southern California. Although these sub-sites made concerted efforts to maintain consistency, they had to rely on their respective local institutions to obtain approval to return research results. While one sub-site of the USC C-CFR eventually did receive IRB approval for ROR, they were not actually able to return results because, by that point, their grant funding had ended.

C-CFR Study Team's Experience with Result Return

Despite differences in the timing and nature of ROR implementation, investigators at the C-CFR sites who made the decision to return results uniformly justified the ROR implementation decision on the basis of the clinical utility of the genetic findings. As one key informant shared,

The strength of evidence that these particular gene mutations [LS-associated MMR pathogenic variants] were highly penetrant and that there was evidence that one could do something preemptively to help ward off some of the disease, i.e., colonoscopy, hysterectomy, and so forth. So it's a very, and I hate the word, clinically actionable disorder and we have a high level of confidence that the mutations that we were seeing was real. [P6, PI]

In addition, key informants described an ethical and moral obligation to return results because the clinical utility of the information extended beyond the individual CRC patient to unaffected family members. Hence, ROR implementation was motivated by a commitment toward “duty to warn” or “duty to care” for the participants enrolled in their respective registries. As shared by another key informant:

We felt like we had a moral and ethical obligation to people to give them information that we had gained as a result of their participation in the research. And that part of being responsible as researchers involved allowing them access to this kind of information...So really it was ... that would have been irresponsible not to give them something that might be actionable in terms of their choices. [P4, PM]

In many instances, key informants shared that registry participants expressed their gratitude for having the opportunity to receive research results. At one site, for example, investigators realized that approximately 70% of participants identified with LS in their registry had not been previously referred to clinical genetic services. They received this feedback anecdotally from the participants who had elected to receive results. Interestingly, one key informant shared that some participants (in locations outside the US) reported that they did not want to receive their results because they thought that their US-based relatives would be adversely affected [e.g., have difficulty obtaining insurance coverage] if a hereditary cancer syndrome was identified in the family. As this key informant passionately shared,

There was an existing litigation to fear of—it's fear, fear, fear and that's what we did in the current world, it's all about fear...[So] the fear of litigation is driving the agenda around the issues of human health, which is why apparently it's such a bloody mess of our own when it comes to health. [P7, PI]

Finally, in the course of the interviews it became clear that notwithstanding the recognition that result return was justified, a local “champion” was often necessary to advocate for the ROR policy development and implementation at the respective sites. When specifically asked what they would have done if their site had not moved forward with ROR protocol implementation, these two key informants expressively shared:

I could not have lived with myself! I would have gone to the mat to try to offer these results back to people. I would have found some end run here. I just...I just don't think that's acceptable. [P6, PI]

I can't imagine that even happening except for maybe funding, where we didn't have funding, or we had no one to do it. That would be—I don't think it would happen because we would just—there is such a strong forces of physicians and other people who were proactive in people giving their results. So I just think that somehow there would be funding. But if it did it happen, I think for me I'd find it difficult. [I] wouldn't... stop doing the job, but it—I would find it difficult. [P10, PM]

Despite challenges (e.g., funding, time to receive IRB approval) faced by some C-CFR staff when developing their site-specific ROR protocols, they all made a concerted effort during participant re-contact for the ROR opportunity. They learned from their experiences, specifically on what worked and what did not work as well, during the implementation of their varying ROR protocols.

Discussion

This qualitative investigation of the views and experiences of C-CFR principal investigators, genetic counselors, and program managers/study coordinators identified a number of underlying motivations for result return as well as the numerous challenges faced by individual sites in the course of ROR implementation across the international cancer registry consortium. Specifically, three main factors were identified as relevant to implementation: the training and prior experience of C-CFR staff, access to a robust public health infrastructure, and the influence of local regulatory norms and/or informed consent. Site-specific differences with regard to these factors led to significant differences in the timing of ROR implementation and meant that the use of genetic counselors for result return varied as well. Implementation varied even though investigators at all sites recognized the clinical actionability of the information and felt an ethical obligation to return relevant results to registry participants.

These findings have several important implications for the implementation of ROR protocols in similar settings. First, they emphasize that even with clear guidelines recommending result return, local barriers including lack of experience with ROR can impede implementation. For example, although the National Bioethics Advisory Commission recommended in 1999 that “IRBs should develop general guidelines for the disclosure of the results of research to subjects and require investigators to address these issues explicitly in their research plans” [49], not all IRBs at local institutions have such guidelines [71-73]. For example, Dressler et al. interviewed 31 IRB professionals representing four major academic centers and two research hospitals in the United States [71]. All the interviewed IRB professionals in that study agreed that research results with clinical actionability should be returned, but most were not comfortable developing policies at their local institutions, given their lack of professional expertise in genomic research. Further, because academic institutions may have multiple genetic research teams, Maschke et al. suggested a committee is needed, separate from the IRB, to ensure equal participant access to genomic data from genetic research [54].

Second, these findings underline the relevance of surrounding health care infrastructure and its role in ensuring the cost-effectiveness and feasibility of research result return. Besides prior experience and regulatory differences, the main factor that allowed the AU and ON C-CFR sites to implement their ROR protocols nearly a decade sooner than the other C-CFR sites was their ability to draw on a robust public health infrastructure in the course of result return. Specifically, they were able to utilize their provincial- and/or government-funded genetic counselors by referring select registry participants for clinical genetic counseling consultations. During these appointments, the genetic counselors facilitated verification of

research results and the cost of clinical genetic testing was covered by their national health care systems.

Finally, this close investigation of the experience of this international CRC cancer registry suggests features of ROR implementation that will need to be addressed as other cancer registries attempt to implement similar ROR protocols. For example, as reported here and previously by Keogh et al. [34], informed consent differences across C-CFR sites added to the challenge of gaining permission from their institution's IRB to re-contact their registry participants for ROR. Moving forward, principal investigators initiating cancer registries with a genetic research component should have clear plans in place at the outset regarding their intention to return research results [18, 19]. Similarly, it will be important to ensure that sufficient resources are set aside to support result return, including the possible CLIA validation of non-CLIA genetic research findings and the use of genetic counselors as part of the return protocol. Because registry participants are often contacted every five years to update their epidemiological information and family medical histories, some aspects of the return process may be easier for registries than other types of research studies.

In cancer registries, emerging ethical considerations may also need to be addressed in future ROR implementation efforts. For example, recent discussion has centered on whether it is worthwhile to offer relevant clinically actionable results to biological relatives' deceased research participants [74-77]. This possibility may be especially important to consider in the context of cancer registries where a significant proportion of cases may be deceased by the time that pathogenic variants in cancer genes are discovered. Of course, in some respects, this problem is counter-balanced by the fact that family members are often enrolled registry participants themselves.

Study Limitations

The purposive sampling method used in this study may have led to an incomplete description of the C-CFR ROR protocol development and implementation experience and, in particular, may have over-represented the views of key informants who were more inclined to advocate for result return. C-CFR staff members who were no longer employed by the registry, who may have held different perspectives, were also not available for interview. Another limitation was that the information about the financial implications of the ROR protocol implementation was based upon the impressions of those interviewed and not on a consideration of registry budgets or related data that would have allowed an estimate of the true cost to each registry site of the return research results to their respective participants.

Conclusion

In summary, individual C-CFR sites implemented their ROR protocols in different ways, with non-US-based registry sites implementing result return nearly a decade before other sites. This suggests that while the ethical impetus to pursue ROR was broadly shared among registry investigators, perceived obligations were enacted with a varying degree of urgency and according to the prior professional experience of the C-CFR staff, available public and health care infrastructure, and existing regulations at local institutions and informed consent. This experience of implementation heterogeneity provides insights on ROR policy development and implementation that will be relevant to other cancer registries.

CHAPTER 3: Participant Characteristics Influencing the Acceptance of Lynch Syndrome Genetic Research Results

Abstract

Purpose: The Colon Cancer Family Registry (C-CFR) sites offered individual participants return of results (ROR) from genetic research relevant to Lynch syndrome (LS). The aim of this study was to identify the proportion of participants who accepted individual LS-related genetic research results and examined which participant characteristics influenced the likelihood of research result acceptance.

Methods: We obtained de-identified demographic information of participants approached for LS-related genetic research result return at four C-CFR sites (N=1792). By including only participants who either accepted or declined research results (N=763), we calculated the proportion of participants who accepted results within and across sites. Using logistic regression analysis, we examined which characteristics among these participants (N=763) predicted the likelihood of acceptance of individual research results relevant to LS.

Results: Across the four C-CFR sites, 63.0% of participants (481/763) that were approached accepted LS-related genetic research results. Participants older than 50 years of age were 64% less likely to accept research results (OR, 0.36; 95% CI, 0.25–0.52) than participants who were less than 50 years old. Participants who were currently or living as married were 67% more likely to accept results than those who were not (OR, 1.67; 95% CI, 1.06–2.63). Further, a participant's race/ethnicity also influenced acceptance, with non-Caucasian "other" participants 3.17 times more likely to accept research results than Caucasians (OR, 3.17; 95% CI, 1.22–8.27). These associations were observed after adjusting for C-CFR site, sex,

reproductive history, number of family members with cancer, whether a participant was a case or relative, and if a family member had pursued clinical genetic testing.

Conclusions: Participant age, marital status, and race/ethnicity were significantly associated with the likelihood of accepting research results. Site-specific ROR protocols may have had an impact on the identified differences in the proportion of participants accepting LS-related research results and the participant characteristics identified.

Introduction

The Colon Cancer Family Registry (C-CFR) is an international consortium composed of six registry sites located in Australia, Canada, and the United States [2]. Initial research by the C-CFR to understand the etiology of colorectal cancer (CRC) began by testing CRC tumor blocks for microsatellite instability (MSI) and then by immunohistochemistry (IHC) staining for the mismatch repair (MMR) proteins [78-80]. As a result, some registry participants were found to have MSI-high CRC tumors, as well as missing expression of the MMR proteins. The biospecimens from these cases were then tested for pathogenic variants in the MMR genes and family members who had provided a biospecimen were also tested to see if they inherited the same (i.e., presumed familial) variant. The genetic tests were performed at either the Australia or Mayo C-CFR research laboratories, and tests were conducted using standardized protocols for quality control. Due to the high predictive value of known pathogenic variants and accepted clinical utility of LS genetic testing [8, 81, 82], most C-CFR sites ultimately elected to return individual results (return of results or ROR) directly to participants. These efforts were initiated in a site-specific fashion, beginning in 1998, and launched following each site's respective institutional review board (IRB) approval.

Lynch Syndrome (LS), a hereditary colon cancer syndrome also known as Hereditary Non-Polyposis Colon Cancer (HNPCC), is responsible for 2% to 4% of CRC and 2% of endometrial cancer cases [11, 59, 83]. The lifetime risk of developing CRC for an individual with LS is in the range of 52% to 82%, with a mean age at diagnosis of 44 to 61 years. To compare, the general population lifetime CRC risk is approximately 5%, with a median age at diagnosis of 69 years. As such, LS-affected individuals are advised to pursue earlier and more frequent screenings (colonoscopy surveillance to begin in early to mid-20s) when compared to unaffected individuals in the general population (colonoscopy surveillance to begin at age 50). Studies have shown that routine colonoscopy screenings in LS-affected individuals decrease the overall CRC incidence by 62% and mortality by 65% to 70% [84]. Compliance with recommended routine surveillance is important because there is a 16% to 30% chance of developing a second primary CRC within 10 years of the first CRC diagnosis. Additional increased cancer risks include a 25% to 60% lifetime risk for endometrial cancer, 6% to 13% for gastric cancer, and 4% to 12% for ovarian cancer [85]. LS is attributable to pathogenic variants in one of several MMR genes (i.e., *MLH1*, *MSH2*, *MSH6*, and *PMS2*). These genes are part of a molecular system that recognizes and repairs errors during DNA replication [86]. Molecular testing for the MMR genes is clinically available [11]. In light of increasing evidence in support of the effectiveness of cancer surveillance in individuals with LS [84, 87-90], the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group recommended in 2009 to screen all newly diagnosed CRC patients for LS so that unaffected and/or undiagnosed family members could become aware of their enhanced risk and pursue options for cancer screening and prevention [81].

Although researchers have returned individual genetic results to participants in diverse contexts [27, 55, 91], there are currently few empirical data reporting the acceptance of research results returned in the context of an international cancer registry consortium. Better data, particularly with regard to LS-related genetic testing, are available in clinical settings [26]. For example, despite one study indicating strong interest in receiving genetic research findings among CRC cases and relatives [19], other research has suggested that not all individuals who meet the criteria for genetic testing actually choose to be tested [57, 92, 93]. Sharaf et al., in a systematic review of available literature, found that fewer than 52% of at-risk relatives pursued recommended genetic testing [94].

To date, two prior studies have described experiences with result return in the C-CFR [34, 55]. Graves et. al. investigated whether the Mayo Clinic C-CFR participants shared their research results with family and health care providers [55], while Keogh et. al. reported how C-CFR researchers manage ROR endeavors in practice [34]. However, neither of these studies described the proportion of registry participants across the C-CFR consortium who accepted research results specifically for LS, or investigated which participant characteristics influenced the likelihood of accepting offered research results. In this study, we address these C-CFR ROR outcomes with the aim of identifying which participant characteristics, if any, are related to the likelihood of LS-related research result acceptance.

Study Purpose and Hypothesis

The purpose of this study was to determine which variables predict the likelihood of participants' acceptance of LS-related genetic research results. The three categories of variables that were examined were 1) participant demographic characteristics (i.e., age, sex,

reproductive history, marital status, education level, race/ethnicity, 2) personal medical history (i.e., affected with cancer or not), and 3) family history (i.e., number of family members with cancer, a family member pursued clinical genetic testing). These variables were selected based on their perceived clinical significance and/or availability of previously published data indicating that these underlying characteristics influence an individual's decision-making whether to know or not know their genetic status.

The outcome of interest was the acceptance of an offered genetic research result. We hypothesized that age, reproductive history, education level, and personal and family history of cancers would each be associated with an increased likelihood of accepting research results. Specifically, we expected that younger participants would be more likely to accept their research results as they might want to use the information for early and more routine cancer screening and for family planning purposes. Participants with a personal and/or family history of cancer were expected to be more likely to accept their results because they would want to know what caused their personal diagnosis of cancer or other significant cancer diagnoses in their family. Participants with children were also expected to be more likely to accept research results because they would want to share the information with their children, while participants with a higher education level were expected to be more likely to accept research results because they would understand better the clinical implications of the information they might receive. We expected to observe no association between the participant's sex, status of either being a case or relative, if a family member had pursued clinical genetic testing, and the likelihood of accepting LS-related research results within and across C-CFR sites.

Methods

The University of Washington Institutional Review Board (IRB # 45998) approved the protocol and informed consent procedures. This study was conducted with the approval of the C-CFR consortium (C-CFR Project ID: C-EX-0412-04).

Study Population

This study examined de-identified demographic information of participants who were offered LS-related genetic research results. Four of the six C-CFR sites were investigated: (1) the University of Hawaii, Honolulu, HI (HI); (2) the Mayo Clinic, Rochester, MN (MA); (3) the Fred Hutchinson Cancer Research Center, Seattle, WA (SE); and (4) the University of Melbourne, Melbourne, Australia (AU) [2, 3]. The Lunenfeld-Tanenbaum Research Institute (2013–present); Cancer Care Ontario 1997–2012), Toronto, Ontario, Canada (ON) C-CFR site; and reportedly some sub-sites of the University of Southern California, Consortium, Los Angeles, CA (USC) also returned genetic findings but complete data were not available so those sites were excluded from the analysis.

For the SE, HI, MA and AU C-CFR sites, data use agreements (DUA) were obtained prior to requesting data for those cases (participants diagnosed with CRC and typically the first person in the family to enroll in the registry) and their enrolled relatives (with and without CRC and related cancer diagnoses) whom were offered genetic research results. Following receipt of DUAs, a C-CFR investigator from each site securely sent to ML the coded data containing the participant identification number and their ROR decision (recorded as accepted, declined, lost to follow-up, status pending, or already underwent clinical testing). Demographic variables for the same coded IDs were provided by the C-CFR informatics

center, (Appendix B for data dictionary of terms) and these data were then merged with the ROR decision variable to create the complete dataset.

Inclusion Criteria

A preliminary dataset of 1,792 C-CFR participants belonging to families with an identified pathogenic variant in a MMR gene for LS who were approached for ROR was used to calculate the proportion of those who accepted research results within and across the four C-CFR sites. These participants had either accepted or declined research results, were lost to follow-up, described as status pending, or had previously pursued clinical genetic testing. For the multivariable logistic regression model, data from only the subset of 763 participants who either declined or accepted research results were used (i.e., those who were lost to follow-up, status pending, or had previously undergone clinical genetic testing, were excluded from further consideration). Some C-CFR participants had unknown information for some variables (e.g., marital status, education and race/ethnicity) and these variables were recoded as “unknown” in order to keep these participants in the dataset.

Statistical Analysis

The study participants’ demographic information was tabulated using STATA14 statistical software package [95] and descriptive statistics, including means, standard deviations, range, and frequencies, were generated. The proportion of C-CFR participants who accepted research result was calculated by dividing the number of participants who received results by the overall number of participants who either declined or accepted research results. Observed proportions were compared across sites using the Pearson χ^2 test statistic or Fisher’s exact test when appropriate.

Logistic Regression Model Analysis

A multivariable logistic regression model was used to predict the association of participant characteristics and ROR acceptance. The dependent outcome variable, result acceptance, reflecting those participants who chose to receive research results, was “dummy coded.” Independent categorical variables were “dummy coded” and included age, sex, reproductive history (i.e., had children or not), personal history of cancer, number of family members with cancer, education level, race/ethnicity (self-reported), marital status and whether a family member was known to have previously pursued clinical genetic testing. As mentioned, the variables education level, race/ethnicity, and marital status, were recoded to include an “unknown” category for those participants missing information. To compare, two logistic regression model analyses were performed. The first logistic regression model included the “unknown” categories, while the second logistic regression model excluded them. Descriptive statistics were calculated for each covariate, consisting of means, standard deviation, range, and frequencies. Odds ratio with 95% confidence interval (CI) and *p*-value of < .05 was generated for the logistic regression model, which was performed within and across C-CFR sites for comparison.

Results

Across the SE, HI, MA, and AU C-CFR sites, there were a total of 1792 participants approached with regard to the return of LS-related genetic research findings (Supplemental Table S2). Across these C-CFR sites (Figure 4), we observed variability in the proportion of participants who accepted or declined research results, were lost to follow-up, were described as status pending, or who reported having previously pursued clinical genetic testing. The HI

C-CFR site had the highest proportion of participants (42 of 49; 85.7%) who accepted research results and AU C-CFR had the lowest (174 of 366; 47.5%). When only those participants who had actively accepted or declined results were considered (Supplemental Table S3), the overall participant acceptance of the offered LS-related research result was 63.0% (481/763).

Figure 4: The Return of Lynch Syndrome Genetic Research Results to Colon Cancer Family Registry Participants (1999-2010)

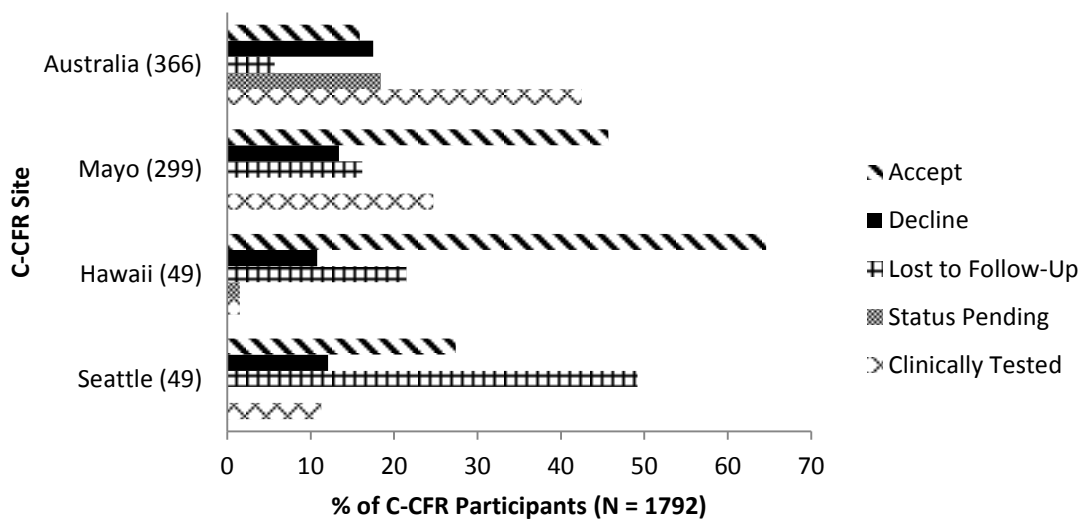


Table 4 summarizes the participant characteristics. In total, there were 81 (10.6% of 763) cases and 682 (89.4% of 763) relatives. For these participants, the mean age was 49.2 years \pm 15.8, with a range of 18 to 87 years. Over half of the sample (51.8 %, 395 of 763) were less than 50 years old, 52.3 % (399 of 763) were female, 63.8 % (487 of 763) had children, 63.8% (487 of 763) had no prior cancer diagnosis, 68.4% (522 of 763) had more than three family members with cancer, 68.3% (521 of 763) had less than or had some college education, and 88.9% (678 of 763) were of self-reported Caucasian race/ethnicity. Further,

43.4% (324 of 763) of participants were currently or living as married and 58.2% (444 of 763) reported having a family member who had previously pursued clinical genetic testing.

Table 4: *Colon Cancer Family Registry Participant Characteristics (1999-2010)**

	SE	Registry Site [N (%)]			Total
		HI	MA	AU	
Age, years [49.2 mean, 15.8 std dev, range: 18-87]					
< 50y	24 (49.0)	26 (53.1)	132 (44.2)	213 (58.2)	395 (51.8)
≥ 50y	25 (51.0)	23 (46.9)	167 (55.9)	153 (41.8)	368 (48.2)
Sex					
Male	19 (38.8)	26 (53.1)	146 (48.8)	173 (47.3)	364 (47.7)
Female	30 (61.2)	23 (46.9)	153 (51.2)	193 (52.7)	399 (52.3)
Had Children					
No	15 (30.6)	28 (57.1)	97 (32.4)	136 (37.2)	276 (36.2)
Yes	34 (69.4)	21 (42.9)	202 (67.6)	230 (62.8)	487 (63.8)
Personal History of Cancer					
None	30 (61.2)	30 (61.2)	164 (54.9)	263 (71.9)	487 (63.8)
Colon Cancer	14 (28.6)	17 (34.7)	87 (29.1)	57 (15.6)	175 (22.9)
Other Cancers**	5 (10.2)	2 (4.1)	48 (10.1)	46 (12.6)	101 (13.2)
# of Family Members with Cancer					
1≤ 3	25 (51.0)	27 (55.1)	75 (25.1)	114 (31.2)	241 (31.6)
> 3	24 (49.0)	22 (44.9)	224 (74.9)	252 (68.9)	522 (68.4)
Education Level					
Less/Some college	36 (73.5)	24 (48.9)	182 (60.9)	279 (76.2)	521 (68.3)
College graduate	12 (24.5)	22 (44.9)	101 (33.8)	76 (20.8)	211 (27.6)
Unknown	1 (2.0)	3 (6.1)	16 (5.4)	11 (3.0)	31 (4.06)
Race/Ethnicity					
Caucasian	36 (73.5)	7 (14.3)	276 (92.3)	359 (98.1)	678 (88.9)
Other	13 (26.5)	39 (79.6)	8 (2.7)	7 (1.9)	67 (8.8)
Unknown	0	3 (6.1)	15 (5.0)	0	18 (2.4)
Currently or Living as Married					
No	14 (28.6)	46 (93.8)	8 (2.8)	108 (29.5)	176 (23.6)
Yes	33 (67.4)	0	35 (12.2)	256 (69.9)	324 (43.4)
Unknown	2 (4.1)	3 (6.0)	243 (84.9)	2 (0.5)	247 (33.1)
Participant**					
Case	10 (20.4)	14 (28.6)	38 (12.7)	19 (5.2)	81 (10.6)
Relative	39 (79.6)	35 (71.4)	261 (87.3)	347 (94.8)	682 (89.4)
MMR Gene Status***					
Positive for a pathogenic variant	30 (61.2)	29 (59.2)	147 (49.2)	164 (44.8)	370 (48.5)
Negative for a pathogenic variant	19 (38.8)	20 (40.8)	152 (50.8)	202 (55.2)	393 (51.5)
At least One Family Member had Clinical Testing					
No	41 (43.7)	47 (95.9)	132 (44.2)	99 (27.1)	319 (41.8)
Yes	8 (16.3)	2 (4.1)	167 (55.9)	267 (72.9)	444 (58.2)

Percentages may not add up to 100% due to rounding; * data obtained from baseline epidemiological participant survey conducted between 1999-2010; **participants diagnosed with biliary/renal, ovarian, stomach, pancreas, bile duct, or small bowel cancers; ** Case = participant with colon cancer and first enrollee of the family; Relative = enrolled family member; *** MMR genes = *MLH1*, *MSH2*, *MSH6* & *PMS2*

Table 5: Colon Cancer Family Registry Participant Characteristics (1999-2010) Comparison of those Who Accepted with those Who Declined Research Results*

	Decline [N (%)]	Accept [N (%)]	Total [N]
Age, years	[48.2 ± 17.06; 19-87]	[47.2 ± 14.58; 18-84]	
	<50y	273 (69.1)	395
	≥50y	208 (56.5)	368
Sex			
	Male	229 (62.9)	364
	Female	252 (63.2)	399
Had children			
	No	178 (64.5)	276
	Yes	303 (62.2)	487
Personal History of Cancer			
	None	299 (61.4)	487
	Colon Cancer	114 (65.1)	175
	Other Cancers ^a	68 (67.3)	101
# of Family Members with Cancer			
	1 ≤ 3	146 (30.4)	241
	> 3	335 (69.7)	522
Education Level			
	Less/Some college	308 (59.1)	521
	College graduate	149 (70.6)	211
	Unknown	24 (77.4)	31
Race/Ethnicity			
	Caucasian	410 (60.5)	678
	Other	58 (86.6)	67
	Unknown	13 (72.2)	18
Currently or Living as Married			
	No	97 (55.1)	176
	Yes	182 (56.2)	324
	Unknown	190 (76.9)	247
Participant ^b			
	Case	60 (74.1)	81
	Relative	421 (61.7)	682
MMR gene status ^c			
	Positive for a pathogenic variant	253 (68.4)	370
	Negative for a pathogenic variant	228 (58.0)	393
At least One Family member had Clinical Testing			
	No	212 (66.5)	319
	Yes	269 (60.6)	444

*Information from SE, HI, MA and AU C-CFR sites and data obtained from baseline epidemiological participant survey conducted between 1999-2010; Percentages may not add up to 100% due to rounding; ^aParticipants diagnosed with biliary/renal, ovarian, stomach, pancreas, bile duct, or small bowel cancers; ^bCase = participant with CRC and first enrollee for the registry; Relative = enrolled family member; ^cMMR genes = *MLH1*, *MSH2*, *MSH6*, or *PMS2*

Table 5 summarizes the characteristics of participants across all four C-CFR sites who accepted (N = 481) with those who declined (N = 282) research results. The subset of participants who accepted results had a mean age of 47.2 ± 14.58 (range 18 to 84), compared to 48.2 ± 17.06, (range 19 to 87) for those who declined. Approximately 63.2% (252 of 399)

of female participants and 62.9% (229 of 364) of male participants had accepted research results. Of the 81 cases, 60 (74.1%) accepted results, and 421 of the 682 (61.7%) relatives did as well. Of the participants who tested positive for a pathogenic variant for LS, 253 participants (68.4% of 370) accepted their results, while 117 (31.6% of 370) had declined. Of the participants who reported having at least one family member who previously pursued clinical genetic testing, there were 175 participants (39.4% of 444) had declined their individual research results, whereas 269 participants (60.6% of 444) had accepted their research results.

Logistic Regression Model Analysis Results

The likelihood of accepting a LS-related genetic research result was significantly associated with participant age, marital status, and race/ethnicity (Table 6). Participants older than 50 years of age were 64% less likely to accept research results (OR, 0.36; 95% CI, 0.25–0.52) than participants who were less than 50 years old. Participants who were currently or living as married were 67% more likely to accept results than those who were not (OR, 1.67; 95% CI, 1.06 – 2.63). Further, a participant’s race/ethnicity also influenced acceptance, with non-Caucasian (other) participants 3.17 times more likely to accept research results when compared to Caucasians (OR, 3.17; 95% CI, 1.22–8.27). Participants in the “unknown” category for the education level variable were also found to have a statistically significant association with the likelihood of accepting research results when compared to participants with less/some college education (5.68 OR; 95% CI, 1.38-23.25). However, the meaning of this association is challenging to interpret given its underlying limitation. There was no significant association identified with the rest of the covariables (i.e., sex, reproductive

status, personal history of cancer, status as case or a relative, or knowing at least one family member had clinical testing) and the likelihood of a participant accepting the offered individual genetic research results.

We also examined the association of C-CFR site with likelihood of result acceptance. Our study found that the participants in the SE, HI and MA C-CFR were more likely to accept LS-related genetic research results when compared to the participants in the AU C-CFR sites, with odds ratios 2.75 [95% CI, 1.30-5.81], 6.36 [95% CI, 1.86-21.76] and 4.63 [95% CI, 1.89-11.31] respectively.

A second logistic regression model analysis (Supplemental Table S8) was conducted excluding the unknown categories of the education level, race/ethnicity, and marital status variables. The likelihood of accepting a LS-related genetic research result was still significantly associated with the participant age, marital status, and race/ethnicity (p -value < 0.05). Specifically, participants older than 50 years of age were 72% less likely to accept research results (OR, 0.28; 95% CI, 0.18–0.44) when compared to participants who were less than 50 years old. Participants who are currently or living as married were 74% more likely to accept results when compared to those who were not (OR, 1.74; 95% CI, 1.09–2.79). Further, a participant's race/ethnicity also influenced acceptance, with non-Caucasian (other) participants 3.61 times more likely to accept research results when compared to Caucasians (OR, 3.61; 95% CI, 1.25–10.43).

Table 6: *Multivariable Logistic Regression Model Analysis of Participant Characteristics Across C-CFR Sites [Australia, Seattle, Mayo and Hawaii] Accepting Lynch Syndrome Genetic Research Results*

Variables (N)	Odds Ratio [95% CI]	P value
Age, years		
<50y (395)	[Reference]	
≥50y (368)	0.36 [0.25-0.52]	0.00
Sex		
Male (364)	[Reference]	
Female (399)	1.07 [0.77-1.49]	0.67
Had Children		
No (276)	[Reference]	
Yes (487)	0.97 [0.66-1.42]	0.87
Personal history of cancer		
None (487)	[Reference]	
Colon Cancer (175)	0.81 [0.49 -1.34]	0.42
Other cancers* (101)	1.62 [0.96-2.72]	0.07
# of family members with cancer		
1 ≤ 3 (241)	[Reference]	
> 3 (522)	1.21 [0.84-1.74]	0.30
Education Level		
Less/Some college (521)	[Reference]	
College graduate (211)	1.14 [0.78-1.67]	0.50
Unknown (31)	5.68 [1.39-23.26]	0.02
Race/Ethnicity		
Caucasian (678)	[Reference]	
Other (67)	3.17 [1.22-8.27]	0.02
Unknown (18)	0.29 [0.04-2.31]	0.24
Participant**		
Case (81)	[Reference]	
Relative (682)	0.59 [0.27-1.30]	0.19
Currently/Living as Married		
No (176)	[Reference]	
Yes (324)	1.67 [1.06-2.63]	0.03
Unknown (247)	1.61 [0.61-4.26]	0.34
At least one family member had clinical testing		
No (319)	[Reference]	
Yes (444)	1.39 [0.95-2.04]	0.09
C-CFR Site		
Australia (366)	[Reference]	
Seattle (49)	2.75 [1.30-5.81]	0.01
Hawaii (49)	6.36 [1.86-21.76]	0.00
Mayo (299)	4.63 [1.89-11.31]	0.00

* participants diagnosed with biliary/renal, ovarian, stomach, pancreas, bile duct, or small bowel cancers

** Case = participant with colon cancer and first enrollee of the family; Relative = enrolled family member

Discussion

In this study, we investigated the proportion of C-CFR participants who accepted LS-related genetic research results within and across the C-CFR consortium and identified the participant characteristics most closely associated with the likelihood of research result acceptance. Overall, the proportion of participants accepting LS research results across the four C-CFR sites was 63% (481/763). Adjusted by C-CFR site, we found that participant age, marital status, and race/ethnicity were statistically significantly associated with the likelihood of genetic research result acceptance (p -value < .05). Participants at the SE, HI and MA C-CFR sites were more likely to accept their research results compared to participants at the AU C-CFR site. The C-CFR participant characteristics of sex, reproductive history, personal history of cancer, number of family members with cancer, participant status as a case or a relative, and whether a participant had a family member who pursued clinical genetic testing did not statistically significantly influence the likelihood of accepting research results.

The observed variation in ROR acceptance across C-CFR sites may be partially explained by the differences in site-specific ROR implementation [34]. For example, the AU C-CFR site offered result return starting in 1998 (initially offering the return of IHC and MSI results rather than MMR genetic findings). In contrast, the other sites (SE, HI, and MA C-CFR sites) began offering results in 2008 or later. Compared to other C-CFR sites, the AU site showed the largest number of participants who already knew their genetic status from clinical testing (Figure 4). This may reflect the AU C-CFR site's initial effort to return MSI and IHC findings to their participants, which may have prompted the pursuit of clinical genetic testing

much sooner and meant that comparably fewer registry participants were interested in receiving genetic results once they became available.

In terms of the acceptance of LS genetic test results by relatives, our investigation found that 61.7% (421/682) of family members chose to accept their research results. This is slightly higher than the previously reported 51% (56/111) acceptance rate of relatives offered clinical LS genetic testing [58], as well as other studies investigating the pursuit of cancer-related genetic testing by first-degree relatives. This level of interest is especially important given current public health efforts aimed at identifying individuals with LS as an avenue to informing family members who may also be at increased cancer risk [101]. Knowledge of MMR gene status may motivate affected family members to pursue recommended cancer screenings for prevention and early detection.

Our study suggested that younger participant age (<50 years) was associated with an increased likelihood of accepting genetic research results. Previous published studies noted similar results [58, 102, 103]. It is also important to note that although our results suggested Non-Caucasian (other) race/ethnicity participant characteristics were statistically more likely to accept research results than Caucasians, this result largely reflects the impact of the HI C-CFR site who focused their recruitment on Asian and Pacific Islander minorities [106].

Prior research has suggested that individuals pursue genetic testing, especially in the cancer setting, in order to share such knowledge with their at-risk relatives, including their children [58, 102, 107-111]. However in this study, the C-CFR participants' reproductive history (i.e., whether they had children or not) was not significantly associated with an increased likelihood of accepting research results. The C-CFR is a family-based registry [2] and so it is

possible that registry participants assumed that their family members (e.g., their siblings and/or children participating in the registry) had similarly been offered the opportunity to receive individual genetic research results. If so, their desire to know their own result would not have been influenced by a desire to share their findings with relatives. Additional research is needed to confirm this possibility.

Study Limitations

Several limitations are worth noting. First, we were unable to examine specific participant characteristics that may have had an influence on result acceptance on a site-specific basis due to the variable, and often relatively small, number of participants within each site re-contacted for result return. We therefore had to restrict our analysis to the combined dataset, possibly overlooking relevant site-specific findings. Problems with data completeness also meant that a significant fraction of those contacted for ROR, including ON C-CFR participants, were not included in our analysis. Further, the limited racial/ethnic diversity in the study sample means that the observed association with race/ethnicity should be regarded with caution and that generalization of the results from this study to other research settings may be unwarranted. We also had a significant number of participants with unknown marital status (mostly from the MA Site). We decided to include these participants in the analysis in order to keep the rest of their information in the dataset. However, the incorporation of a variable with significant amounts of missing data makes the interpretation of the association of marital status with the likelihood of acceptance of research results difficult. Finally, the inclusion of relatives in the logistic regression model is another relevant study limitation. This problem was addressed by creating a variable that described whether a participant had at least one member of the family with a prior clinical genetic testing finding. This variable

allowed us to investigate the potential influence of family members' previous pursuit of genetic testing on the likelihood of a registry participant to accept or decline their research result.

Conclusion

Our study identified differences in the proportion and characteristics of participants accepting LS-related research results at four C-CFR sites. An analysis of the registry participants who accepted or declined ROR suggests that participant age, marital status, and race/ethnicity were associated with the likelihood of accepting a genetic research result. These findings provide an assessment of the role of participant characteristics in the acceptance of genetic research results offered by an international cancer registry. There is a need to conduct additional research to determine if the site-specific ROR protocols had an impact on participant acceptance of research results within each registry site.

CHAPTER 4: Clinical Confirmation of Non-CLIA Genetic Research Results Returned to Participants in a Population-Based Colon Cancer Registry

Abstract

Purpose: Few data exist regarding the extent to which participants clinically confirm results of non-CLIA genetic tests received in a research context. To address this gap, we examined whether and why participants in one research study, the population-based Seattle Colon Cancer Family Registry (C-CFR), adhered to the recommendation to verify their genetic non-CLIA research results in a CLIA-compliant laboratory.

Study population: In February 2011, the Seattle C-CFR began re-contacting registry participants (cases and their enrolled relatives) in families identified as having Lynch Syndrome (LS) from C-CFR research-related genetic testing. A total of 119 registry participants who had tested either positive or negative for a familial mismatch repair (MMR) gene pathogenic variant for LS were approached for individual result return.

Methods: We invited participants who accepted their non-CLIA genetic research results to participate in a two-month and 12-month post-test disclosure surveys. These surveys included questions about clinical validation of non-CLIA genetic results and whether results had been shared with family members or health care providers. A subset of participants who accepted or declined non-CLIA genetic research results were also interviewed to obtain information about their decision-making with regard to result acceptance and clinical validation.

Results: Twenty-six of 34 participants (76.5%) who accepted non-CLIA genetic research results completed the 12-month post disclosure survey. Of these, 4 (15.4%) reported having

clinically verified their results, 22 (84.6%) reported having shared the results with family members, and 15 (57.7%) with their health care provider. Among 11 participants interviewed, the reasons for pursuing clinical validation included acting on the recommendation of the research team and informing future clinical care. Those who did not clinically verify their non-CLIA genetic research results cited lack of insurance coverage and limited perceived personal benefits of clinical validation.

Conclusion: While the majority of participants in this study shared their non-CLIA genetic research results with their family members and health care providers, relatively few clinically verified their results in a CLIA-compliant laboratory. Participants who did not clinically confirm their results often had a prior diagnosis of colon cancer or were aware of other family members with clinically verified findings. Additional research will be needed to assess whether similar rates of compliance with the recommended CLIA confirmation are observed in other genetic research settings.

Introduction

The Clinical Laboratory Improvement Amendments of 1988 (CLIA) require that laboratories meet quality standards to ensure patients receive accurate, reliable, and timely results [112]. Notwithstanding an emerging ethical consensus that it is desirable to return clinically actionable results from genetic research to participants [18, 19, 36], controversy continues over whether results obtained from genetic research need to be confirmed in a CLIA-compliant laboratory prior to return [18, 20, 38, 113]. While some have argued that non-CLIA-validated results should not be returned [35], a CLIA research exception does exist, allowing the results of tests performed in non-CLIA-compliant laboratories to be returned

with the caveat that such results must be clinically verified before taking any clinical action [43, 44]. However, to date, no study has examined the extent to which participants, after receiving non-CLIA genetic research results, pursue verification in a CLIA-compliant laboratory. If the primary ethical rationale for result return is clinical benefit, it is important to consider whether participants pursue these recommendations.

The Seattle Colon Cancer Family Registry (C-CFR) is one of six sites in an international research cancer registry which has pursued research-related genetic testing using biospecimens donated by registry participants [2]. To date, 5 of the 6 C-CFR sites have returned genetic research findings related to cancer predisposition. After local Institution Review Board (IRB) approval, the Seattle C-CFR began returning results to their respective participants in February 2011. Participants selected for returning individual results belonged to families identified as segregating a Lynch Syndrome (LS) related pathogenic variant in one of the mismatch repair (MMR) genes (i.e., *MLH1*, *MSH2*, *MSH6*, and *PMS2*) [60, 81, 114]. Briefly, LS is a hereditary colon cancer syndrome, also known as hereditary non-polyposis colon cancer (HNPCC), that increases an affected individual's risk for cancers of the colon, rectum, stomach, hepatobiliary tract, endometrium, and ovaries [11, 83, 85, 115]. The Seattle C-CFR's decision to offer these findings to registry participants was based on the high predictive value of the identified MMR gene pathogenic variants and the known clinical utility of LS genetic testing.

During the return of results (ROR) implementation, Seattle C-CFR participants to whom results were offered were told that any genetic finding they might receive was a preliminary result to be used for information purposes only because the result had been generated in a non-CLIA research laboratory. Participants who chose to receive individual results provided

informed consent of this understanding, as well as the importance of clinically verifying the result received.

The objective of this sequential mixed-method study was to identify, using post-test disclosure surveys and semi-structured qualitative interviews, why participants elected to receive genetic research results and what participants did with the findings they received. In particular, we were able to determine whether participants acted on the recommendation to verify their non-CLIA genetic research results in a CLIA-compliant laboratory.

Methods

This study was approved by the C-CFR consortium (C-CFR Project # C-EX-0806-05), and IRB approval was obtained from the University of Washington (IRB # 45998). We chose a sequential mixed-method design, with a longitudinal 2-month and 12-month post-test disclosure survey followed by a semi-structured qualitative interview, in order to enhance the interpretation of our results [116, 117]. Post-test disclosure surveys included questions about verification of non-CLIA genetic research results in a CLIA-compliant laboratory and family and health care provider communication. Interview questions focused on how and why participants made the decision to receive research results and how they chose (or did not choose) to act on the information received.

Seattle C-CFR Participant Recruitment

The informed consent signed by Seattle C-CFR participants stated, “Test results will not be available on an individual basis since the tests are for research purposes only. That is, they have no verified clinical relevance at this time” [34] (Supplemental Table S1). Therefore,

Seattle C-CFR investigators obtained a second IRB approval from the Fred Hutchinson Cancer Research Center (FHCRC) prior to re-contacting participants for ROR. After this approval, cases (i.e., participants affected with CRC and typically the first person to join the registry) for whom genetic testing had revealed a LS-related pathogenic variant in one of the *MLH1*, *MSH2*, *MSH6*, or *PMS2* genes, and their enrolled family members who had been tested for the same pathogenic variant (with both positive and negative results), were approached for result return. Three additional criteria were used to identify eligible participants: (a) DNA fingerprinting results were available to confirm relationships of family members; (b) living registry participants (case or relatives) had previously consented to receive periodic contact with Seattle C-CFR regarding their participation; and (c) the MMR pathogenic gene variant had been identified twice (i.e., either the case had been tested two times or the same mutation was found in both a case and a family member).

Genetic Counseling and Recommendation for CLIA Confirmation

Participants interested in receiving LS-related results were invited to attend two individual genetic counseling appointments (Figure 4). The first session was designed to discuss issues associated with learning genetic testing results from the Seattle C-CFR. Results were not offered at the first session; instead, participants were asked to attend a second genetic counseling session at which results were returned. However, over the course of implementation, Seattle C-CFR investigators received feedback from participants that it would have been appropriate to convey results at the end of the first session. Therefore, an IRB amendment was submitted to accommodate this protocol change. Accordingly, 67.6% (23 of 34) of the participants received their results during the second genetic counseling

session, and later, 32.4% (11 of 34) received their results at the end of their first genetic counseling session.

The first genetic counseling session covered six major topics: (a) previous genetic counseling and testing history; (b) an overview of the C-CFR and the MMR pathogenic variant project; (c) a discussion on the pros and cons of knowing a genetic test result; (d) an explanation of the difference between findings generated in a research or CLIA-compliant laboratory underscoring the need to confirm any result received in a clinical laboratory; (e) an explanation of the importance of sharing results with at-risk relatives (who may not be in the registry) as well as with health care providers; and, (f) participant confidentiality.

The Seattle C-CFR participants were told they could take as much time as they needed to decide whether to receive their results. The informed consent form to receive research results (which was provided during the genetic counseling session when the participant received his or her result) contained the following statement:

I certify that I have met with a genetic counselor and have received information about the possible results of testing, the implications of receiving these results, and the accuracy and sensitivity of specific tests. I have also been encouraged to repeat these findings in a certified clinical laboratory as the available results were obtained in a research laboratory. I have had the opportunity to ask questions and have them answered to my satisfaction, and that I understand the benefits and the risks of receiving my test results.

For those participants who received non-CLIA genetic research results, the genetic counselor sent a follow-up summary letter as well as a letter to the participant's health care provider, in care of the participant, who was responsible for sharing the letter with his or her provider. In the participant's letter, the recommendation to verify research results clinically was further emphasized with this statement:

Your testing was performed in a research setting. This specific gene mutation should be verified in a clinical laboratory using a fresh blood specimen. As we had discussed, [you plan to pursue confirmation testing through [CENTER NAME] or your [PROVIDER]

In addition, the participant provider's letter stated,

These results were generated in a research laboratory, not a certified clinical laboratory. Your patient has been counseled that this result should be verified in a clinical laboratory using a fresh blood specimen. Retesting to verify our research result is a vital step to take as important medical decisions may depend on the reliability of this result. As a research project, we are not able to provide clinically certified testing to confirm this result. Confirmation testing can be obtained through a cancer genetics clinic, such as [CLINIC NAME(S)].

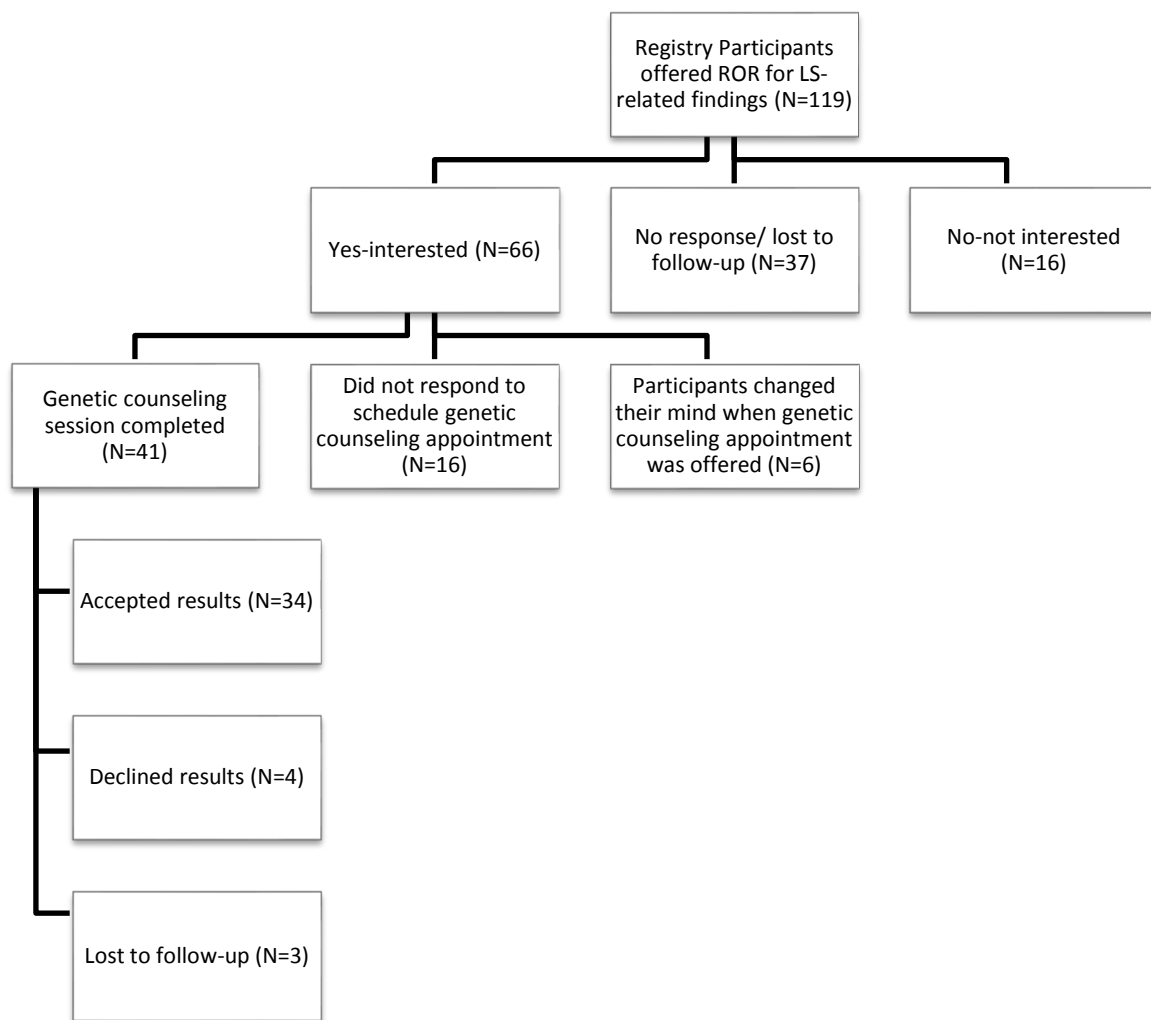
Upon request, the genetic counselor provided each participant with contact information for clinical genetic counseling services located near his or her residence.

Participant Surveys

Figure 5 illustrates the Seattle C-CFR ROR implementation process, showing the number of participants who were approached, the number who elected to receive research findings, and the number who declined or were otherwise lost to follow-up. Participants who expressed interest in receiving research results were asked to participate in a baseline survey (Appendix C) prior to their first genetic counseling session. Participants who received individual research results were asked to complete two follow-up surveys: a 2-month survey (Appendix D) and a 12-month survey (Appendix E). The decision to participate in these surveys did not affect the opportunity to receive results. Participants who did not want to receive results indicated their choice by returning the response card, calling to let us know, or telling us of their lack of interest on a follow-up call. These participants were designated “decliners” and were asked to complete a short decliner survey (Appendix F). The decliner survey consisted of four questions to collect the reasons for declining ROR. Decliners were asked about

previous genetic counseling and testing and perceived personal and family benefit of potential results. Some decliner surveys were completed immediately after the initial invitation was declined while others were completed only after the first genetic counseling session. The decliner, baseline, 2-month post-test result disclosure, and 12-month post-test result disclosure surveys were all conducted over the phone by a C-CFR study interviewer between April 2011 and April 2014.

Figure 4: Seattle C-CFR Return of Results Outcome (February 2011-April 2013)



Participant Interviews

In order to explore in greater detail how research participants chose to act on information received, especially the recommendation to clinically verify the non-CLIA genetic research results, participants who accepted results were invited to participate in a semi-structured qualitative interview (Appendix G). Participant interview recruitment began in April 2014 and was completed in October 2014.

Participants were approached for interview shortly after the conclusion of their 12-month post-test disclosure survey. Of the 21 invitations mailed to those who had chosen to receive research results, 11 participants responded and completed interviews, for a final response rate of 52%. We also planned to interview 10 participants who declined research results.

However, of 14 decliners approached, only two (14%) accepted our invitation, and four (28.6%) indicated that they were not interested. The remaining eight of 14 (57.1%) did not respond to the invitation letter or to two follow-up phone calls. To increase the number of potential participants for interviews in the “decliner” category, we sent an additional 15 invitation letters to participants considered to be passive decliners, i.e., those who had indicated interest in result return but who did not schedule a genetic counseling session. Of those 15, three (20%) indicated their willingness to participate. However, all three people missed their scheduled interview times and did not respond to requests to reschedule. Five of the 15 (33.3%) indicated they were not interested in participating and the remaining were non-responders (46.7%, 7 of 15). Accordingly, the final response for the “decliner” interviews was 6.9% (2 of 29).

After informed consent, all the interviews were conducted by telephone and audio-recorded by the C-CFR study interviewer. The average length of interview time was 19 minutes for those who accepted and 13 minutes for those who declined. The semi-structured interview guide (Appendix G) focused on how and why participants made the decision to receive research results (e.g., what they learned or thought they might learn as a result of receiving research results) and how they had chosen (or not chosen) to act on the information received (i.e., pursuing verification of results in a CLIA-compliant laboratory). Questions included:

1. How long ago were you contacted to learn of research results from your participation in the registry?
2. What was your experience when you were initially contacted?
3. Can you please describe how you came to decide that you wanted to know (or not know) your genetic research results?
4. If relevant: As recommended when you spoke with the genetic counselor, did you have your research results confirmed in a clinical laboratory?
 - a. If yes, what was the process like? If no, why did you decide not to pursue confirmation?

Data Analysis

Quantitative Analyses

Post-test disclosure survey responses were captured on paper or entered directly into the secure Seattle C-CFR Call Track database. These data were cross-checked to ensure accuracy. Survey data were de-identified, downloaded, and transformed for analysis with STATA14 statistical software [95]. Participant demographic information, including age, sex, education, marital status, education level, and self-described race/ethnicity was obtained. Descriptive statistics (e.g., participant characteristics, survey completion status, participant interview status, and reports of CLIA validation) were calculated, including frequencies,

means, and standard deviations. Proportions were compared using the Pearson χ^2 test statistic or Fisher's exact test when appropriate.

Qualitative Analyses

The Seattle C-CFR participant interviews were audio-recorded and transcribed verbatim. Transcripts were checked for accuracy and uploaded to Atlas.ti [68], a computer-assisted qualitative software package, for directed content thematic analysis [69]. Two research team members (ML and AT) independently coded the transcripts by constant comparison of the generated codes [70]. The directed content analysis provided a systematic approach to identifying the ROR experiences of the Seattle C-CFR participants. A preliminary code list was created based on the topics discussed during the interview and additional codes were added based on the themes shared by the participants.

Results

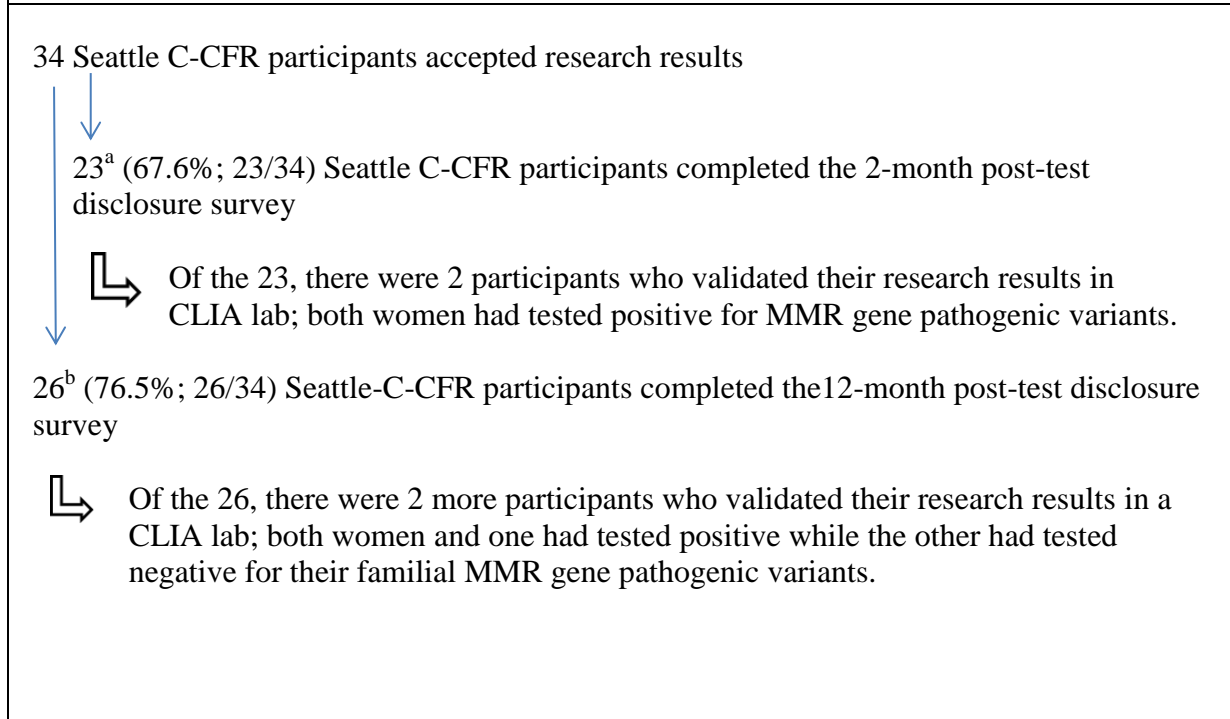
Of the 34 Seattle C-CFR participants who accepted genetic research results, six (17.7%) were cases and 28 relatives (82.4%) (Table 7). Nineteen participants (55.9%, 19 of 34) tested positive for the familial MMR gene pathogenic variant and 15 participants (44.1%, 15 of 34) tested negative. Twenty-three (73.5%) of these 34 participants completed the 2-month post-test disclosure survey, and 26 (76.5%) completed the 12-month post-test disclosure survey (Figure 5). One participant completed the 2-month survey but not the 12-month survey; four participants completed the 12-month but not the 2-month survey. Of the 34 participants, seven (20.6%) did not complete either the 2-month or 12-month surveys (Table 8 for participant characteristics).

Table 7: Seattle C-CFR Participants Who Accepted Research Results (Feb 2011-April 2013)

	Sex	MMR Gene Research Result	Survey Completed		CLIA verified	Interviewed		Sex	MMR Gene Research Result	Survey Completed		CLIA verified	Interviewed
			2-month	12-month						2-month	12-month		
Family 1							Family 9						
Affected Relative	M	Neg	Yes	Yes	No	No	Unaffected Relative	F	Neg	-	-	-	No
Unaffected Relative	F	Pos	Yes	Yes	No	No	Unaffected Relative	F	Neg	Yes	Yes	No	No
Unaffected Relative	F	Pos	Yes	Yes	No	Yes ^a	Family 10						
Unaffected Relative	M	Pos	-	-	-	No	Case	F	Pos	Yes	-	-	Yes ^e
Unaffected Relative	F	Neg	Yes	Yes	No	No	Family 11						
Family 2							Unaffected Relative	F	Pos	-	Yes	No	No
Unaffected Relative	M	Neg	-	-	-	No	Family 12						
Family 3							Case	M	Pos	Yes	Yes	No	Yes ^d
Affected Relative	F	Pos	Yes	Yes	No	No	Unaffected Relative	F	Pos	Yes	Yes	Yes	Yes ^b
Unaffected Relative	M	Neg	Yes	Yes	No	No	Unaffected Relative	M	Neg	-	Yes	No	No
Unaffected Relative	F	Neg	Yes	Yes	No	No	Unaffected Relative	M	Neg	Yes	Yes	No	No
Family 4							Unaffected Relative	F	Pos	-	-	-	No
Case	F	Pos	Yes	Yes	Yes	Yes ^b	Family 13						
Unaffected Relative	M	Neg	Yes	Yes	No ^c	No	Case	M	Pos	-	Yes	No	No
Unaffected Relative	M	Neg	-	-	-	No	Unaffected Relative	M	Pos	Yes	Yes	No	No
Family 5							Family 14						
Unaffected Relative	F	Neg	Yes	Yes	No	No	Unaffected Relative	M	Pos	Yes	Yes	No	No
Family 6							Family 15						
Unaffected Relative	M	Neg	Yes	Yes	No	No	Affected Relative	F	Pos	-	-	-	Yes ^f
Family 7							Unaffected Relative	F	Neg	Yes	Yes	No	No
Case	F	Pos	Yes	Yes	No	Yes ^d	Family 16						
Unaffected Relative	F	Pos	Yes	Yes	Yes	Yes ^b	Affected Relative	M	Pos	Yes	Yes	No	No
Unaffected Relative	F	Neg	-	Yes	Yes	-	Family 17						
Family 8							Unaffected Relative	F	Neg	-	-	-	No
Unaffected Relative	F	Neg	Yes	Yes	No	Yes ^e							

Case = affected with CRC and first family member recruited; Affected Relative = enrolled family member diagnosed with CRC or other cancers; Unaffected Relative = enrolled family member with no known cancer hx; ^a participant shared that she wants to verify results but does not have any insurance at the moment; ^b participant shared that she confirmed results for clinical decision-making regarding recommended cancer surveillance and/or surgery; ^c participant had his blood drawn for clinical verification but was later cancelled due to insurance test cost non-coverage; ^d participant shared that clinical verification research result was not necessary since she already had cancer and a family member clinically verified their results; ^e participant did not remember if she had her research results clinically verified; ^f participant accepted research results and shared during the interview that that she already had clinical genetic testing

Figure 5: Seattle C-CFR Participants Who Completed Post-Test Disclosure Surveys



^a 1 participant completed the 2-month but not the 12-month post-test disclosure survey

^b 4 participants completed the 12-month but not the 2-month post-test disclosure survey

Table 8: Seattle C-CFR Participant Characteristics of those who Completed the Post-Test Disclosure Survey, Decliner Survey, Participated in the Interview, and those Who did not Complete any Survey

	Completed 2-month*	Completed 12-month**	Participated in the Qualitative Interview	Decliner Survey	No survey
	[N (%)]	[N (%)]	[N (%)]	[N (%)]	[N (%)]
Age, years	[48.8 ± 14.5;20-73]	[48 ± 13.6; 20-73]	[47.9 ± 10.9; 36 - 72]	[54.4 ± 16.7; 23 – 77]	[54.4 ±15.8;34-74]
Sex					
Male	9 (39.1)	11(42.3)	1 (9.1)	4 (22.2)	3 (42.9)
Female	14 (60.9)	15 (57.7)	10 (90.9)	14 (77.8)	4 (57.1)
Had Children					
No	8 (34.8)	8 (30.8)	4 (36.4)	8 (44.4)	2 (28.6)
Yes	15 (65.2)	18 (69.2)	7 (63.6)	10 (55.6)	5 (71.4)
Personal history of cancer					
Colon	6 (26.1)	6 (23.1)	4 (36.4)	7 (38.9)	0
Other Cancers ^a	2 (8.7)	2 (7.7)	3 (27.3)	3 (16.7)	2 (28.6)
None	15 (65.2)	18 (69.2)	4 (36.4)	10 (55.6)	5 (71.4)
# of family members with cancer					
≤ 1	5 (21.7)	5 (19.3)	1 (9.1)	3 (16.7)	2 (28.6)
2-3	18 (78.3)	21 (80.8)	10 (90.9)	15 (83.3)	5 (71.4)
Education Level					
less than college	6 (26.1)	8 (30.8)	3 (27.3)	6 (33.3)	2 (28.6)
Some college	10 (43.5)	10 (38.5)	3 (27.3)	6 (33.3)	1 (14.3)
College graduate	7 (30.4)	8 (30.8)	5 (45.5)	5 (27.8)	3 (42.9)
Unknown	0	0	0	1 (9.1)	1 (14.3)
Race/ethnicity					
Caucasian	15 (65.2)	17 (26.9)	10 (90.9)	17 (94.4)	5 (71.4)
Other	2 (8.7)	2 (7.7)	1 (9.1)	0	2 (28.6)
Unknown	6 (26.1)	7 (26.9)	0	1 (9.1)	0
Participant ^b					
Case	4 (17.4)	4 (15.4)	4 (36.4)	6 (33.3)	0
Affected Relative	2 (8.7)	3 (11.5)	3 (27.3)	5 (27.8)	2 (28.6)
Unaffected Relative	16 (69.6)	19 (73.1)	4 (36.4)	7 (38.9)	5 (71.6)
MMR Gene Status ^c					
Positive for pathogenic variant	13 (56.5)	14 (53.8)	10 (90.9)	13 (72.2)	3 (42.9)
Negative for pathogenic variant	10 (43.5)	12 (46.2)	1 (9.1)	5 (27.8)	4 (57.1)

* 1 participant completed the 2-month but not the 12-month post-test disclosure survey; ** 4 participants completed the 12-month but not the 2-month post-test disclosure survey; ^aparticipants diagnosed with biliary/renal, ovarian, stomach, pancreas, bile duct, or small bowel cancers; ^bCase = participant with colon cancer and first enrollee of the family; Relative = enrolled family member; ^cMMR gene = MLH1, MSH2, MSH6 or PMS2

CLIA Confirmation of Non-CLIA Genetic Research Results

At 2-months post-test disclosure, two of the 23 (8.7%) participants surveyed (both of whom tested positive for a pathogenic variant) reported having clinically verified their non-CLIA genetic research results. At 12-months post-test disclosure, two additional participants reported verification of their non-CLIA genetic research results in a CLIA-compliant laboratory. Therefore, four of the 26 (15.4%) participants surveyed (three testing positive and the other negative) reported having clinically verified their results. All those who reported clinical verification of their non-CLIA genetic research results were women, and two of the four who confirmed their results belonged to the same family. Respondents reported that the research and clinical results were in each case concordant (Table 7).

Seven of the 34 participants who accepted non-CLIA genetic research results (20.6%) did not complete either a 2-month or a 12-month post-test disclosure survey. Of these, there were four females and three males and all but one were unaffected (no prior cancer diagnosis) relatives. Three of these participants tested positive while four participants tested negative for the MMR gene pathogenic variant in their family. We had the opportunity to interview one of the participants who had tested positive and she shared that she accepted her research results in order to verify her clinical genetic test result.

Twenty-two of the 26 participants who completed the 12-month post-test disclosure survey reported that they had not clinically verified their non-CLIA genetic research results in a CLIA-complaint laboratory. Of these 22, ten tested positive for the non-CLIA genetic research result of the pathogenic variant in their families (45.5%) and 12 (54.5%) tested negative. Five of the 22 (22.7%) participants, who indicated on the 12-month survey that

they did not obtain CLIA confirmation, belonged to families in which another family member had clinically verified their non-CLIA genetic research result.

For those participants who did not clinically verify their non-CLIA genetic research results at 2-months (Table 9), one participant shared that s/he had not found time to schedule an appointment with a health care provider, another participant explained that s/he did not have insurance coverage, while another participant shared s/he did not want the insurance company to know the genetic result. In addition, seven of the ten participants reported feeling that they did not need to validate their non-CLIA genetic research results. For those who did not clinically verify their research results at 12-months (Table 9), two participants shared that they did not have insurance coverage and two other participants shared they had not found a time to schedule with their health care providers. In addition, two participants (both of whom tested negative for their familial variant) reported that they had wanted to pursue clinical testing but their insurance company did not cover the test cost. Finally, eight of the 14 participants felt they did not need to clinically verify their results.

Table 9: Reasons Shared for Not Verifying Non-CLIA Genetic Research Results in a CLIA-compliant Laboratory

Reasons	2-month Post-Disclosure Survey* N (%)	12-month Post-Disclosure Survey** N (%)
I have not found a time to schedule an appointment with my health care provider.	1 (10.0)	2 (14.3)
I don't have insurance	1 (10.0)	2 (14.3)
My insurance will not pay for confirmation test	-	2 (14.3)
I don't want my insurance company to know	1 (10.0)	-
I believe the results you gave me	-	-
I don't feel the need to repeat my test results	7 (70.0)	8 (57.1)
Total	10	14

CLIA Confirmation Decision-Making: Findings from Interviews

Eleven Seattle C-CFR participants who accepted non-CLIA genetic research results completed qualitative interviews (Table 8 for participant characteristics). Of the 11, two had received research results without initially being approached as part of the ROR protocol (i.e., they independently called the SE C-CFR to request their research result). Of those interviewed, ten (90.9%) participants tested positive for a MMR gene pathogenic variant.

Reasons Participants Chose to Clinically Confirm Non-CLIA Research Results

We interviewed three participants (all women) who reported clinical validation of their LS positive non-CLIA genetic research results. Each participated in the 2-month and/or 12-month post-test disclosure survey. These participants gave two major reasons for choosing to clinically verify their results: (1) acting on the recommendation of the research team and (2) informing future clinical care.

Acting on the recommendation of the research team

These participants scheduled their consultations at genetic services as recommended by the Seattle C-CFR genetic counselor and reported that clinical confirmation was arranged by a medical geneticist, a clinical genetic counselor, or by their health care provider (e.g., gastroenterologist, gynecologist).

She [the genetic counselor] said that we need to test you just to confirm that you, in fact, carry the gene. So right there, they sent me to the lab and had blood work done, and I just confirmed that I carry the gene. (P6, participant with Lynch syndrome)

These participants chose to act on the recommendation of the clinical team, and they were subsequently told that the clinical and research results were concordant.

Informing future clinical care

Another important reported rationale for confirming research results was the recognition of the clinical utility of findings, which could help health care providers make recommendations about appropriate cancer screening surveillance and prophylactic surgery. For example, one of the participants who tested positive for a LS-associated pathogenic variant had already had her uterus removed for cancer prevention, but still considered the information useful for other surgical decision-making.

I don't have my uterus already because I had a hysterectomy prior to knowing this, but I still have my ovaries, so they also recommended that I [clinically confirm] to remove the ovaries and fallopian tube. (P8, participant with Lynch syndrome)

All the interviewed participants reported pursuing the recommended cancer surveillance in light of their genetic test findings.

Reasons Participants Chose Not to Clinically Confirm Non-CLIA Research Results

Four participants (1 male and 3 female) reported they had not had their non-CLIA genetic research findings validated in a CLIA-compliant lab by the time of the interview. These respondents gave two major reasons for not confirming their research findings as recommended: (1) lack of insurance coverage or concerns about insurance; and (2) perceived limited personal and/or clinical utility.

Lack of insurance coverage or concerns about insurance

Two participants shared that lack of insurance or limited finances prevented them from pursuing the recommendation. However, both indicated they understood the importance of clinical confirmation and said that they planned to follow up with their health care provider soon.

I can't. I checked with a doctor but if it's going to cost me, then no but otherwise I'll just go with what I know and so next time I'll go to the doctor I'll check to see what she thinks and take it from there. [P9, participant with Lynch syndrome]

Perceived limited personal and/or clinical utility

Two participants reported feeling that they did not need to confirm their non-CLIA genetic research results because they already had colon cancer. These participants knew of enrolled family members who had elected to receive their results and who had subsequently clinically confirmed those findings.

Because I didn't see any reason to ... I already had cancer figured out. I got the syndrome, what's the big deal? (P4, participant with Lynch syndrome)

I didn't. No, my sister did. I experienced having colon cancer at a young age. I just felt that the study was adequate enough. [P3, participant with Lynch syndrome]

The rest of the participants interviewed (36.4%, 4 of 11) either did not recall if they had their non-CLIA genetic research results clinically verified or they had already pursued clinical genetic testing prior to receiving research results.

Family and Health Care Provider Communication: Interview Findings

Table 10 illustrates the number of survey participants who shared their research results with their family members and their health care providers. In addition, we asked the 11 participants who received results from the Seattle C-CFR about their experiences when communicating their research findings to their family members and health care providers. From analysis of the transcripts, three major themes emerged: (1) this is a family affair, (2) informing the health care provider, and (3) knowledge is power.

This is a family affair

All of the interviewed participants reported being aware of family members enrolled in the registry. They were all aware that Seattle C-CFR recruitment was initiated because they were (or had a family member) diagnosed with colon cancer.

Yes, my sister ... had colon cancer. I believed when she was over in Seattle after she had the surgery, I think the Fred Hutchinson had contacted her and asked if they could do a study with her and her family in which case then she referred to me and my sisters and brother and so that's basically how we kind of got hooked up.
[P7, participant with Lynch syndrome]

Overall, the participants shared they were glad their family members were part of the registry. They also said they knew that family members were being contacted for the ROR opportunity. Although the majority of the interviewed participants indicated it was easy to share the information with their family members, two participants noted their difficulty with informing some of their family members (one had a terminally ill brother who had cancer, and the other had a teenage daughter who was not yet ready to hear the results). Otherwise, other participants shared their ease in communicating the results with their parents, siblings,

spouses, and friends. Further, their intent to share results with family members was unrelated to whether they had chosen to clinically verify their result. This observation was in concordance with the majority of survey respondents (84.6%, 22 of 26) who reported sharing their results with their family members on the 12-month post-test disclosure survey.

Informing the health care provider

Except for one participant who had yet to see a health care provider, the majority (90.1%, 10 of 11) of those interviewed reported sharing their research findings with their providers.

Two (18.2%, 2 of 11) participants mentioned that they gave the Seattle C-CFR letter to their physicians as documentation. The participants' motivation to inform their health care provider was to ensure that they received the recommended cancer screening for individuals with LS. As one participant shared,

Well, number one is that most doctors still recommend that you get a colonoscopy like every ten years or something like that and I think I wanted to make sure that the doctors knew that I needed to have a colonoscopy every two to three years. That was probably one of the most important reasons to share it with them. And I think it's important they know what my medical history is and what's going on?
[P4, participant with Lynch Syndrome]

With some concern, one participant shared that her doctor appeared to show a lack of awareness regarding LS and to be unaware of screening recommendations. She explained,

I gave her a copy of my letter [and] that she looked kind of clueless, frankly, to what it meant. So I gave her a copy of the letter that I got the results, and I don't remember if I gave her much anything else and she... she's interested enough to take a look at it ... That I—that was last year, and I haven't been back to her yet, so I don't know.
[P9, participant with Lynch Syndrome]

Overall, participants reported having shared their research results with at least one provider, primarily their general physician, who then sent referrals to multidisciplinary cancer care

clinics for the participant's yearly cancer screenings and surveillance. Similarly, 15 of 26 (57.7%) survey respondents who completed the question reported sharing their results with their health care providers.

Knowledge is power

All the participants shared that they were glad to know their results so they could make proactive choices to prevent cancer in themselves. As one participant clearly advocated,

Yeah, I just think it's so important. I was lucky enough 14 years ago to find out about my colon cancer, and it was just by fluke. I have no symptoms. So I think that it's really important to just stay on top of your health because I think there're a lot of kinds of cancer that are silent and that the only way we're going to know is through research and what we can... do the exercise and eat properly to fight it because I don't think it's all medical. [P6, participant with Lynch syndrome]

Interviewed participants also indicated that they felt a responsibility to warn other family members who may be at risk to have LS. They all understood the importance of pursuing early and more frequent cancer screening, and that screening could save lives.

I think my dad's brother got his letter about his genetic testing. He did not want to know the results and I had a conversation with him which I told him I thought that was selfish because he may not want to know because he doesn't want to worry about it, but it may save the lives of his children and/or grandchildren and that he should maybe rethink that. [P10, participant with Lynch syndrome]

Some participants expressed gratitude that family members who were not part of the Seattle C-CFR pursued clinical testing after research results were offered to the family.

Well, it was a relief. It was just like a load lifted off me. Because [my son] being Downs syndrome, I knew it might be a little bit more challenging. If he carried that gene, he needs to have a colonoscopy and kind of go through some of that process. So, I was just very glad to know, to find out that he didn't carry that gene. [P5, participant with Lynch syndrome]

In addition, all the interviewed participants shared that it was not a difficult decision to choose to accept the research results. Although some did not expect to receive such results, it was considered a “bonus” for being a research participant, and participants reported being grateful to have received the information.

So when we first did the study there was no expectation that we were having this genetic [testing] and the results of that or any benefits to ourselves. I was just participating on the study to help the study in any way that I could. And then I think it was, maybe two years ago, or it may have been a year ago when we agreed, both my brother and myself, we were offered the results, and we are happy to have the opportunity to do all of that. [P10, participant with Lynch syndrome]
 If it hadn’t been for the Fred Hutchinson Cancer Research, I never would have known. [P6, participant with Lynch syndrome]

Table 10: *Family and Health Provider Communication of Lynch Syndrome Genetic Research Results*

	2-month Post-Disclosure Survey*	12-month Post-Disclosure Survey**
	N (%)	N (%)
Participants who shared with their family members	19 (82.6)	22 (84.6)
Participants who shared with their health care provider	10 (43.5)	15 (57.7)
Total surveys completed	23	26

Decliner Survey and Interview

Eighteen decliner surveys were completed (15.1%, 18 of 119) (Table 8 for participant characteristics). From these responses, we found that 12 of 18 (67%) had previously undergone genetic counseling and testing in a clinical setting. This result was supported by the interviews with two decliners (1 male and 1 female), who both shared that they had declined the offered research results due to previous pursuit of clinical testing. Both had tested negative for their familial pathogenic variant for LS.

Of the six decliners who did not report prior genetic counseling, two (33.0%) declined because they were already affected by cancer, and one (17%) declined because s/he already knew his/her risk of cancer was low. Unfortunately, we do not know why this participant believed that his/her cancer risk is low. The rest (3 of 6, 50%) reported that genetic counseling was not relevant to them. Four participants (66.7%, 4 of 6) indicated that they lacked personal time to pursue genetic counseling. We were not able to interview any registry participants who actively declined research results without the prior pursuit of clinical genetic testing.

Discussion

In this study, we found that 15.4% (4 participants in 3 families of 26 participants in 17 families who had non-CLIA genetic research results returned) of the Seattle C-CFR participants who received LS-related non-CLIA genetic research results and completed a post-disclosure survey had verified their non-CLIA genetic research result in a CLIA-compliant laboratory within 12 months of receiving their results. For those who participated in follow-up qualitative interviews, participants who clinically confirmed their non-CLIA genetic research results explained that acting on the recommendation of the research team and informing future clinical care were the main reasons they pursued verification of their research results in a CLIA-compliant laboratory. Participants who did not clinically confirm non-CLIA genetic research results explained that lack of insurance coverage and the limited perceived personal and/or clinical benefits had prevented them from pursuing clinical confirmation. To our knowledge, this is the first study to examine the extent to which participants pursue non-CLIA genetic research result verification in CLIA-compliant laboratories.

The Clinical Laboratory Improvement Amendments of 1988 (CLIA) research exception explicitly states that results of tests performed in non-CLIA-compliant laboratories should be used for informational purposes only [43, 44], and with the expectation that participants will subsequently clinically verify their results. However, in this study some Seattle C-CFR participants reported feeling that they did not need to clinically confirm their research results given their personal history of cancer and/or because they knew of other enrolled family members who had received and clinically verified their research results. While health care providers should not alter clinical care on the sole basis of a non-CLIA research finding, it is possible that a non-confirmed result could be interpreted in the context of the participant's medical and family medical history of cancer, as well as in light of knowledge about family members' clinical results. In such cases, even unvalidated information could be valuable.

Controversy continues about whether non-CLIA genetic research results should be verified in a CLIA-compliant laboratory prior to return [18, 20, 38, 113]. Evans recently conducted a legal analysis pertaining to the return of research results from non-CLIA research laboratories to willing participants and argued that a researcher's First Amendment rights may be violated if he or she is prevented from communicating non-validated findings [43]. In addition, as was the case here, research conducted on older samples may not always be CLIA-compliant, such that the sharing of non-CLIA research results may be the only feasible way to return clinically important information to research participants. Moving forward, if confirmation of non-CLIA genetic research results in CLIA-compliant laboratories becomes the norm for ROR endeavors, researchers ought to receive additional resources from funding agencies to support the practice.

However, routine CLIA validation of non-CLIA genetic research findings may pose other concerns. Burke et al. recently emphasized that the ROR process “should be focused on clarity, appropriate caveats and, most important, appropriate referrals when the results may be helpful to consider in clinical care” in order to minimize the risk of therapeutic misconception [44]. In other words, when researchers return clinically actionable research findings, participants may mistakenly believe that the main purpose of their participation was to provide them with medical benefit rather than to advance knowledge [39, 40, 44]. For example, Miller et al. [41] showed that the disclosure of research results to participants in a cancer clinical trial made their research participation seem like clinical care. In the Seattle C-CFR ROR, care was taken to distinguish research from clinical care by providing participants and their health care provider with information on clinical services to facilitate verification of their research results in a CLIA-compliant laboratory. Participants also provided informed consent of their understanding that they were receiving non-CLIA genetic research results and information about the importance of clinical validation. However, some surveyed participants still shared that they did not intend to confirm their findings. In addition, with or without CLIA confirmation, most of the Seattle C-CFR participants reported willingly sharing their non-CLIA genetic research results with their family members and health care providers. While this outcome supports current public health endeavours to identify individuals with LS in order to prevent cancer or to detect it early in their at-risk relatives [8, 81, 89, 118], this issue will need further investigation if CLIA validation of non-CLIA genetic research results is a goal prior to returning to participants.

Study Limitations

The Seattle C-CFR returned LS-related non-CLIA genetic research results to a limited number of participants, some of whom were related, and the small number of participant survey responses limited our ability to draw statistically significant inferences. We addressed this shortcoming by conducting a sequential mixed-method investigation to enhance the interpretation of the data. For the qualitative portion of the study, we were unable to interview participants who had not previously pursued clinical genetic testing yet also declined research result return. In addition, our interview findings were likely influenced by recall bias since the participants were interviewed at least a year after they had received their research results. Finally, the responses we received were possibly influenced by underlying participant and/or family characteristics (e.g., belonging to families who willingly share genetic information). We tried to minimize this bias by offering the interview opportunity to all eligible participants re-contacted for ROR who met the inclusion criteria.

Conclusion

Despite relatively few Seattle C-CFR participants who had clinically verified their non-CLIA genetic results in a CLIA-compliant laboratory, and some faced challenges when pursuing clinical verification, the majority of participants shared their findings with family members and health care providers. Additional research is needed to determine if clinical verification of non-CLIA genetic research result is necessary prior to returning individual results to research participants.

CHAPTER 5: CONCLUSION

Overall Summary

The Colon Cancer Family Registry (C-CFR), an international research cancer registry consortium returned genetic research results to participants. The C-CFR includes sites at the University of Hawaii, Honolulu, HI (HI); the Mayo Clinic, Rochester, MN (MA); the Fred Hutchinson Cancer Research Center, Seattle, WA (SE); the University of Southern California, Consortium, Los Angeles, CA (USC); the Cancer Care Ontario, Canada (ON); and the University of Melbourne, Melbourne, Australia (AU). The similarities and differences between the six C-CFR site-specific return of results (ROR) protocols provided a unique opportunity to describe the ROR experience at each registry site and to document site-specific outcomes of result return. Qualitative and quantitative methods were utilized to investigate the complexity of ROR implementation across the registry and to determine which participant characteristics influenced the likelihood of acceptance at four C-CFR sites. Using data from the Seattle C-CFR, a sequential mixed-methods study design was used to investigate the impact of result return on registry participants. Overall, the results of this dissertation study should help guide the development and implementation of future national and international policies regarding the return of individual results from genetic research.

Three broad sets of factors that contributed to varying C-CFR site-specific ROR protocol development and implementation were identified using key-informant interviews with C-CFR staff. These factors included: 1) the clinical and/or research experience of the C-CFR staff; 2) the public and health care system infrastructure; and 3) existing regulations at local institutions and/or informed consent. Together, these factors help explain why the ON and

AU C-CFR sites were able to implement their ROR protocols in the late 1990's, nearly a decade before other C-CFR sites. The MA, HI, SE and USC C-CFR sites, in contrast, experienced multiple barriers in each of these domains and hence, were unable to implement their ROR protocols as quickly. Despite these challenges, key informants at all six C-CFR sites agreed on the importance of returning research results with clinical utility and they all made a concerted effort to enable result return once they were able to allocate funds and the ROR protocol was approved by their local institutions.

The outcomes of ROR implementation were explored in four C-CFR sites (AU, MA, HI and SE). We found that the overall proportion of participants choosing to accept research results was 63% (481/763). We found that participant age, marital status, and race/ethnicity were significantly associated with the likelihood of acceptance of individual genetic research results, while adjusting for the C-CFR site, participant sex, reproductive history, personal history of cancer, family history of cancer, status as a case or relative, and whether a family member had pursued clinical genetic testing. Site-specific ROR protocols may have had an impact on the identified differences in the proportion of participants accepting LS-related research results and the underlying participant characteristics.

We looked more closely at the impact of result return using a sequential mixed-methods investigation of Seattle C-CFR registry participants. While the majority of those surveyed reported that they had shared their research findings with their family members and health care providers, only four of 26 (15.4%) participants who completed the 12-month post-test disclosure survey reported having clinically verified their non-CLIA genetic research results. Some of the participants who did not validate their non-CLIA genetic research results shared that they did not plan to pursue the recommendation because of the perceived lack of

personal utility. Others who wanted to confirm their non-CLIA genetic research results reported not completing their clinical genetic testing because their insurance companies did not cover the test cost. Despite challenges faced by some SE C-CFR participants when pursuing clinical verification of their non-CLIA genetic research results, many participants expressed their gratitude for having had an opportunity to learn their genetic research results.

In sum, these results highlight the complexity encountered by an international cancer registry overcoming site-specific challenges to returning individual genetic research results to participants.

Revisiting the Return of Research Results Debate

In Chapter 1, we discussed the arguments for and against the return of individual results from genetic research with respect to the ethical principles of respect for autonomy, beneficence, nonmaleficence, and justice by using previously published articles. With valuable insights obtained from the results of this dissertation study, we revisit this debate in the context of the C-CFR's experience, across and within registry sites, on ROR protocol and implementation.

Respect for Autonomy

A central ethical consideration in arguments surrounding return of research results is respect for autonomy and the ways in which participants' preferences for the receipt of potentially actionable genetic information are elicited and honored. In this study, we had an opportunity to learn from the experience of Seattle C-CFR participants who made an autonomous decision to accept individual non-CLIA genetic research results offered by the registry. They shared during follow-up interviews that this was important information to know – not just for

their personal health benefit but for their family members as well. Of course, whereas direct registry participants were given the option to freely decide whether or not to know their research findings, respect for autonomy may have been challenged as participants took what they learned back to their family members. For example, one participant described a conversation with her uncle who had initially chosen not to receive his individual research result from the registry, and who eventually changed his mind in the face of her advocacy. She felt that for his children's sake, it was important for him know this information and to share his results with his immediate family. It is therefore possible that her uncle felt "coerced" to accept his individual research result from the study team. In this case (and possibly others about which we are unaware), the registry did not directly impose on his autonomy, but the decision to offer genetic research findings to registry participants may have indirectly affected his "right not to know" genetic information about himself.

In addition, we were also interested to learn from participants who had autonomously declined to receive their individual research results. Unfortunately, we were not able to interview any participants in this category, so we do not know the reasoning behind their decision to decline.

Beneficence

Another important ethical rationale for the return of individual research results to participants is the idea of beneficence, or returning information of clear clinical utility with immediate health relevance [21]. Accordingly, there is strong ethical consensus that any results offered be analytically valid, and a related regulatory expectation that medical decision-making be based on clinically validated (i.e., performed in a CLIA-compliant laboratory) information.

C-CFR investigators/genetic counselors, especially in the United States where CLIA policy applies, had therefore emphasized to their respective participants the importance of clinically confirming their non-CLIA genetic research results prior to changing their lifestyle behaviors and/or medical management (e.g., colonoscopy screenings, pursuing prophylactic removal of uterus, etc.). The extent to which participants at most C-CFR sites acted on this recommendation is unknown. At the Seattle C-CFR site, where all participants who received non-CLIA genetic research results gave verbal consent of their understanding of this recommendation, a significant proportion had chosen not to clinically validate their findings 12 months post-disclosure. This does not mean, however, that these participants did not benefit from the ROR. Instead, in certain cases, the perceived personal utility of confirmation was low, either because of the participant's age, personal history of cancer, and/or the knowledge that a family member had previously clinically confirmed the familial pathogenic variant. Interestingly, several of the participants contacted by the Seattle C-CFR reported using their genetic research result to informally confirm their results from prior clinical genetic test findings. Further, in most cases, participants reported communicating with family members about their non-CLIA genetic research results even in the absence of clinical validation, suggesting indirect benefits with respect to raising awareness among family members about a possible cancer predisposition. These findings suggest that the return of non-CLIA genetic research results may still satisfy ethical requirements for beneficence.

Nonmaleficence

While there was no evidence that the ROR protocols implemented across the C-CFR led to direct participant harms, the ethical obligation of nonmaleficence, or the “obligation not to

inflict harm on others”[21], may have been indirectly violated in terms of the effects of uneven and, at times, significantly delayed, implementation of ROR protocols across C-CFR sites. For example, interviews with C-CFR investigators and staff repeatedly referenced a perceived pressure to implement ROR protocols based on the experience of early-adopting registry sites. This required investigators to surmount numerous financial (e.g., hiring a genetic counselor) and oversight (e.g., IRB approval process) obstacles and, in some cases, led to an experience of disappointment (emotional concerns) when it took years for some C-CFR sites to fully implement their ROR protocols. Nevertheless, collaboration and support provided among C-CFR sites (e.g., sharing of ROR protocols) helped ease some of these ill-effects. It is impossible to know if any participants were indirectly harmed, e.g., by delayed cancer diagnosis, as function of site delayed in ROR implementation.

Justice

Finally, the ethical principle of justice in the ROR context primarily refers to the equitable distribution of resources to enable result return [13, 15], as well as equal participant access to the research findings of potential clinical relevance. Despite a common (National Institutes of Health) funding structure, this study shows that the success of ROR implementation had more to do with local contextual considerations, such as the availability of a public health infrastructure to enable result return. Therefore, participants at some C-CFR sites (ON, AU) had access to clinically relevant research findings much sooner than others, whereas participants at another registry site (USC) were never offered the opportunity to learn about research findings that were held by their local investigators. If we believe that registry participants were helped by the offer of CRC-related genetic research findings, these differences in the experience of participants at different registry sites are, arguably, unjust

and ideally would not have occurred. Either ROR should not have occurred at any site until all sites had the ability to proceed, or research support to enable the prompt offer of results at sites without the ancillary infrastructure should have been made available at an earlier stage in registry development. This said, it would be challenging to quantify if there was “harm” experienced by the participants and to re-emphasize, the C-CFR had no legal obligation to return individual research results to their participants.

Lessons Learned: C-CFR ROR Experience

Despite concerted efforts to return clinically actionable results in a manner consistent with existing research policy recommendations [18, 19, 66, 67, 119], the C-CFR ROR protocol implementation was complex, heterogeneous, and of uncertain clinical impact. While belonging to the same consortium, ROR implementation varied considerably among registry sites, in terms of the timing of return, the way that registry participants were approached, and what results were offered. In accordance with available financial and regulatory support at their local institutions, the variability of the site-specific ROR protocols may have had an impact on timely participant access to clinically relevant findings. However, without access to data about the effects of ROR on cancer surveillance and survival, it is challenging to know exactly what impact these differences had on registry participants’ health outcomes. Indeed, the most important impact may have been on the C-CFR investigators themselves, as ROR protocols adopted successfully in some sites may have imposed untoward pressures on other sites to make major adjustments that allowed them to offer results when they had not initially planned to do so. In the future, it may be preferable to create a consistent ROR protocol across all C-CFR sites, and to provide for uniform process evaluation when investigating the impact of ROR endeavors.

Moving forward, it will be important for cancer registries, such as the C-CFR, to have a well-designed infrastructure to ensure a successful and sustainable ROR protocol implementation. For those cancer registries contemplating the adoption of ROR to participants, three essential elements will need to be addressed proactively. First, funding agencies will need to agree to set aside additional resources for cancer registries to implement ROR protocols (e.g., funding for participant re-contact, personnel accountable for result return). Second, information about the potential for re-contact and the offer of clinically relevant results must be included at the time registry participants provide their informed consent to participate in the registry. Third, and most importantly, cancer registries must also ensure that participant risks are minimized (e.g., quality in sample handling, labeling, and IRB approval for the ROR process). Only when these essential elements of result return are addressed can a cancer registry, like the C-CFR, be assured that its intention to benefit participants is honored.

SUPPLEMENTAL TABLES AND FIGURES

Figure S1: Hierarchical Coding of C-CFR Key Informant Interviews

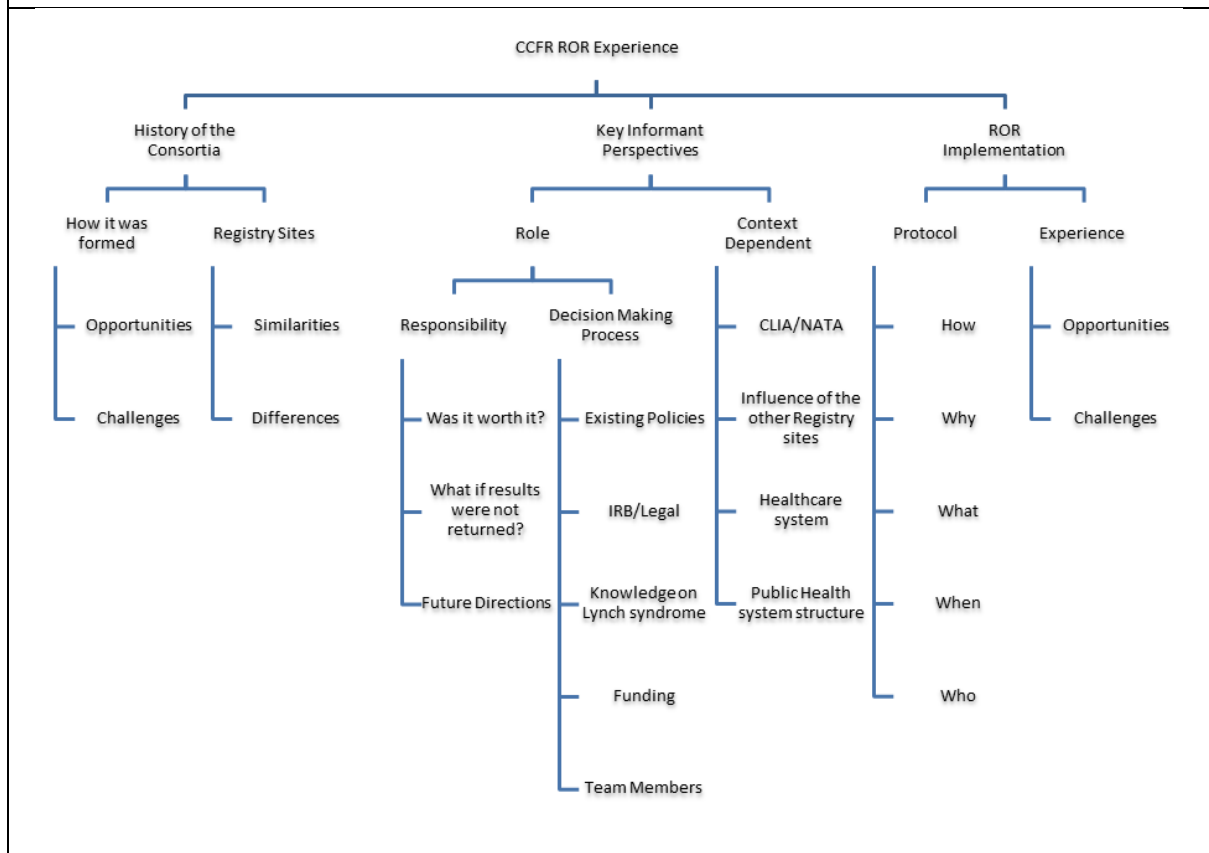


Table S1: Excerpts from the Original Informed Consent Forms Given to Participants at each C-CFR Site

Ontario (ON)

“You may be given the opportunity to be informed of research results that may affect your personal risk of colon polyps/cancer If individual results are available, the Ontario Familial Colon Cancer Registry, consisting of a group of health-care professionals will review the quality of research results and decide when, and if, they should be available to the study participants. If you do not want to know the results from research, please let us know.”

Australia (AU)

“It is becoming possible to test for specific Colon cancer genes and we are undertaking some work in this area, on a research basis. Should we find information relevant to you and your family, we will offer to give this information to you through the Victorian Clinical Genetic Service.”

Mayo Clinic (MA)

“No results will be given to you unless researchers at Mayo Clinic find something important that could be useful for you to know. If this occurs, you will be notified in writing of the option of learning of this research result and would be given an opportunity to learn more about the risks and benefits of learning about a test result before actually getting a result.”

Hawaii (HI)

“If I want to know how these research findings (from the FR) would make a difference for me personally, especially about genetic factors, I can have counseling and possible testing outside this research study. These services would have to be at my own cost. The Registry staff can give me a list of names and addresses of certified cancer genetic specialists.”

University of Southern California (USC)

“Results of gene studies will not be made available to you or any other individual participants. We hope that the knowledge gained from this and future research studies will be of benefit to you, your relatives, and future generations by improving screening, prevention and treatment of Colon cancer.”

Fred Hutchinson Cancer Research Center (SE)

“Test results will not be available on an individual basis since the tests are for research purposes only. That is, they have no verified clinical relevance at this time.”

Source: Keogh, L.A., et al., How do researchers manage genetic results in practice? The experience of the international Colon Cancer Family Registry. J Community Genet, 2013.

Table S2: Overall Outcomes of Participant Re-contact to Return Lynch Syndrome Genetic Research Results Across C-CFR Sites

C-CFR SITES [N (%)]					
Return of Results	SE	HI	MA	AU	Total
Decline	15 (12.1)	7 (10.8)	68 (13.4)	192 (17.5)	282 (15.7)
Accept	34 (27.4)	42 (64.6)	231 (45.7)	174 (15.9)	481 (26.8)
Lost to F/U	61 (49.2)	14 (21.5)	82 (16.2)	63 (5.7)	220 (12.3)
Status Pending	-	1 (1.5)	-	202 (18.4)	203(11.3)
Already Tested	14 (11.3)	1 (1.5)	125 (24.7)	466 (42.5)	606 (33.8)
Total	124 (100)	65 (100)	506 (100)	1097 (100)	1792 (100)

Table S3: Participant Acceptance of Lynch Syndrome Genetic Research Results Across C-CFR Sites

C-CFR SITES [763 (%)]					
Return of Results	SE	HI	MA	AU	Total
Decline	15 (30.6)	7 (14.3)	68 (22.7)	192 (52.5)	282 (37.0)
Accept	34 (69.4)	42 (85.7)	231 (77.3)	174 (47.5)	481 (64.0)
Total	49 (100)	49 (100)	299 (100)	366 (100)	763 (100)

Table S4: Multivariable Logistic Regression Model Analysis Comparison between All Sites with Seattle C-CFR Site

<i>Across C-CFR Sites [Australia, Seattle, Mayo and Hawaii] Accepting Lynch Syndrome Research Results</i>			<i>Seattle CCFR Participants Accepting Lynch Syndrome Research Results*</i>		
Variables (N)	Odds Ratio [95% CI]	P value	Variables (N)	Odds Ratio [95% CI]	P value
Age, years			Age, years		
<50y (395)	[Reference]		<50y (24)	[Reference]	
≥50y (368)	0.36 [0.25-0.52]	0.00	≥50y (25)	0.02 [0.00-0.49]	0.02
Sex			Sex		
Male (364)	[Reference]		Male (19)	[Reference]	
Female (399)	1.07 [0.77-1.49]	0.67	Female (30)	0.35 [0.04-3.22]	0.35
Had Children			Had Children		
No (276)	[Reference]		No (15)	[Reference]	
Yes (487)	0.97 [0.66-1.42]	0.87	Yes (34)	24.46 [1.13-530.18]	0.04
Personal History of Cancer			Personal history of cancer		
None (487)	[Reference]		None (30)	[Reference]	
Colon Cancer (175)	0.81 [0.49 -1.34]	0.42	Colon Cancer (14)	5.52 [0.11-276.16]	0.39
Other cancers* (101)	1.62 [0.96-2.72]	0.07	Other cancers* (5)	0.97 [0.46-20.43]	0.98
# of Family Members with Cancer			# of family members with cancer		
1≤ 3 (241)	[Reference]		1≤ 3 (25)	[Reference]	
> 3 (522)	1.21 [0.84-1.74]	0.30	> 3 (24)	0.07 [0.01-0.79]	0.03
Education Level			Education Level		
Less/Some college (521)	[Reference]		Less/Some college (36)	[Reference]	
College graduate (211)	1.14 [0.78-1.67]	0.50	College graduate (12)	6.01 [0.61-59.15]	0.12
Unknown (31)	5.68 [1.39-23.26]	0.02	Unknown (1)	-	-
Race/ethnicity			Race/Ethnicity		
Caucasian (678)	[Reference]		Caucasian (36)	[Reference]	
Other (67)	3.17 [1.22-8.27]	0.02	Other (13)	26.40 [1.08-642.5]	0.04
Unknown (18)	0.29 [0.04-2.31]	0.24	Unknown (0)	-	-
Participant**			Participant**		
Case (81)	[Reference]		Case (10)	[Reference]	
Relative (682)	0.59 [0.27-1.30]	0.19	Relative (39)	12.71 [0.25-647.33]	0.21
Currently/Living as Married			Currently/Living as Married		
No (176)	[Reference]		No (14)	[Reference]	
Yes (324)	1.67 [1.06-2.63]	0.03	Yes (33)	3.13 [0.39-25.4]	0.29
Unknown (247)	1.61 [0.61-4.26]	0.34	Unknown (2)	-	-
At least one family member had clinical testing			At least one family member had clinical testing		
No (319)	[Reference]		No (41)	[Reference]	
Yes (444)	1.39 [0.95-2.04]	0.09	Yes (8)	4.42 [0.15-130.02]	0.39
C-CFR Site					
Australia (366)	[Reference]				
Seattle (49)	2.75 [1.30-5.81]	0.01			
Hawaii (49)	2.75 [1.30-5.81]	0.00			
Mayo (299)	2.75 [1.30-5.81]	0.00			

*participants diagnosed with biliary/renal, ovarian, stomach, pancreas, bile duct, or small bowel cancers; ** Case = participant with colon cancer and first enrollee of the family; Relative = enrolled family member

*associations were not calculated for covariates with collinearity and those that predicted success perfectly

Table S5: Multivariable Logistic Regression Model Analysis Comparison between All Sites with Mayo C-CFR Site

<i>Across C-CFR Sites [Australia, Seattle, Mayo and Hawaii] Accepting Lynch Syndrome Research Results</i>			<i>Mayo CCFR Participants Accepting Lynch Syndrome Research Results</i>		
Variables (N)	Odds Ratio [95% CI]	P value	Variables (N)	Odds Ratio [95% CI]	P value
Age, years			Age, years		
<50y (395)	[Reference]		<50y (132)	[Reference]	
≥50y (368)	0.36 [0.25-0.52]	0.00	≥50y (167)	0.49 [0.25-0.97]	0.04
Sex			Sex		
Male (364)	[Reference]		Male (146)	[Reference]	
Female (399)	1.07 [0.77-1.49]	0.67	Female (153)	1.28 [0.71-2.30]	0.42
Had Children			Had Children		
No (276)	[Reference]		No (97)	[Reference]	
Yes (487)	0.97 [0.66-1.42]	0.87	Yes (202)	0.65 [0.31-1.37]	0.26
Personal history of cancer			Personal history of cancer		
None (487)	[Reference]		None (164)	[Reference]	
Colon Cancer (175)	0.81 [0.49 -1.34]	0.42	Colon Cancer (87)	0.75 [0.35-1.62]	0.47
Other cancers* (101)	1.62 [0.96-2.72]	0.07	Other cancers* (48)	1.24 [0.53-2.87]	0.62
# of family members with cancer			# of family members with cancer		
1 ≤ 3 (241)	[Reference]		1 ≤ 3 (75)	[Reference]	
> 3 (522)	1.21 [0.84-1.74]	0.30	> 3 (224)	2.12 [1.11-4.04]	0.02
Education Level			Education Level		
Less/Some college (521)	[Reference]		Less/Some college (182)	[Reference]	
College graduate (211)	1.14 [0.78-1.67]	0.50	College graduate (101)	1.04 [0.54-2.01]	0.91
Unknown (31)	5.68 [1.39-23.26]	0.02	Unknown (16)	0.38 [0.03-5.43]	0.48
Race/ethnicity			Race/ethnicity		
Caucasian (678)	[Reference]		Caucasian (276)	[Reference]	
Other (67)	3.17 [1.22-8.27]	0.02	Other (8)	3.57 [0.33-38.48]	0.29
Unknown (18)	0.29 [0.04-2.31]	0.24	Unknown (15)	0.32 [0.04-2.81]	0.30
Participant**			Participant**		
Case (81)	[Reference]		Case (38)	[Reference]	
Relative (682)	0.59 [0.27-1.30]	0.19	Relative (261)	0.32 [0.05-1.94]	0.21
Currently/Living as Married			Currently/Living as Married		
No (176)	[Reference]		No (8)	[Reference]	
Yes (324)	1.67 [1.06-2.63]	0.03	Yes (35)	1.67 [0.25-11.07]	0.60
Unknown (247)	1.61 [0.61-4.26]	0.34	Unknown (243)	2.54 [0.28-22.75]	0.41
At least one family member had clinical testing			At least one family member had clinical testing		
No (319)	[Reference]		No (132)	[Reference]	
Yes (444)	1.39 [0.95-2.04]	0.09	Yes (167)	0.99 [0.52-1.87]	0.97
C-CFR Site					
Australia (366)	[Reference]				
Seattle (49)	2.75 [1.30-5.81]	0.01			
Hawaii (49)	2.75 [1.30-5.81]	0.00			
Mayo (299)	2.75 [1.30-5.81]	0.00			

*participants diagnosed with biliary/renal, ovarian, stomach, pancreas, bile duct, or small bowel cancers; ** Case = participant with colon cancer and first enrollee of the family; Relative = enrolled family member

Table S6: Multivariable Logistic Regression Model Analysis Comparison between All Sites with Hawaii C-CFR Site

<i>Across C-CFR Sites [Australia, Seattle, Mayo and Hawaii] Accepting Lynch Syndrome Research Results</i>			<i>Hawaii CCFR Participants Accepting Lynch Syndrome Research Results*</i>		
Variables (N)	Odds Ratio [95% CI]	P value	Variables (N)	Odds Ratio [95% CI]	P value
Age, years			Age, years		
<50y (395)	[Reference]		<50y (26)	[Reference]	
≥50y (368)	0.36 [0.25-0.52]	0.00	≥50y (23)	0.26 [0.02 – 4.20]	0.35
Sex			Sex		
Male (364)	[Reference]		Male (26)	[Reference]	
Female (399)	1.07 [0.77-1.49]	0.67	Female (23)	0.73[0.05-10.62]	0.82
Had Children			Had Children		
No (276)	[Reference]		No (28)	[Reference]	
Yes (487)	0.97 [0.66-1.42]	0.87	Yes (21)	1.76 [0.10-30.6]	0.70
Personal history of cancer			Personal history of cancer		
None (487)	[Reference]		None (30)	[Reference]	
Colon Cancer (175)	0.81 [0.49 -1.34]	0.42	Colon Cancer (17)	-	-
Other cancers* (101)	1.62 [0.96-2.72]	0.07	Other cancers* (2)	-	-
# of family members with cancer			# of family members with cancer		
1≤ 3 (241)	[Reference]		1≤ 3 (27)	[Reference]	
> 3 (522)	1.21 [0.84-1.74]	0.30	> 3 (22)	1.85 [0.11-30.17]	0.67
Education Level			Education Level		
Less/Some college (521)	[Reference]		Less/Some college (24)	[Reference]	
College graduate (211)	1.14 [0.78-1.67]	0.50	College graduate (22)	4.60 [0.17-127.00]	0.37
Unknown (31)	5.68 [1.39-23.26]	0.02	Unknown (3)	-	-
Race/ethnicity			Race/ethnicity		
Caucasian (678)	[Reference]		Caucasian (7)	[Reference]	
Other (67)	3.17[1.22-8.27]	0.02	Other (39)	0.95 [0.03-29.5]	0.98
Unknown (18)	0.29 [0.04-2.31]	0.24	Unknown (3)	-	-
Participant**			Participant**		
Case (81)	[Reference]		Case (14)	[Reference]	
Relative (682)	0.59 [0.27-1.30]	0.19	Relative (35)	-	-
Currently/Living as Married			Currently/Living as Married		
No (176)	[Reference]		No (46)	[Reference]	
Yes (324)	1.67 [1.06-2.63]	0.03	Yes (0)	-	-
Unknown (247)	1.61 [0.61-4.26]	0.34	Unknown (3)	-	-
At least one family member had clinical testing			At least one family member had clinical testing		
No (319)	[Reference]		No (47)	[Reference]	
Yes (444)	1.39 [0.95-2.04]	0.09	Yes (2)	-	-
C-CFR Site					
Australia (366)	[Reference]				
Seattle (49)	2.75 [1.30-5.81]	0.01			
Hawaii (49)	2.75 [1.30-5.81]	0.00			
Mayo (299)	2.75 [1.30-5.81]	0.00			

*participants diagnosed with biliary/renal, ovarian, stomach, pancreas, bile duct, or small bowel cancers; ** Case = participant with colon cancer and first enrollee of the family; Relative = enrolled family member

*associations were not calculated for covariates with collinearity and those that predicted success perfectly

Table S7: Multivariable Logistic Regression Model Analysis Comparison between All Sites with Australia C-CFR Site

<i>Across C-CFR Sites [Australia, Seattle, Mayo and Hawaii] Accepting Lynch Syndrome Research Results</i>			<i>Australia CCFR Participants Accepting Lynch Syndrome Research Results</i>		
Variables (N)	Odds Ratio [95% CI]	P value	Variables (N)	Odds Ratio [95% CI]	P value
Age, years			Age, years		
<50y (395)	[Reference]		<50y (213)	[Reference]	
≥50y (368)	0.36 [0.25-0.52]	0.00	≥50y (153)	0.34 [0.21-0.56]	0.00
Sex			Sex		
Male (364)	[Reference]		Male (173)	[Reference]	
Female (399)	1.07 [0.77-1.49]	0.67	Female (193)	1.03 [0.67-1.60]	0.88
Had Children			Had Children		
No (276)	[Reference]		No (136)	[Reference]	
Yes (487)	0.97 [0.66-1.42]	0.87	Yes (230)	0.92 [0.56-1.52]	0.76
Personal history of cancer			Personal history of cancer		
None (487)	[Reference]		None (263)	[Reference]	
Colon Cancer (175)	0.81 [0.49 -1.34]	0.42	Colon Cancer (57)	0.89 [0.43-1.86]	0.76
Other cancers* (101)	1.62 [0.96-2.72]	0.07	Other cancers* (46)	2.01 [0.99-4.12]	0.06
# of family members with cancer			# of family members with cancer		
1 ≤ 3 (241)	[Reference]		1 ≤ 3 (114)	[Reference]	
> 3 (522)	1.21 [0.84-1.74]	0.30	> 3 (252)	1.05 [0.65-1.71]	0.84
Education Level			Education Level		
Less/Some college (521)	[Reference]		Less/Some college (279)	[Reference]	
College graduate (211)	1.14 [0.78-1.67]	0.50	College graduate (76)	1.05 [0.62-1.78]	0.87
Unknown (31)	5.68 [1.39-23.26]	0.02	Unknown (11)	11.9 [2.12 -6.54]	0.01
Race/ethnicity			Race/ethnicity		
Caucasian (678)	[Reference]		Caucasian (359)	[Reference]	
Other (67)	3.17 [1.22-8.27]	0.02	Other (7)	2.48 [0.45-13.58]	0.29
Unknown (18)	0.29 [0.04-2.31]	0.24	Unknown (0)	-	-
Participant**			Participant**		
Case (81)	[Reference]		Case (19)	[Reference]	
Relative (682)	0.59 [0.27-1.30]	0.19	Relative (347)	0.46 [0.14-1.49]	0.20
Currently/Living as Married			Currently/Living as Married		
No (176)	[Reference]		No (108)	[Reference]	
Yes (324)	1.67 [1.06-2.63]	0.03	Yes (256)	1.73 [1.04-2.88]	0.04
Unknown (247)	1.61 [0.61-4.26]	0.34	Unknown (2)	0.69 [0.03-18.93]	0.83
At least one family member had clinical testing			At least one family member had clinical testing		
No (319)	[Reference]		No (99)	[Reference]	
Yes (444)	1.39 [0.95-2.04]	0.09	Yes (267)	1.77 [1.04 -3.01]	0.04
C-CFR Site					
Australia (366)	[Reference]				
Seattle (49)	2.75 [1.30-5.81]	0.01			
Hawaii (49)	2.75 [1.30-5.81]	0.00			
Mayo (299)	2.75 [1.30-5.81]	0.00			

*participants diagnosed with biliary/renal, ovarian, stomach, pancreas, bile duct, or small bowel cancers; ** Case = participant with colon cancer and first enrollee of the family; Relative = enrolled family member

Table S8: Multivariable Logistic Regression Model Analysis Comparison when Unknown Categories are Included versus Excluded

<i>Across C-CFR Sites [Australia, Seattle, Mayo and Hawaii] Accepting Lynch Syndrome Research Results- Inclusion of Unknown Categories</i>			<i>Across C-CFR Sites [Australia, Seattle, Mayo and Hawaii] Accepting Lynch Syndrome Research Results[without the unknown variable]- Exclusion of Unknown Categories</i>		
Variables (N)	Odds Ratio [95% CI]	P value	Variables (N)	Odds Ratio [95% CI]	P value
Age, years			Age, years		
<50y (395)	[Reference]		<50y (278)	[Reference]	
≥50y (368)	0.36 [0.25-0.52]	0.00	≥50y (211)	0.28 [0.18-0.44]	0.00
Sex			Sex		
Male (364)	[Reference]		Male (235)	[Reference]	
Female (399)	1.07 [0.77-1.49]	0.67	Female (254)	0.96 [0.64-1.43]	0.83
Had Children			Had Children		
No (276)	[Reference]		No (182)	[Reference]	
Yes (487)	0.97 [0.66-1.42]	0.87	Yes (307)	1.14 [0.72-1.81]	0.57
Personal history of cancer			Personal history of cancer		
None (487)	[Reference]		None (313)	[Reference]	
Colon Cancer (175)	0.81 [0.49 -1.34]	0.42	Colon Cancer (122)	0.80 [0.41-1.58]	0.52
Other cancers* (101)	1.62 [0.96-2.72]	0.07	Other cancers* (54)	1.95 [0.99-3.83]	0.05
# of family members with cancer			# of family members with cancer		
1≤ 3 (241)	[Reference]		1≤ 3 (168)	[Reference]	
> 3 (522)	1.21 [0.84-1.74]	0.30	> 3 (321)	1.01 [0.66-1.58]	0.93
Education Level			Education Level		
Less/Some college (521)	[Reference]		Less/Some college (368)	[Reference]	
College graduate (211)	1.14 [0.78-1.67]	0.50	College graduate (121)	1.06 [0.66-1.69]	0.81
Unknown (31)	5.68 [1.39-23.26]	0.02			
Race/Ethnicity			Race/Ethnicity		
Caucasian (678)	[Reference]		Caucasian (432)	[Reference]	
Other (67)	3.17[1.22-8.27]	0.02	Other (57)	3.61 [1.25-10.43]	0.02
Unknown (18)	0.29 [0.04-2.31]	0.24			
Participant**			Participant**		
Case (81)	[Reference]		Case (76)	[Reference]	
Relative (682)	0.59 [0.27-1.30]	0.19	Relative (413)	0.61 [0.25-1.50]	0.28
Currently/Living as Married			Currently/Living as Married		
No (176)	[Reference]		No (174)	[Reference]	
Yes (324)	1.67 [1.06-2.63]	0.03	Yes (315)	1.74 [1.09-2.79]	0.02
Unknown (247)	1.61 [0.61-4.26]	0.34			
At least one family member had clinical testing			At least one family member had clinical testing		
No (319)	[Reference]		No (204)	[Reference]	
Yes (444)	1.39 [0.95-2.04]	0.09	Yes (285)	1.54 [0.94-2.51]	0.09
C-CFR Site			C-CFR Site		
Australia (366)	[Reference]		Australia (354)	[Reference]	
Seattle (49)	2.75 [1.30-5.81]	0.01	Seattle (47)	2.82 [1.29-6.20]	0.01
Hawaii (49)	2.75 [1.30-5.81]	0.00	Hawaii (46)	6.89 [1.89-25.19]	0.00
Mayo (299)	2.75 [1.30-5.81]	0.00	Mayo (42)	5.19 [1.96-13.75]	0.00

*participants diagnosed with biliary/renal, ovarian, stomach, pancreas, bile duct, or small bowel cancers; ** Case = participant with colon cancer and first enrollee of the family; Relative = enrolled family member

APPENDICES

APPENDIX A: Interview Guide: Registry-Affiliated Researchers

The Return of Genetic Results in the Context of an International Colon Cancer Family Registry

INTERVIEW GUIDE: REGISTRY-AFFILIATED RESEARCHERS

May 21, 2013

INTRODUCTION

Thank you very much for taking the time to speak to me about your experience in the decision making when your registry site developed your return of results policy.

Your participation in this interview is voluntary. You can refuse to answer any questions, and end this interview at any time. I will digitally record the interview to enable thematic analysis for the study. These recordings will not be shared with anyone outside of my dissertation committee and all transcribed data will be anonymized and secured.

Does that all sound reasonable? Do you have any questions before we begin?

SECTION 1: Respondent's Role in Colon CFR Consortium

To get us started, I would like to ask a little bit about your role in the Colon CFR Consortium.

You are [*info received from Colon CFR staff listing regarding position/title*], correct?

1. Could you tell me – briefly – what this position means? How long have you worked as part of the Consortium? What are your key responsibilities?
2. In what ways do your areas of responsibility relate to the development of the Return of Results protocol at your registry site?

Thank you for clarifying your roles and responsibility. It is very helpful. Now, I am going to ask you questions specifically about the Return of Results Policy.

SECTION 2: Current Registry's Return of Results Policy

Though it continues to be a much-debated issue, offering the return of results identified to have important research results, directly to registry participants, has been initiated within the Colon CFR consortium.

3. Does your registry site have a policy with regard to the return of individual genetic findings? If so, what is that policy exactly? To which registry participants are results offered? What types of results are deemed eligible for return?
4. Was this policy already in place at the inception of your registry site? If this has not always been the policy, what was the initial policy that this current return of results policy replaced? How long has this been the policy of the registry?

SECTION 3: Decision-Making Process that Led to Return of Results Policy

Think back to when discussions first started at [*your registry site*] about developing an ROR policy.

5. How did you first hear about it? How were you involved in the process? What was your role?
6. What were the factors going on at the time that established the need for an ROR policy? *Possible Prompts:* What do you think influenced this request for a policy change?
7. What factors weighed in for you personally during your decision-making process when the return of results of policy was being developed? (Possible Factors: ethical frameworks, legal policies, health system infrastructures, etc.) *Possible Prompts:* Which of these factors felt more significant for you? How come? Which ones were insignificant? How come?

APPENDIX B: Data Dictionary

Return of Results Data Set Column	Description
SITE	C-CFR sites AU, SE, MA, HI
AGE	Continuous variable
GENDER (SEX)	Male, Female
CHILDREN	Participant's Reproductive History
CANCER_HX	Diagnosed with colon cancer, or other cancers (e.g., biliary/renal, ovarian, stomach, pancreas, bile duct, or small bowel cancers), or no cancer diagnosis
Ca1_2_deg	Participants reported the # of family members with cancer
EDUCATION_LEVEL	Some or less college education, College graduate or unknown
ETHNIC_BACKGROUND	Caucasian, Non-Caucasian "Other" (African/Black, Hispanic, Asian, Native American, Other), and Unknown
MARSTAT	Marital status for each participant; either NO, Yes or Unknown
PARTICIPANT	C-CFR participants are either the initial case (proband) or a family member
GENETIC_TEST	MMR gene for Lynch syndrome that was found to have a pathogenic variant; A participant either tested positive or negative of their familial mutation
HAD_GT	At least one family member had clinical genetic testing
ROR	Participants either choosing to accept, decline research results, or they are either lost to follow-up, status pending or had clinical testing

APPENDIX C: Pre-Counseling Baseline Survey

Thank you for taking the time to do this brief genetic counseling survey. Your responses to this survey will help us improve the quality of our research and better meet the needs of family members in CORE Family Studies / the Colon Cancer Family Registry.

SECTION 1: QUALITY OF LIFE

EQ5D

Please tell me which statement best describe your own health state today.

1.1 Mobility

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

1.2 Self-Care

- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

1.3 Usual Activities (*eg, work, study, housework, family or leisure activities*)

- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

1.4 Pain/Discomfort

- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

1.5 Anxiety/Depression

- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

1.6 Your own health state today

To help people say how good or bad a health state is, we have a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

I would like you to tell me on this scale how good or bad your own health is today, in your opinion. Please do this by indicating a number between 100 (Best imaginable health state) and 0 (worst imaginable health state) that indicates how good or bad your health state is today.

SECTION 2: GENERAL ANXIETY

PROMIS Emotional Distress – Anxiety Short Form 1

Please answer each of the following questions. In the past 7 days.....

2.1 I felt fearful

- Never
- Rarely
- Sometimes
- Often
- Always

2.2 I felt anxious

- Never
- Rarely
- Sometimes
- Often
- Always

2.3 I felt worried

- Never
- Rarely
- Sometimes
- Often
- Always

2.4 I found it hard to focus on anything other than my anxiety

- Never
- Rarely
- Sometimes
- Often

- Always

2.5 I felt nervous

- Never
- Rarely
- Sometimes
- Often
- Always

2.6 I felt uneasy

- Never
- Rarely
- Sometimes
- Often
- Always

2.7 I felt tense

- Never
- Rarely
- Sometimes
- Often
- Always

SECTION 3: CANCER SPECIFIC WORRY

Adapted from Lerman *et al.* 1991

3.1 How much do you currently worry about getting cancer some day?

- Not at all
- Rarely
- Sometimes
- Often
- Almost all the time

3.2 How much do worries about cancer impact your mood?

- Not at all
- A little
- Somewhat
- A lot

3.3 How much do worries about cancer impact your daily activities?

- Not at all
- A little
- Somewhat
- A lot

3.4 What is your current level of anxiety about the results of future cancer tests?

- Not at all
- A little
- Somewhat
- A lot

SECTION 4: HEALTH BEHAVIOURS

Selected items from Centers for Disease Control and Prevention (CDC) Behavioral Risk Factor Surveillance System Questionnaire 1984-2010

BMI

4.1 About how much do you weigh without shoes? *Note: If respondent answers in metrics, circle kilograms.*

Round fractions up
 _ _ _ _ Weight (*pounds/kilograms*)

- Do not read:**
- Don't know / Not sure
 - Refused

4.2 About how tall are you without shoes? *NOTE: If respondent answers in metrics, circle meters or centimeters.*

Round fractions down
 _ _ / _ _ Height (*ft / inches / meters / centimeters*)

- Do not read:**
- Don't know / Not sure
 - Refused

EXERCISE

4.3 During the past month, other than your regular job, did you participate in any physical activities or exercises such as running, calisthenics, golf, gardening, or walking for exercise?

- Yes
- No

Do not read:

- Don't know / Not sure
- Refused

TOBACCO USE

4.4 Have you smoked at least 100 cigarettes in your entire life? NOTE: 5 packs = 100 cigarettes

- Yes
- No [Go to Q 4.8]

Do not read:

- Don't know / Not sure [Go to Q 4.8]
- Refused [Go to Q 4.8]

4.5 Do you now smoke cigarettes every day, some days, or not at all?

- Every day
- Some days
- Not at all [Go to Q 4.7]

Do not read:

- Don't know / Not sure [Go to Q 4.8]
- Refused [Go to Q 4.8]

4.6 During the past 12 months, have you stopped smoking for one day or longer because you were trying to quit smoking?

- Yes [Go to Q 4.8]
- No [Go to Q 4.8]

Do not read:

- Don't know / Not sure [Go to Q 4.8]
- Refused [Go to Q 4.8]

CATI note: If Q 4.5 = 3 (Not at all); continue. Otherwise, go to Q 4.8.

4.7 How long has it been since you last smoked cigarettes regularly?

- Within the past month (less than 1 month ago)
- Within the past 3 months (1 month but less than 3 months ago)
- Within the past 6 months (3 months but less than 6 months ago)
- Within the past year (6 months but less than 1 year ago)
- Within the past 5 years (1 year but less than 5 years ago)
- Within the past 10 years (5 years but less than 10 years ago)
- 10 years or more

Never smoked regularly

Do not read:

Don't know / Not sure

Refused

4.8 Do you currently use chewing tobacco, snuff, or snus every day, some days, or not at all?

Snus (rhymes with 'goose') NOTE: Snus (Swedish for snuff) is a moist smokeless tobacco, usually sold in small pouches that are placed under the lip against the gum.

Every day

Some days

Not at all

Do not read:

Don't know / Not sure

Refused

COLONSCREENING

The next questions are about Colon cancer screening.

4.9 Sigmoidoscopy and colonoscopy are exams in which a tube is inserted in the rectum to view the colon for signs of cancer or other health problems. Have you ever had either of these exams?

Yes

No [Go to next section]

Do not read:

Don't know / Not sure [Go to next section]

Refused [Go to next section]

4.10 For a SIGMOIDOSCOPY, a flexible tube is inserted into the rectum to look for problems. A COLONOSCOPY is similar, but uses a longer tube, and you are usually given medication through a needle in your arm to make you sleepy and told to have someone else drive you home after the test. Was your MOST RECENT exam a sigmoidoscopy or a colonoscopy?

Sigmoidoscopy

Colonoscopy

Do not read:

Don't know / Not sure

Refused

4.11 How long has it been since you had your last sigmoidoscopy or colonoscopy?

Read only if necessary:

- Within the past year (anytime less than 12 months ago)
- Within the past 2 years (1 year but less than 2 years ago)
- Within the past 3 years (2 years but less than 3 years ago)
- Within the past 5 years (3 years but less than 5 years ago)
- Within the past 10 years (5 years but less than 10 years ago)
- 10 or more years ago

Do not read:

- Don't know / Not sure
- Refused

WOMEN'S HEALTH

CATI note: If respondent is male, END OF INTERVIEW. Thank you again for taking the time to complete this survey. We will call you two months and 12 months after your 2nd genetic counseling session.

The next questions are about breast and cervical cancer.

4.12 A mammogram is an x-ray of each breast to look for breast cancer. Have you ever had a mammogram?

- Yes
- No [Go to Q 4.14]

Do not read:

- Don't know / Not sure [Go to Q 4.14]
- Refused [Go to Q 4.14]

4.13 How long has it been since you had your last mammogram?

Read only if necessary:

- Within the past year (anytime less than 12 months ago)
- Within the past 2 years (1 year but less than 2 years ago)
- Within the past 3 years (2 years but less than 3 years ago)
- Within the past 5 years (3 years but less than 5 years ago)
- 5 or more years ago

Do not read:

- Don't know / Not sure
- Refused

4.14 A clinical breast exam is when a doctor, nurse, or other health professional feels the breasts for lumps. Have you ever had a clinical breast exam?

- Yes
- No [Go to Q 4.16]

Do not read:

- Don't know / Not sure [Go to Q 4.16]
- Refused [Go to Q 4.16]

4.15 **How long has it been since your last breast exam?**

Read only if necessary:

- Within the past year (anytime less than 12 months ago)
- Within the past 2 years (1 year but less than 2 years ago)
- Within the past 3 years (2 years but less than 3 years ago)
- Within the past 5 years (3 years but less than 5 years ago)
- 5 or more years ago

Do not read:

- Don't know / Not sure
- Refused

4.16 **A Pap test is a test for cancer of the cervix. Have you ever had a Pap test?**

- Yes
- No [Go to Q 4.18]

Do not read:

- Don't know / Not sure [Go to Q 4.18]
- Refused [Go to Q 4.18]

4.17 **How long has it been since you had your last Pap test?**

Read only if necessary:

- Within the past year (anytime less than 12 months ago)
- Within the past 2 years (1 year but less than 2 years ago)
- Within the past 3 years (2 years but less than 3 years ago)
- Within the past 5 years (3 years but less than 5 years ago)
- 5 or more years ago

Do not read:

- Don't know / Not sure
- Refused

CATI note: If participant is pregnant; then END OF INTERVIEW. Thank you again for taking the time to complete this survey. We will call you two months and 12 months after your 2nd genetic counseling session.

4.18 **Have you had a hysterectomy?**

Read only if necessary: A hysterectomy is an operation to remove the uterus (womb).

- Yes
- No

Do not read:

- Don't know / Not sure
- Refused

Thank you again for taking the time to complete this survey. We will call you two months and 12 months after your 2nd genetic counseling session.

APPENDIX D: 2-Month Post-Counseling Survey

Thank you for participating in the Genetic Counseling Survey. This is your 2-month follow-up survey assessment.

SECTION 1: CONFIRMATION OF RESEARCH TEST RESULTS

(Interviewer note. Pull this data from the database before the interview.) When you spoke with our genetic counselor, she told you the results of genetic testing with your blood. She said:

- You have a disease causing mutation in the _____ gene.
- You have a variant of unknown significance.
- You do not have a disease causing mutation or variant of unknown significance.

1.1 Our genetic counselor recommended that you confirm the findings of your research genetic test results in a clinically-approved laboratory. Were you able to pursue this recommendation?

- Yes (next question 1.2)
- No (next question 1.5)

1.2 Who helped you coordinate confirming your research results?

- Primary care provider
- Genetic Counselor
- Gastrointestinal provider
- Other: Please specify

1.3 Did the results confirm similar genetics findings that you were told by our genetic counselor?

- Yes (next question Q. 2.1)
- No

1.4 What were the results?

- I have a disease causing mutation in the _____ gene.
- I have a variant of unknown significance.
- I do not have a disease causing mutation or variant of unknown significance.
- I don't remember the confirmation results.

(Go to question 2.1)

1.5 Are you planning to pursue this recommendation?

- Yes (Go to Section 2)
- No

1.6 Please tell us the reason why you decided not to pursue confirmation testing at this time

- I have not found a time to schedule an appointment with my health care provider
- I don't have insurance
- My insurance will not pay for confirmation test
- I don't want my insurance company to know
- I believe the results you gave me
- I don't feel the need to repeat my test results

SECTION 2: FAMILY AND HEALTH PROVIDER COMMUNICATION

2.1 Did you share the test results provided by our genetic counselor with your family?

- Yes
- No (next question 2.4)

2.2 With whom did you share your results?

- My mom
- My dad
- My children
- My brothers
- My sisters
- My extended relatives
- Others: please specify

2.3 How did you share your results?

- In person
- Over email
- Over the phone
- Other: please specify. _____

2.4 Did you share your test results with your friends?

- Yes
- No (go to 2.7)

2.5 How did you share your results?

- In person
- Over email
- Over the phone
- Other: please specify

2.6 Using "True" or "False", which of the following statements apply to you

a. I discussed how the result affects the cancer risk of my children

- True
- False

Do not read:

- Don't know / Not sure
- Refused

b. I discussed whether or not I should have children in the future

- True
- False

Do not read:

- Don't know / Not sure
- Refused

c. I discussed how this result will affect my insurance

- True
- False

Do not read:

- Don't know / Not sure
- Refused

d. Is there anything I have missed?

Do not read:

- Don't know / Not sure
- Refused

2.7 Have you discussed your genetic test results with a health care provider?

- Yes
- No (next question Q 3.1)

Do not read:

- Don't know / Not sure
- Refused

2.8 Using “yes”, “no” or “not applicable”, which of the following statements applies to you?

a. I made an appointment to discuss screening recommendations

- Yes
- No
- Not applicable

Do not read:

- Don't know / Not sure
- Refused

b. I discussed how my result would change my cancer screening options

- Yes
- No
- Not applicable

Do not read:

- Don't know / Not sure
- Refused

c. I made an appointment for Colon screening or follow-up screening

- Yes
- No
- Not applicable

Do not read:

- Don't know / Not sure
- Refused

d. Is there anything else you discussed with a health care provider that I haven't asked?

Do not read:

- Don't know / Not sure
- Refused

SECTION 3: QUALITY OF LIFE

EQ5D

Please tell me which statement best describe your own health state today.

3.1 Mobility

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

3.2 Self-Care

- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

3.3 Usual Activities (*eg, work, study, housework, family or leisure activities*)

- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

3.4 Pain/Discomfort

- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

3.5 Anxiety/Depression

- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

3.6 Your own health state today

To help people say how good or bad a health state is, we have a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

I would like you to tell me on this scale how good or bad your own health is today, in your opinion. Please do this by indicating a number between 100 (Best imaginable health state) and 0 (worst imaginable health state) that indicates how good or bad your health state is today.

SECTION 4: GENERAL ANXIETY

PROMIS Emotional Distress – Anxiety Short Form 1

Please answer each of the following questions. In the past 7 days.....

4.1 I felt fearful

- Never
- Rarely
- Sometimes
- Often
- Always

4.2 I felt anxious

- Never
- Rarely
- Sometimes
- Often
- Always

4.3 I felt worried

- Never
- Rarely
- Sometimes
- Often
- Always

4.4 I found it hard to focus on anything other than my anxiety

- Never
- Rarely
- Sometimes
- Often
- Always

4.5 I felt nervous

- Never
- Rarely
- Sometimes
- Often
- Always

4.6 I felt uneasy

- Never
- Rarely

- Sometimes
- Often
- Always

4.7 I felt tense

- Never
- Rarely
- Sometimes
- Often
- Always

SECTION 5: CANCER SPECIFIC WORRY

Do not read: Adapted from Lerman et al. 1991

5.1 How much do you currently worry about getting cancer some day?

- Not at all
- Rarely
- Sometimes
- Often
- Almost all the time

5.2 How much do worries about cancer impact your mood?

- Not at all
- A little
- Somewhat
- A lot

5.3 How much do worries about cancer impact your daily activities?

- Not at all
- A little
- Somewhat
- A lot

5.4 What is your current level of anxiety about the results of future cancer tests?

- Not at all
- A little
- Somewhat
- A lot

This is the end of your 2-month genetic counseling follow-up survey. Thank you for your time and participation. We will be calling you in the future for your 12-month follow-up assessment.

APPENDIX E: 12-Month Post-Counseling Survey

Thank you for participating in the Genetic Counseling Survey. This is your 12-month follow-up survey assessment.

Interviewer note: *Please skip Section 1 if the respondent already reported confirmation of the genetic test results during the 2-month survey.*

SECTION1: CONFIRMATION OF RESEARCH TEST RESULTS

(Interviewer note. Pull this data from the database before the interview.) When you spoke with our genetic counselor, she told you the results of genetic testing with your blood. She said:

- You have a disease causing mutation in the _____ gene.
- You have a variant of unknown significance.
- You do not have a disease causing mutation or variant of unknown significance.

1.7 Our genetic counselor recommended that you confirm the findings of your research genetic test results in a clinically-approved laboratory. Were you able to pursue this recommendation?

- Yes (next question 1.2)
- No (next question 1.5)

1.8 Who helped you coordinate confirming your research results?

- Primary care provider
- Genetic Counselor
- Gastrointestinal provider
- Other: Please specify

1.9 Did the results confirm similar genetics findings that you were told by our genetic counselor?

- Yes (next question Q. 2.1)
- No

1.10 What were the results?

- I have a disease causing mutation in the _____ gene.
- I have a variant of unknown significance.
- I do not have a disease causing mutation or variant of unknown significance.
- I don't remember the confirmation results.

(Go to question 2.1)

1.11 Are you planning to pursue this recommendation?

- Yes (Go to Section 2)
- No

1.12 Please tell us the reason why you decided not to pursue confirmation testing at this time

- I have not found a time to schedule an appointment with my health care provider
- I don't have insurance
- My insurance will not pay for confirmation test
- I don't want my insurance company to know
- I believe the results you gave me
- I don't feel the need to repeat my test results

SECTION 2: FAMILY AND HEALTH PROVIDER COMMUNICATION

Introduction. We asked you the following questions about family and health care provider communication at your last interview. We are asking them again in case you have new information for us since we last talked.

2.3 Did you share the test results provided by our genetic counselor with your family?

- Yes
- No (next question 2.4)

2.4 With whom did you share your results?

- My mom
- My dad
- My children
- My brothers
- My sisters
- My extended relatives
- Others: please specify

2.3 How did you share your results?

- In person
- Over email
- Over the phone
- Other: please specify. _____

2.4 Did you share your test results with your friends?

- Yes
- No (go to 2.7)

2.5 How did you share your results?

- In person

- Over email
- Over the phone
- Other: please specify

2.7 Using “True” or “False”, which of the following statements apply to you

e. I discussed how the result affects the cancer risk of my children

- True
- False

Do not read:

- Don't know / Not sure
- Refused

f. I discussed whether or not I should have children in the future

- True
- False

Do not read:

- Don't know / Not sure
- Refused

g. I discussed how this result will affect my insurance

- True
- False

Do not read:

- Don't know / Not sure
- Refused

h. Is there anything I have missed?

Do not read:

- Don't know / Not sure
- Refused

2.7 Have you discussed your genetic test results with a health care provider?

- Yes
- No (next question Q 3.1)

Do not read:

- Don't know / Not sure
- Refused

2.8 Using “yes”, “no” or “not applicable”, which of the following statements applies to you?

e. I made an appointment to discuss screening recommendations

- Yes
- No
- Not applicable

Do not read:

- Don't know / Not sure
- Refused

f. I discussed how my result would change my cancer screening options

- Yes
- No
- Not applicable

Do not read:

- Don't know / Not sure
- Refused

g. I made an appointment for Colon screening or follow-up screening

- Yes
- No
- Not applicable

Do not read:

- Don't know / Not sure
- Refused

h. Is there anything else you discussed with a health care provider that I haven't asked?

Do not read:

- Don't know / Not sure
- Refused

SECTION 3: QUALITY OF LIFE

EQ5D

Please tell me which statement best describe your own health state today.

3.1 Mobility

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

3.2 Self-Care

- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

3.3 Usual Activities (*eg, work, study, housework, family or leisure activities*)

- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

3.4 Pain/Discomfort

- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

3.5 Anxiety/Depression

- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

3.6 Your own health state today

To help people say how good or bad a health state is, we have a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

I would like you to tell me on this scale how good or bad your own health is today, in your opinion. Please do this by indicating a number between 100 (Best imaginable health state) and 0 (worst imaginable health state) that indicates how good or bad your health state is today.

SECTION 4: GENERAL ANXIETY

PROMIS Emotional Distress – Anxiety Short Form 1

Please answer each of the following questions. In the past 7 days.....

4.1 I felt fearful

- Never
- Rarely
- Sometimes
- Often
- Always

4.2 I felt anxious

- Never
- Rarely
- Sometimes
- Often
- Always

4.3 I felt worried

- Never
- Rarely
- Sometimes
- Often
- Always

4.4 I found it hard to focus on anything other than my anxiety

- Never
- Rarely
- Sometimes
- Often
- Always

4.5 I felt nervous

- Never
- Rarely
- Sometimes
- Often
- Always

4.6 I felt uneasy

- Never
- Rarely
- Sometimes
- Often
- Always

4.7 I felt tense

- Never
- Rarely
- Sometimes
- Often
- Always

SECTION 5: CANCER SPECIFIC WORRY

Do not read: Adapted from Lerman et al. 1991

5.1 How much do you currently worry about getting cancer some day?

- Not at all
- Rarely
- Sometimes
- Often
- Almost all the time

5.2 How much do worries about cancer impact your mood?

- Not at all
- A little
- Somewhat
- A lot

5.3 How much do worries about cancer impact your daily activities?

- Not at all
- A little
- Somewhat
- A lot

5.4 What is your current level of anxiety about the results of future cancer tests?

- Not at all
- A little
- Somewhat
- A lot

SECTION 6: HEALTH BEHAVIOURS

Selected items from Centers for Disease Control and Prevention (CDC) Behavioral Risk Factor Surveillance System Questionnaire 1984-2010

BMI

6.1 About how much do you weigh without shoes? *Note: If respondent answers in metrics, circle kilograms.*

Round fractions up

___ Weight (*pounds/kilograms*)

Do not read:

- Don't know / Not sure
- Refused

6.2 About how tall are you without shoes? *NOTE: If respondent answers in metrics, circle meters or centimeters.*

Round fractions down

__ / __ Height (*ft / inches / meters / centimeters*)

Do not read:

- Don't know / Not sure
- Refused

EXERCISE

6.3 During the past month, other than your regular job, did you participate in any physical activities or exercises such as running, calisthenics, golf, gardening, or walking for exercise?

- Yes
- No

Do not read:

- Don't know / Not sure
- Refused

TOBACCO USE

6.4 Do you now smoke cigarettes every day, some days, or not at all?

- Every day
- Some days
- Not at all [Go to Q 4.6]

Do not read:

- Don't know / Not sure [Go to Q 4.7]
- Refused [Go to Q 4.7]

6.5 During the past 12 months, have you stopped smoking for one day or longer because you were trying to quit smoking?

- Yes [Go to Q 4.7]
- No [Go to Q 4.7]

Do not read:

- Don't know / Not sure [Go to Q 4.7]
- Refused [Go to Q 4.7]

CATI note: If Q 4.4 = 3 (Not at all); continue. Otherwise, go to Q 4.7.

6.6 How long has it been since you last smoked cigarettes regularly?

- Within the past month (less than 1 month ago)
- Within the past 3 months (1 month but less than 3 months ago)
- Within the past 6 months (3 months but less than 6 months ago)
- Within the past year (6 months but less than 1 year ago)

Do not read:

- Don't know / Not sure
- Refused

6.7 Do you currently use chewing tobacco, snuff, or snus every day, some days, or not at all?

Snus (rhymes with 'goose') NOTE: Snus (Swedish for snuff) is a moist smokeless tobacco, usually sold in small pouches that are placed under the lip against the gum.

- Every day
- Some days
- Not at all

Do not read:

- Don't know / Not sure
- Refused

COLONSCREENING

The next questions are about Colon cancer screening.

6.8 Sigmoidoscopy and colonoscopy are exams in which a tube is inserted in the rectum to view the colon for signs of cancer or other health problems. Have you ever had either of these exams in the last 12 months?

- Yes
- No [**Go to next section**]

Do not read:

- Don't know / Not sure [**Go to next section**]
- Refused [**Go to next section**]

6.9 For a SIGMOIDOSCOPY, a flexible tube is inserted into the rectum to look for problems. A COLONOSCOPY is similar, but uses a longer tube, and you are usually given medication through a needle in your arm to make you sleepy and told to have someone else drive you home after the test. Was your MOST RECENT exam a sigmoidoscopy or a colonoscopy?

- Sigmoidoscopy
- Colonoscopy

Do not read:

- Don't know / Not sure
- Refused

COST OF COLONSCREENING

6.10 How much time, if any, did you take off from work to have this test, and/or to recover after the test?

Round fractions up

____ Time (*Hours/Days*)

Do not read:

- Don't know / Not sure
- Refused

6.11 How far did you have to travel to have this test?

Round fractions up

____ Distance (*Miles/Kilometers*)

Do not read:

- Don't know / Not sure
- Refused

6.12 How did you travel to have this test?

Mode of transport

Do not read:

- Don't know / Not sure
- Refused

6.13 Did you have any out-of-pocket expenses to have this test and if so what were they?

- Yes ----- [Record item and cost]
- No

Do not read:

- Don't know / Not sure
- Refused

6.14 How much time, if any, did a family member or friend have to take off from work to assist you to have this test?

Round fractions up

----- Time (*Hours/Days*)

Do not read:

- Don't know / Not sure
- Refused

6.15 How much time, if any, did a family member or friend have to take off from work to help you recover after you had this test?

Round fractions up

----- Time (*Hours/Days*)

Do not read:

- Don't know / Not sure
- Refused

WOMEN'S HEALTH

CATI note: If respondent is male, END OF THE INTERVIEW. This ends your 12-month follow-up interview. Thank you again for your participation with the Colon Cancer Family Registry.

The next questions are about breast and cervical cancer.

BREAST SCREENING MAMMOGRAPHY

6.16 A mammogram is an x-ray of each breast to look for breast cancer. Have you ever had a mammogram in the last 12 months?

- Yes
- No [Go to Q 4.23]

Do not read:

- Don't know / Not sure [Go to Q 4.23]
- Refused [Go to Q 4.23]

COST OF BREAST SCREENING MAMMOGRAPHY

6.17 How much time, if any, did you take off from work to have this test, and/or to recover after the test?

Round fractions up

_____ Time (*Hours/Days*)

Do not read:

- Don't know / Not sure
- Refused

6.18 How far did you have to travel to have this test?

Round fractions up

_____ Distance (*Miles/Kilometers*)

Do not read:

- Don't know / Not sure
- Refused

6.19 How did you travel to have this test?

Mode of transport

Do not read:

- Don't know / Not sure
- Refused

6.20 Did you have any out-of-pocket expenses to have this test and if so what were they?

- Yes _____ [Record item and cost]
- No

Do not read:

- Don't know / Not sure

Refused

6.21 How much time, if any, did a family member or friend have to take off from work to assist you to have this test?

Round fractions up

_____ Time (*Hours/Days*)

Do not read:

Don't know / Not sure

Refused

6.22 How much time, if any, did a family member or friend have to take off from work to help you recover after you had this test?

Round fractions up

_____ Time (*Hours/Days*)

Do not read:

Don't know / Not sure

Refused

BREAST SCREENING EXAMINATION

6.23 A clinical breast exam is when a doctor, nurse, or other health professional feels the breasts for lumps. Have you ever had a clinical breast exam in the last 12 months?

Yes

No [Go to Q 4.30]

Do not read:

Don't know / Not sure [Go to Q 4.30]

Refused [Go to Q 4.30]

COST OF BREAST SCREENING EXAMINATION

6.24 How much time, if any, did you take off from work to have this test, and/or to recover after the test?

Round fractions up

_____ Time (*Hours/Days*)

Do not read:

Don't know / Not sure

Refused

6.25 How far did you have to travel to have this test?

Round fractions up

_____ Distance (*Miles/Kilometers*)

Do not read:

- Don't know / Not sure
- Refused

6.26 How did you travel to have this test?

Mode of transport

Do not read:

- Don't know / Not sure
- Refused

6.27 Did you have any out-of-pocket expenses to have this test and if so what were they?

- Yes _____ [Record item and cost]
- No

Do not read:

- Don't know / Not sure
- Refused

6.28 How much time, if any, did a family member or friend have to take off from work to assist you to have this test?

Round fractions up

_____ Time (*Hours/Days*)

Do not read:

- Don't know / Not sure
- Refused

6.29 How much time, if any, did a family member or friend have to take off from work to help you recover after you had this test?

Round fractions up

_____ Time (*Hours/Days*)

Do not read:

- Don't know / Not sure
- Refused

CERVICAL SCREENING

CATI note: If the respondent had a hysterectomy, END OF THE INTERVIEW. This ends your 12-month follow-up interview. Thank you again for your participation with the Colon Cancer Family Registry.

6.30 A Pap test is a test for cancer of the cervix. Have you ever had a Pap test in the last 12 months?

- Yes
- No [Go to Q 4.37]

Do not read:

- Don't know / Not sure [Go to Q 4.37]
- Refused [Go to Q 4.37]

COST OF CERVICAL SCREENING

6.31 How much time, if any, did you take off from work to have this test, and/or to recover after the test?

Round fractions up

_____ Time (*Hours/Days*)

Do not read:

- Don't know / Not sure
- Refused

6.32 How far did you have to travel to have this test?

Round fractions up

_____ Distance (*Miles/Kilometers*)

Do not read:

- Don't know / Not sure
- Refused

6.33 How did you travel to have this test?

Mode of transport

Do not read:

- Don't know / Not sure
- Refused

6.34 Did you have any out-of-pocket expenses to have this test and if so what were they?

- Yes ----- [Record item and cost]
 No

Do not read:

- Don't know / Not sure
 Refused

6.35 How much time, if any, did a family member or friend have to take off from work to assist you to have this test?

Round fractions up

_____ Time (*Hours/Days*)

Do not read:

- Don't know / Not sure
 Refused

6.25 How much time, if any, did a family member or friend have to take off from work to help you recover after you had this test?

Round fractions up

_____ Time (*Hours/Days*)

Do not read:

- Don't know / Not sure
 Refused

CATI note: If participant is pregnant; END OF THE INTERVIEW. This ends your 12-month follow-up interview. Thank you again for your participation with the Colon Cancer Family Registry.

HYSTERECTOMY

6.26 Have you had a hysterectomy in the last 12 months?

Read only if necessary: A hysterectomy is an operation to remove the uterus (womb).

- Yes
 No [Go to next section]

Do not read:

- Don't know / Not sure [Go to next section]
 Refused [Go to next section]

COST OF HYSTERECTOMY

6.27 How much time, if any, did you take off from work to have this surgery, and/or to recover after the surgery?

Round fractions up

____ Time (*Hours/Days*)

Do not read:

Don't know / Not sure

Refused

6.28 How long did you have to stay in hospital to have this surgery, and/or to recover after the surgery?

Round fractions up

____ Time (*Hours/Days*)

Do not read:

Don't know / Not sure

Refused

6.29 How far did you have to travel to have this surgery or any follow-up appointments?

Round fractions up

____ Distance (*Miles/Kilometers*)

Do not read:

Don't know / Not sure

Refused

6.30 How did you travel to have this surgery or any follow-up appointments??

Mode of transport

Do not read:

Don't know / Not sure

Refused

6.31 How many follow-up appointments did you have?

Number of appointments

Do not read:

Don't know / Not sure

Refused

6.32 Did you have any out-of-pocket expenses to have this surgery or afterwards and if so what were they?

Yes _____ [Record item and cost]

No

Do not read:

Don't know / Not sure

Refused

6.33 How much time, if any, did a family member or friend have to take off from work to assist you to have this surgery?

Round fractions up

_____ Time (*Hours/Days*)

Do not read:

Don't know / Not sure

Refused

6.34 How much time, if any, did a family member or friend have to take off from work to help you recover after you had this surgery?

Round fractions up

_____ Time (*Hours/Days*)

Do not read:

Don't know / Not sure

Refused

6.35 How much time, if any, did a family member or friend have to take off from work to help attend follow-up appointments following your surgery?

Round fractions up

_____ Time (*Hours/Days*)

Do not read:

Don't know / Not sure

Refused

This is the end of your 12-month genetic counseling follow-up survey. Thank you again for your participation.

APPENDIX F: Decliner Survey

1. Have you ever had genetic counseling? (By counseling we mean speaking with a provider about genetics. Questions about actually having a genetic test are different and come after these questions about genetic counseling.)

- Yes (Please continue just below.)
- No (Please go to question 2.)

I had genetic counseling with my

- Primary care provider
- Genetic counselor
- Geneticist
- Oncologist
- Nurse practitioner
- Other: Please specify. _____

Did they recommend that you pursue genetic *testing*?

- Yes (Please continue just below.)
- No (Go to question 3.)

2. I have chosen not to speak with a genetic counselor at CORE Family Studies / the Colon Cancer Family Registry or anywhere else because:

- It's not relevant to me when
 - I already know I have a low risk for cancer
 - I already know I have a high risk for cancer
 - I've already had cancer
 - I'm already getting appropriate cancer screening
- I'm worried that / about
 - this will have a negative impact on my health insurance
 - this will have a negative impact on my life insurance
 - I will not cope well with the test result
 - privacy and/or confidentiality issues surrounding genetics
 - emotional impact on myself
 - emotional impact on my family members
 - possible consequences for my future plans (starting a family, choice of career)
- There's no benefit
 - to me
 - to my family
- I don't have the time now to pursue genetic counseling
- I am not interested in genetic counseling at this time
- One or more relatives do not want me to participate

- I will wait for results from other family members before I pursue this for myself
- It was difficult to schedule or get an appointment with the genetic counselor
- Other, please specify. _____

3. Have you ever had genetic testing?

- Yes (Please continue just below.)
- No (Please go to question 4.)

What genetic testing was done?

- Lynch syndrome (MLH1, MSH2, MSH6, or PMS2 gene)
- MAP (MYH associated polyposis) (MYH gene)
- FAP (familial adenomatous polyposis) (APC gene)
- I don't remember
- Other _____

Did you get your results?

- Yes (Please continue just below.)
- No (Please go to question 2)

What were your results?

- I was found to have a disease causing mutation
- I was found to have a variant of unknown significance
- No mutation was found
- I don't remember
- Other _____

To your knowledge, what sample was used for your genetic testing?

- Blood
- Saliva or buccal swab
- I don't remember

Would you be willing to share your results with us by signing a consent form giving us permission to get a formal copy of that information?

- Yes (We will mail a consent form to you right away.)
- No (Go to question 2)

4. What were your reasons for deciding not to have genetic testing?

- It's not relevant to me when
 - I already know I have a low risk for cancer
 - I already know I have a high risk for cancer
 - I've already had cancer
 - I'm already getting appropriate cancer screening
- I'm worried that / about
 - this will have a negative impact on my health insurance

- this will have a negative impact on my life insurance
- I will not cope well with the test result
- privacy and/or confidentiality issues surrounding genetics
- emotional impact on myself
- emotional impact on my family members
- possible consequences for my future plans (starting a family, choice of career)

- There's no benefit
 - to me
 - to my family

- I don't have the time now to pursue genetic counseling
- I am not interested in genetic counseling at this time
- One or more relatives do not want me to participate
- I will wait for results from other family members before I pursue this for myself
- It was difficult to schedule or get an appointment with the genetic counselor
- Other, please specify. _____

Thank you for taking the time to complete this survey.

Please remember you can contact us at any time if you change your mind about wanting genetic counseling.

APPENDIX G: Interview Guide: Seattle C-CFR Participants

The Return of Genetic Results in the Context of an International Colon Cancer Family Registry

INTERVIEW GUIDE: SEATTLE C-CFR PARTICIPANTS May 21, 2013

INTRODUCTION

Thank you very much for taking the time to speak to me about your experience of receiving or declining genetic test results generated from your participation in the registry. This study is specifically interested in learning more about the factors that led to your decision making, as well as what you have chosen to do with any information you might have received.

Your participation in this interview is voluntary. You can refuse to answer any questions, and end this interview at any time. I will digitally record the interview to enable in-depth analysis for the study. These recordings will not be shared with anyone outside of the study staff and all transcribed data will be anonymized and secured.

Does that all sound reasonable? Do you have any questions before we begin?

SECTION 1: Respondent's Involvement with the Colon Cancer Family Registry

To get us started, I would like to ask a little bit about your participation in the Fred Hutchinson Colon Cancer Family Registry.

1. Could you tell me what you remember about how you were recruited?
2. Do you know if other members of your family recruited as well? What was this experience like for you?
3. About how long ago were you contacted to learn research results based on your participation in the registry? What was your experience when you were initially contacted?

Thank you for sharing this information. It is very helpful. Now, I am going to ask you questions specifically about your experience regarding the Return of Results.

SECTION 2: Decision-Making Process

4. Can you please describe how you came to decide that you wanted to know (or not know) your genetic research results? Would you say that this was an easy or hard decision for you?
 5. What would you say were the main reasons that you made that decision? Can you please say a little bit more about that?
 6. What was this experience like for you? Can you say a little bit more about that?
-

SECTION 3: Familial and Health Care Provider Communication

7. Did you share your results with any of your family members? If yes, with whom did you share your findings and why did you choose to share with them? If no, why did you choose not to share the information?
 8. What was the experience of sharing your results with specific family members like for you? Was it easier to tell some family members but not others? How so?
 9. Did you share your results with any of your health care providers? If yes, what made you choose to share your findings with him or her? If no, what are the reasons why you have not shared ?
-

SECTION 4: CLIA-Confirmation of Research Results

10. Did you have your research results confirmed in a CLIA-compliant laboratory?
 - a. If yes, what was that process like? Did a genetic counselor facilitate this or did your health care provider order the testing?
 - b. If no, why did you decide not to pursue confirmation?
 11. Did you share with more/different family members after receiving confirmation of your registry findings?
-

SECTION 4: Cancer Screening Recommendations

12. What specific recommendations were made for you following result confirmation?
 13. Did you pursue additional cancer (or much earlier) screenings?
 14. Did you make any specific lifestyle or dietary changes upon learning your results?
 - a. If yes, what are some of the things you are doing now?
 - b. In no, do you plan to make any lifestyle or dietary changes based on the results in the future? What do you think has prevented you from making these changes thus far?
-

WRAP-UP

Thank you very much for your time today.

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