THE HIDDEN COSTS: A QUALITATIVE STUDY OF FINANCIAL TOXICITY IN HEREDITARY CANCER SYNDROMES ACROSS CANADA

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Abstract

Identifying financial toxicity (FT) following a cancer diagnosis is critical for providing interventions and support to patients. There is virtually no research on FT in patients with hereditary cancer syndromes (HCS), which account for approximately 10% of all cancers. This thesis examines FT related to two common types of HCS: hereditary breast and ovarian cancer syndrome (HBOC) and Lynch syndrome (LS). A qualitative interpretative description study was employed. Patients across three provinces in Canada with a confirmed molecular diagnosis of HBOC or LS were invited to participate in semi-structured interviews. Data saturation was achieved after interviewing 73 participants diagnosed with HBOC (n= 39) or LS (n= 34). Thematic analysis employing constant comparison was used to analyze the transcripts. Participants described several aspects of FT categorized under three primary themes: 1) objective financial burden (direct out-of-pocket (OOP) medical costs, direct OOP non-medical costs, indirect costs); 2) evaluation of financial resources; 3) subjective financial distress (distress due to financial resource management, basic needs insecurity, future financial insecurity). Findings revealed many interrelated objective and subjective aspects of FT. Evaluation of one's financial resources emerged as a key factor in the experience of financial distress. Developing policies that facilitate solutions to mitigate FT experienced by patients with HCS is urgently needed.

Keywords: Hereditary cancer syndromes (HCS), Financial toxicity (FT), Out-of-pocket (OOP) costs, Subjective financial distress

General Summary

This thesis investigates the healthcare-related costs and financial difficulties faced by patients and families affected by hereditary cancer syndromes. Specifically, it focuses on the out-of-pocket expenses and perceived financial distress associated with screening and treatment for hereditary breast and ovarian cancer syndrome and Lynch syndrome. The research incorporates a comprehensive qualitative interview study in Newfoundland and Labrador (NL), Ontario (ON), and British Columbia (BC). Results revealed that despite living in a country with a universally funded healthcare system, many patients face challenges and changes in their financial condition as a result of their lifelong hereditary cancer risk. Findings reveal areas of financial toxicity (including out-of-pocket costs, productivity loss, and financial distress) that can inform anticipatory guidance and support for patients. Findings also highlight existing gaps in healthcare practice and policies, which can inform future studies to reduce the financial hardship experienced by patients with hereditary cancer syndromes and their caregivers.

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List of Abbreviations

AFEs	Adverse Economic Events
BC	British Columbia
BMI	Body Mass Index
CPP	Canada Pension Plan
CRC	Colorectal Cancer
EI	Employment Insurance
EI-SB	Employment Insurance Sickness Benefit
FAMM	Familial Atypical Multiple Mole Melanoma Syndrome
FAP	Familial Adenomatous Polyposis
FT	Financial Toxicity
HBOC	Hereditary Breast and Ovarian Cancer
HCS	Hereditary Cancer Syndromes
HRQoL	Health-Related Quality of Life
IVF	In vitro Fertilization
LS	Lynch Syndrome
MEN	Multiple Endocrine Neoplasia
MLH1	MutL Protein Homolog 1
MMR	Mismatch Repair
MRI	Magnetic Resonance Imaging
MSH2	MutS Homolog 2
MSH6	MutS Homolog 6
MSI	Microsatellite Instability

NF1	Neurofibromatosis type 1
NL	Newfoundland and Labrador
ON	Ontario
OOP	Out-of-Pocket
PGT	Preimplantation Genetic Testing
PMS2	Postmeiotic Segregation Increased 2
SDH	Social Determinant of Health
TSC	Tuberous Sclerosis Complex
VHL	Von Hippel-Lindau Disease
WHO	World Health Organization

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Glossary of Terms Related to Financial Toxicity

Term	Definition
Financial Toxicity	Objective financial burden and subjective financial distress experienced by patients with cancer as a result of their treatment.
Objective Financial Burden	Individuals' inability to meet financial demands is measured as paying out-of-pocket for direct and indirect costs to patients and their caregivers.
Subjective Financial Distress	Individuals' emotional responses and perceived distress due to higher costs which are assessed through perceived money management distress.
Direct Out-of-pocket Costs	Include the monetary value of resources in preventing, diagnosing, and treating disease.
Direct Out-of-pocket Medical Costs	Cover services directly related to diagnosis or treatment. Those not covered by third parties, which the patient and their family must face (e.g., drugs, surgeries, etc.).
Direct Out-of-pocket Non-medical Costs	These include several OOP costs not directly tied to purchasing medical services (e.g., travel costs for screening and treatment, special diets, counselling for mental health concerns, etc.).
Indirect Costs	The economic and time resources shifted from everyday activities (e.g., time off work, career changes, etc. in patients and their family members).

Declaration of Publication Intent

These chapters have not been published in a peer-reviewed journal; therefore, no figures or tables are copyrighted except for a table in Chapter 2 (Table 2-1), for which copyright permission has been received from the journal. However, the main chapter (Chapter 3) will be submitted to an open-access, peer-reviewed journal for publication. All co-authors have provided email consent to the senior author for their names to be included in this thesis version of the manuscript.

Chapter 1: Introduction

1-1 Introduction

Cancer impacts patients and their families not only physically and emotionally but also economically, imposing substantial financial challenges (1). The World Health Organization (WHO) discusses the global impact of cancer, underscoring its continuing clinical and financial burden across genders (2). With the number of new cancer cases rising rapidly (3), the projected economic impact of cancer is only expected to increase (4).

Measuring the financial impacts of cancer is crucial for medical resource allocation, reimbursement decisions, and evaluation of specific programs throughout cancer care to set future healthcare budgets and support decision-making for cancer control systems (5–7). The economic impact of the disease is measured in terms of costs, which represent the monetary value of resources allocated for disease treatment or the economic opportunities lost due to the presence and treatment of the disease (8).

Based on a recent study in Canada, the cost of cancer to the health system (CAD 18.4 billion) would increase by almost 30% if expenses that are paid by patients and families (CAD 7.8 billion) were included (9). In the US, the national patient economic burden in 2019 associated with cancer care was $21.09 billion, comprised of out-of-pocket costs of $16.22 billion and patient time costs of $4.87 billion (10). According to a systematic review in the US, 49% of patients with cancer reported experiencing financial hardship (11). Patients with cancer are 2.65 times more likely to experience adverse economic events, including filing for bankruptcy and being at risk of other adverse credit and financial events (12).

The economic burden of cancer extends beyond patients themselves, affecting families, caregivers,

friends and the whole society (13), which could not only profoundly impact the patients' and caregivers' quality of life, psychological well-being, and overall health outcomes (14–16) but also potentially hinder adhering to essential cancer care, particularly for individuals from low socioeconomic backgrounds or those residing in rural areas (17–19).

In the context of hereditary cancer syndromes (HCS), which account for up to 10% of all cancers (20), studies have highlighted cost as a primary barrier to genetic testing for patients (21–24). Additionally, some research has evaluated the cost-effectiveness of genetic-based screening and treatment strategies (25). However, there is a large and notable gap in the literature concerning the perceived financial impacts experienced by patients with HCS.

Aiming to highlight the economic effects of cancer on the lives of patients, the concept of financial toxicity (FT) emerged in the US after a group of experts in chronic myeloid leukemia wrote an editorial highlighting the prices of cancer drugs and discussed long-term healthcare policies in order to make this price more affordable for patients and families (26). This crucial concern was supported by a commentary of 115 American scientists (27) in 2015 and the American Society of Clinical Oncology (28) in 2017. Following this, Zafar (29) introduced the term FT in 2013 in oncology, followed by different studies addressing this issue in the US (11,16,30–34), which does not have a publically funded healthcare system. FT refers to an unexpected, though often foreseeable, financial strain that cancer patients face, encompassing both direct monetary burdens and the emotional distress related to their treatment costs (35).

Work on financial toxicity in countries with predominantly publicly funded healthcare systems, such as Canada (36), started later than in the US. A recent study in Canada (37) indicated that FT profoundly impacted patients' everyday lives and quality of life, emphasizing the need for further research in this area.

Regardless of the type of healthcare system, patients with hereditary cancer syndromes can experience FT to varying degrees, given their high lifetime risks of multiple cancers. Given the significant impact of FT already established in oncology and the lack of research on the personal economic burden in hereditary cancers, there is a need for a deeper understanding of FT from the perspective of HCS patients in Canada. Identifying the different aspects of FT perceived by patients with hereditary cancer can enhance our understanding of this concept in countries with universal healthcare and address the specific needs of these patients and their families. Therefore, in this thesis, I aim to explore the distinct domains of FT in HCS to identify the knowledge gaps in this area.

1-2 Study Objectives

Given the dearth of research and knowledge about FT in HCS populations, this is the first national study to explore FT from HCS patients' perspectives, specifically patients affected by HBOC and LS.

Specific objectives:

1- To explore the direct and indirect costs endured by HBOC and LS carriers

2- To explore the subjective financial distress perceived by HBOC and LS carriers

3- To better understand the construct of financial toxicity in HBOC and LS carriers

1-3 Outline of Thesis

This thesis consists of four chapters to achieve the objectives mentioned above.

This first chapter provides a brief introduction to the study's key concept of FT and outlines the study objectives. The second chapter provides a literature review and identifies knowledge gaps

related to financial toxicity in cancer and hereditary cancer syndromes, domains and examples of financial toxicity, existing financial toxicity models in cancer, risk factors, and mitigating strategies. The third chapter presents a manuscript based on qualitative interviews investigating financial toxicity in hereditary cancer syndromes across three provinces in Canada. The fourth chapter concludes the thesis, outlining its implications and offering suggestions for further research.

Chapter 2: Background and Literature Review

The research described in this thesis focuses on the financial toxicity experienced by individuals who are affected by the two most common hereditary cancer syndromes, hereditary breast and ovarian cancer and Lynch syndromes. The purpose of this chapter is to provide an overview of the available literature related to the main concepts in this thesis. This chapter will also highlight gaps in the literature, which form the rationale for conducting the current study.

2-1 Hereditary Cancer Syndromes

2-1-1 Etiology and Epidemiology

Cancer is a significant cause of illness and death worldwide (38). In 2020, there were approximately 19.3 million new cancer cases and almost 10 million cancer-related deaths globally (38). In Canada, the number of cancer deaths is also substantial and is expected to increase by 44% from 2020 to 2040 (39).

Hereditary cancer syndromes (HCS) are caused by genetic mutations in tumour suppressor genes or proto-oncogenes (40) transmitted across generations within families (41,42). These mutations substantially increase the probability of developing specific cancers throughout carriers' lifetimes (43). Since the phenotypic expression of genetic mutations can exhibit considerable variation, the clinical manifestations of HCS may be characterized by a substantial degree of heterogeneity (43). However, all HCSs are marked by significantly high lifetime risks of developing cancer (44), often affecting multiple organs (45) and typically occurring at younger ages (46,47).

There are more than 100 unique hereditary cancer susceptibility syndromes, most of which are considered to be rare diseases (48). Nonetheless, more than 200,000 individuals in Canada are estimated to carry pathogenic genetic variations in over 100 genes associated with HCS (44). Despite being rare, HCS is among the most common inherited diseases, comprising 5-10% of all cancer cases (20,49) and as high as 20% of some cancers (48,50).

This thesis focuses on two HCSs: hereditary breast and ovarian cancer (HBOC) and Lynch syndrome (LS).

2-1-2 Hereditary Breast and Ovarian Cancer (HBOC)

Breast cancer was the most commonly diagnosed cancer among women in 2023 in Canada (51). Regarding new cancer cases, globally, female breast cancer has surpassed lung cancer to become the most frequently diagnosed cancer in 2020, with an estimated number of 2.3 million new cases, accounting for 11.7% of all cancer cases (38).

Ovarian cancer ranks as the seventh most malignant tumour and the eighth cause of cancer-related deaths in women worldwide (52). Each year, ovarian cancer is diagnosed in 3,000 individuals across Canada (53). Among Canadian women, ovarian cancer is the ninth most common cancer diagnosed (54), with a five-year survival rate of 45% (55). Ovarian cancer has the highest death rate among all cancers of the female reproductive system (54).

Hereditary Breast and Ovarian Cancer (HBOC) is a genetic condition associated with a substantially elevated breast and ovarian cancer risk. In most cases, mutations in the *BRCA-1* and *BRCA-2* genes are linked to this condition (56). The pathogenic variants in the breast cancer susceptibility genes are considered the most significant hereditary risk factors, especially in early-

onset breast cancer cases. The presence of HBOC is suspected when there is a diagnosis of breast cancer before menopause or when a patient has a notable family history of the disease (48).

The gene that carries the pathogenic variant affects the levels of cancer risk. For example, women who inherit a pathogenic *BRCA-1* variant have a 55%–72% risk of developing breast cancer by the age of 70–80 years, while those who inherit a harmful *BRCA-2* variant have a 45%–69% risk (57–59). Women with pathogenic *BRCA-1* or *BRCA-2* variants also have an elevated risk of developing cancer in the opposite breast following a breast cancer diagnosis (57–59). Men with a *BRCA* mutation face a 7% to 8% increased risk of breast cancer and up to a 20% increased risk of prostate cancer by the age of 80 years (60). Women who inherit a pathogenic *BRCA-1* variant face a 39%–44% risk of developing ovarian cancer, and those with a pathogenic *BRCA-2* variant have an 11%–17% risk by the age of 70–80 years (57–59). Of note, HBOC syndrome accounts for 15-20% of ovarian cancer cases (61). Managing HBOC is essential in reducing incidence, morbidity, and mortality because of these cancers and improving patient well-being and health outcomes.

2-1-3 Lynch Syndrome (LS)

Colorectal cancer (CRC) is among the three major cancers globally (62) as well as in Canada; 1 in 37 Canadians die from CRC, with the highest age-standardized mortality rates for both males and females reported from NL (63). CRC is classified into three categories (64): sporadic (with no family history or inherited gene mutations), familial (happens more often in families due to shared genetic, environmental, or lifestyle factors but is not directly inherited), and hereditary (with inherited gene mutations passed from parent to child) (65). It is estimated that 20-30% of all CRCs fall under the familial category, including CRCs with multifactorial inheritance (64). Inherited, highly penetrant single-gene mutations may account for an additional 5% of colon cancer cases

(66). Among the inherited CRC types, Lynch Syndrome (LS), previously known as hereditary non-polyposis CRC, is characterized by defective mismatch repair (MMR), leading to a tumour microsatellite instability (MSI) phenotype (67).

LS is the most frequently inherited CRC, caused by mutations in the MMR genes such as *MLH1, MSH2, MSH6*, and *PMS2*, and it follows an autosomal dominant inheritance pattern. Familial cases that meet the Amsterdam criteria but lack MMR gene mutations and exhibit MSI-low or MSI-stable tumour profiles are now classified as CRC type X, a separate and likely genetically heterogeneous group of disorders (20, 21).

According to a recent systematic review and meta-analysis of 51 studies (70), LS accounts for 2-3% of global CRC cases. A higher prevalence (~5%) is reported in germline testing studies of CRC participants (70). The cumulative lifetime risk of developing CRC for individuals affected by LS can reach up to ~52 % in women and ~69% in men (71). Cancer risks vary according to the MMR gene with the pathogenic variant. For example, the cumulative risks of CRC in heterozygous mutation carriers, at age 70 years, for male and female carriers, respectively, are around 44% and 37% for *MLH1*, 54% and 39% for *MSH2*, and 12% and 12 % for *MSH6* (72). LS carriers are also at risk of developing cancer in other organs; for example, there is a lifetime cumulative risk of 40%-60% in endometrial cancer in women (73).

2-1-4 Beyond HBOC and Lynch Syndrome: Other Relevant Syndromes

While the most common HCS is hereditary breast and ovarian cancer, followed by Lynch Syndrome, there are other syndromes with lower prevalence, such as Neurofibromatosis Type 1, Familial Atypical Multiple Mole Melanoma Syndrome, Tuberous Sclerosis Complex, Neuroblastoma, Familial Adenomatosis Polyposis, Li-Fraumeni Syndrome, Hereditary

Retinoblastoma, Multiple Endocrine Neoplasia Type 1, Multiple Endocrine Neoplasia Type 2, and Von-Hippel Lindau Disease (43,74,75) (Table 2-1). As also evident from Table 2-1, in most HCS cases, more than one organ is at risk of developing cancer.

Table 2-1 Epidemiology of the Most Common Hereditary Cancer Syndromes

Syndrome	Mutated genes	Prevalence	The main type of cancers
Hereditary breast and ovarian cancer*	*BRCA-1* and *BRCA-2*	1 in 300-500	Breast, ovary, pancreas, prostate
Lynch syndrome (Hereditary non-polyposis colorectal cancer)	MMR genes**	1 in 400-500	Colorectal, endometrial, gastric, ovarian, hepatobiliary tract, small bowel, ureter, bladder, glioblastoma, prostate, breast, pancreas, sebaceous neoplasms
Neurofibromatosis type 1	*NF1*	1 in 3,000	Peripheral nerves, optic nerve, pheochromocytoma, nephroblastoma (Wilms tumour), neuroblastoma, leukemia
FAMM (Familial atypical multiple mole melanoma syndrome)	*CDKN2A* and others	1 in 3,000-7,000	Melanoma, pancreas
Tuberous sclerosis complex	*TSC1* and *TSC2*	1 in 6,000	Brain, renal
Neuroblastoma	*ALK* and *PHOX2B*	1 in 7,000-10,000	Neuroblastoma, adrenal
FAP (Familial Adenomatosis Polyposis)	*APC*	1 in 6,000-13,000	Colorectal, gastric, small intestine, thyroid, pancreas, brain, hepatobiliary tract
Li-Fraumeni syndrome	*p53*	1 in 5,000-20,000	Breast, soft tissue sarcoma, brain, osteosarcoma, adrenocortical
Hereditary retinoblastoma	*RB1*	1 in 17,000	Retinoblastoma
MEN 1 (Multiple Endocrine Neoplasia type 1)	*MEN1*	1 in 5,000-50,000	Parathyroid, pancreas, gastronome, anterior pituitary
MEN 2 (Multiple Endocrine Neoplasia type 2)	*RET*	(in white population)	Thyroid, parathyroid, pheochromocytoma
Von-Hippel Lindau disease	*VHL*	1 in 31,000	Central nervous system, retinal hemangioblastomas, endolymphatic sac tumours, pancreas, renal

*All syndromes included in this table are inherited in an autosomal dominant manner. **MMR: Mismatch DNA Repair Mechanism. Adapted from "Fertility counselling in women with hereditary cancer syndromes. Critical Reviews in Oncology/Hematology" by Somigliana et al., 2022, reproduced by permission provided by Elsevier, copyright license number# 5794731034499 (Appendix 1).

2-1-5 Management and Identification of HCS

Early detection and management of HCS improve outcomes and reduce mortality rates (76). Several methods help identify families affected by HCS, including family history assessments, clinical genetic evaluations, and genetic testing. Family history assessments can identify individuals with a higher risk of HCS based on specific cancers and other criteria in their family history (e.g., age of onset/diagnosis and number of affected relatives). Clinical genetic evaluations involve a physical examination and a genetic specialist's medical and family history review. Genetic testing can confirm the presence of a specific mutation and provide important information about cancer risk and management options (76).

Based on personal and familial cancer history, the National Comprehensive Cancer Network developed criteria to identify individuals who should be tested for cancer predisposition mutations (77). However, a significant proportion of individuals with cancer predisposition mutations were not identified using this guideline, indicating the need for broader testing criteria to prevent missed opportunities for early detection and prevention of inherited cancers (78). Manchanda et al. concur, highlighting that current guidelines fail to detect many carriers of deleterious variants. Many high-risk individuals are currently missed, with only about 20% of carriers identified. They advocate for a paradigm shift towards a direct-to-patient model, where genetic testing services are provided directly to individuals, bypassing traditional healthcare intermediaries (79). Identifying patients with an inherited cancer predisposition syndrome is vital to enable proactive care for patients and at-risk relatives and patient empowerment (80). Clinicians have critical roles in identifying the individuals and families at risk of HCS. They may recommend genetic testing following a clinical risk assessment to diagnose the syndrome. They can also explain the outcomes of genetic tests to families to assist them in comprehending their cancer risks and the advantages of tailored screening

schedules and lifestyle modifications (48). Genetic testing, however, needs in-depth preliminary genetic counselling, valid and long-standing psychological support, and a multi-disciplinary clinical environment to face the complex necessities of these patients (75). In Canada, there are significant regional differences for individuals with HBOC in access to genetic testing, gynecologic oncologists, and the likelihood of being offered participation in clinical trials (81). There is a need for standardized national guidelines and improved access to genetic testing, clinical trials, and specialized care for all at-risk individuals, regardless of their geographic location or socioeconomic status (81). For example, in Newfoundland and Labrador, significant challenges exist for individuals and families at risk of HCS. These include the current referral process for genetic testing, prolonged wait times to access genetic testing, lack of appropriate referral knowledge, and the inability of the provider to order baseline genetic testing, all of which contribute to low satisfaction and high frustration for patients and families (82).

2-1-6 Hereditary Cancer Syndromes Across Canada

In Canada, healthcare is delivered provincially, and there is no national approach to identifying and managing people who carry hereditary cancer pathogenic variants (83). Even in this study, the three study sites identified and managed at-risk individuals differently. As a result, we do not know the exact number of people who carry mutations across the country. Dragolovic et al. (84) recently reviewed the provisions of genetic healthcare across Canada. They found many differences across provinces regarding which were (or were not) ready to deliver genomic medicine. For example, Ontario has recently adopted a provincial genomic strategy (85). Between 2007 and 2016, the number of patients referred to genetics clinics in Ontario for cancer-related assessments nearly tripled. Among women who underwent BRCA1/BRCA2 testing during this period, 2,134 were

found to carry pathogenic mutations, while 1,527 had variants of uncertain significance (86). In BC, care is provided through the provincial cancer program (87). In NL, all genetic testing is coordinated through the Provincial Medical Genetics Program, which serves the entire province (88). A recent study protocol noted that between 500-600 patients are estimated to carry BRCA and Lynch syndrome in NL (89), though exact numbers could not be found.

Canada's readiness for genomic medicine in the context of hereditary cancer services is challenged by the projected increase in workforce requirements and the variability of cancer services across the country (84). In 2020, the Canadian clinical genetics workforce made up about half of the total genetic workforce, hinting at a possible strain on resources; the model also predicts that by 2030, the increasing demand for hereditary cancer services in Canada is likely to greatly strain or even exceed the capacity of the clinical genetics' workforce (84). These findings suggest a need for coordinated action at the health system level and innovations in service delivery to meet the growing demand for hereditary cancer assessment (84,90).

While several systematic reviews have been conducted on the psychosocial aspects of genetic testing and the identification of hereditary cancer syndromes (91–95), little attention has been given to these conditions' financial impacts on individuals and families. This gap underscores the importance of the current project's focus on the financial impact of hereditary cancers across Canada. With the already-projected future demand for clinical genetics services (77), a better understanding of the economic burden faced by these patients could allow for improved resource management and tailored support systems.

2-2 Financial Toxicity in Cancer

2-2-1 Definition

Over the last decade, the term Financial Toxicity (FT) has received considerable attention in the literature (29). FT is now a well-recognized issue in cancer, offering a comprehensive concept of the impacts of cancer healthcare costs on patients (32,96–98). Carrera and Zafar (35) conceptualized FT as the unintended, but not necessarily unanticipated, objective financial burden and subjective financial distress experienced by patients with cancer as a result of their treatment, particularly as they relate to newer classes of drugs and concomitant health services (Figure 2-1). Moreover, FT is viewed as a condition in which patients perceive themselves as unable to maintain their preferred living standards and economic independence (99), which has negative impacts on well-being (29,100), health-related quality of life (6,101), and social functioning (40,67).

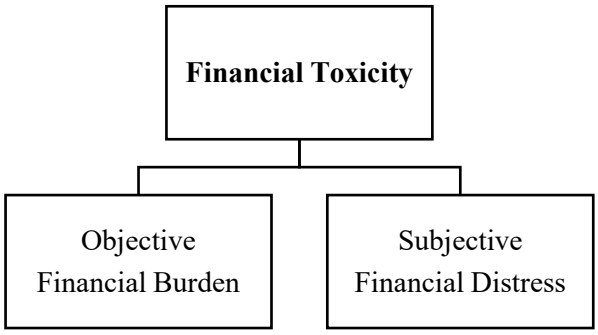

Figure 2-1 Financial Toxicity Cancer-related Domains

Reviewing the current conceptual frameworks on cancer-related financial toxicity (104–112), a unified understanding of the concept of FT remains elusive. Despite the large number of publications on this topic, there is a variation in understanding of this construct in cancer (109). The sole consensus lies in the clear distinction between the two primary determinants of FT:

objective financial burden and subjective financial distress (106,113). Besides the variety in the conceptualization of FT, there is a considerable inconsistency in the terminology used when describing FT, encompassing terms such as "financial toxicity", "financial hardship", "financial burden", and "financial distress". Therefore, to gain a better understanding, in section 2-2-3, "Comparing FT conceptual framework", I will discuss some existing conceptualizations of FT and their proposed terminology in detail, following an outline of some common FT domains.

2-2-2 Domains of Financial Toxicity

2-2-2-1 Objective Financial Burden

Objective financial burden refers to an individual's inability to meet financial demands (114). In cancer, the objective financial burden, as indicated in Figure 2-2, is often measured as paying out-of-pocket (OOP) for direct medical and non-medical costs and lost productivity (indirect costs) of patients and their caregivers (35,106).

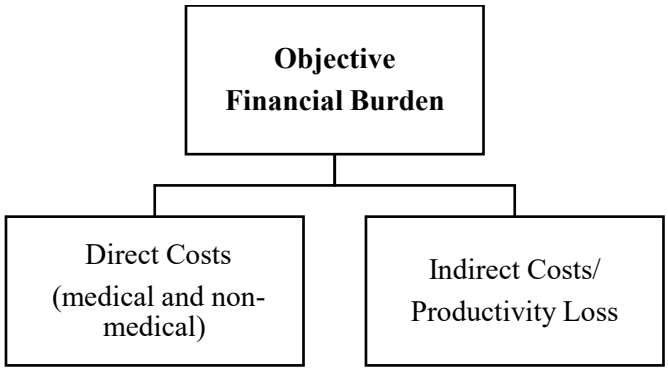

Figure 2-2 Domains of Objective Financial Burden

2-2-2-1-1 Direct OOP costs

Direct healthcare costs include the monetary value of resources in preventing, diagnosing, and treating disease. The direct OOP costs comprise both direct medical and direct non-medical costs.

Direct OOP Medical Costs: The direct OOP medical costs cover services directly related to diagnosis or treatment. These medical and health service expenses are partly paid for by third-party payers such as the public health system and/or private health insurance coverage. Direct OOP medical costs are those not covered by third parties, which the patient and their family must face. They typically include OOP costs for hospital stays, medications, diagnostic tests, medical supplies, outpatient doctor visits and consultations, and various medical procedures (115,116). Direct OOP medical costs are often the more visible expenses incurred by patients and their families, which have implications for the affordability and accessibility of health care for patients (117).

Direct cancer care in the US is substantial; in 2018, patients with cancer were responsible for $5.6 billion in out-of-pocket expenses for their treatments. This amount covered a range of services, including surgical interventions, radiation therapy, and chemotherapy medications (117,118). In Canada, direct OOP medical costs incurred by cancer patients are expenses for prescribed medications that are not fully covered by publicly funded insurance. Monthly OOP costs for cancer within Canada ranged from US $15-400 (117). In low- and middle-income countries, cancer patients and their caregivers allocated 42% and 16% of their annual income to OOP expenses (117).

The findings of qualitative studies on the direct medical costs of cancer also emphasize that patients with cancer incur a wide range of health-related expenditures. Direct medical costs that

were noted in several qualitative studies include hospital bills (119), consultant fees (119), primary care physician fees (119), diagnostic costs (119,120), prescription charges (119,121–123), over-the-counter medications for symptom control and side effect treatment (119,123,124), complementary therapies (119,121), home-use medical devices.

Direct OOP Non-medical Costs: In addition to out-of-pocket medical expenditures, several OOP costs are not directly tied to purchasing medical services (116). These include expenses related to transportation to healthcare providers and the costs associated with temporarily or permanently relocating to access specific treatments or facilities. Also, illness may compel a family to bear additional costs in caring for an ill member. These costs encompass additional expenses for everyday household tasks, special diets or clothing, and items for rehabilitation and comfort (such as exercise bikes and vaporizers). Modifications to properties, such as installing elevators or other specialized housing adaptations, as well as vocational, social, and family counselling services, are also significant costs; furthermore, expenses related to retraining or reeducation and financial losses from withdrawn savings or interest charges on borrowed funds to cover illness-related costs are considered direct non-medical costs (8,116,117,125).

In Canada, public health systems do not fully cover direct OOP non-medical costs, with considerable variation across provinces (126). About 33% of patients with cancer in Canada reported high levels of financial burden, and patients who reported the "worst burden" spent approximately 50% of their monthly income on out-of-pocket costs (127). A systematic literature review (117) estimates OOP cancer costs in Canada for a typical family of four with employer-sponsored health insurance to be $8,333 in 2024. The review further noted that non-medical costs were among the highest out-of-pocket costs faced by patients with cancer in countries with national

health insurance that provide universal coverage of cancer care, such as Canada and Australia (117). In Germany, although most medical costs are covered by health insurance, patients faced co-payments for prescription drugs, rehabilitation measures, hospitalization, travel expenses, and non-prescription drugs or housekeeping; the majority of those (81%) faced out-of-pocket expenses, but these did not usually exceed €200 monthly (128).

Based on a systematic review in 2021 (129), high OOP non-medical costs arise from travel to access medical care, parking, childcare, food and special diet. Also, for young adult women, paying for fertility preservation is considered a financial non-medical OOP difficulty (130,131). The findings of qualitative studies on direct non-medical costs of cancer care align with the quantitative studies, which illustrate that patients with cancer incur a wide range of cancer-related expenditures. Direct non-medical costs that were noted in several qualitative studies include personal items (119,121,122,124), transportation and travel costs (112), healthy foods (119,121,123) and fertility preservation (130,132).

In the hereditary cancer syndrome literature, existing studies on healthcare systems mention that surveillance and preventive surgeries can be cost-effective for healthcare systems (133). The second group of studies on HCS are from the patients' perspective, focused on addressing the OOP cost barrier to genetic testing (21–24).

However, to the best of our knowledge, while a significant amount of data is available on the OOP cost of cancer for patients and families, there is a complete absence of literature exploring OOP costs perceived by patients with *hereditary* cancer syndromes.

2-2-2-1-2 Indirect Costs

Indirect costs are the economic and time resources shifted from everyday activities, including work, housekeeping, volunteer efforts, and leisure, due to disease occurrence and treatment (8). Though not reflected in direct monetary transactions, these costs signify the economic resources that could have been utilized otherwise if the disease was absent; they typically involve the patients' loss or reduction of usual activities due to morbidity, disability, or mortality related to the illness (8,134). Additionally, family members and others may need to forgo personal activities to care for the patient, possibly facing unwanted job changes or missed opportunities for advancement and education (116). Other indirect costs include the time the patient and family spend visiting physicians and other health professionals (115).

A systematic literature review (135) on indirect costs of breast cancer in women from 2000 to 2020 reported the cost of lost productivity due to premature death ranged from $22,386 to $52 billion (135). In a more extensive Canadian study of indirect costs of cancer in 2021 (36), non-work-related costs, encompassing factors such as patient time, diminished leisure time, and losses in home productivity, were incorporated alongside productivity losses directly linked to employment. The study reported lost earnings among self-employed patients and higher costs for females. Caregiver costs were estimated at $15,786 to $20,414, household productivity losses at up to around $240,000 per household per year, patient time (leisure) costs at $13,000 and $18,704, total direct and indirect costs incurred by employers at $6,400 and $23,987, and societal productivity losses ranging from $75 million to $317 million (36). In a French population-based cohort (136), indirect costs were €22,722 and €7,724 per patient; 93% of patients had at least one period of sick leave, averaging 186 days of sick leave, and 24% of patients had a part-time work resumption after their sick leave periods, averaging 114 days. Indirect costs, therefore, can be substantial.

Patient and family experiences of indirect costs and reduced productivity related to cancer care are also supported by qualitative studies. An extensive qualitative study on cancer burden in Canada (112) reported a key theme of "reduced income and reserves" in its data; this referred to changes in work status as a significant impact of cancer, along with incurred cost, that could intensify financial strain for patients and families. Most categories emerging in qualitative studies of cancers' indirect costs are consistent with quantitative findings, such as job losses (119–121,124), reduction in working time (14,110,119,121), and childcare costs (111,119,124). Notable differences emerging in qualitative studies include domestic costs (e.g., housekeeping, grocery shopping, maintenance) (111,119–124), loss of surcharges for shift work (110), and waiting time for transfer payments (110).

Just as with direct burden, there is a lack of research exploring the indirect financial costs associated with hereditary cancer syndromes, highlighting a significant gap in current research

2-2-2-2 Subjective Financial Distress

Subjective financial distress refers to an individual's emotional response and perceived distress due to higher costs, assessed through perceived money management stress (137). It is conceptualized as having two primary dimensions: 1) current money management stress and 2) meeting expected *future* financial goals, which involves worry about current financial obligations and the ability to meet future financial goals based on the desired lifestyle (137). Subjective financial distress can also be considered as the individual's perception of objective debt burden among households, including perceptions of repayment difficulties, financial distress in the future, or overborrowing (138). Despite some level of agreement on explanations of objective financial burden, FT frameworks (104–112) usually differ in *how* they categorize the elements thought to comprise subjective financial distress. For example, some models capture psychological responses

(105) or subjective measures (104) of distress due to cancer costs and meeting expenses. Others measure psychological financial burden (107), "worry" about future costs and "rumination" about past and current financial burdens. Subjective financial distress (106), the decline of households' wealth and non-medical spending, and worry about the effectiveness of employee coping strategies have also been a part of subjective financial distress. Material (spending, resources), psychological, and behavioural (support seeking, coping care, coping lifestyle) responses of patients with cancer have also been reported as domains of subjective financial distress (109,111,139); for further details, see Figure 2-3. All of these mirror the findings of a systematic review study that recognized subjective financial distress as a multidimensional construct lacking a generally accepted definition (108). Indeed, a literature review suggests that the FT construct and the relationship between objective and subjective elements is somewhat heterogeneous in FT models. In the following section, I will discuss FTs' existing conceptual frameworks.

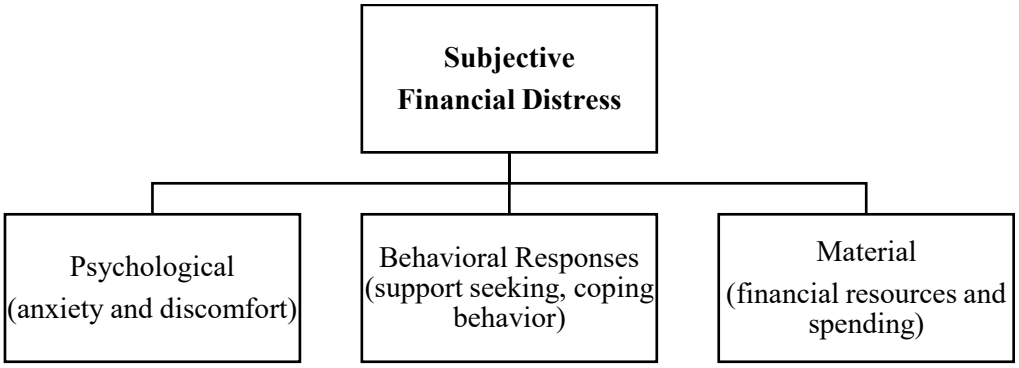

Figure 2-3 Domains of Subjective Financial Distress

2-2-3 Analyzing Existing Conceptual Frameworks of Financial Toxicity in Cancer

Over the past decade, many studies have focused on clarifying the concept of financial toxicity

and developing a clear framework for this issue in cancer. As mentioned earlier, identifying previous models can be very helpful because there is still no consensus on the FT construct. This section presents all the existing models of FT, compares them, and highlights their specific aspects. Additionally, figures have been included to provide a clearer understanding of these concepts. For a summary of these studies, please see Table 2-2.

Table 2-2 Summary of Financial Toxicity Models

First author	Year	Type of study	Financial toxicity domains		
Francour (140)	2005	cross-sectional	objective financial stress (measurable medical and non-medical expenses)	subjective financial "strain" (concerns about the adequacy of health insurance and financial resources to meet future health needs)	
Altic (105)	2017	systematic review	material conditions (OOP expenses and lower income)	psychological responses (distress due to costs of cancer, increased households, concerns about wages/ income)	coping behaviours (to manage expenses)
Gordon (4)	2017	systematic review	objective measures (coping behaviours and material conditions)	subjective measures (psychological responses)	monetary measures
Jones (107)	2020	theoretical model	material financial burden (financial consequences and financial coping behaviours)	psychological financial burden ("worry" about future costs)	psychological financial burden ("rumination" about past and current costs)
Carrera (106)	2018	narrative review	objective financial burden (quantifiable expenditures)	subjective financial distress (decline of the households' wealth and non-medical spending, and worry about the effectiveness of employed coping strategies)	
Witte (109)	2019	systematic review	objective financial burden (direct costs/ indirect costs)	subjective financial distress (material conditions, psychosocial response and coping behaviour)	
Gharazi (111)	2020	qualitative study	objective financial burden (direct costs/ indirect costs)	subjective financial distress	
Lueckmann (141)	2022	qualitative study	higher costs	four mediators: evaluation of financial adjustments, assessment of the ability to make ends meet, burden of applied financial adjustments, bureaucracy	subjective financial burden

Francoeur (140) was one of the pioneers in describing the financial impacts of cancer on patients. In this model, objective financial stress (financial resources and illness-related financial costs) is distinguished from subjective financial "strain" (concerns about the adequacy of health insurance and financial resources to meet future health needs). This model also highlights that objective financial stress significantly influences certain aspects of subjective financial strain. Francour suggests that objective financial stress contributes to subjective financial strains (140).

One of the most frequently cited models by Altice and colleagues (105) emphasized the inconsistency in the terminology and used "financial hardship" instead. This model delineates three domains: (1) material conditions (out-of-pocket costs, missed work, reduced income, medical debt, or bankruptcy), (2) psychological responses (distress due to costs of cancer, increased household, concerns about wages/ income), and (3) coping behaviours (skipped or delayed medications). This model considers coping behaviours responding to economic burden as a separate domain not directly linked to material conditions or psychological responses.

The model by Gordon and colleagues (104) outlined three domains: 1- objective measures (coping behaviours and material conditions), 2- subjective measures (psychological response), and 3- monetary measures (financial stress including direct and indirect medical expenses and the amount of household income). This model includes at least some of the material conditions and psychological responses included in the Altice model and the financial strain element of Francoeur's model. Coping strategies, however, are classified under objective measures, representing a novel approach to measuring and assessing this concept.

Another model by Jones and colleagues published in 2020 (107) includes two dimensions: a material financial burden and a psychological financial burden versus a healthcare-specific-general burden. The psychological financial burden is divided into "worry" about future costs and

"rumination" about past and current financial burdens. The material financial burden is categorized into financial consequences and financial coping behaviours. It also introduces moderators and outcomes, such as quality of life and mortality, to be affected by financial burden. Concerns about past and current financial situations were part of the psychological responses to financial hardship among cancer survivors in Altice, which is aligned with the "rumination" type of psychological financial burden in Jone's model.

The FT framework of Carrera & Zafar (35,106) conceptualizes financial objective and subjective burden, resulting in FT (Figure 2-4). Previously, models primarily concentrated on the domains of financial hardship and did not address the subsequent effects of these domains, which are defined as financial toxicity. Based on this model (35), objective financial burden refers to quantifiable expenditures, including drug costs, other direct medical costs, and related treatment costs; this would correspond with the material conditions component of Altice's model. Subjective financial distress includes anxiety and reduction in wealth that patients with cancer experience. In the framework of Carrera and Zafar, "coping behaviour" also belongs to subjective financial distress. Their model highlighted the complex role of coping mechanisms in response to direct and indirect costs, which impact health outcomes and quality of life. However, Gordon's model defined coping as belonging to objective measures, covering tangible solutions to ease the financial burden and subjective measures as patients' perceptions.

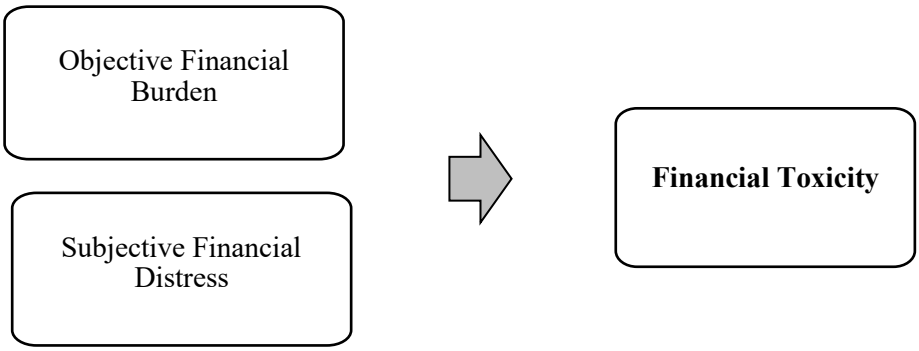

Figure 2-4 Financial Toxicity Model by Carrera and Zafar

Following the model of Carrera & Zafar, Witte and colleagues (109) suggested a new sequence of developing financial toxicity, where FT is the potential consequence of subjective financial distress only and subjective financial distress results from objective financial burden (Figure 2-5). This model identified direct and indirect costs that define objective burden. Also, subjective financial distress is comprised of three domains: (1) material conditions (active financial spending, passive financial resources), (2) psychosocial response and (3) coping behaviour (support seeking, coping with care, and coping with one's lifestyle). Coping strategies reported in this model, as a subgroup of subjective burden, are consistent with the Carrera & Zafar model and the model of Altice.

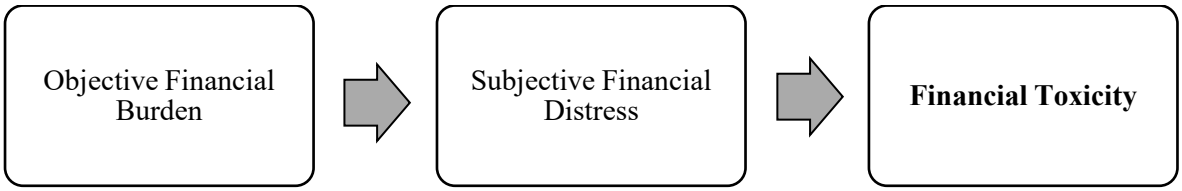

Figure 2-5 Financial Toxicity Model by Witte

The conceptual framework of Witte changes the main contributors to FT as it proposes a different sequence in shaping FT, which represents a different conceptualization than the model of Carrera & Zafar but also different from some conceptualizations such as Longo (142) and Fitch (143). Longo et al. (142) consider an objective financial burden comprising out-of-pocket costs and income losses the primary contributor to financial toxicity (Figure 2-6). The conceptual model from a systematic review (143) of qualitative studies on financial toxicity experienced with cancer in publicly funded healthcare systems by Fitch et al. (2022) also mirrors the findings by Longo (142), indicating OOP direct and indirect cancer-related costs as predictors of FT.

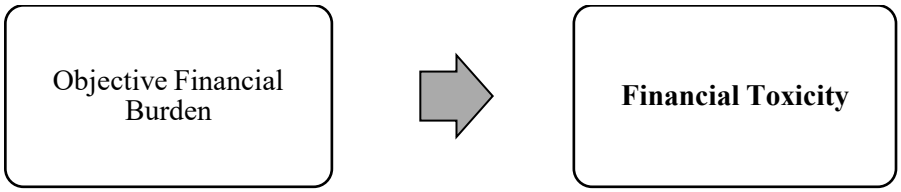

Figure 2-6 Financial Toxicity Model by Longo

It is important to note that the synthesized emerging themes in explaining FT in the Fitch model and Longo may be incomplete in identifying FT, as there is a need for developing standard measures focusing on other aspects of financial impacts besides increased costs, particularly in countries with publicly funded healthcare (11).

A recent qualitative study by Gharazi et al. (111) supported the FT model proposed by Witte. The novel addition of Gharazi is the concept of "expectation". Expectation refers to a patient's uncertainty related to treatment that impacts financial planning and causes objective and subjective burdens. Their findings suggest that objective burden and "expectations" together result in subjective financial distress, and subjective financial distress leads to FT.

A recent qualitative study by Lueckmann et al. (110) in Germany proposed a new interpretation of

"expectation" in the FT framework that emphasized four mediators between higher costs and subjective financial distress. In a systematic review of qualitative and quantitative studies, Pauge (108) assessed this interpretation of Lueckmann (110) and highlighted the crucial role of sociodemographic risk factors in shaping subjective financial distress. Pauge also emphasized that previous reviews might have been misleading, suggesting that FT is mainly the result of higher costs and largely overlooked perceived financial distress.

Reviewing the existing frameworks on the FT construct indicated that even though there appears to be some consensus on the two main domains of FT, objective financial burden and subjective financial distress, there are divergent understandings of how these domains contribute to the manifestation of FT. Recent studies suggest that a better understanding of subjective financial distress and its domains could significantly contribute to our knowledge of FT. Specifically, some socioeconomic risk factors, outcomes, and mitigating factors could also assist us in a more comprehensive understanding of FT; I will review them in the next section.

2-2-4 Socioeconomic Risk Factors of Financial Toxicity

According to a recent systematic review, socioeconomic risk factors predicting FT include insurance coverage, unemployment and lower-income (11).

2-2-4-1 Insurance Coverage

Insurance coverage is considered one of the main risk factors for experiencing FT in patients with cancer (11). Patients in countries with universal national health insurance programs like Canada,

compared to those with a mix of private and public insurance (144), usually report lower out-of-pocket costs for cancer medical treatment (117). In countries with national health insurance, non-medical expenses are among the highest out-of-pocket costs for patients with cancer (36). On the other hand, having insurance does not always mean that cancer treatment is affordable. For example, even though an insurance company might cover 80% of medical costs in cost-sharing medical plans, the patients' 20% share can amount to tens of thousands of dollars for some treatments, leading to thousands of dollars in out-of-pocket expenses (145). Another example is in Canada, where public coverage for supportive care medications varies by jurisdiction, and the fragmented coverage of take-home cancer drugs often poses a significant barrier to cancer drug access (146). Moreover, individuals with private insurance report higher costs and less access to care than those with public insurance in the same country, as private insurance typically involves higher premiums, deductibles, and co-payments (147).

2-2-4-2 Unemployment and Lower Income

Being unemployed is an independent risk factor for FT in those with cancer (11). Those who are unemployed, employed part-time, early retired, or on disability support might face higher FT compared to those who are employed full-time (125). Income and work participation changes are also linked to increased FT (104). Similarly, a reduction in income and missing work due to illness are connected to financial difficulties (105). In one study, self-employed patients with cancer reported a higher percentage of lost earnings (43%) compared to those who were employed (24%) (36).

2-2-4-3 Social Determinants of Health

As noted in the preceding paragraphs, FT among patients with HCS is significantly shaped by social determinants of health (SDH) and underlying health inequities; factors such as inadequate insurance coverage, unemployment, and reduced income contribute to a heightened financial burden, often amplifying pre-existing disparities in access to care (148,149). Individuals with stronger SDH, such as those older (150), with stable employment and comprehensive insurance coverage, generally experience better access to healthcare and are better equipped to manage FT (151). In contrast, younger people (150) face unemployment, lower income, or inadequate insurance and are more vulnerable to financial strain, leading to disparities in healthcare access and the management of FT (151).

For example, findings from a qualitative study by Sayani et al. (152) highlighted significant FT experienced by patients with cancer in Canada, particularly because of inadequate income support and precarious employment conditions. SDH components, such as employment status and access to social benefits, are crucial in exacerbating FT. Patients without comprehensive workplace benefits often rely on insufficient social income programs such as Employment Insurance Sickness Benefits (EI-SB), which provide limited financial relief. This financial strain forces many to make difficult trade-offs between essential needs and returning to work before full recovery, further entrenching social inequities. These findings align with those of other studies, which emphasize the loss of employability and the fragmented income support programs that contribute to increased stress, deepening financial toxicity (106), and poorer cancer-related health outcomes (153,154). These studies underscore the need for targeted policy interventions to address the systemic inequities that underlie FT in the HCS population.

2-2-5 Outcomes Associated with Financial Toxicity

In oncology, health-related quality of life (HRQoL) is an important outcome, and its improvement can impact patient prognosis and survival (155). Research has consistently shown that increased financial toxicity reduces quality of life (11,16,30–32,34,98,142). All forms of FT, including direct and indirect financial and psychological burden, are linked to reduced HRQoL dimensions in various studies (52, 98, 99, 100–104). Additionally, the psychosocial aspects of cancer, such as mental health, social functioning, and role functioning, are essential components of HRQoL (155). While socioeconomic risk factors and outcomes of FT contribute to the heightened risk, understanding them is crucial for developing effective strategies to mitigate FT. The following section explores various mitigating factors that can help reduce the impact of FT.

2-2-6 Mitigating Factors of Financial Toxicity

Mitigating FT in cancer involves a variety of approaches that patients and families could consider: altering lifestyle coping strategies (127), access to financial counselling, and some proposed interventions such as insurance literacy for survivors.

To cope with FT related to treatment, patients and families may be more inclined to adopt approaches that alter their lifestyle (156); first, they may reduce their expenses (112,113) and prioritize their treatment bills. For example, patients may pay for basic needs like heat or groceries instead of non-essential items such as recreational activities (106,109,156,157). Second, patients may enhance their resources (158) by saving less (156,158), selling their home, taking out a loan (156,158), moving in with other family members (99,127), or seeking subsidies from governmental or nonprofit organizations (159).

Patients rarely discuss their financial situation with healthcare professionals (37); however, research studies have shown that medical oncologists can provide high-quality treatment and help manage financial toxicity (160). They could serve as a focal point in helping to identify the financial distress of their patients (160), and fostering cost-consciousness among healthcare providers can play a pivotal role in alleviating FT experienced by patients (73). Communication by oncologists and patient health literacy are critical components of any intervention designed to reduce the FT of cancer care in families (113). Insurance literacy is another proposed service that enhances survivors' knowledge of choosing health insurance and understanding coverage details, plans and insurance terminologies (161). A systematic review of qualitative studies emphasized the importance of providing healthcare information support facilities and financial discussion about costs (32).

Even though potential interventions have demonstrated beneficial outcomes in cancer, a recent scoping review (97) on reducing FT in patients with cancer, along with a qualitative analysis of strategies for mitigating FT (111), affirmed the need for studies to evaluate interventions' effectiveness and identify financial support resources.

Regarding mitigating the disease burden associated with HCS, research studies have concentrated on enhancing accessibility to genetic information services and formulating interventions to promote effective family communication among individuals undergoing HBOC susceptibility genetic testing (162,163). However, in our literature review, I found no specific intervention studies designed to mitigate financial toxicity in patients with HCS. This is in keeping with the lack of research on FT in HCS more broadly.

2-3 Chapter Summary

2-3-1 Literature Gaps

The literature review in this chapter indicates that the financial hardships, specifically the costs and perceived distress experienced by patients with HCS and their caregivers, have been overlooked in research. Although numerous studies have examined cancer costs in healthcare systems (164,165), there is comparatively less information about the patients' share and how these costs are perceived and borne by patients and families (and with what impacts). Additionally, despite the growing research over the last decade on the financial impacts of cancer, these studies often lack a unified or consistent theoretical and measurement framework of financial toxicity. This may be due, in part, to many studies being conducted in the US and a lack of consideration in review studies for variations in funding provided by different health systems.

2-3-2 Literature Insights

Reviewing the existing literature indicates that:

-All consistently address two aspects of FT: higher costs (direct and indirect costs) and perceived financial distress.

-These models generally report similar domains of high costs, referred to as objective financial burdens or expenditures.

-They primarily differ in categorizing subjective financial distress and how they define coping strategies.

-There is a divergence in understanding the FT pathway, which is how objective financial burden and distress contribute to FT manifestation.

-Considering recent patient reports and systematic review data, subjective financial distress is

increasingly acknowledged for its foundational contribution to defining financial FT.

-It is essential to acknowledge the heterogeneous nature of the measurement and conceptualization of FT, which is a shared limitation of all the studies

2-3-3 Thesis Contribution

This thesis offers the first comprehensive review of existing conceptual models in the financial toxicity pathway and domains, synthesizing research on financial hardship in cancer and hereditary cancer syndromes. It introduces a qualitative study that is the first to explore FT in hereditary cancer syndromes across three provinces in Canada. This study will enable researchers to identify the elements of FT in patients with HCS and contribute to the theoretical and methodological discussion on FT more broadly.

Chapter 3: Manuscript of Qualitative Study

Revealing the Hidden Costs: Exploring the Financial Toxicity of Hereditary Cancer Syndromes in Canada

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* Patient Partners
** Co-Principal Investigators

3-1 Statement of Co-authorship

All authors are co-investigators on a large CIHR team grant, of which this work is a separate and specific sub-study. All authors contributed to identifying the grant's research foci and reviewed and approved this draft manuscript. Patient partners further reviewed and contributed to developing the research interview guide. Sepideh Rajeziesfahani conducted all 24 interviews in NL, while other analysis team members conducted interviews in ON and BC. Sepideh, Jordan Sam, Emma Reble, Brooklyn Sparkes, Carly Butkowsky, Marc Clausen and Ridhi Gopalakrishnan comprised the analysis team for the grants' large dataset and co-developed an initial codebook, deductively driven by the content sections of the interview guide (e.g., financial impact, psychosocial impacts, healthcare system impacts, lifestyle changes). Sepideh solely developed the specific codebook for the analysis of FT data for this sub-study and extracted all data related to FT for the current analysis. The codebook was initially categorized according to the common FT constructs seen in all models of FT (e.g., objective financial burdens, subjective financial burdens). Data were then inductively analyzed solely by Sepideh, with repeated and frequent verification discussions with HE. Here, the third high-level theme (a potential mediator of FT), the numerous subcategories of FT, and the postulated relationship among high-level themes to produce the experience of FT rose inductively from the data using thematic analysis. Holly Etchegary, Kasmintan Schrader, and Yvonne Bombard are the team grant Co-PIs; Holly Etchegary is the supervisor for the FT sub-project, and Sevtap Savas is the co-supervisor.

3-2 Abstract

Background: Identifying financial toxicity (FT) following a cancer diagnosis is critical if patients are to be supported in preparing for and lessening financial impacts. There is limited research on FT in patients with hereditary cancer syndromes (HCS), which account for up to 10% of cancers. This paper examines the out-of-pocket (OOP) direct and indirect costs and financial distress related to two common types of HCS: Hereditary Breast and Ovarian Cancer Syndrome (HBOC) and Lynch Syndrome (LS).

Methods: A qualitative study was conducted guided by interpretive description. Patients across three Canadian provinces (NL, ON, BC) with a confirmed molecular HBOC or LS diagnosis were invited to semi-structured interviews by providers in their circle of care. Thematic analysis with constant comparison was employed to analyze the transcripts.

Results: 73 participants with HBOC (n= 39) or LS (n= 34) completed an interview. Participants described numerous aspects of FT categorized under three primary themes: 1) objective financial burden (direct OOP medical costs, direct OOP non-medical costs, indirect costs); 2) evaluation of financial resources; 3) subjective financial distress (distress arising from financial resource management, basic needs insecurity, future financial insecurity).

Conclusion: FT is a significant additional burden faced by patients with HCS. While there was some variation across provinces, most HCS carriers experienced FT, with travel costs and income loss being the primary contributors. Findings suggest that high costs contributed to subjective financial distress through patients' evaluation of their financial resources. Results highlight the need to develop strategies that mitigate the FT experienced by HCS carriers in universal healthcare systems.

Keywords: Hereditary cancer syndromes, Financial toxicity, Out-of-pocket costs, Financial

distress, Breast and ovarian cancer, Lynch syndrome

3-3 Introduction

Cancer is a leading cause of early morbidity in Canada (63) and globally (166), with 2 in 5 Canadians expected to develop cancer in their lifetime (167). Cancer care costs significantly impact patient outcomes, even in highly developed countries with publicly funded healthcare systems (143,168,169). In Canada, one-third of the financial burden of cancer is borne by patients and families (9), with 33% experiencing significant out-of-pocket (OOP) costs for cancer treatment (127).

Highlighting the adverse economic impacts of cancer, the concept of financial toxicity (FT) emerged a decade ago in oncology (26,29), followed by many studies exploring the concept in sporadic cancers (11,16,30–34). However, little is known about the patient-reported financial difficulties in Hereditary Cancer Syndromes (HCS). HCS accounts for 5-10% of all cancers caused by inherited mutations in cancer predisposition genes (20,49). The most common HCSs are Hereditary Breast and Ovarian Cancer syndrome (HBOC) and Lynch Syndrome (LS) (43,74). These syndromes can lead to additional costs since they necessitate specialized testing to diagnose (170), more frequent screening and surveillance (45), higher health insurance premiums (171), and prophylactic surgeries (172,173). They are typically marked by an early age of onset (148) compared to sporadic cancers. Despite this, there is a dearth of research on the nature of FT in HCS populations.

FT includes both the objective and subjective dimensions of costs incurred by patients and families. The objective financial burden is often measured as paying out-of-pocket (OOP) for direct medical and non-medical costs and losing productivity (indirect costs) (35,106). Subjective

financial distress refers to an individual's emotional response and perceived distress due to higher costs (137). For example, Witte et al. (102) suggest it has three domains: 1) impacts of financial spending and financial resources used by individuals, 2) psychosocial responses to objective financial burdens, and 3) coping strategies for objective financial burdens. Despite some agreement on what comprises objective financial burden, recent FT frameworks (104–112) differ in categorizing the elements thought to comprise subjective financial distress.

Moreover, limited information is available on *how* objective and subjective elements become FT. Earlier studies reported the primary contributing factors to FT as out-of-pocket costs and lost income (174–176). Other studies (104) proposed that both objective and subjective financial burdens contribute to the manifestation of FT. According to Witte et al. (109), supported by some recent qualitative studies (111) and a systematic review (108), financial objective burden leads to subjective financial distress; thus, FT emerges as a direct consequence of subjective financial distress. However, a recent study by Lueckmann et al. (132) highlights the evaluation of financial adjustments, the ability to make ends meet, the burden of applied financial adjustments, and bureaucracy as factors more important than higher costs when measuring subjective financial distress. This suggests that financial distress may arise independently of increased costs and could also directly contribute to FT.

Previous research on FT has used variable measurement tools, limiting comparison across studies (11,108). Moreover, most FT research has been conducted in the US, potentially limiting generalizability to publicly funded healthcare systems (142) such as Canada. Some recent studies with patients affected by cancer in Canada (35) indicated that high levels of OOP costs and FT exist (1,2), and FT has a profound impact on patients' everyday lives and quality of life (37). However, as noted, virtually, no research has explored FT in patients with HCS.

The overall objective of this study is to better understand the FT experienced by individuals with HBOC and LS in three Canadian provinces. Identifying the diverse aspects of FT as perceived by these patients will enhance our understanding of FT and inform future policy and practice solutions to address their financial needs.

3-4 Methods

3-4-1 Setting and Design

We conducted a qualitative interpretative descriptive study using semi-structured interviews in the Canadian provinces of Newfoundland and Labrador (NL), Ontario (ON), and British Columbia (BC). A qualitative approach allowed an in-depth exploration of patients' perceptions of the economic impacts of living with an HCS, generating rich data in participants' own words (177). Given the relative lack of data in the literature on FT in this patient population, these features of a qualitative approach aligned well with the study objectives.

This study is part of a larger, mixed-method study investigating the health system experiences and psychosocial and economic impacts of HCS in Canada. The current research focuses on the experience of FT as described by patients affected with HCS.

3-4-2 Participant Selection

Eligible participants were those with molecularly confirmed LS and HBOC, with or without a history of cancer, aged 18 years or older, who could read and speak English and who lived in either NL, ON, or BC, the three study sites. Interviews continued until thematic saturation was reached

(n=73); no new ideas or codes arose in the data (178,179).

Sampling was purposive (180,181) and sought variation in geographic location (across the three provinces, as well as rural vs. urban), sex, age and clinical characteristics (e.g., cancer history, LS and HBOC) to gather information from a diverse range of participant experiences. Preliminary analysis of roughly the first third of interviews revealed missing perspectives (e.g., males, rural respondents); thus, theoretical sampling (180,182) was subsequently used to allow maximum variation in the patients' experience of FT across three provinces.

Participants were mainly recruited through partnered hereditary cancer clinics and healthcare providers, including oncologists, gastroenterologists, and genetic counsellors at the three study sites. Providers in the circle of care shared information about the study, and all interested participants were given study team contact information. Study adverts were also shared at some sites via social media and by email to professional and research networks of team members. When participants made initial contact with a study team member, a copy of the study consent form was forwarded before scheduling an interview.

3-4-3 Patient Partner Engagement

Six patient partners, two each from NL, ON and BC, affected by HBOC or LS were recruited from team members' networks at the start of the study. Initial meetings with patient partners confirmed that financial impacts were an important issue for patients and families with HCS. Partners helped modify the interview guide (e.g., ensuring language was not solely negative and focused on burdens) and finalize probing questions. Patient partners also reviewed emerging themes in the data for the larger project, including financial impacts, and they are co-authors on all study outputs.

3-4-4 Interview Procedure

We conducted semi-structured interviews between July 2022 and February 2023 with 73 patients: NL (n=24), ON (n=26), and BC (n=23).

Interviews were conducted by three members of the research team (SR, CB, JS). Interviewers met before the start of interviews to ensure a standard interview guide was used, to discuss and choose standard prompts, and to ensure the same interview process was followed for all participants (e.g., provision and discussion of consent form, gift card thank you discussion). It is acknowledged that qualitative data collection is a co-constructed process between interviewer and respondent (183); however, these practices helped ensure a standard interview process and the same open-ended questions were administered to all participants.

According to participant preference, interviews were conducted over a videoconferencing platform (e.g., Cisco WebEx, Zoom Health) or by phone to allow equitable participation from anywhere in the study provinces. Interviews lasted 30 to 60 min and were about 45 minutes on average. Verbal consent was obtained and documented at the start of all interviews. The interviewers provided a brief presentation on the study's aims and explained that the interview included multiple questions on assessing socioeconomic burden and psychosocial and health implications of living with HCS. At the end of the interview, the following demographic questions were collected: education level, employment status, living location (urban, rural), number of years with molecularly confirmed HCS, family history with molecularly confirmed HCS and previous experience with cancer. Participants were also advised that a small gift card ($20) was available as a token of appreciation. All interviews were transcribed verbatim using the online transcription service (Rev.com). Approximately 70 hours of recordings were transcribed for analysis. Given the large volume of data and the large number of participants in this qualitative study, transcripts were not returned to participants for comments or correction. However, we reviewed

findings with the study's six patient partners to ensure emerging themes made sense in the context of their lived experience.

3-4-5 Interview Guide

The development of the interview guide (Appendix 2) was an iterative process, informed by relevant literature on the psychosocial, health system and financial impacts of HCS and regular discussion of the study team, including patient partners. The interview guide was refined through a pilot test involving three mock interviews with patient partners, which helped adjust its content and length while incorporating additional prompts and probing questions.

3-4-6 Data Analysis

Thematic analysis (184) using constant comparison (179) was employed to analyze transcripts. An interpretive description approach (177) directed the study procedures. This method avoids theoretical assumptions about the data and presents data in the participants' own words. These results in a comprehensive summary of findings to inform practical and relevant applications in clinical settings (177,185). This is consistent with our aim to explore FT in HCS populations and make recommendations for practice and policy.

Using constant comparison (179), data gathering and analysis occurred simultaneously and continuously during the study. Categories in the initial codebook (Appendix 3) arose deductively guided by the content sections in the interview guide (e.g., emotional impacts, financial impacts, lifestyle changes, FT). These data were extracted for the specific analysis of each impact. As the analysis advanced, the codebook was updated to incorporate newly identified codes and themes

derived from the data. The six analysis team members continuously evaluated new and existing findings, making iterative refinements to the interview guide, coding framework, and sampling strategy based on these insights. This iterative process was enhanced through peer debriefing and collaborative team discussions over six months, which offered valuable interpretative perspectives. Discrepancies between investigators were resolved through discussion and, when necessary, by including additional coders (supervisors). Initial themes were generated by examining relationships between codes. Themes were revised and developed through iterative discussions among the analysis team. Quotations from each interview were listed under headings to summarize study data so that all authors could have an overview of critical data from the whole sample. A separate framework was created by SR for the current FT analysis, with high-level categories corresponding to FT frameworks (e.g., objective burdens). Additional codes and themes specific to FT were inductively added by SR as they emerged during the thematic analysis and review of the FT frameworks in the literature (Appendix 4). All analytical decisions were documented. Throughout the analysis, team members practiced reflexivity (186) by examining beliefs and experiences related to the HCS care journey that could affect the analysis. Team members discussed how these facets may have affected the interviews or interpretations of findings. The collaborative analysis process allowed the analysis to progress to a higher level of data conceptualization.

3-4-7 Reflexivity

Reflexivity involves critically reflecting on how the researcher's background, experiences, and assumptions may influence the study. It helps ensure transparency and reliability by

acknowledging potential biases that could shape data collection, analysis, and interpretation (186–188). The lead author's reflexivity in this study is outlined below:

First, I began my analysis by reading all the existing models on FT and deliberately chose to categorize the data deductively, focusing on two primary constructs: objective financial burden and subjective financial distress. These key concepts are central to the FT frameworks, and I recognize that this influenced how I initially coded the data. While this approach could mean that some data were excluded from the analysis, all relevant FT-related data was thoroughly identified, extracted from the interviews, and compiled into an Excel sheet for coding. Each piece of data was carefully scrutinized and analyzed over an extended period of several months, ensuring comprehensive data treatment and that all emergent themes were captured.

Second, much of the literature reviewed originated from the United States, where qualitative data on hereditary cancer syndromes is more common. However, the U.S. healthcare system significantly differs from Canada's publicly funded system. These differences raised concerns in that they could have affected the approach to analyzing the data (e.g., a heavy focus on out-of-pocket medical costs that are common in the US literature). To mitigate this, the literature review was purposely broadened to include countries with healthcare systems that closely resemble Canada’s, such as publicly funded or partially funded systems. This helped ensure that my perspective remained aligned with the context of the Canadian healthcare system.

Third, I was aware that it would have been easy to assume that individuals with better insurance coverage, full-time jobs or higher incomes would not experience FT. However, I remained cautious to avoid this bias, ensuring that all data was carefully considered. Through this thorough analysis, I discovered that even those with more financial resources, though not reporting *objective* financial burdens, still experienced subjective financial distress.

Fourth, it would have been straightforward to follow the prevailing narrative in most of the existing literature, which suggests that subjective financial distress is merely a consequence of objective financial burden. However, I consciously avoided this assumption, focusing solely on what the data revealed. As a result, I identified a distinct group of individuals who, despite not facing objective financial burdens, still reported subjective financial distress. This finding led to the emergence of a potential mediator within our model that differs significantly from what has been suggested in previous literature.

3-4-8 Ethical Concerns

This study received ethics approval from the Newfoundland and Labrador Health Research Ethics Board, HREB # 20222386, the Research Ethics Boards at Unity Health in Toronto REB # 3855, and BC Cancer in Vancouver REB # H21-03579, Canada (Appendix 5). Study procedures were strictly followed according to the approved ethics applications across the three study sites. All participants received a copy of the study's consent form before their interviews and were advised of their right to stop the interview at any time. Participants' transcripts were shared only via a secure platform for transcription and were deidentified upon return. All interview data was stored on a secure university platform and was not shared with anyone else outside of the analysis team.

3-5 Findings

3-5-1 Demographic Characteristics of the Participants

In total, 73 participants (NL=24, ON=26, BC=23), with half between 28-47 years, were interviewed (Table 3-1). Most (70%) were women, and nearly half had a university education; most were married and working. The majority (80%) were Canadian and self-identified as white.

Table 3-1 Demographic Characteristics of the 73 Participants

Demographic Variable	**Total**
HCS diagnosis	
HBOC	39
LS	34
Age (average age/ range)	50yrs /25-80
NL (average)	47
ON (average)	50
BC (average)	53
Gender	
Female	51
Male	21
Different identity	1
Marriage	
Married/ common-law	59
Single	10
Divorced	4
Employment Status	
Employed	50
Self-employed	2
Retired	19
Unemployed	2
Race/ Ethnicity	
White/European	54
Asian	7
Others	12

Following analysis, participants were categorized into four groups based on the presence or absence of objective financial burden and subjective financial distress (Table 3-2). Objective financial burdens were determined by participant-reported direct or indirect out-of-pocket (OOP) costs. Participants reporting such costs were coded as having objective financial burdens. Subjective financial distress was categorized as present or absent based on participants' narratives.

Table 0-2 Number of Participants Reporting FT Across Provinces

Province			Reported subjective financial distress		Total
			Yes	No	
NL	Reported high costs	Yes	10	8	18
		No	4	2	6
	Total		14	10	24
ON	Reported high costs	Yes	10	1	11
		No	4	11	15
	Total		14	12	26
BC	Reported high costs	Yes	7	3	10
		No	1	12	13
	Total		8	15	23

Out of the total participants, 39 reported high costs (53%) (NL=18, ON=11, BC=10). Among these, 27 participants (NL=10, ON=10, BC=7) indicated experiencing high costs and subjective financial distress, while 12 participants (NL=8, ON=1, BC=3) reported only high costs without experiencing financial distress. Additionally, 9 participants (NL=4, ON=4, BC=1) experienced only subjective financial distress without reporting high costs. Accordingly, nearly 50% of the total participants, 36 participants (NL=14, ON=14, BC=8), reported high costs with or without subjective financial distress. The following sections describe these costs in detail.

3-5-2 Themes

Three primary themes (Fig 3-1) arose during data analysis: 1) Objective financial burden, 2) Evaluation of financial resources, and 3) Subjective financial distress. These themes are themselves comprised of sub-themes. The evaluation of financial resources is divided into two groups: financial distress reported and no financial distress reported. Subjective financial distress is described as a series of three subthemes. These are presented in turn.

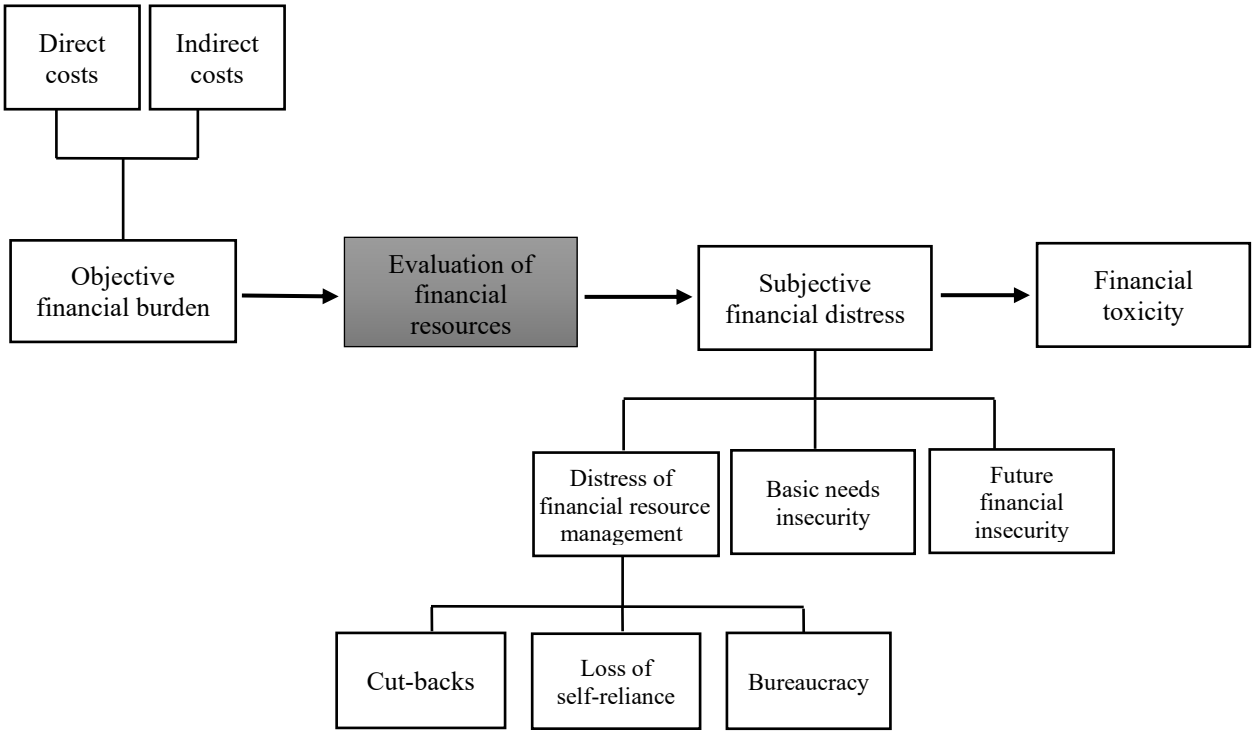

Figure 3-1 Model of Financial Toxicity Based on the Hereditary Cancer Syndrome Participants' Experiences

3-5-2-1 Objective Financial Burden

3-5-2-1-1 Direct OOP Medical Costs

Healthcare: Participants reported that they did not incur out-of-pocket (OOP) costs for medical care related to hospitalization, chemotherapy and radiation, surgeries, services of physicians and specialists, genetic testing, and preventive screenings, as the public health system covers these. However, participants reported several direct OOP medical costs, including over-the-counter drugs, hormone replacement therapy, prostheses, physiotherapy, and psychotherapy (Table 3-3). Those with private insurance were sometimes partially reimbursed for these costs.

Accessing Magnetic Resonance Imaging (MRI): An OOP medical cost related to accessing MRI screening for those patients with elevated body mass index (BMI), affecting at least two obese participants. These participants reported that due to their body size, they were unable to undergo breast MRI screening in NL, as the available machines do not accommodate them (Table 3-3). Both participants avoided this screening modality because of the high travel costs to other provinces but recognized they were missing a recommended and important screening.

3-5-2-1-2 Direct OOP Non-medical Costs

Travelling: Many participants experienced direct OOP non-medical costs related to travel for ongoing and lifelong risk management. Travel costs were generally higher for participants who lived in rural areas, needed an overnight stay, and had a family member(s) who accompanied them. Childcare costs were also increased with travel for screening (Table 3-4), as were the costs associated with airline tickets for those patients living far away from tertiary centres. While some participants reported partial reimbursement for travel through their private health insurance, most travel costs associated with managing hereditary risk were borne by patients (Table 3-4).
Participants living in urban areas also reported transportation costs, mainly encompassing the cost of gas to travel to treatments and screenings, pharmacies and rehabilitation centers (Table 3-4).

Parking: Paying OOP for hospital parking was reported by many participants and could sometimes be substantial. One participant noted that parking fees alone could be as high as almost $2000 (Table 3-4).

Diet (foods to eat, foods to avoid): A healthy diet is recommended for HCS mutation carriers. However, participants noted that healthy foods are costly in Canada, making a healthy diet a significant out-of-pocket expense (Table 3-4). Some tried to incorporate a healthy diet by making cutbacks on other expenses such as non-grocery shopping or vacations.

Fertility interventions for embryos predisposed to HCS: A unique OOP cost, particularly for younger mutation carriers, was a gene-sensitive fertility intervention for HCS-predisposed embryos. Pre-implantation genetic testing (PGT) is an assisted fertilization technique using in

vitro fertilization (IVF), where embryos are frozen while waiting for genetic testing results. The goal is to select embryos free of pathogenic mutations to prevent inheriting hereditary cancer. This procedure is expensive and could cost thousands of dollars per cycle (Table 3-4), typically not covered by funded health systems or private insurance.

Table 0-3 Direct Out-of-pocket Medical Costs

Costs	**Illustrative quotes**
Healthcare (over-the-counter)	…some of the medicine was like $1400 every week...So some of it's covered, but then there's all the little things that you need to help you survive each day that are not covered and you don't have an income coming. BC13
Healthcare (hormone therapy)	…we don't have a drug plan, so none of my hormone replacement therapy that I'm on...is covered. And so we have to pay for that out-of-pocket. NL6
Healthcare (physiotherapy)	Paying [OOP] for physiotherapy after my different surgeries and whatnot has not been cheap. NL15
Healthcare (psychotherapy)	Well I get like $500 a year for psychotherapy, but a therapists' appointment is $100 or more for the appointment, so there's definitely some out of pocket expense. ON23
Healthcare (prosthetics)	And the prosthetics, I bought them, the costly one was $1,000, and the government pays part of it. $190, I think they pay on each one. ON1
Accessing MRI for elevated BMI	I'm very large, I'm morbidly obese, and Newfoundland does not have an MRI machine that I will fit in. So I've continued to have my mammograms arranged through my family doctor annually, but I have not had an MRI...I've not had an MRI on my breasts since 2013, 2014. NL4
	I'm not able to have a breast MRI in the province of Newfoundland...Our machines are not built for plus size or larger people...I should be getting breast MRIs yearly, and I'm not...I'm going to need to leave the province to get this testing...This is a restriction, MRI, I'm not getting the full screening I should be getting. NL20

Table 3-4 Direct Out-of-pocket Non-medical Costs

Costs	Illustrative quotes
Travelling (transportation, accommodation, airline tickets, gas)	…the transportation thing, it will always be an ongoing issue because you have to have two people who have time off work. Sometimes we would use an Airbnb... ON12
	I have to take time off. My partner has to take time off. We would have to pay for gas money...close to $200 to $300, a place to stay out...$500 to $600 so we'd end up...between the two of us not working, gas money and everything, probably out $5,000 just to go for a two-minute appointment. NL23
	I had spent so much money to get out there to arrange all the care for my kids, time off work, my husband, hotel. NL5 [on travelling for surgery]
	…yes, all those things, the airport costs, hotel costs, I can't even imagine...they'd have to apply through the Medical Transportation Assistance program. NL22
	So hotel bills and food bills and everything will be racking up. But I think we're middle class. So far, we haven't had to sell the house or nothing. BC8
Parking	The only thing we were really out of pocket on, and it was huge, was parking. I'm not kidding. It was probably $1,800 in parking. Luckily we could afford it...But still parking at hospitals is insane. BC12
	I think is a big impediment to healthcare is the price of parking. That's probably kind of ridiculous...If I need blood work, if I needed to get into the clinic, having mammograms, everything, MRIs I used to have, Sunnybrook parking is super expensive… that's definitely a challenge for a lot of people. ON23
Diet	And even eating healthier, to be honest, fruits and vegetables are extremely expensive. I'm not exaggerating when I say I'll spend about, I don't know, $600 a week on groceries. It's expensive. It's really, really expensive to eat healthy... I would say that's the biggest cost to me. ON22
Fertility interventions for embryos predisposed to HCS	I feel like another financial impact that...will happen, is when I get that meeting to see about the embryos and removing the embryos that has the *BRCA1* gene. I don't know how much it costs yet. I know that my counselor did tell me it was around 5,000...It could be more than that. ON7
	my brother and I talk about this…And I knew that when they decided to do the, I guess IVF, to get rid of the Lynch and to, said probably the same thing I said to you, I'm sure Jen and I would have a very strong consideration to do this. We certainly would have the financial means to do it. I know for them a little more. But they also had the means to say this is important. ON8
	...if he decides to go ahead with in vitro down the road, like we're looking at potentially $20,000, and I understand the importance for him, because if I had a choice, I would've certainly never passed on this gene…but still it has got to come out of their pockets, which is really unfair. NL1

3-5-2-1-3 Indirect Costs

Loss of income: Loss of income emerged as a significant financial stressor impacting patients and primary caregivers. Loss of income was sometimes the result of participants being unable to work due to cancer treatment or having to take jobs that paid less (Table 3-5).

Participants who lost their jobs mostly transitioned to income support programs. The programs described in our study included Employment Insurance (EI) sickness benefits, the Canada Pension Plan (CPP), and short-term and long-term disability benefits (Table 3-5). The coverage varied widely among participants, and the inclusion criteria were influenced by the type of employment contracts, years worked, and accumulated insured hours.

Some participants characterized income support duration as short and insufficient, often necessitating a premature return to the job market before being physically well enough to do so (Table 3-5). Demonstrating eligibility for transition between income support programs was also challenging for some. (Table 3-7).

Those who were employed in precarious conditions with limited access to health benefits were generally younger and had fewer years of employment. Those residing in areas with fewer full-time, well-paying job opportunities, such as NL, described more economic difficulties and distress (Table 3-7).

Career choices: Some participants could not return to their prior employment because of the impact of HCS on their overall health, meaning they took less physically demanding and stressful jobs. Others described prioritizing their health or spending quality time with family rather than making money, leading to a different career choice, notably an easier or part-time job (Table 3-5). One young HCS participant decided to stay in Canada to have access to a funded health system

rather than move to the U.S. for employment (Table 3-5).

Taking time off work: Another source of indirect costs included taking sick leave, vacation time, or unpaid leave days for healthcare related to HCS (Table 3-5).

Some participants reported having limited access to sick leave, especially those new to their jobs, resulting in leisure time costs and absence from employment through vacation leave or unpaid sick days (Table 3-5).

Employer support, flexible working hours, benefits, and remote jobs allowed participants to adapt their work schedules around screening and treatment times. Participants with paid sick leave described how these afforded substantial financial relief following an HCS diagnosis and treatment (Table 3-5).

Families' or friends' productivity loss: Several participants described how their families or friends had to request vacation time or unpaid leave to accompany them to ongoing appointments and screenings (Table 3-5). This results in lost productivity for family members and friends. Some participants reported that a family member even left their job to support them during their HCS healthcare (Table 3-5).

Self-employed: Patients or families who were self-employed reported there were no employers to ask for support or sick days, and they lost their clients or customers as a result of being off work during treatment (Table 3-5).

Table 3-5 Indirect Costs

Costs	Illustrative quotes
Loss of income	My salary was really good. I had a large team. And then when I was diagnosed, I immediately had to leave work...there was no way I could lead a team so I left work immediately… So I stepped back. $20,000 I've lost in salary. ON5
	I just have EI, sick, and then onto CPP disability, which would be very limited for me and the amount of contributions I've been able to make over time. NL15
	I don't know how anybody lives off that. So it was very hard for us. I probably needed more time. It was recommended I needed more time, but I returned for financial reasons. ON22
Career Choice	I can't really work the same types of jobs I used to work, in very heavy customer service, very escalated issues. My stress levels are just off the charts all the time so I am seeking more mellow terms of employment. NL 23
Taking time off work	The coming off of work, having to leave work. Having a lot of appointments booked, because there was at one point when all that stuff was going on with the lymph node that was swollen that I had to leave work early. ON7
	…when I was getting paid by the hour, you miss a day of work, that's a day you don't get paid. NL10
	…I had a hospital stay…I've taken holidays, and so then I didn't have holidays to do family things. NL12
	I'm fortunate that the career path I was already headed towards when I got this diagnosis was one that kind of is an easy one to get time off when I need it. And I have really good health coverage. ON24
Families' or friends' productivity loss	…when you have no other family here to help you take care of your children… and your wife is on modified bedrest, he had to take three weeks of either unpaid leave or holiday. I mean, that wouldn't have been his choice of how to take two to three weeks of holiday. BC1
	…when I had my hysterectomy done…I was there for four or five days and my husband was there…My husband takes holidays to try and be there. NL2
	I also had another friend travel with me…it was something that I felt I'd be comfortable with…she traveled from the island in Newfoundland...I can't remember if she was coming to St. John's for something, but she agreed to stay with us. NL5
	…my husband had to leave work. He left work with me for the surgery part. NL14
Self-employed	I have a [business] in the house and clients came to the home and a lot of them were very understanding, but I mean you lose clients. BC13

3-5-2-2 Evaluation of Financial Resources

Almost all participants reported reasons for experiencing financial distress (or not) as they managed increased direct and indirect costs. These reasons were linked to their evaluation of available financial resources to manage these healthcare-related costs. The evaluation focused on 1) the perceived adequacy and accessibility of financial resources and 2) the perceived effectiveness of strategies to cope with high health-related costs.

The "financial resources" are those things that help alleviate FT. In this study, they included a partner's job, retirement pensions and free time, savings, supportive employers and flexible work hours, private insurance, income support programs, financial support of family and friends, fundraising, and access to a funded health system (Table 3-6). Described coping behaviors – what participants did to help manage their FT - including budgeting, financial dependence on partners, seeking help from family and friends, utilizing savings, selling property, relying on retirement pensions, requesting employer assistance, reducing non-essential spending, discontinuing medical screenings, and applying for income support programs (Table 3-6).

Participants' evaluation of financial resources appeared to mediate the relationship between objective financial burden and subjective financial distress. Participants were categorized into two groups:

No financial distress reported: About half of the participants (n=37) did not describe subjective financial distress as they reported sufficient financial resources to manage the increased costs. The availability of sufficient resources enabled participants to plan purposeful actions to cope effectively with increased expenses. Therefore, although they had almost similar higher costs related to HCS health care, they did not report financial distress.

Financial distress reported: About half of the other participants (n=36) reported subjective financial distress. However, the data suggested two sub-groups here:

-For the majority of these, coping effectively with higher costs was challenging because they did not have adequate financial resources, which led to financial distress (Table- 3-6).

-For a smaller group (n=9), subjective financial distress was reported because they were concerned about what might happen in the *future*. Despite having access to enough financial resources currently, these participants still experienced financial distress (Table- 3-7).

Table 0-6 Reported Financial Resources

Financial resources	**Illustrative quotes**
Partners' job	…because I quit my job and everything. I am reliant on my partner. BC5
Retirement	Well, not really me because I'm retired now. BC19 [on reason for no financial impact]
	Didn't affect me, no. Really, no. Yes, I had less money, but I mean, my husband still works a little bit, we were both on pension, so we were okay. BC18
Savings	…we did have to draw down on our savings. Fortunately we had a degree of savings, so we didn't have to necessarily change our lifestyle, or sell the car. ON14
	I'm also lucky that I sold my house and I had a little bit more money to play around with for other healthcare professionals. If I didn't sell my house, it would've been really hard for me to be able…to get some of the other self care that is so important. ON5
Supportive employer	They really supported. They asked me not work too hard and take the treatment first and work the second. BC2
	…but my work was very accommodating and everything to let me have the time off with no problem, no questions about that. ON6
Private insurance	My mom worked for the county and had benefits as well. If we didn't have benefits, it would to an extent. ON18
	At the hospital, when I was having chemo, I did have an injection of Neulasta after every chemo treatment and that was quite a bit. It was like $3,000 for each injection and my insurance actually covered the whole amount. ON19
Income support programs	I had long term disability benefits, so even though it was still, I guess there's still always a financial burden on myself and my family because I was off work for well over a year, it could have been a lot worse, for sure. ON14
Families' and friends' financial support	My parents took care of me, I was eternally thankful for that. I had a spot, they fed me, that kept a roof over my head. NL10
	…thank goodness I do live with my girlfriend and my mom, who could back me up here...they both have vehicles, so I do have access to a vehicle. ON12
Fundraising	I had a GoFundMe and my community supported me with $10,000,...I got private donations too...so it was probably closer to $11,000. ON12
	I had some amazing friends that put together fundraiser and stuff. BC23
Funded health system	I live in a country that has great medical care and everything they did was covered through B.C. Medical. So it wasn't like in the States where you would also have a financial worry on top of your health worry. BC16
	Of course, it's not like the US where a trip to the hospital could bankrupt you as an example.ON17

3-5-2-3 Subjective Financial Distress

Data analysis revealed three domains of subjective financial distress.

The distress of financial resource management: Several participants described distress due to trying to manage objective financial burdens with insufficient available resources. First, this included reducing spending on non-necessities, primarily reported in vacations and non-grocery shopping contexts (Table 3-7). Secondly, a loss of financial self-reliance occurred through moving back to their parent's home, receiving financial support, or not working and relying on their families. These situations led to feelings of being a financial burden on their families, feeling devalued, or, as one participant put it, "feeling like shit" (Table 3-7). Third, some other participants were distressed by the existing bureaucracies and administrative burden when navigating healthcare with private insurance systems and income support programs. These challenges include dealing with time-consuming paperwork, meeting the inclusion criteria to access support programs and the amount of coverage for which they qualified (Table 3-7).

Basic needs insecurity: For some participants, deep distress resulted from the inability to make ends meet (Table 3-7). In our study, this theme mainly occurred in patients' ongoing struggle to balance the indirect costs of necessary medical treatments and their daily living expenses.

Future financial insecurity: Despite having adequate financial resources to manage their current financial burden, these participants still reported financial distress. However, their distress was not directly tied to immediate financial expenditures or debts but was instead related to *future* financial uncertainties and potential financial risks and vulnerabilities (Table 3-7). Participants reported they

were worried about unexpected occurrences of HCS in the future and would only be prepared if they had access to adequate resources (Table 3-7). For example, being self-employed with no pension, passing away, and their families not having access to enough supportive resources or not having enough savings, which they face again, were specific sources of future worry. This led to changes in financial behavior to increase their resources, such as buying a house, saving more money or purchasing life insurance (Table 3-7).

Table 0-7 Subjective Financial Distress

Financial distress	**Illustrative quotes**
Distress of financial resource management (cut-backs)	So obviously that's a stress. You've still got mortgage payments to make, you've still got all the things you need to pay for that don't change even though your income's been cut almost in half. ON14
	we've got to cut back...I was having a family dinner once a week, just so that I could have family time with my children. And he would be like, maybe we shouldn't do this every week. Maybe we should just do it once a month to cut back. BC13
Distress of financial resource management (loss of self-reliance)	I became very financially dependent on my family...I moved back home. I lived with them. I was entirely dependent on them for financial support. NL 15
	I quit my job and everything. I am reliant on my partner…I had to take sick leave. I took about six months off and that impacted me in my life. BC4 [on financial impact]
Distress of financial resource management (bureaucracy)	I have worked for almost eight years. No, more than eight years now…I was in contracts for a long time…They kicked in one month before my first appointment with my nurse practitioner where we talked about what this [HCS] could be. I was diagnosed within the first year of my benefits, and therefore I wasn't covered for long term disability, which was a huge fight and really alarming and sneaky. ON12
	When my dad was diagnosed, he was off work for a long time with no income. He wasn't approved for disability through the government so he really had no income. NL9
Basic needs insecurity	You can't work, you can't pay your rent, right. You could end up homeless- So it's pretty scary. …. I live month to month. NL11
	I got divorced...and it's not easy to survive now here in BC, prices so high and I don't have a very payable job, so it's made me nervous about it. BC17
	Food, rent, childcare, bills, just bills, things people have, cable, phone bills, heat bill, whatever. And then your credit score is gone. Just, there's all kinds of repercussions. NL11
Future financial insecurity	…with a young family and being self-employed, I had no pension. So, I had to make sure that, being somebody who was in a vulnerable position of maybe the opportunity of getting cancer and leaving my family earlier than what I would like to, is making sure that they were financially stable ...make sure that my family was looked after once... If I was gone. NL24
	if anything happens to me in the short term my wife is on her own for the most part…. I imagine, she would end up having to sell the house and do a bunch of things that way, which is awful. NL10
	I definitely see that it impacts her. Financially, I know she worries about it. Ever since when it happened she went out and got herself another property because she's like, "I need to make sure. ON22

3-5-3 Findings Across Provinces

Approximately half the participants were categorized as having objective financial burdens, with the highest being in NL, with similar levels reported in ON and BC (Table 3-2). Participants who reported both objective financial burden and subjective financial distress, and those who reported only subjective financial distress, were higher in NL and ON, whereas financial distress was observed less in BC. Participants from NL, who were younger on average, described having less access to employment benefits and being less likely to own their homes and, therefore, more likely to have a mortgage. Those in BC, who were older on average, reported more access to retirement pensions. Participants in both BC and ON described having more access to a secure, supportive job (a critical financial resource) than NL. In both NL and BC, participants residing in rural areas experienced greater travel costs for accessing medical centers than the more dispersed healthcare services across a larger geographic area in ON. Participants reported some costs, such as hormone replacement therapy or psychotherapy (e.g., CBT), in NL as OOP expenses. In contrast, these costs were not covered by the universal healthcare system but were covered by third parties, such as particular hereditary cancer clinics in ON and BC. A comprehensive set of illustrative quotes from all analyses is presented in Appendix 6.

3-6 Discussion

To the best of our knowledge, this is the first investigation of FT experienced by people affected by HCS. Approximately 50% of participants reported substantial OOP and indirect costs, extending the FT construct to HCS populations. Results describe the previously underreported aspects of HCS-related costs, identify areas of subjective financial distress for affected individuals, and describe elements of the FT construct in HCS. Findings suggest that subjective financial distress is the consequence of an individual's evaluation of their financial resources impacting the experience of FT.

3-6-1 Objective Financial Burden

People affected by HCS experience a wide range of direct and indirect OOP costs. The majority of these have been reported in patients with non-genetic cancers (32,122,189), although fertility interventions for embryos predisposed to HCS appear to be a unique OOP cost for this population. The sheer volume of patient-reported OOP expenditures and indirect costs underscores the gap in coverage and support available for these patients, particularly for travel to access medical services and support for income loss. Data also revealed that some HCS carriers in NL with elevated BMIs had no access to local MRI screening, causing delays in, or discontinuation of, recommended screening.

This study extends cancer-related OOP expenditures and indirect costs (32,110,111,122,157,190,191) to the HCS population but also reveals a unique cost for patients with HCS. About 65% of young adult cancer survivors are worried about passing on a cancer genetic risk to their children (192), and studies highlight the high cost of IVF with pre-implantation

genetic testing, with an average price of about $30,000 for patients (193–195). In non-genetic cancers, financial difficulties of fertility preservation are associated with oocyte, sperm, or embryo cryopreservation prior to cancer treatment, which may cause infertility (130,131). Our findings regarding fertility interventions for embryos predisposed to HCS indicate a different financial challenge than those in previous studies. In this study, high costs are linked with PGT and IVF, which aim to select embryos free of pathogenic mutations to prevent hereditary cancers. This distinct challenge emphasizes the need for policy interventions and support programs specifically designed to address the unique needs of HCS patients.

Patients also faced a wide range of non-medical costs (e.g., parking, diet), with treatment-related travel expenses being particularly significant. These findings are consistent with other literature (e.g., 115, 116) and suggest that these non-medical costs should be incorporated into the formal evaluation of patients' cancer-related OOP expenses. Failure to do so could underestimate the overall FT burden. In HCS populations, travel expenses could be considerable, given lifelong screening requirements and prophylactic surgeries that are often a part of risk management guidelines for many pathogenic variant carriers.

Consistent with other studies in Canada (15) and Germany (110), the majority of patients who were employed at the time of screening could not maintain their previous work level during treatment; this led to job loss, a reduction in income, the loss of career choices, and losing financial productivity for families. This underlines the prominence of OOP *indirect* costs for HCS patients living in Canada. This is different from other health systems. For example, the main contributors to OOP costs in non-publicly funded health systems are *direct* medical expenditures (111,196). Findings suggest that even though the health system is publically funded in Canada, social determinants of health are interconnected to experiencing more FT and access to equity healthcare

(152). For example, patients still report high health-related OOP costs, particularly for vulnerable groups such as those living in rural areas, younger patients, and those without supportive employers. Additionally, patients in NL may require extra assistance from support agencies to address objective financial burdens. This is consistent with the findings of Longo et al. (189), who indicated that levels of OOP costs and lost income in cancer vary provincially in Canada. These findings suggest that the benefits of the funded healthcare system are not equally distributed (197,198) and highlight the necessity of different policy strategies within provincial jurisdictions to mitigate these costs (189).

3-6-2 Subjective Financial Distress

Our findings and others (e.g., 132) suggest a potential mediating factor, the evaluation of available financial resources, between objective financial burden and experiencing subjective financial distress. The presence of higher costs, on its own, did not directly lead to subjective financial distress for all participants. Instead, assessing what resources were available to cope with costs emerged as a determinant of financial distress. Access to sufficient financial resources (e.g., partner's job, time in retirement, family support) was an effective coping strategy for adjusting to increased expenditures. Subjective financial distress, significantly influenced by sociodemographic factors such as family status that affect the availability of financial resources to manage costs, is supported by reviews (11,98,108) and aligns with our findings.

However, our findings are inconsistent with the FT framework of Carrera and Zaffar (35), where financial distress is not an outcome of an objective financial burden. Our results also differ from the FT framework of Witte et al. (109) and Gharazi et al. (111), where subjective financial distress results directly from objective financial burden.

While most studies agree on the direct OOP and indirect cost domains of objective financial burden (36,105,109–112,129,136,199), there remains a divergence in how subjective financial distress is categorized across frameworks (109). For example, concerns about the adequacy of health insurance and financial resources to meet future health needs (140), distress due to costs of cancer, increased household expenses (nonmedical costs, daily living expenses, debts), concerns about income (105), psychological responses (4), worry about future costs and rumination about past and current costs (107), a decline of the households' wealth and non-medical spending (106), material conditions, psychosocial response and coping behavior (109,111) have all been identified in the literature as contributing to subjective financial distress. Furthermore, Lueckmann et al. (141) is the only study that has incorporated the concept of mediating elements influencing the impact of objective financial burdens on financial distress, identifying four key mediating factors: evaluation of financial adjustment, the burden of applied financial adjustment, perceived ability to make ends meet and bureaucracy.

The current study suggested three subdomains of financial distress: distress following financial resource management, basic needs insecurity, and future financial insecurity. These findings correspond with the literature that has also documented the distress of financial resource management, worry about the ability to make ends meet and worry about future-focused psychological and financial burdens (16, 24–28). Contrary to Lueckmann et al. (141), our results suggest that the distress of financial resource management, the ability to make ends meet and bureaucracy should be classified under subjective financial distress, and the evaluation of available financial resources serves as the sole potential linking factor. Our research identifies a fourth domain of financial distress, termed future financial insecurity, characterized by concerns about financial vulnerability in future; this is consistent with Jones et al. (107), who reported that even

patients who did not report higher costs and currently had access to adequate financial resources could also feel vulnerable to future financial threats following HCS. These findings caution health providers against assuming that patients who are not currently experiencing FT are immune to future financial worries.

Despite universal healthcare in Canada, FT impacted carriers with HCS across the three study provinces with lower reporting of FT in BC. Participants in BC had different demographic backgrounds, including older age, retirement status, access to stable retirement pensions, and less risk of unemployment or job change. Multiple studies (125,202–207) have associated these factors with lower FT, while employment change, reduced income and early retirement (11,174) are linked to higher FT. These sociodemographic factors suggest a basis for identifying patients at risk for FT.

3-6-3 Implications

Our results indicate that although not all patients with HCS will face FT, a significant proportion will experience adverse financial consequences of hereditary cancer in Canada. Creating an environment that proactively addresses patients' financial difficulties and ensures that appropriate strategies are available for mitigation is essential.

Policy changes at the national level can ease the burden of FT for patients and families. Such interventions could include increasing the distribution of healthcare services in rural areas to reduce travel time and regional disparities in access to medical care. Given that healthcare spending is provincially dictated in Canada, assistance from the federal government or national agencies could help ensure equitable solutions for FT for all patients across Canada. Federal policies could consider creating an income supplement program for patients' families to retain

their current salary or enact policy changes to federal support programs such as EI or medical assistance travel programs. All income support programs should work to reduce eligibility complexities and paperwork. Policies covering IVF and PGT for HCS carriers would substantially benefit these patients and help mitigate this source of FT.

In practice, patients with HCS should be informed about potential healthcare OOP costs, possible income reductions, public and private insurance coverages, and financial management strategies on budgeting and navigating insurance through workshops, educational sessions and access to financial counsellors. Perhaps some of this could be delivered through national agencies (e.g., the Canadian Cancer Society). Hospitals and clinics could consider granting free parking to these patients, given their lifelong need for regular screening and appointments. Charities should consider assistance programs that address specific uncovered expenses such as hormone therapy, prostheses, physiotherapy, or psychotherapy; they could also consider partnerships with airlines allocating special fares and discounts for treatment-travel patient costs. FT represents a significant concern for patients, families and healthcare systems. Multimodal interventions that involve collaboration across all key stakeholders at municipal, regional and national levels will be essential to help address the burden of FT.

3-6-4 Limitations

Participation bias is possible, with those volunteering for the study being more likely to have financial burdens or be more willing to talk about them, potentially overestimating the amount of FT or limiting generalizability. However, given that not all participants were categorized as having high FT, we believe this is unlikely. Additionally, we did not have a diverse sample; the study participants were predominantly white, female, married, and Canadian citizens, with about half

having a university education. This may limit the generalizability of the findings to other demographic groups and restrict our ability to explore fully how the social determinants of health (SDH) interact with or influence the experience of FT. In turn, this limits our ability to provide robust practice and policy recommendations related to the SDH and FT. The interview guide was designed as part of a broader project on the impacts of HCS, focusing on capturing essential concepts related to not only financial but also health system and psychosocial impacts. This focus might have resulted in fewer questions and responses addressing specific financial impact domains. Future research using the FT construct and subjective financial distress as primary analytical lenses would benefit from employing a more detailed interview guide.

Additionally, the primary interviewers varied across the three provinces. While every effort was made to standardize the interview process, they might not have consistently asked probing questions or used the same probes, potentially impacting responses. Finally, qualitative research typically employs small samples, limiting generalizability. This is mitigated somewhat in the current study, given the fairly large sample size and purposive sampling to ensure diversity in responses.

3-7 Conclusion

This research has illuminated the various direct and indirect high costs, three domains of subjective financial distress and a potential mediating link between increased expenditures and financial distress associated with hereditary cancer syndromes. High costs contribute to subjective financial distress, influenced by patients' evaluation of their financial resources. This connection underscores the need for a deeper understanding of patient perceptions in FT studies, highlighting the pivotal role of patients' evaluation of their financial resources. Compared to non-genetic

cancers, fertility intervention for embryos predisposed to HCS is a unique consideration for carriers with HCS. Individuals living in rural areas, those facing travel costs, and working-age individuals experiencing income loss exhibit higher rates of FT. The results suggest that current financial protections for hereditary cancers, even within government-funded healthcare systems, remain inadequate and require improvement. Provincial differences provide a basis for identifying patients vulnerable to FT and highlight the impact of varying policies across jurisdictions in mitigating costs. This study underscores the need for additional research and policy development on FT in HCS. The findings can inform the development and implementation of support programs for patients with HCS and families at risk for FT.

Chapter 4: Discussion and Conclusion

4-1 Overall Thesis Summary

The overall objective of this thesis was to explore the financial toxicity (FT) among individuals with hereditary cancer syndromes (HCS). Approximately half the sample experienced increased costs (50%) and FT (53%) following their diagnosis. FT varied somewhat across provinces, with the greatest increased costs observed in NL and the highest reported FT in both NL and ON.

Direct out-of-pocket (OOP) medical costs reported by participants were payments for over-the-counter drugs, hormone therapy, prostheses, physiotherapy and psychotherapy. Travel expenses to access healthcare services, especially significant for those living in rural areas, were the most considerable direct *non-medical* OOP cost, followed by high costs for medical center parking and healthy food. Fertility interventions for embryos predisposed to HCS were identified as a particular OOP non-medical cost for these patients. The lack of access to MRI machines for participants with elevated BMIs was revealed as a particular OOP medical cost in NL, a challenge not reported by participants at other study sites. Indirect costs, including loss of income, time off work, and family members' income loss, were identified by individuals in all three provinces.

The evaluation of financial resources to manage increased expenditures appeared to be a potential connecting link between objective financial burden and the experience of subjective financial distress. The financial resources identified by patients in this thesis to mitigate FT were many and included relying on a partner's income, access to retirement pensions and free time, savings, having a supportive employer with flexible work hours, access to private insurance or income support programs, receiving financial aid from family and friends or fundraising, and access to a funded health system. For some participants, insecurity in meeting even basic needs was another

form of financial distress reported. Future financial insecurity was another domain of financial distress, and it was mainly identified in individuals not experiencing distress from current costs. This thesis suggests an FT model wherein financial distress is not a direct consequence of objective financial burdens but the result of one's evaluation of financial resources. When evaluations suggested adequate financial resources, participants reported no financial distress; however, those who appraised their financial resources as insufficient reported financial distress.

4-2 Thesis Contributions to Literature

The findings of this thesis fill current gaps in the literature by exploring FT from the perspective of patients with HCS for the first time. Despite the growing body of research on FT in cancer over the past decade (98,208–211), no study has explicitly focused on patients with HCS, and existing studies lack a consistent definition and measurement of FT. This issue is further compounded by the fact that much of the research is based in the U.S. (104), often failing to consider how partial or universal healthcare systems might affect the experience of FT in patients with cancer. Literature on the FT model (35,105–107,109–111,141) mostly varies in how models define financial distress and conceptualize the FT pathway. Recent studies (108,109,111,141) acknowledge subjective financial distress as a primary contributor to FT, emphasizing the need for a deeper understanding of FT pathways across different cancer types and healthcare systems. This thesis addresses this gap by identifying a model of FT that highlights the pathway from an objective financial burden to subjective financial distress through a potential mediating link, supporting the FT framework of Lueckmann et al. (141).

Additionally, this thesis highlights the connection between FT and SDH, emphasizing that FT is particularly prevalent among younger patients who face less secure employment, limited savings,

and lower incomes (148,151). Patients who already have unmet social needs—such as inadequate housing, food insecurity, and lack of reliable transportation—along with those lacking strong social support networks (e.g., supportive family, friends, or employers), are more vulnerable to experiencing FT, beyond the additional burden of an HCS. These individuals are disproportionately affected by gaps in health coverage, further exacerbating existing health inequities. Study findings reveal how these SDH interact with carrying heightened genetic cancer risks, particularly in populations with heightened vulnerability. Thus, future research and policies related to HCS carriers should focus on not only FT but also the SDH to help mitigate existing health inequities and ensure future inequities are not imposed on individuals with HCS.

Also, this thesis confirms the findings that living in a country with a funded healthcare system does not necessarily protect patients from experiencing FT (112,212). While patients in non-publicly funded systems, such as the U.S., pay substantial OOP medical costs (117), our study shows that patients in Canada struggle more with OOP non-medical and indirect costs despite facing lower medical OOP costs. Finally, provincial differences in financial hardship experience provide a basis for identifying more vulnerable patients for FT, particularly those who are living in rural areas and are younger and working age (146,189).

4-3 Thesis Implications for Practice and Policy-making

Findings support developing policies and strategies addressing FT in hereditary cancer populations. Recognizing fertility preservation and pre-implantation genetic testing (PGT) as relevant considerations, particularly for younger patients with HCS, subsidy programs should be developed to cover these costs, helping to select embryos free of pathogenic mutations to prevent hereditary cancer. More broadly, findings suggest that people with cancer should be informed

about the wide range of potential healthcare OOP costs, both direct and indirect, in an effort to provide anticipatory guidance. Workshops and educational sessions could be designed and offered to patients to provide information and advice on managing income reductions, navigating support programs and insurance coverages and providing a supportive environment for talking about FT. Further, there is a need for a comprehensive review of healthcare coverage under the public system to identify and address gaps such as prostheses, psychotherapy, physiotherapy, and hormone therapy.

Legislation could ensure the availability of MRI machines for all patients (including those with elevated BMIs) in Canada. This would reduce patients' need to travel inter-provincially for medical screenings, thereby alleviating FT. Alternatively, policies should be implemented to subsidize (or completely cover where services are not available) travel costs for patients requiring treatment far from home, potentially through partnerships with transportation services and local hotels. Airlines could also offer special fares or discounts to these patients to further ease travel costs.

Hospital and clinic decision-makers should consider offering free parking to patients attending appointments to reduce the indirect costs of treatment. These costs can be significant for patients affected by HCS requiring lifelong screening. Governments could consider creating a targeted income supplement program for families affected by HCS, aiming to retain their current salary levels, extend the duration of support, and simplify eligibility criteria.

Healthcare organizations and patient advocacy groups could work together to develop and share guidelines and programs to educate employers on supporting their employees through flexible work arrangements, remote work options, and protected leave. This support is crucial during the challenging periods of dealing with the disease, but in the case of hereditary cancer, it is also relevant during regular and ongoing screenings. Charities should allocate specific funds to provide

temporary financial relief to self-employed individuals during medical leave.

Additionally, integrated mental health support programs should be developed to focus on coping with the psychological impacts of financial distress and helping patients manage the adverse effects of financial distress, including feelings of dependency and loss of self-reliance. Collaboration and co-development among all relevant stakeholders, including governments, healthcare organizations, charities, societies, and patient advocacy groups, will be required to mitigate FT for patients and families with HCS. This effort will help promote a more uniform healthcare service across various provinces and territories, ensuring all patients are supported.

4-4 Unique Policy Recommendations for the HCS Population

Findings suggest several unique challenges faced by carriers of HCS pathogenic variants that imply unique policy recommendations for this population. A first unique challenge includes fertility-related interventions such as IVF and pre-implantation genetic testing to ensure cancer mutations are not present in developing embryos. Second, unlike a person who develops sporadic cancer, individuals with HCS are more likely to be burdened by FT throughout their entire lives. They face lifelong, high cancer risks and are more likely to develop multiple cancers across numerous organs compared to a single sporadic cancer. Third, and relatedly, individuals with an HCS often develop cancers at young ages. Thus, this population may encounter the financial consequences of their genetic risk at a younger age, when they are more likely to have lower incomes, less savings, and job insecurity. Given these specific challenges, the following specific policy recommendations need to be better planned, tailored and implemented to address FT in the HCS population:

1. Create specific policies and health services that address the fertility costs that are unique to this

population (e.g., preimplantation genetic diagnosis). If costs are not fully covered, at the least some kind of subsidy program should be available to these patients 2. Patients with HCS need access to financial planning resources over a lifetime that are designed to help them manage *long-term* financial challenges associated with ongoing screening, preventive care, and potential cancer treatments. A specific policy could involve offering government-supported or employer-based financial planning programs. For example, policies should be developed to offer tailored EI programs for the HCS population, who may require more flexible work arrangements and periods of medical leave throughout their lives. These programs should account for the fact that HCS patients may face recurring medical needs and have fewer opportunities to build stable, long-term savings. 3. To empower HCS patients with knowledge on how to manage FT, online webinars and educational resources specifically tailored to this group should be developed. These could include sessions on long-term financial management, navigating insurance options, creating a comprehensive information package for newly diagnosed HCS carriers and understanding workplace rights for individuals at higher genetic cancer risk. These recommendations emphasize the importance of addressing the specific needs of the HCS population, which is distinct from patients with sporadic cancer.

4-5 Future Research Studies

Future studies on FT in cancer should focus on creating better tools to measure the complex nature of FT. Research is still needed across various cancer types to determine if elements of FT differ or if common elements emerge regularly. Research should include both qualitative and quantitative methods to fully understand the varied, personal experiences of subjective financial distress that patients with cancer and their families face. Efforts should be directed toward developing a

common understanding of FT that covers financial costs and subjective financial distress. Additionally, exploring the relationships between financial toxicity, risk factors, indirect costs, and psychosocial costs will help create more effective clinical and policy solutions to reduce financial harm.

To overcome the limitations seen in the qualitative approach of this thesis, such as potential bias from volunteer sampling and the influence of participant traits like extroversion, future research should use a more diverse recruitment strategy that includes a broader range of participants and focus more on the relationship between FT, SDH, and the experience of health inequities.

Survey studies allowing for anonymous responses would also include a larger sample of perspectives and help mitigate reluctance to discuss financial challenges.

This study was part of a larger research project that explored many impacts of hereditary cancer syndromes, including the financial and emotional, lifestyle, familial, and social impacts. Using a more detailed and specifically tailored interview guide focused solely on FT will ensure that all important FT areas are covered. Probing, focused questions could also improve the quality and depth of the data collected. These methodological improvements are essential for a better understanding of FT and for developing targeted interventions to reduce the financial toxicity of patients with cancers.

4-6 Thesis Conclusion

This thesis presents the first investigation into the FT experienced by patients with hereditary cancer syndromes. Overall, this thesis fills a gap in the current literature on FT in HCS, revealing patient experiences of FT and what factors help to mitigate it. Results indicate that financial protections for hereditary cancers within universal healthcare systems are insufficient and need

improvement. Integrating considerations of the SDH into HCS-related healthcare delivery is essential for reducing FT and achieving health equity. Provincial differences provide a basis for identifying at-risk patients for FT. These insights can assist providers and decision-makers as they try to create and implement supportive FT programs and policies for patients with hereditary cancers more appropriately.

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Appendices

Appendix 1: Copyright Permission (Table 2-1)

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Table 1 Main characteristics of the most common hereditary cancer syndromes (HCS)

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Appendix 2: Interview Guide

Interview Guide

Instructions for the interviewer: The purpose of this interview is to explore the socioeconomic impacts of individuals living with a confirmed risk for hereditary cancer syndrome. This guide acts as a prompt reminding you of necessary topics to cover, questions to ask and areas to probe. It is not intended to read word-for-word, nor is it intended to occur in the sequence depicted below. Please refer to the qualitative training materials folders for more information.

Introduction script: *Thank you very much for agreeing to participate in our study and allowing us to speak with you. The goal of our study is to explore the impacts on individuals living with a cancer risk diagnosis that are not usually captured by the healthcare system. These impacts can be both positive and negative. Throughout this interview, we will ask you questions about how your hereditary cancer diagnosis affects your life. Your responses to our questions are strictly confidential, and you may refuse to answer any questions you're not comfortable with and to share as little or as much as you want.*

Domain 1: Background

1. Can you tell me about your cancer risk journey?
    - *Probes: Which cancers? How long ago? Family history? Who was involved? When/where genetic testing? Which genes?*
2. When you found out about your cancer risk, what was the course of action by your healthcare provider/ family doctor?
    - *Probes: Care path, access to genetic testing, care programs, managing risk for cancer, recommendations from health care providers, frequency of screening*

Domain 2: Systems-level Impact

1. Can you tell me about your experience receiving medical care related to your cancer risk diagnosis?
    - *Probes: What has worked well? What has made it easier? What challenges are faced? Wait times, geographic location, challenges scheduling appointments, challenges accessing genetic testing, lack of coordinated screening program, COVID-19 pandemic, implications to family members that also tested positive, feelings about increased health screening/surveillance?*
    - *Prophylactic surgery (if applicable): How has prophylactic surgery impacted you? (Probes: sense of loss, family planning, regret, physical changes, additional costs, positive outcomes such as feelings of empowerment or taking control of risk)*
2. What are your thoughts about the quality of care provided by doctors or other healthcare workers involved in managing your cancer risk?
    - *Probes: satisfaction with the current care plan? Received enough information? Family doctor? Oncologist? Changes in relationship/dynamic with physicians/HCWs?*
3. How has managing your medical appointments related to your cancer risk affected you or your family's ability to see other healthcare professionals or manage other health problems?
    - *Probes: dentist, optometrist, chiropractor, difficulties with coordination of care or facilitated/heightened attention to other health issues?*

Domain 3: Economic Impact

1. How has your cancer risk impacted you or your family financially?

- *Probes: Financial benefits? Time off work? Out-of-pocket payments for care? Insurance? Costs to travel for medical care? Family spending? Non-essential spending (vacations, social activities)? Cost to other family members?*

2. How has your cancer risk impacted you or your family's ability to work or decisions about work?
    - *Probes: Positive impacts to work? Better productivity? Decreased productivity? Career trajectory, part-time vs full-time, retirement decisions, support from the employer, location for work (rural vs urban), secondary insurance, education decisions?*

Domain 4: Emotional Impact

1. How has your cancer risk impacted you emotionally throughout your journey?

    Probes: Regaining control, anxiety, mental health, depression, Coping strategies (support groups, key family and friends)/ empowerment, *worry, sense of relief, sense of loss*

    - Follow-up question: How have you managed your emotions? How did you access help?

      Probes: experience accessing help, barriers to mental health services

2. Since learning of your cancer risk, can you describe your emotions towards medical appointments? *Probes: better preparedness/resilience, increased anxiety, resentment, sense of appreciation*

Domain 5: Lifestyle Impact

1. How has your cancer risk impacted your life decisions?

- *Probes: marital, behavioral and lifestyle changes, physical activity; changes in diet, family planning, actions to take control of cancer, naturopathy (non-Western medicine), travel*

Domain 6: Relationships

1. Can you describe how living with a cancer risk affected your relationship with your family and your community?
    - *Probes: feeling closer to each other, children/grandchildren, sense of guilt (e.g. causing relatives in different provinces/countries needing to undergo screening), worry for others health*
    - Follow up questions: How about friends? Coworkers? Associates in your community?

Domain 7: Unfair treatment/ stigmatization

1. What are your thoughts about sharing your cancer risk diagnosis with others?
    - Probes: *breach of privacy, stigma/worry of stigmatization, insurance, advocacy, employer/work supervisor, friends, relatives*

Final Thoughts:

Probe about COVID if it has not already been discussed

Probe about economics if not already discussed

If you had a magic wand that could magically fix anything… within the healthcare system… what are the issues within this system that you would change?

After interview:

Collect demographic information not already answered

Discuss gift card and ways of getting that, “Do we have your permission to share the email with MUN finance team?”

Appendix 3: Initial Codebook for Entire Study

Domain	Code	Definition
Health-care system Impacts	Provider knowledge	Amount of knowledge that a healthcare provider has in terms of genetic testing and hereditary cancer syndromes/ Effective medical care/effective knowledge about all aspects of HCS care (including management/follow-up) - includes patients' interpretation of providers' knowledge
	--->subcode - provider communication	
	Access to care/ access to genetic services	Distance to clinics for screening or consultation, lack of providers/ Barriers or easy access to genetic testing, information, counsellors, specialists/ Lack of providers/ screening program eligibility
	Navigation of care/ Uncertainty with care/ Lack of follow-up care	The people (providers or not) who help the patients coordinate various appointments and see the appropriate specialists for their HCS/ Lack of follow-up care/ guidance after prophylactic surgery
		Confusion, lack of guidance, or conflicting information on HCS care
		No follow-up care was provided after diagnosis or prophylactic surgery, or limited actionable information was given
	Self-advocacy	Patient-initiated referrals, appointments, or follow-up care - frustration with having to be my own advocate - acceptance/eagerness to be own advocate
	Alternative medicine/therapy	"Non-western" medicine, e.g. naturopathy - seeking out alternative medicine instead of or in addition to "traditional" medical care
	Impact of comorbidities	
	Cancer vs cancer risk	

	Health literacy	Patient knowledge of genetic testing, their HCS, or follow-up care plans - SES/education/career may impact this - family history of cancer/disease may also impact this
	Attitude about care	Satisfaction with care
	Trust in care	Acceptance with care
	Prophylactic surgery	
Financial Impacts	Financial distress	* This can be a higher level theme *Level of distress related to finances (no distress, some distress, a lot of distress/financial burden)
	Spending behaviour	e.g. taking money from home savings and using it elsewhere for treatment, IVF, change in priorities
	Spending autonomy	Lack of choice for financial spending, Saving transfer (Lack of autonomy for savings, financial planning), money spent on childcare while at surgery/appointments, sacrificing, well-being autonomy
	Undermine financial burden	Minimizing the effect of costs associated with HCS, not wanting to inconvenience family, financial resiliency, guilt feeling
	Career choice	e.g., change in career field, role, schedule
	--> career flexibility	
	Geographic location	e.g., costs with access to patient-centred care, parking, travel costs associated with coming to town (gas, babysitter, etc.), fewer/different job opportunities, and more financial burden?
	Retirement decision	Influences or changes in retirement plans
	Family planning cost/child birth	Example: IVF, egg freezing, additional screening?
	Insurance coverage	Limited insurance
	Bills	Mortgage, insurance
	Cost for care	Out-of-pocket cost for care, e.g. paying for genetic testing
	--> screening costs	
	--> On-going costs	Out-of-pocket, e.g. physiotherapy, Alternative medicine/therapy (naturopathy), Counselling costs
	--> cancer cost	The financial burden associated with cancer treatment

		Lack of autonomy for savings, financial planning
	FT impacts on partner and family	e.g. partner takes a day off to take pt to appts, family role
	Wealth	Wealth accumulation; saving and bankruptcy salaries or replacement
	Unidentified financial prospects (future)	Financial impacts of cancer on their or their family's life in the future
	FT support	
	---> seeking financial support	Financial balance: changing the plans, cutting spending, borrowing money; official and unofficial supports: friends, grant free accommodation, free parking or transportation, workplace support, insurance information, providers (genetic specialists)
	---> unsatisfied/ unaddressed needs	Information: lack of information on financial resources, cancers' potential effects on their financial life. Pragmatic: lack of a social worker to navigate financial issues, a virtual navigator, or a family member to borrow money
	---> unexpected supports	Health advocates, employer who gives additional benefits such as additional sick days, fundraising
	---> unpreparedness and unexpected financial issues	
	The stigma surrounding talking about money	
Psychosocial Impacts-Lifestyle	Family planning	Decisions made in regards to having children, adopting children, and/or medical intervention to have children (e.g. IVF)
	Health changes	Changes to diet, exercise, and habits (e.g. smoking, drinking, etc)
	Stigmatization	Treated differently by others, e.g. friends, family, coworkers, employer, insurance. This can include being judged or the feeling of being judged differently
	Sense of burden	One's presence, needs, or requests may be imposed on others, causing them inconvenience, stress, or discomfort
	Family connections	e.g. reconnecting with family, new connections, estranged

	Caretaking	Needing a caretaker or cannot take on a caretaker role
Psychosocial Impacts-Emotional	Cancer worry	Experience of anxiety or fear related to the possibility of developing cancer
	subcode to Cancer Worry-> family cancer worry	Experience of anxiety or fear related to the possibility of a family member developing cancer
	subcode to Cancer Worry -> worry for anticipated costs	Experience of distress/anxiety for upcoming costs related to HCS, e.g. surgery, testing, etc
	subcode to Cancer Worry -> Bodily Distress	Physical symptoms (unrelated to cancer) are distressing but do not have a clear medical association with cancer risk. E.g. having a cold and thinking it could be cancer
	subcode -> emotional impact of cancer	
	Personal outlook	Individuals' perspectives or attitudes towards life, their beliefs about the world, and their expectations for the future have been shaped by their hereditary cancer and career influences—changes to personal outlook related to HCS experience
	Carrier guilt	The guilt associated with having a disease-causing variant and possibly passing it onto future generations
	Social support	Emotional support an individual receives from their social network or community
	Coping mechanisms	Behaviors, thoughts, and emotions that individuals use to manage and adapt to stressors, challenges, or difficult situations, e.g., seeking social support, engaging in relaxation or mindfulness techniques, activities or hobbies, using avoidance or denial, seeking counselling, drugs and/or alcohol usage
	subcode to Coping mechanisms -> placebo effect	Action, treatment, or intervention that an individual undergoes thinking it would mitigate their cancer risk, but it does not necessarily do so

	Alienation	Sense of detachment or disconnection from others because of cancer risk that not many others have. Alienation can also lead to feelings of isolation and loneliness
	Empowerment	Acts enabling individuals to gain control over their cancer risk
	Body image	How an individual views their body in response to cancer, cancer risk, or prophylactic surgery This can include body betrayal
	Uncertainty	Lack of certainty in regards to how their cancer risk will impact their life in the future

Appendix 4: FT Codebook

Main Theme	Code	Definition
Objective financial burden	Direct OOP medical costs	Healthcare (over-the-counter)
		Healthcare (hormone therapy)
		Healthcare (physiotherapy)
		Healthcare (psychotherapy)
		Healthcare (prosthetics)
		Accessing MRI for elevated BMI
	Direct OOP non-medical costs	Travelling (transportation, accommodation, airline tickets, gas)
		Parking
		Diet
		Fertility interventions for embryos predisposed to HCS
	Indirect costs	Loss of income
		Career Choice
		Taking time off work
		Families' or friends' productivity loss
		Self-employed
Evaluation of financial resources	Financial resources	Partner's job
		Retirement
		Savings
		Supportive employer
		Private insurance
		Income support programs
		Families' and friends' financial support
		Fundraising
		Funded health system
Subjective financial distress	Distress of financial resource management	Cut-backs
		Loss of self-reliance
		Bureaucracy
	Basic needs insecurity	
	Future financial insecurity	

Appendix 5: Ethics Approval

Ethics Approval - NL site

Research Ethics Office
Suite 200, Eastern Trust
Building 95
Bonaventure Avenue
St.Joh's, NL A1B 2X5

March 08, 2022

Craig Dobbin Centre for Genetics Dear Dr Etchegary:

Researcher Portal File # 20222386 Reference # 2022.014

RE: Variations in care for hereditary cancer syndrome families: direct and indirect socio-economic impacts

Your application was reviewed by a subcommittee under the direction of the HREB and your response was reviewed by the Chair and the following decision was rendered:

X	Approval
	Approval subject to changes
	Rejection

Ethics approval is granted for one year effective March 8, 2022. This ethics approval will be reported to the board at the next scheduled HREB meeting.

This is to confirm that the HREB reviewed and approved or acknowledged the following documents (as indicated):

- Application, approved
- Research proposal approved
- Appendix 9 Consent form qualitative study, approved

- Appendix 8 Demographics, approved
- Appendix 5 Survey information sheet, approved
- Appendix 3 Qualitative study information sheet, approved
- Appendix 2 Contact log, approved
- Appendix 10 master linking log, approved
- Appendix 7 Survey advert, approved
- Appendix 6 Study Measures, approved
- Appendix 4 Study advert qualitative, approved
- Appendix 1 Recruitment scripts, approved
- Budget, approved Please note the following:
- This ethics approval will lapse on March 8, 2023 It is your responsibility to ensure that the Ethics Renewal form is submitted prior to the renewal date.
- This is your ethics approval only. Organizational approval may also be required. It is your responsibility to seek the necessary organizational approvals.
- Modifications of the study are not permitted without prior approval from the HREB. Request for modification to the study must be outlined on the relevant Event Form available on the Researcher Portal website.
- Though this research has received HREB approval, you are responsible for the ethical conduct of this research.
- If you have any questions please contact info@hrea.ca or 709 777 6974.

The HREB operates according to the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2), ICH Guidance E6: Good Clinical Practice Guidelines (GCP), the Health Research Ethics Authority Act (HREA Act) and applicable laws and regulations.

We wish you every success with your study.

Sincerely,

Dr Debra Bergstrom, Chair Genetics Committee Health Research Ethics Board

You Have Received Ethics Approval, Now What?: HREB Reporting Requirements

Once a study has received ethics approval from the Health Research Ethics Board (HREB), there are still associated reporting requirements. In the conduct of approved research researchers are required to report to the HREB, in a timely manner, proposed changes from approved research that affect participants at any stage of the process. This includes, but is not limited to, changes to the consent form, changes to the tasks or interventions involved in the research, or changes to measures to protect privacy and confidentiality.

Any substantive change to the research should not be implemented prior to documented approval by the HREB, except when necessary to eliminate an immediate risk(s) to the participants. Below are examples of post approval documentation that must be submitted to the HREB:

Amendments

Any proposed change in the conduct of a study must be submitted to the HREB, and approved, before the change may be implemented. Such changes might include modification of recruitment procedures, inclusion or exclusion criteria, revised sample size, addition or deletion of study sites, changes to an intervention, consent forms, questionnaires or scripts, etc. If there are changes in project team members or changes to funding source(s)/sponsor(s), there are specific forms to complete to report this to the HREB.

Adverse Event

Serious and unanticipated adverse events that occur within Newfoundland and Labrador are required to be reported to the HREB. Such events may occur in both clinical trials and in other types of research, e.g. collapse during a rehabilitation program, emotional breakdown requiring follow up care during an interview, or breach of privacy during correspondence. Serious adverse events that are fatal or life-threatening are required to be reported to the HREB as soon as the research team is aware of the event.

Protocol Deviations

Deviations from an approved study protocol must be reported to the HREB. Changes that eliminate immediate hazards to participants do not require prior approval, but must be reported soon as reasonably possible.

Safety Reports

Safety reports providing information on all serious adverse events (SAEs) occurring in a clinical trial must be provided by the sponsor to the HREB, normally on a three or six monthly basis (i.e. in accordance with the specified reporting timelines that were outlined in the approved ethics application).

Investigator Brochure (IB) and Product Monograph (PM)

Throughout the course of a clinical trial, changes may be implemented to study documents. All revisions to approved study documents must be submitted to the HREB to ensure the record is up to date. If the revisions include new risk or safety information there may be a requirement to notify research participants.

Ethics Renewal/Study Closure

Ethics approval lasts for one year. Ethics renewal is required annually, on the anniversary of the

date of the HREB notification of approval. Once data collection is no longer ongoing, a study closure form is required to be submitted to the HREB for the study to remain active or to be closed in good standing.

Ethics Approval- ON sit

Date: 27 January 2022

To: Dr. Yvonne Bombard, St. Michael's Hospital CTO Project ID: 3855

Study Title: Variations in care for hereditary cancer syndrome families: direct and indirect socio-economic impacts

Sponsor Study ID: NA

Study Sponsor: St. Michael's Hospital

Application Type: Clinical Trial Provincial Initial/CHEER Initial Application Review Type: Delegated

Date Approval Issued: 27/Jan/2022 11:48 Study Approval Expiry Date: 27/Jan/2023

Dear Provincial Applicant,

Thank you for submitting the above-referenced study on behalf of all Ontario centres through the Clinical Trials Ontario Streamlined Research Ethics Review System. The Unity Health Toronto Research Ethics Board has reviewed the study and granted initial provincial approval as of the date noted above.

Provincial documents approved:

Document Name	Document Date	Document Version
HCS Protocol	06/Jan/2022	
Appendix 1 Scripts	06/Jan/2022	
Appendix 3 Info Letter - Aim 1 Qual	19/Jan/2022	
Appendix 4 Info Letter - Aim 1 Survey	06/Jan/2022	
Appendix 5 Measures	19/Jan/2022	
Appendix 6 Info Letter - Aim 2 Qual	06/Jan/2022	
Appendix 8 Consent - Aim 1 Qualitative	06/Jan/2022	
Appendix 9 E-Consent - Aim 1 Survey	19/Jan/2022	
Appendix 10 Consent - Aim 1 Survey	19/Jan/2022	
Appendix 12 Consent - Aim 2 Qualitative	06/Jan/2022	
Appendix 14 Demographics	06/Jan/2022	

Provincial documents acknowledged:

Document Name	Document Date	Document Version
Appendix 2 Contact Form	09/Nov/2021	
HCS Grant Budget Spring 2021 Appendix 13 Master Linking Log	09/Nov/2021	

Note: Provincial REB approval does not confer ethics approval for participating centres. Each participating centre, including that of the Provincial Applicant, must submit the "Centre Initial Application" and receive approval from this REB prior to the conduct of the study at that centre. All other required institutional approvals must also be obtained prior to the conduct of the study.

No deviations from, or changes to, the protocol should be initiated without prior written approval from Unity Health Toronto Research Ethics Board, except when necessary to eliminate immediate hazard(s)

to study participants or when the change(s) involves only administrative or logistical aspects of the trial (such as a change in telephone number).

Unity Health Toronto Research Ethics Board operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. Unity Health Toronto Research Ethics Board is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP).

Please do not hesitate to contact us if you have any questions.

Sincerely

David Mazer, MD Chair, Research Ethics Board	Michael Szego, PhD Vice Chair, Research Ethics Board	Zoe von Aesch, MD Vice Chair, Research Ethics Board	Melanie Tsang, MD Vice Chair, Research Ethics Board