

THE PSYCHOSOCIAL AND BEHAVIORAL IMPACT OF GENETIC TESTING FOR
LYNCH SYNDROME

by

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Abstract

The focus of this doctoral research was to investigate the long-term psychosocial and behavioral implications of genetic testing for and living in families with Lynch syndrome (LS). A primary purpose of the research was to develop a clinical monitoring tool capable of assessing psychosocial adjustment and conduct a psychometric evaluation of the Psychosocial Adjustment to Hereditary Diseases (PAHD) scale. This dissertation consists of five chapters including an introductory and discussion chapter. The middle three chapters focus on the long-term psychosocial and behavioral adjustment to LS and development of the PAHD. Collectively, the studies and resulting manuscripts constitute a thesis that forms the basis for an ongoing and future program of research for monitoring adjustment to hereditary diseases.

Adjustment to the presence of hereditary cancer is best described as an evolving state that ebbs and flows in response to changing personal and family experiences in the management of long-term cancer risk and emergence of cancer in the self and/or others. The findings indicate that both carriers and non-carriers experience long-term personal and family challenges in living with the presence of LS. In fact, the findings suggest that the management of LS has implications for many individuals and families that extend well beyond the initial genetic testing event. The results also suggest the importance of personal resources and the family context in facilitating or impeding adjustment. Importantly, a confirmed presence of LS requires lifelong cancer screening and/or

surveillance to reduce morbidity and mortality. Therefore, it is crucial to assess how individuals and families are adjusting to hereditary cancer in the long-term.

Psychometric testing of the PAHD scale was based on the work of Ware and Gandek (1998). Steeped in the experiences of those living in families with LS, the PAHD was found to be a psychometrically sound scale that is capable of assessing psychosocial adjustment. Preliminary findings support the convergent, discriminant and construct validity of the subscales. It is concluded that the PAHD may be a valuable monitoring tool to identify individuals and families who may require therapeutic interventions.

The findings have implications that can be utilized to enhance the clinical management of individuals and families with LS. Individuals living in these families may need supportive interventions to effectively manage their cancer risks and minimize adjustment difficulties. From a policy perspective, resources are needed to enhance the coordination, continuity and provision of health care services that promote optimal health functioning and a quality of life. The familial and lifelong nature of LS necessitates long-term resources to ensure availability and accessibility of interventions that result in improved health outcomes.

Dedication

This dissertation is dedicated to my father, the late Gordon Roy Watkins, whose incredible work ethic, integrity and sense of humor have inspired me throughout life.

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List of Abbreviations

ARVC	Arrhythmogenic right ventricular cardiomyopathy
BAHD	Behavioral Adjustment to Hereditary Diseases
BK	Burden of Knowing
BMI	Body Mass Index
CIHR	Canadian Institutes for Health Research
CRC	Colorectal cancer
FC	Family Connectedness
FCCTX	Familial colorectal cancer type – x
GC	Genetic counselor
GT	Genetic testing
HD	Huntington’s Disease
HD-GT	Hereditary Diseases and Genetic Testing
HD-PBA	Hereditary Diseases – Psychosocial and Behavioral Adjustment
HGP	Human Genome Project
HNPCC	Hereditary non-polyposis colorectal cancer
KMO	Kaiser – Meyer – Olkin
LS	Lynch syndrome
MAP-R	Multitrait/Multi-item Analysis Program – Revised
MICRA	Multidimensional Impact of Cancer Risk Assessment
MMR	Mismatch repair

NFCCR	Newfoundland Familial Colorectal Cancer Registry
NL	Newfoundland and Labrador
PAGIS	Psychological Adaptation to Genetic Diseases Scale
PAHD	Psychosocial Adjustment to Hereditary Diseases
PMGP-NL	Provincial Medical Genetics Program of Newfoundland and Labrador
RHA	Regional Health Authority
SMOG	Simple Measure of Gobbledygook

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List of Publications

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Papers

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Abstracts

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CHAPTER 1

Introduction

The Human Genome Project (HGP) and rapid developments in genomic medicine have provided individuals with genetic risk information that can identify susceptibility to many health alterations. In fact, genetic predisposition has become a significant determining factor of chronic diseases and disability [1]. The identification of causal genes responsible for adult-onset diseases such as cancer, neurodegenerative disorders and heart disease have enabled individuals and families to determine their level of risk.

Depending on the clinical trajectory of the disease, knowledge of genetic predisposition can offer potential benefits. It can facilitate health care decisions, motivate behavior change and, in some cases, individualize presymptomatic and/or prophylactic treatments [2]. While this new genetic knowledge can offer possibilities for health promotion and early interventions, it can have a lifetime of consequences for those identified as living “at-risk”. A confirmed genetic link to disease can bring much uncertainty to families as individual members face many unknowns and deal with an often unpredictable and evolving disease state.

In recent years, ongoing gene discovery has resulted in the confirmation of various hereditary cancer syndromes and an increasing research base on the implications of having a genetic link to cancer. Living with lifelong cancer risk requires psychosocial and emotional adjustment as well as behavioral change. Importantly, identifying individuals at risk for cancer could facilitate targeted screening, health promotion and prevention strategies, early interventions and quality outcomes.

The focus of the research addressed in this dissertation is on the psychosocial and behavioral implications of living in families with a confirmed presence of hereditary cancer, specifically Lynch syndrome (LS). A primary purpose of the overall program of research was to develop clinical monitoring tools that are capable of assessing the impact of the genetic testing process and long-term psychosocial and behavioral adjustment. A focus of this researcher's doctoral work was to conduct a secondary analysis of a qualitative data base for the purpose of identifying the psychosocial and behavioral implications of living in families with LS. A second focus was to develop and conduct preliminary testing of the Psychosocial Adjustment to Hereditary Diseases (PAHD) scale.

This dissertation is presented in a manuscript format with an introductory chapter and a final chapter acting as bookends to the three manuscripts (chapters 2, 3, and 4). Chapter 1 provides the reader with an introduction to the research, including the rationale and background information on the program of research. It also provides an overview of the team's research to date and this researcher's role as part of the research team. Chapter 2 presents the qualitative findings on the long-term emotional and psychosocial impact of LS for carriers and non-carriers. Chapter 3 details the various phases and steps involved in the development and preliminary testing of the PAHD scale. Chapter 4 summarizes the second qualitative paper on how carriers of LS experience disease management and view the quality of interactions with health care providers and the overall health care system. Chapter 5 presents a general discussion of the findings and implications for clinical practice, policy and research.

Background and Rationale

The discovery of a genetic marker for Huntington's disease (HD) in 1983 facilitated the use of linkage analysis to identify carriers and non-carriers of a genetic-based disease [3]. Subsequently, the identification of the gene mutation for HD in 1993 led to the development of genetic testing protocols within a multidisciplinary framework that included careful consideration of potential negative outcomes [4]. These discoveries prompted an expanding research base on the implications of genetic testing and living with knowledge of disease risk.

Several authors emphasize the need to understand the long-term psychosocial, emotional and behavioral implications of harbouring a genetic predisposition [2,3,5]. In particular, health care providers must have knowledge of the complexities of living with a genetic-based disease so that clinical practice can be informed when planning care for those affected [2,6]. Further, hereditary disease is a family matter with significant implications for all members [2,7]. It is essential to understand how families are burdened by hereditary disease and develop a more familial approach to genetics-based health care [2,8].

One disease with a confirmed genetic link is colorectal cancer (CRC). As the second leading cause of cancer deaths in Canada, CRC is of significant concern to all Canadians. It is of particular interest in Newfoundland and Labrador (NL) as this province has the highest incidence of CRC in Canada [9,10]. In fact, the age-standardized incidence rate in

2010 was reported to be 138 cases per 100,000, which was 36% higher than the Canadian average of 102 cases per 100,000 [9]. About 95% of the NL population (517,000) can trace their origins to either Southeast Ireland or Southwest England, thus limiting its ethnic and racial diversity [10].

A major form of inherited CRC is hereditary non-polyposis colorectal cancer (HNPCC). Families with HNPCC meet the Amsterdam criteria (Appendix A) which were originally devised in 1991. HNPCC is considered to be present if at least three family members in two generations had CRC, one affected person was a first degree relative of the other two, and at least one affected individual was diagnosed before 50 years of age [11]. The Amsterdam I criteria were revised in 1999 (Amsterdam II criteria) to include some of the extracolonic cancers associated with HNPCC [11]. Lynch syndrome represents a subset of HNPCC with most tumors evidencing microsatellite instability but molecular testing is required to document the presence of a DNA mismatch repair (MMR) gene mutation (i.e., MSH2, MLH1, MSH6, PMS2) [10,12,13]. MSH2 and MLH1 account for nearly 50% and 40%, respectively, of the mutations associated with LS. MSH6 accounts for 7-10% while PMS2 is found in less than 5% of the alterations [14]. The underlying gene defect for LS was discovered in 1993 facilitating the availability of genetic testing for known mutations [15].

Evidence indicates that there may be differences in cancer risks for mutation carriers depending on gender and the LS genotype. When compared to females, male carriers

with MSH2 and MLH1 mutations have a higher risk of CRC [13], a finding that is supported in those with a MSH2 mutation in the NL population [16]. MSH2 mutations are associated with a higher risk of extracolonic cancers [17], especially endometrial [17], ovarian [18] and urological tumours [19,20,21], when compared with mutations in the other MMR genes. Those with a MLH1 mutation seem to present with less extracolonic cancers and an excess of CRCs, when compared with the MSH2 type [17,22]. Individuals with a MSH6 mutation appear to have a milder clinical phenotype with a later onset of CRC but an increased incidence of endometrial carcinoma [17,21,23]. Finally, the cancer risks in individuals with a PMS2 mutation remain largely unknown [24] but there does seem to be a later age onset of CRC in those families [19].

Lynch syndrome accounts for approximately 1-3% of all cases of CRC worldwide [21]. In NL over 50% of incident CRC cases come from high- and intermediate-risk families, of which 2.7% have LS [25]. In addition to LS, an heterogeneous group of families, labeled familial colorectal cancer type-X (FCCTX), fulfill the Amsterdam criteria but do not evidence microsatellite instability in tumors or have known MMR mutations [11]. Similar to what has been reported by others [13,26], FCCTX accounts for a high proportion of HNPCC in the NL population [10].

Confirmation of LS means that all family members are encouraged to undergo predictive testing and/or follow recommended cancer screening. Regardless of carrier status, evidence suggests that the presence of hereditary cancer can have psychosocial,

emotional and behavioral impacts for all family members. Despite a growing number of studies, the full extent and specifics of these impacts are still unknown. A confirmed presence of hereditary cancer can bring much uncertainty to families as members face the realities of whether, when and where cancer will develop. When cancer does emerge, the indeterminacy of its treatment and outcome can have far-reaching emotional and psychosocial consequences for the entire family. Some studies have highlighted the strain hereditary disease can place on the family and its members [27,28].

To date, the focus of research efforts has been on the psychosocial implications of genetic testing with less emphasis on living with and managing cancer risk and/or cancer over the lifespan. The conclusion of meta-analyses and literature reviews is that genetic testing for hereditary cancer causes minimal psychological consequences [5,8,29,30]. Despite this, some quantitative evidence indicates that a subgroup of individuals experience difficulty in adjusting [1,31,32]. Further, qualitative findings suggest that certain individuals have difficulty adjusting in the short- and long-term following confirmation of genetic predisposition [27,33-36].

An important contextual factor that seems to buffer the impact of hereditary cancer on family members is strong and open communication patterns [28,37]. Currently, researchers and theorists are placing more emphasis on exploring how variations in the family context may impact short- and long-term adjustment for those at risk for hereditary cancer [2,37-41]. Importantly, it is suggested that individuals with greater

social supports and who belong to families with open communication may have less psychosocial distress [28,42,43] and adjust better over the long-term [44].

Given its high cancer risks, LS has important behavioral implications. Evidence indicates that individuals can benefit from highly targeted screening and management strategies [45,46]. Colonoscopy screening, the only surveillance protocol in LS deemed to be effective [45], can reduce CRC-mortality by detection and removal of adenomas, the precursor of most CRCs [47]. In the NL population, colonoscopy screening prevented CRC and delayed the age of onset by more than 10 years for both male and female LS carriers [46]. Findings indicated an improvement in life expectancy of more than 15 years for females and four years for males [46]. Despite the documented benefits of colonoscopy screening in reducing CRC-mortality, morbidity related to the management of LS is a concern. Colonoscopic screening can result in serious adverse events such as perforation and bleeding [48,49] and less serious complications such as abdominal pain and bloating [48], all of which could be barriers to long-term, regular screening and/or surveillance.

For female carriers of LS, the risk of developing endometrial cancer is high and can equal or exceed the risk of CRC [21]. Despite the lack of evidence-based data on the survival benefit of screening for endometrial and ovarian cancer, some recommend annual transvaginal ultrasound and endometrial biopsy starting at age 35-40 years [21]. Others propose this annual screening start earlier at 30-35 years of age [13,50]. The authors of

the NL study concluded that screening did not result in earlier detection of gynecological cancers [51]. What is proposed is a hysterectomy and oophorectomy once childbearing is complete, particularly after the age of 40 [21].

LS also predisposes at-risk individuals to extracolonic cancers such as gastric, small bowel, urinary tract and pancreatic. A recent study concluded that 61% of cancer deaths in LS were related to non-CRC and non-endometrial cancers [52]. While some authors propose regular screening for mutation carriers with a family history of gastric, small bowel and/or urinary tract cancers [53], recently revised guidelines suggest that surveillance for these cancers should only be performed in a research setting as the benefits remain unknown [21]. However, some authors maintain that cancer screening be tailored to the extracolonic expression history of the specific LS mutation [24].

Even though individuals with LS have to make important decisions about screening and disease management, only a limited number of studies have identified behavioral adjustment in the post-genetic testing phase as an important area for research inquiry [2,5,29,30,54,55]. In addition, most of this research is quantitative and more focused on screening adherence rates than barriers to and/or facilitators of timely access to recommended screening and follow through from diagnostic testing to treatment and ongoing surveillance. There is some qualitative evidence which suggests that the health care system itself can be a significant barrier to individual and family willingness and ability to follow recommended protocols for LS. Specific reference has been made to

challenges such as ineffective coordination, non-person centered care, limited provider knowledge and expertise, and inadequate provider/clinician communication skills, among others [36]. A recent review on colonoscopy screening in primarily average risk populations concluded that challenges with the bowel preparation, lack of knowledge about the importance of CRC screening and practical issues (e.g., transportation, costs, scheduling) are major barriers to participation [55]. The authors also suggested that a positive attitude towards screening, physician recommendation and having a family history of CRC facilitate screening [55].

What also remains unclear is how psychosocial, emotional and familial factors impact health-related behavior following confirmation of risk. There is some evidence to suggest that psychological distress may interfere with an individual's ability to adhere to recommended disease management strategies [56,57]. Findings from a study of carriers of LS found that those who did not undergo a colonoscopy within six months following genetic test results were six times more likely to have depressive symptoms compared to those who did participate in screening [58]. These results suggest that cancer screening may facilitate adaptation to living with LS and may moderate emotional distress [58]. It is also conjectured that individuals living in supportive families with open communication are more likely to follow recommended protocols [59-62]. Clearly there is a need to further assess whether psychological and familial factors are impacting an individual's ability to manage LS over time.

Perceptions of risk have been another area of research focus in relation to hereditary cancer. Some authors have suggested that awareness of familial cancer patterns, personal/family experiences with cancer and communication within the family influence risk perceptions. Risk perceptions could then in turn impact behavioral adjustment to the disease, particularly recommended screening and health promotion strategies [63,64]. A recent review on risk perceptions in high-risk populations concluded that psychosocial factors such as worry, distress and depression were consistently associated with perceptions of risk [65]. The authors also indicated that worry could influence screening behaviors [65].

Summary

While there is an expanding research base on the psychosocial implications of genetic testing and a confirmed presence of hereditary cancer, less is known about psychosocial and behavioral adjustment in the long-term. Given the uncertainty of when and where cancer could develop and the necessity of adhering to screening protocols and/or cancer treatment and surveillance, adjustment may be influenced by multiple, interacting factors. Furthermore, the familial nature of LS can result in implications for the entire family. Currently, there is a paucity of research on the roles played by family dynamics, communication and support in influencing adjustment. While screening behavior adherence rates have been explored, little is known about whether they are maintained over time or how personal, health care provider and system factors facilitate or impede

adherence. Finally, there is a dearth of literature on whether psychosocial and emotional factors influence adherence to recommended disease management strategies.

Program of Research

The intent behind this section is to provide the reader with an insightful overview of the research program to date. The program of research, from which the doctoral work emerged, was comprised of several empirical studies. The studies were components of a multiphase program of research funded by the Canadian Health Services Research Foundation, the Canadian Institutes for Health Research (CIHR) through the Colorectal Cancer Interdisciplinary Health Research Team at the University of Toronto and Memorial University and the Atlantic Medical Genetics and Genome Initiative, funded by Genome Canada.

As an initial step to facilitate a program of research on CRC, the Newfoundland Familial Colorectal Cancer Registry (NFCCR) was established in 1999 [10], which served as a major infrastructure component for all subsequent CRC research. The multiphase program of research across Newfoundland and Labrador and Ontario aimed to advance knowledge about the determinants, impact and control of familial colorectal cancer. Phase I (2000-2008) of the research entitled “*Interdisciplinary Studies of the Determinants, Impact and Control of Colorectal Cancer: A Genetic-Epidemiological and Population-Based Approach*” consisted of infrastructure development, research projects, capacity (training) building and knowledge translation. Phase II (2006-2011), entitled

“CIHR Team in Interdisciplinary Research on Colorectal Cancer”, was designed to build on Phase I findings and focused on the impact of genetic and non-genetic factors on CRC etiology, clinical outcomes, screening and psychosocial functioning. As part of the Phase II funding this researcher received a CIHR studentship (2006-2007) and, from September 2006 onward, was an active and contributing member of the interdisciplinary research team.

As part of the larger interdisciplinary research team, team members took a leadership role in systematically examining the psychosocial, emotional and behavioral impact of participating in genetic testing for and living with hereditary cancer. The principle driver behind the current research agenda was to explore individuals and families experiences with a high cancer presence and confirmation of a hereditary link, and to highlight care needs, as well as potential/actual barriers to necessary health care services. The overarching objective was to use findings from both quantitative and qualitative studies to identify modifiable factors that could be potential targets of innovative strategies to improve disease prevention and management. The target outcome was to develop a framework to guide the delivery of clinical genetics services in the province’s four regional health authorities (RHAs). It was anticipated that such a framework would help clinicians involved in various aspects of the cancer care continuum to better determine individual and family needs and preferences and to use this information to deliver timely and appropriate care.

Phase I

The team's research in Phase I consisted of a quantitative and qualitative study. The *first* study under Phase I, "*Psychosocial and Behavioral Impact of Predictive DNA Testing for Hereditary Non-Polyposis Colorectal Cancer (HNPCC)*" was conducted in 2004. Ethics approval for the full study and consent protocol were received in July 2003 (Appendix B). The primary objective of the quantitative study was to systematically investigate the psychosocial and behavioral impact associated with genetic counseling/testing for hereditary non-polyposis colorectal cancer, also known as LS. The study involved a quantitative survey, using standardized and researcher-developed scales, of 120 carriers and non-carriers of LS who were accrued from a population-based registry in NL.

The target population was individuals from high risk families who were referred to the Provincial Medical Genetics Program of Newfoundland and Labrador (PMGP-NL). Eligible participants for the study were in families who had participated in predictive DNA testing and received confirmation of a MSH2 mutation on intron 5 and exon 8 [16]. With the exon 8 mutation identified more recently (early 2000's) than the intron 5 mutation (early 1990's), there was a larger cohort available from the latter group for research purposes when data collection commenced in 2004. Details on the sampling plan for this study are outlined in Appendix C.

Preliminary analysis of the quantitative study results indicated that insufficient information was available on the psychosocial and behavioral impact of genetic testing

on individuals living in families with hereditary colorectal cancer. In summary, the findings provided the research team with limited insight into the role played by variant/similar family contexts and personal experiences in motivating individuals to become involved in genetic testing for LS, in shaping perceptions of the process and reactions to test results, and in facilitating or hindering adjustment to a being a carrier or non-carrier.

The *second* study under Phase I was a two-stage qualitative study (2004-2007) designed to clarify and augment quantitative findings. Ethics approval for the study and consent protocol were received in April 2004 (Appendices D and E). The main objectives of the “*Psychosocial and Behavioral Impact of Predictive DNA Testing for Hereditary Non-Polyposis Colorectal Cancer (HNPCC)*” were to explore individual and families’ experiences with cancer, reactions to and communications around being informed about the potential hereditary basis for the familial cancer, experiences with genetic testing, and psychosocial and behavioral outcomes in the short- and long-term following genetic testing. A second aim of the study was to determine the clinical services (genetic counseling, screening/surveillance, therapies and interventions) needed by individuals and families residing in each of the provinces’ four RHAs and highlight barriers to care. The long-term goal was to develop useful strategies for removing/modifying perceived/actual barriers to clinical genetic services and healthy living (illness prevention/health promotion behaviors).

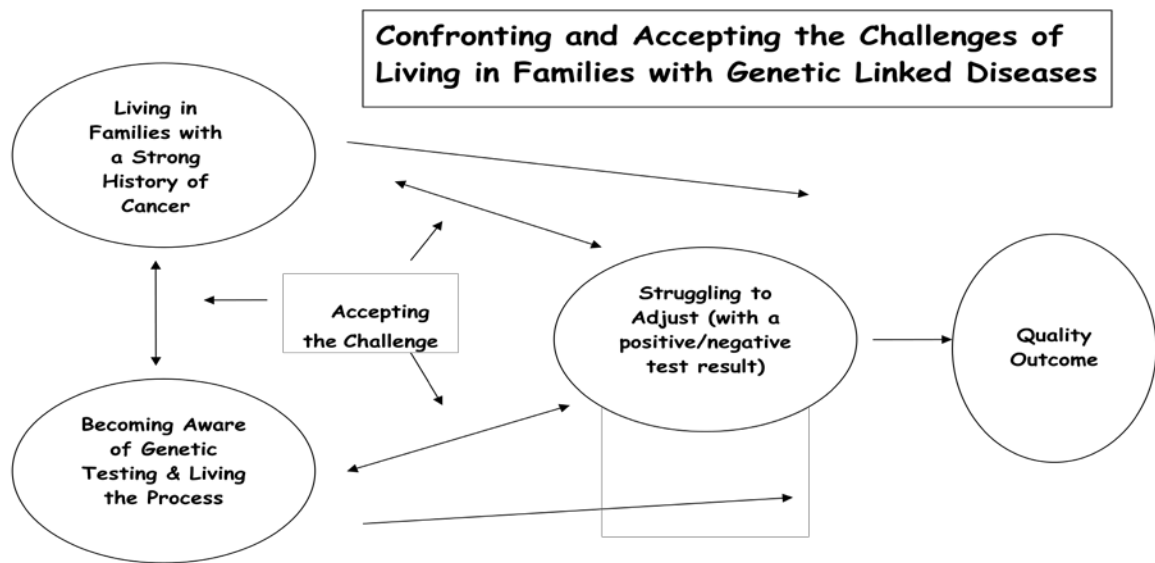
This study used a grounded theory approach to data collection and analysis. In this instance, common perceptions shared by individuals in families with LS were explored. The inductive approach to studying phenomenon is focused on generating as opposed to testing theory and, as conceptualized by Glaser and Strauss (1967) [66], substantive theory is seen as emerging from a substantive area of inquiry. The strength of this approach is that the interest is not on merely describing how individuals experience a particular phenomenon but rather how information is received and assimilated into existing belief structures in a way that it becomes a stimulant for desired behavior. It was also conjectured that by using a grounded theory approach to data collection relevant theoretical constructs would be identified and developed in such a manner that quantitative measures could subsequently be generated to measure them. In grounded theory, theoretical sampling is an important tool for data collection and analysis. This form of sampling involves the deliberate selection of participants based on their experience with the area of interest and the needs of the emerging theory [67]. Details on the sampling plan for the qualitative study are provided in Appendix C.

The majority of these participants were from families with the intron 5 splice site of the MSH2 gene and had participated in genetic testing eight to ten years prior to being interviewed. With the identification of an additional MSH2 mutation, exon 8 deletion, family members were now available to be interviewed closer to the time of genetic testing. Stage two of the qualitative study involved using a modified grounded theory approach, designed for a Masters thesis, and was conducted with an additional seven

individuals from families with the exon 8 deletion [68]. The purpose of the study was to augment the conceptualizations of the constructs generated in stage one of the study. The findings supported the proposed constructs and indicated that living in a family with a strong history of cancer shaped personal beliefs, risk perceptions and emotional readiness for genetic testing. While acknowledging the helpful support received from genetics personnel, the real work of emotionally adjusting to the results of genetic testing occurred at the individual and family levels. Personal and family challenges in managing LS interfered with the psychosocial and emotional adjustment of both carriers and non-carriers. Being open to and having family support emerged as being significant. Interactions with health care providers and the system also had implications for the psychosocial, emotional and behavioral adjustment of individuals and families.

The substantive theory, “*Confronting and Accepting the Challenges of Living in Families with Genetic-Linked Diseases*” (see Figure 1.1), was generated from both qualitative data bases from interviews with carriers and non-carriers in LS families. The theory broadly conjectures that the situational and experiential contexts defining familial cancer are important forces influencing how well individuals accept the hereditary link to cancer, are motivated to become involved in genetic testing and adjust to their carrier or non-carrier status in the short- and long-term. The psychosocial and behavioral processes captured by the theory suggest three major constructs: (a) living in families with a strong history of cancer, (b) becoming aware of genetic testing and living the process, and (c) struggling to adjust.

Figure 1.1: Confronting and Accepting the Challenges of Living in Families with Genetic-Linked Diseases



The first construct, *living in families with a strong history of cancer*, describes the phase prior to genetic testing for LS. It provides insight into the relevancy of the family context for shaping cancer risk perceptions and, ultimately, preparing family members for becoming involved in genetic testing. It depicts what it is like to live in families where there is an ominous presence of cancer and to eventually awaken to the idea that the cancers could be hereditary.

The second major construct, *becoming aware of genetic testing and living the process*, provides insight into a complex process that individuals living in high risk families are

required to navigate to confirm their LS status and provide guideposts for future actions. It outlines how family members decide to become involved in genetic testing, react to being informed about their carrier status, perceive the supportiveness of genetics personnel, understand their risk and are willing to communicate genetic testing findings within and outside the family network. The degree of involvement in the genetic testing process is heavily influenced by how well individuals understand their risk for LS, accept the utility of genetic testing for confirming that risk, are willing to assume the psycho-emotional repercussions in the short- and long-term, and feel supported by members of formal and informal networks.

The third construct, *struggling to adjust*, focuses on the psychosocial, emotional and behavioral adjustment in LS families in the short- and long-term post-genetic testing. Adjustment is best defined as an evolving process that ebbs and flows in response to changing personal and family experiences in the management of long-term cancer risk and emergence of cancer in the self and/or others. Personal characteristics (e.g., attitudes, beliefs, practical knowing based on prior experiences, openness to knowing the implications of LS) and the family environment (e.g., supportiveness, availability of resources, dynamics, communication patterns) interact to influence psychosocial and emotional adjustment. Psychosocial and behavioral adjustments also waver in response to evolving experiences and critical events (e.g., personal and family challenges, progression to affected states, the suffering and early deaths of affected relatives). Finally, adjustment is influenced by interactions with health care providers/system,

particularly in relation to screening/treatment, and ease of access to a supportive health care system (meaningful information, timely screening/treatment, psychosocial supports). These experiences can act as barriers to or facilitators of adjustments. The construct focuses on the personal and family challenges of managing LS over time, the importance of openness and support within the family, dealing with recommended screening/treatment and health care providers/system, and managing risks for younger family members.

The first two constructs, *living in families with a strong history of hereditary cancer and becoming aware of genetic testing and living the process*, are conjectured to exert a direct impact on each other and a direct and indirect impact on struggling to adjust. It is also proposed that accepting the challenge is the unifying thread that links the constructs, signifying that a change in one area has repercussions for other areas. Finally, all three constructs are believed to exert a direct impact on quality outcome, which is seen as an evolving state. The third construct, *struggling to adjust*, is also conjectured to mediate the effects of living in a family with a strong history of cancer and becoming aware of genetic testing and living the process on quality outcome.

Phase II

In Phase II of the program of research a proposal for psychometric testing was successfully submitted to CIHR for funding as part of the larger research project “*CIHR Team in Interdisciplinary Research on Colorectal Cancer*” (CIHR # - FRN-79845)

(2006-2011). The sub-project, “*Psychometric Testing of Scales for Monitoring the Psychosocial and Behavioral Impact of Genetic Testing for Hereditary Non-Polyposis Colorectal Cancer*” (2008-present), was designed to build on the previous quantitative and qualitative studies. Ethics approval for the study and consent protocol were received in February 2008 (Appendices F and G). The target population for this study was individuals at 50% risk for inheriting LS who had participated in predictive DNA testing and were informed of their carrier status. The participants were recruited from population-based probands comprising the PMGP-NL.

Immediately prior to the study, 272 carriers and 295 non-carriers had been confirmed from the PMGP-NL and entered into a Cancer Screening Data Base. This data base was developed for a component of the larger study which retrospectively profiled the actual screening practices of carriers and non-carriers following genetic testing. The rationale for using this data base was that actual screening practices will be, ultimately, linked to the psychosocial and behavioral self-report data obtained over time following confirmation of the psychometric properties of the monitoring tools.

At the time of the study, the information available on registrants comprising the Cancer Screening Data Base was reviewed to identify potential participants. Registrants excluded from consideration included those who did not have a confirmed carrier status (i.e., obligate carriers, presumed positive, or inconclusive results with unknown risk), had not participated in genetic testing, had died since their name was entered into the data base,

had no contact information, or had refused to be contacted for research purposes. Details on the sampling plan for this study are provided in Appendix H.

Relying on the qualitative study data, the research team used the operational indicators comprising the descriptors of each property defining each category of the substantive theory to draft several scales. The first two constructs, *living in families with a strong history of hereditary cancer and becoming aware of genetic testing and living the process*, of the model were used to develop the Hereditary Diseases and Genetic Testing (HD-GT) scale which is capable of assessing experiences prior to, during and immediately following genetic testing. Comprising the research for a Masters thesis [69], the HD-GT was piloted tested in 75 carriers and non-carriers of LS (Appendix H).

Psychometric testing of the HD-GT scale was based on the work of Ware and Gandek (1998) [70]. Preliminary findings indicated good data quality and potential usability of the scale under variant administrative conditions. All of the HD-GT subscales met the criteria for Likert scaling assumptions (i.e., approximate equivalence of means and variances, use of all response choices in the rating scale, amount of missing data, approximate symmetry in response distribution, linearity, item-convergent validity and item-discriminant validity) and evidenced very good reliability and validity. The various subscales of the HD-GT augmented what has been reported in the literature and provided new insights into the psychosocial impact of genetic testing for individuals and families with LS. Study findings suggested that a family history of cancer does have a significant

impact on decision-making regarding genetic testing. There were also indications that study respondents placed high value on having all potentially at-risk family members participate in genetic testing, but were often challenged trying to convince them to accept the need for testing.

With regard to the genetic testing process, results indicated that most respondents placed high value on being emotionally prepared for genetic testing and having appropriate information, but not everyone required health care provider or family/friends support. As well, despite experiencing some emotional difficulty while waiting for test results, not everyone required support prior to and during the receipt of results. Finally, most family members wanted information about LS, and were perceived to understand it, but encountered some difficulties in communicating the information to other family members. In summary, study findings indicated that the subscales appeared to be sensitive enough to measure the wide-range of psychosocial implications of genetic testing.

Analysis of the third construct of the model, *struggling to adjust*, revealed two dominant themes – one focusing on psychosocial and emotional adjustment and the other on behavioral adjustment in LS families. The Hereditary Diseases-Psychosocial and Behavioral Adjustment (HD-PBA) scale was developed to measure psychosocial and behavioral adjustment and is divided into two scales. The psychosocial adjustment data matrix provided the content for item generation for the Psychosocial Adjustment to

Hereditary Diseases (PAHD) scale, designed to assess the personal and family burden of LS and the perceived role of family in buffering its impact. The behavioral adjustment data provided the content for the Behavioral Adjustment to Hereditary Diseases (BAHD) scale. This scale, which is currently being tested, is designed to assess the experiences with screening/treatment, perceptions of health care quality, management of children who are at risk and what is needed to promote effective disease management post-genetic testing.

Following pilot testing of all three scales in 2008, ongoing recruitment and data collection continued between July 2008 and July 2010. The HD-GT, PAHD and BAHD scales were administered to an additional 168 participants giving a final sample size of 243 (140 carriers and 103 non-carriers of LS) (Appendix H). Preliminary testing indicates that the HD-GT and PAHD are psychometrically sound, reliable and valid scales.

Program of Research for Dissertation

This section is intended to provide the reader with details on this researcher's personal contribution to the program of research and a clear distinction between individual and team effort. Upon joining the research team in 2006, this researcher was directly involved in: (a) analysis of the 2004 survey data for NL participants, (b) secondary analysis of the first two constructs of the substantive theory to collapse categories and generate items for the HD-GT, (c) development of a proposal for ethics review, and (d) pilot testing of the HD-GT and data analysis. As part of the CIHR studentship (2006-2007) and onward, this

researcher assumed the lead role for: (a) secondary analysis of the *struggling to adjust* construct of the qualitative data base, (b) using this data to develop two multidimensional instruments capable of assessing long-term psychosocial, emotional and behavioral adjustment to the presence of LS, and (c) the recruitment of additional participants, data collection and analysis for the psychometric testing of scales following the pilot study.

Rationale for Dissertation Research

In families with a confirmed LS presence, individual members have to deal with a complex disease which has multi-organ targets, variant familial trends with first cancer sites, highly variable potential onset times over the lifespan, and uncertain effectiveness of recommended screening/surveillance and treatment protocols. These evolving and, at times, challenging realities require individuals to adjust psychosocially, emotionally and behaviorally. Given the far-reaching psychosocial and emotional impacts for the entire family and behavioral implications for carriers, it is imperative that health care providers be able to assess short- and long-term adjustment to hereditary disease.

Living with and managing lifelong cancer risk requires adjustment on many levels to achieve quality outcomes. Therefore, clinical monitoring tools that can evaluate adjustment are needed. These tools must be able to: (a) determine the presence and pervasiveness of personal/family burden in the short- and long-term, (b) identify a supportive milieu and communication openness in families, (c) identify barriers to and facilitators of screening/surveillance, and (d) assess the interaction of psychological and

behavioral factors in determining outcomes (e.g., health-related quality of life, morbidity/co-morbidity, mortality).

Importantly, the clinical practice implications of this program of research are significant. Effectively managing LS with targeted, individualized screening and/or surveillance protocols are critical to quality health outcomes in this population. The provision of genetics services in primary health care must include support and resources for the entire family that go well beyond the immediate post-genetic testing period. A growing evidence base indicates that monitoring the short- and long-term adjustment of individuals is necessary in identifying those who may be experiencing challenges. Providing individuals with genetic testing results and information about recommended management protocols may be insufficient. Some individuals and families will need ongoing supports in dealing with psychosocial and emotional issues and assistance in accessing, coordinating and managing recommended screening/treatment.

Finally, the clinical monitoring tools developed will need to be incorporated in cancer genetics services at various points before, during and following genetic testing. This will allow the researcher to assess the clinical utility of the tools in identifying and assessing those at risk for poor psychological and behavioral outcomes. It is anticipated that the data gleaned from the monitoring tools can be used to inform health care interventions for individuals and families facing the confirmed presence of a hereditary disease.

Research Objectives

The specific research objectives guiding the dissertation work were as follows:

1. To explore the long-term psychosocial and emotional impacts of living in a family with a hereditary disease.
2. To explore the role of the family context in facilitating/impeding psychosocial and behavioral adjustment to LS.
3. To identify the facilitators of and barriers to screening and disease management in those with a confirmed mutation for LS.
4. To determine how facilitators of and barriers to screening can be augmented or addressed.
5. To develop items for the PAHD and assess its psychometric properties.

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Co-authorship Statement

Chapter 2

Dr. Christine Way and Dr. Mary Jane Esplen conceived and designed the study. Dr. Way and Jacqueline Fiander interviewed the participants. Dr. Way, Jacqueline Fiander, Dr. Robert Meadus, Valerie Ludlow and Kathy Watkins were involved in data analysis. Kathy Watkins and Dr. Way drafted the manuscript. Dr. Patrick Parfrey critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Chapter 3

Dr. Christine Way, Dr. Mary Jane Esplen, Dr. Deborah Gregory and Dr. Patrick Parfrey conceived and designed the study. Dr. Way, Kathy Watkins, Holly LeDrew and Valerie Ludlow constructed the items for the scales. Dr. Way, Kathy Watkins, Dr. Deborah Gregory, Holly LeDrew, Valerie Ludlow and Jeffrey Dowden were involved in data analysis. Kathy Watkins and Dr. Way drafted the manuscript. Dr. Deborah Gregory, Dr. Patrick Parfrey, Dr. Mary Jane Esplen, Holly LeDrew, Valerie Ludlow, Janet Cox and Dr. G. William Fitzgerald critically reviewed the manuscript for important intellectual content. All authors read and approved the final manuscript.

Chapter 4

Dr. Christine Way and Dr. Mary Jane Esplen conceived and designed the study. Dr. Way and Jacqueline Fiander interviewed the participants. Dr. Way, Jacqueline Fiander, Dr. Robert Meadus, Valerie Ludlow, and Kathy Watkins were involved in data analysis. Kathy Watkins and Dr. Way drafted the manuscript. Dr. Patrick Parfrey, Dr. Jane Green and Dr. Holly Etchegary critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

CHAPTER 2

Living with Lynch Syndrome: Beyond Genetic Testing

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Background: Lynch syndrome (LS) is an inherited cancer syndrome with high risks of colorectal and extracolonic cancers. With its familial nature and uncertain clinical trajectory, LS has significant implications for individuals as well as all family members. The objective of this paper is to examine the long-term psychosocial and emotional adjustment to LS for carriers and non-carriers.

Methods: A grounded theory study was part of a multiphase project examining the psychosocial and behavioral impact of predictive genetic testing for LS. Individual and small group interviews were conducted with 39 unaffected carriers, affected carriers and non-carriers from 15 families with the intron 5 splice site mutation or exon 8 deletion.

Results: The study highlights the long-term personal and family strengths/challenges for both carriers and non-carriers who have been living in families with hereditary cancer many years beyond the initial genetic testing event. The findings indicate that carriers and non-carriers in LS families have variant experiences that are influenced by diverse personal and familial factors that can act as facilitators of and barriers to adjustment.

Conclusions: Being at risk for LS is a condition that affects the individual and family with both requiring support over time. Genetic testing is one event along a continuum of lifelong disease management. The supportive and informative roles of genetic counselors and other health care providers, knowledgeable about managing LS, will be critical in promoting successful psychosocial adjustment and a reasonable quality of life.

Background

Hereditary non-polyposis colorectal cancer, also known as Lynch syndrome (LS), is an inherited cancer syndrome with significant risks of colorectal (CRC) and related cancers for carriers of the gene mutation. With an unpredictable clinical trajectory and the importance of engaging in lifelong preventive health behaviors, LS has the potential to impact the psychosocial, emotional and behavioral adjustment of entire families affected by this condition. The focus of this paper will be on the long-term psychosocial and emotional adjustment to LS for carriers and non-carriers.

Adjustment to the presence of hereditary cancer is defined as an evolving process that ebbs and flows in response to changing personal and family experiences in the long-term management of cancer risk and emergence of cancer in the self and/or others [1]. To understand adjustment in the short- and long-term it is necessary to examine a number of interactive factors defining it. Personal characteristics (e.g., attitudes, beliefs, practical knowing based on prior experiences, openness to knowing the implications of LS) and the family environment (e.g., supportiveness, availability of resources, dynamics, communication patterns) interact to influence psychosocial and emotional adjustment. Experiences with health care providers and the system can also interact with individual and family-based factors to influence behavioral adjustment to LS [2].

Confirmation of hereditary cancer can bring lifelong uncertainty to all family members [3,4]. Carriers are faced with a syndrome characterized by an 85-90% penetrance rate [5]

in the development of variant and, often multiple, colorectal and extracolonic cancers. Lifetime risk estimates for a cohort of families within Newfoundland and Labrador (NL) have been determined to hover around 98.2% and 92.8% for male and female carriers, respectively [6]. LS accounts for approximately 1-3% of CRC cases worldwide [7,8]. In NL over 50% of incident CRC cases come from high- and intermediate-risk families, of which 2.7% have LS [9].

Clustering of certain cancers in families [10], in addition to early age onset, compounds the complexity and uncertainty of the disease. For some individuals, the reality of living with LS over time can involve a multitude of experiences that deviate far from expected norms. Despite evidence suggesting that hereditary cancer risk can be burdensome, existing data provides limited insight into how psychosocial and emotional adjustment is influenced by the complex interplay of individual, familial and health care factors.

Furthermore, there is limited evidence on how psychosocial and emotional factors impact surveillance behaviors which are critical to effective disease management and reduced morbidity and mortality. While the benefits of colonoscopy screening have been demonstrated in the NL population [11] and others [12,13], there is a paucity of literature on the role played by psychosocial factors in facilitating or impeding adherence to recommended screening. The findings of one study examining the association between psychosocial outcomes and screening one month following receipt of genetic testing results suggest that those who fear dying soon tend to delay colonoscopy beyond the

recommended interval [14]. Qualitative evidence indicates that some individuals who feel burdened and overwhelmed in managing LS may take “time out” periods from recommended screening regimes [2].

One identified gap in research on hereditary cancer is the presence of useful and reliable information on long-term outcomes [3,15,16]. Several authors have emphasized the need to better understand the psychosocial, emotional and behavioral implications of harboring a genetic predisposition [14,17-19]. Quantitative studies focusing on short-term psychological outcomes post-genetic testing suggest minimal psychological impact [19-23]. Most of these studies used standardized instruments for data collection which have been criticized for their limited sensitivity in detecting psychological distress in at-risk, non-clinical populations [21,24] or fully exploring the diverse experiences influencing individual responses to hereditary cancer [25]. As well, most quantitative studies, to date, have been limited to short-term follow up of individuals (i.e., 1-12 months) without consideration of the familial context or long-term adjustment [26].

A recent review on the psychosocial impact of genetic testing for LS concluded that testing does not cause long-term distress in carriers unaffected with cancer but suggest that little is known about the impact on those who have developed cancer [27]. Given the earlier age of onset and emergence of variant cancers in LS, it is critical to conduct longitudinal studies so that experiences of those who develop cancer can be captured. To

fully understand the implications of living in families with LS, it is important to explore the lifelong experiences of carriers, affected and unaffected with cancer, and non-carriers.

Although it may be difficult to draw conclusions about the long-term psychosocial and emotional impact of hereditary cancer [3,16,20,28], there are indications that a small, but significant group of individuals experience adjustment difficulties and perhaps distress [27-30]. Some individuals may have difficulty adjusting to living with hereditary cancer in the short- and long-term [2,3,31-34].

A research area that has received limited attention is the role of the family environment in influencing adjustment to genetic-based diseases. There is evidence that the family context may impact individual well-being, risk perceptions and health behaviors [35], in that individuals with greater social supports and who belong to families with open communication may be less prone to experience psychosocial distress [30,36,37] and adjust better over the long-term [16]. As well, it has been suggested that older family members can support younger family members [38,39] and encourage them to follow recommended cancer screening [38], and women may assume the role of coordinator and support [32], particularly when communicating important information about genetic counseling and testing [40].

What these findings suggest is that reliance on individual-focused approaches to genetic counseling, without considering the family context, may be ineffective for long-term

management of genetic conditions, like hereditary cancer [3,26,36,41]. Personal and family resources have been shown to impact the psychosocial and emotional well-being of all members in the short- and long-term [4,23,24,28,35,42-44]. From a clinical perspective, it is imperative that we develop greater insight into how the family context impacts adjustment and use this information to develop a family-based approach to health care for individuals with genetic-based diseases [36,41].

The Present Study

The goal of the present study was to examine the long-term psychosocial and emotional adjustment to LS among carriers and non-carriers. This study is unique because, to date, there is limited data available on both carriers and non-carriers who have been living with cancer risk within the self and/or others for many years beyond the initial genetic testing event. To our knowledge, this is the first study to provide adjustment data for carriers, affected or unaffected with cancer, and non-carriers for several years following confirmation of hereditary cancer (Table 2.1). The study highlights the long-term personal and family challenges for both carriers and non-carriers living in families with hereditary cancer, as well as the facilitators of and barriers to adjustment.

Table 2.1 Participant characteristics (N = 39)

<i>ID</i>	<i>Family</i>	<i>Gender</i>	<i>Post-GT^a</i>	<i>Age^b</i>	<i>Carrier</i>	<i>Onset Age</i>	<i>Cancer Types^c</i>
23	1B	Female	6.42	57	Yes	---	---
24	1B	Female	6.42	78	Yes	46	CRC/EC
25	1B	Male	8.50	52	Yes	42	CRC/GA
26	1B	Female	2.42	32	Yes	---	---
31	1B	Male	7.50	47	Yes	45	CRCx2
8	1C	Male	3.67	28	Yes	---	---
22	1C	Male	6.50	26	Yes	---	---
30	1C	Male	7.42	57	Yes	---	---
2	2A	Male	7.83	38	No	---	---
7	2A	Male	8.33	37	No	---	---
9	2A	Female	8.08	41	Yes	39	CRCx2
32	2A	Female	9.58	69	Yes	35	CRCx2/EC/GA/SK
20	2B	Female	9.08	50	Yes	33	EC/BR/VA
21	2C	Male	9.08	50	Yes	---	---
6	2D	Female	6.92	53	No	---	---
15	2E	Female	2.75	78	No	72	CRC
16	2E	Female	2.75	79	No	74	CRC
10	3A	Female	7.00	42	Yes	---	---
27	3A	Female	8.17	51	Yes	43	Ovarian
28	3A	Male	8.17	43	Yes	45	CRC/DUO
29	3A	Female	7.50	33	Yes	---	---
11	3B	Male	8.42	76	Yes	39	CRCx2/SK/KD
12	3B	Female	7.42	55	No	26	CX
13	4	Female	8.42	59	No	---	---
14	4	Male	6.42	45	No	---	---
18	5	Male	7.42	42	No	---	---
1	6	Female	0.75	43	No	---	---
3	6	Female	0.92	50	No	---	---
4	6	Female	0.75	48	Yes	49	CRC
19	6	Female	0.08	63	Yes	54	SK
5	7	Female	2.33	52	No	---	---
37	7	Female	3.17	50	Yes	46	KD/EC
38	7	Male	3.08	46	Yes	---	---
39	7	Male	3.25	55	No	---	---
33	8	Male	2.25	66	No	---	---
34	8	Female	2.83	43	Yes	40	EC
35	8	Female	3.75	44	No	---	---
36	8	Female	3.75	42	Yes	---	---
17	9	Female	2.75	75	No	---	---

Note. Families 1B to 3B, 4, 5 and 9 have the intron 5 mutation and families 6 to 8 have the exon 8 deletion. The use of A, B, C, D or E after the family number denotes separate nuclear families within a particular extended family.

^a Years since genetic testing.

^b Age at first interview.

^c CRC=colorectal; CX=cervix; EC=endometrial; GA=gastric; SK=skin; BR=breast; VA=vaginal; KD=kidney; DUO=duodenal.

Methods

Study Design

A grounded theory study [2] was part of a multiphase project examining the psychosocial and behavioral impact of predictive genetic testing for LS. The Health Research Ethics Board, Memorial University, approved the study protocol. The rationale for using grounded theory is presented in Watkins et al. (2011) [2].

Participants

Details on the target population and predictive genetic testing have been reported elsewhere [2]. A purposive sample of 39 individuals from 15 families who had participated in genetic testing and knew their status was selected from the accessible population. This article focuses on the 23 carriers and 16 non-carriers (Table 2.1) from 12 families with the intron 5 splice site mutation and three families with the exon 8 mutation. The mean time from genetic testing to initial interview was 5.4 (± 2.6) years (range .1 to 9.6) and age at the first interview was 51.2 (± 13.8) (range 26 to 79).

Procedure

Following initial contact and informed written consent, two interviewers conducted 60 to 90 minute interviews with participants either individually or in small groups. Information on the procedure, interview questions and data analysis are presented in a previous publication [2]. Data analysis revealed a substantive theory, “*Confronting and Accepting the Challenges of Living in Families with Genetic-Linked Diseases*” which is comprised

of three major constructs (living in families with a strong history of cancer, becoming aware of genetic testing and living the process, and struggling to adjust) which exert separate and interactive effects on each other. The data presented in this article are restricted to examining the construct, *struggling to adjust*, specifically the psychosocial and emotional impact of hereditary cancer for individuals and families.

Results

Living in families with hereditary cancer may have psychosocial and emotional implications for all family members. The implications go well beyond individual genetic test results to the family environment where many interactive factors influence how carriers and non-carriers manage a genetic-based disease. The interactive effects of genetic and environmental factors can facilitate or impede psychosocial and emotional adjustment to living with familial cancer.

Similarities and discrepancies were observed in how study participants and their families responded to the presence of LS. The findings revealed a family meaning context, with members having shared similar/differing experiences and/or reactions to the confirmation of a genetic link to cancer. Although most individuals and families deal with the ominous presence of hereditary cancer in a positive manner, the potential exists for significant personal and family burden.

Adjusting to Lynch Syndrome – Personal and Family Implications

Wide variations were observed in how the study sample perceived personal and family impacts of LS. While most acknowledged the importance of knowing about their cancer risk, some were burdened by this reality. Periods of intense exposure to familial cancer seemed to provide participants with an extensive practical knowing that appeared to be both informative and burdensome. Some individuals and families were empowered to effectively manage the condition, whereas others were challenged to do so and struggled to grasp an understanding of its implications personally and for significant others.

Personal Strengths/Challenges

Confirmation of LS in a family involves adjusting to an unfolding, complex disease state as individuals struggle to come to terms with the uncertainty of who will get cancer, the timing/location of cancer episodes and disease outcomes. Dealing with the threat of cancer or its development, caring for others with cancer, adhering to recommended screening, enduring cancer treatment and contemplating children's risk are potential sources of psychosocial and emotional burden. The current study findings suggest that, on a personal level, the challenge is to embrace a positive attitude and not dwell on the uncertainties of hereditary cancer. Most family members recognize the importance of maintaining a positive outlook and accepting the unknowns: "We don't dwell on it [LS] and we don't let it get to us. It is one of those things where we know it's there and we're just going to accept it." [I23, Fam1B]

A sense of inner personal strength and resilience were evident in the narratives of many carriers. This observation held for both those affected and unaffected with cancer. The findings suggest that most accepted the realities of LS and endeavored to think positively and face each day without focusing on the uncertainties. One male participant, who had not developed cancer, had this to say: “I don’t dwell on anything since I had this [LS]. I don’t even think about it. No, I live a day at a time. I live a good happy life. I am not interested in negative things.” [I30, Fam1C]. Another participant, who had experienced cancer twice, made a similar comment: “We just got to carry on and be strong.” [I11, Fam3B]

Another male carrier, who was also unaffected, firmly believed that attitude plays a significant role in shaping health outcomes. For him, psychosocial and emotional factors can affect disease onset even when there is a genetic predisposition for it.

I think people’s attitude really has an effect upon outcomes as well. I think stress plays a part in the illness. ...Who’s to say that my attitude has probably helped keep me from developing something? When I do become ill, if I’m able to maintain the attitude that I have now, I think I would have a better chance of survival. [I21, Fam2C]

Some carriers, who were unaffected with cancer, had reached critical milestones in that they had surpassed the age at which most of their family members had developed and/or

succumbed to cancer. This reality could potentially evoke anxiety and fear but also reassurance that one had “beat the odds”. One of male carriers had this to say: “I’ve heard of some families of my cousins, the entire generation in their 40’s were wiped out so obviously that must be very frightening if you’re 30. ...my father was in his 20’s you know, I’m 50.” [I21, Fam2C]

Many carriers struggle to reconcile the gap between the cognitive awareness of risk status and emotional acceptance while waiting for the disease to manifest. Being aware of and caring for others who develop cancer are stark reminders of things to come. The narratives of unaffected carriers contained evidence of personal struggles, especially during reflective periods.

Will I ever be faced with cancer? If I do, then how will I feel? I always look back when I’m talking to her [mother]. What if this was me? Would I feel any different by what someone is saying to me? ...I struggle with that. I can’t relate to that because I couldn’t say what I would or wouldn’t do in that situation. [I36, Fam8]

The reality of LS is that it does not occur in isolation. The narratives of some carriers are reflective of how the burden of managing LS can be compounded by stressful life events and other illnesses. Despite being cancer free, one female carrier had to deal with the interactive and cumulative effects of dealing with LS, cancer screening for over 20 years, heart disease and diabetes, among others. Due to previous abdominal surgery,

recommended colonoscopies have become more difficult for physicians to perform and for her to endure. Her words capture the toll on her physical and emotional well-being and her challenge to maintain a positive outlook.

Looking at me now, you wouldn't say I had a care in the world. And some days if you could see me, you'd swear I had one foot in the grave. ...And there's days like yesterday I kept saying, 'Lord I don't know if I can do this. I don't know if I can make it through another day and try to act as if everything is okay. It's hard to wear a smile when you feel like you're falling apart at the seams.' [I10, Fam3A]

The intensity of reactions to being affected with cancer seems to be influenced by the number of personal bouts and exposure to cancer in immediate family members. For most, there is the realization that when cancer surfaces initially and is treated successfully, this is only the beginning of a lifelong journey filled with uncertainty about future health states. One woman who followed recommended screening based on her family history had two primary early stage cancers. Even though she tried not to dwell on her situation, her words reflect concern for her future well-being: "I don't sit and dwell. Yes, we all do; especially last year when I sort of got down and got cancer again. ...What else is going to happen to me now? Oh God, when is it going to break out next?" [I37, Fam7]

A similar story was related by a male participant. His recent experience with cancer, signs and symptoms of health changes, and cancer onset and death among younger family members fueled heightened distress and anxiety propelling him to take action.

But after I had my operation [colon cancer] I phoned up for another appointment [for diagnostic testing] and they told me that it could be another 6 months before I get in and my year was up then right. ...So I phoned the doctor that operated on me and I got in within 2 weeks. I couldn't wait another 6 months. I was frightened. [I31, Fam1B]

Long-term cancer survivors seem to have developed a sense of resilience characterized by a positive attitude and increased emotional strength. One woman who had survived for 35 years and endured four previous primary cancers spoke about her fifth bout. Despite significant long-standing challenges with cancer and its complications, her words capture an approach to living that has enhanced her emotional, social and physical well-being.

Now that episode with stomach cancer was 15 years ago and I was living alone. So then I had the ileostomy but that didn't bother me psychologically because it was such a relief after spending so much time in the washroom. I recovered from that. I was fine. I was getting a new lease on life. I was 54. Apart from having cancer I am a real physical fitness sort of person. ...I am a survivor because during these years I got a black belt in karate and that has helped me. [I32, Fam2A]

Similar to carriers, the stories of non-carriers reflect the need to stay positive in order to face the challenges of LS. One non-carrier echoed the sentiments of others when he suggested that a positive attitude is important to the person facing cancer: “You got to have a good outlook or you are not lasting. I think that it [positive attitude] has a lot to do with it [survival].” [I33, Fam8]

Some non-carriers are challenged by having to give up regular screening for cancer. While most experience relief, others find it difficult to discontinue recommended screening for LS. It seems that screening, particularly for those who did it for years prior to genetic testing, provided a safety net and reassurance that all is well. One participant spoke about how her loss has not dampened the need to be vigilant. “Now that the crutch is gone, I just watch myself a little bit more carefully. If there is any change in my bowel habits, then I think, I suppose it’s been a little while since I had that colonoscopy done.” [I3, Fam6]

In contrast, other non-carriers, who had screened for years prior to genetic testing, concluded that further action could be taken to reduce a person’s overall risk of cancer. Following receipt of negative genetic testing results one participant realized that he should be taking better care of his health: “Alright, I’ll pay a little bit more attention to what I’m doing with myself. At that point maybe I did lead a more healthy lifestyle.” [I2, Fam2A]

Family Burden

Hereditary cancer is a family matter that can create psychosocial and emotional challenges for all members. Striving to be positive and enduring one's lot are not easily achievable for everyone, particularly when considering the broader implications of LS. Living with the uncertainty of cancer, losing younger family members at an early age and dealing with the challenges of regular screening can be overwhelming and emotionally taxing. The only certainty is that any family member at risk can be diagnosed with cancer at any point in time: "Nobody likes the idea of worrying and wondering if this test is going to show that I got something wrong this time." [I10, Fam3A] Depending on the person's inner strength and resilience, too much worry and concern has the potential to evolve into an emotional barrier impeding effective disease management. Study findings highlight the fact that hereditary cancer is a family-focused disease which can evoke burden in close and extended members regardless of one's carrier status.

A source of burden for carriers is non-accepting children. One female carrier expressed concern for her children and wondered if exposure to her struggles will prevent them from accepting and managing their cancer risk: "I don't think they want to know [carrier status] because they've seen me go through it – the screening, prep, and prognosis because I have had two cancers. I think that's what's going to hold my children back." [I20, Fam2B]

Other carriers spoke about the impact of LS on young family members. With cancer-related deaths occurring at younger and younger ages, parents are worried about what the future might hold for their children. One woman's words capture the sentiments expressed by many: "When I think of the cousins who are gone and the families they have left. The young men ... every time we get together for family gatherings especially Christmas and you see all those young family members and you wonder what becomes of them." [I19, Fam6]

Carriers also found it challenging to deal with children who have experienced the suffering and death of young family members. The following text exemplified the significant burden that hereditary cancer can bring to a family: "They [children] just lost their cousin, 17 years old. How do they deal with that? We're finding it difficult to deal with and, not only that, we watched her die." [I38, Fam7]

While not at risk personally, non-carriers in LS families are an integral part of the social and familial contexts and often have to endure the emotional implications of caring for others at-risk or with cancer and dealing with the loss of significant others. Thinking about who would be affected next is emotionally draining as individuals struggle to adjust to a constantly evolving condition: "It is very upsetting. When I find out that they [relatives] have cancer, it really makes me think, 'Who's going to be next?' That fear is always there." [I13, Fam4]

Non-carriers struggle to remain optimistic and not dwell on what is happening around them. However, this can prove to be very difficult as more and more family members develop cancer. One woman who tested negative for LS had this to say:

Since I've had this wonderful news that I don't have the mutation, two of my younger cousins are now having problems. ...So like you go along in this family and you're thinking. ...It's not just off there in the distance. It's right up there in your face all the time. [I3, Fam6]

Summary

While most participants strived to maintain a positive outlook in dealing with LS, confirmation of this syndrome had personal and family psychosocial and emotional implications. As conveyed by the words of study participants, it is sometimes a struggle to maintain a positive outlook when dealing with a disease that has an uncertain trajectory, time of onset and outcome for the self and others. While a small number are able to face the disease with incredible strength and resilience, the majority of carriers and non-carriers are burdened. Although the presence of LS is manageable for most, there is a subgroup that struggle with it. While carriers have to confront challenges that go beyond worrying about personal cancer risk, the findings also suggest that non-carriers have to endure the emotional consequences of living in LS families.

Family Connectedness

Family connectedness plays a crucial role in helping individuals deal with the adversities of living with hereditary cancer. As defined by study participants, family connectedness involves having a supportive environment, access to resources and open communications to help manage the many challenges posed by LS. Any one member's ability to adjust to being a carrier or non-carrier is shaped, in part, by what is happening in the family. Strength in numbers is a function of close ties between and among extended family members.

When family relations have always been characterized by a special closeness and open communication, there is no change following confirmation of LS. In such instances, individuals maintain ongoing contact for the purpose of keeping everyone current on what is happening to family members, facilitating openness and providing support: "As soon as one finds out something else about the other – look out the phone don't stop ringing. Because if you tell one it's like the pony express, everybody knows it ... That's part of getting us through it [LS]." [I27, Fam3A]

All of the carriers referenced the comfort derived from having at least one person who knows and understands what it means to live with hereditary cancer. The commonality of interests, risks and concerns often means more frequent contact and open discussions. It seems that when a supportive milieu is present, carriers are helped to become more open to and accepting of their high cancer risk. From the perspective of one young man, the

presence of LS has helped facilitate greater sharing of experiences: “In some sense it has created a kind of unique bond in our family – you got something in common with some of your cousins’ and uncles’. Things that you’re going through together ... You can ... talk about things.” [I8, Fam1C]

A parent with several children with the LS mutation also observed that more open communication and greater access to supportive others not only buffers the impact of LS syndrome but also encourages more effective disease management.

The only thing I find now, the children who are positive, they’re more supportive toward each other. ...They’re checking on each other and they talk about it when they’re together for their socials. ...and they’re making sure that they get their screening done. [I37, Fam7]

A recurrent theme in the interviews of both carriers and non-carriers was the importance of being available to and supportive of those at high risk for cancer. One non-carrier commented thus: “I think it has made our family a lot closer. We are very close with my mother’s siblings and I think it is because, every day, it could be anybody. You just need to be there for them.” [I1, Fam6]

From a practical knowing perspective, living through multiple bouts of cancer with a parent and providing care for them during the terminal stage can enhance or weaken

family ties. One non-carrier who had assisted with the cancer care of both parents perceived a positive change in relations with his siblings.

There's only the three of us siblings and you kind of lean on each other more now that our parents are gone. You keep closer contact and involved in each other's life more than you would normally if you didn't know about the others risk [for cancer]. [I18, Fam5]

Cancer can also have negative repercussions for family connectedness when the early years have been emotionally traumatic due to a parent's experience with cancer. The children may develop a strong sense of self-sufficiency that, to a degree, runs counter to a perceived need for openness. One non-carrier reflected upon the time when his mother experienced multiple bouts of cancer. This male participant perceived that family communications were compromised and have had pervasive, lifelong effects on all of the children.

We sorted things out for ourselves but as a result you know became very separate from each other. Home was not a place necessarily of security, there was always that doubt there. ...We all became very independent. ...We are all good people but as a result we are not very close. [I2, Fam2A]

Early deaths of multiple family members also could mean that there are less people to provide support. As more and more relatives succumb to the disease, there is not only a diminishing support base but also an erosion of family connections.

I didn't have a lot of awareness of cousins of my father who became ill because I had lost that connection with them. ...those people are strangers. ...I thought it was interesting that they were ending up with the same problems that my father had. But it was not that emotional attachment to it. [I21, Fam2C]

In summary, many of the study participants acknowledged the importance of being open about the cancer risk in the family and having access to resources and family supports in sharing the burden of cancer. While most were able to openly communicate, be there for each other and receive support, some families were challenged by the burdens imposed by LS.

Discussion

The current study highlights the psychosocial and emotional adjustment of 39 carriers and non-carriers in LS families. What is unique is that some of the carriers and non-carriers had been having screening/surveillance and living with the risk of and/or cancer for almost 20 years prior to the availability of genetic testing. Very few studies have examined how individuals adjust in the long-term to hereditary cancer [3,14,15,26,45]. Most studies have focused on psychological outcomes for individuals immediately or in

the early months following genetic testing as opposed to how families are adjusting to their high cancer risk over time.

The current study provides informative insight into key personal and family strengths/challenges that may facilitate/impede the adjustment of carriers and non-carriers. The findings highlight the complexity of living in families with a strong history of hereditary cancer and the interactive impact of individual and family factors on adjustment. Following confirmation of LS, most individuals strive to be positive in facing the uncertainties associated with hereditary cancer. This attitude, although challenging to maintain at times, did enable most study participants to deal with cancer risk, the development of cancer, and recommended screening and treatment.

Despite deliberate efforts to maintain a positive attitude, some participants struggled to adjust to the constant challenges imposed by new cancer episodes in the self or other family members. These findings concur with those of others who assert that there are challenges to long-term adjustment in families with hereditary cancers [3,41,46].

Nevertheless, there were a few instances where individuals who were diagnosed with cancer several times displayed incredible resilience. Previous research findings have also documented how a strong sense of resilience helps some family members adapt to hereditary disease [46] and cancer [47,48].

Similar to the findings from other studies, the current study suggests that the major challenges for family members include adjusting to being a carrier or non-carrier for LS [26,31,33] dealing with cancer in the self and/or others [33] and worrying about other family members who may be at risk [32,33]. For the carriers, the emotional toll of waiting for cancer to surface for the first time or to recur oscillated in response to one's inner strength and the perceived supportiveness of family and others. This finding supports the growing body of qualitative evidence on the psychosocial and emotional implications of living in families with hereditary cancer [3,31-33,49,50].

The findings also provide data on how carriers who have developed cancer one or more times are managing in the long-term, an area identified by others as lacking research [27]. Those who had experienced cancer had already confronted the reality of what it means to be a LS carrier. Despite the implications, most strived to maintain a positive attitude in facing the diagnosis and treatment. However, encounters with cancer served to remind some of their high-risk status and the possibility of future bouts.

Non-carriers are not spared the emotional and psychosocial burdens associated with a strong cancer presence in families. In the present study, this was especially evident when a parent experienced and survived multiple cancers during the children's early years. Previous authors have identified that non-carriers can be burdened by caring for others with cancer and worrying about others at-risk [31,33]. In fact, just being a member of a

family with hereditary cancer can create burden, a sense of loss and isolation for non-carriers [31].

A key finding is that hereditary cancer not only impacts the individual but also has implications for immediate and extended families. This finding is supported by other authors [3,26,32,33,49]. Family relationships are impacted in diverse ways. Some families are able to maintain close relations or strengthen family ties while others experience distancing and a weakening of relationships. Other researchers have noted the variable impact that genetic conditions can have on family relationships [3,4,31-34].

The current study also highlights how family supports may buffer the overall burden of LS. Having someone to share experiences with plays an important role in managing a multitude of issues that can surface following confirmation of cancer risk. Both carriers and non-carriers in the current study acknowledged the need for support to help them deal with the uncertainty and realities of cancer. The importance of family support in adjusting to hereditary cancer has been reported previously [3,16,30] and family support and encouragement may play roles in adherence to recommended screening [51,52].

Family members, particularly carriers, have to deal with unique challenges concerning future generations, a concern highlighted in other studies [3,4,32,33,50]. Many members are burdened by the possibility of their children testing positive and then having to endure

screening/treatment. The level of worry and concern fluctuates back and forth from the self to the children and other family members.

In conclusion, the presence of LS has implications for carriers, non-carriers and children within families. All family members must adjust to living with hereditary cancer. Family dynamics play a key role in buffering the challenges of effective disease management. Hereditary cancer has variable impact on family relations.

Despite the limitations of a small sample size and the inherent biases in having participants recall how they experienced and responded to various events and situations, the findings provide practical insight into the long-term personal and family implications of hereditary cancer. The findings suggest that the variant experiences of carriers, non-carriers and their families are influenced by diverse personal and familial factors.

Clinical and Policy Implications

This study has examined the long-term psychosocial and emotional impact of LS on individuals and families. By referencing a qualitative data base derived from carriers and non-carriers, we argue that most family members will need support that extends far beyond the immediate genetic testing period to successfully integrate the burden of multiple demands [3]. Other authors have questioned the adequacy of health care system support for non-carriers and unaffected carriers of hereditary cancer and recognize the importance of providing care even in the absence of a cancer diagnosis [41].

Ideally, genetic counseling should explore the psychosocial and emotional impact of hereditary cancer and assist individuals and families in adopting effective strategies to lessen the burden of the disease. The variation and complexity of personal experiences and experiential knowledge from living in families with LS necessitates a family-centered approach to the provision of genetic services. Further, psychosocial and emotional adjustment over time must be considered, particularly when cancer emerges in the self and/or others. Adjustment must also be assessed in terms of the impact on adherence to recommended screening and treatment. The barriers to and facilitators of screening in this population have been documented [2]. The findings suggest a complex interaction of the emotional and physical burden of managing LS and the practical demands of everyday living [2]. Given the documented benefits of screening in this population [11], it is imperative that ongoing assessment of the psychosocial and emotional impact be inclusive of implications for effective disease management.

The quality of family relations and the availability of supports to share the cancer burden are important factors influencing overall adjustment to LS. Assessing family functioning can help shed light on an individual's level of awareness and acceptance of high-risk status [32]. Knowledge gained from this assessment can help genetics personnel identify those with strong and weak family support systems [49]. Strong family systems suggest the presence of sufficient resources to help buffer stress and facilitate adjustment. Conversely, weak family systems should indicate to genetics personnel that there is a

need to provide additional cognitive and emotional support regarding risk and disease prevention.

Being at risk for LS is a condition that affects the individual and family with both requiring support over time. Genetic testing for LS is one event along a continuum of lifelong disease management. The years prior to and following the event are very significant to families in terms of psychosocial and emotional impact and require further study and exploration [46] The concerns for future generations suggest the need for supportive interventions. Health care providers need to understand that even though individuals may accept and adjust to their carrier status, they can experience periodic challenges over the long-term.

Importantly, LS has implications for public health policy [53]. The ultimate plan should be to provide a coordinated system of health care services that includes continuing assessment and support well beyond the immediate genetic testing period. Formal health care supports must be readily available particularly when existing personal and family resources are inadequate to facilitate adjustment to the hereditary condition.

In order to ensure that health care services are tailored to meet individual and family needs, clinical monitoring tools should be in place to evaluate adjustment to the evolving psychosocial and emotional challenges of hereditary diseases. Our team has developed a reliable and valid scale that is capable of capturing how carriers and non-carriers are

adjusting to hereditary cancer at any point in time [1]. The scale is designed to elicit data on the psychosocial and emotional impact (personal and family strengths/challenges) of receiving confirmation of a carrier or non-carrier status, and the importance of being part of a supportive family network. Preliminary results indicate that there is a core group of individuals in all families who are struggling to adjust. The significance of the family environment and dynamics in members' adjustment to LS was also confirmed.

In conclusion, the supportive and informative roles of genetic counselors and other health care providers, knowledgeable about managing LS, will be critical in promoting successful psychosocial adjustment and a reasonable quality of life.

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Authors' contributions

CW and MJE conceived and designed the study. CW and JF interviewed the participants. CW, JF, RM, VL and KW were involved in data analysis. KW and CW drafted the manuscript. PP critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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CHAPTER 3

Development and Preliminary Testing of the Psychosocial Adjustment to Hereditary Diseases Scale

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Background: The presence of Lynch syndrome (LS) can bring a lifetime of uncertainty to an entire family as members adjust to living with a high lifetime cancer risk. The research base on how individuals and families adjust to genetic-linked diseases following predictive genetic testing has increased our understanding of short-term impacts but gaps continue to exist in knowledge of important factors that facilitate or impede long-term adjustment. The failure of existing scales to detect psychosocial adjustment challenges in this population has led researchers to question the adequate sensitivity of these instruments. Furthermore, we have limited insight into the role of the family in promoting adjustment.

Methods: The purpose of this study was to develop and initially validate the *Psychosocial Adjustment to Hereditary Diseases (PAHD)* scale. This scale consists of two subscales, the *Burden of Knowing (BK)* and *Family Connectedness (FC)*. Items for the two subscales were generated from a qualitative data base and tested in a sample of 243 participants from families with LS.

Results: The Multitrait/Multi-Item Analysis Program-Revised (MAP-R) was used to evaluate the psychometric properties of the PAHD. The findings support the convergent and discriminant validity of the subscales. Construct validity was confirmed by factor analysis and Cronbach's alpha supported a strong internal consistency for BK (0.83) and FC (0.84).

Conclusion: Preliminary testing suggests that the PAHD is a psychometrically sound scale capable of assessing psychosocial adjustment. We conclude that the PAHD may be

a valuable monitoring tool to identify individuals and families who may require therapeutic interventions.

Background

Lynch syndrome (LS) is an autosomal dominant disease characterized by the development of colorectal (CRC) and extracolonic cancers [1]. Individuals living with LS may be faced with cancer onset in themselves and other family members, lifelong cancer screening, extensive treatment regimes and early deaths of family members.

Confirmation of LS through predictive genetic testing can bring a lifetime of uncertainty to an entire family as members adjust to living with an indeterminate or evolving disease state. The research base on how individuals and families adjust to genetic-linked diseases following predictive genetic testing has increased our understanding of short-term impacts but gaps continue to exist in knowledge of important factors that facilitate or impede long-term adjustment.

In studies focusing on the impact of genetic-based diseases, the adjustment construct assumes many forms. Psychological/psychosocial adjustment is used interchangeably with psychological/psychosocial functioning, impact, distress, consequences and outcomes, among others. What is evident from a review of the scientific literature is a lack of consensus on how psychological adjustment is defined and operationalized [2].

Quantitative studies that focus on hereditary cancer have primarily assessed short-term psychological functioning (i.e., cancer specific distress, anxiety, and depression) by using such standardized scales as the State-Trait Anxiety Inventory [3-9], Impact of Events [3,5-8,10], Hospital Anxiety and Depression Scale [5,9,10], and the Center for Epidemiologic Studies Depression Scale [6-8]. The evidence suggests that individuals who are part of LS families are not distressed (intrusive thoughts about cancer, anxiety and depression) in the short-term post-genetic testing. Prospective studies monitoring changes in psychological functioning during genetic testing show slight elevations in carriers distress levels immediately post-testing which return to baseline levels within a year, but decrease immediately for non-carriers and remain relatively stable over time [3,4,6,11]. Investigations of impact for longer periods revealed no differences in psychosocial outcomes between carriers and non-carriers at three [5,12] or five years post-testing [13]. The conclusion of meta-analyses and literature reviews is that genetic testing for hereditary cancer causes minimal psychological consequences [14-17].

Absent from this quantitative research base is prospective data on long-term psychosocial adjustment. Specifically, there is minimal consideration of the psychosocial and emotional impact of living with hereditary cancer, personal and family challenges over time, and the role played by family functioning and supports in reducing the impact of hereditary cancer and facilitating adjustment. In 2004, our research team administered a battery of standardized and researcher-developed scales to a convenience sample of 120 carriers and non-carriers from LS families in Newfoundland and Labrador at different

times post-genetic testing (i.e., 0.1 to 9.2 years). Baum and colleagues theoretical model of stress and adaptation (1997) [18], previously described by Esplen et al. (2007) [8], was used to guide data collection. Table 3.1 presents a summary of the objectives, methods and select findings of this initial survey. Study findings revealed that most respondents were not psychologically distressed (anxious, depressed, intrusive and avoidant thoughts) from being involved in genetic testing for LS, did not convey worry/concern about cancer risk for the self/others, were part of healthy functioning families with adequate internal strengths, were satisfied with available social supports, relied equally on emotion-focused and problem-focused coping, and were satisfied with valued aspects of life (family, health and functioning, psychological spiritual and social/economic). Although most individuals seemed well adjusted, a subgroup had elevated distress levels, compromised family functioning and lower quality of life.

There is additional support from the literature that a small, but significant, group of individuals experience adjustment problems and may be classified as having borderline distress [8,13,17]. Problems with psychological functioning may negatively impact long-term adjustment, particularly adherence to recommended screening protocols crucial for the prevention and early detection of cancer. Importantly, the evidence suggests that individuals with greater social supports and who belong to families with open communication are more likely to follow recommended protocols [19-21], have less psychosocial distress [22-24] and adjust better over the long-term [10].

Table 3.1: Objectives, instruments used and results of two preliminary studies undertaken prior to the current study

Study	Objectives	Instrumentation	Results
Phase I: Survey	<p>1) to investigate psychosocial and behavioral impact of genetic testing (GT) process for at-risk individuals in LS families</p> <p>2) to examine key factors (i.e., age, gender, education, supportive relationships, familial & personal cancer history, CRC knowledge, satisfaction with GT decision, time since GT) associated with difficulties in psychosocial and behavioral adjustment (reaction to GT results, perception of risk, willingness to disclose and to whom) in individuals affected/unaffected with cancer</p>	<p>Standardized scales (Impact of Events Scale [28], Center for Epidemiologic Studies Depression Scale [29], State-Trait Anxiety Inventory [30], McMaster Family Assessment Device [31], Family Hardiness Index [32], Quality of Life Index [33], Social Support Questionnaire [34], Ways of Coping Questionnaire) [35]; researcher-developed items (medical history, worry/concerns, demographics, cancer experiences, reaction to & disclosure of results, screening & healthy living)</p>	<p><i>Sample characteristics:</i></p> <ul style="list-style-type: none"> - mean age of 47.4 (SD = 12.9), range 22 to 78 years - female (57.5%), carriers (51.7%) of intron 5 splice site mutation (93.3%) and unaffected (77.5%) - average of 6 years post-genetic testing <p><i>Key findings:</i></p> <ul style="list-style-type: none"> - over 33% had moderate to severe avoidance/intrusive thoughts post-GT; - small percent above clinical cut-off score for depression and anxiety - small percent with quality of life issues and lower family functioning (role execution & communication) - no significant impact for time since GT, gender, age, carrier or cancer status
Phase II: Qualitative	<p>1) to explore meanings of genetic testing for individuals at risk for colorectal and related-cancers in LS families</p> <p>2) to understand psychosocial and behavioral impact of genetic testing for carriers and non-carriers of LS</p> <p>3) to use emergent data to improve existing counseling programs</p>	<p>Semi-structured interviews focused on: familial cancer experiences (exposure in close/distant members, first aware of hereditary link, perceived risk for self, screening/healthy living motivation) and pre/post GT (decision-making pre and post testing, experience with genetic counseling, reaction to GT results, understanding risk for self/others, impact on family, role/importance of supports, adjusting to status & experiences with health care)</p>	<p><i>Constructs:</i></p> <ul style="list-style-type: none"> - Living in families with a strong history of hereditary cancer (familial cancer context & emergence of hereditary link) - Becoming aware of genetic testing and living the process (decision-making, reactions to results, understand risk, supportiveness of genetic counselors, disclose results) - Struggling to adjust (personal/family challenges, family dynamics/support, barriers/facilitators of adjustment)

With the sensitivity and specificity of standardized scales for detecting and monitoring psychosocial adjustment in this population questioned [4,14], Read et al. (2005) [25] developed the Psychological Adaptation to Genetic Diseases (PAGIS) scale to evaluate the efficacy of genetic counseling and identify individuals requiring additional support. These researchers propose that psychological adaptation to genetic information is a multidimensional phenomenon comprised of non-intrusiveness, support, self-worth, certainty and self-efficacy. While the PAGIS demonstrated acceptable internal consistency and content validity in preliminary testing, there is no further reference to its use in subsequent studies. The Multidimensional Impact of Cancer Risk Assessment (MICRA) questionnaire [26] was developed to measure positive and negative responses to genetic testing for cancer. The MICRA was initially validated among women at risk for breast cancer but, to our knowledge, has not been used in subsequent studies. Despite these disease-specific scales, there is no empirical evidence suggesting that they are capable of monitoring how well individuals adjust to genetic-based diseases in the short- and long-term [27].

Critical appraisal of the research evidence on adjustment challenges for LS families from studies using quantitative versus qualitative methodologies can lead to very different conclusions. Reliance on qualitative methods helps researchers identify areas of psychosocial impact that have implications for affective and behavioral outcomes. The evidence suggests that certain individuals have difficulty adjusting in the short- and long-term following confirmation of hereditary cancer [36-40], feel burdened about

communicating genetic risk information to family members [40], worry about cancer risk in others [36,37], perceive that health care system supports post-genetic testing are inadequate [38,39], struggle to adhere to recommended screening protocols [38,39] and experience difficulty in coping with cancer in the self/others [37].

Following the 2004 survey, our research team designed a grounded theory study to explore the meaning of genetic testing for individuals (N=39) in LS families and develop a greater understanding of psychosocial and behavioral impacts for confirmed carriers and non-carriers. Data collection spanned the years 2004 to 2007. Purposive samples were recruited from 15 family groupings: (a) 2004 survey respondents with an interest in further research (n=22), (b) additional individuals from families with the intron 5 splice site mutation to augment evolving family, carrier/non-carrier or affected/non-affected themes (n =10), and (c) individuals from families with the more recently identified exon 8 deletion to ensure comparability of experiences in families with the intron 5 splice site mutation families (n=7). Details on the sample and data analysis have been described elsewhere [39]. Semi-structured schedules guided data collection via face-to-face interviews. A second interview confirmed the interpretive summaries constructed from each transcript, augmented gaps in the data and corroborated conceptual categories and properties. Table 3.1 summarizes study objectives, methods and key findings.

The conceptual model “*Confronting and Accepting the Challenges of Living in Families with Genetic-Linked Diseases*” emerged from analysis of the qualitative data. The model

broadly conjectures that the situational and experiential contexts are important forces influencing how well individuals accept the hereditary link to cancer, are motivated to become involved in genetic testing, and adjust to living with a confirmed presence of LS in the family in the short- and long-term. The *struggling to adjust* construct focuses on psychosocial and behavioral adjustment in LS families. The findings suggest that while most individuals acknowledge the importance of knowing about their cancer risk, some are burdened by having to manage LS over time (i.e., struggle to adhere to recommended screening) and having to deal with cancer episodes in the self and/or others. Importantly, the impact of LS is not limited to carriers but extends to all family members. Family functioning and openness of communications seem critical in helping individuals deal with the ongoing challenges. Finally, the findings provide further support for the premise that some individuals in these families experience difficulty adjusting in the short- and long-term and, at times, struggle to effectively manage their disease.

Based on the research literature and quantitative and qualitative findings from the two projects conducted by the research team, it was concluded that reliable and valid clinical tools capable of identifying subgroups of individuals, as well as their families, who may be at-risk for psychosocial and emotional challenges post-genetic testing are needed for use in genetics clinics. Monitoring tools are needed to assess adjustment to LS (i.e., positive affect and well-being, motivation to follow recommended protocols and modify health behaviors, and the buffering impact of supports). It was also evident from the literature and our findings that health care providers tend to not only have limited insight

into the extent of individual and family burden posed by genetic-based diseases but also fail to understand the level of support that might be needed to mitigate long-term effects.

In summary, emphasis on short-term outcomes, without thorough consideration of the social and familial contexts, can limit our understanding of long-term psychosocial adjustment. We argue that adjustment to hereditary cancer is broader than psychological outcomes and is an evolving process that ebbs and flows in response to changing personal and family experiences in the management of long-term cancer risk and emergence of cancer in the self and/or others. Personal and/or family experiences can facilitate or impede adjustment.

Purpose

The purpose of the current study was to develop and initially validate a tool for monitoring long-term psychosocial adjustment. Using the data generated from a grounded theory study, the Psychosocial Adjustment to Hereditary Diseases (PAHD) scale was developed as part of an ethically approved program of research. The PAHD is designed to assess the personal and family burden of LS and the perceived role of family in buffering its impact. The specific objectives for this component of the larger project are to: (a) test the feasibility of using the PAHD scale under variant conditions, (b) reduce item numbers, (c) validate subscale and overall scale structure, and (d) examine scaling (rating) methods.

Methods

The study was conducted in three phases. Phase I consisted of item generation and refinement. Phase II consisted of a pilot study designed to generate data for preliminary assessment of the psychometric properties of the PAHD scale. Phase III was designed to generate additional data to facilitate final item selection and initial scale validation.

Phase I: Scale Development

Interview transcripts from the grounded theory study provided the data base for scale development. The grounded theory method facilitated theoretical construct identification in such a manner that operational indicators defining the properties of each construct could be used to generate items. Initially, data matrices were created for the struggling to adjust construct by collating all data from the interviews into relevant descriptors of properties and re-writing the text until a clear decision trail emerged. Two dominant themes emerged from these analyses - one focusing on psychosocial adjustment and the other on behavioral adjustment. The psychosocial adjustment data matrix provided the content for item generation for the PAHD.

The approach taken to item generation and refinement consisted of several steps which are summarized in Table 3.2. The first step involved item generation and refinement. The focus was on identifying potential stems, reducing the number of stems and reworking and finalizing the text. The items were grouped into two subscales based on theoretical content. The first subscale dealt with personal burden issues (i.e., psychosocial distress and emotional well-being), and the second with family dynamics and the importance of

openness and supports. At the second step, efforts focused on selecting the best rating scale format to use with this population. Following consideration of multiple selection options, the research team decided to use one rating scale (not at all, a little bit, moderately, quite a bit, extremely). The fifth and final steps focused on assessing the scale's readability and subjecting it to content validation. The readability level of the PAHD was at an acceptable level and genetic counselors and individuals from LS families validated the content of the PAHD, as well as the usefulness of the rating scale.

Table 3.2: PAHD scale development

Item stem identification	A four-member research team was responsible for item generation and refinement. Initially, the team became immersed in the data matrices of the <i>struggling to adjust</i> construct. Independent raters created a profile of frequency and priority ratings of construct properties and descriptors (e.g., dwelling on carrier status, positive outlook, concern for young family members, importance of openness, strain on relations, emotional burden of suffering & death) by participant and group. Team members used these profiles to generate item stems for 5 groups and the principal investigator validated the process. At this stage, the team had 59 potential items.
Item stem reduction	Multiple drafts of items for the scale were reviewed and modified by the researchers. Team meetings were held frequently to collate, prioritize and refine item stems for potential scale inclusion (emphasis on conciseness, avoidance of negative wording, ambiguous terminology, jargon, value-laden words and double-barreled questions). A final set of 17 items were identified for potential inclusion in the PAHD scale.
Rating scale development	Initial rating scales focused on the frequency of occurrence (never, rarely, sometimes, often, or almost always), and ‘the importance/difficulty/receptiveness of’ or ‘how satisfied/concerned/confident/certain one was with’ select events/situations (not at all, a little bit, moderately, quite a bit, extremely). The multiple selection options made things cumbersome and confusing. The decision was made to rework the items and use one rating scale. Despite recognizing that a 5-point scale might not be sufficient for maximum reliability, the group consensus was that it would be difficult to devise unambiguous additional ordinal adjectives.
Scale readability	Several tools (i.e., Flesch-Kincaid Grade Level and Flesch Reading Ease, Fog index and SMOG) were used to assess the PAHD’s reading level at less than or equal to Grade 10. Although a grade less than 10 is recommended to ensure maximum reading ease and material comprehension, the PAHD is developed to assess the experiences of individuals who have had predictive DNA testing. These individuals have had repeated exposure to terms such as LS, hereditary non-polyposis colorectal cancer, carriers/non-carriers, inherited, generations, genetic and geneticist/genetic counselor. These polysyllabic words and others are used frequently throughout the scale which does increase the final readability score.
Content validation	<i>First</i> , two genetic counselors (GCs) who work with individuals during the genetic testing process reviewed the PAHD. A brief written synopsis of the conceptual model and construct definitions, along with a copy of the scales, were given to the GCs to prepare them for this task. Input was requested on item content relevancy (extremely, moderately, slightly, or irrelevant) in terms of its ability to measure the properties of targeted constructs, and effectiveness (very, moderately, poorly or not at all effective) of the 5-point Likert rating scale for ease of item rating. Minor changes to select items were made based on their recommendations. <i>Second</i> , the PAHD was administered to individuals (carrier & non-carrier) who had participated in the survey and qualitative studies. Respondents were asked to comment on item clarity/relevancy, and rating scale usefulness. No changes were made at this stage.

Phase II: Pilot Study

Using a descriptive correlational design with longitudinal components the PAHD scale was initially tested in individuals from LS families. The approach to scale testing was based on the work of Ware and Gandek (1998) [41], a method used by others [42,43].

Methods

The pilot study was designed to assess the integrity of subscale and scale structures, item clarity and difficulty, time required for completion and the feasibility of using different administrative methods. It also provided data for a preliminary assessment of the PAHD scale. Following creation of a descriptive profile for each item (i.e., frequencies, means, standard deviation, skewness and missing data), a correlation matrix was generated and the strength and significance of inter-item correlations assessed. A summary table was constructed of inter-item correlations falling within set cutoff ranges (i.e., $>.40$ and $.30$ to $.40$) which was the primary basis for initial subscale item selection. The final steps included factor analysis and reliability analysis using Cronbach's alpha.

Population and Sample

The target population was individuals at 50% risk for inheriting LS who had participated in genetic testing and informed of their carrier status. Survey respondents were recruited from families attending the Provincial Medical Genetics Program of Newfoundland and Labrador (PMGP-NL). Three large pedigrees with MSH2 mutations on intron 5, exon 8 or exon 4 to 16 have been identified with 272 carriers and 295 non-carriers confirmed

and entered into a Cancer Screening Data Base. This data base provided the resource for subject recruitment for the pilot study which occurred between February and June of 2008. Of the 120 individuals contacted, 75 (45 carriers and 30 non-carriers) completed the survey, resulting in a 62.5% response rate.

Procedure

Ethical approval of the study protocol was granted by the Human Investigation Committee, Faculty of Medicine, Memorial University as well as Eastern Health where the PMGP-NL is located. Telephone contact was initiated with potential respondents to inform them about the study and ascertain their willingness to receive additional information. Consenting individuals were forwarded packages consisting of a cover letter, a brief summary of the study, two consent forms and the survey instrument. Following receipt of consent, a follow-up telephone call was made to determine the preferred mode of participation (face-to-face, telephone or self-administered) and to schedule a mutually agreed upon time for survey completion.

Preliminary Results

Importantly, data completeness was similar for all three methods of PAHD administration, indicating that it is possible to administer this scale under variant conditions. Preliminary findings indicated that the two subscales appeared to be sensitive enough to measure a range of factors influencing psychosocial adjustment. For most items, there was evidence of fair spread across the response choices. Although factor

analysis indicated that item sampling was less than desired, no further analyses were pursued until further subject recruitment.

Post-Pilot Findings

Following recruitment of additional respondents, the PAHD subscale structure was reexamined. The items comprising the two subscales were merged with items from the subscales of the Hereditary Diseases and Genetic Testing (HD-GT), a second scale developed by the research team to assess the impact of the genetic testing process (pre, during and post receipt of results), and a correlational matrix generated. It was anticipated that this approach would help the research team determine if meaningful divisions existed between the subscales of the HD-GT dealing with psychological and emotional issues from engaging in genetic testing compared to those of the PAHD which focus on assessment of more long-term effects. The correlation matrices confirmed the uniqueness of the PAHD subscales and identified additional items not loading on any HD-GT subscales but theoretically similar in content to PAHD items.

The final PAHD scale (Appendix 1) contained two subscales with 17 items (Table 3.3). The *Burden of Knowing (BK)* and *Family Connectedness (FC)* subscales are in line with the psychosocial and emotional component of the construct *struggling to adjust*. The conceptual definition highlights the importance of capturing: (a) the perceived personal and/or family burden following confirmation of LS, and (b) the role played by family supports in promoting status acceptance and buffering the impact of challenges posed by

the disease. The BK scale is comprised of 10 items that recognize the personal and family aspects of adjustment to hereditary cancer with higher scores reflecting lesser burden.

Additional items from the HD-GT scale address how the stress of cancer in younger family members may impact family relations (BK19_R) and how regular screening may heighten cancer worries (BK20_R, BK27_R).

Table 3.3: Item descriptive statistics for Burden of Knowing (BK) and Family Connectedness (FC) scales (N = 243)

Scale & Items	X	SD	Missing (%)	Response Values Frequency				
				0	1	2	3	4
Burden of Knowing (BK)	24.8	8.4	9.5%					
• Dwelling on carrier status (BK11_R)	3.1	1.1	0.8	5	24	36	65	111
• Difficulty modifying screening regime (BK14_R)	2.8	1.4	1.6	28	17	41	34	119
• Concerns with non-acceptance by others (BK15_R)	3.4	1.2	2.5	13	14	12	27	171
• Difficulty dealing with young people (BK17_R)	1.8	1.4	3.3	59	43	59	28	46
• Worry about young people’s future (BK18_R)	1.4	1.3	1.2	80	58	49	39	14
• Stress of cancer alters family relations (BK19_R)	2.8	1.3	1.6	17	33	39	40	110
• Screening reminder of personal risk (BK20_R)	2.2	1.5	1.2	50	37	44	39	70
• Concerns about impact on family relations (BK24_R)	3.3	1.2	0.4	13	15	24	25	165
• Worry about burden of cancer on family (BK25_R)	2.3	1.4	0.8	30	44	54	49	64
• Screening heightens cancer worry (BK27_R)	1.9	1.5	0.8	63	46	41	45	46
Family Connectedness (FC)	20.4	5.6	4.5					
• Encourage young people to talk about cancer (FC16)	3.0	1.1	1.2	10	18	49	60	103
• Feeling supported facilitates acceptance (FC21)	2.9	1.2	0.4	13	21	41	77	90
• Easy to seek help from family (FC22)	3.0	1.2	0.8	13	18	34	67	109
• Important to openly discuss family cancer (FC23)	3.4	0.8	0.4	0	8	27	62	145
• Caring for others promotes personal acceptance (FC26)	2.3	1.4	1.6	37	31	50	66	55
• Relieved by availability of genetic testing (FC28)	2.9	1.2	1.6	10	21	42	66	100
• Supportive others promotes healthy behaviors (FC29)	3.0	1.1	0.4	11	16	33	78	104

Comparatively, the seven-item FC scale assesses family connectedness with higher scores reflecting the importance of having open discussions and access to resources to handle the challenges posed by LS. Additional items from the HD-GT scale address feelings of relief concerning the availability of genetic testing (FC28) and the role of supportive others in promoting acceptance of healthy behaviors (FC29). Two items dealing with emotional well-being (BK12) and not dwelling on the hereditary cancer (BK13) failed to load on either subscale but were retained as test items for future scale administrations.

Phase III: Initial Validation

Ongoing recruitment and data collection continued between July 2008 and July 2010. Data were collected by face-to-face interviews, telephone interviews and self-administered surveys. Of the additional 253 individuals contacted, the scale was administered to another 168 participants. In total, 373 individuals agreed to receive study materials during the two phases giving a total sample size of 243 (140 carriers and 103 non-carriers of LS) and a response rate of 65.1%.

Study respondents were mostly females (63.8%) and from families with a confirmed MSH2 gene mutation (92.6%). Of the MSH2 mutations (intron 5 splice site, exon 8 deletion or exon 4-16 deletion), the dominant type was the intron 5 splice site (62.1%). The remaining participants had mutations in either MLH1 (6.6%) or MSH6 (0.8%). The mean age was 48.80 (SD =13.60), with a range of 19 to 83 years. Most participants were

carriers (57.6%) but unaffected by cancer at the time of the study (72.8%). Although study respondents and non-responders were similar with regard to gender (χ^2 (1, N=)=2.08, $p>0.05$), non-responders tended to be non-carriers (χ^2 (1, N=)=4.79, $p<0.05$) and younger (t (361)= -2.63, $p<0.01$) than respondents.

Data Analysis

Data were coded and entered into the Statistical Package for the Social Sciences (SPSS) for analysis. Descriptive statistics were used to create a profile of respondents' scores on all study scales. The Multitrait/Multi-Item Analysis Program-Revised (MAP-R) assessed how well the PAHD met Likert scaling assumptions [44]. At the first step, the assumption concerning the appropriateness of using particular items to create a summative score (approximate equivalence of means and variances, use of all response choices in the rating scale, amount of missing data, and approximate symmetry in response distribution) was assessed. At the second step, a multitrait/multi-item correlation matrix was generated to assess three additional assumptions (linearity, item-convergent validity and item-discriminant validity). At the third step, subscale scores were assessed in terms of ceiling and floor effects, approximate symmetry, internal consistency and inter-correlations. Finally, factor analysis examined the construct validity of the 17-item PAHD scale. The appropriateness of the factor analytic model was tested using the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy and Bartlett's test of sphericity. Principal component and maximum likelihood analysis were the factor extraction methods. The

scree test was used to determine the number of factors to retain. The preferred rotation method was orthogonal using varimax rotation.

Results

Data Quality and Item-Level Summated Scale Assumptions

Data Quality

Item descriptives for the PAHD scale are displayed in Table 3.3. Missing data for individual items were random and minimal, ranging from 0.4% to 3.3%. Although there is no consensus on what constitutes extensive missing data (from 10%-40%) on any given item or variable, it is generally agreed that what is more important is whether the pattern is systematic or random in nature [45].

The majority of respondents had complete data for the two subscales. The percent of respondents with complete data ranged from 90.5% for BK to 95.5% for FC (data not shown). The minimum and random amount of missing data for this study suggests that overall the scale items were not difficult to understand or interpret [41].

All response choices were used for most items (94.1%). The data also depict variability across the rating scale and approximate a symmetrical distribution. The subscale items with minimal to no use of certain response choices were expected. For example, most individuals are expected to attach high importance to having family members talk openly about the high cancer risk (FC23).

Item-Level Scaling Assumptions

Items means and standard deviations within each subscale are approximately equivalent (Table 3.3). There are important exceptions, however, which require further elaboration. In the BK subscale, items 17, 18 and 27 have lower mean scores and greater variance than the remaining items. This finding is expected given that these items are more focused on personal worries and interaction difficulties. The higher mean scores and lower variances observed for items 11, 15 and 24 were also expected since their content focuses on the personal and family implications of knowing one's carrier status and dealing with LS. Similarly, the higher score and lower variance observed for item 23 of the FC subscale was also expected as most individuals attach importance to open discussion of high cancer risk among family members.

Scale Level Assumptions

Item Internal Consistency

Table 3.4 outlines Pearson item-scale correlations corrected for item overlap [41,46]. Item-scale correlations were used to examine the relationship of each item to its hypothesized scale (i.e., internal consistency). Correlations for all items within their respective scales are larger than correlations between items and competing scales. In addition, all item-scale correlations are 0.42 or larger indicating a substantial and satisfactory item internal consistency [41].

Table 3.4: Factor scores and final item to scale correlations

Scale item	Factor 1	Factor 2	BK§	FC§
BK11_R	.620	-.121	0.58*	-0.25
BR14_R	.555	-.051	0.45*	-0.16
BK15_R	.516	-.080	0.46*	-0.20
BK17_R	.531	-.150	0.49*	-0.26
BK18_R	.562	-.412	0.55*	-0.46
BK19_R	.520	-.160	0.48*	-0.28
BK20_R	.583	-.218	0.55*	-0.32
BK24_R	.473	-.055	0.42*	-0.16
BK25_R	.612	-.188	0.56*	-0.32
BK27_R	.533	-.209	0.50*	-0.32
FC16	-.263	.524	-0.36	0.46*
FC21	-.103	.769	-0.29	0.70*
FC22	.001	.706	-0.19	0.59*
FC23	-.180	.798	-0.36	0.73*
FC26	-.237	.503	-0.34	0.51*
FC28	-.162	.537	-0.28	0.48*
FC29	-.180	.600	-0.32	0.58*

Abbreviations: *BK* = Burden of knowing, *FC* = Family connectedness.

Extraction Method: Maximum likelihood; Number of factors to retain: Scree test;
Rotation method: Varimax.

§ Item-scale correlation corrected for overlap (relevant item removed from its scale for correlation). *Denotes item correlations with hypothesized scales.

Equality of Item-Scale Correlations

This assumption addresses the proximity of values for all item-scale correlations within a hypothesized scale. The best scale contains item-scale correlations that are roughly equal and ideally fall within the 0.40 to 0.70 range [41]. The reader is again referred to the corrected item-total correlations for individual items and their subscales in the columns with asterisks in Table 3.4.

For the majority of items in the two subscales, the corrected-item total correlations fall within an acceptable range. There are some exceptions however. The items that appear to be contributing more to their various scales than other items include items 21 and 23 of the FC subscale. These items deal with emotional content which may be responsible for the observed discrepancies. This finding is expected to a degree since item content is focused on the importance of feeling supported by family/friends in coming to terms with being a carrier/non-carrier and the importance of family members openly discussing the cancer risk.

Item Discriminant Validity

This assumption examines the strength of item correlations with other scales with the objective that each item has a stronger correlation with its hypothesized scale than with other related scales. Study findings are summarized in Table 3.4. Four score categories (-1, -2, +1 or +2) are possible for each test with the standard error of correlation setting the criterion. Values of a -1 and a -2 indicate that an item has failed the test of item discriminant validity. In this study, all item scale discriminant tests (data not shown)

scored +2 indicating item-scale correlations were significantly higher for the hypothesized scale than for a competing scale.

Scale Level Descriptive Statistics

Total subscale scores were constructed for each participant following confirmation of item scaling assumptions. Consideration was first given to the impact of select sample characteristics on subscale scores. At the second step, the properties of the subscales were examined with special attention given to the logic of mean and standard deviation scores.

Comparability of Scale Scores

It was hypothesized that subscale means should be approximately equal within the sample based on demographic and illness-related characteristics. The reader is reminded that the BK subscale is reversed scored. The *t*-test of difference and correlation tests assessed the impact of select factors on subscale scores. No significant effect was detected for carrier status, exon type, cancer presence, age or time since genetic testing ($p > .05$) (data not shown). However, females tended to report significantly higher levels of burden than men on the BK subscale. Women also had significantly higher mean scores than men on the FC subscale suggesting that women attach greater importance to having access to family support and resources in dealing with LS.

Scale Properties

Subscale means, standard deviations, lowest and highest scores and score ranges were examined for both raw and transformed scores. The focus here was on the logic behind the distribution of subscale scores. For the BK subscale, a higher score is reflective of less personal and family burden associated with adjustment to hereditary cancer. Higher scores on the FC subscale are reflective of better family connectedness in dealing with the challenges posed by LS.

The pattern of mean scores and standard deviations for each subscale is summarized in Table 3.5. The transformed mean score (62 ± 20.9) on BK suggests that participants, on average, reported experiencing *a little to moderate* amount of burden. The transformed mean score (73 ± 19.9) on the FC subscale suggests that respondents, on average, gave high ratings to having open discussions and access to family resources/supports to handle the challenges posed by LS.

Table 3.5: Descriptive statistics using transformed scores for Burden of Knowing (BK) and Family Connectedness (FC) scales

Scale	Mean	SD	Range	% Missing	% At floor	% At ceiling
BK	62.0	20.9	0-100	9.5	0.5	0.5
FC	73.0	19.9	14.3-100	4.5	0.4	6.5

Reliability and Validity of PAHD

Cronbach's alpha coefficient was used to assess internal consistency. Correlations among the subscales are useful preliminary measures of the construct validity of the entire scale. Reliability ranged from 0.83 for BK to 0.84 for FC. The reliability coefficients were above the minimum 0.70 level suggested for group level comparisons [47]. These findings suggest that the two subscales have good internal consistency.

The findings support the premise that each of the two subscales is making a distinct contribution to the overall PAHD scale. The alpha coefficients for each of the subscales are larger than the Pearson's r values (data not shown). The subscales of the PAHD depict significant low to moderate, negative correlations with each other. That is, higher levels of family connectedness are associated with lower levels of personal and family burden in adjusting to LS.

The 243 participants provided an adequate sample for conducting factor analysis of the 17-item PAHD scale. The KMO value was 0.85 exceeding the minimally acceptable level of 0.6 [48]. Bartlett's test of sphericity was also acceptable ($p = 0.000$), indicating the feasibility of using a factor model for the analysis. These two measures of psychometric adequacy suggested that the PAHD correlation matrix was suitable for factor analysis.

Factor analysis revealed four distinct dimensions. Based on the scree plot, it was possible to force a two-factor solution which accounted for 45.4% of the variance (Table 3.4). The

first 10-item factor, BK, included items with loadings greater than 0.47. The scale had a reliability of 0.83. Item BK18_R appeared to be factorially complex. While its highest loading is on factor 1, it also loads on factor 2. Using a $\pm .33$ as the minimal level of practical significance for factor loadings [49], our team could either delete the item from the analysis or rewrite it [50]. At this stage of scale development, it was decided to retain the item for further investigation. The second 7-item factor, FC, included items with loadings greater than 0.50. The scale had a reliability of 0.84. Overall, the factor analysis supports the qualitative and quantitative findings.

Discussion

The PAHD scale was the outcome of a program of research that relied on survey and qualitative methods to inform the research team about psychosocial adjustment challenges in LS families. The scale was developed from content defining the struggling to adjust construct of a theoretical model generated from grounded theory. A four-member research team developed the scale by generating a large set of potential items, refining the items, and validating item content using experts and individuals from families with hereditary cancer.

By developing the PAHD from a qualitative data base, the content is steeped in the personal experiences of individuals from families with hereditary cancer. Various authors argue that instrument item-content generated from qualitative data is more likely to capture the experiences of targeted groups [51,52]. It is also argued that clinical tools

developed in this manner have better content and face validity and excellent psychometric properties [53].

The current study provides initial evidence to support the psychometric properties of the PAHD scale. The pilot study supported the relevancy of item content and logic of the two subscale structure. Application of the MAP-R to findings from the larger sample suggests that the PAHD has acceptable internal consistency reliability, item-convergent validity and item-discriminant validity [44]. Intrascale correlations compared with scale Cronbach's alphas indicate that the two subscales (BK and FC) of the PAHD are measuring distinct but interrelated concepts.

The BK scale is intended to capture the subjective perception of individual and family burden from knowing about the presence of LS in the family. The mean BK score suggests that participants, on average, reported experiencing *a little to moderate* burden. Although no significant differences were observed for carrier and affected status or time since genetic testing, women tended to report higher levels of burden than men. Despite the limited insight from existing literature on the depth and scope of the long-term struggles of individuals living within LS families, several authors acknowledge that their complexity is shaped by the interaction of experiential cancer-based knowledge from the past and present as well as individual coping styles [14,52,54-57]. Results from the current study support previous qualitative findings that a subgroup of individuals

experience psychosocial distress in the long-term following confirmation of hereditary cancer [39,40].

The second subscale, FC, is intended to capture the importance of having access to resources and family supports in sharing the burden and challenges of hereditary cancer. The mean score suggests that respondents, on average, gave high ratings to the presence of supportive family structures. Again study findings did not vary based on carrier and affected status or time since genetic testing, but women tended to value family supports more than men.

The low to moderate correlation between the two subscales support the multidimensional nature of the PAHD scale. Given that the correlations between the two scales of the PAHD are less than their reliability coefficients, there is evidence of unique reliable variance measured by each scale. A major premise of the model from which the PAHD was developed is that living in families characterized by open, supportive relationships facilitates psychosocial and emotional adjustment and decreases the burden associated with the presence of hereditary cancer. Therefore, it was expected that the subscales of the PAHD would correlate well with each other.

The findings suggest that individuals with more perceived support from family and friends tended to be less burdened from dealing with the challenges posed by hereditary cancer in the family. The value of the strength and stability of family support systems for

facilitating positive coping and adjustment at the individual and family level is receiving increased attention in the research literature on genetic-based diseases [13,52,55,57].

The results of these analyses provide support for the uniqueness of the PAHD subscales and add further credence to its validity. Future studies are needed to determine the scale's potential for monitoring the long-term psychosocial adjustment.

Limitations

While the initial validation results are promising, there are a number of limitations to consider. First the study was cross-sectional and thus it is not possible to evaluate the scale's monitoring capabilities. Second, the use of mixed methods for data collection may have influenced the findings. Further, the responders were significantly older than non-responders thus potentially limiting our knowledge of the experiences of younger individuals. Finally, it is also possible that the higher proportion of non-carriers among the non-responders may have altered the findings.

Conclusion

The use of qualitative data to develop the PAHD has produced a scale that is steeped in the experiences of individuals and families with hereditary cancer. Initial testing suggests that the scale is psychometrically sound and capable of assessing psychosocial adjustment. Although study results support other findings reported in the literature, the PAHD scale is unique in that it is specific to hereditary cancer. As a clinical monitoring

tool for use following genetic testing, it has the potential to identify those who are experiencing psychosocial challenges and who may require additional support for optimal adjustment.

The PAHD scale has been adapted and is being piloted in a second population with hereditary disease. A focus of this pilot is to examine the psychosocial impact of arrhythmogenic right ventricular cardiomyopathy (ARVC) on individuals and families post-genetic testing. The next stage of research for the project team will focus on implementing the PAHD scale in Community Familial Cancer Genetics Clinics throughout Newfoundland and Labrador.

Appendix 1

Psychosocial Adjustment to Hereditary Diseases (PAHD) Scale.

We are interested in the long-term effects of a confirmed HNPCC or Lynch syndrome presence in families. Everyone goes through periods of trying to make sense of inner feelings about what the future might hold for the self and other family members. Using the scale given, you are asked to rate how well each statement reflects your situation (Table 3.6).

Table 3.6: Psychosocial Adjustment to Hereditary Diseases (PAHD) Scale

	0	1	2	3	4
	Not at all	A little bit	Moderately	Quite a bit	Extremely
1. I think about being a carrier/non-carrier more than I should. (BK11_R).....				0 1	2 3 4
2. I try to be positive about my future health and overall well-being. (BK12)				0 1	2 3 4
3. It is important for my future health not to dwell on the hereditary link to cancer in the family. (BK13)				0 1	2 3 4
4. It was hard changing how often I had to screen for cancer. (BK14_R)				0 1	2 3 4
5. It bothers me when others do not accept my carrier/non-carrier status. (BK15_R)				0 1	2 3 4
6. Younger people need to be encouraged to talk about all the cancer in the family. (FC16)				0 1	2 3 4
7. I find it hard dealing with younger family members who get cancer. (BK17_R)				0 1	2 3 4
8. I worry about what the future might hold for younger family members. (BK18_R)				0 1	2 3 4
9. The stress of so much cancer in the family, more so in younger members, pulled some of us closer together but pushed others apart. (BK19_R)				0 1	2 3 4
10. Regular screening for cancer became a constant reminder of my cancer risk by being in this family. (BK20_R)				0 1	2 3 4

Some families handle the challenges of a strong cancer presence better than others do. We want to know how well individuals in your family support one another. Using the scale given, you are asked to rate how well each statement reflects your situation.

11. Feeling supported by family and friends has helped me accept being a carrier/non-carrier. (FC21)				0 1	2 3 4
12. I find it easy to seek help from family members when I need it. (FC 22) ..				0 1	2 3 4
13. It is important for everyone to talk openly about the high cancer risk in the family. (FC23)				0 1	2 3 4
14. I am concerned that the presence of hereditary cancer has hurt family relations. (BK24_R)				0 1	2 3 4
15. I worry that all the suffering and death from cancer is placing too much burden on family members. (BK25_R)				0 1	2 3 4
16. Providing care to other family members with cancer has helped me become more accepting of my future. (FC26)				0 1	2 3 4
17. With so much cancer in the family, I worried that something would show up on my next screening test. (BK27_R)				0 1	2 3 4
18. When I knew there was a test to see if my family had the cancer gene, I was relieved. (FC28)				0 1	2 3 4
19. Encouragement and support from family and friends helps one accept the need for healthy living and cancer screening. (FC29)				0 1	2 3 4

Note: R indicates items to be reverse coded. BK = Burden of Knowing. FC = Family Connectedness

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Authors' Contributions

CW, ME, DG and PP conceived and designed the study. CW, KW, HL and VL constructed the items for the scales. CW, KW, DG, HL, VL and JD were involved in data analysis. KW and CW drafted the manuscript. DG, PP, ME, HL, VL, JC and GWNF critically reviewed the manuscript for important intellectual content. All authors read and approved the final manuscript.

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CHAPTER 4

Lynch Syndrome: Barriers to and Facilitators of Screening and Disease Management

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Background: Lynch syndrome is a hereditary cancer with confirmed carriers at high risk for colorectal (CRC) and extracolonic cancers. The purpose of the current study was to develop a greater understanding of the factors influencing decisions about disease management post-genetic testing.

Methods: The study used a grounded theory approach to data collection and analysis as part of a multiphase project examining the psychosocial and behavioral impact of predictive DNA testing for Lynch syndrome. Individual and small group interviews were conducted with individuals from 10 families with the MSH2 intron 5 splice site mutation or exon 8 deletion. The data from confirmed carriers (n = 23) were subjected to re-analysis to identify key barriers to and/or facilitators of screening and disease management.

Results: Thematic analysis identified personal, health care provider and health care system factors as dominant barriers to and/or facilitators of managing Lynch syndrome. Person-centered factors reflect risk perceptions and decision-making, and enduring screening/disease management. The perceived knowledge and clinical management skills of health care providers also influenced participation in recommended protocols. The health care system barriers/facilitators are defined in terms of continuity of care and coordination of services among providers.

Conclusions: Individuals with Lynch syndrome often encounter multiple barriers to and facilitators of disease management that go beyond the individual to the provider and health care system levels. The current organization and implementation of health care services are inadequate. A coordinated system of local services capable of providing

integrated, efficient health care and follow-up, populated by providers with knowledge of hereditary cancer, is necessary to maintain optimal health.

Introduction

The increased use of predictive DNA testing to determine the hereditary basis of familial cancer has important implications for cognitive, affective and behavioral outcomes of high risk individuals. Investigations into the impact of genetic testing have focused more on cognitive and affective responses and less on factors facilitating optimal disease management. Our understanding of behavioral responses is a significant gap in the research literature.

The most common hereditary colon cancer is Lynch syndrome [1-4] which is an autosomal dominant disease accounting for 2-5% of all colorectal cancers (CRCs) worldwide [1,5], with geographical clusterings observed [5,6]. A puzzling and unexplained feature of the disease is the variable expressivity (differing ages of onset, cancer sites) and incomplete penetrance (not all carriers develop the disease) [6,7]. Lynch syndrome has a lifetime CRC risk of about 80% [7,8] and is also associated with extracolonic cancers of the uterus, ovary, kidney, urinary tract, stomach, biliary tract, small intestine and brain [8]. Gynecologic cancers are important for female carriers who have a lifetime risk of 40-60% for endometrial and 10-21% for ovarian cancers [4,6].

Confirmation of Lynch syndrome means that all family members should undergo predictive DNA testing and/or be strongly encouraged to regularly screen. The effectiveness of screening in reducing morbidity and mortality from CRC is well supported [9,10]. Despite this, there is suboptimal uptake of screening by high-risk individuals [11-13]. Wide variability in adherence rates have been reported, with colonoscopy screening ranging from 53-100% [11,14-20], transvaginal ultrasonography from 69-86% [14,20,21] and endometrial biopsies around 54% [21].

From a clinical management perspective, it is important to know why some high risk individuals fail to follow recommended guidelines. Few research inquiries have attempted to identify facilitators of, or barriers to, behavioral change following confirmation of hereditary disease [22-28]. Merely informing individuals of their cancer risk may not motivate behavior change [25] and could possibly impede screening if perceived to be uncontrollable [29,30].

Some authors have conjectured that awareness of familial cancer patterns and personal/family cancer experiences influence risk perceptions which, in turn, impact acceptance of a carrier status and engagement with screening [25-27,30-32]. Other authors have used social cognition theory as a template for conceptualizing cognitive and emotional factors that impact reactions to predictive DNA testing and, ultimately, behavioral responses [25,30,31]. Nevertheless, it remains unclear how risk perceptions are shaped by disease-related experiences and impact behavior.

High risk individuals are expected to manage their cancer risk [16,21,33]. This can be difficult without consensus on the scope, frequency, and age of initiation of screening for CRC [4,34-37] and extracolonic cancers [4,34,35,38]. Despite the documented benefits of prophylactic interventions, like gynecologic surgeries, for reducing cancer risk [4,34,38], these strategies have not been fully integrated into the clinical management of Lynch syndrome families.

Health care providers play a key role in encouraging high risk individuals to become involved in disease management [4,34,35,39]. It is critical that all providers are adequately informed about Lynch syndrome, obtain comprehensive medical and family histories [39-41], make referrals to genetics services [4] and recommend appropriate screening and management [3,34,36]. However, significant gaps exist in providers knowledge [12,42] and many fail to identify at-risk individuals and/or advise them appropriately [39,42].

The evidence suggests that the health care system can pose barriers to screening. Ineffectual coordination and continuity of care [43], inadequate access to and availability of screening/specialty services [44], and variation in provider recommendations [39,43] can impede effective clinical management. Currently, there is a paucity of research on how individuals interact with the health care system as they adjust to living with a confirmed hereditary cancer risk.

This article reports on findings derived from a grounded theory study on the psychosocial and behavioral impact of genetic testing on individuals at high risk for Lynch syndrome. In this paper we focus on how confirmed carriers experience disease management and view the quality of interactions with health care providers and the overall health care system. We include recommendations on how to improve disease management and facilitate quality outcomes.

Methods

Study Design

A grounded theory study was part of a multiphase project examining the psychosocial and behavioral impact of DNA testing for Lynch syndrome. The Human Investigation Committee, Memorial University, approved the study protocol.

Grounded theory was used during data collection and analysis [45]. This approach is considered appropriate as the focus is not solely on how health threats, diagnostic procedures or treatment protocols are experienced, but also on how this information is received and assimilated into belief structures, and how this integration becomes a stimulant for actions needed to achieve optimal health functioning. The strength of this inductive approach is the emphasis placed on identifying and describing the social-psychological processes grounded in the data emerging from participant interviews [46].

Population and Predictive Genetic Testing

The target population was individuals from high and intermediate risk families registered in the Provincial Medical Genetics Program of Newfoundland and Labrador (NL) and participating in the larger case control study. Eligible participants for the grounded theory study were those living in families with a confirmed MSH2 mutation-the intron 5 splice site mutation (942+3A > T) (12 families) or exon 8 deletion (5 families). Details on this population have been reported elsewhere [6].

A purposive sample of 39 individuals from 10 families who had completed genetic testing and knew their status was selected from the accessible population (N = 276). Predictive DNA testing is offered to individuals in high and intermediate risk families. Follow-up counseling sessions are held with those interested in testing for known mutations. Testing results are normally reported in face-to-face sessions. Follow-up letters summarizing the results are forwarded to participants and their physicians. Clinical screening programs are adjusted according to test results.

This article focuses on 23 confirmed carriers (14 female, 9 male) from three families with the intron 5 splice site mutation and three families with the exon 8 deletion (Table 4.1). The mean time from genetic testing to the initial interview was 6.0 (\pm 2.8) years (range .1 to 9.6) and age at the first interview was 48.9 (\pm 13.6) years (range 26 to 78). Thirteen participants developed cancer at a mean age of 43 (\pm 5.8) years (range 33 to 54). Significantly, those who had reached the affected stage experienced a total of 27 primary

cancers with CRC occurring at least once in 61.5% of the cases. Of the 14 female carriers, five developed endometrial cancer (35.7%) and four (28.6%) had prophylactic hysterectomies and/or oophorectomies.

Table 4.1: Participant characteristics (N = 23)

<i>ID</i>	<i>Family</i>	<i>Gender</i>	<i>Post-GT^a</i>	<i>Age^b</i>	<i>Affected</i>	<i>Onset Age</i>	<i>Cancer Types^c</i>
23	1B	Female	6.42	57	No	---	---
24	1B	Female	6.42	78	Yes	46	CRC/EC
25	1B	Male	8.50	52	Yes	42	CRC/GA
26	1B	Female	2.42	32	No	---	---
31	1B	Male	7.50	47	Yes	45	CRCx2
8	1C	Male	3.67	28	No	---	---
22	1C	Male	6.50	26	No	---	---
30	1C	Male	7.42	57	No	---	---
9	2A	Female	8.08	41	Yes	39	CRCx2
32	2A	Female	9.58	69	Yes	35	CRCx2/EC/GA/SK
20	2B	Female	9.08	50	Yes	33	EC/BR/VA
21	2C	Male	9.08	50	No	---	---
10	3A	Female	7.00	42	No	---	---
27	3A	Female	8.17	51	Yes	43	Ovarian
28	3A	Male	8.17	43	Yes	45	CRC/DUO
29	3A	Female	7.50	33	No	---	---
11	3B	Male	8.42	76	Yes	39	CRCx2/SK/KD
4	6	Female	0.75	48	Yes	49	CRC
19	6	Female	0.08	63	Yes	54	SK
37	7	Female	3.17	50	Yes	46	KD/EC
38	7	Male	3.08	46	No	---	---
34	8	Female	2.83	43	Yes	40	EC
36	8	Female	3.75	42	No	---	---

Note. Families 1B to 3B have the intron 5 mutation and families 6 to 8 have the exon 8 deletion. The use of A, B or C after the family number denotes separate nuclear families within a particular extended family.

^a Years since genetic testing.

^b Age at first interview.

^c CRC = colorectal; EC = endometrial; GA = gastric; SK = skin; BR = breast; VA = vaginal; KD = kidney; DUO = duodenal.

Procedure

After initial contact, interested individuals were forwarded a cover letter, brief study summary and consent form, and re-contacted to schedule interviews. Following informed, written consent, two interviewers (principal investigator and research assistant) conducted 60 to 90 minute interviews with participants. Individual or small group interviews (immediate family only) took place in participants' homes or conference rooms. Open-ended questions elicited commentary on experiences with cancer in the family (first awareness of hereditary link, perceived personal risk, screening motivation) and genetic testing (decision-making, counseling experiences, reaction to status, understanding implications, impact on family). Additional questions evolved from the thematic content analysis (adjusting to carrier status, screening experiences, health care service needs). A second interview provided participants with an opportunity to comment upon and confirm their interpretive summaries. Information from the second interview also helped the research team augment gaps in the data, and the conceptual categories and properties of the emerging substantive theory.

Data Analysis

Data analysis proceeded in several phases. First, interviews were transcribed verbatim and perused independently by a three-member team. The focus was on interpreting the meaning of words and sentences through reading and re-reading the text, and assigning substantive codes to recurrent themes. Team discussions focused on achieving consensus on emerging themes. Second, mid-way through data collection, interviewing was

temporarily stopped and the constant-comparative method of analysis applied to the data sets by two members working independently. The objective was to identify relationships between and among substantive codes. As potential category relationships were tested within the data, a substantive theory began to emerge.

Third, in-depth analysis of the first 18 transcripts revealed a family context (i.e., experiential base and degree of burden and sense of resilience), differences between carriers and non-carriers of Lynch syndrome (views of screening protocols and timelines to diagnosis, coping approaches to short/long term prognosis, implications for children) and differences between affected and unaffected carriers (intensity of reactions to cancer onset/recurrences). The focus shifted to purposive selection of an additional 14 carriers from family groupings with many ($n = 9$) having reached the affected stage. This approach to subject selection facilitated confirmation of the substantive codes and refinement of their properties.

In the later stages of analysis, length of time since discovery of the family-based gene mutation and the availability of and actual involvement in genetic testing surfaced as potential influencing factors on individual and family perceptions. The decision was made to sample additional individuals to determine the importance of time. Data collection continued ($n = 7$) until the research team was confident that the experiences of this group would not alter existing properties or categories. At the final step, the data and

resulting theory were examined by an independent consultant to enhance credibility and accuracy. This resulted in a more parsimonious and refined set of themes and codes.

Results

Data analysis revealed several personal, provider and health system barriers to and/or facilitators of effective disease management. Risk perceptions and acceptance of the genetic link to cancer influenced individuals' ability to adjust to their carrier status and accept recommended regimes. Despite the importance of risk perceptions and acceptance, interactions with the health care system and providers clearly affected overall adjustment.

Person-Centered Barriers/Facilitators

The most important personal factors were emotional and psychosocial states, physical health status, prior experiences with cancer screening and/or treatment, and accepting the need for prophylactic interventions. These factors are categorized as risk perceptions and decision-making, and enduring screening/disease management.

Risk Perceptions and Decision-Making

Risk perceptions play a crucial role in motivating individuals to become involved in disease management. A meaningful balance must be forged between the cognitive and emotional spheres for decision-making. Full engagement seems to be highly contingent upon emotionally accepting potential threats to the self and understanding the benefits of ongoing monitoring and timely interventions.

Participants spoke about the emotional and physical challenges of living with Lynch syndrome. Despite understanding the importance of following recommended protocols, the burden of dealing with this disease can be overwhelming.

Like I can sit here and say to you, 'Oh yeah, all the knowledge in the world, it's great to know. But look at it from the human part of it, your own self going through this every single day'. Every time someone goes to a doctor, my crowd is like, 'Who is next, right?' It gets to you after a while. [I10, Fam3A]

All participants echoed the importance of screening while being ever mindful of the challenge of living with high cancer risk. Only one participant had not engaged in cancer screening following a positive genetic test result. However, not all of the participants were participating in the full scope of cancer screening and/or adhering to recommended intervals. Oscillating cognitive and emotional forces impinge on individuals' willingness to become fully involved in the process.

Although some participants had misgivings about knowing their status, these doubts soon subsided when screening detected cancer. Several individuals alluded to the potential benefits of regular screening.

I started seeing [gynecologist] on a regular basis. I was constantly being screened; it [uterine cancer] was picked up. I had the Pap smear and then the endometrial

biopsy and both of that came back abnormal. It [cancer] was just in the early stages. [I37, Fam7]

Participants also recognized the need to accept and assume responsibility for healthy living and self-monitoring for signs and symptoms of an impending illness. Some perceived this as critical for disease management.

Since I found out that I have the gene, I try to eat a little better and ... exercise a little better. You watch for things and you're a little more conscious of the things you're putting in your body. [I26, Fam1B]

How well individuals adjusted to the burden of the disease had important implications for their willingness to follow recommended guidelines. Everyone who accepted having Lynch syndrome recognized the benefits of disease management. For some, the motivation to do so was enhanced following early cancer detection.

Enduring Screening and Disease Management

Participants often experienced conflicting emotions about knowing what had to be done, wanting to do it and actually doing it. For many, scheduling appointments and waiting for diagnostic test results became physically draining, time consuming, and burdensome. Successful adjustment seemed highly contingent upon living as normal a life as possible without being constantly reminded of cancer risk. The anxiety and worry associated with

the probability of cancer detection created emotional barriers that impeded actions, forcing some to use "time out" periods.

I'm after falling off the wagon a bit, where I've had a couple of surgeries. ... I couldn't do one test because I was doing something else. ...Then after one of the surgeries, I guess you kind of reach your tolerance level. It was a conscious decision. ...I just had to give it up for a while. [I9, Fam2A]

Participants relayed stories of endurance and perseverance. Although the full scope of physical and emotional difficulties was individual specific and time dependent, many commented on the challenges of regular screening. Even when highly motivated, the emotional strain of upcoming procedures can be quite burdensome especially when prior experiences evoke unpleasant memories: "It's just as well to tell the truth, I cry. I'm weeks before thinking about it and I'm dreading it. I'm dreading the day that the test will come." [I37, Fam7]

For many participants, the type and frequency of screening protocols and recommended prophylactic interventions increased with evolving knowledge and/or emerging cancer patterns within the family. The increasing demands often became a struggle: "It [screening] is cumulative and I find more and more. I don't dwell on it, but it's changing and I find I'm really, really sick of having to have this..." [I34, Fam8]

Ongoing disease management requires adequate resources to support everyday living. The significance of this for any one person can be influenced by their financial status, family responsibilities and employment history, among others. For many, accessing appropriate cancer care involves having the means and willingness to travel outside of their communities, taking time off work and/or having adequate support to deal with family responsibilities. Practical issues are important because they may interfere with one's willingness and ability to access recommended screening/treatment.

I'm a year in the hole on my sick leave here now. So if I got a flu or anything like that, I can't just stay home. Every appointment [for diagnostic tests], where I'm running to town is over so many hours ... it is sick leave. Then I had surgeries where you take off six weeks. [I9, Fam2A]

When early stage cancer is identified, physical and psychological benefits occur immediately following treatment. These benefits may not be so obvious for individuals asked to consider prophylactic surgery in the absence of signs and symptoms of disease. Female family members are encouraged to have prophylactic hysterectomy and bilateral salpingo-oophorectomy because of their high risk for endometrial and ovarian cancer, especially when parents or sisters have had these cancers. In the current study, four women had prophylactic surgery without having symptoms of disease whereas another two had hysterectomies for benign gynecological disease.

The "present" for many participants reflects a story of survivorship and endurance. It was apparent from listening to their stories that the burden of screening/treatment sometimes became a deterrent to continuance. This burden was augmented or lessened by the scope of family and work responsibilities.

Provider-Centered Barriers/Facilitators

The perceived knowledge and skills of health care providers surfaced as key factors facilitating or impeding participation in regular screening and disease management. Participants wanted to receive care from physicians/specialists familiar with their family cancer history. Trust seemed to increase when physicians were intimately aware of the family history and acknowledged the importance of monitoring high risk cancer sites.

When you get a doctor like that [open and engaging] it means something because you don't feel like you're just a number, like they know you personally. They seem like they care and you don't come across too many like that. I felt like a number for so long. [I27, Fam3A]

Most disconcerting for participants was the perceived tendency for some physicians to discount age of onset of first cancers in families as a benchmark for screening initiation and follow-up. When physicians failed to do this, participants distrusted their knowledge: "The problem is they are young and because they are young the doctors aren't testing

[screening] them properly for bowel cancer. Not testing them early enough. They're not realizing that even now after all this." [I23, Fam1B]

Integral to effective monitoring is having knowledge of the natural history of the disease. Following encounters with physicians who seemed to have limited understanding of Lynch syndrome, some participants felt the need to become better informed and share this knowledge with them.

Every time I go to him [physician] I say, 'Now do you know that these lesions are sometimes flat? ...Don't look for bumps. Look for these flat lesions which are the Lynch II'. Even now I don't know if he hears me. Because they'll always talk about removing polyps and I don't know if that's set out enough in the literature. [I20, Fam2B]

Similar concerns were expressed about physicians not perceived to be attentive enough to the extracolonic cancers.

It would be nice if we knew it was being monitored and we were all getting the proper checks. But not only just for bowel. I mean they do a colonoscopy, that's not going to show if you have anything in your ovaries or kidneys or anywhere else. [I23, Fam1B]

From a clinical management perspective, participants assessed physicians in terms of the completeness of medical care and quality of communications. Medical care was evaluated by the thoroughness of history taking and physical examinations. If unsure about a physician's approach, participants felt the need to enlighten them.

Unless you can tell a doctor what is wrong with you he can't see through you and know, unless you recognize symptoms yourself. Gone are the days when ... they [physicians] do a complete physical and chest x-ray. ...They don't look at it [cancer] as coming from a history. [I32, Fam2A]

Quality of communications was defined in terms of effective interpersonal skills.

Participants wanted providers who were sincere and took the time to facilitate understanding. Some commented on the limited communication of an informative nature and the lack of perceived support: "When I go for a colonoscopy, it's the quicker you're in and out the better. It's no such thing as sit down for any discussion. We got no support system." [I25, Fam1B]. Other participants presented a contrasting perspective.

When they found things that he [specialist] has been suspicious about, he showed me the pictures and he sits down. 'This is what we are going to do'. ...So he's always been very informative. ...I appreciate that, I want that honesty. ...So I can be actively involved with what happens to me. [I21, Fam2C]

In essence, living with Lynch syndrome is an independent journey that requires being attentive to physical changes, appreciative of their implications for future health, and assertive about receiving care from knowledgeable, caring providers.

Health Care System Barriers/Facilitators

Continuity of care at the provider and system levels seemed to pose great difficulty for participants. Continuity of care is dependent upon continuous information flow (disease and person-focused), strategic coordination of services (complementary and timely), and accessing a consistent provider mix over time. Restricted continuity of care can play havoc with successful disease management.

Especially vital is ongoing collaboration among primary and specialty care sectors during the planning and delivery of services. As the number of diagnostic procedures and potential cancer sites increase, there is a concomitant increase in the number of specialists involved in providing care and, thus, the greater potential for inconsistencies in recommended screening intervals. A couple of participants voiced their frustrations following interactions with different aspects of the health care system: "But my family doctor argued that it [colonoscopy] should be every year. I feel it should be done every year. Every three years the [specialist] wants it done." [I38, Fam7]; "I haven't been done since two years ago. That extra six months could mean a lot to me. So what am I supposed to do?" [I27, Fam3A]

Study participants were of the opinion that poor communication among providers could be detrimental to a person's well-being, quality of life and, ultimately, long-term survival. An important message conveyed is that greater consensus is needed on acceptable screening intervals and targets, especially in families with a higher than usual penetrance rate for CRC and associated cancers.

Participant comments also conveyed a vivid picture of limited organization and coordination of health care. Individuals confront challenges navigating the health care system particularly when having to deal with different institutions and physicians/specialists. At times, this requires a tenacious, persistent approach and a working knowledge of the system.

Every six months I ... have the ultrasound done. ...Then I have to make an appointment to see the specialist ... for what? It is a negative ultrasound. Then you're supposed to ... get another ultrasound but they can't get an appointment set up that far in advance. ...then you need a requisition. [I9, Fam2A]

Everyone echoed the need for a more coordinated approach that lessens the demands on personal time and coping resources. One participant commented thus, "I would like to have one stop shopping. It seems like I am running around doing all this and I don't want this. I don't need this." [I4, Fam6]

Timely access to services can become a major liability, with delays especially upsetting for individuals subject to heightened uncertainty and worry. Participants suggested that carriers should be given priority access to screening and specialty services.

After I had my operation [for colon cancer] I phoned up for another appointment [with specialist] and they told me that it could be another six months before I get in and my year was up then right. ...So I phoned the doctor that operated on me and I got in within two weeks. ...I was frightened right. [I31, Fam1B]

Despite being aware of requisite health care services, system challenges often prevented participants from 'being ahead of the game'. Especially critical is a coordinated system of care which provides timely access and follow-up. Without adequate resources, individuals are at greater risk to be burdened by the disease.

Discussion

The current study highlights the many personal, provider and system level barriers to and facilitators of engaging in effective disease management. Study findings suggest that participants seem to be well-informed about Lynch syndrome, have accurate risk perceptions and acknowledge the benefits of regular screening. Nevertheless, the interaction of the emotional and physical burden of disease management with the practical demands of everyday living (family and work) and provider and health care system challenges may also significantly influence behavior.

Only a few studies have stressed that the behavioral impact of genetic testing is an important area for research [2,22,23,28]. Most studies have focused on psychological outcomes as opposed to potential barriers to and facilitators of informed decision-making concerning screening/treatment regimes. The current study provides informative insight into some of these factors. The findings highlight the physical and psycho-emotional obstacles (worries/concerns about potential test results/prophylactic interventions, intensity and scope of screening, preparation for and experiences with diagnostic procedures, scheduling issues) that can increase the burden of disease management. Other researchers have noted that physical and psychological barriers can add to the burden of screening, and pose deterrents to regular participation [11,14,20,32,47].

The importance of disease-related experiences for facilitating adjustment and determining the appropriateness and relevancy of healthy behaviors is not new. This finding supports, in part, the argument put forth by others that behavioral responses are a function of perceived risk which is influenced by health threat representations that continuously evolve in response to experiences with the disease in the self and/or others [25,30,31].

The current study also supports how interactions with health care providers can impact the overall burden of Lynch syndrome. Ratings of the quality of provider care are a function of perceived knowledge levels and clinical management approaches. A growing body of evidence supports the significant role played by physicians and other providers in

improving adherence in this population [13,16,33,34,43]. It is therefore important that all providers become informed about current screening and treatment protocols [16,35,48]. Several authors confirm the controversy over suitable time intervals for colonoscopy [34,35,40,41] and the variable attention given to extracolonic cancers [17,38]. These inconsistencies are worrisome. Previous research has found that those at increased risk for CRC receive insufficient information on screening intervals, risk assessment and procedures, and inadequate emotional support between diagnostic tests [20,43]. This situation not only impedes development of best practice guidelines but also creates problems for physicians involved in disease management [49,50].

Experiences with and reactions to encounters with the health care system can impede effective disease management. Our findings suggest that existing counseling and disease management resources are inadequate to meet the demands that follow predictive DNA testing. An important source of dissatisfaction is gaining timely access to needed services. Ineffective coordination of diagnostic, treatment and specialists' appointments creates unnecessary delays, enhances worry, and propels some to distance themselves from the whole process. It is apparent that referral protocols need to be simplified and more coordinated. Some authors have highlighted the need for a single service [12] or a multidisciplinary team comprised of providers committed to following evidence-informed clinical guidelines [12,20,38,39,50].

Our research illuminates the possibility of new roles for health care providers in cancer genetics. In Canada there is no national registry, as provided in some smaller countries. In the province of NL four regional health authorities (RHAs) are responsible for delivering a range of health care services in hospitals, clinics and community health programs within their respective geographic areas. Recently, genetics clinics have been established in three of these RHAs. These clinics will be linked to the Provincial Medical Genetics Program which will integrate clinical care with the evaluation of interventions directed toward improving clinical outcomes. Other researchers concur that familial cancer registries and genetics service centers are perceived to be effective mechanisms for facilitating quality outcomes [12,34,35].

Despite the limitations of a small sample size and inherent biases in having participants recall how they experienced and reacted to specific events and situations, the findings do provide practical insight into barriers and facilitators that may be individual, provider and/or system based.

Conclusions and Policy Implications

This study has further illuminated the psychosocial and behavioral impact of predictive DNA testing for Lynch syndrome. Many participants were confronted with serious issues in managing their disease. These issues require preventive strategies to help maintain optimal health and a reasonable quality of life. What is important for families is the

presence of providers with the necessary knowledge and skill base and a coordinated system of local services capable of providing integrated health care and timely follow-up.

Ideally, genetic counseling should facilitate the adoption of appropriate, lifelong disease management strategies. In light of the current findings, genetic counselors may need to assess the family and socio-cultural context of hereditary cancer [24] and its potential influence on decision-making. It is also necessary to explore the emotional aspects of living with cancer risk so that the burden of the disease can be lessened.

Importantly, Lynch syndrome has significant implications for public health policy [4]. The ultimate plan should be to provide resources that enable individuals in high risk families to develop a strong sense of resilience and maintain a balanced screening schedule. In particular, this cohort requires timely and appropriate health care services, including:

- A critical mass of genetic counselors to provide timely services to high risk families before, during and following genetic testing.
- Service providers to coordinate and streamline diverse screening and treatment resources.
- Health care providers, especially primary care physicians, informed about the risk of cancer within families and reinforcing the importance of maintaining recommended screening and initiating referrals to appropriate specialists.

- Clinical monitoring tools designed to evaluate the impact of predictive testing and the ongoing psychosocial and behavioral adjustment to living in families with hereditary cancer.

The current uncoordinated, physician dependent organization of screening for individuals with Lynch syndrome in Canada is inadequate. Given the incidence and prevalence of these hereditary cancers and the clinical benefits of screening, there is a critical need to provide integrated health care and timely follow-up in a manner that facilitates navigation of and access to the health system.

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Authors' Contributions

CW and MJE conceived and designed the study. CW and JF interviewed the participants. CW, JF, RM, VL and KW were involved in data analysis. KW and CW drafted the manuscript. PP, JG and HE critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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CHAPTER 5

General Discussion and Implications for Clinical Practice, Policy and Research

General Discussion

The final chapter provides a summary discussion of the findings, implications for clinical practice, research and policy, and limitations of the research. This program of research was designed to investigate the long-term psychosocial and behavioral adjustment to living in families with LS. Confirmation of hereditary cancer through predictive DNA testing requires adjustment on several levels. Individuals and families experience variant and evolving psychosocial and emotional states in response to being a carrier or non-carrier. Carriers are recommended to follow highly targeted surveillance and management strategies necessitating adjustment on a behavioral level. Adjustment to the presence of hereditary cancer is best described as an evolving state that ebbs and flows in response to changing personal and family experiences in the management of long-term cancer risk and emergence of cancer in the self and/or others. Personal and/or family experiences can facilitate or impede adjustment.

To understand adjustment following genetic testing for LS, it is necessary to examine a complex set of interacting factors that are individual, family and health care system-based. Biesecker and Erby (2008) [1] highlight the importance of viewing adjustment as a multidimensional construct, with many potential interacting factors altering its presentation at any point in time. Other authors suggest that psychological and emotional responses to genetic testing information are influenced by individual, familial, social and medical factors [2].

Since the identification of the mismatch repair genes 20 years ago, significant research has focused on the psychosocial implications of genetic testing for LS. Less research has been focused on living with and managing cancer risk in the long-term, how those at risk adjust behaviorally and how experiences with the health care system impact disease management. Given the lifelong surveillance required for those with LS, it is imperative that facilitators of and barriers to recommended screening and treatment be identified. It is also critical that health care providers be able to identify those at risk for poor adjustment following confirmation of LS so that strategies promoting quality outcomes can be implemented.

The *struggling to adjust* construct of the substantive theory from the qualitative study was used to develop monitoring tools capable of assessing adjustment. Findings from the *first* paper presented in Chapter 2 examining the psychosocial and emotional implications of living in families with LS indicate that carriers, affected and unaffected with cancer, and non-carriers oscillated between positive and negative feeling states. While most were able to adjust psychosocially to cancer risk in the self and/or others, some were burdened by this reality and struggled to adjust. Importantly, our findings provide new knowledge on the long-term adjustment of carriers who developed cancer, an area recently identified by others as lacking research [3]. Some of the participants in our study had two or more cancer episodes resulting in the experiential knowledge that LS is often a challenging, evolving entity that brings much uncertainty to individuals and families.

The presence of LS in a family can involve diverse, complex experiences that can occur concurrently at any point in time [4]. While some members may be coming to terms with being at risk, others may be undergoing genetic testing and/or cancer screening. Other members may be adapting to genetic test results, facing a cancer diagnosis, dealing with cancer treatment, managing other co-morbidities and/or experiencing the loss of a family member. Those with a confirmed mutation may be confronting issues with the testing and/or screening of children. Our findings support these ever-changing and cumulative situations within a family. These experiences can present individual and cumulative challenges, impact psychosocial responses [4] and result in continued uncertainty over the lifespan [5].

Our qualitative findings indicating that a subgroup of carriers and non-carriers experience psychosocial and emotional distress in living with LS has important implications for the management of those with hereditary cancer syndromes. Assisting individuals and families to adjust to hereditary cancer requires understanding of the potential psychosocial issues that could arise during the genetic testing process and beyond [6]. Knowledge of the complex and, often unpredictable, issues that individuals and families have to confront over time following confirmation of LS can assist health care providers in intervening in a timely manner. It is also important to understand how personal or family psychosocial factors impact health behaviors that are deemed essential in reducing morbidity and mortality associated with LS. Other researchers have suggested that psychological well-being is linked to clinically relevant outcomes in LS [4].

Our findings also suggest that hereditary cancer has implications for the entire family. Participants valued having a supportive family environment, access to resources and open communications to help manage the many challenges imposed by LS. While most families were able to communicate openly about their cancer risk, be there for each other and receive support, some were challenged in dealing with the burdens associated with hereditary cancer. These findings suggest that health care interventions for those at risk should extend beyond the individual to the family, a finding supported by others [7,8]. However, those providing care should also be aware of the individuality of family member's responses to the confirmation of hereditary cancer [9] and anticipate similar and disparate reactions among members of the same family. It is also crucial to recognize that individual adjustment to LS can be significantly shaped by the family context and dynamics [8,9].

In summary, it was apparent from the interviews in the qualitative study that individuals living in LS families experience a wide range of emotional, psychological and social issues that have important implications for their health and quality of life. These findings and the inability of previously used standardized instruments to consistently identify those experiencing adjustment difficulties led the research team to use the qualitative data base to design clinical monitoring tools. It is anticipated that these tools be used to inform the delivery of cancer genetics services.

As discussed in paper *two* in Chapter 3 the PAHD scale was developed from content defining the struggling to adjust construct of a theoretical model generated from grounded theory and tested in 243 carriers and non-carriers of LS. Using a descriptive correlational design the PAHD scale was psychometrically tested using the Multitrait/Multi-Item Analysis Program-Revised (MAP-R) [10], a method used by others [11,12].

The PAHD, steeped in the experiences of those living in families with LS, was found to be a psychometrically sound scale that is capable of assessing psychosocial adjustment. Clinical monitoring tools are needed to evaluate the impact of genetic testing and the ongoing psychosocial and behavioral adjustment to living in families with hereditary diseases. Currently, instruments commonly used in research on the psychosocial implications of genetic testing have focused on identifying symptoms such as depression, anxiety and/or cancer specific distress. This approach can be limiting in that the instruments are not specific to hereditary diseases and may not capture the unique impacts brought on by genetic knowledge and cancer risk. Others conclude that screening tools specific to hereditary diseases, used during the genetic testing process, can help genetic service providers identify those who may require interventions and/or follow-up [7].

Results from the development and preliminary testing of the PAHD support the qualitative findings that a subgroup of individuals experienced psychosocial distress in

the long-term and were burdened by the presence of LS. In fact, our findings indicated that over one third of the 243 participants experienced personal and family burden associated with adjusting to LS. Approximately two thirds of the participants experienced moderate to extreme difficulty in dealing with young people who developed cancer with non-carriers experiencing significantly more burden than carriers. The majority of carriers and non-carriers had moderate to extreme worry in relation to the future of younger family members. These findings suggest that individuals living in LS families may need support in dealing with the impact on younger family members. Overall, the findings provide support for the qualitative study and insight regarding the burdensome situations that LS families may have to endure. Previous research on LS indicates that parents are concerned about how their children will be impacted [9,13] and worry about children getting cancer at a young age [9].

Results also indicated that nearly two thirds of participants in the quantitative study perceived that screening tests heightened their worry about cancer. Some of the participants in the qualitative study also reported worrying about the possibility of finding cancer during their screening/surveillance tests. Other researchers suggest that fear of finding cancer [14,15] and worry may influence screening behaviors [16].

The quantitative findings also highlight the significance of the family's supportive structure, resources and openness in dealing with and managing LS. The majority of participants perceived that access to resources and having open communications were

very important in dealing with LS, a finding confirming our qualitative results. These findings also provide further evidence that openly discussing the presence of hereditary cancer in the family is highly valued [14,17] and plays a significant role in managing cancer risk [9] Previous research supports the influence of family resources and a positive family environment on the psychological well-being of individuals in LS families [17-20].

The results reinforce the need to identify those who may be at risk for psychosocial and emotional challenges in adjusting to LS. Therefore, the next step is to assess the clinical utility of the PAHD. It is proposed that the tool be used within the context of providing genetic testing services. It is planned that individuals seeking genetic counseling and testing for LS will be administered the PAHD. It is anticipated that the scale will assist in identifying those who may be at risk for poor psychosocial adjustment following confirmation of LS in the family. Identifying those who are experiencing or may be at risk for adjustment difficulties can facilitate the provision of health care services that focus on specific individual and family needs. Knowledge gleaned from the PAHD could also assist genetics personnel to plan and implement appropriate interventions and follow-up care.

Secondary analysis of the struggling to adjust construct in the qualitative study also indicated a second dominant theme, one focusing on behavioral adjustment to LS in the short- and long-term. The *third* paper in Chapter 4 focused on behavioral implications for

confirmed carriers. To date, investigations on the impact of genetic testing and living in families with LS have concentrated more on psychosocial and emotional implications and less on behavioral outcomes. Given the CRC cancer risks and mounting evidence on the development of extracolonic cancers in those with specific mutations [21], investigations on behavioral adjustment are critical. The benefits of cancer screening in the LS population have been documented [22,23] and published guidelines for clinical management have recently been updated [21]. Research on the effectiveness of surveillance for CRC and extracolonic cancers is expanding as researchers and clinicians attempt to propose best practice guidelines that are based on sound evidence. While colorectal surveillance is highly recommended and deemed effective, screening for select extracolonic cancers is suggested despite their lack of documented effectiveness [21,24].

Importantly, individuals with a confirmed LS mutation should be provided with screening recommendations and encouraged to comply [3]. While the research base on screening behaviors and adherence rates following confirmation of LS is expanding [25-30], minimal research has focused on identifying factors which could impact an individual's long-term adherence and behavioral adjustment. The qualitative findings discussed in Chapter 4 highlight the many personal, health care provider and system level barriers to and facilitators of screening and disease management in LS. Our findings are unique in that this is the first study, to our knowledge, to comprehensively investigate personal, health care provider and system factors that can impact the overall burden of LS. Study findings suggest that a number of factors can individually impact or interact to influence

behavioral outcomes. While some participants were able to overcome barriers to effectively managing LS, many were confronted with serious issues and struggled to adhere to recommended guidelines. Health care providers and the system should support individual and family efforts to manage LS. Therefore, the findings have significant implications for the clinical management of individuals and families with LS.

The struggling to adjust construct also provided data for the development and preliminary testing of a second adjustment scale for confirmed carriers. The Behavioral Adjustment to Hereditary Diseases (BAHD) scale addresses the perceived burden of screening/treatment, perceptions of quality health care, management of children who may be at risk and perceptions of what is needed to promote effective management of LS. Further analysis is currently being conducted on this scale and a publication on its development is planned. It is proposed that the clinical utility of the scale will be assessed within the context of genetic testing for individuals with a confirmed gene mutation for LS.

Clinical Practice Implications

In this section the implications for clinical practice, policy and research will be addressed. It is acknowledged that, given the relationship between clinical practice, policy and research, there are implications presented which could be applicable to all three areas. In the past decade information about the identification and management of LS has grown exponentially. With cancer genetics services being offered in primary care

and increased availability of genetic testing, health care providers must have the appropriate knowledge and skills to assist individuals and families with effective disease management. Findings from the studies in this dissertation have practice implications that serve to enhance the provision of genetic counseling, genetic testing and overall clinical management of individuals and families with LS.

The variation and complexity of individual and family experiences with LS necessitates a tailored approach to the provision of genetic services. Consideration must be given to all aspects of the disease, including the experiential impact of living in these families and the genetic testing process, as well as the short- and long-term adjustment to living with LS and the concomitant formal and informal support requirements. It is also recognized that some individuals living in LS families may have a lifelong need for support from genetics personnel [3].

Rapid developments in gene discovery and genetic testing for hereditary diseases are placing demands on genetic counselor services that may exceed supply [31]. It is also suggested that in hereditary cancer syndromes where individuals are often cared for by multiple health care providers, other professionals may play a role in meeting psychological support needs [31]. Other researchers suggest training a larger number of mental health professionals to work in cancer genetics clinics [3]. Our qualitative findings also support the possibility of new roles for health care professionals such as

nurses in cancer genetics [32]. Nurses can be educated to provide quality health care services and ongoing support to individuals and families.

Genetics personnel need to be cognizant of the variant levels of awareness of cancer in the family and the closeness of relatives affected as this influences risk perceptions, comprehension, acceptance and emotional readiness to become informed of one's risk. The impact of the familial social environment on adjustment to hereditary cancer is also receiving increased attention. The quality of family relations is also significant in shaping perceptions of risk and managing LS. Assessing family functioning in relation to the impact of familial cancer events can help illuminate an individual's level of awareness and acceptance of high-risk status. Knowledge gained from this assessment can help genetics personnel identify those with strong and weak family support structures. Families with supportive structures and openness to giving/receiving support suggest the presence of sufficient resources to help deal with the challenges of living with LS. However, those with limited family connectedness may be in need of additional interventions to minimize adjustment difficulties.

The use of the PAHD, as a clinical monitoring tool in cancer genetics services, can provide baseline and periodic information on individuals and their families at critical junctures in the delivery of services. It may assist genetics personnel to identify those who are experiencing or may be at risk for psychosocial and emotional challenges following confirmation of LS. This can enable genetics personnel to plan and implement

interventions that are tailored to the needs of the individual and family. It is conjectured that the PAHD can identify those who are feeling burdened by the presence of LS and are struggling to manage their disease effectively in the short- and long-term. It is also conjectured that the tool can identify those who may lack a supportive family structure in dealing with the challenges posed by LS. Recognizing those who may be experiencing challenges on a psychosocial and emotional level can facilitate supportive interventions. It is also suggested that those who are supported emotionally and psychosocially in managing LS may comply with recommended protocols and benefit from life-saving cancer surveillance.

LS is under diagnosed in many families [33]. Therefore, primary care physicians and nurse practitioners informed about the risk of cancer within high-risk families, are needed to identify those at risk, reinforce recommended screening and initiate referrals to appropriate specialists. They need to be cognizant of the features of LS, be aware of the extracolonic cancers associated with the syndrome and be able to do an extensive family history on the patient. These clinicians play an important role in identifying high-risk individuals, encouraging adherence to recommended screening and providing follow-up care after a cancer diagnosis has been made [34,35].

Individuals who are confirmed carriers may encounter challenges when faced with lifelong screening and/or treatment, particularly when there are cumulative effects resulting from the practical demands of daily living. These individuals may need

additional psychosocial and emotional support in dealing with these challenges and assistance in navigating the health care system to ensure access and continuity.

Individuals may also need help in obtaining accurate, evidence-based information, accessing recommended screening and communicating results and information to others. Health care providers with a skill base in cancer genetics have what is required to assist individuals and families in promoting effective disease management.

What is critically important is the provision of accurate and consistent cancer screening information (i.e., type, interval and age of initiation) to individuals and families. It is possible that failing to strictly adhere to current screening recommendations, particularly for CRC, can result in increased mortality. Therefore, it is essential that clinicians have current knowledge of screening and treatment protocols and assist individuals to maintain screening regimes. Although screening recommendations for select extracolonic cancers are not supported with evidence, it is vital that clinicians be aware of the types of cancers in the family and those associated with specific LS gene mutations. Information on cancers more commonly associated with select mutations also needs to be clearly communicated to individuals and families. If screening for other types of cancers is being carried out it is also important to fully inform individuals about the benefits and limitations of such screening [21]. Of significance for female carriers is the incidence of endometrial and ovarian cancer and the lack of effective screening tests for early detection. This situation raises concerns about whether low detection rates can impact a woman's psychosocial adjustment, particularly if they are fully informed about the

benefits and limitations of current screening for these cancers. Low detection rates for various cancers may also be associated with inexperienced health care providers who do not have sufficient knowledge of LS cancer types and presentation.

The incidence of extracolonic cancers in LS also illuminates the need for individuals to be vigilant in monitoring for any health changes and to seek health care immediately. However, timely access to health care providers and the system must be readily available and able to respond when health changes are suspected and/or diagnosed. As highlighted in the qualitative study, access to timely screening, surveillance and treatment and continuity of care were identified as barriers to effective disease management. The important role of familial cancer registries in the management and

Assessing for a family history of cancer in FCCTX families is also crucial given the lack of distinctive morphological features [36]. One study in NL found that of 29 non-LS families who fulfilled the Amsterdam I criteria, 28 of them met the criteria for FCCTX [37]. Given the many individuals with a family history of CRC who have unknown mutations, it is imperative that those working in primary care be aware of the possibilities beyond LS and provide evidence-based cancer screening/surveillance recommendations.

Policy Implications

The research findings have revealed the far-reaching psychosocial, emotional and behavioral implications of genetic testing and living with LS. These findings have

implications that serve to enhance the provision of genetic counseling, genetic testing and overall management of individuals and families with LS. From a policy perspective, the ultimate plan should be to provide a coordinated system of resources capable of providing integrated health care and follow-up in a manner that promotes optimal health functioning and overall well-being. These resources should extend well beyond the initial genetic testing event and encompass all aspects of effective disease management. The findings illuminate the need for health care resources that are responsive to the needs of individuals and families with hereditary cancer. There is a need for adequate resources to identify those with LS as well as assist individuals in adopting and adhering to lifelong cancer screening and treatment protocols.

In particular, this population requires a number of timely and appropriate health care services. A multidisciplinary approach to the provision of services has been proposed, including a single service to coordinate screening [38]. In the province of Newfoundland and Labrador an initiative is being pilot tested to have Community Familial Cancer Genetics Clinics within the regional health authorities. Ideally, these clinics would provide the full gamut of genetics, informational and support services as well as coordinate recommended screening for at-risk individuals. Other researchers report that familial cancer registries and genetics service centers are perceived to be effective mechanisms for facilitating quality outcomes [38]. Since the first polyposis registry established in the United Kingdom in 1925, many familial cancer registries have been established worldwide, including those specific to LS [39]. These registries have an

important role in the ongoing management of LS with many coordinating screening programs and other aspects of multidisciplinary care [39]. Some authors propose that all individuals with LS be managed within the context of a registry [40]. Registries also provide other benefits such as patient-focused care and a database for conducting research [41].

At the first step, these clinics require a critical mass of genetic counselors to provide timely services to at-risk individuals and families about LS before, during and following genetic testing. Health care providers, knowledgeable about the natural history of LS, its disease trajectory and management, must also be available to coordinate and streamline diverse health care services. Within these clinics, a multidisciplinary approach is needed to ensure that individuals' screening/surveillance protocols are maintained and/or modified based on evidence and the evolving family cancer history [38].

Finally, the interface of the environment, epigenetics and colorectal cancer must be given increased attention. Traditional epidemiological research has focused on the roles of genetic, environmental and lifestyle factors in the development of CRC [42]. This body of knowledge continues to support the premise that LS cancers are influenced by environmental and lifestyle as well as genetic factors. A recent review outlined studies investigating the influence of factors such as meat intake, smoking, alcohol, body mass index (BMI) and dietary fibre/fruit on cancer development in LS. The authors of the review conclude that smoking and a higher BMI increase the risk of developing

adenomas and CRC in LS [21], a finding supported by others [3]. A Western diet has also been implicated in an increased risk of CRC [3]. Recently, one study found that aspirin significantly reduced the risk of CRC in LS [43].

Research on epigenetics and LS is also providing evidence to explain the development of cancer in those who do not have a pathogenic mutation [44]. Molecular epidemiology is expanding at a rapid pace and focusing on interactions between genetics and environmental, dietary and lifestyle factors in carcinogenesis [42]. Given the presence of unknown mutations, environmental complexities, variability in the health care environment and inadequate sensitivity and specificity of screening tests for extracolonic cancers in LS, continued attention to these areas is paramount.

Research Implications

The findings presented in the dissertation have implications for future research. At the first step, the clinical utility of the PAHD and its ability to identify those who may be experiencing adjustment challenges in living with LS must be evaluated. Adaptation of the PAHD for use with other hereditary diseases is also anticipated. Currently, it has been modified for a pilot test in a population with arrhythmogenic right ventricular cardiomyopathy (ARVC). A pilot study of the instrument in FCCTX families is also planned.

Given the importance of adhering to recommended cancer surveillance protocols, it is prudent to examine whether there is a relationship between psychosocial implications and behavioral outcomes in LS. Currently, there is an initiative underway to merge data from the psychometric study outlined in chapter 3 and data from a cancer screening study in the same population. The cancer screening data base provides information on the actual screening practices of both carriers and non-carriers. It is conjectured that those who are experiencing high levels of emotional and psychosocial burden in managing LS may experience challenges with engaging in regular screening. Identifying those who are experiencing such difficulties would facilitate the development of supportive interventions.

The psychosocial and behavioral implications of living in families with FCCTX should also be examined. These are families who have multiple members with CRC across several generations but with an unknown genetic etiology [45]. Due to the lack of psychosocial research efforts in this population, it would be important to qualitatively explore how individuals in these families adjust to the high incidence of cancer in the family, perceive barriers to and facilitators of screening and view their support needs. Information gleaned from the qualitative data can then be used to modify the PAHD for use in these families.

Another area for research is with groups who have received less attention [3]. These groups include cultural minorities and adult children of those with a confirmed mutation.

Our research findings unveiled a number of carrier concerns related to the management of children, particularly in terms of genetic testing and screening. As these new generations at risk come of age, it is essential that research findings articulate their support and information needs and understand the long-term perspective of living in LS families [3].

Limitations

The research studies presented in this dissertation have a number of limitations. First of all, many types of selection bias (e.g., ascertainment, volunteer, non-response and loss to follow up) can be present in studies of genetic diseases [46]. In all phases of the quantitative and qualitative studies presented here, the participants were considered to be high-risk based on a combination of clinical and Amsterdam criteria. The use of restrictive criteria to identify those at risk could have caused an ascertainment bias towards families with multiple members who had cancer and a more severe phenotype [46].

It is also conjectured that self-selection bias may have been a limiting factor in that a number of respondents participated in all phases of the research. One of the inclusion criteria for all of the studies was that participants had to have participated in predictive DNA testing. It is possible that those who volunteered to engage in genetic testing and participate in research were more motivated than those who refused and may not be representative of all individuals living in families with LS [46].

Given that the quantitative studies in both phases of the research were cross-sectional and involved questionnaires, it is possible that those who did not respond were more burdened by the presence of LS in the family. In the larger quantitative study on the development and preliminary testing of the PAHD, the responders were significantly older than the non-responders thus potentially limiting our knowledge of the experiences of younger individuals who are living in families with LS. Further, the higher proportion of non-responders among the non-carrier cohort may have also impacted the findings. The findings may have also been limited by the use of mixed methods for data collection. Also, the use of a cross-sectional design precluded the evaluation of the PAHD's monitoring capabilities.

The use of small sample sizes for the qualitative phase of the research may have limited the generalizability of the findings. Further, the results may not be generalizable to ethnic minority individuals. Finally, the inherent biases in having participants recall how they experienced genetic testing and/or responded to specific situations/events may have impacted the findings.

Conclusion

The research findings have revealed the far-reaching psychosocial, emotional and behavioral implications of living in families with LS. Lynch syndrome is a lifelong, evolving disease that requires individuals and families to adjust on many levels. This adjustment should be monitored at various junctures during the genetic testing process

and beyond receipt of results. To assess psychosocial adjustment, the PAHD scale was developed from a qualitative data base. Preliminary testing of the scale indicates that it is psychometrically sound. The subscales and overall scale structure were validated and it was determined that the scale met Likert scaling assumptions. The next step is to test the clinical utility of the scale in cancer genetics services and assess its ability to identify individuals and families who may require therapeutic interventions.

The current organization and provision of cancer genetics and health care services to LS families are inadequate. The barriers identified in the current research must be eliminated so that individuals can access and engage in evidence-based protocols. To ensure that individuals and families are effectively managing LS, a system of integrated and coordinated services should be implemented. Community genetics clinics should be resourced so that genetic counseling, genetic testing, psychosocial support, coordination of screening, timely follow-up care and assistance in navigating the health care system can be provided to those living in families with hereditary cancer.

In conclusion, clinicians and families need to think longitudinally about the course of LS with normative landmark transitions and constantly changing demands. This will help individuals and families achieve a sense of resilience and maintain an optimal quality of life in living with and managing LS.

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Appendix A
Amsterdam Criteria

Appendix A: Amsterdam Criteria

Amsterdam Criteria I

There should be at least three relatives with colorectal cancer

- one relative should be a first-degree relative of the other two
- at least two successive generations should be affected
- at least one tumour should be diagnosed before age 50
- familial adenomatous polyposis should be excluded
- tumours should be verified by histopathological examination

Amsterdam Criteria II

There should be at least three relatives with colorectal cancer or with a Lynch syndrome-associated cancer: cancer of the endometrium, small bowel, ureter or renal pelvis

- one relative should be a first-degree relative of the other two
- at least two successive generations should be affected
- at least one tumour should be diagnosed before age 50
- familial adenomatous polyposis should be excluded in the colorectal cancer case if any
- tumours should be verified by histopathological examination

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Appendix B

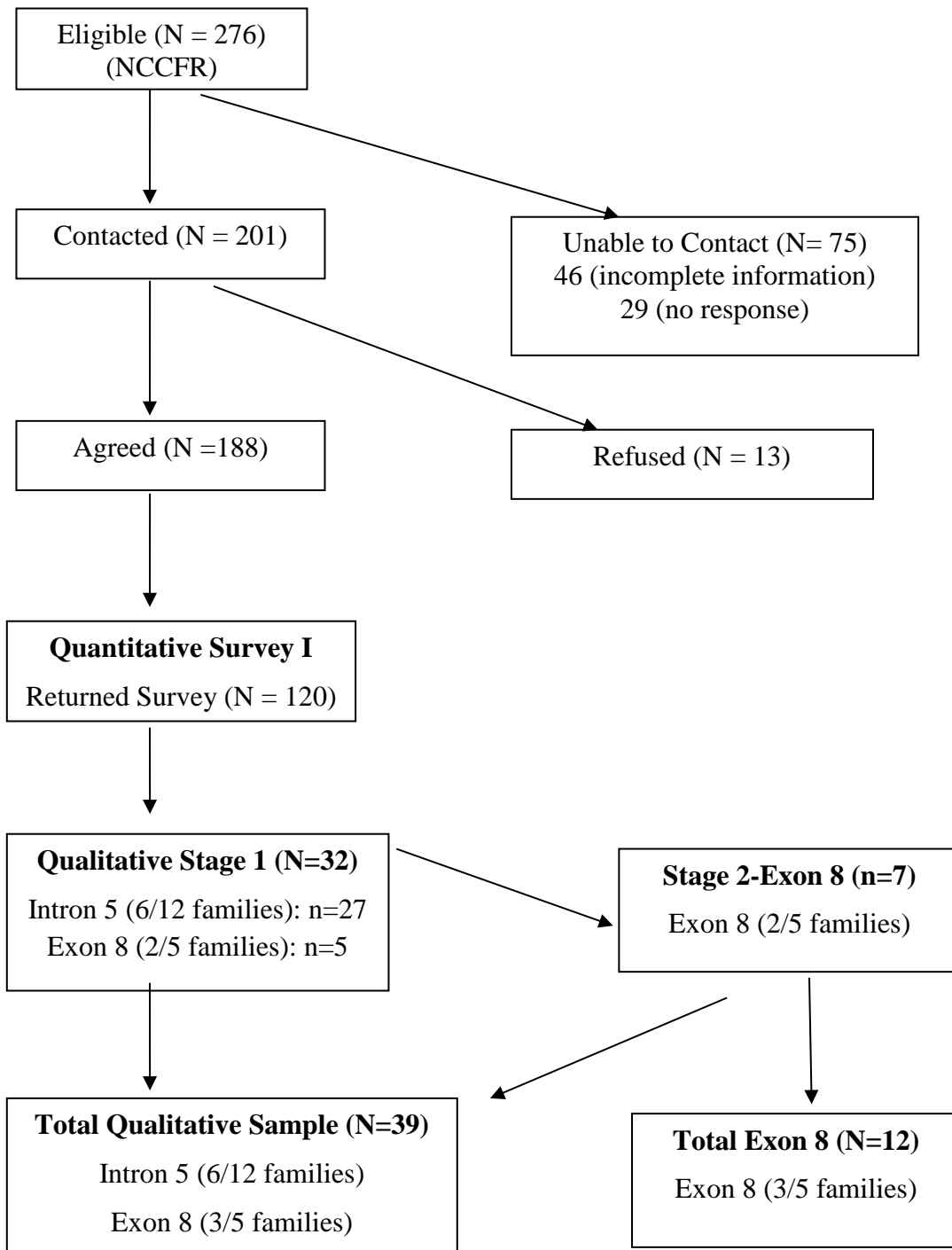
Human Investigation Committee Approval and Consent

Protocol: Phase I (Quantitative)

Appendix C

Sampling Plan – Phase I (Quantitative and Qualitative)

Appendix C: Flow Chart of Sampling Plan - Phase I (Quantitative and Qualitative)



Appendix D

Human Investigation Committee Approval and Consent

Protocol: Phase I (Qualitative)

Appendix E
Research Proposals Approval Committee:
Phase I (Qualitative)

Appendix F

Human Investigation Committee Approval and Consent

Protocol: Phase II (Quantitative)

Appendix G

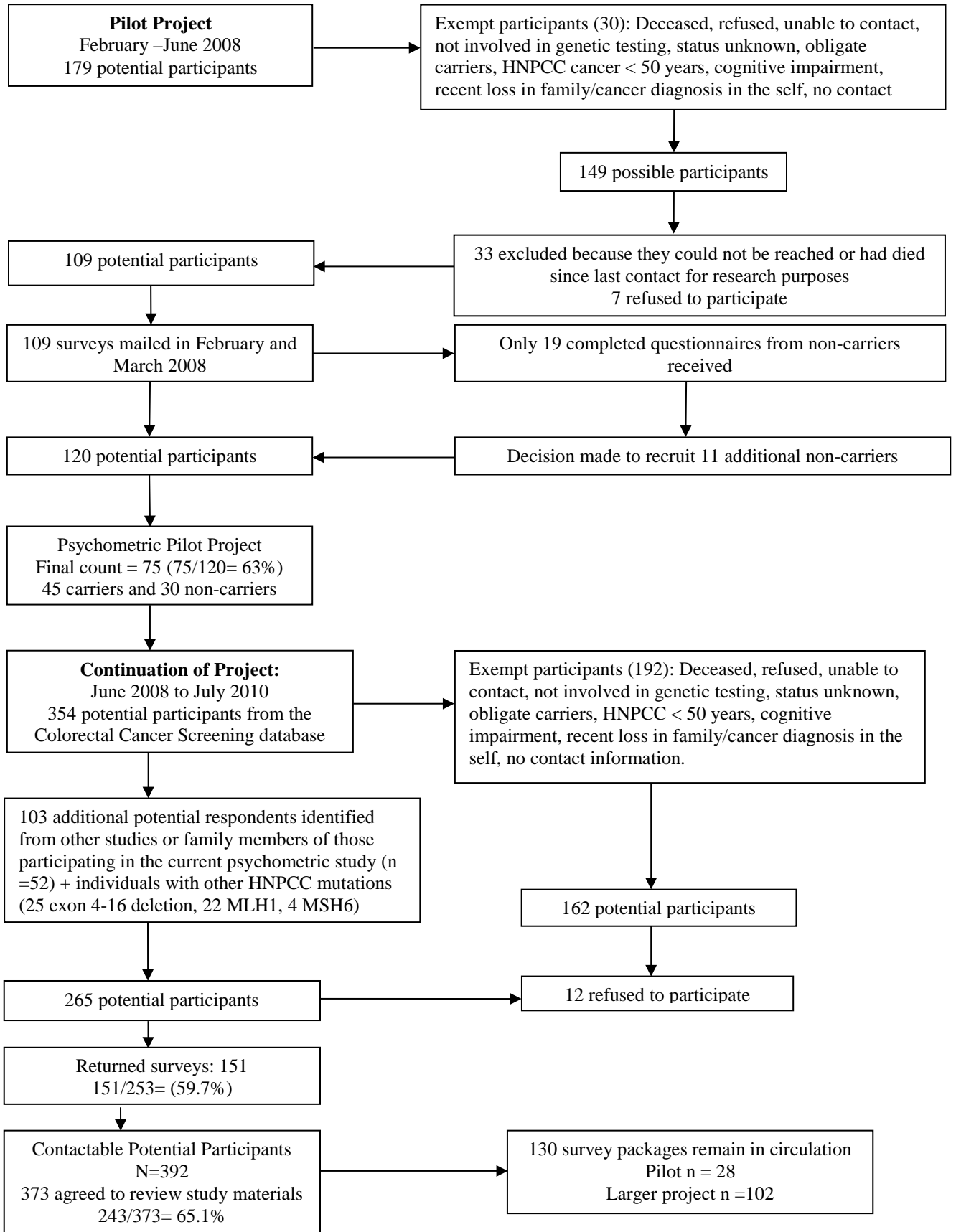
Research Proposals Approval Committee:

Phase II (Quantitative)

Appendix H

Sampling Plan – Phase II (Quantitative)

Appendix H: Flow Chart of Sampling Plan – Phase II (Quantitative)



Appendix I
Hereditary Diseases: Psychosocial and Behavioral
Adjustment Scale