EXAMINATION OF A NEW MODEL OF GENETIC COUNSELLING AND ASSESSING A DEMOGRAPHICALLY DIVERSE PATIENT POPULATION ATTENDING HEREDITARY CANCER GENETIC COUNSELLING SERVICES

by

MATTHEW RICHARDSON

B.Sc., Queen's University, 2016

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(Interdisciplinary Oncology)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

August 2020

The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, a thesis entitled:

Examination of a New Model of Genetic Counselling and Assessing a Demographically Diverse Patient Population Attending Hereditary Cancer Genetic Counselling Services

submitted by Matthew Richardson in partial fulfillment of the requirements for

the degree of Master of Science

in Interdisciplinary Oncology

Examining Committee:

Dr. Kasmintan A. Schrader, Department of Medical Genetics
Co-supervisor

Dr. Sophie Sun, Department of Medicine
Co-supervisor

Dr. Aly Karsan, Department of Pathology and Laboratory Medicine
Supervisory Committee Member

Dr. Daniel Renouf, Department of Medicine
Additional Examiner

Abstract

The popularity of genetic testing and counselling for hereditary cancer syndromes has increased rapidly in the past decade due to a decrease in genetic sequencing costs, increase in public interest, and increase in medically actionable results. As the demand for genetic testing services has increased, the wait times for patients to receive genetic testing and counselling has also increased. In order to increase patient access to genetic testing and counselling, genetics services must examine new genetic counselling models and ensure that historically under-served patient populations are receiving equitable health outcomes.

In this thesis I have examined the impact of a new model of genetic counselling termed oncology clinic-based genetic counselling, examined patient demographics at the Hereditary Cancer Program (HCP) in British Columbia Canada, and assessed patient reported outcome measures (PROMs) from patients receiving genetic testing and counselling. I found that oncology clinic-based genetic testing and counselling significantly reduced patient wait times from referral to return of genetic testing results compared to traditional genetic counselling (403 vs 198 days; $p < 0.001$). Secondly, oncology clinic-based genetic testing and counselling was acceptable to both patients and healthcare providers. Furthermore, I found that all ethnic minority patient populations are under-represented at the HCP, and patients of Asian ethnicity are significantly more likely than patients of European ethnicity to receive a pathogenic variant ($p < 0.001$) or variant of uncertain significance ($p < 0.001$) genetic test result. Lastly, from analyzing PROMs from patients attending the HCP I found that patients of self-expressed Asian ethnicity experience increased distress ($p = 0.003$) and uncertainty ($p < 0.001$) compared to patients of European ethnicity.

These results show that new models for genetic testing and counselling increase patient access by decreasing wait times and are acceptable to patients. As well, ethnic minority patients are underrepresented at the HCP, receive more complicated genetic diagnoses, and experience more negative feelings from genetic testing. In order to increase access to genetic testing and counselling services, increase ethnic minority population participation, and decrease health outcome inequities, new genetic counselling models and the modification of current genetic counselling models are necessary.

Lay Summary

The popularity of genetic testing and counselling for hereditary cancer has dramatically increased over the last decade. Increased patient demand necessitates the evaluation of genetics services quality of care and the consideration of new models of genetic counselling. In this thesis I have examined a new genetic counselling model that increases the utilization of a patient's oncologist and found that the new model decreased patient wait times. I have also found that ethnic minority patients are less likely to receive genetic testing, have more complicated diagnoses from genetic testing, and experience elevated distress and uncertainty during genetic testing. My findings conclude that new genetic counselling models must be considered to meet increased patient demand and that increased representation of ethnic minority patient populations in genetic testing and counselling are necessary to reduce health inequities.

Preface

This thesis contains work in which I was primarily responsible for the design and execution. However, this work would not have been possible without the guidance and research design assistance from my supervisors Dr. Kasmintan Schrader and Dr. Sophie Sun and my committee member Dr. Aly Karsan. Dr. Schrader and Dr. Sun were primarily responsible for the conceptualization and implementation of the oncology clinic-based genetic testing and counselling model (chapter 2). As well, the members of the Hereditary Cancer Program provided invaluable support throughout the course of this thesis. In particular, Hae Jung Min worked with me to develop the research questions for the study on patient responses to the MICRA survey (chapter 4) and was primarily responsible for data collection for the oncology clinic-based genetic testing and counselling model (chapter 2).

Work in this thesis received ethics approval by the UBC Research Ethics Board. Certificate numbers were: H16-02201, H15-02174, and H18-03689.

A version of chapter 2 has been published.

- Richardson M, Min HJ, Hong Q, Compton K, Mung SW, Lohn Z, Nuk J, McCullum M, Portigal-Todd C, Karsan, A, Regier D, Brotto LA, Sun S, Schrader KA. Oncology Clinic-Based Hereditary Cancer Genetic Testing in a Population-Based Health Care System. *Cancers* 2020, 12, 338.

The conceptualization and implementation of the study was conducted primarily by Dr. Kasmintan Schrader, Dr. Sophie Sun, Jennifer Nuk, Hae Jung Min, and Dr. Lori Brotto. Data collection was conducted primarily by Hae Jung Min. I assisted in study conceptualization and data collection. I performed the data analysis, interpretation, and majority of the manuscript

preparation. Quan Hong assisted with data analysis. Dr. Kasmintan Schrader, Dr. Sophie Sun and Hae Jung Min assisted with manuscript preparation. The section on “Clinical Models” was originally drafted by Hae Jung Min.

A version of Chapter 3 has been prepared for submission to publication.

- Richardson M, Min HJ, Mung SW, Swanson L, Young S, Kumar A, Dawson LM, Bedard A, Nuk J, Karsan A, Sun S, Schrader KA. Hereditary Cancer Multigene Panel Testing in a Demographically Diverse Canadian Population (Manuscript in preparation).

I co-led the study conceptualization with Dr. Kasmintan Schrader, Dr. Sophie Sun, and Dr. Aly Karsan. I performed the data collection, analysis, interpretation, and majority of the manuscript preparation. Lucas Swanson, Sean Young, and Dr. Aly Karsan provided the genetic testing data and provided interpretation of the genetic testing data. Angela Bedard, Jennifer Nuk, Dr. Aly Karsan, Dr. Sophie Sun, and Dr. Kasmintan Schrader assisted in manuscript preparation.

A version of chapter 4 has been prepared for submission to publication.

- Richardson M, Min HJ, Canizares G, Mung SW, Lohn Z, Bedard A, Nuk J, Sun S, Schrader KA. Evaluating Patient Psychological Responses to Genetic Testing and Counselling in a Publicly Funded Healthcare System (Manuscript in preparation).

I co-led the conceptualization of the study with Hae Jung Min. I co-led the data collection with Hae Jung Min. I performed the study implementation, data analysis, interpretation, and majority of the manuscript preparation. Hae Jung Min, Angela Bedard, Zoe Lohn, Dr. Sophie Sun, and Dr. Kasmintan Schrader assisted in manuscript preparation.

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List of Abbreviations

ACMG – American College of Medical Genetics and Genomics

BC – British Columbia

BCCA – BC Cancer

CCG – Centre for Clinical Genomics

CGL – Cancer Genetics and Genomics Laboratory

DCS – Decisional Conflict Scale

DNA – Deoxyribonucleic Acid

ENIGMA – Evidence-based Network for the Interpretation of Germline Mutant Alleles

FAP – Familial Adenomatous Polyposis

GCOS-24 – Genetic Counselling Outcome Scale

GNDA – Genetic Non-Discrimination Act

GOS – Genomics Outcome Scale

GWAS – Genome Wide Association Studies

HBOC – Hereditary Breast and Ovarian Cancer

HCP – Hereditary Cancer Program

HDGC – Hereditary Diffuse Gastric Cancer

HGSA – Human Genetics Society of Australasia

HGVS – Human Genome Variation Society

IHC - Immunohistochemistry

MAP – *MUTYH*-Associated Polyposis

MICRA – Multidimensional Impact of Cancer Risk Assessment

MLPA – Multiplex Ligation-dependent Probe Amplification

MSI – Microsatellite Instability

NGS – Next Generation Sequencing

NSGC – National Society of Genetic Counselors

PCR – Polymerase chain reaction

PROM – Patient Reported Outcome Measures

PV – Pathogenic Variant

UK – United Kingdom

UNINF – Uninformative genetic test result

USA – United States of America

VUS – Variant of Uncertain Significance

Acknowledgements

I would first like to thank Dr. Kasmintan Schrader and Dr. Sophie Sun for their guidance, encouragement, and constant support. Their brilliant insights, dedication to their work, and inquisitive attitudes have pushed me to be a better student and helped me grow as a scientist. Without their support this thesis would not have been possible. As well, I greatly appreciate the guidance and valuable feedback provided by my committee member Dr. Karsan in developing this thesis.

I would also like to recognize all of the people at the Hereditary Cancer Program for the support they have given me through the course of this thesis. In particular, I would like to thank Hae Jung for her advice and help in the development of this thesis.

I appreciate the funding support from The Canadian Institute of Health Research, The Michael Smith Genome Science Centre, and AstraZeneca that made the work in this thesis possible.

Finally, I would like to recognize my friends, my mom and dad, my sisters, and Crystal for all of the emotional and moral support they have provided me during the course of this thesis.

Dedication

To my family.

Chapter 1: Introduction

1.1 Hereditary Cancer

1.1.1 Cancer in Canada

Approximately 50% of Canadians will be diagnosed with a cancer at some point in their lifetime, and 25% of Canadians will die from cancer [1] . Breast cancer is the most common cancer in Canadian women, making up 25.5% of diagnoses [1] . The second and third most common cancer diagnoses for Canadian women are lung and colorectal cancer making up 13.8% and 11.5% of total cancer cases respectively. In Canadian men, prostate cancer is the most common diagnosis making up 20.7% of all cancer diagnoses [1]. Similar to Canadian women, colorectal and lung cancer make up the second and third most common cancer diagnosis for Canadian men at 14.5% and 14.0% respectively [1]. Both prostate and breast cancer have high 5-year survival rates (90% and 87% respectively), however they are heavily influenced by the stage at which the cancer is diagnosed [1].

1.1.2 Cancer Diagnosis Stage

Early detection of a cancer is one of the best predictors for patient survival. Patient's diagnosed with localized (TNM Stage 1) breast cancer have a 5-year survival of 98.8% [2]. In comparison, patients diagnosed with a late stage distant (TNM Stage IV) breast cancer have a 5-year survival of 27.4% [2]. Similarly, patients diagnosed with localized ovarian cancer have a 5-year survival of 92.4% versus 29.2% for patients diagnosed with later stage distant ovarian cancer [3]. This trend stays the same for 5-year survival in patients diagnosed with either prostate cancer (Localized: 100% vs Distant (30.5%) or colorectal cancer (Localized: 89.9% vs Distant: 14.2%) [3].

Cancer diagnosis stage also often has an impact on the treatment a patient will receive. For both breast and colorectal cancers, stage I-III are primarily treated with surgery along with chemotherapy to reduce tumor size [4, 5]. In comparison, cancers that are diagnosed in stage IV are considered metastatic and are more difficult to treat. Surgery is often not an option and treatment often consists of chemotherapy, targeted therapies, and hormone therapies [4, 5]. The metastatic nature of stage IV cancers makes surgery difficult and therefore greatly increases the chance of a patient experiencing a recurrence of their cancer even if the initial treatment is successful [6]. Implementing surveillance methods to detect cancers at an early stage allow for more successful treatment of the cancers and a lower risk of recurrence [7].

For example, methods of surveillance such as using mammograms for early detection of breast cancer, has been shown to reduce breast cancer mortality by 30% and reduce the diagnoses of late-stage breast cancers by 25% [8, 9]. In British Columbia (BC), women aged 40+ can receive a mammogram every 2 years to surveil for breast cancer [10]. Furthermore, women are eligible to receive a mammogram every year after 40 if they are identified with a hereditary cancer syndrome from genetic testing, or if they display a strong family history for breast cancer [10]. Prompt identification of families with a hereditary cancer syndrome ensures that all members of a family can increase their cancer surveillance and lower their cancer specific mortality risk.

1.1.3 Hereditary Cancer Syndromes

The majority of cancers (70 – 80%) are from sporadic tumor formation, primarily due to a lifetime accumulation of DNA replication errors. These sporadic cancers do not typically have an identifiable genetic component and are heavily influenced by an individual's environmental exposure. Patients that end up developing a sporadic cancer will hopefully be diagnosed in an early stage from following standard cancer surveillance practices based on their age and

environmental exposures. The remaining 20 – 30% of cancers include a larger genetic component. Familial cancer makes up 10 – 25% of cancers and displays some family clustering of cancer that is most likely due to a combination of multiple low penetrant germline variants along with shared environmental exposures [11]. The final 5 – 10% of cancers have a major genetic component and are classified as hereditary cancers. Hereditary cancers are typically caused by a single moderate to high penetrance germline gene variant that displays an autosomal dominant inheritance pattern [11]. These cancers display heavy family clustering, often present at an earlier age, and are more likely to result in multiple malignancies [11]. It is important to identify patients at risk of developing a hereditary cancer in order to put in place increased cancer surveillance methods to increase patient survival.

Identifying hereditary cancer syndromes largely began with research into Hereditary Retinoblastoma. Retinoblastoma is a rare cancer with only 200 cases a year in the United States of America (USA) and less than half of the cases are determined to be a hereditary cancer [12]. In 1971 Dr. Knudson proposed his two-hit hypothesis developed from his research into differences between hereditary and sporadic retinoblastoma [13]. Knudson's two-hit hypothesis stipulated that in most cancers two mutations or "hits" were required for the development of cancer. In hereditary cancers, the first mutation is already inherited and only one mutation needs to be accumulated. This research explained the earlier onset of hereditary cancer cases and led to the discovery of both cancer-causing genes (oncogenes) and tumor suppressor genes [14].

Hereditary Retinoblastoma played a large part in the understanding of hereditary cancers and paved the way for the discovery of more common hereditary cancer syndromes. The two most common hereditary cancer syndromes are Hereditary Breast and Ovarian Cancer (HBOC) and Lynch Syndrome [15]. Other prevalent, but less common syndromes, include Li-Fraumeni

Syndrome, *MUTYH*-associated polyposis (MAP), Familial adenomatous polyposis (FAP), Cowden Syndrome and Hereditary Diffuse Gastric Cancer (HDGC).

With the discovery of *BRCA1* in 1994 and *BRCA2* in 1995, an identifiable genetic cause for familial patterns of breast cancer was established [16, 17]. HBOC accounts for 5 – 10% of all breast cancer diagnoses, and 80% of HBOC diagnoses are from germline *BRCA1/2* pathogenic variants (PV) [18]. Patients diagnosed with a *BRCA1* or *BRCA2* PV have a 40-80% chance of developing a breast or ovarian cancer over the course of their lifetime. This represents a 5 to-10-fold increase in risk compared to non-carriers of *BRCA1* or *BRCA2* PV [19].Other genes with slightly smaller associated cancer risks such as *CHEK2*, *ATM*, *PALB2*, and *RAD51C* have also been recently associated with HBOC [20-23]. It is also likely that are many other low penetrant genes that contribute to HBOC incidence [24].

Lynch Syndrome was first described in 1895 by Dr. Warthin and further defined as we now understand it by Dr. Lynch in 1971 [25, 26]. Lynch Syndrome is typically phenotypically identified as three or more cases of colorectal cancer in close relatives, spanning two generations, and one relative diagnosed under 50 [27]. To diagnose Lynch Syndrome, a patient's tumor is first assessed for microsatellite instability (MSI) using immunohistochemistry (IHC). MSI is found in 10 – 40% of sporadic colorectal tumors and patients then receive germline genetic testing to confirm a Lynch Syndrome diagnosis [28]. Out of all patients that test positive for Lynch Syndrome, 42% are diagnosed with a PV in *MLH1*, 33% in *MSH2*, 18% in *MSH6*, and 7.5% in *PMS2* [29]. Lynch Syndrome is the most common form of hereditary colorectal cancer and is responsible for 2.8% of all colorectal cancer tumors [30].

1.2 Genetic Testing for Hereditary Cancer

Widespread sequencing of genetic material became more accessible to researchers with the introduction of Sanger sequencing in 1977 [31]. The discovery and cloning of various hereditary cancer genes such as *BRCA1* in 1994, and *BRCA2* in 1995 made available identifiable genetic markers for researchers and clinicians to identify in hereditary cancer patients [16, 17]. In 1995, genetic testing for hereditary cancer began to become widely available in clinical settings rather than solely at research institutions [32]. With the recognition of hereditary cancer syndromes having identifiable genetic alterations it became incredibly valuable to be able to identify which patients in a suspected hereditary cancer family may have inherited a PV. By successfully identifying at-risk family members, proactive measures can be implemented to lower a patient's cancer-specific mortality.

1.2.1 Multigene Panel Testing

As the technology for genetic testing progressed and next generation sequencing (NGS) technologies were developed and refined it became practical to sequence multiple genes simultaneously. NGS improved upon Sanger sequencing by making it feasible to perform parallel sequencing of multiple genes in a shorter time frame at a reasonable cost [33, 34]. Once NGS was shown to meet the same specificity and sensitivity requirements for HBOC diagnosis as Sanger sequencing, it was only a matter of time before it became the clinical standard for genetic testing [34-36]. In 2005 NGS became commercially available and in 2012 multigene panels using NGS began to become widely available for clinical use [37, 38]. New multigene panels have allowed for a more comprehensive risk assessment of patients as well as increasing the number of patients that may qualify for genetic testing [39].

Some hereditary cancer syndromes exhibit overlapping phenotypes and without multigene panel testing a PV may be missed [40]. Studies have shown that using a single-gene testing approach in an iterative fashion can miss between 47%-61% of patient mutations [41]. Similarly, research has shown that non-*BRCA1/2* PV can have PV detection rates between 3.9%-9.2% in patients with a personal history of breast cancer [41-44]. Without utilizing multigene panels nearly half of patients and their families with HBOC indications may not fully understand their true cancer risk factor.

1.3 Genetic Testing Psychological Burden and Genetic Counselling

1.3.1 Psychological Burden of Hereditary Cancer Genetic Testing

It is increasingly established in literature that patients who receive a diagnosis of a PV for HBOC or Lynch Syndrome do not experience long-term clinically relevant increases in psychological distress or depression [45-49]. Many studies find that distress and anxiety in patients diagnosed with a PV may be elevated immediately after receiving results but steadily decreases over time [49-51]. However, every patient that receives genetic testing will have a different experience and come into the process with different expectations and assumptions. Often the best predictor of post-genetic testing distress are a patient's baseline distress levels before receiving testing [50]. Although the majority of patients who receive genetic testing and a PV diagnosis do not experience clinical depression or anxiety, there are still measurable negative psychological impacts of a PV diagnosis.

Hereditary cancer syndromes disproportionately impact entire families due to their genetic cause. Families diagnosed with a hereditary cancer syndrome will often see multiple close family members diagnosed with cancer in their lifetime. This can lead to high psychological distress among families such as feelings of guilt for "passing on" the gene

mutation to children and survivor's guilt amongst family members not diagnosed with a genetic mutation [52, 53]. Some families diagnosed with Lynch Syndrome have reported that Lynch Syndrome is so distressing they can no longer have family reunions because the grief of seeing a sick family member is so high [52].

Similarly, families with HBOC often experience feelings of guilt, emotional distress, and anxiety in relation to their genetic test or hereditary cancer syndrome diagnosis. After being diagnosed with a *BRCA1* or *BRCA2* PV, both men and women experienced higher levels of guilt over potentially passing the gene down to their children [54-57]. Patients have also been shown to harbor survivor's guilt after discovering that they are not a carrier for a PV when one of their siblings is identified as a carrier [58, 59]. The feelings of survivor's guilt can range from men feeling that their family would be better off if they had inherited a PV rather than their sister, to men and women feeling guilty that their sibling will have to go through the process and experience of a PV diagnosis alone [56, 59].

Many patients that go through genetic testing for hereditary cancer also exhibit increased personal feelings of grief, emotional distress, and anxiety [52, 55, 56, 60]. Patients diagnosed with a PV often display increased feelings of anxiety and cancer-specific distress when assessed shortly after receiving their genetic testing result [46, 61, 62]. Some studies have also indicated that carriers of a PV show significantly higher levels of general distress than non-carriers [63]. Furthermore, patients diagnosed with a PV have been shown to experience increased uncertainty and indicate they have had a less positive experience with genetic testing [64].

For many patients the diagnosis of a PV is one of the first steps in proactively managing their cancer risk. Many women diagnosed with a *BRCA1* or *BRCA2* pathogenic variant decide to pursue prophylactic surgery and are satisfied with their decision [65]. However, there is also

evidence that many women that have chosen a prophylactic mastectomy have been shown to experience higher distress than women who have chosen increased surveillance [46]. Moreover, women who have had a prophylactic mastectomy have reported a worse sense of their body image, and a worsening of their sexual lives [46, 65]. Patients that have undergone pre-menopausal prophylactic oophorectomy have reported more severe menopausal complaints and increases in sexual dysfunction [66]. Although clinical depression and anxiety are rare in patients that undergo genetic testing, receive a PV, and pursue risk reducing surgeries, there are still numerous negative psychological outcomes that can result from the patient's experience. Negative psychological outcomes that are a product of genetic testing highlight the importance and necessity of genetic counsellors in managing patient outcomes.

1.3.2 Genetic Counselling

After the eugenics practices during and after World War II many geneticists publicly disavowed eugenics and sought to distance the field of genetics from eugenics by developing clinical genetics [67, 68]. The profession of genetic counselling emerged from clinical genetics in 1947 with Sheldon Reed coining the term genetic counselling to describe "a kind of genetic social work without eugenic connotations" [69]. Although a cornerstone of genetic counselling and clinical genetics was to distance itself from eugenics, much of the early work in the field and by the practitioners supported similar goals to the original eugenics movement [68, 70]. The measures of success for genetic counselling at this time were mostly a reduction in genetic disease, not if the counselling helped family members understand and cope with their diagnosis of a genetic disease [68].

In the mid-1980s, there was a shift within genetic counselling from medical interventions to a more psychological and counselling-based approach [71]. The first graduate level training

programs in Canada began during this time [72]. The American Board of Genetic Counsellors (now the Accreditation Council for Genetic Counselling) in 1993 began a certification process for genetic counsellors [72]. As the genetic counselling profession shifted towards a less paternalistic medical interventionist approach to a more patient-focused approach, a new definition for the field was required. The National Society of Genetic Counselors (NSGC) in 2006 released a definition for genetic counselling: "genetic counselling is the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease" [73].

1.4 Barriers to Accessing and Utilizing Genetic Testing and Counselling Services

1.4.1 Patient Wait Times

The pressure on clinical genetic services has increased as scientific and public awareness of the influence of genetics on cancer development grew [74]. The expansion in multigene panels, decrease in costs for genetic testing, and demand from the public has led to a documented shortage in the number of medical geneticists with 50% of medical genetics residency positions remaining vacant each year [75, 76, 77]. The increase in demand placed on clinical genetics services compounded with a lack of medical geneticists creates strain on genetic counsellors to help fill the demand for genetic expertise [78].

Problematically, there is also a shortage of genetic counsellors in North America [79, 80]. The lack of genetic counsellors has been identified by the American Society of Human Genetics as a major barrier preventing broader incorporation of genetics into general clinical practice [81]. Furthermore, the lack of genetic counsellors has led to increasing wait times for patients in both the USA and Canada [82-84]. Although there are no guidelines in Canada for the timeframe that a patient should receive genetic counselling, the Human Genetics Society of Australasia (HGSA)

suggests that patients should see a genetic counsellor within 12 weeks of being referred [85]. In stark contrast to the HGSA guidelines, some provinces in Canada experience wait times of up to three years for genetic counselling services. The average wait time to see a genetic counsellor in the province of Ontario is approximately 26 weeks, wait times have increased to three years in the province of Newfoundland and Labrador, and average wait times have increased to approximately 57 weeks in the province of British Columbia [83, 84]. High wait times for genetic counselling have been documented to both reduce patient satisfaction with the care they eventually receive and dissuades patients from attending their appointment when they receive one [86, 87].

1.4.2 Health Inequities Among Ethnic Minority Populations

Genetics as a field has had a checkered history that includes research into eugenics practices on ethnic minority populations beginning in the 1920's. Eugenics practices in BC were legal through 1933 – 1973 although sterilization records have been thought to be lost or destroyed [88, 89]. Indigenous populations in Alberta were disproportionately targeted and sterilized as part of the province's eugenics program from 1929 – 1972 and over 1000 sterilizations of Indigenous people took place in Ontario over a similar timespan [89-91]. Furthermore, unethical research practices such as the exploitation of First Nations blood samples and the intentional mistreatment of African Americans in the USA with syphilis have contributed to feelings of mistrust surrounding healthcare research by some ethnic minority populations [92, 93]. Both African American and Hispanic patients display higher levels of mistrust that their genetic information will be misused [94].

Common explanations for the lack of ethnic minority participation in health research is mistrust of the medical system, lack of knowledge of clinical trials, and cultural differences that

stigmatize discussion around health outcomes [95-97]. There are also significant institutional barriers that prevent ethnic minority populations from participating in health research. These institutional barriers include cultural racism, implicit and explicit racial biases by healthcare workers, and segregated neighborhoods [98-100]. A review of institutional barriers to health research participation for ethnic minorities has shown that a lack of access to primary medical care and the alienation of ethnic minority healthcare workers from other members of the health community are major barriers [101]. The review also found that amongst researchers there is an incorrect stereotype that ethnic minority populations are more difficult to recruit and that researchers were less likely to actively recruit ethnic minority patients [101]. Other studies have also shown that one of the greatest barriers to ethnic minority populations participation in research is researchers not actively recruiting them [102, 103]. These findings support other research done in the USA that has shown that ethnic minority patients are equally willing as white patients to participate in health-related research [99, 104].

The lack of representation of ethnic minority populations is particularly pronounced in genome-wide association studies (GWAS) in which participants are overwhelmingly (80%) of European ethnicity [105]. Furthermore, most of the geographically-specific population descriptions are for European populations and European cohorts are often far larger and better characterized than their ethnic minority counterparts [105, 106]. Participants of Asian ethnicity make up only 14% of participants in GWAS and other ethnic minority populations make up the remaining 6% [105]. Indigenous patients make up only 0.05% of all GWAS genomes on record [105]. Although representation of ethnic minorities in GWAS has increased from 4% to 20% over seven years from 2009 to 2016, the vast majority of the improvement in representation is from increased genetics research in Asian countries [105, 107]. The lack of research into the common genetic

diversity of ethnic minority patients means they are more likely to receive an indeterminate result from genetic testing [108]. This makes it more difficult and complicated for genetic counsellors to provide patients with useful advice and information [109].

The inequities seen in genetics research persists in access to clinical genetic testing and counselling. Ethnic minority populations are less likely to receive genetic testing after surviving breast cancer [110, 111]. A study in the USA found that in a cohort of African American breast cancer patients who all qualified for genetic testing and counselling only 51% of the patients were referred to genetic counselling services [112]. Moreover, ethnic minority patients have been shown to rate their experience with genetic counselling more negatively than white patients [113]. To further complicate the access to genetic testing and counselling services, approximately 90% of genetic counsellors in North America are white [114]. Previous research has found that the majority of genetic counsellors display moderate to strong pro-white biases and use less emotionally responsive communication methods when counselling ethnic minorities [115]. Altogether, ethnic minority patients have a lower access to genetic testing and counselling services than similar patients of European ethnicity.

1.4.3 Other Barriers to Genetic Testing and Counselling

Further barriers to accessing genetic testing and counselling services include travel distance to clinics and lack of physician knowledge regarding genetics. Previous research has identified travel distance as being one of the most significant barriers to access for genetic testing and counselling [116, 117]. Travel distance to genetics services that are primarily located in urban areas is a prominent barrier for access in Canada where between 14 – 53% of Canada's population lives in a rural area [118]. Similarly, lack of physician knowledge about genetics and available genetic testing opportunities has been described as another large barrier to access for

genetic testing and counselling [116]. A review examining primary care providers knowledge of and attitudes towards genetic testing found that many physicians felt their knowledge of genetics was lacking [119]. The same review also determined these care providers were interested in gaining genetics knowledge and that targeted education programs are necessary to improve genetic testing knowledge [119].

1.5 New Genetic Counselling Models to Address Patient Access

As genetic testing became available for Huntington's disease, genetic counselling involved time consuming, in-depth counselling sessions for patients to understand and cope with the potential diagnosis of an untreatable terminal disease [120]. Genetic counselling for hereditary cancer syndromes has often been similarly as intensive despite diagnosis with a hereditary cancer syndrome being treatable. The traditional genetic counselling model includes two in-person 1-on-1 counselling sessions between the patient and genetic counsellor. In the first session a patient's hereditary cancer risk is conveyed to them and informed consent is obtained for genetic testing. In the second session a patient's genetic testing results are returned and the test implications are explained to the patient. Because of the lower risk for severely negative psychological outcomes from hereditary cancer genetic counselling when compared to Huntington's it is possible to consider alternative models of genetic counselling that may reduce the significant burden that in-person 1-on-1 genetic counselling places on a clinical genetics program.

To combat barriers to access, many new genetic counselling models have been developed. Telephone genetic counselling and videoconference genetic counselling (telegenetics) have been trialed and implemented in Canada, Australia, the USA, and Europe [121-132]. A major benefit of telephone genetic counselling and telegenetics models is that they can

provide increased access to patients that would normally have to travel long distances to receive genetics services [125, 127, 131]. The majority of studies that examine telephone genetic counselling and telegenetics have found that both models were just as satisfactory to patients as an in-person genetic counselling appointment and there was no increase in patient distress or anxiety [121, 122, 125-132]. Telephone genetic counselling has also been shown to improve ethnic minority patients satisfaction with genetics services thereby reducing ethnic minority patients' barriers to access [133]. A study trialing telephone genetic counselling in the USA found that African American women displayed higher satisfaction with telephone genetic counselling rather than in-person genetic counselling and the authors suggested it may have been due to reduced implicit bias from genetic counsellors and other clinical staff [133]. One potential limitation of telephone genetic counselling is that genetic testing uptake rates may be lower in patients with high baseline distress that receive telephone genetic counselling [124].

New genetic counselling models seeking to increase the efficiency of the genetic testing and counselling process have also been developed. Group genetic counselling models have been demonstrated to reduce the cost of providing genetic counselling services [134]. Furthermore, group models can increase efficiency by decreasing the average time per patient spent with genetic counsellors [134, 135]. Group genetic counselling has also been demonstrated to reduce patient wait times to access genetic testing and counselling services [83]. Similarly to other new genetic counselling models, group genetic counselling has shown to be satisfactory to patients [134, 136, 137]. Trials have revealed that group genetic counselling does not increase cancer-specific distress [134-136]. A potential limitation of group genetic counselling models is that some studies have shown that some patients would actively prefer a 1-on-1 appointment over a group appointment [136, 137].

Other new genetic counselling models such as genetic counsellor embedded models, genetic counselling extender models, and mainstream genetic testing models have sought to further streamline genetic counselling processes by modifying healthcare professionals' roles. Embedded genetic counsellor models involve placing a genetic counsellor directly into an oncology clinic [138, 139]. Embedded genetic counsellor models have been shown to reduce patient wait times and improve genetic testing uptake rates [138, 139]. Genetic counsellor extender models involve training a healthcare professional (e.g. nurses) to perform some of the responsibilities of a genetic counsellor [138]. These responsibilities can include risk assessment for patients, obtaining informed consent when genetic tests are ordered by a doctor, and the return of genetic testing results [138]. Results from these models have shown that genetic counsellor extenders can increase access to genetic testing fourfold and are able to provide access to genetic testing services for patients in geographically distant locations [138, 139]. Finally, mainstreaming genetic testing was pioneered in the United Kingdom (UK) and involves oncologists directly obtaining informed consent for genetic testing, and patients only seeing a genetic counsellor to receive their genetic testing results [140]. Mainstreamed genetic testing and counselling has been shown to reduce patient wait times and has been deemed satisfactory by patients [140].

Finally, further models such as direct genetic testing and tumor first genetic testing models have also been introduced. Direct genetic testing involves the consent of patients to genetic testing with no pre-test discussion with a genetic counsellor and instead, may include only written or pre-recorded video materials [141]. Direct genetic testing models have been shown to be satisfactory for patients when compared to traditional genetic counselling models [142, 143]. Direct genetic testing models can also reduce genetic testing and counselling costs and wait times [141, 143]. Tumor first genetic testing models involve the genetic testing of a patients' tumor

and follow up germline genetic testing and counselling if a PV is discovered [144-147]. Tumor first genetic testing models have primarily been trialed for Lynch Syndrome where all patients diagnosed with colorectal cancer or certain gynecological cancers are referred for genetic testing [144, 146]. A major benefit of tumor first genetic testing instead of targeted genetic testing and counselling is that patients with a hereditary cancer syndrome will not be missed due to not meeting specific family history criteria [144]. Patient satisfaction with tumor first genetic testing models has been shown to be high [145, 146].

1.6 Thesis Rationale and Aims

1.6.1 Thesis Rationale

Genetic counsellors facilitate genetic testing for hereditary cancer syndromes in order to identify families at a high risk of developing cancer so that patients can improve cancer specific health outcomes. The increase in prevalence and demand of genetic testing and counselling for hereditary cancer has made it clear that increased access to genetic counselling services are required in Canada. There are currently numerous barriers to patient access for genetic testing and counselling that new or modified genetic counselling models may be able to address. Wait times for genetic counselling services in many Canadian provinces are extremely long and new genetic counselling models are needed reduce this barrier to access. Increased investigation into identifying specific patient populations in BC that are experiencing reduced access and may benefit from new or modified genetic counselling models is also needed.

1.6.2 Thesis Aims

In this thesis, the overall aim is to analyze the effectiveness of a new genetic counselling model on reducing patient barriers to access at the BC HCP and to identify specific patient populations facing increased barriers to genetic testing and counselling at the BC HCP. I will

specifically be analyzing a new genetic counselling model, analyzing the demographic data of the patient population at the BC HCP, and analyzing patient psychological responses to genetic testing and counselling at the BC HCP. To achieve this aim I have three hypotheses.

Hypothesis 1: New genetic counselling models can reduce patient barriers to access and are acceptable to patients and healthcare providers.

Hypothesis 2: There are specific and identifiable patient populations at the BC HCP experiencing increased barriers to access for genetic testing and counselling.

Hypothesis 3: There are specific and identifiable patient populations at the BC HCP experiencing increased psychological distress, and uncertainty.

For the first hypothesis, I aim to show that a new model of genetic counselling trialed at the BC HCP, termed oncology clinic-based genetic testing and counselling, is effective at reducing barriers to genetic testing and is acceptable to patients. The surge in use of genetic testing and counselling services necessitates the development and trialing of new genetic counselling models to manage patient demand. I have analyzed the results from the new oncology clinic-based genetic testing and counselling model trialed at the BC HCP. The specific aims are as follows:

Aim 1: Determine if oncology clinic-based genetic testing and counselling reduces patient wait times.

Aim 2: Analyze patient reported outcome measures to determine if oncology clinic-based genetic testing and counselling provides similar psychological benefits as traditional genetic counselling.

Aim 3: Analyze healthcare provider responses to determine if oncology clinic-based genetic testing and counselling is acceptable to them.

Aim 4: Determine if there are demographic factors associated with patient reported outcome measure responses.

For my second hypothesis, I aim to identify specific patient populations at the BC HCP that are under-served. There are many barriers to accessing genetic testing and counselling services and some patient populations experience larger barriers to access then others. By identifying patient populations facing barriers to access, future research can be targeted to determine how to alleviate barriers these populations face. For this hypothesis I have three aims:

Aim 1: To describe the demographics of patients attending the BC HCP and determine if specific patient populations are under-represented compared to the general BC population.

Aim 2: To describe the genetic testing results of patients attending the BC HCP

Aim 3: To determine if there are demographic factors associated with genetic testing results.

For my final hypothesis, I set out to analyze patient responses to the MICRA survey from the general clinical practice at the BC HCP. Although most patients that receive genetic testing and counselling for hereditary cancer do not experience long-term clinical distress or anxiety, there are differences in patient psychological responses. Identifying specific patient populations experiencing worse psychological outcomes is important in order to further understand barriers to genetic testing and counselling. If specific patient populations are having a worse experience

with the genetic testing and counselling process, this may negatively impact future patient participation. For this hypothesis I have a single aim.

Aim 1: Determine if there are demographic factors associated with patient responses on the MICRA survey.

All together my work aims to reduce patient barriers to accessing genetic testing and counselling services and identify specific patient populations experiencing increased barriers to genetic testing and counselling. This work can be used to identify patient populations at the BC HCP that would particularly benefit from new and modified genetic counselling models to decrease barriers to genetic testing and counselling.

Chapter 2: Oncology-Clinic Based Genetic Testing and Counselling

2.1 Introduction

Emerging use of genetic testing to guide cancer therapies, combined with greater public and health care provider awareness, has led to rising demand for publicly funded cancer genetic services [148, 149]. This has resulted in longer wait times for patients to access genetic counselling and testing. Given the rapidly expanding indications for genetic testing to guide oncologic treatment decision-making, alternative genetic counselling models must be explored to ensure timely access to results.

Newer approaches to cancer genetic counselling have recently been described. These new approaches have included telephone, videoconference, and group genetic counselling [137, 150]. These approaches have all been demonstrated to be as equally acceptable to patients as in-person genetic counselling [137, 150]. A new streamlined model from the United Kingdom with oncologists providing pre-test counselling and consenting patients for genetic testing has also been recently described [140]. This study demonstrated that oncology clinic-based genetic testing reduced overall patient wait times for genetic testing services, reduced costs, and was satisfactory for patients [140].

A similar international prospective study in the United States, Italy, and Spain found that ovarian cancer patients were highly satisfied with oncology clinic-based genetic testing for *BRCA1* and *BRCA2* [151]. Other similar models have recently been described in Australia, Canada, and Malaysia. In Australia oncologists provided *BRCA1* and *BRCA2* genetic testing and found that specialists were comfortable with administering genetic testing [152]. As well, they found that genetic counselling times were decreased by the new model [152]. In Canada surgeons provided genetic testing in ovarian cancer patient populations and found that the new model increased access to genetic testing by increasing the uptake percentage for genetic testing [153]. In Malaysia,

ovarian cancer patients were provided genetic testing by non-genetic counsellor clinicians and it was determined that this model was also satisfactory to patients [154].

To improve access to genetic testing, I analyzed the results of oncology clinic-based genetic testing and counselling using a multi-gene hereditary cancer panel for selected patients with breast and ovarian cancer at the BC HCP. The primary objectives of this study were to evaluate wait times and patient reported outcome measures for the new streamlined oncology clinic-based model as compared to traditional genetic counselling. The secondary objectives of this study were to evaluate oncologist and genetic counsellor acceptability and experience as well as to investigate demographic factors affecting patient survey responses. I hypothesized that the oncology clinic-based approach would be feasible, decrease wait times, and not affect patient reported outcome measures. As well, I hypothesized that demographic factors would influence patient reported outcome measures.

2.2 Methods

2.2.1 Clinical Models

Women age ≥19 undergoing index testing, matching provincial HBOC testing criteria, and attending the HCP from June 2015 to August 2017 were eligible to participate in the traditional model. The traditional model is the standard genetic counselling process at the HCP and first involved the referral of the patient to the HCP, followed by a one-on-one 45-minute pre-test counselling session with a genetic counsellor prior to genetic testing referral. This was followed by a scheduled 30-minute results disclosure appointment approximately one month after the patients' blood sample was submitted for genetic testing. Pre- and post-test genetic counselling sessions were conducted in person, by videoconference, or by telephone.

Women age ≥19 attending their regularly scheduled oncology appointment from June 2015 to August 2017 and meeting a subset of provincial HBOC criteria (non-mucinous ovarian cancer, under 35 breast cancer, or under 60 triple-negative breast cancer) were eligible to participate in the oncology clinic-based model. A subset of the provincial HBOC criteria were used to streamline the process for oncologists when identifying patients that qualify for genetic testing. Patients were consented to participate in the new oncology clinic-based model by their oncologist. The oncology clinic-based model involved pre-test counselling and genetic testing referral by an oncologist in clinic. This was followed by a scheduled 60-minute post-test results session with a genetic counsellor conducted either in person, by videoconference, or by telephone approximately one month after the patients' blood sample was submitted for genetic testing (Figure 2.1). Patients in the oncology clinic-based model had a longer results session with a genetic counsellor to review both family and personal history that may have impacted the interpretation of the patients' genetic test results.

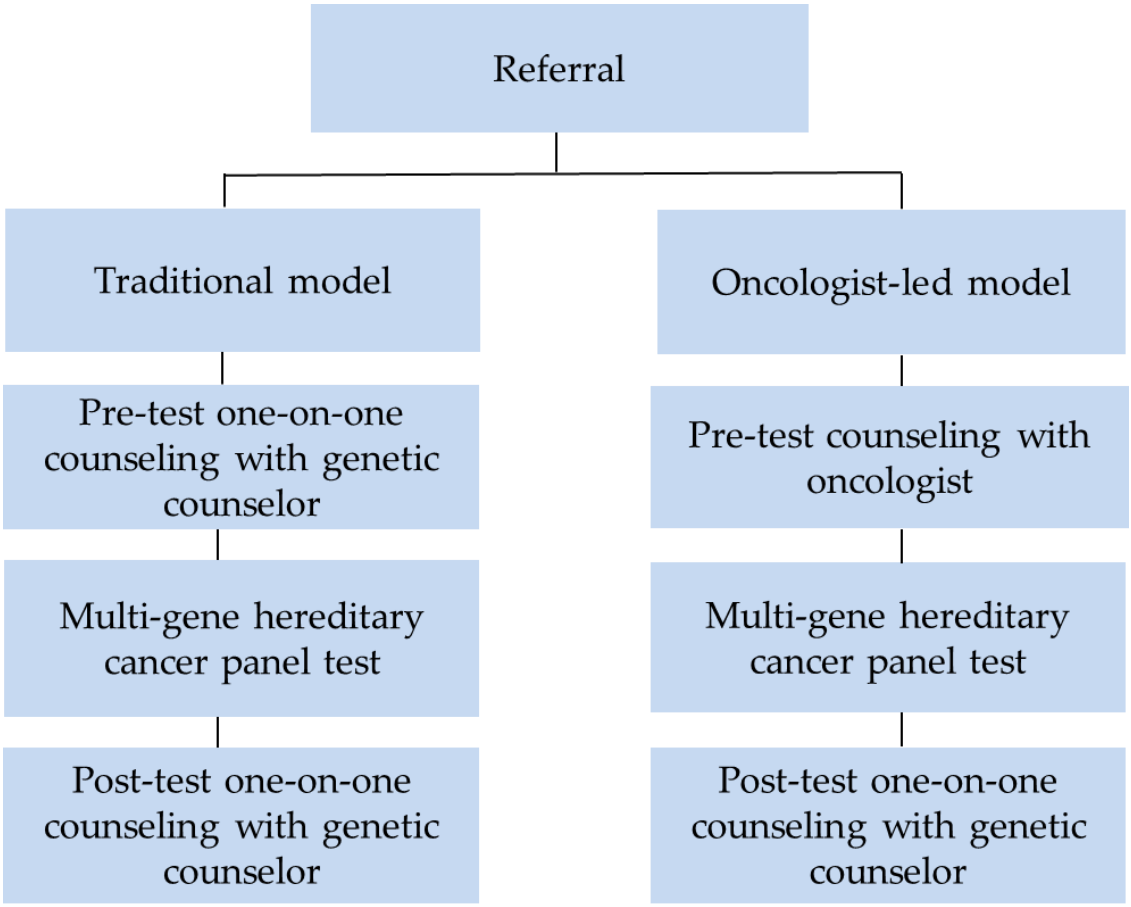

Figure 2.1. Progression of the oncology clinic-based genetic testing and counselling model compared to the traditional genetic counselling model

All patients received a results appointment with a genetic counsellor regardless of their genetic test result. Due to British Columbia's geographical layout and variable patient availability, all patients were given the option for an in person, telephone, or videoconference session. All oncologists were trained by one of the HCP medical directors to provide genetic testing information to patients and consent patients for genetic testing. Oncologists were also provided with reference material including a frequently asked questions information sheet and were provided continued HCP support as needed. Oncologists initially received a standardized script outline and used a standardized patient consent form.

2.2.2 Genetic Testing

Genetic testing was performed using next-generation sequencing of a multi-gene hereditary cancer panel and Multiplex Ligation-dependent Probe Amplification (MLPA) for *BRCA1* and *BRCA2* on peripheral blood samples. A minority of patients were offered additional expanded panel testing based on clinical presentation and provincial testing guidelines.

2.2.3 Study Questionnaires

Patients in both models were contacted by a research assistant over telephone approximately two business days after their genetic testing results appointment to consent them for study questionnaires. Informed consent was obtained, and survey packages were mailed to patients. If patients were unable or unwilling to complete a paper survey package the research assistant offered to complete the survey package with them over the phone. Patients in the traditional model who did not meet the oncology clinic-model's HBOC subset criteria were excluded from the survey analysis. These patients were excluded to maintain similar patient eligibility criteria in both models.

Patients were mailed the survey package and were instructed to complete the package one month after the results appointment date. Patients completed five questionnaires: Genetic Counselling Outcome Scale (GCOS-24) [155], Decisional Conflict Scale (DCS) [156], Multidimensional Impact of Cancer Risk Assessment (MICRA) [157], Genetic Knowledge Questionnaire [158] and Patient Acceptability Scale. Patients were asked to complete their survey package one month after their results appointment to match the procedures in the original validation of MICRA and GCOS-24.

Oncologists and genetic counsellors were invited to complete surveys to assess feasibility and acceptability of the streamlined model. Oncologists were invited to complete two questionnaires to evaluate their experiences and acceptability: Oncologist Questionnaire [151] and Oncologist Experience Scale. Genetic counsellors completed a questionnaire to measure their perceptions of patient preparedness, time taken for both models, and to obtain direct feedback.

2.2.4 Questionnaire Scoring

Four validated surveys were administered to patients and one unvalidated survey was administered. The unvalidated survey was an internally developed acceptability survey to assess patients perceived acceptability of the HCP's genetic testing services.

The first validated survey administered to patients was a knowledge test adapted from Hughes et al. 1997. This survey was scored by summing all of the patients correct answers.

The second validated survey administered to patients was the MICRA [157]. The MICRA is comprised of three subscales that measure patient distress, uncertainty, and positive experiences. Patients have the option of responding to each question with Never (0), Rarely (1), Sometimes (3), and Always (5). The MICRA survey is assessed by first reverse scoring the positive experience subscale. Then each subscale questions are summed, multiplied by the number of

questions on the subscale, and then divided by the number of questions the patient answered. For all subscales a high MICRA score represents a negative psychological response and a low MICRA score represents a positive psychological response.

The third validated survey was the DCS [156]. The DCS contains five subscales measuring how informed patients are, what values are important to patients, if patients feel supported, patient uncertainty, and whether the patient is comfortable with the decisions they've made. Patients responded to each question with Strongly Agree (1), Agree (2), Neither Agree nor Disagree (3), Disagree (4), and Strongly Disagree (5). The DCS is analyzed by first reverse scoring negatively worded items, subtracting 1 from each response, summing all patient responses, dividing by the number of questions and then multiplying by 25.

The final validated survey completed by patients was the GCOS-24 [155]. The GCOS-24 was developed to evaluate patient empowerment when participating in clinical genetics services. Patients are able to respond to questions on a scale with Strongly Disagree (1), Disagree (2), Slightly Disagree(3), Neither Disagree nor Agree (4), Slightly Agree (5), Agree (6), and Strongly Agree (7). Questions that are worded in the negative are reverse scored and then all 24 responses are summed with higher scores equating to increased feeling of empowerment. GCOS-24 is typically administered once before the genetic counselling session and once afterwards and then the first score is subtracted from the second score to determine if there was an increase in patient empowerment after genetic counselling. For our study we were only able to administer GCOS-24 once after the genetic counselling session and therefore we only used descriptive statistics on the GCOS-24.

Missing data for GCOS-24 and the DCS was assessed using the methods outlined for GCOS-24. If less than 20% of the survey items were missing, the answered items were averaged,

and the average value was imputed for the missing items. If more than 20% of the survey items were missing the survey was excluded from the analysis. For the MICRA survey, missing data is accounted for by the scoring method.

2.2.5 Statistical Analysis

Data for wait times from referral to return of genetic test results, indication for genetic testing, method of genetic testing, patient demographics, and personal and family cancer history were obtained through review of the BC Cancer and HCP electronic chart and pedigree databases.

Descriptive statistics were presented for both categorical and continuous variables. Categorical variables were summarized as frequencies with percentages, and continuous variables were described as means with standard deviations.

An independent sample *t*-test was used to compare wait times for the two clinical models. Generalized linear model analyses were performed to compare psychological outcomes. The MICRA Uncertainty subscale was assessed with a multiple linear regression. The Distress and Positive Experiences subscales were assessed with multiple censored linear regressions due to an over-abundance of zero answers from patients. All DCS subscales were assessed with multiple censored regressions due to an overabundance of zero answers from patients. A log or cube root transformation was applied for continuous outcomes if needed. For survey analyses, the traditional model (n = 99) and oncology clinic-based model (n = 49) patients were compared. Patient demographic and genetic testing factors were analyzed to identify any potential confounding factors associated with survey results. The factors analyzed included, knowledge (as measured by the Genetic Knowledge Questionnaire), age at referral, genetic test result, oncology clinic-based testing criteria met, results appointment disclosure genetic counselling

modality, and patient ethnicity. For the regression analysis patients with a pathogenic or likely pathogenic variant genetic test result were assigned to a high, moderate, or low penetrance PV. Patients with a likely benign variant genetic test result were assigned to UNINF.

All statistical tests were two-tailed with a p-value of 0.05 indicating significance. Statistical analysis was performed using R V.3.5.1**.**

2.3 Results

2.3.1 Study Population

A total of 702 patients that were seen in the HCP from August 2015–July 2017, were invited to take part in this study. Three hundred and twenty two of the 537 patients who received through the traditional model elected to participate, 78 of the 165 patients who received oncology clinic-based services elected to participate (n = 400). Of the 400 consented participants, 259 completed the study survey package. One hundred and forty-eight patients (99 traditional and 49 oncology-clinic based) with a personal history of breast/ovarian cancer met the study inclusion criteria and were included in our evaluation of the patient survey package responses (Figure 2.2).

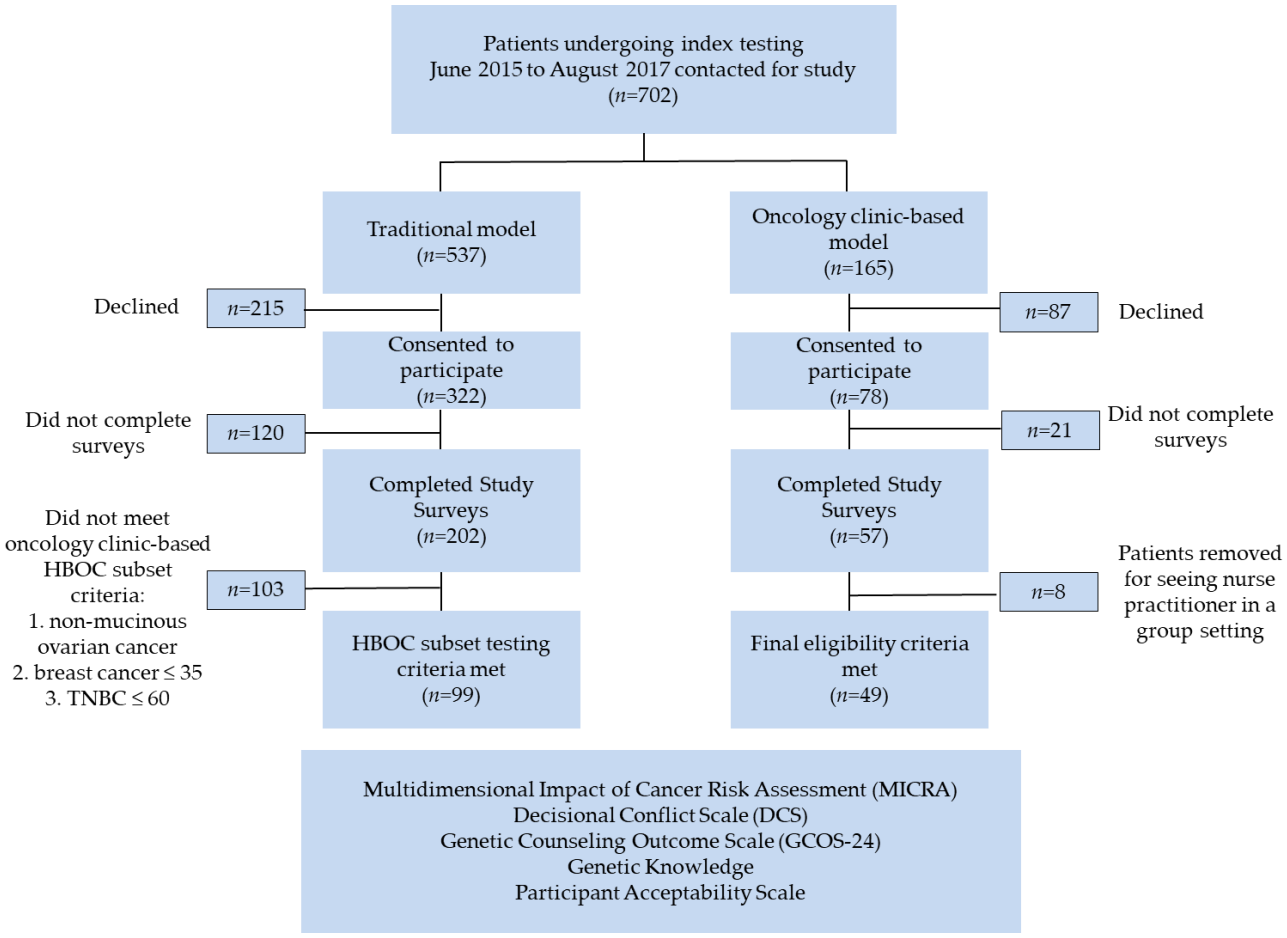

Figure 2.2. Oncology clinic-based genetic testing and counselling patient inclusion criteria

2.3.2 Wait Times

Wait times were calculated from the date of referral to the date of return of genetic test results for the 400 individuals seen at the HCP that consented to participate in the study. The mean wait time in days for oncology clinic-based (n = 78) model patients (M = 191 days; SD = 174 days) was significantly shorter (t = 8.05; $p < 0.001$) as compared the traditional (n = 322) model (M=403, SD=312).

2.3.3 Patient Demographics

Patient demographics for the traditional and oncology clinic-based models are outlined in Table 2.1. The mean age of referral for all patients was 58 years and all patients were female. Patient age, cancer diagnosis, method of testing, test results, and results appointment format are summarized in Table 2.1. Patients undergoing testing through the traditional model were younger as compared with the oncology clinic-based group (56.5 vs 62.2, p = 0.010).

For the traditional model, pre-test counselling sessions were in-person for 41.4% (n = 41) of patients, and by videoconference or telephone for the remaining. Most post-test results counselling sessions for patients in the traditional model were conducted by telephone (n = 91; 91.9%). In comparison, all pre-test sessions were in person at oncology clinics for oncology clinic-based patients and post-test sessions with the genetic counsellor were done by videoconference (n = 21; 42.9%), telephone (n = 4; 8.2%) or in person (n = 24; 42.9%). Patients in the oncology clinic-based model were significantly more likely to receive in-person or videoconference appointment types than traditional model patients ($p < 0.001$).

Table 2.1. Patient demographics for oncology clinic-based genetic testing and counselling

	Total Patient Population	Oncology clinic-based	Traditional	P-Values
Wait time (days) Referral to return of genetic test results (SD)		191(174)	403(312)	$p<0.001$*
Age (years, SD)		62.2(12.0)	56.7(12.0)	$p=0.013$*
Gender (n, %)				
Female	148 (100)	49(100)	99(100)	N/A
Personal history (n, %)				$p=0.006$*
Ovarian cancer	86 (58.1)	38(80.7)	48(48.0)	
Breast cancer ≤ 35	15 (10.1)	3(5.3)	12(13.0	
Triple negative breast cancer ≤ 60	46 (31.1)	8(14)	38(38.0)	
Breast ≤35 and ovarian cancer	1 (0.7)	0	1(1.0)	
Family history of breast/ovarian cancer (n, %)				$p=1$
No	89 (60.1)	29(59.2)	60(60.6)	
Yes	59 (39.9)	20(40.8)	39(39.4)	
Pre-test appointment type (n, %)				$p<0.001$*
In-person	90 (60.8)	49(100)	41(41.4)	
Telephone	24 (16.2)	0	24(24.2)	
Videoconference	34 (23.0)	0	34(34.3)	
Results appointment type (n, %)				$p<0.001$*
In-person	32 (21.6)	24(48.9)	8(8.1)	
Telephone	95 (64.2)	4(8.2)	91(91.9)	
Videoconference	21 (14.2)	21(42.9)	0	
Genetic testing (n, %)				$p=0.015$*
14-gene panel	55 (37.2)	21(42.9)	34(34.3)	
17-gene panel	77 (52.0)	28(57.1)	49(49.5)	
Prior *BRCA1* and *BRCA2* uninformative	3 (2.0)	0	3(3.0)	
Other	13 (8.8)	0	13(13.1)	
Additional expanded panel testing (n, %)				$p=0.086$
No	116 (78.4)	43(87.78)	73(73.7)	
Yes	32 (21.6)	6(12.2)	26(26.3)	
Genetic test results[1] (n, %)				$p=0.470$
Pathogenic or likely pathogenic	18 (12.2)	6(12.2)	12(12.1)	
Pathogenic monoallelic *MUTYH*[2]	3 (2.0)	1(2.0)	2(2.0)	
Variant of uncertain significance	31 (20.9)	12(24.5)	19(19.2)	
Likely benign	14 (9.5)	7(14.3)	7(7.1)	
Uninformative	82 (55.4)	23(46.9)	59(59.6)	

[1] Patients are reported based on their most clinically relevant variant diagnosis (if diagnosed with both a variant of uncertain significance (VUS) and pathogenic variant then the patient is categorized in 'Pathogenic or likely pathogenic'). [2] One patient was diagnosed with a pathogenic BRCA1 variant and a pathogenic monoallelic *MUTYH* variant and the patient is classified in the "Pathogenic or likely pathogenic" row. * Indicates significance. Patient demographics are for the 148 patients that completed survey packages. For the purpose of this study, an uninformative test result was defined as a negative test result for pathogenic or likely pathogenic variants in an individual who had index genetic testing and patients with VUS were considered separately.

2.3.4 Genetic Testing

Most patients received genetic testing through the in-house hereditary cancer gene panel through the BC Centre for Clinical Genomics that was expanded from 14 to 17 hereditary cancer predisposition genes in November 2016 (Table 2.2). Among 148 patients, 55 underwent 14-gene panel testing (37.2%), 77 had 17-gene panel testing (52.0%), and 16 traditional model patients either had only prior *BRCA1* and *BRCA2* testing (*n* = 3; 3.0%) or prior self-funded private-pay testing (*n* = 13; 13.1%). Thirty-one patients (21.6%) met provincial criteria for additional expanded panel testing via send-out to outside laboratories (Including the 13 traditional model patients that only utilized prior private-pay-testing) (Table 2.1).

Overall, genetic testing identified a disease causing pathogenic or likely pathogenic variant in 14.2% of patients (*n* = 21) and variant detection rates were comparable across both models (Table 2.1). *BRCA1* (*n* = 6; 4.1%) and *BRCA2*, (*n* = 6; 4.1%) were the most commonly identified variants. Pathogenic or likely pathogenic variants in monoallelic *MUTYH*, 2.0% (*n* = 3), *PALB2*, 1.4% (*n* = 2), *CHEK2*, 0.7% (*n* = 1), *PTEN*, 0.7% (*n* = 1), *TP53*, 0.7% (*n* = 1), and *APC*, 0.7% (*n* = 1) were also identified. Testing was uninformative for 55.4% of patients (*n* = 82). 23 likely benign variants were identified in 9.5% (*n* = 13) of patients. 42 variants of uncertain significance (VUS) were identified in 20.9% (*n* = 31) of patients. Further, one patient originally reported with a germline pathogenic variant in the *NF1* gene, was found to have it likely as a result of clonal hematopoiesis.

Table 2.2. Hereditary cancer program 17-gene panel

Gene	Syndrome
BRCA1, BRCA2	Hereditary breast and ovarian cancer
*PALB2**	Hereditary breast and pancreatic cancer
TP53	Li Fraumeni syndrome
PTEN	*PTEN* hamartoma tumor syndrome (Cowden Syndrome)
CDH1	Hereditary diffuse gastric and lobular breast cancer
MLH1, MSH2, MSH6, PMS2	Lynch syndrome
MUTYH	*MUTYH*-associated polyposis (MAP)
APC	Familial adenomatous polyposis (FAP)
*POLE**	Hereditary colorectal cancer and colonic polyposis
*POLD1**	Hereditary colorectal and uterine cancer; colonic polyposis
STK11	Peutz-Jeghers syndrome
SMAD4, BMPR1A	Juvenile polyposis syndrome

* The 14-gene panel includes high-penetrant genes: *BRCA1, BRCA2, TP53, PTEN, CDH1, STK11, MLH1, MSH2, MSH6, PMS2, MUTYH, APC, SMAD4, BMPR1A* with multiplex ligation-dependent probe amplification of *BRCA1* and *BRCA2*. *PALB2, POLD1,* and *POLE* were added in November 2016 to create the 17-gene panel.

2.3.5 Patient Reported Outcome Measures

There were no significant differences between the oncology-clinic based model and the traditional model on the MICRA survey (Figure 2.3a) or on the DCS survey (Figure 2.3b). Results from study questionnaires are summarized in Table 2.3.

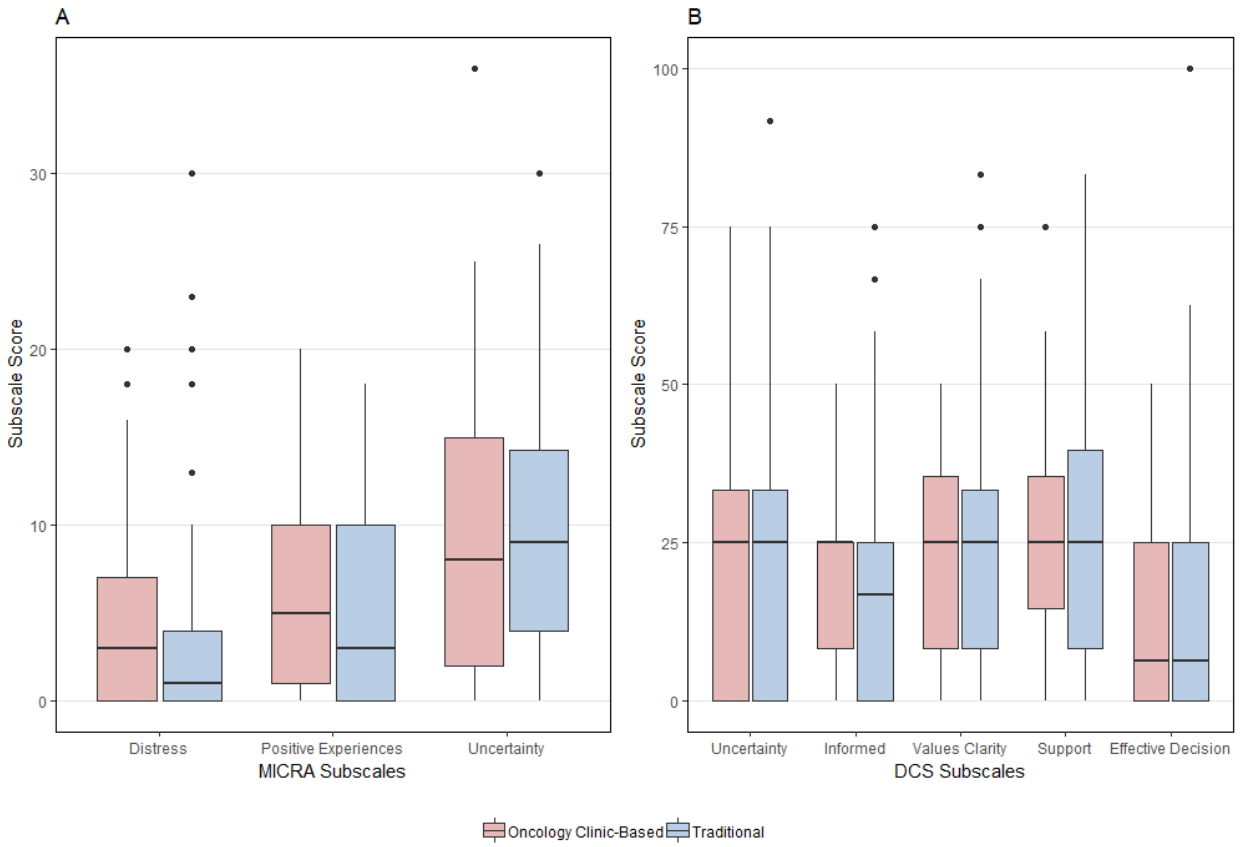

Figure 2.3. Patient MICRA and DCS survey scores for patients attending the oncology-clinic based and traditional genetic counselling models

Table 2.3. Oncology clinic-based genetic testing and counselling patient survey outcomes

Survey	Oncology clinic-based model		Traditional model		Population Total	
	n	mean (SD)	n	mean (SD)	n	Mean (SD)
Genetic Knowledge	49	8.46(1.79)	99	8.67(1.52)	148	8.60 (1.59)
Patient Acceptability Scale	49	4.54(0.71)	92	4.52(0.69)	141	4.53 (0.70)
Decision Conflict Scale						
Uncertainty	48	22.57(19.52)	98	23.36(21.25)	146	23.10 (20.63)
Informed	48	19.71(14.04)	97	18.04(17.38)	145	18.59 (16.32)
Values Clarity	48	24.13 (17.04)	97	24.22(19.73)	145	24.19 (18.82)
Support	48	25.18(18.23)	97	26.61(20.94)	145	26.13 (20.03)
Effective Decision	48	13.16(14.32)	97	15.21(19.43)	145	14.53 (17.88)
Multidimensional Impact of Cancer Risk Assessment						
Distress	49	4.53(5.65)	99	3.37(5.24)	148	3.75 (5.39)
Uncertainty	49	9.51(8.19)	99	10.02(6.88)	148	9.85 (7.32)
Positive experience	49	6.00(5.78)	99	4.45(4.66)	148	4.96 (5.09)
Genetic Counselling Outcome Scale	49	120.17(16.78)	98	120.93(15.15)	147	120.67 (15.66)

2.3.5.1 Knowledge Questionnaire

Overall, there were no significant differences in responses between the traditional and oncology clinic-based models (Table 2.3.).

2.3.5.2 Multidimensional Impact of Cancer Risk Assessment Survey

On the Distress subscale, patients of a younger age were associated with a significantly ($\beta = -0.18$, $t = -2.37$, $p = 0.018$) higher distress score. There was no significant difference between patients in the traditional or oncology clinic-based models ($p = 0.829$). A total of 19 (38.78%) patients in the oncology clinic-based model and 35 (35.35%) patients in the traditional model scored zero on the Distress subscale indicating they felt no distress from genetic testing and counselling.

There were no significant demographic predictors for patients on the Uncertainty subscale. There was no significant difference between patients in the traditional or oncology clinic-based models ($p = 0.194$).

On the Positive Experiences subscale, patients with a high penetrance PV ($\beta = 5.61$, $t = 3.37$, $p < 0.001$), moderate penetrance PV ($\beta = 20.94$, $t = 2.62$, $p = 0.009$), and VUS ($\beta = 2.85$, $t = 2.19$, $p = 0.029$) were associated with a significantly higher score than patients with an uninformative genetic test result. Patients with no known ethnicity data were associated with significantly ($\beta = 5.89$, $t = 2.11$, $p = 0.035$), higher Positive Experience scores than patients of self-reported European ethnicity. There was no significant difference between patients in the traditional or oncology clinic-based models ($p = 0.058$). A total of 11 (22.45%) patients in the oncology clinic-based model and 31 (31.31%) patients in the traditional model scored zero indicating they had a completely positive experience with genetic testing and counselling.

2.3.5.3 The Decisional Conflict Scale

For the Uncertainty subscale, patients of self-reported Asian ethnicity were associated with significantly ($\beta = 23.03$, $t = 3.22$, $p = 0.001$) higher uncertainty scores than patients of European ethnicity. As well, patients that were referred for both non-mucinous ovarian cancer and under 35 breast cancer were associated with significantly ($\beta = 85.99$, $t = 3.46$, $p < 0.001$) higher Uncertainty subscale scores than patients referred for only meeting under 35 breast cancer. On the Uncertainty subscale there was no significant difference between the traditional and oncology clinic-based models ($p = 0.082$) (Figure 2.4).

There were no significant demographic predictors for the Informed subscale. There was no significant difference between the traditional and oncology clinic-based models ($p = 0.502$).

Similar to the Uncertainty subscale, on the Values Clarity subscale patients of Asian ethnicity were associated with significantly ($\beta = 20.36$, $t = 3.07$, $p = 0.002$) higher scores than patients of European ethnicity. There was no significant difference between the traditional and oncology clinic-based models ($p = 0.067$) (Figure 2.4).

Again, patients of Asian ethnicity were associated with significantly ($\beta = 22.64$, $t = 3.78$, $p < 0.001$) higher scores on the Support subscale than patients of European ethnicity. As well, patients referred for triple negative breast cancer under age 60 were associated with significantly ($\beta = 14.30$, $t = 2.01$, $p = 0.045$) higher scores than patients referred for under 35 breast cancer. There was no significant difference between the traditional or oncology clinic-based model ($p = 0.102$) (Figure 2.4).

Finally, on the Effective Decisions subscale, patients of Asian ethnicity were associated with significantly ($\beta = 26.64$, $t = 3.10$, $p = 0.002$) higher scores than patients of European ethnicity. As well, patients that received genetic counselling through videoconference were

associated with a significantly ($\beta = 20.13$, $t = 2.14$, $p = 0.033$) higher score than patients that received in-person genetic counselling. There was no significant difference between the traditional and oncology clinic-based models ($p = 0.176$) (Figure 2.4).

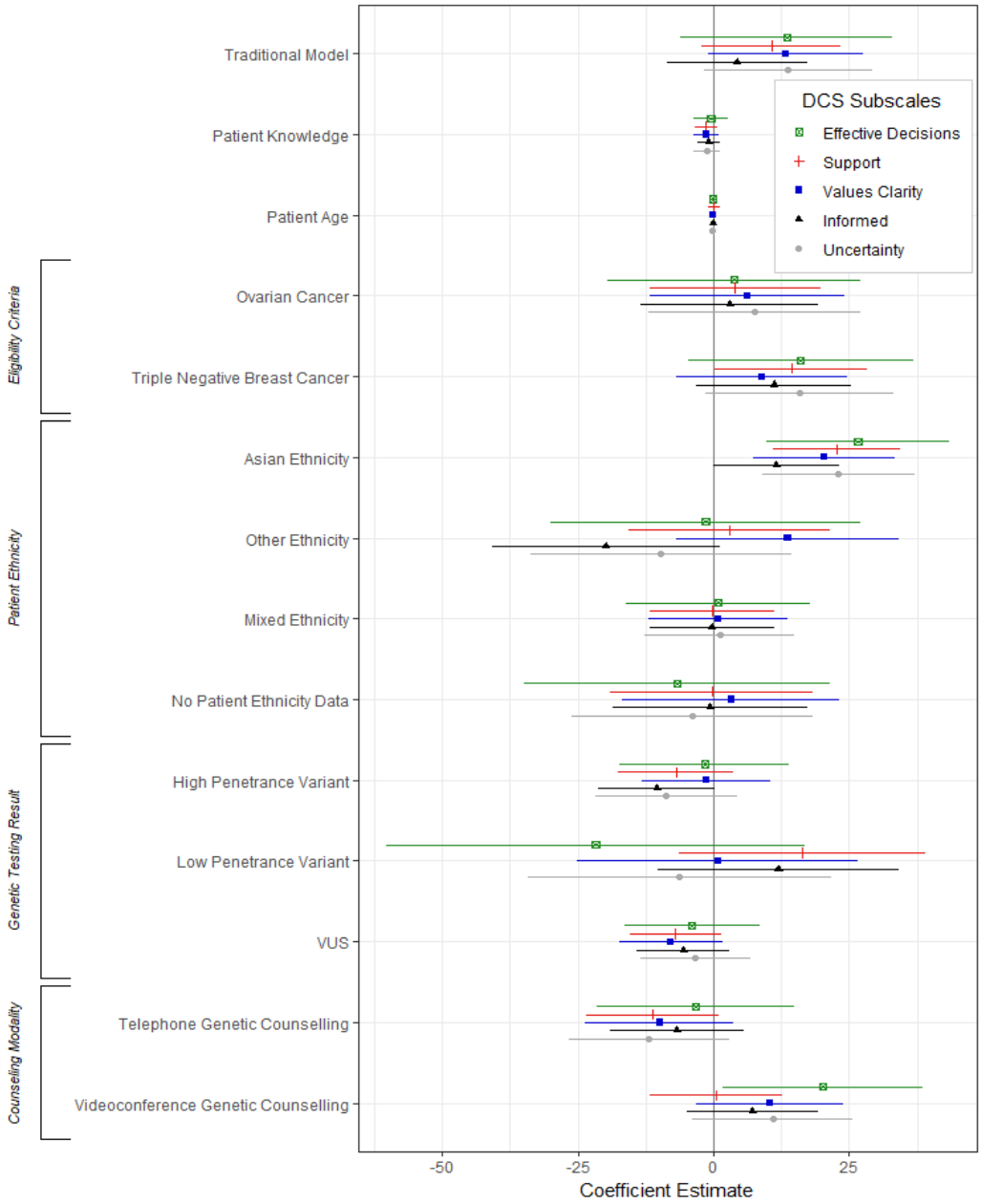

Figure 2.4. Forest plot of DCS subscales regression analyses results

The results from the five regression analyses are presented in this figure as a forest plot. For categorical variables the center line represents a baseline value that each level within the variable is compared against. Points on the right side of the center line indicate a higher DCS score (negative psychological outcome) and points on the left indicate a lower DCS score (positive psychological outcome). Baseline levels for each variable are, Eligibility Criteria: Breast Cancer under age 35, Patient Ethnicity: European, Genetic Testing Result: Uninformative, Sex: Female, Counselling Modality: In-Person. The dots represent the regression coefficient and the whiskers represent 95% confidence intervals. The eligibility criteria of having both ovarian cancer and breast cancer under age 35, and the genetic testing result of moderate penetrance PV were removed from the figure due to overly large error bars.

2.3.5.4 Patient Acceptability Scale

Overall, patients indicated that they were comfortable with the genetic testing process, and that this was acceptable, with no difference between the two models (mean responses 4.54 and 4.53 for the oncology clinic-based model and the traditional model, respectively).

2.3.5.5 The Genetic Counselling Outcome Scale

The GCOS-24 was administered after genetic counselling and genetic testing with similar mean scores between the two models (traditional model = 121.07, oncology clinic-based model = 120.17).

2.3.5.6 Oncologist and Genetic Counsellor Experience

Among 19 oncologists participating in oncology clinic-based testing, 8 (42%) completed an online survey. Clinician years of practice ranged from 2 to greater than 10 years. The number of oncology clinic-based patients per oncologist ranged from 2-30. An 11-question survey was adapted from George et. al. [12] to reflect use of a multi-gene panel. When oncologists were asked if they felt 'the process for carrying out multi-gene panel testing worked well', 4 indicated 'strongly agree', 3 'agree', and 1 'disagree'. Oncologists reported that their pre-test counselling appointments with patients took on average 17 minutes.

Six out of 14 (43%) genetic counsellors completed surveys. The number of oncology clinic-based patients seen per genetic counsellor ranged from 4-65. Genetic counsellors estimated that genetic testing result disclosures for patients undergoing the traditional model on average were 16.7 minutes (SD = 2.6) (scheduled for 30 minutes) as compared to 43.3 minutes (SD = 10.3) (scheduled for 60 minutes) for the oncology clinic-based patients. Among the 6 genetic counsellors, 4 indicated that their oncology clinic-based patients were 'usually prepared', and 2 indicated 'sometimes prepared' for their results

2.4 Discussion

Oncology clinic-based genetic testing and counselling using a multi-gene hereditary cancer panel approach in a publicly funded population-based health care setting in BC, Canada was implemented. I evaluated the patient wait times, patient reported outcome measures, oncologist and genetic counsellor experience, and compared the streamlined oncology clinic-based model to traditional one-on-one genetic counselling and genetic testing.

The oncology clinic-based model significantly shortened mean wait times from referral to return of genetic test results; 191 days as compared to 403 days for the traditional model. Similarly, other groups have reported reduced time to results with oncology clinic-based *BRCA1* and *BRCA2* testing for ovarian cancer patients [140, 151].

Other models including DNA-direct, telephone, videoconference, and group genetic counselling have been reported and these approaches are also acceptable for patients and reduce wait times [137, 150, 159, 160]. An advantage of the oncology clinic-based model is that this can potentially be combined with alternative streamlined approaches such as DNA-Direct to increase efficiency and further decrease wait times.

As compared to previous streamlined studies with *BRCA1* and *BRCA2* testing in ovarian cancer patients only [140], in this study, genetic testing was performed using a multi-gene panel approach in patients with a personal history of breast and/or ovarian cancer. The overall pathogenic variant detection rate was 14.2% (n = 21), similar in both models, and comparable to previous reports using multi-gene panel testing in a similar population [161, 162].

Monoallelic pathogenic variants were identified most commonly in *BRCA1* and *BRCA2* (n = 12; 8.1%). As expected with multi-gene panel testing, VUS were common (n = 31; 20.9%) and non-*BRCA1* or *BRCA2* pathogenic or likely pathogenic variants comprised 42.9% (n = 9) of

positive findings. The high proportion of non-*BRCA1* or *BRCA2* pathogenic variants and the discovery of the somatic *NF1* variant likely due to clonal hematopoiesis, highlights the importance of educating clinicians and patients about the broad range of results possible with multi-gene panel testing.

Patients completed five questionnaires to assess various psychosocial outcomes. Independent factors associated with greater distress and/or positive experiences based on the MICRA responses included: high and moderate penetrance PV, VUS, and younger patient age. These results are similar to studies that have found that *BRCA1* and *BRCA2* carriers display higher levels of concern immediately after genetic testing and counselling [155, 156]. As well, previous studies have shown that both women diagnosed with cancer at a younger age, and women that receive genetic testing at a younger age, display higher distress [163, 164]. Controlling for demographic variables there were no differences in, uncertainty, distress, and experience between the two clinical models. Finally, the large number of zero answers on the Distress and Positive Experiences sub-scales indicated that a large proportion of patients felt completely positive and non-distressed about their genetic testing and counselling.

On the DCS there was also no difference between the oncology clinic-based model and traditional model. However, patients of Asian ethnicity scored higher on four out of the five DCS subscales. These results suggest that patients of Asian ethnicity felt that they were more uncertain, had less clarity about what values were important to them in decision making, felt less supported in their decision making, and that they had made less effective decisions regarding their care. Previous studies have also found that ethnic minority patients are more likely to express dissatisfaction with their decisions regarding cancer treatment [165, 166]. Further, studies have found that values that are important to patients in regard to their decision-making process

may differ between ethnicities [166-168]. Ethnic minority women have been shown to put a larger emphasis on family, religiosity, and the cost of treatments as important factors in their decision-making process [166, 168, 169]. Patients of Asian ethnicity in this study may feel more uncertain and less supported in their decision-making process because of differences in communication with genetic counsellors. A previous study has shown that ethnic minority patients participating in discussions with non-ethnic minority doctors were more passive in their discussions and doctors were less likely to offer in-depth information and discussions to the patients [170]. These results suggest that genetic counsellors and oncologists may need to modify their communication models to better support ethnic minority patients and that increased recruitment of ethnic minority genetic counsellors is necessary.

Patients with a personal history of both ovarian cancer and breast cancer under age 35 experienced greater uncertainty than patients referred for only breast cancer under age 35. As well, patients referred for triple negative breast cancer under age 60 experienced feelings of less support in their decision making than patients referred for breast cancer under age 35. The association of greater uncertainty for patients with both ovarian cancer and breast cancer under age 35 and the association of triple negative breast cancer with a lack of support in decision making suggests that these may represent vulnerable patient populations; however, further studies are needed to better understand other factors that may be associated with greater uncertainty and lack of support (eg. advanced stage diagnosis or undergoing active oncologic treatment). Collectively, these findings suggest that a subgroup of patients may benefit from additional support before and after genetic testing.

Overall, oncologists had a favourable experience with a majority indicating that they felt that the oncology clinic-based process worked well. These findings are similar to a previous

report by George et al. [140] that showed that oncology clinic-based genetic testing was feasible and favourable among oncologists. Similarly, 80% of oncologists participating in a study in the US and Europe felt that this was an efficient use of their time [151]. These results support previous studies indicating that oncologists are accepting and willing to offer genetic counselling and initiate genetic testing. Among 6 genetic counsellors surveyed, most indicated that they felt that patients were prepared for the genetic test results appointment.

The 30%–40% survey response rates from patients and health care providers in this study are lower than some previously reported studies [151] but are similar to internal survey response rates at BC Cancer. Key limitations to our study include small numbers of oncologist, genetic counsellor, and patient responses, as well as heterogeneity among the patient population and variable genetic testing approaches. In addition, measurement of patient empowerment by the GCOS-24 was completed only once, after the genetic counselling results appointment, therefore only descriptive statistics were applied. Similarly, patient genetic knowledge measured by the genetic knowledge questionnaire was only able to be assessed post-genetic counselling appointment and therefore may not address the potential difference in knowledge from the pre-test modalities. As the interaction with a genetic counsellor was common to both models, it remains unclear as to the degree it impacted patient empowerment. This may be relevant when considering oncologist-led genetic testing models that do not include a genetic counsellor-led results appointment.

In summary, streamlined oncology clinic-based genetic counselling and genetic testing resulted in similar outcomes for patient reported outcome measures, was acceptable to their health care providers, and significantly reduces wait times for genetic testing. Future directions include implementing surveys online, implementing pre- and post-genetic counselling surveys as

part of clinical care to measure empowerment, and to evaluate patient reported outcome measures and clinician acceptability when introducing new models. As well, future directions will increase testing to include hereditary cancer syndromes other than HBOC. The field of cancer genetic counselling is rapidly evolving due to recent advances in personalized cancer treatments for patients with hereditary cancer and new rapid genetic testing and counselling approaches are needed to better serve patient populations.

Chapter 3: Identifying Demographic Differences Between Patient Populations

3.1 Introduction

With the advent of next generation sequencing, it has become possible to test patients for multiple hereditary cancer syndromes at once. The use of multigene panel testing has almost doubled the identification of the number of germline pathogenic variants in patients when compared to single gene testing in an iterative fashion [161, 171]. Identifying a greater proportion of patients with pathogenic variants allows for more targeted cancer treatments and increased surveillance for unaffected patients and their families.

As many hereditary cancer syndromes have overlapping phenotypic presentations, it can be cost and time saving to perform hereditary cancer genetic testing with a multigene hereditary cancer panel approach rather than single gene testing in an iterative fashion [40, 171]. The advantage of a multigene panel testing approach can be demonstrated when examining specific clinical scenarios, such as when performing genetic testing for familial breast cancer. While a family history of breast cancer is more commonly associated with HBOC, breast cancer has increasingly also been associated with Lynch Syndrome [172]. As Lynch Syndrome is typically associated with germline mutations in *MSH1*, *MSH2*, *MSH6*, and *PMS2* and is characterized by endometrial and colorectal cancer, a patient with a personal history of breast cancer would not traditionally be tested for Lynch Syndrome [173]. By performing limited genetic testing of *BRCA1* and *BRCA2* for a patient with a pattern of familial breast cancer, individuals and families with hereditary cancer may be missed.

The HCP in British Columbia has routinely conducted multiplex gene panel testing in a population-based healthcare system since October 2014, and expanded from a 14-gene panel to a 17-gene panel in November 2016. All patients referred for the hereditary cancer syndromes of

HBOC, Lynch Syndrome, FAP, MAP, Cowden Syndrome, Li-Fraumeni Syndrome, Juvenile Polyposis Syndrome, Peutz-Jeghers Syndrome, Hereditary Diffuse Gastric Cancer and Lobular Breast Cancer have all received the same gene panel since its inception at the HCP.

In order to better understand potential barriers to genetic testing and counselling faced by the BC population I aimed to characterize the current state of the patient population receiving genetic testing and counselling at the HCP. In this observational, retrospective population-based study I examined the results of standardized multigene panel testing with three primary objectives: 1) To describe the patient population attending hereditary cancer genetic testing and counselling services in BC; 2) To describe the frequency of PV and VUS among patients undergoing hereditary cancer genetic testing in BC; 3) To identify and examine demographic factors that influence the PV and VUS detection rates.

3.2 Methods

3.2.1 Demographic Data

Patients undergoing genetic testing and counselling at the HCP between October 2014 and August 2017 who met criteria for index testing and were ≥ age 18 were included as part of the study cohort. Demographic data for patients was obtained through the BC Cancer and HCP electronic databases and by additional chart review if required. Patient age was defined as age at first cancer diagnosis. Ethnicity was defined as the self-reported patient's "self-expressed racial identity" as indicated using a patient ethnicity questionnaire [174]. Specific self-expressed racial identity populations were categorized using the broad identifiers European, Asian (East Asian, South Asian, Southeast Asian) Latin American, African Canadian, Middle Eastern, Pacific Islander, Indigenous, and Ashkenazi Jewish. If a patient self-expressed more than one racial identity they were placed into a mixed category.

3.2.2 Genetic Testing

The exonic and limited flanking intronic sequences of the 14 or 17 genes was determined from peripheral blood derived gDNA supplied by CGL. Identified variants were submitted by report to the Cancer Genetics and Genomics Laboratory (CGL). Variants submitted to CGL were interpreted according to ACMG guidelines and annotated using HGVS nomenclature. Pursuant to HGVS convention, cDNA nucleotide numbering begins at the A of the initiating codon (ATG). The sequence of any pathogenic or likely pathogenic variant was confirmed by Sanger sequencing. This test was developed and its performance characteristics determined by the Centre for Clinical Genomics (CCG) and further validated at the BC Cancer (BCCA) CGL.

Pathogenic or likely pathogenic variants were confirmed by determining the gene sequence from peripheral blood derived gDNA via standard dideoxy sequencing using gene specific intronic PCR amplification and sequencing primers. Analysis was performed using an AB1 3730 DNA analyzer and associated analysis software (Applied Biosystems). This test was developed and its performance characteristics determined by the CGL at the BCCA.

The presence or absence of copy number differences in *BRCA1* and *BRCA2* genes or portions thereof was determined by multiplex Ligation-dependent Probe Amplification (MLPA) according to the manufacturer's protocol. Analysis of the resulting amplification products was performed using an ABI 3730 DNA analyzer and associated analysis software. Large scale insertions and deletions which lie outside the regions assessed by the individual MLPA probes are not detectable by this method. Genetic variants lying within individual probe binding sites may lead to false positive MLPA results. Single exon deletions are independently confirmed.

Genetic testing results were provided by the CCG and cross-validated with patient results from the internal HCP database. If data discrepancies between the laboratory and HCP database

were identified, further review of individual genetic test reports were performed. A minority of patients consented to further private-pay testing for expanded gene panel testing, and the PV and VUS results from additional testing were included in the PV and VUS detection rates.

3.2.3 Statistical Analysis

Descriptive statistics were used for all continuous and categorical variables. I performed multiple Chi-square tests while using the Holm-correction to account for multiple comparisons in order to compare population proportions. I also conducted a subset analysis of the HBOC specific referral criteria using multiple Chi-square tests. Fisher's exact test was used to compare the pathogenic variant detection rates for each HBOC referral criteria against a pre-specified guideline variant detection rate. I used a logistic regression analysis to identify demographic predictors for pathogenic variant and VUS status. In the logistic regression analysis potential confounding demographic factors I took into account included patient age, sex, ethnicity, cancer diagnosis, and referral reason. For the Asian subset analysis I used the two original logistic regression models but expanded Asian Ethnicity into East Asian, South Asian, Southeast Asian, and Mixed/Other Asian ethnicity. All statistics were performed in R version 3.5.1 using base packages.

3.3 Results

3.3.1 Genetic Testing Detection Rates

The majority of the 2,051 patients who received index testing at the HCP from September 2014 to August 2017 were female (n = 1936; 94.39%) with a minority being male (n = 115; 5.61%). The overall pathogenic variant (PV) detection rate in this cohort of patients was 15.21% (n = 312). Male patients had a 27.83% (n = 32) PV detection rate that was significantly higher than the 14.46% (n = 280) PV detection rate in females ($p < 0.001$). However, there was no

difference in VUS rates between males (41.74%, *n* = 48) and females (31.87%, *n* = 617) (Table 3.1).

Table 3.1. Patient demographics receiving genetic testing and counselling at the BC HCP

Patient Demographics	Total Population	UNINF	VUS	PV
Patient Age at First Cancer Diagnosis – years (SD)	52.0 (13.5)	53.4 (13.4)	49.9 (13.7)	49.6 (12.7)
Sex – N (%)				
Female	1936 (94.39%)	1131 (58.42%)	617 (31.87%)	280 (14.46%)
Male	115 (5.61%)	48 (41.74%)	48 (41.74%)	32 (27.83%)
Ethnicity – N (%)				
European	1418 (69.14%)	892 (66.87%)	387 (27.29%)	188 (13.26%)
Asian	359 (17.50%)	146 (41.95%)	172 (47.78%)	78 (21.67%)
Middle Eastern	36 (1.76%)	19 (59.38%)	13 (36.11%)	8 (22.22%)
Pacific Islander	5 (0.24%)	1 (33.33%)	2 (50.00%)	1 (25.00%)
African Canadian	8 (0.39%)	3 (42.86%)	5 (62.50%)	1 (12.50%)
Indigenous	4 (0.20%)	0 (0)	3 (75.00%)	2 (50.00%)
Ashkenazi Jewish	36 (1.76%)	17 (48.57%)	12 (33.33%)	10 (27.78%)
Latin American	18 (0.88%)	5 (29.41%)	13 (72.22%)	3 (16.67%)
Mixed	66 (3.22%)	34 (55.74%)	28 (42.42%)	9 (13.63%)
No Patient Ethnicity Data	101 (4.92%)	62 (65.26%)	30 (29.70%)	12 (11.88%)
Cancer Diagnosis – N (%)				
Breast	1019 (49.68%)	604 (59.27%)	330 (32.38%)	126 (12.37%)
Ovarian	438 (21.36%)	276 (63.01%)	121 (27.63%)	58 (13.24%)
Fallopian Tube	29 (1.41%)	19 (65.52%)	9 (31.03%)	2 (6.70%)
Uterine	52 (2.54%)	18 (34.62%)	25 (48.08%)	14 (26.92%)
Colorectal	74 (3.61%)	28 (37.84%)	30 (40.54%)	25 (33.78%)
Colon Polyposis	29 (1.41%)	15 (51.72%)	12 (41.38%)	4 (13.79%)
Pancreatic	7 (0.34%)	3 (42.86%)	4 (57.14%)	1 (14.29%)
Prostate	8 (0.39%)	6 (75.00%)	1 (12.5%)	1 (12.5%)
Other	31 (1.51%)	16 (51.61%)	13 (41.94%	4 (12.90%)
Multiple Cancers	340 (16.58%)	185 (54.41%)	107 (31.47%)	71 (20.88%)
Unknown	5 (0.24%)	1 (20.00%)	4 (80.00%)	1 (20.00%)
No Cancer	6 (0.29%)	3 (50.00%)	2 (33.33%)	2 (33.33%)

Monoallelic *MUTYH* PV and the *APC* c.3920T>A, (p.Ile1307Lys) PV were included in the PV detection rate. In total, 2.14% (*n* = 44) of patient's were diagnosed with a monoallelic *MUTYH* PV. In this cohort two common European founder mutations in *MUTYH* c.536A>G, (p.Tyr179Cys) (*n* = 8; 18.18%) and c.1187G>A, (p.Gly396Asp) (*n* = 15; 34.09%) accounted for the majority of monoallelic *MUTYH* PV identified. Another 13 (29.55%) patients harbored the East Asian ethnicity founder mutation *MUTYH* c.(934-2A>G). Four patients (0.04%) were identified with an *APC* c.3920T>A PV, the majority (3 out of 4) of these individuals were of Ashkenazi Jewish ethnicity. Excluding the low penetrance monoallelic *MUTYH* PV, and the *APC* c.3920T>A PV, the total number of PV was 263, representing a 12.82% PV detection rate.

3.3.2 Patient Ethnicity

Among 2,051 index patients undergoing broad panel genetic testing at the HCP, 69.14% (*n* = 1418) self-expressed their racial identity as European. Asian ethnicity was the second most commonly self-reported racial identity with 17.50% of patients (*n* = 359). Among all patients, 4.92% (*n* = 101) had no reported ethnicity data available, and 3.22% (*n* = 66) self-expressed multiple racial identities.

Patients of Indigenous (*n* = 4; 0.20%), African Canadian (*n* = 8; 0.39%), Pacific Islander (*n* = 5; 0.24%), Latin American (*n* = 18; 0.88%), and Asian (*n* = 359; 17.50%) ethnicity were all under-represented at the HCP when compared with the BC population from the 2016 BC Census (5.42%; 1.07%; 0.74%; 1.70%; 21.69% respectively) (all $p < 0.001$). In comparison, the proportion of patients attending the HCP of European (*n* = 1418; 69.14%) and Middle Eastern (*n* = 36; 1.76%) ethnicity were not significantly different from the population of BC (67.29%; 1.78% respectively) ($p = 0.076$; $p = 0.997$ respectively). Further, patients of Ashkenazi Jewish (*n*

= 36; 1.76%) ethnicity were significantly over-represented at the HCP compared to the BC population (0.31%) ($p < 0.001$) (Table 3.1).

The proportion of detected VUS among patients of Asian ($n = 172$; 47.78%) and Latin American ($n = 13$; 72.22%) ethnicity were significantly higher than the VUS rates of patients of European ethnicity ($n = 387$; 27.29%) ($p < 0.001$; $p = 0.018$ respectively). Further, the proportion of PV in patients of Asian ethnicity ($n = 78$; 21.67%) were significantly higher than patients of European ethnicity ($n = 187$; 13.9%) ($p = 0.026$). All other ethnicities had similar VUS and PV detection rates.

To further explore the difference in PV and VUS rates between patients of European and Asian ethnicity, I examined HBOC referral criteria and cancer diagnosis patterns between patients of European and Asian ethnicity. The proportion of patients diagnosed with breast and ovarian cancer were similar: breast cancer, $n = 847$; 59.73% vs $n = 216$; 60.00% and ovarian cancer, $n = 410$; 28.91% vs $n = 109$; 30.28% for those with European and Asian ethnicity, respectively. However, patients of Asian ethnicity ($n = 203$; 64.24%) were significantly more likely than patients of European ethnicity ($n = 531$; 42.93%) to be referred for an HBOC referral criteria related to a primarily personal diagnosis of cancer ($p < 0.001$). In comparison, patients of European ethnicity ($n = 505$; 40.66%) were significantly more likely than patients of Asian ethnicity ($n = 82$; 25.95%) to be referred for a HBOC referral criteria primarily related to a familial pattern of cancer diagnoses ($p < 0.001$).

3.3.2.1 Asian Ethnicity Subset Analysis

Demographics for Asian ethnicity subgroups can be seen in Table 3.2. The proportion of PV among patients that self-expressed East Asian ($n = 48$; 22.97%), and South Asian ($n = 17$; 22.67%) ethnicity was significantly higher than the proportion of PV among patients of

European ethnicity (n = 188; 13.26%) ($p < 0.001$ and $p = 0.037$ respectively). There was no significant difference in PV detection rates between patients of Southeast Asian (n = 9; 15.00%) and European ethnicity. The proportion of detected VUS among patients of self-expressed East Asian (n = 102; 48.80%), South Asian (n = 29; 38.67%), and Southeast Asian (n = 31; 51.67%) ethnicity were all significantly higher than the proportion of detected VUS in patients of European ethnicity (n = 387; 27.29%) ($p < 0.001$; $p = 0.035$; $p < 0.001$ respectively).

Table 3.2. Patient demographics for Asian ethnicity subset analysis

Asian Ethnicity Subset Demographics	Total Population	UNINF	VUS	PV
Ethnicity – N (%)				
East Asian	209 (58.22%)	80 (39.41%)	102 (48.80%)	48 (22.96%)
South Asian	75 (20.89%)	34 (47.89%)	29 (38.67%)	17 (22.67%)
Southeast Asian	60 (16.71%)	27 (46.55%)	31 (51.67%)	9 (15.00%)
Mixed/Other Asian	15 (4.18%)	4 (26.67%)	10 (66.67%)	14 (26.67%)

3.3.3 Patient Reason for Referral

Patients who received genetic testing for Lynch Syndrome (n = 51; 28.33%) were significantly more likely to be diagnosed with a PV than patients referred for HBOC (n = 224; 13.01%) ($p < 0.001$). All patients tested had similar VUS detection rates regardless of the indication for referral. Out of the total 311 patients with a PV, 69 (22.19%) patients were diagnosed with a secondary finding that would not have been identified if the patient had only received single gene testing. Excluding monoallelic *MUTYH* PV, out of the total 267 patients with a PV, 28 (10.19%) patients were diagnosed with a secondary finding.

The most common HBOC testing criterion met by patients at the HCP was "isolated history of non-mucinous ovarian cancer" (n = 371; 21.13%). The second most common testing criterion was "3 or more cases of breast cancer in close relatives with one under 50" (n = 307; 17.48%) (Table 4.3).

Notably, 11 (44%) out of the 25 PV diagnoses for the HBOC referral criteria "3 or more cases of breast cancer in close relatives with one under 50" were from a low penetrant monoallelic *MUTYH* variant. Similarly, 5 (62.5%) out of the 8 PV diagnoses for the referral criteria of "isolated history of invasive breast cancer < 35" were from low penetrant monoallelic *MUTYH* variants. These two HBOC referral criteria had the highest proportion of monoallelic *MUTYH* PV. (Table 4.3).

Table 3.3. Patient referral criteria that recieved genetic testing and counselling at the BC HCP

Patient Referral Criteria	Total Population - N (%)	UNINF – N (%)	VUS - N (%)	PV – N (%)	Monoallelic *MUTYH* PV – N (%)
Hereditary Cancer Referral Syndrome					
HBOC	1722 (83.96%)	1038 (60.28%)	528 (30.66%)	222 (12.89%)	40 (2.32%)
Lynch Syndrome	180 (8.78%)	73 (40.56%)	180 (38.89%)	56 (31.11%)	2 (1.11%)
HDGC	5 (0.24%)	4 (80.00%)	1 (20.00%)	0 (0%)	0 (0%)
FAP or MAP	42 (2.05%)	18 (42.86%)	19 (45.24%)	8 (19.05%)	1 (2.38%)
Cowden Syndrome	4 (0.2%)	3 (75.00)	1 (25.00%)	1 (25.00%)	0 (0%)
PJS	1 (0.05%)	0 (0)	1 (100%)	0 (0%)	0 (0%)
Li-Fraumeni Syndrome	12 (0.59%)	6 (50.00%)	6 (50.00%)	2 (16.67%)	0 (0%)
Familial Pancreatic Cancer	3 (0.15%)	1 (33.33%)	2 (66.67%)	1 (33.33%)	1 (33.33%)
Carrier Testing	7 (0.34%)	4 (57.14%)	3 (42.86%)	2 (28.57%)	0 (0%)
Other Hereditary Cancer Syndrome	5 (0.24%)	1 (20.00%)	3 (60.00%)	1 (20.00%)	0 (0%)
Multiple Syndromes	70 (3.41%)	31 (44.29%)	31 (44.23%)	18 (25.71%)	0 (0%)
HBOC Referral Criteria					
One breast and one ovarian in close relatives	202 (11.50%)	132 (65.35%)	57 (28.22%)	17 (8.42%)	1 (0.50%)
3 or more cases of breast cancer in close relatives with one under 50	307 (17.48%)	190 (61.89%)	96 (31.27%)	25 (8.14%)	11 (3.58%)
More than 1 primary breast cancer with the first under 50	78 (4.44%)	48 (61.54%)	26 (33.33%)	8 (10.26%)	0 (0%)
Only two cases of breast cancer in close relatives both under 50	87 (4.95%)	50 (57.47%)	34 (39.08%)	7 (8.05%)	2 (2.30%)
Carrier testing	1 (0.06%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)
Primary breast and ovarian cancer in the same person	44 (2.51%)	20 (45.45%)	15 (34.09%)	11 (25.00%)	1 (2.27%)
Other	21 (1.20%)	15 (71.43%)	5 (23.81%)	1 (4.76%)	0 (0%)
Personal history of triple negative breast cancer diagnosed under 60	208 (11.85%)	128 (61.54%)	60 (28.85%)	30 (14.42%)	8 (3.85%)
Isolated history of invasive breast cancer under 35	91 (5.18%)	47 (51.65%)	38 (41.76%)	8 (8.79%)	5 (5.49%)
Ashkenazi Jewish and diagnosis of breast and/or ovarian cancer	10 (0.57%)	5 (50.00%)	2 (20.00%)	2 (20.00%)	0 (0%)
Approved at clinic lab	28 (1.59%)	15 (53.57%)	11 (39.29%)	3 (10.71%)	1 (3.57%)
Isolated history of non-mucinous ovarian cancer	371 (21.13%)	228 (61.46%)	107 (28.84%)	54 (14.56%)	7 (1.89%)
One male breast cancer and one breast or ovarian cancer in close relative	21 (1.20%)	11 (52.38%)	5 (23.81%)	5 (23.81%)	0 (0%)
2 or more cases of ovarian cancer in close relatives	28 (1.59%)	16 (57.14%)	9 (32.14%)	5 (17.86%)	1 (3.57%)
Adopted and breast cancer under 50	1 (0.06%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)
Multiple Criteria Met	258 (14.69%)	146 (56.59%)	75 (29.07%)	55 (21.32%)	3 (1.16%)

3.3.4 Logistic Regressions

Both Ashkenazi Jewish ethnicity ($p = 0.021$; OR=2.48) and Asian ethnicity ($p < 0.001$; OR = 1.83) were significant predictors of more likely being diagnosed with a PV than European ethnicity. As well, younger patients were significantly more likely to be diagnosed with a PV ($p = 0.001$). Patients who received genetic testing for Lynch Syndrome ($p = 0.003$; OR = 2.39) and multiple hereditary cancer syndromes ($p = 0.023$; OR = 2.03) were both significantly more likely to be diagnosed with a PV than patients referred for HBOC (Figure 3.1).

Similar to the PV results, Asian ethnicity ($p < 0.001$; OR = 2.37) was again a significant predictor of being more likely to harbor a VUS than European ethnicity. The ethnicities of African Canadian ($p = 0.044$; OR = 4.42) and Latin American ($p < 0.001$; OR = 8.27) were also both significant predictors of identifying a VUS. As well, patients of a younger age were significantly more likely to be identified with a VUS ($p < 0.001$). Finally, patients referred for multiple hereditary cancer syndromes were significantly more likely to be identified with a VUS than patients referred for only HBOC ($p = 0.049$; OR = 1.69) (Figure 3.1).

3.3.4.1 Subset Asian Ethnicity Logistic Regression Analysis

Similar to the Fisher's exact tests, East Asian ($p < 0.001$; OR = 1.92) and South Asian ethnicity ($p = 0.017$; OR = 2.06) were significant predictors of being diagnosed with a PV. As well, East Asian ($p < 0.001$; OR = 2.36), South Asian ($p = 0.013$; OR = 1.86), and Southeast Asian ethnicity ($p < 0.001$; OR = 2.71) were significant predictors of being diagnosed with a VUS (Figure 3.2).

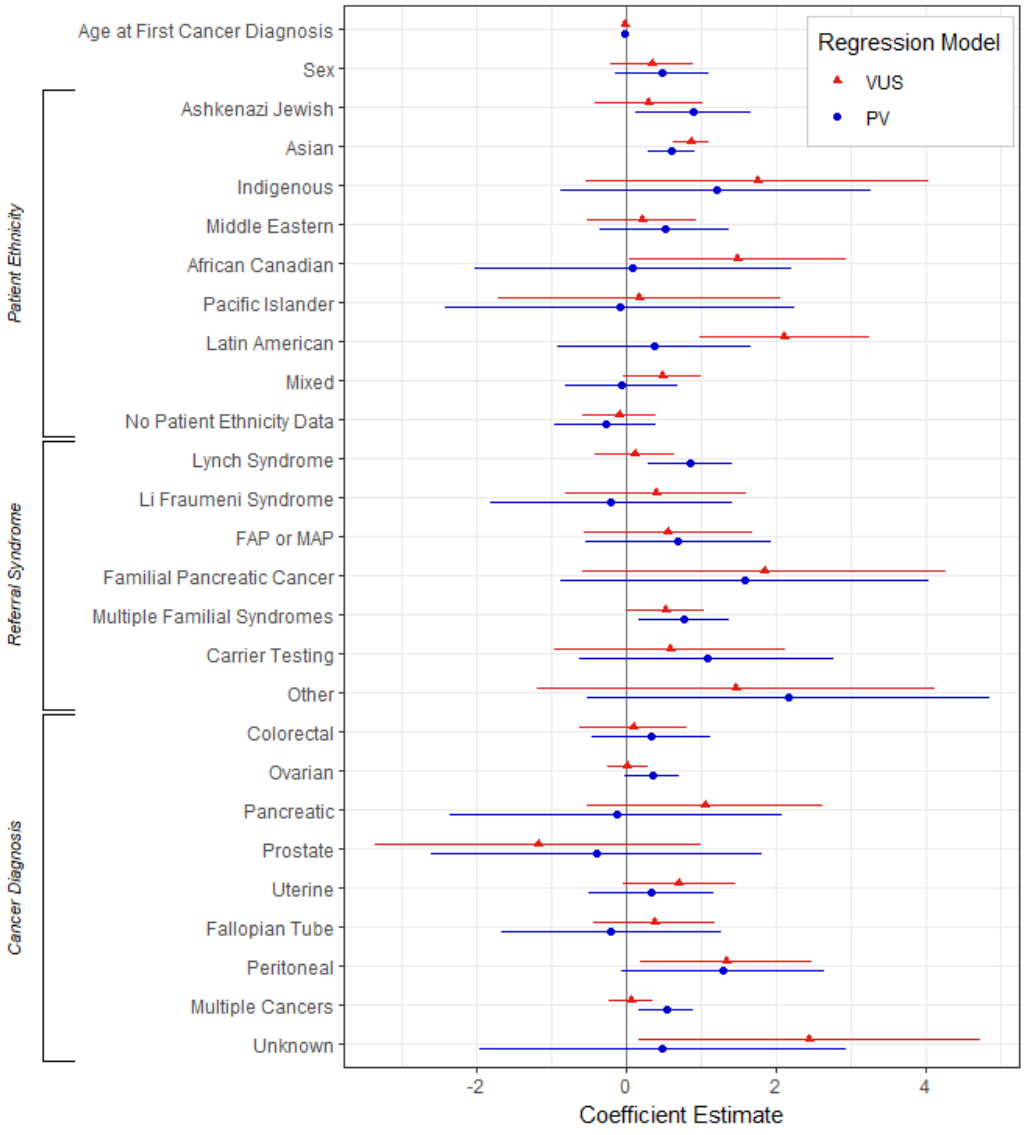

Figure 3.1. Forest plot of logistic regressions to predict PV or VUS status

The results from the two regression analyses are presented in this figure as a forest plot. For categorical variables the center line represents a baseline value that each level within the variable is compared against. Points on the right side of the center line indicate a higher MICRA score (negative psychological outcome) and points on the left indicate a lower MICRA score (positive psychological outcome). Baseline levels for each variable are, Genetic Testing Result: Uninformative, Patient Ethnicity: European, Cancer Diagnosis: No Cancer, Sex: Female, Referral Syndrome: HBOC. The dots represent the regression coefficient and the whiskers represent 95% confidence intervals. Cowden Syndrome, HDGC, and Colon polyposis levels were removed from the figure due to overly large error bars.

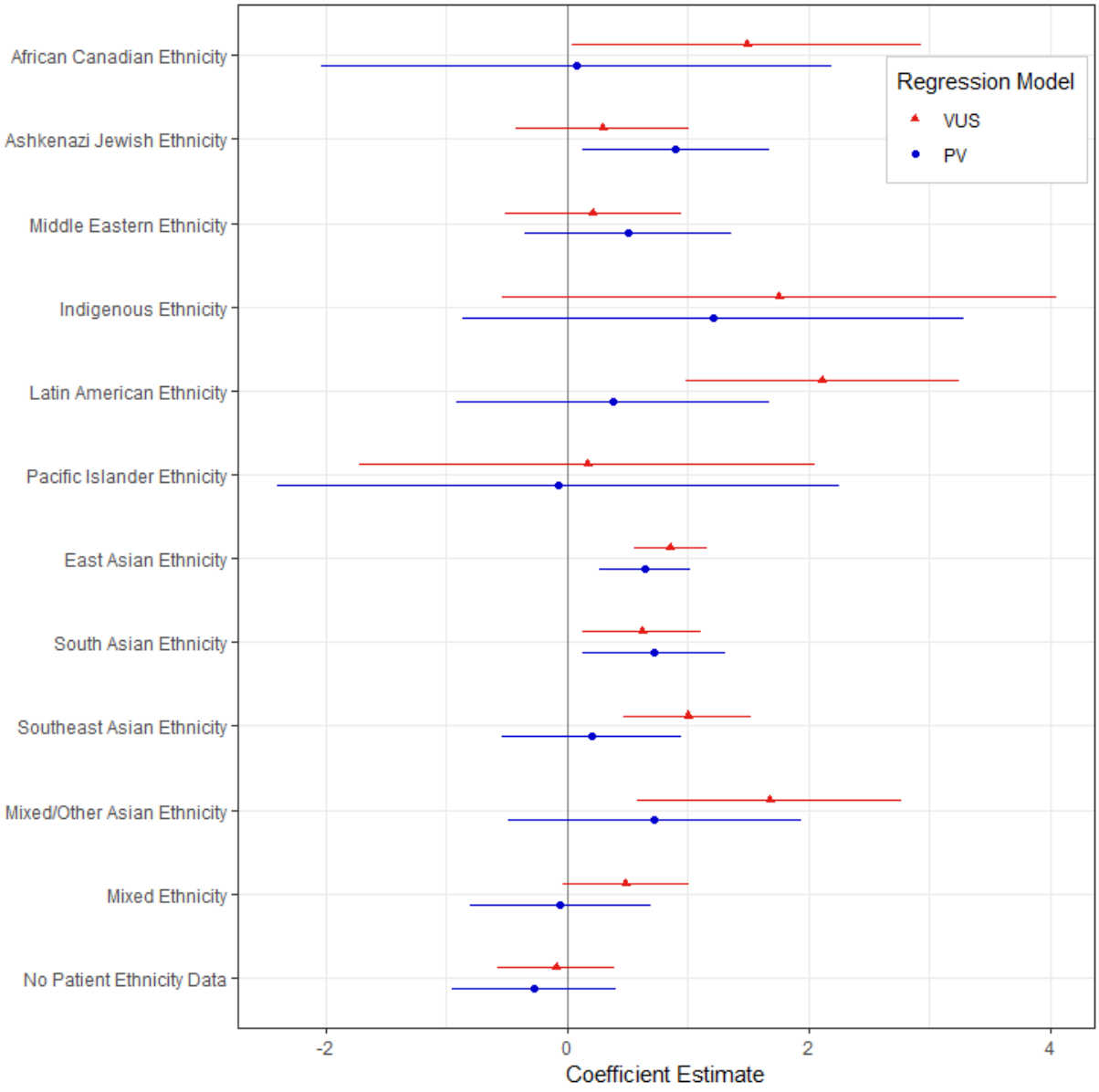

Figure 3.2. Forest plot of logistic regressions to predict PV or VUS status for Asian ethnicity subset analysis

Presented here is a forest plot of only patient ethnicity from the two regression analyses I performed for the subset analysis of Asian ethnicity. The center line represents a baseline value that each level within the variable is compared against. Points on the right side of the center line indicate a higher MICRA score (negative psychological outcome) and points on the left indicate a lower MICRA score (positive psychological outcome). Baseline level is European ethnicity. The dots represent the regression coefficient and the whiskers represent 95% confidence intervals.

3.4 Discussion

By characterizing the genetic testing results for the patient population attending the HCP, I have found differences in both the PV and VUS detection rates amongst patient ethnicity, patient age of first cancer diagnosis, hereditary cancer referral syndrome, and specific HBOC referral criteria.

The PV detection rate of 15.21% (*n* = 312) and the VUS detection rate of 32.42% (*n* = 665) amongst the 2,051 HCP patient cohort were similar to other studies utilizing multigene-panel tests [161, 175]. As variant detection programs have reported on more variants, VUS rates across the literature have begun to decline [161, 176]. Similarly, among our cohort, the VUS rates declined year over year since 2015. The decline in VUS rates can most likely be attributed to the BC Cancer Genetics and Genomics Laboratory's increased experience in classifying variants, the increase in the size of the BC CGL's variant database, and the increased availability of shared variant databases such as ClinVar and ENIGMA.

Increased VUS detection rates in ethnic minorities were commonly seen across studies [171, 177, 178]. Similarly, I found that patients of Asian and Latin American ethnicity have increased VUS detection rates compared to patients of European ethnicity. The difference in VUS detection rates is most likely due to a lack of information in public databases and research into the common genetic diversity present in individuals of non-European ethnicity [179]. The majority of genetics research significantly over represents participants of European ethnicity [105, 106]. This lack of research has led to health professionals being less able to provide medically actionable advice to patients of diverse ethnic backgrounds [179].

I observed that Asian ethnicity patients were also more likely to receive a PV. This difference in PV detection rates between Asian ethnicity and European ethnicity patients may be

due to differences between the specific HBOC referral criteria met by patients of each ethnicity. Patients of Asian ethnicity more often met criteria for only a significant personal cancer history and European ethnicity patients were more likely to meet criteria for a significant familial cancer history. Taking both of these results together, it may be that patients of Asian ethnicity in our cohort were more likely to only be referred for genetic testing when there was an extremely clear indication for hereditary cancer. This is supported by research in the USA that showed that African American women are less likely than White women to be referred for genetic testing and counselling, even when meeting similar criteria [110, 112]. Racial stereotypes and implicit racial biases from healthcare providers may heighten the bar for ethnic minority patients to receive a referral for genetic counselling services [98, 180]. These experiences may dissuade patients without a strong personal history of cancer from continuing to utilize any genetic counselling services that are offered [98]. As well, it is possible that cultural differences may have an impact on patient utilization of genetic testing services [97, 167]. Previous research has shown that cancer diagnoses were often under-reported within ethnic minority families [181]. Further, research examining health information communication amongst families has found that ethnic minority patients were more likely to have a more holistic understanding of family health history, rather than having precise physical records of health information [182]. These cultural differences can result in truncated family history information that can impact how genetic counsellors interpret a patient's hereditary cancer risk [181, 182]. It is important for genetic counsellors to realize this potential when assessing a patient for criteria met to receive genetic testing.

I also found that patients of Asian, Latin American, African Canadian, Pacific Islander, and Indigenous ethnic groups were underrepresented at the HCP when compared to the population frequencies present in BC. Similarly, the under representation of ethnic minorities has

been seen in many facets of healthcare including genetics research and clinical care [105, 107, 183]. Implicit biases from healthcare providers, patient mistrust, and cultural differences may all contribute to the under representation of ethnic minority patients [167, 184-186]. Further, research in the United States has shown that cultural racism, discrimination, and community segregation all contribute to reduced access to healthcare [98, 100, 187]. Although Canadian universal healthcare may increase the social equity of healthcare access, there are still many healthcare inequities seen in Canada [188-190]. As well, there is a notable lack of healthcare research in Canada that includes ethnic minority patients and examines health outcome inequities [188].

Among all HBOC patients seen in our cohort, patients referred for the criteria of "three or more family members with breast cancer with one under 50" were the least likely to be diagnosed with a high or moderate penetrance PV (n = 14; 4.53%). Among our patient cohort this was the worst performing criterion for detecting patients with a high/moderate penetrance PV. As well, the PV detection rate of 4.53% for this referral criterion was not statistically different from the 3.1% PV detection rate found in a study providing genetic testing to breast cancer patients unselected for family history [191]. This indicates that the "three or more family members with breast cancer with one under 50" criterion may not be a powerful predictor in identifying HBOC patients with a high or moderate penetrance PV. However, the inclusion of low penetrance PV such as monoallelic *MUTYH* increased the PV detection rate for this criterion substantially. Similarly, other studies investigating HBOC referral criteria have found that the criterion of multiple family members with breast cancer (two or more) has the poorest PV detection rate [192-194].

In contrast, both the HBOC referral criteria of "isolated diagnosis of non-mucinous ovarian cancer" and "one male relative with breast cancer and one female relative with ovarian

cancer" both had a PV detection rate significantly higher than 10%. This further confirms that all non-mucinous ovarian cancer patients should continue to be offered germline genetic testing. Based on projections by BC Cancer and known proportions of ovarian cancer subtypes, approximately 352 patients a year (29 per month) will be diagnosed with non-mucinous ovarian cancer in BC [195, 196]. Although more work is still required, it is encouraging that efforts to increase the referral rate for women in BC with non-mucinous ovarian cancer appear to be working as referral rates have increased over the 3 years of this study from 11 to 14 patients per month. As well, these results suggest that the HCP was correct to broaden referral criteria in 2019 to include all males with breast cancer. Many males with breast cancer who are identified to be *BRCA2* carriers have no other family history of breast or ovarian cancer [197, 198].

In this retrospective population-based study I found significant predictors of a patient's PV or VUS status included patient ethnicity, age at first cancer diagnosis, and a patient's reason for referral. As well, I found that multiple ethnic minority populations are under-represented at the HCP in BC for genetic testing and counselling. These results highlight the differences in HBOC referral criteria in identifying patients with high or moderate penetrance PV within the BC population. As well, these results show the clinical utility in utilizing multigene panel testing to identify PV in patients where single gene testing would have not been informative. Finally, these results highlight the need to increase engagement with patients that self-identify as an ethnic minority to identify barriers to access they face in genetic testing, counselling, and research. Future genetics studies will be necessary to increase the knowledge of common genetic variation in ethnic minority populations and future qualitative studies will be necessary to identify the reasons for low ethnic minority population referral rates to the HCP.

Chapter 4: Identifying Patient Populations Experiencing Negative Psychological Outcomes During Genetic Testing and Counselling

4.1 Introduction

Multigene panel testing for hereditary cancer patients allows for better coverage of overlapping cancer syndrome phenotypes and has increased the identification of germline pathogenic variants by over 40% [199]. This has allowed for increased treatment opportunities for patients and increased surveillance for their families [200].

Numerous studies have assessed patient reported outcome measures (PROM's) from patients receiving genetic testing, and those with a pathogenic variant (PV) are consistently identified with higher distress, anxiety, and uncertainty [64] immediately following testing. However, the majority of these studies have focused on single gene genetic testing, with fewer studies assessing multigene panels [201] . Further, few studies have examined PROM's from genetic testing in ethnically diverse populations [202, 203].

Ethnic minorities are often excluded from research which makes findings from ethnically homogenous studies non-generalizable [105]. The exclusion of ethnic minorities in research has been documented as a reason for some medications having unintentional side-affects or unexpected low efficacy when prescribed to ethnic minority patients [105]. Studies that do not included ethnically diverse populations within their study cohorts may miss important variation in patient responses. It is important for genetic testing and counselling services to assess the current treatment of ethnic minority patients to ensure that all patients regardless of age, sex, or ethnicity are receiving equal care and health outcomes.

The HCP is a population-based program serving British Columbia and the Yukon and has utilized the MICRA [157] Survey to measure patient distress, uncertainty, and positive/negative experiences from multigene panel testing since September 2015. I have assessed and analyzed patient MICRA scores with the hypothesis that there are identifiable differences in the scores between populations of patients at the HCP.

4.2 Methods

4.2.1 Patient Inclusion Criteria

Patients included in the analysis underwent index multigene panel testing or single gene carrier testing between September 2015 to November 2018, completed the MICRA survey, did not require an interpreter, and were ≥ 18. All patients were mailed or emailed the MICRA survey 4 weeks after the return of their genetic testing results. Patient demographic data was collected from the HCP clinical database and from the cancer registry database at BC Cancer.

A total of 1,671 patients were sent MICRA surveys and 917 patients completed them (response rate of 55.1%). Patients that received testing to confirm a PV detected in a solid tumor (n = 2), received testing to confirm a research finding (n = 1), and received testing to confirm a direct-to-consumer test finding (n = 1), were excluded. Finally, a (n = 1) survey was left out for being largely incomplete.

4.2.2 Genetic Testing

Patients' genetic test results were queried from the HCP clinical database and cross-validated with their genetic test results in the BC Cancer database. Patients genetic test results were separated by variant status (high penetrance PV, moderate penetrance PV, low penetrance PV, recessive PV, VUS, UNINF) and by whether a patient received index or carrier testing. Genetic test result demographic numbers were reported as the most serious test result. If a patient

was diagnosed with both a VUS and a high penetrance PV they were only counted as a high penetrance PV. Genetic testing pipeline can be seen in section 3.2.4. All patients received genetic testing using the 14-gene or 17-gene panel at the HCP. Some patients were offered additional expanded private-pay panel testing based on clinical presentation and provincial testing guidelines.

4.2.3 MICRA Survey

The MICRA survey is described in section 2.2.4.

4.2.4 Statistical Analysis

The internal consistency of the MICRA Survey's three subscales was assessed using Cronbach's α. All subscales did not meet assumptions for a linear regression. The Uncertainty subscale was cube root transformed and analyzed with a multiple linear regression. The Distress and Positive Experiences subscales were log transformed and analyzed with multiple censored regressions. The three regression analyses examined differences in MICRA subscales scores while adjusting for the demographic factors of age, sex, cancer diagnosis, referral reason, ethnicity and genetic test results.

I also conducted four subset analyses to specifically examine HBOC referral criteria, impact of secondary findings, patient insurance concerns, and Asian subpopulations. For the HBOC subset analysis I examined only HBOC patients and added HBOC referral reason as a variable to the regression model. For the secondary findings analyses I assigned either expected diagnosis or unexpected diagnosis for each patient based on their cancer presentation and the germline PV and added this variable into the original regression models. For the Asian subset analyses I used the three original regression models but expanded Asian Ethnicity into East Asian, South Asian, Southeast Asian, and Mixed/Other Asian ethnicity. Finally, for the insurance

concerns subset analysis the Genetic Non-Discrimination Act (GNDA) was passed in Canada in 2017 and I wanted to examine if the passing of the GNDA had an effect on patient insurance concerns. I used a single regression model with the same demographic factors as the original regression analyses and I used the MICRA question "Feeling concerned about how my test results will affect my insurance status" as the response variable. A *p*-value of 0.05 was used to determine significance. All analysis was completed in R version 3.5.1.

4.3 Results

4.3.1 Patient Demographics

The majority of patients were female (*n* = 544; 86.1%), of European ethnicity (*n* = 424; 67.1%), and had a single previous cancer diagnosis (*n* = 406:64.2%) (Table 4.1). Of the 912 patients in this study 237 (26.0%) were diagnosed with a high (*n* =175; 19.2%), moderate (*n* = 40; 4.4%), low (*n* = 21; 2.3%), or recessive penetrance PV (*n* = 1; 0.1%). A total of 112 (12.3%) patients were diagnosed with a VUS. Out of the 912 survey responses, 860 (94.3%) surveys had zero blanks, and 53 (5.7%) surveys had between one and three questions left blank.

HBOC (*n* = 414; 45.4%) was the most common referral reason for patients attending the HCP and carrier testing was the second most common referral reason (*n* = 280; 30.7%) (Table 4.2). Patients of European ethnicity represented the highest number of patients at the HCP (*n* = 618; 67.8%) and patients of Asian ethnicity were the second most common ethnicity (*n* = 74; 8.1%). Patients of East Asian (*n* = 42), Southeast Asian (*n* = 6), South Asian (*n* = 13), and other Asian (*n* = 13) ethnicity made up the 74 patients that self-expressed their ethnicity as Asian. Further, a large proportion of patients that attended the HCP self-expressed multiple ethnicities and were categorized as Mixed ethnicity (*n* = 151; 16.6%).

Table 4.1. Patient demographics and MICRA scores

Patient Demographics	Index N (%)	Carrier N (%)	MICRA – Total (SD)	MICRA – Distress (SD)	MICRA – Positive Experiences (SD)	MICRA – Uncertainty (SD)
Sex						
Female[a]	544 (86.1%)	198 (70.7%)	17.06 (13.58)	3.68 (5.51)	4.86 (5.21)	8.52 (7.45)
Male	88 (13.9%)	82 (29.3%)	15.69 (11.88)	2.61 (4.10)*	5.99 (5.49)*	7.09 (7.22)*
Ethnicity						
European[a]	424 (67.1%)	194 (69.3%)	16.39 (13.10)	3.31 (5.24)	5.12 (5.26)	7.96 (7.28)
Asian	57 (9.0%)	17 (6.1%)	22.39 (14.86)*	5.32 (6.19)*	5.38 (5.68)	11.69 (7.99)*
Middle Eastern	8 (1.3%)	2 (0.7%)	15.55 (11.60)	3.82 (5.04)	3.00 (3.90)	8.73 (7.02)
Pacific Islander	N/A	1 (0.4%)	15.00 (N/A)	7.00 (N/A)	0 (N/A)	8.00 (N/A)
African	1 (0.2%)	N/A	41.00 (N/A)	10.00 (N/A)	2.00 (N/A)	29.00 (N/A)*
Indigenous	3 (0.5%)	1 (0.4%)	15.75 (18.28)	3.00 (6.00)	7.00 (9.45)	5.75 (7.80)
Ashkenazi Jewish	11 (1.7%)	4 (1.4%)	12.13 (7.61)	1.53 (2.20)	3.40 (3.87)	7.20 (5.28)
Mixed	110 (17.4%)	41 (14.6%)	16.55 (12.85)	3.33 (5.06)	5.19 (5.40)	8.04 (7.23)
No Patient Ethnicity Data	18 (2.8%)	20 (7.1%)	14.29 (13.61)	3.45 (5.22)	4.32 (4.47)	6.53 (7.96)
Cancer Diagnoses						
No Diagnoses[a]	59 (9.3%)	201 (71.8%)	14.95 (13.07)	3.41 (5.14)	5.25 (5.51)	6.29 (6.50)
One Diagnosis	406 (64.2%)	66 (23.6%)	17.71 (13.41)*	3.69 (5.40)*	4.81 (5.07)	9.20 (7.76)*
Multiple Diagnoses	167 (26.4%)	13 (4.6%)	17.10 (13.08)*	3.04 (5.21)	5.8 (5.46)	8.58 (7.27)*
Genetic Test Result						
UNINF (Index Test)[a]	400 (63.3%)	N/A	13.86 (10.84)	2.06 (3.81)	4.08 (5.06)	7.72 (7.12)
High Penetrance PV (Index Test)[b]	74 (11.7%)	N/A	27.87 (15.61)*	8.09 (7.38)*	7.81 (3.82)*	11.98 (8.08)*
High Penetrance PV (Carrier Test)[b]	N/A	101 (36.1%)	27.79 (14.34)*	7.65 (6.80)*	9.28 (4.34)*	10.86 (7.48)*
Moderate Penetrance PV (Index Test)[c]	26 (4.1%)	N/A	22.41 (18.90)*	5.20 (7.38)*	8.32 (6.40)*	8.89 (9.46)
Moderate Penetrance PV (Carrier Test)[c]	N/A	14 (5.0%)	29.03 (10.91)*	7.50 (5.43)*	9.64 (3.43)*	11.88 (7.53)*
Low Penetrance PV (Index Test)[d]	20 (3.2%)	N/A	18.12 (11.92)	3.87 (5.03)	4.20 (3.53)	10.05 (7.61)
Low Penetrance PV (Carrier Test)[d]	N/A	1 (0.4%)	12.00 (N/A)	0.00 (N/A)	10.00 (N/A)	2.00 (N/A)
Recessive[e]	N/A	1 (0.4%)	7.00 (N/A)	1.00 (N/A)	6.00 (N/A)	0 (N/A)
VUS (Index Test)	112 (17.7%)	N/A	16.16 (11.99)	2.69 (4.27)	4.31 (5.28)	9.16 (7.82)
True Negative (Carrier Test)	N/A	163 (58.2%)	10.28 (8.13)	2.06 (3.29)	3.24 (4.85)	4.98 (5.34)

* Significantly (p=0.017) associated with a higher MICRA score than the baseline outcome
a. Baseline outcomes for each variable are the first outcome in their respective variable section
b. *APC*, *ATM* (c.7271T>G), *BRCA1*, *BRCA2*, *CDH1*, *CDKN2A*, *DICER1*, *FH*, *FLCN*, *MLH1*, *MSH2*, *MSH6*, *MUTYH* biallelic, *PALB2*, *PMS2*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *TP53*
c. *ATM*, *BRIP1*, *CHEK2*, *MITF*, *NBN*, *PTEN*, *RAD51C*, *RAD51D*
d. *APC* (c.3920T>A), *AXIN*, *CHEK2* (c.470TC), *MSH6* (c.3117C>G), *MUTYH* monoallelic
e. *FH* (c.1431_1433dupAAA). All scores are the averaged unadjusted raw MICRA scores.

Patient demographics and patient responses to the MICRA Survey for each demographic are presented in table 1. A high MICRA score represents a negative psychological response and a low MICRA score represents a positive psychological response. All scores are the averaged unadjusted raw MICRA scores.

Table 4.2. Patient referral criteria and genetic counselling modality

Patient Demographics	Index N (%)	Carrier N (%)	MICRA – Total (SD)	MICRA – Distress (SD)	MICRA – Positive Experiences (SD)	MICRA – Uncertainty (SD)
Reason for Referral						
HBOC[a]	414 (65.5%)	N/A	17.05 (13.26)	3.33 (5.36)	4.75 (5.11)	8.97 (7.50)
Lynch Syndrome	97 (15.3%)	N/A	17.21 (12.77)	3.27 (4.80)	5.12 (5.78)	8.82 (7.51)
FAP	14 (2.2%)	N/A	10.14 (11.61)	1.86 (5.19)	3.50 (3.92)	4.79 (4.59)
HDGC	3 (0.5%)	N/A	16.67 (11.59)	6.67 (8.33)	3.33 (4.16)	6.67 (0.58)
Li-Fraumeni Syndrome	4 (0.6%)	N/A	33.00 (21.77)	8.25 (8.66)	4.00 (2.94)	20.75 (13.50)
Familial Pancreatic	33 (5.2%)	N/A	17.18 (10.34)	2.41 (3.29)	6.26 (5.36)	8.50 (7.60)
Carrier Testing	N/A	280 (100%)	15.84 (12.62)	3.73 (4.94)	5.36 (5.46)	6.75 (6.57)
Other Inherited Cancer Syndromes	37 (5.9%)	N/A	15.19 (12.30)	2.91 (4.60)	5.37 (5.58)	6.90 (7.16)
Multiple Hereditary Cancer Syndromes	30 (4.7%)	N/A	21.78 (19.56)	5.45 (8.37)	5.96 (4.75)	10.38 (9.56)
Genetic Counselling Modality						
In-Person Session[a]	300 (48.86%)	149 (%)	17.10 (13.80)	3.70 (5.56)	4.87 (5.16)	8.53 (7.60)
Telephone Session	186 (30.29%)	73 (%)	16.00 (12.71)	2.96 (4.75)	5.20 (5.49)	7.83 (7.39)
Videoconference Session	117 (19.06%)	58 (%)	17.29 (12.99)	3.79 (5.38)	5.34 (5.23)	8.16 (6.96)
Group Session	11 (1.79%)	N/A	15.18 (9.27)	1.55 (2.50)	5.82 (6.40)	8.69)

a. Baseline outcomes for each variable are the first outcome in their respective variable section

Patient responses to the MICRA Survey for the factors of Patient Reason for Referral and Genetic Counselling Modality. A high MICRA score represents a negative psychological response and a low MICRA score represents a positive psychological response. All scores are the averaged unadjusted raw MICRA scores.

4.3.2 Internal Consistency

All three subscales displayed good internal consistency ($\alpha > 0.7$) with Cronbach's α = 0.85 for the Distress subscale, 0.78 for the Uncertainty subscale, and 0.72 for the Positive Experiences subscale.

4.3.3 Linear Regression

4.3.3.1 Uncertainty Subscale

Patients with a high penetrance ($\beta = 0.33$, $t = 4.69$, $p < 0.001$), and low penetrance ($\beta = 0.25$, $t = 1.99$, $p = 0.047$) PV from index testing, along with patients with a high penetrance ($\beta = 0.48$, $t = 5.11$, $p < 0.001$), and moderate penetrance ($\beta = 0.52$, $t = 3.21$, $p = 0.001$) variant from carrier testing were significantly more likely than patients with an UNINF genetic test result to score higher on the Uncertainty subscale. As well, patients with one cancer diagnosis ($\beta = 0.26$, $t = 4.36$, $p < 0.001$) and patients with multiple cancer diagnoses ($\beta = 0.25$, $t = 3.54$, $p < 0.001$) were significantly more likely than patients with zero cancer diagnoses to score higher on the Uncertainty subscale. As well, patients of Asian ($\beta = 0.23$, $t = 3.35$, $p < 0.001$) and African ethnicity ($\beta = 1.15$, $t = 2.07$, $p = 0.038$) were significantly more likely than patients of European ethnicity to score higher on the Uncertainty subscale. Further, patients that were referred for Li-Fraumeni Syndrome ($\beta = 0.74$, $t = 2.67$, $p = 0.008$) were significantly more likely to score higher on the Uncertainty subscale than patients referred for HBOC Syndrome. Patients that were male ($\beta = -0.12$, $t = -2.23$, $p = 0.026$) were significantly more likely than female patients to score lower on the Uncertainty subscale (Figure 4.1).

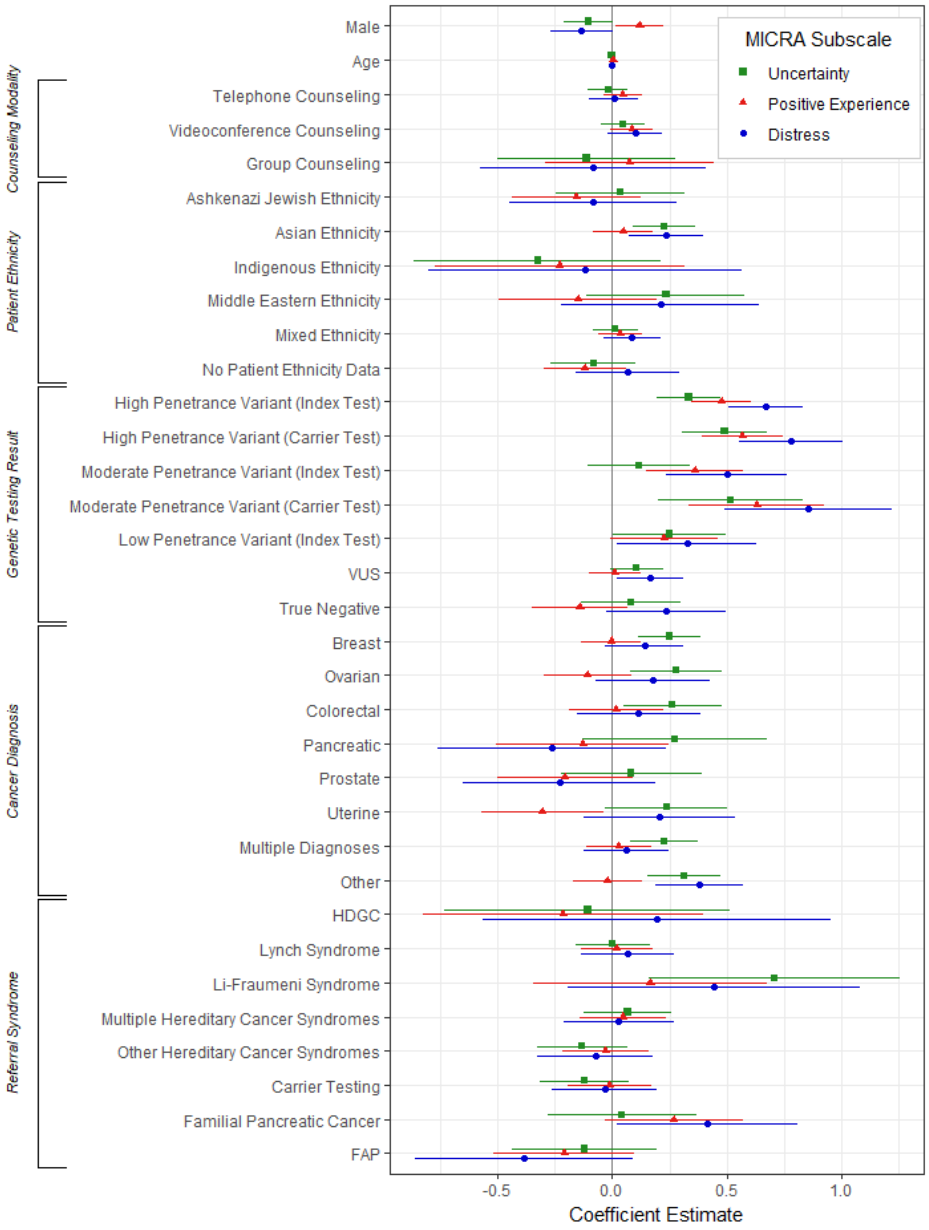

Figure 4.1. Forest plot of MICRA regression analysis

The results from the three regression analyses are presented in this figure as a forest plot. For categorical variables the center line represents a baseline value that each level within the variable is compared against. Points on the right side of the center line indicate a higher MICRA score (negative psychological outcome) and points on the left indicate a lower MICRA score (positive psychological outcome). Baseline levels for each variable are, Genetic Testing Result: Uninformative, Patient Ethnicity: European, Cancer Diagnosis: No Cancer, Sex: Female, Counselling Modality: In Person, Referral Syndrome: HBOC. The dots represent the regression coefficient and the whiskers represent 95% confidence intervals. Low penetrance variant (carrier test), recessive variant, African ethnicity, and Pacific Islander ethnicity levels were removed from the figure due to overly large error bars.

4.3.4 Censored Regressions

4.3.4.1 Distress Subscale

Patients with a high penetrance (β = 0.66, t = 7.81, p < 0.001), moderate penetrance (β = 0.50, t = 3.67, p < 0.001), and low penetrance (β = 0.33, t = 2.13, p = 0.033) variant from index testing were significantly associated with scoring higher on the Distress subscale than patients that received an UNINF result. As well, patients that received a high penetrance (β = 0.78, t = 6.80, p < 0.001) and moderate penetrance (β = 0.87, t = 4.57, p < 0.001) variant from carrier testing were significantly associated with scoring higher on the Distress subscale than patients that received an UNINF result. Further, patients that received a VUS (β = 0.16, t = 2.10, p = 0.036) from index testing were significantly associated with scoring higher on the Distress subscale than patients with an UNINF result. It is notable though that patients who received a VUS (β = -0.50, t = -5.02, p < 0.001) from index testing were significantly associated with a lower MICRA score when compared to patients that received a high penetrance variant. Patients referred for familial pancreatic cancer were significantly (β = 0.41, t = 2.05, p = 0.040) associated with scoring higher on the distress subscale than patients referred for HBOC. As well, patients of Asian ethnicity (β = 0.56, t = 2.48, p = 0.003) were significantly associated with scoring higher on the distress subscale than patients of European ethnicity. Further, increases in patient's age (β = -0.01, t = -3.23, p = 0.001) were significantly associated with a decrease in patient's Distress subscale score. Finally, male patients (β = -0.18, t = -2.67, p = 0.008) were significantly associated with scoring lower on the Distress subscale than female patients (Figure 4.1).

4.3.4.2 Positive Experiences Subscale

Similar to the previous two sub-scales, patients with a high penetrance (Index $\beta = 0.48$, $t = 7.20$, $p < 0.001$; Carrier $\beta = 0.57$, $t = 6.30$, $p < 0.001$) and moderate penetrance (Index $\beta = 0.36$, $t = 3.36$, $p < 0.001$; Carrier $\beta = 0.63$, $t = 4.18$, $p < 0.001$) variant from index or carrier testing scored significantly higher on the Positive Experiences subscale than patients that received an UNINF result. Separately from the previous subscales, patients previously diagnosed with uterine cancer ($\beta = 0.22$, $t = 1.98$, $p = 0.047$) scored significantly higher on the Positive Experiences subscale than patients not diagnosed with cancer. Finally, male patients ($\beta = 0.12$, $t = 2.22$, $p = 0.027$) scored significantly higher on the Positive Experience Subscale than female patients (Figure 4.1).

4.3.5 HBOC Subset Analysis

For all 3 sub-scales there were no significant associations between HBOC referral criteria and MICRA scores. To ensure that there were no differences amongst HBOC referral criteria I collapsed the referral criteria into a variable that included familial, personal, carrier, and other criteria. Patients referred for carrier testing scored significantly lower than patients referred for familial criteria on the total MICRA score ($\beta = -0.40$, $t = 2.42$, $p = 0.025$), and the Positive Experiences subscale ($\beta = -0.91$, $t = 3.24$, $p = 0.001$). As well, patients referred for mixed criteria ($\beta = -0.74$, $t = 2.25$, $p = 0.025$) were significantly more likely than patients referred for familial criteria to respond as having a “Positive Experience”.

4.3.6 PV Patient’s Subset Analysis

There was no significant difference between primary and secondary findings on any of the MICRA subscales after re-running all models.

4.3.7 Asian Ethnicity Subset Analysis

After re-running the previous regression models with the new ethnicity subpopulation categories there was once again no difference between patient ethnicities on the Positive Experience subscale. Only patients of South Asian ethnicity ($\beta = 0.49$, $t = 2.66$, $p = 0.008$) were significantly more likely than patients of European ethnicity to score higher on the Distress subscale. Finally, patients of East ($\beta = 0.20$, $t = 2.28$, $p = 0.023$), Southeast ($\beta = 0.60$, $t = 2.66$, $p = 0.008$), and South ($\beta = 0.36$, $t = 2.32$, $p = 0.021$) Asian ethnicity were all significantly more likely than patients of European ethnicity to score higher on the Uncertainty subscale. These results suggest that the majority of patients of Asian ethnicity experience increased uncertainty, and specifically patients of South Asian ethnicity experience increased distress when receiving genetic testing and counselling.

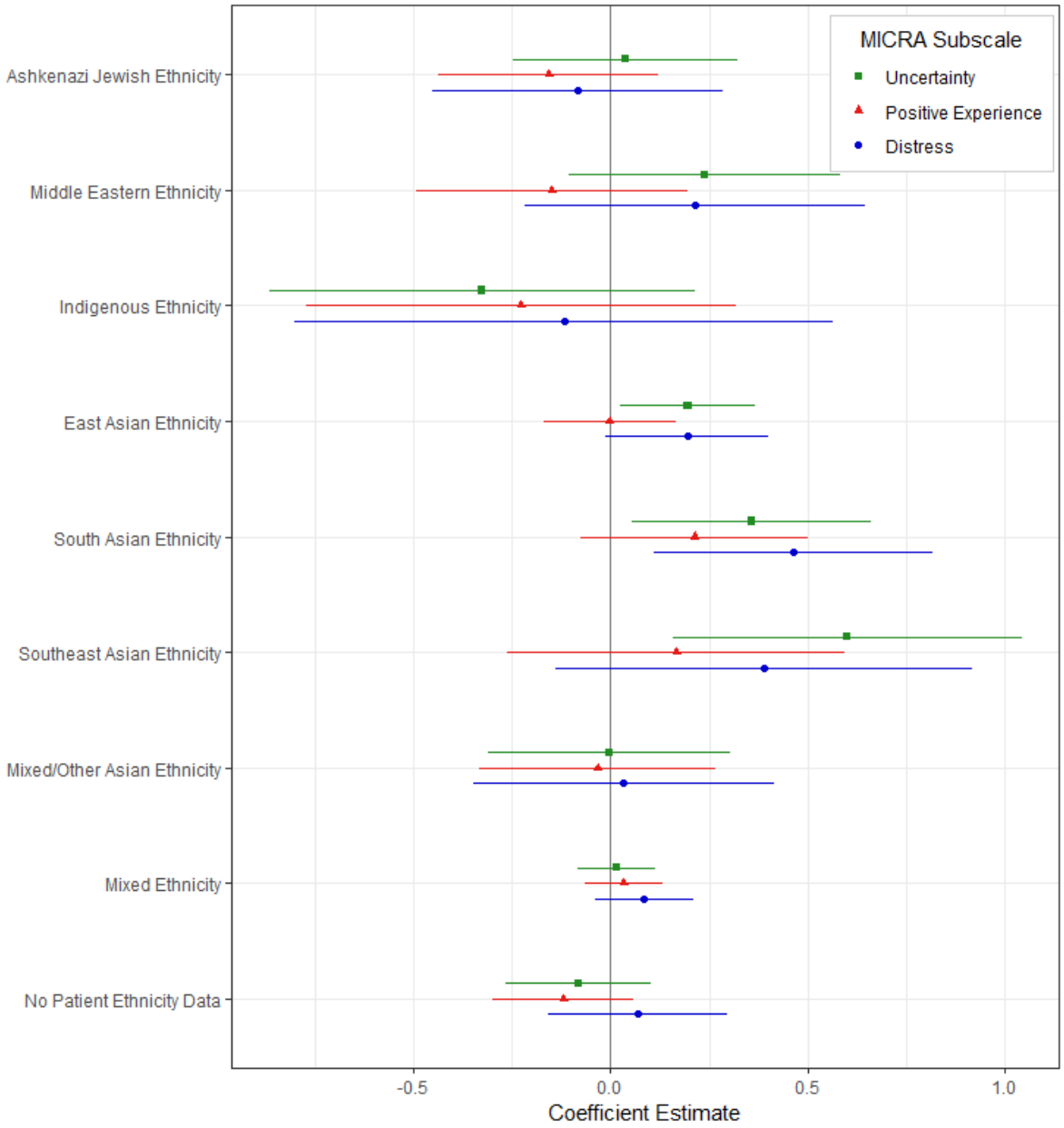

Figure 4.2. Forest plot of MICRA regression analysis for Asian ethnicity subset analysis

The results from the three regression analyses for the Asian ethnicity subset analysis are presented in this figure as a forest plot. The center line represents a baseline value that each level within the variable is compared against. Points on the right side of the center line indicate a higher MICRA score (negative psychological outcome) and points on the left indicate a lower MICRA score (positive psychological outcome). The baseline level is European ethnicity. The dots represent the regression coefficient and the whiskers represent 95% confidence intervals. African ethnicity, and Pacific Islander ethnicity levels were removed from the figure due to overly large error bars.

4.3.8 Patient Insurance Concerns

Patients that had their initial genetic counselling session before the passing of the GNDA trended towards scoring higher ($p = 0.087$) on the question "Feeling concerned about how my test results will affect my insurance status" than patients who attended genetic counselling after the passing of the GNDA.

4.4 Discussion

By assessing the MICRA scores of patients undergoing multigene panel testing in a population-based program, I have identified specific patient groups that are having a poorer experience from their genetic testing and counselling appointments. Factors with a negative influence on psychological outcomes included genetic test result, age, ethnicity, and sex.

Patients in this cohort diagnosed with a high or moderate penetrance PV experienced higher distress, uncertainty, and feelings of negative experiences. Previous work has also concluded that patients diagnosed with a high penetrance PV experience an increase in negative psychological outcomes shortly after their diagnosis [64, 163, 204]. However, research into low penetrance PVs has been limited. As well, results from the return of VUS show mixed psychological effects [204, 205]. From these findings, patients with either low penetrance PV or VUS trended towards scoring worse on one of the MICRA subscales. Research into larger sample sizes of patients diagnosed with a VUS or low penetrance PV will be needed to better elucidate the potential psychological impact of these results. As multigene panels continue to expand, more patients will be diagnosed with a low penetrance PV or VUS and these patients may need additional support for adverse psychological reactions.

With the use of multigene panel testing there are also concerns that receiving a secondary finding will lead to greater distress and uncertainty for patients [206]. I found no difference in

psychological outcomes between primary and secondary genetic test findings. This may indicate that genetic counsellors are managing patient uncertainty rising from a secondary finding, or that patients do not feel these secondary findings are concerning.

Encouragingly, the factor of genetic counselling modality (in-person, telephone, videoconference, or small group) had no significant influence on patient responses. This adds to previous research that has shown patients are receptive to new genetic counselling models [127, 131, 135, 140, 150]. Continued research into new genetic counselling models to improve patient access and reduce barriers to genetic counselling will be important as demand for genetic testing and counselling grows.

Patients of Asian ethnicity scored higher than those of European ethnicity on the distress and uncertainty subscale. Previous research using the MICRA Survey has suggested that patients from an ethnic minority population score higher on the MICRA uncertainty and positive experiences subscale, with those of African ethnicity scoring higher on the distress subscale [207, 208]. These disparities are not unique to the MICRA scale [208]. As well, from a subset analysis I also identified differences in patient responses between Asian ethnicity subregions. These findings mirror results from previous studies showing diversity amongst Asian ethnicity patients in cancer prevalence, and no-show rates for genetic counselling services [87, 209]. As well, research examining patient responses to genetic testing in ethnically diverse Asian ethnicity populations has demonstrated variations in patient attitudes and perceptions [210, 211]. A review from Gee et al. (2009) has noted that a major problem in health research on patients of Asian ethnicity is the lumping together of ethnically diverse patient populations into a single identifier [212].

Health disparities amongst ethnic minorities are well documented and have been reinforced by their historical underrepresentation in clinical genetics research [212, 213]. Patients of

Asian ethnicity specifically, are often underrepresented in clinical genetics research, even in the context of other ethnic minority populations [62, 202]. As well, historical experience with the healthcare system has led some patients within ethnic minority groups to be distrustful of the healthcare system which may influence patient experiences with genetic testing [214]. Further, underrepresentation of ethnic minority populations in research can make it difficult to assess psychological outcomes, since instruments such as the MICRA Survey were validated in a primarily ethnically European population [157].

It is important to increase community outreach towards ethnic minority communities to improve their representation in genetic testing and research, and to ensure that genetic counselling services are improving upon multiculturally competent practices. Important multiculturally competent practices that can continuously be improved include hiring ethnic minority staff, providing training to staff for increased cultural awareness, and incorporating culture-specific values into healthcare practices and promotion tools [215]. As well, it is important for healthcare professionals to continuously reflect upon and recognize their own historical, societal, and cultural experiences that may influence their interactions with patients or their interpretation of research findings [216].

In the past, the potential impact of genetic testing on insurance status has acted as a barrier for patients looking to access genetic testing [217]. The passing of the GNDA aimed to directly prevent insurers, or employers from accessing an individuals' genetic testing results in Canada. Therefore, it is encouraging that patients in our study who received genetic testing after the passing of the GNDA trended towards feeling less concerned about the impact of genetic testing on their insurance eligibility.

Overall, these results indicate that there are measurable psychological differences amongst the patient populations that receive genetic testing and counselling for multigene hereditary cancer panels. These psychological differences indicate that patient populations such as ethnic minority groups may benefit from increased community outreach, genetic counselor resources, and better delivery of multiculturally competent care. As the demand for genetic testing for both treatment and cancer-risk reduction utility rapidly increases so does the use of new models of genetic counselling. Analysis of quantifiable psychological outcomes in patient populations allows genetic counselling services to assess patient experiences and determine specific patient populations experiencing increased barriers to benefits of genetic counselling.

Chapter 5: Conclusion

5.1 Significance

An increasing number of patients are receiving genetic testing which has placed further stress on genetic counselling services. As genetic testing increases in popularity, it is important to assess the effectiveness of genetic counselling service delivery and identify barriers to receiving genetic testing and counselling. Throughout the three previous chapters of this thesis, I have sought to highlight three areas of importance for the genetic testing and counselling services at the BC HCP. First, to assess if new models of genetic testing and counselling improve patient wait times and are acceptable to patients. Second, to examine the patient demographics at the HCP to identify patient populations that are underrepresented and identify patient populations receiving differential genetic testing diagnoses. Third, to identify patient populations at the HCP that are experiencing increased psychological distress and uncertainty. By examining these three areas, I have shown that oncology clinic-based genetic testing and counselling is an effective model to reduce patient wait times, and that there are identifiable populations at the HCP that experience increased barriers to accessing genetic testing and counselling services.

In Chapter 2, I analyzed results from the new model of genetic testing and counselling at the HCP, oncology clinic-based genetic testing and counselling. As attendance at the HCP and other publicly funded hereditary cancer services have increased, it has become necessary to develop new or modified genetic counselling models to reduce wait times. I found that the oncology clinic-based genetic testing and counselling model significantly reduced patient wait times and was acceptable to patients. Reducing the significant barrier of patient wait times has important implications in patient care. Identifying patients and their family members with PV allows for increased cancer surveillance and earlier detection thereby leading to increased patient

survival. Decreasing patient wait times also improves patient utilization of genetic testing and counselling services and alleviates a major barrier to access [87].

Further to the benefits of decreased patient wait times, my analysis indicated that patients receiving oncology clinic-based genetic testing and counselling scored no differently on validated survey measures than patients that participated in the traditional genetic counselling model. These findings support previous work done in the field of genetic counselling indicating that patients are flexible in accepting different models of genetic testing and counselling. Furthermore, participating oncologists and genetic counsellors indicated that they believed the new model was acceptable and a good use of their time. My analysis has shown the clinical utility for implementing new genetic counselling models in general clinical practice to reduce patient barriers to genetic testing and counselling.

In Chapter 3, I examined the demographics of the HCP to determine if specific patient populations are underrepresented and if specific patient populations receive differential genetic testing results. My analysis has found that patients who attend the HCP are predominantly female and of European ethnicity and all ethnic minority patients are under-represented. Furthermore, patients of Asian ethnicity are more likely to be referred to the HCP for personal diagnoses of cancer rather than familial diagnoses of cancer. This may partially explain why my analysis found that patients of Asian ethnicity at the HCP have significantly higher PV detection rates than patients of European ethnicity. My analysis also showed that patients of Asian ethnicity have significantly more VUS diagnoses than patients of European ethnicity which can create ambiguity in patient's understanding of the implications of their genetic testing results. These findings indicate that ethnic minority populations face significant barriers when it comes

to accessing genetic testing and counselling and when it comes to receiving targeted health recommendations based on their genetic testing results.

To further investigate differences between patient populations attending the HCP, I assessed patient reported outcomes from patients receiving genetic testing and counselling using the MICRA survey. In Chapter 4, I found that patients who were diagnosed with both moderate and high penetrance PV experienced increased feelings of distress and uncertainty. Furthermore, I found that patients diagnosed with a low penetrance PV or a VUS trended towards feeling significantly more distressed. As multi-gene panels continue to become the standard for genetic testing, an increasing number of genes will be added to them. This will increase the chances of patients being diagnosed with a low penetrance PV or VUS and my findings suggest it will be important to monitor patient psychological responses to these findings in order to mitigate negative patient experiences.

More importantly, my analysis found that patients of Asian ethnicity indicated they were significantly more distressed and uncertain from genetic testing and counselling than patients of European ethnicity. Specifically, I found that East Asian patients felt more distressed, and East, South, and Southeast Asian patients felt more uncertain. These results further the extensive research into health disparities amongst ethnic minorities. Poorer psychological outcomes amongst ethnic minority patients may influence a patient's willingness to promote genetic testing within their family and friends and represents a further barrier to accessing genetic testing and counselling services. The results from analyses in Chapters 3 and 4 taken together indicate that being a member of ethnic minority population represents a major barrier to receiving genetic testing and counselling services. At the BC HCP, ethnic minority patients are less likely to

receive genetic testing, are more likely to receive a distressing test result, and are more likely to experience distress and uncertainty from their genetic testing and counselling experience.

5.2 Limitations

There are several limitations to the work I have shown here. In Chapter 2, the 30-40% response rate for surveys from patients and healthcare providers are lower than some previously reported studies. The lack of responses by patients may mean that my analysis does not capture the full spectrum of patient responses. Heterogeneity amongst the patient populations and variable genetic testing approaches may have also been confounding factors in my analysis of the new genetic counselling model.

In Chapter 2, interactions with a genetic counsellor were common to both counselling models. It is therefore unclear what impact genetic counsellors may have had on patient psychological outcomes. The results from my analysis may not be applicable if oncology clinic-based genetic counselling models are implemented without genetic counsellor-led results appointments in the future. Furthermore, patients in the oncology clinic-based genetic counselling model were provided a longer results appointment with a genetic counsellor. It is therefore uncertain if longer results appointments will always be necessary for patients that receive oncology clinic-based genetic testing and counselling. Due to small sample sizes in Chapter 2 and due to data recording and collection limitations in Chapter 4, I was unable to group patients by their genetic counsellor. It is unclear what affect if any, specific genetic counsellors may have had on patient outcomes.

In both Chapters 2 and 4, I analyzed PROM data. The DCS, MICRA, and GCOS surveys were all validated in patient populations that were primarily female, and of European ethnic origin. Because of this, these surveys may not accurately reflect male patients or patients of other

ethnicities. Furthermore, all three surveys were validated and provided to patients in English. Although patients that required an interpreter were excluded from my analyses, if English was a patient's second language the surveys may have not accurately captured their responses. Further, because patients that required an interpreter were excluded from my analyses this means that recent immigrants and older immigrants that have not learned English were completely excluded from my analyses.

Although I have analyzed numerous demographic factors in each of these three chapters, I was unable to collect socioeconomic status data for patients. Socioeconomic status has been shown to affect patient health outcomes, with reports in Canada suggesting as much as 50% of patient health outcomes can be explained by socioeconomic status [218]. Without socioeconomic data there may have been confounding factors that influenced my analyses.

Finally, a limitation in my analyses for both Chapters 3 and 4 is that I have only retrospectively analyzed quantitative data. Although my analyses show differences between patient populations for patient attendance rates, variant detection rates, and psychological outcomes, my analyses are unable to say why these differences occur. Therefore, my findings may be context dependent for patient populations and will need to be paired with qualitative patient studies in the future.

5.3 Future Directions

Moving forward, future research will be necessary to better understand new genetic testing and counselling models, and the barriers behind ethnic minority patients having poorer psychological outcomes and being under-represented at the HCP.

Efforts to further expand and evaluate the oncology clinic-based genetic testing and counselling model are underway, with recent expansion to include additional oncologists, nurses,

nurse practitioners, and general practitioners with oncology expertise. Future directions include implementing surveys online, implementing pre- and post-genetic counselling surveys as part of clinical care to measure patient empowerment, and to evaluate patient reported outcome measures and clinician acceptability when introducing new models. Future directions will also increase testing to include hereditary cancer syndromes other than HBOC.

Secondly, new models of genetic counselling will need to be investigated to further improve access and reduce barriers to service for all patients, especially ethnic minority patients. Initiatives such as Babylon telehealth links doctors to patients in remote communities [219]. Initiatives such as telehealth and others could be paired with oncology clinic-based genetic testing and counselling to improve geographic access for genetic testing and counselling. Initiatives such as these may particularly benefit Indigenous communities that are often located far from genetic testing and counselling services.

Thirdly, it will be necessary to determine the reason for the under representation of ethnic minorities at the HCP. Future research will need to determine at what stage of the genetic testing referral process ethnic minority patients are facing the greatest barriers. It will need to be determined if ethnic minority patients are not coming forward to primary care physicians to be evaluated for referral to genetics services, are not receiving referrals to the HCP, are not attending HCP sessions, or face barriers to access at all three stages.

The HCP is continuing to assess patient responses to genetic testing and counselling through assessment of the MICRA survey and will also begin routinely assessing patient empowerment through use of the GOS survey [220]. Being able to utilize results from multiple patient surveys will be important to better investigate and understand differences in patient psychological outcomes. Furthermore, future qualitative studies will be necessary to determine

the specific reasons for ethnic minority patients scoring lower on the MICRA scale. Only through prospective patient interviews can the quantitative survey data I have analyzed be fully placed in context and used to directly improve genetic counselling models.

Finally, it will be important moving forward for the HCP to further assess and interrogate their policies regarding cultural competency and to incorporate cultural competency into new genetic counselling models. Discrimination in healthcare is often not an active form of discrimination but rather an implicit bias found in multiple aspects of the healthcare system. In many instances, cultural competency alone may not be adequate in addressing healthcare disparities amongst patients. As health policy continues to evolve in BC, services such as the HCP may benefit from investigating the utility of putting in place cultural safety policies along with cultural competency policies [221].

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