UNIVERSAL TUMOR SCREENING FOR LYNCH SYNDROME: PATIENT PERSPECTIVES AND PREFERRED MODEL OF CONSENT.

by

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ABSTRACT

Lynch Syndrome (LS) is associated with an increased risk of colorectal (CRC) and other cancers. High risk individuals can be detected by testing all CRC tumors for findings such as microsatellite instability suggestive of LS, known as 'universal tumor screening'. Patient interest in screening and preferences for consent remain largely unknown. To explore the perspectives of CRC patients about universal tumor screening, a postal survey was administered to patients in NL diagnosed with CRC from 2014-2016 (n=698). Response rate was 47.6%. A large majority of patients (81.4 %) were willing to have their tumors tested if such a program were available in NL. Nearly all were willing to discuss their test result with family members and healthcare professionals, and the majority (62.6%) preferred informed consent be obtained prior to screening. While patients were supportive of tumor screening to identify LS, they expected some form of consent to be obtained, contrary to current practice across Canada. Findings can help guide the implementation of a universal tumor screening program in NL.

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AAPC	Attenuated Adenomatous Polyposis Coli
AC	Amsterdam Criteria
AJCC	American Joint Committee on Cancer
APC	Adenomatous Polyposis Coli
ATT	Attitude scale
CIHR	Canadian Institute of Health Research
COMM	Communication Scale
CRC	Colorectal Cancer
EGAPP	Evaluation of Genomic Applications in Practice and Prevention
EWG	Evaluation of Genomic Applications in Practice and Prevention – Working Group
EPCAM	epithelial cell adhesion molecule
FAP	Familial Adenomatous Polyposis
HNPCC	Hereditary non-polyposis colorectal cancer
HCP	Healthcare professional
IHC	Immunohistochemistry
ICG-HNPCC	The International Collaborative Group on HNPCC
LS	Lynch Syndrome
LSEW	Lynch Syndrome Educational Workshop
LSPAN	Lynch Syndrome Patient Advocacy Network
LSSN	The Lynch Syndrome Screening Network
MLH1	MutL homolog 1
MMR	Mismatch Repair

MSH2	MutS homolog 2
MSH6	MutS homolog 6
MSI	Microsatellite Instability
MSI-H	Microsatellite Instability-high
MSI-L	Microsatellite Instability-low
MSS	Microsatellite stable
NL	Newfoundland and Labrador
NCCN	National Comprehensive Cancer Network
NICE	National Institute of Health and Care Excellence
NCI-CCC	National Cancer Institute - Comprehensive Cancer Centers
NLCHI	Newfoundland and Labrador Center for Health Information
PCP	Primary care physician
PMS2	PMS1 homolog 2
USMSTF	United States Multi-Society Task Force

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CHAPTER 1

INTRODUCTION

This chapter begins with an overview of the epidemiology of colorectal cancer (CRC) and hereditary colorectal cancer syndromes. The history of Lynch syndrome (LS), its clinicopathological features and various screening criteria, including molecular screening methods, are then described. In the subsequent sections, universal tumor screening for LS, and a literature review of various aspects of universal screening including its implications, barriers, and stakeholder perspectives are described. The final section of the chapter describes the objectives of the study.

1.1 Epidemiology

Colorectal carcinoma (CRC) is the third most common malignancy in the world (Ferlay et al., 2015). In 2012, an estimated 1.4 million new CRC cases were diagnosed worldwide. It is the fourth most common cause of cancer-related death in the world. CRC, together with lung, prostate and breast cancer, accounts for

about half of all the cancer burden and is more common in areas with a high Human Development index (Bray, Jemal, Grey, Ferlay, & Forman, 2012).

In Canada, CRC is the second most common cancer, accounting for about 13% of all cancers (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2017). Roughly 29,000 new cases were projected for the year 2017. Although the mortality rates of CRC have decreased in Canada, it is still the second leading cause of cancer death among males and third most common cause of cancer death among females and accounts for about 12% of all cancer deaths (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2017). Newfoundland and Labrador (NL), has the highest incidence of CRC in the country. Canadian Cancer Statistics estimates roughly 620 new cases of CRC diagnosed in 2017 in NL (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2017). It was estimated that the average lifetime cost of managing CRC patients in Canada ranged from $20,319 per case in stage I colon cancer to $39,182 per case for stage III rectal carcinoma. The lifetime treatment cost in Canada for all patients was over $333 million in the year 2000 (Maroun et al., 2003).

The vast majority of CRCs are sporadic in nature, caused due to environmental and lifestyle factors. However, kindred and twin studies revealed that 20-30% of colorectal cancers have a potentially identifiable genetic or familial origin

(Lichtenstein et al., 2000; Wells & Wise, 2017). These conditions are collectively called Hereditary Cancer Syndromes. Lynch Syndrome is the most common familial cancer, accounting for 3-5% of all CRC cases. This project will focus on tumor testing in the context of Hereditary Non-Polyposis Colorectal Cancer (HNPCC), also known as Lynch syndrome (LS).

1.2. Hereditary cancer syndromes

Classically, the hereditary cancer syndromes are classified based on the presence and type of intestinal polyps. They vary in their penetrance (i.e., lifetime risk of developing CRC if one carries a mutation), histological features, risk of extracolonic malignancies and other extra intestinal features (Jasperson, Tuohy, Neklason, & Burt, 2010). Lynch Syndrome is a non-polyposis colon cancer syndrome. Other types include polyposis colon cancer syndrome and hamartomatous colon cancer syndromes. The important subtypes are briefly described below.

1.2.1 Polyposis Colon Cancer Syndromes (PCCS)

These syndromes are characterised by the development of adenomatous polyps along the gastrointestinal tract in varying numbers and site. Familial Adenomatous Polyposis (FAP), the second most common type of hereditary CRC, is an autosomal dominant genetic condition characterised by the development of hundreds of thousands of colonic polyps with a high rate of malignant transformation, normally in the second or third decade of life. The genetic basis lies in the mutation to the Adenomatous Polyposis Coli (APC) gene and the recommended management includes prophylactic total colectomy (Strate & Syngal, 2005). The variants of this condition include: Gardner syndrome, which features desmoid tumors, dental abnormalities, osteomas and soft tissue tumors; Turcot syndrome, characterised by additional central nervous system tumors such as astrocytoma; and Attenuated Adenomatous Polyposis Coli (AAPC) which is similar to FAP, but manifests as fewer (<100) intestinal polyps with later onset and lower risk of CRC (Strate & Syngal, 2005; Wells & Wise, 2017).

1.2.2 Hamartomatous Colon Cancer Syndromes

Hamartomatous polyposis syndromes are a group of uncommon conditions characterized by the development of intestinal hamartomas in childhood or in early adulthood. Peutz-Jeghers Syndrome, caused due to mutations in gene LKB1 (STK11), is characterized by hamartomatous polyps in the entire gastrointestinal tract and other extra intestinal features such as mucocutaneous pigmentation and cancers of the breast, pancreas, thyroid and cervix. Juvenile polyposis caused due to mutations in the PTEN gene, consists of congenital abnormalities, including cardiac, craniofacial and bowel rotations and has about 10-40% penetrance. Other less common types include Cowden syndrome, Ruvalcaba– Myhre–Smith syndrome and Hereditary mixed polyposis (Strate & Syngal, 2005)

1.2.3 Non-Polyposis Colon Cancer Syndromes

Non-polyposis colon cancer Syndromes include Lynch Syndrome (LS) and Muir -Torre syndrome. Lynch Syndrome accounts for about 3-5% of all CRC cases, making it the most common type of inherited colon cancer.

Individuals with LS have up to a 78% lifetime risk of developing CRC and typically present at an earlier age (less than 50 years of age). There is a high risk of developing cancers in extra colonic sites, such as the endometrium, renal pelvis,

ureter and small bowel. The condition is caused by mutations in the Mismatch repair genes (MMR) namely, *MLH1*, *MSH2*, *MSH6* and *PMS2*(H. Lynch et al., 2009; Vasen, 2007). LS is described in detail in the following sections. Muir - Torre syndrome, a clinical variant of Lynch syndrome, is an autosomal dominant condition associated with skin lesions such as sebaceous adenomas, carcinomas, keratoacanthomas along with gastrointestinal cancers. It is associated with DNA mismatch repair mutations in genes MLH1 and MSH2 (Ponti & de Leon, 2005).

1.3 Lynch Syndrome

1.3.1 History of Lynch Syndrome

The history of Lynch Syndrome goes back to a little over 100 years, when Dr. Aldred Warthin, Chairman of the Department of Pathology at the University of Michigan in Ann Arbor, described the family of a Michigan seamstress who reported several early onset cancers in her family (Boland & Lynch, 2013; P. M. Lynch, 2017). Warthin created a pedigree of the family, indicating who did or did not develop cancer, making possible the first formal study of the condition. He named the family as 'Family G' and identified that there was "some influence of heredity on cancer" (Warthin, 1913). In 1925, he reported a further study on family

G, identifying higher incidence of colorectal and endometrial cancers, and the development of early onset cancer in the family (Warthin, 1925). There was not much development until the sixties, when Dr. Henry T. Lynch. MD, after whom the condition is named, identified the early onset cancers and the autosomal dominant inheritance pattern. After learning about Dr. Warthin's efforts, Lynch arranged a reunion of the G family and termed the pattern of observed cancers the Cancer Family Syndrome. However, the use of that term was later discontinued to avoid confusion with Cancer Family Syndrome of Li and Fraumeni (now referred to as Li Fraumeni Syndrome) (P. M. Lynch, 2017). The term Hereditary Non-Polyposis Colorectal Carcinoma was coined by Dr. Lynch himself in 1985. He coined the term to differentiate it from FAP, but the term was lengthy and excluded extracolonic manifestations (Boland, 2005). In 1973, Boland used the term Lynch Syndrome for the first time to honor the work of Dr. Lynch. He used the terms Lynch Syndrome I and II to differentiate between families with CRC only and with extra colonic cancers. It was after the understanding of the genetic basis, years later, that the term Lynch Syndrome was decided to be used for all spectrum of conditions with Microsatellite Instability (Boland, 2005) .

Continuing from this early work, the ground-breaking discovery in the history of LS was made in 1993, when an international consortium of scientists identified the genetic basis and the microsatellite instability characteristic of LS. The team was

working on samples from several large families from New Zealand and Newfoundland (P. M. Lynch, 2017). Lauri Aaltonen identified significant linkage for LS on chromosome 2p, using the microsatellite marker, D2S12 (Aaltonen, Peltomaeki, Pylkkaenen, & Chappelle, 1993; Peltomaeki, Aaltonen, Pylkkaenen, & Chappelle, 1993). This breakthrough discovery was followed by intense and focused research effort in the western world which led to the identification of the four genes related to LS mutations as *MLH1*, *MSH2*, *PMS1*, and *PMS2*. Later, *PMS1* was identified as not related to LS, and *MSH6* was concluded as the fourth LS gene. (Miyaki et al., 1997)

During the late eighties and nineties, there were efforts to develop clinical criteria for the identification of Lynch Syndrome families. The International Collaborative Group on HNPCC (ICG-HNPCC) developed the Amsterdam criteria in 1990, later revised in 1998 as Amsterdam II criteria. Bethesda guidelines were established in 1997 and revised in 2004. The limitations of these guidelines and criteria are well documented, and efforts continued to develop a system to identify all individuals with LS mutations irrespective of family history and clinical features. This ultimately led to the Jerusalem conference in 2010 and the EGAPP Working group (Evaluation of Genomic Applications in Practice and Prevention [EWG]) recommendations, and the introduction of Universal tumor Screening strategies

(Berg, Armstrong, & Botkin, 2009). These criteria are discussed in detail in later sections.

1.4 Clinical features of Lynch Syndrome

LS is caused due to mutations in MMR genes and inherited in an autosomal dominant fashion. LS accounts for 3-5% of all cases of colorectal cancers and has a prevalence of about 1 in 440 in the general population (Rubenstein, Enns, Heidelbaugh, & Barkun, 2015). Chappelle et al. estimated the incidence of LS in the general population to be between 1 in 2000 to 1 in 660 and suggested it as one of the most common highly deleterious heritable conditions in man (de la Chapelle, 2005).The cardinal features of Lynch Syndrome are given in table 1.1

Table 1.1 Cardinal features of Lynch Syndrome

- Autosomal dominant inheritance.
- Associated cancers: cancer of colorectum, stomach, ovary, ureter/renal pelvis, central nervous system, small bowel, hepatobiliary tract, skin (sebaceous adenoma)
- Early age of cancer onset (Less than 50 years of age)
- Features of colorectal cancer: predilection for proximal colon, improved survival, multiple colorectal cancers, poorly differentiated tumors and Crohn's-like infiltration of tumor by lymphocytes
- Features of adenomas: the numbers vary from one to a few, increased proportion of adenomas with a villous growth pattern, high degree of dysplasia, rapid progression from adenoma to carcinoma, proximal location and flat or sessile morphology
- High frequency of microsatellite instability
- Immunohistochemistry: loss of *MLH1*, *MSH2*, *MSH6* and *PMS2* protein expression.

1.5 Malignancies associated with Lynch Syndrome

Lynch Syndrome (LS) is associated with a spectrum of malignancies, beyond CRC alone. There is also increased risk for extracolonic malignancies including cancers of the endometrium, ovaries, stomach, small intestine, hepatobiliary, urinary tract and the Central Nervous System (Kanth, Grimmett, Champine, Burt, & Sammader, 2017). Some types of LS cancers may be more prevalent in some populations than others. For example, Korean HNPCC families were found to have a higher incidence of gastric and pancreatic cancers than Dutch HNPCC families, indicating some gene-environment interaction in LS cancer expression (Park, Park, Wijnen, & Vasen, 1999).

1.5.1 Colonic Manifestations

CRC is the most common cancer associated with Lynch Syndrome. Lifetime risk of developing CRC in LS has been reported from 30-80% by various studies (Cohen & Leininger, 2014; Syngal et al., 2015). Early age of onset of CRC is a key feature of LS. The average age of onset has been described varyingly by different studies ranging from 44-48 (Cohen & Leininger, 2014; Kanth et al., 2017; Vasen, 2007). Hampel et al. re-examined the penetrance of HNPCC by analysing the combined data set of several Finnish HNPCC families. In mutation-positive family

members, age of onset of CRC was found to be 53-68 years, much later than described in the literature. However, age of onset was 41-46 years considering only probands (i.e., those first identified in the family). It was also found that the lifetime risk was lower than earlier reported (Hampel, Stephens et al., 2005). The CRCs in LS are associated with proximal colonic involvement. Seventy percent of the colonic malignancies in LS arise proximal to splenic flexure. A small adenoma can develop into a malignant tumor in a short time of two to three years, compared to eight to ten years in sporadic cases. This accelerated carcinogenesis leads to a higher incidence of interval cancers in LS carriers (Jass et al., 2002; Rijcken, Hollema, & Kleibeuker, 2002; Vasen, Nagengast, & Khan, 1995). Interval CRC is defined as CRC diagnosed after a cancer-detecting test in which no cancer was detected and before the date of the next suggested test (Sanduleanu et al., 2015). CRC tumors in LS are often poorly differentiated, with an excess of mucoid and signet cell features. LS CRCs tend to be diploid in nature and show Chron's-like reaction and lymphocyte predominance (Jass et al., 2002). Synchronous and metachronous cancers are another key feature of LS. Synchronous tumors are defined as a second primary tumor identified at the same time or within six months of diagnosis of the first primary tumor. Metachronous tumors are diagnosed after 6 months or later, in a different part of the organ (H. Lynch et al., 2009; Vasen, 2007).

1.5.2 Extra Colonic Manifestations

Lynch Syndrome (LS) is associated with increased risk of several extra colonic malignancies. Endometrial carcinoma in women is the most common extracolonic manifestation of LS. The lifetime risk of developing endometrial carcinoma in female mutation carriers is 30-60% (Vasen, 2007). They have an age of onset ten years earlier than the general population, which is between 50-60 years of age (Cramer, 2012; Pessoa et al., 2014). The histopathologic features related to MMR mutation include solid-cribriform growth, mucinous differentiation and necrosis. Mutations in *MSH6*, *MLH1* and *MSH2* are found to be associated with endometrial carcinoma, with the *MSH6* and *MSH2* having the highest risk of up to 44% (Cohen & Leininger, 2014).

The lifetime risk of developing ovarian cancer is 6.7% - 12% with a slightly higher risk in *MSH2* carriers (Cohen & Leininger, 2014). Gastric cancer occurs in up to 13% of cases but is more common in the Asian countries of Japan, South Korea and China (Park et al., 1999). Small bowel cancers and cancers of the ureter/renal pelvis occur less frequently in up to 6% of LS cases. It was found that brain cancers were the third most frequent cause of cancer death in LS (6.7%) after CRC (50.3%) and endometrial carcinoma (6.7%) (de Jong et al., 2006).

1.6. Genetic Basis of Lynch Syndrome

Lynch syndrome occurs due to mutations in the Mismatch Repair (MMR) genes. The Mismatch repair proteins detect and repair the errors that may occur after DNA replication in cells. Therefore, it plays an important role in maintaining the genetic integrity in somatic cells where cell turnover is very rapid, such as the intestinal epithelium. Defective MMR genes can result in the accumulation of DNA replication errors in somatic cells. There are five MutS genes (*MSH2*, *MSH6*, *MSH3*, *MSH4*, and *MSH5*) and four MutL genes (*MLH1*, *PMS2*, *PMS1*, and *MLH3*) in human cells which can mediate mismatch repair in various heterodimeric combinations (Peltomäki, 2016). Among these four are conclusively associated with Lynch Syndrome, namely *MLH1*, *MSH2*, *MSH6* and *PMS2* (Peltomäki, 2016). There are more than 5000 pathogenic variations of these genes associated with LS as listed in the International Society for Gastrointestinal Hereditary Tumors (InSiGHT) database (https://www.insight-group.org/syndromes/lynch-syndrome/) (Peltomäki, 2016; Plazzer et al., 2013). Among these, 70-90% are attributed to *MLH1* and *MSH2* and the remaining 10-30% to *MSH6* and PMS2. Up to 3% of LS is associated with the *EPCAM* gene, whose mutations will result in the hypermethylation of *MSH2* promoter, resulting in Lynch Syndrome. (Cohen & Leininger, 2014; Tutlewska, Lubinski, & Kurzawski, 2013)

The occurrence of malignancy in Lynch Syndrome follows Knudson's two hit hypothesis of carcinogenesis in hereditary conditions (Knudson, 1971). The inheritance of the faulty gene constitutes the first hit, and the somatic mutations make the second hit resulting in cancer. The mutations in the MMR genes' errors lead to the carcinogenesis in LS. There is evidence to suggest that in Lynch Syndrome cancers, both hits could be genetic or epigenetic (Peltomäki, 2014). The epigenetic mechanisms identified so far include deletion of the *EPCAM* gene combined with hypermethylation of MSH2 promoter, and methylation of *MLH1* (Cohen & Leininger, 2014; Peltomäki, 2014; Tutlewska et al., 2013). Lifestyle and environmental factors have also been implicated in Lynch syndrome, suggesting possible areas where primary and secondary preventive strategies can be employed (Park et al., 1999; van Duijnhoven et al., 2013).

1.7 Molecular Basis of Lynch Syndrome

Microsatellites are repetitive DNA sequences of either a single nucleotide (mono) or more than one nucleotide (bi-, tri-, tetra-, or penta-). There are over 500,000 microsatellites in the human genome (Chapelle & Hampel, 2010; de la Chapelle, 2003). Normally, the number of repeats in a microsatellite will be the same for every cell. When the microsatellites gain or lose repeat units in one or

two alleles and vary between cells, it is said to have Microsatellite Instability or MSI (Chapelle & Hampel, 2010). Usually they can be detected if they are present in a relatively high number of cells, which is typical in the case of a neoplasm. MSI is the hallmark phenotype in Lynch Syndrome and was identified by Aaltonen et al. in 1993 (Aaltonen et al., 1993). MSI can be detected in over 90% of all Lynch Syndrome cases, but in 15% of all CRC cases as well (H. T. Lynch et al., 2006). MSI in sporadic CRC occurs due to hypermethylation of the *MLH1* promoter region (Aaltonen et al., 1998; H. T. Lynch et al., 2006). Identification of MSI can be used as a screening test for Lynch Syndrome in patients diagnosed with CRC.

1.8 Molecular screening tests for Lynch Syndrome

1.8.1 Microsatellite instability testing (MSI testing)

MSI can be identified by testing for several markers, including mononucleotide repeats or for higher nucleotides. The National Cancer Institute guidelines for determination of MSI in colorectal cancers recommended a panel of five markers for testing MSI known as the Bethesda panel. They include two mononucleotide repeats (*BAT26, BAT25*) and three dinucleotide repeats (*D2S123, D5S346,*

D17S250) (Boland et al., 1998). Depending on the number of markers showing instability, the result can be categorized into High Instability MSI-H, if there is MSI in two or more markers (>30-40%), Low Instability MSI-L if there is instability in less than 2 markers (<30%) and no Instability, MSS (Microsatellite Stability) in cases where there is no instability detected (Boland et al., 1998). There are different test kits available using varying type and number of markers. Murphy et al. compared the most frequently used one, the Microsatellite Instability Analysis System (Promega Corp), with the Bethesda panel and found 85% concordance between the two systems (Murphy et al., 2006). The EGAPP Working Group (EWG) found adequate evidence showing 90.2% specificity for MSI testing (Berg et al., 2009). There was also adequate evidence showing that the sensitivity of MSI testing was 89% for *MLH1* and *MSH2* mutations, and 77% for *MSH6* mutations (Palomaki, Mcclain, Melillo, Hampel, & Thibodeau, 2009). Microsatellite instability testing can be a useful tool in identifying individuals at risk of having Lynch Syndrome.

1.8.2 Immunohistochemistry

An alternative to MSI testing is the use of Immunohistochemistry testing (IHC) on resected tumor tissue and biopsy samples. Immunohistochemistry testing employs monoclonal and polyclonal antibodies to visualize the presence or absence of MMR proteins using fluorescence or similar methods. Loss of one or more of the MMR proteins suggests the possibility of mutation in the associated genes, potentially indicative of LS. In 1996, Leach et al. developed monoclonal antibodies for *MSH2*, paving the way for IHC analysis in MMR deficiency (Leach et al., 1996). Thibodeau et al. later examined *MSH2* and *MLH1* mutations using Immunohistochemistry testing (Thibodeau et al., 1996). Several reports of the involvement of *MSH6* mutations were subsequently published. *MLH1* and *MSH2* protein expression in IHC in CRC tumors were studied and IHC testing was found to be a valuable tool for detecting possible LS mutations in young patients (Paraf et al., 2001). Stone et al. compared Microsatellite stable (MSS) and Microsatellite instable tumors using IHC and discussed the potential of IHC in the detection of MMR deficiency in routine clinical practice (Stone, Robertson, & Houlston, 2001). CRC patients were tested for germ-line mutations *MLH1*, *MSH2*, and *MSH6* by employing a mixed method of clinical measures and IHC analysis, and a positive predictive value of 80 percent and a sensitivity of 62 percent for mutation carriers

were estimated (Barnetson et al., 2006). In another study, paraffin embedded tumor samples of 85 individuals with CRC collected from 1979 to 1999 were examined using IHC for *MSH2*, *MSH6* and *MLH1* mutations. The sensitivity for predicting a pathogenic mutation was 89%, despite a non-standardized fixing of the tissue samples (Hendriks et al., 2002). The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (EWG) conducted a series of extensive reviews to evaluate various screening methods and their clinical validity. The sensitivity of IHC in identifying MMR was found to be 78% (65-88), *MSH2* to be 80% (62-90), *MSH6* to be 74 % and the overall sensitivity to be 77% (69-84). The specificity of IHC testing was found to be 88.8% with an adequate level of evidence (Berg et al., 2009; Palomaki et al., 2009). The sensitivity of IHC as an indication of MMR mutation has been estimated as 83%, with 90% specificity (Chubak, Heald, & Richard, 2011; South et al., 2009).

There are several advantages for Immunohistochemical screening for Lynch Syndrome. Firstly, IHC is readily available in most laboratory facilities and is therefore convenient for pathologists as well as patients in terms of accessibility. Secondly, IHC is thought to be more cost efficient than MSI screening. IHC was found to be three times less expensive than MSI testing with no change in sensitivity (Debniak et al., 2000). Thirdly, it has been shown that IHC could be

helpful in identifying MMR missed by MSI testing (Shia, 2008). Studies have shown that the sensitivity and specificity of IHC testing is similar or higher to MSI.

However, there is no scientific consensus yet as to which of these testing methods should be used in identifying patients at risk of having LS, IHC or MSI testing. Existing guidelines recommend the use of either of these methods for CRC tumor screening for LS (Berg et al., 2009).

1.9 Diagnostic and Clinical Criteria for Lynch syndrome

Families at risk for developing Lynch syndrome are conventionally identified based on clinical and family history, such as those used in the Amsterdam I and II criteria and both the original and revised Bethesda guidelines. In recent years, various predictive models and Universal tumor screening strategies have been suggested to help identify more individuals at risk of having Lynch syndrome. Individuals tested fulfilling these criteria or tested positive using screening tests would undergo germline analysis to diagnose Lynch Syndrome.

1.9.1 Amsterdam Criteria

The International Collaborative group on HNPCC developed a set of guidelines in 1990 to help identify families at risk of having LS. They came to be known as Amsterdam criteria, after the venue of the meeting. To be identified as at risk, an

individual should have met all three criteria: 1) At least three relatives should have histologically verified colorectal cancer; one of them should be a first degree relative to the other two. Familial adenomatous polyposis should be excluded. 2) At least two successive generations should be affected. 3) In one of the relatives, colorectal cancer should be diagnosed under 50 years of age (Vasen, Mecklin, Khan, & Lynch, 1991). The extracolonic manifestations of LS were not taken into consideration and the Amsterdam criteria failed to identify some LS families. Therefore, in 1999, ICG-HNPCC issued a revised set of diagnostic guidelines, known as the Amsterdam II criteria, including the extracolonic cancers namely endometrium, small bowel, ureter or renal pelvis (Vasen, Watson, Mecklin, & Lynch, 1999)

The validity of Amsterdam criteria I and II has been widely studied. In a large cohort of CRC patients in Scotland, Barnetson et al. tested 890 patients for MMR mutations (*MLH1*, *MSH2* and *MSH6*) using DNA analysis. They found that 52% of participants who were carrier-positive did not fulfil the ACII criteria. (Barnetson et al., 2006). Vasen et al. reviewed the literature in 2007 and found that only 41% of the mutation carriers fulfilled the Amsterdam criteria (Vasen, 2007). Syngal et al. found that the sensitivity and specificity of ACI were 61% and 67%, and that of ACII were 72% and 50%, respectively in *MLH1* and *MSH2* carriers (Syngal, Fox, Eng, Kolodner, & Garber, 2000). While better than ACI, ACII still missed 22% of

the mutations, thus excluding those patients and their families from surveillance and access to confirmatory genetic testing. Although Amsterdam Criteria were successful in the detection of HNPCC families, their limitation in identifying *MSH2* and *MLH1* mutations make them less efficient for identifying all high-risk individuals (Syngal et al., 2000).

1.9.2 Bethesda Guidelines.

By 1996, the association of LS with Microsatellite Instability and MMR mutations was known to the scientific community. The Bethesda guidelines were developed to identify the individuals who needed MSI testing. Later in 2004, the Revised Bethesda guidelines were introduced (Rodriguez-Bigas et al., 1997; Umar et al., 2004). The Bethesda and the revised guidelines are shown in Table 1.2.

Table 1.2 Bethesda and the Revised Bethesda criteria for Hereditary Non-Polyposis Colorectal Cancer (Lynch Syndrome)

Bethesda guidelines
1.Individuals with cancer in families that meet the Amsterdam criteria.
2.Individuals with two HNPCC-related cancers, including synchronous and metachronous colorectal cancers or associated extracolonic cancers. [a]
3.Individuals with colorectal cancer and a first-degree relative with colorectal cancer and/or HNPCC related extracolonic cancer and/or a colorectal adenoma; one of the cancers diagnosed at age < 45years, and the adenoma diagnosed at age < 40 y.
4.Individuals with colorectal cancer or endometrial cancer diagnosed at age <45 y.
5.Individuals with right sided colorectal cancer with an undifferentiated pattern (solid/cribriform) on histopathology diagnosed at < 45 y. [b]
6.Individuals with signet-ring-cell-type colorectal cancer diagnosed at age <45 y. [c]
7.Individuals with adenomas diagnosed at age <40 y.
Revised Bethesda guidelines
1.Colorectal cancer diagnosed in a patient <50 years of age.
2.Presence of synchronous, metachronous colorectal, or other Lynch syndrome-related tumors, regardless of age. [d]
3.Colorectal cancer with MSI-H [e] histology [f] diagnosed in a patient <60 years of age.
4. Patient with colorectal cancer and a first-degree relative with a Lynch syndrome-related tumor, with one of the cancers diagnosed under age 50 years.
5. Patient with colorectal cancer with two or more first-degree or second-degree relatives with a Lynch syndrome-related tumor, regardless of age.

[a] endometrial ovarian, gastric, hepatobiliary, or small bowel cancer or transitional cell carcinoma of the renal pelvis or ureter.

[b] Solid/cribriform defined as poorly differentiated or undifferentiated carcinoma comprised of irregular solid sheets or large eosinophilic cells and containing small gland-like spaces.

[c] Composed of >50 % signet ring cells.

[d] Hereditary nonpolyposis colorectal cancer (HNPCC)-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratoacanthomas in Muir–Torre syndrome, and carcinoma of the small bowel.

[e] MSI-H = microsatellite instability–high in tumors refers to changes in two or more of the five National Cancer Institute-recommended panels of microsatellite markers.

[f] Presence of tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.

A handful of studies have evaluated the Bethesda guidelines. According to a review by Vasen et al., 89% of the mutation carriers fulfilled Bethesda guidelines (Vasen, 2007). Syngal et al. classified 70 LS families by Amsterdam and Bethesda guidelines to estimate their clinical validity. The sensitivity and specificity of the Bethesda guidelines were estimated as 94% and 25% respectively, showing the low specificity (Syngal et al., 2000). However, the revised guidelines were found to have a sensitivity of 94% and specificity of 49%. Studies have shown that using Bethesda guidelines alone could lead to mutation positive individuals being ruled out. In a study of 870 CRC patients, among the participants who fulfilled Bethesda guidelines, 62% tested negative for a *MLH1* or *MSH2* mutation, (Barnetson et al., 2006). Similarly, in a French study, it was found that the revised Bethedsa guidelines failed to detect two of eight probands, while molecular testing identified

all eight of them with no significant increase in workload (Julié et al., 2008). A later age of onset of cancers than earlier reported was observed among two cohorts of Dutch HNPCC families, indicating that if the revised Bethesda guidelines were employed, some patients would still be missed (Hampel et al., 2005).

1.9.3 Predictive models

Predictive models are tools developed based on regression models using clinical and family history to predict the probability of a germline mutation in an individual. They calculate a "numerical risk" or likelihood of having MMR mutations. A handful of these evidence-based models have been developed and validated for Lynch Syndrome. One of them, the PMMRpro, developed by Chen et al. predicts the risk of *MLH1*, *MSH2* and *MSH6* mutations (Chen et al., 2006). A clinically-driven predictive model has been developed to predict DNA mismatch repair mutations in *MLH1*, *MSH2* and *MSH6* (Barnetson et al., 2006) called MMRPredict. This model has the best specificity (90%) among predictive models (Giardiello et al., 2014). The PREMM 1,2,6 (Kastrinos, 2011) model which predicts risk of *MLH1*, *MSH2* and *MSH6* germline mutations has a sensitivity of 90% and specificity of 67%. (Giardiello et al., 2014; Kastrinos, 2011). The model has recently been expanded to PREMM5 to include *PMS1* and *EPCAM* mutations

also (Kastrinos et al., 2017). However, because these predictive models rely at least in part on family and clinical history, much like the Amsterdam and Bethesda criteria, they have similar limitations.

Identification of individuals and families with germline mutations in the MMR genes remains a critical clinical and public health challenge. The limitations and poor performance of the criteria based on family history led to the emergence of universal tumor screening recommendations.

1.10 Universal tumor Screening for Lynch Syndrome

Universal tumor screening for Lynch Syndrome (LS) refers to the strategy of screening every newly diagnosed CRC patient using MSI or IHC testing, irrespective of family history. For those testing positive in the initial screen, germline testing is then recommended to confirm the diagnosis of LS. Hampel et al. conducted a study to evaluate various screening methods for LS by performing MSI testing on 1066 CRC patients in Ohio. IHC analysis was done for the patients with high microsatellite instability, which was followed by germline mutational analysis. It was concluded that large scale screening of CRC patients was a feasible option and the authors recommended MSI screening for every newly diagnosed CRC patient (Hampel, Frankel et al., 2005). A workshop was held in Jerusalem in 2009 to discuss the screening and management of Lynch Syndrome; subsequently,

the Jerusalem guidelines were published. It was recommended to screen all CRC patients younger than 70 years of age for LS mutations, (Boland & Shike, 2010). The universal screening strategy implies the screening to be 'automatic' or reflexive in nature, where all newly diagnosed CRC patients are automatically tested. The screening strategy is also referred to as reflex testing. (Beamer et al., 2011). The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working Group (EWG), based on a review of available evidence on population level screening and outcomes, found sufficient evidence to recommend genetic testing to detect LS in all newly diagnosed CRC patients (Berg et al., 2009; Palomaki et al., 2009). This recommendation by EWG sparked a movement towards universal tumor screening for identifying at risk individuals as a routine practice, which was followed by several studies exploring its feasibility.

In 2008, a study was conducted comparing screening based on revised Bethesda guidelines and molecular screening using MSI for all patients. It included 214 patients, among which Bethesda guidelines failed to detect two of the eight probands, whereas the MSI detected all mutations. It was concluded that the universal tumor screening strategy using MSI testing was more effective in identifying at risk individuals LS mutations and that the germline testing workload was only slightly higher for such screening (Julié et al., 2008).

In a prospective multicenter study of 1137 CRC patients, MSI testing and IHC analysis were conducted on all 1117 patients; germline mutation analysis followed for those patients with MSI or MMR deficiency. Among the participants, 83% referred to counselling after testing positive had not fulfilled any family history-based criteria. The LS incidence in the study population was 4.5%, concordant with the existing literature, and routine MSI screening of every newly diagnosed CRC patient up to the age of 70 was suggested (Van Lier et al., 2012).

Universal tumor screening for LS and revised Bethesda guidelines were also compared in a Spanish cohort. IHC or MSI testing was performed on 2093 CRC patients, and those with loss of MMR expression or high MSI were followed up with genetic testing. Among the patients identified with LS mutations, 14.3% did not fulfill revised Bethesda guidelines and would have been missed if family history-based criteria were used. Universal tumor screening strategy with immunohistochemistry or MSI testing was found to be more effective (Perez-Carbonell et al., 2012).

Similarly, Bethesda guidelines failed to detect up to 37% of potential LS-affected individuals in a prospective study involving 1040 CRC patients (Canard et al., 2012). A pooled data analysis of four cohorts from the US and Finland assessed a strategy of germline mutation testing for MSI positive individuals in 10,019 CRC patients. Germline mutational analysis was done for those probands with positive

MSI, and it was found that 3.1% of all the participants carried LS-associated mutations. Only universal screening had 100% sensitivity and was concluded to be the most effective compared to alternative strategies including Bethesda guidelines and Jerusalem criteria (Moreira et al., 2012). Thus, evidence from several large studies shows that universal tumor screening strategies using MSI or IHC is beneficial in identifying patients with Lynch Syndrome. Based on these studies and the recommendation from the EGAPP Working Group (EWG), universal tumor screening for Lynch Syndrome has been recommended by a number of international organizations and health systems.

The United States Multi-Society Task Force (USMSTF) for colorectal cancer endorsed MMR deficiency testing for all CRC cases using IHC testing for *MLH1*, *MSH2, PMS2* or *MSH6* proteins or using MSI testing. They recommend testing for all CRC cases, or in CRC patients diagnosed at younger than 70 years of age, and in individuals older than 70 who have a family history (Giardiello et al., 2014). The National Comprehensive Cancer Network (NCCN) also recommends screening all CRC patients, or CRC under 70 years and in those over 70 who meet the Bethesda guidelines, using either IHC or MSI (Provenzale & Gupta, 2015). The American Gastroenterological Association Institute and the American College of Gastroenterology recommend screening for LS in patients diagnosed with CRC using MSI or IHC (Rubenstein et al., 2015; Syngal et al., 2015). One of the

genomics objectives of the initiative of Healthy People 2020 is to increase the number of patients diagnosed with CRC who undergo screening for LS in accordance with the EGAPP and US Task Force recommendations (Green, Dotson, Bowen, Kolor, & Khoury, 2015). The National Society of Genetic Counselors and the Collaborative Group of the Americas on Inherited Colorectal Cancer Joint Practice Guideline recommends MSI or IHC testing for all newly diagnosed CRC and endometrial cancer patients (Weissman et al., 2012). Additionally, similar strategies were also recommended by the National Institute of Health and Care Excellence (NICE) (Newland, 2017).

Since the recommendations of EGAPP and USMSTF, there has been a trend toward universal tumor screening in the US. The Lynch Syndrome Screening Network (LSSN) was initiated in 2011 with 35 participating institutes with aim to promote universal screening and to facilitate institutions to implement screening programs (Mange, 2015). In the United States, even though Lynch Syndrome screening protocols for CRC and endometrial carcinomas are prevalent and have been increasing in recent years (Cohen, 2014; Cragun et al., 2014), there is still room for improvement. A survey of cancer centers in the US found that only 70% of the National Cancer Institute–designated Comprehensive Cancer Centers (NCI-CCCs) were utilising a universal reflex testing strategy (Beamer et al., 2011). In Canada, an integrated approach in LS screening among CRC patients is lacking

(Bombard et al., 2017). A survey of pathologists across Canada suggests that most of the MMR deficiency tests are requested by clinicians and highlights the lack of standardized guidelines regarding LS screening (Kalloger et al., 2012). Lynch Syndrome is under-recognized, with centres still relying on family history-based Amsterdam and Bethesda guidelines to identify at risk individuals (Pi, Nap-Hill, Telford, & Enns, 2017).

In Newfoundland, where the incidence of familial CRC is very high, it was found that a screening approach based on family history was inefficient. For 48% of incident cases, family history information was not available or provided, resulting in failure to assess those cases for LS risk (Parfrey et al., 2017). These studies suggest a lack of standardized universal tumor screening guidelines and irregularities in practice, meaning some individuals at risk of having LS remain unidentified. This is a crisis not only at a patient level where adequate risk identification and preventive surveillance are not provided due to a lack of screening, but also at population level, with high mortality and morbidity of LS-associated malignancies.

1.10.1 Economic feasibility of universal tumor screening.

A universal tumor screening strategy involves testing a large number of individuals compared to any other screening criteria. In any such large-scale program, cost effectiveness and economic feasibility are important issues that need to be addressed. Evidence from the literature suggests that population-level screening is a cost-effective method in identifying LS carriers. In an American cost-effectiveness study, it was found that the incremental cost effectiveness ratios for universal tumor screening for LS using IHC or MSI ranged from $12,332 to $49,272 per life year saved compared to no testing, and from $18,778 to $85,391 per life year compared to screening based on age. IHC screening was found to have 40% lower costs compared to MSI testing. IHC screening followed by germline testing was found to be the most effective strategy, and it was concluded that universal tumor screening of all newly diagnosed CRC patients was a cost-effective option in the country (Mvundura, Grosse, Hampel, & Palomaki, 2010). In another feasibility analysis of various screening strategies for LS, including family history-based and germline testing, it was found that screening of newly diagnosed CRC patients could provide clinical benefits at an acceptable cost. The cost effectiveness was dependent on screening of the relatives and their risk reduction strategies. IHC testing with subsequent germline testing in positive individuals, was the most effective strategy. MSI testing followed with

germline testing in positive individuals was found to be the second-best strategy. It was also found that limiting the screening strategy to patients younger than 50 presented a more cost-effective option, but at the risk of having older LS patients being left undetected (Ladabaum et al., 2011). In a systematic review, MSI testing and IHC testing were both cost effective strategies in screening for LS. The cost effectiveness is dependent on various factors such as utilization of genetic testing and screening of relatives to provide their risk reduction strategies (Di Marco et al., 2017; Grosse, 2015; Snowsill et al., 2014; Snowsill et al., 2017).

1.10.2 Preventive and therapeutic implications of screening

Screening for LS mutations among CRC patients has several benefits to the patients themselves and their family members. Firstly, understanding genetic risk of LS has prognostic and therapeutic implications for the patients themselves. Individuals with LS are at higher risk of developing several extracolonic malignancies. In patients with LS, therefore, frequent cancer surveillance and screening at younger ages (e.g., colonoscopic surveillance) may be required in order to detect these malignancies at an early stage. Options for preventive procedures, including hysterectomy or salpingo-oophorectomy for affected females, could help patients in reducing cancer risk (Hampel, 2018). Secondly,

microsatellite instability status of CRC tumors could have prognostic implications for the patients (Gryfe et al., 2000; Kang et al., 2018). MSI-CRCs have been found to have a better prognosis and overall survival (HR= 0.69; 95% CI: 0.56 to 0.85) compared to MSS CRCs (Popat, Hubner, & Houlston, 2005). Thirdly, therapeutic implications of MSI status have been highlighted by a handful of studies. It has been shown that patients with high MSI status had a better survival and prognosis with surgery alone, compared to surgery and adjuvant chemotherapy with fluorouracil (Popat et al., 2005; Ribic et al., 2003; Smyth et al., 2017). Furthermore, recent evidence about the clinical benefits of immunotherapeutic agents such as pembrolizumab in MMR deficient tumors, shows the importance of identifying the genetic and molecular status of CRC patients (Hampel, 2018; Le et al., 2015). Thus, there are several benefits for CRC patients themselves in determining MSI or MMR deficiency.

While the benefits to the patients are important, the identification of at risk individuals through cascade testing of relatives has implications for current and future generations and confers a public health benefit. Evidence suggests a higher likelihood of relatives undergoing cancer screening and surveillance procedures if the LS mutation status of the patient is known (Bonis, Trikalinos, & Chung, 2007). At risk family members who undergo regular colonoscopic surveillance have lower incidence of CRC, lower CRC mortality and increased overall survival. It has been

shown that colonoscopic surveillance can decrease CRC incidence by 59-62%, preventing a conservative estimate of up to 5000 colon cancer cases in the US (Bellcross, 2012). CRC-associated mortality rates are reduced in those patients who undergo regular colonoscopic screening. Additionally, LS patients who underwent regular cancer surveillance were found to have an increased life expectancy by 23 years, compared to no surveillance (Stupart, Goldberg, Algar, & Ramesar, 2009). The extent of these benefits is directly associated with the efficiency of screening programs in identifying at risk individuals, as well as the extent to which their family members are screened for LS and subsequently followed up with cancer surveillance.

Universal tumor screening has been shown to benefit at risk individuals (Berg et al., 2009). Perspectives of key stakeholders on universal tumor screening are critical since the success of screening programs is reliant on patient and family engagement with follow-up diagnostic testing and adherence to cancer surveillance behaviors recommended for high-risk family members.

In 1968, "Principles and Practice of Screening" from the World Health Organization introduced a set of ten criteria to be met by screening programs before being established as a public health measure (Wilson & Jungner, 1968). Universal screening for LS meets most of the original public health screening criteria. Notably, one of the Wilson-Jungner criteria that is not met was, "The test

should be acceptable to the population" (Cragun, DeBate, & Pal, 2015). Cragun et al. argued that a lack of research about public perceptions of tumor screening precluded meeting this criterion. A newer set of population screening criteria was introduced decades later to reflect the scientific advancements and change since Wilson and Jungner's seminal work (Andermann, Blancquaert, Beauchamp, & Déry, 2008). One of the newer criteria for population screening suggests that the program should ensure informed choice and patient autonomy. Since patient perceptions on informed consent for universal screening is relatively under-researched and the current practice is non-requirement of a consent, this criteria is not met (Cragun et al., 2015). The following sections outlines these areas, overviews the available literature and identifies the gap in existing knowledge.

1.11 Perspectives of stakeholders regarding benefits and barriers

The key stakeholders of a universal tumor screening program include CRC patients and healthcare providers including surgeons, pathologists, genetic counsellors, gastroenterologists, and primary care providers. The studies exploring their perspectives are limited in number but aim at highlighting the facilitators and barriers of universal screening, consent protocols and the role of communication of genetic risk.

1.11.1 Perspectives of healthcare providers

The healthcare professionals who would be involved in a universal tumor screening program for LS range from primary care physicians, surgeons, gastroenterologists, oncologists, pathologists and genetic counselors. Their perspectives would be crucial in establishing evidence-based guidelines and policy initiatives regarding the program. In a qualitative study, Bombard et al. interviewed 27 Canadian health providers. The participants were generally in favour of a universal tumor screening program, but identified some challenges, including lack of patient awareness, longer wait times, lack of genetic counselor resources and the need for a co-ordinated, ongoing system of cancer surveillance. The study also noted the lack of a universal practice guideline regarding LS screening across the country (Bombard et al., 2017). In the US, where universal tumor screening is becoming routine, genetic counselors identified barriers to implementing the program such as collaboration of stakeholders, cost, and convincing the medical staff about the necessity of the program (Cohen, 2014). A survey of clinical and laboratory staff revealed support for universal screening but noted barriers such as the need for infrastructural support and effective interdepartmental collaboration and communication (Schneider et al., 2015). Other identified barriers to tumor screening included the need and process for informed consent, the psychosocial burden for patients with cancer and undergoing

treatment, and barriers related to communication between healthcare providers and family members (Hall, 2010).

1.11.2 Need for informed consent

Informed consent requires that patients understand the risks, benefits and alternatives to the procedure or test prior to the test or procedure, enabling them to make informed decisions about their health in accordance with their values (Annas, 1977; Faden, 1986). Explicit informed consent is required prior to colon cancer screening or diagnostic procedures, including colonoscopy. However, there is no similar consent requirement for testing biopsy samples or resected tissue samples (Feld, 2002). The consent model often used in this situation is of implied consent. Germline genetic tests require explicit informed consent because of their implication in the patient's, as well as their family's health and future (Feld, 2002). There are no detailed guidelines available on consent for tumor testing for LS and it is a topic of debate in the literature. (Beamer et al., 2011; Bombard et al., 2017; Shipman, Arribas-Allyon, Murray, & Gaff, 2013). The reflexive or automatic nature of the universal screening has implications for the role of informed consent and its protocol. One of the arguments is that MSI testing can be considered as a genetic test, and as such, the EGAPP Working Group (EWG) suggests the use of

informed consent prior to MSI testing, whilst noting the contrasting views from the literature. IHC testing is not viewed as 'genetic testing' and thus, informed consent is not a requirement (Berg et al., 2009). Some authors disagree with this, suggesting IHC testing has more in common with genetic tests because of the information the test provides (Chubak et al., 2011). Chubak et al. conclude that explicit informed consent is not required for MSI testing because the testing does not affect patients in "potential harmful ways" that necessitates an informed consent. Bombard et al., in a survey among healthcare providers, similarly found that healthcare providers did not see the need for consent for universal tumor screening but endorsed an opt-out option for further germline mutation testing. To date, the consent protocols regarding universal tumor testing are not well established and the issue of consent is widely debated (Bombard et al., 2017; Chubak et al., 2011; Janet & Marc, 2011; Shipman et al., 2013).

1.11.3 Perspectives of patients

Very few studies have explored the perspectives of patients regarding universal tumor screening, but existing literature suggests a generally favorable attitude. A telephone survey of 145 CRC patients who consented to screening were followed up with a second questionnaire after results of the screening test were provided.

Participants had a positive attitude towards screening, understood the benefits of testing and were willing to communicate the results to family members and health care providers. Participants of that study had low prior knowledge about screening and LS. In a follow up survey after screening and germline testing, most of the patients were consistent with their initial answers and had shared their results with family members. Though the study was conducted among patients who consented to participate in screening, and therefore did not necessarily reflect the attitudes of CRC patients in general, the findings of the study establish the significance of understanding the patient perspective (Hunter et al., 2015; J. Hunter et al., 2017). In a cross-sectional survey of 91 CRC patients, it was found that 67% of the participants expressed interest in genetic screening. The benefits of screening were found to be more important to patients compared to barriers, among which the main barrier was economic (Cragun, Malo, Pal, Shibata, & Vadaparampil, 2012). In another survey among 125 individuals who met the Bethesda criteria, it was found that patients generally had low levels of knowledge about MSI testing but had an overall positive attitude about screening (Manne S., Chung D., & Weinberg D., 2007). To our knowledge, no research has explored the opinions of patients in Canada about universal tumor screening for LS.

In all, this small body of literature highlights gaps in our understanding of both patient and healthcare provider perspectives about universal tumor screening, as well as the lack of data from a Canadian context.

1.12 Summary

Lynch Syndrome is the most common cause of hereditary colon cancer, affecting 3-5% of all CRC cases. Universal tumor screening for LS among CRC patients using MSI testing or IHC is recommended by several organizations and groups internationally, though no Canadian guidelines or consensus statement exists. Understanding the perspectives of key stakeholders is important in the successful implementation of any screening program. Patients' interest in a universal tumor screening program and their need for and preferred form of consent has been largely unexplored, and there are no studies in the Canadian context.

1.13 Objective

This study is part of a larger project exploring the perspectives of key stakeholders including CRC patients, pathologists and genetic counselors regarding the benefits and barriers of universal tumor screening for LS.

The objective of this patient-oriented research project is to explore the perspective of CRC patients regarding universal tumor screening, especially their attitude, willingness to communicate with healthcare professionals and family members about test results, and their perspectives on the need for, and preferred mode of, informed consent.

CHAPTER 2

METHODS

This population-based survey was part of a larger project exploring the perspectives of key stakeholders regarding universal tumor screening. The initial phases of the study consisted of web-based national surveys of pathologists and genetic counselors. The present study encompasses a mail-out survey of patients with CRC in Newfoundland and Labrador, Canada. This cross-sectional survey was conducted with the objectives of understanding the patients' attitudes towards universal tumor screening for Lynch Syndrome, the perceived benefits and barriers of screening and the need for (and preferred form of) informed consent. The data for this mail-out survey was collected and analysed entirely by the author of this thesis.

2.1 Study Setting

This study was conducted at Memorial University of Newfoundland, Canada with the survey administered through the Dr. H. Bliss Murphy Cancer Centre in the Eastern Health Authority in St. John's Newfoundland (NL). The period of the

study was from January to December 2017. Ethics approval was obtained from the Newfoundland and Labrador Health research ethics Board (HREB), ref no: 2016.277.

2.2 Patient Oriented Research

Patient Oriented Research involves patients as research partners, rather than solely as study subjects (CIHR-strategy for patient-oriented research.2017). The current research was designed with patient engagement to meet several objectives: 1) to include a patient perspective in the overall design and conduct of the study; 2) to make the survey content and language more appropriate and understandable to the participants; 3) and to obtain a patient perspective on study conclusions and knowledge translation activities (e.g., an end-of-study patient workshop). The patient partner for the current study was identified for the larger project through personal networks of the study team. His lived experience was as a person who has had colon cancer and would be eligible to complete the survey. He was actively involved from the design and development of the survey, to the dissemination of results at the end of the study. The PI and her supervisor met regularly with the patient partner over the course of the study as decisions on content, language, administration, analysis and dissemination were made.

2.3 Sampling

The target population for this study was all living patients diagnosed with CRC in Newfoundland and Labrador over a three-year period preceding the survey administration (2017). This time frame was suggested by the Cancer Centre as having the most up-to-date data in the provincial cancer registry, the database used to recruit eligible respondents. As such, all living patients diagnosed with CRC from 2014 to 2016 were deemed eligible for the current study irrespective of age, gender and stage of tumor. The broad eligibility criteria were set to increase the sample size and to capture a wide range of responses. Eligible participants were identified from the Provincial Cancer Registry by Cancer Center staff within the patients' circle of care. Mortality Clearance of these patients was obtained by the Cancer Centre from the Newfoundland and Labrador Center for Health Information (NLCHI) before survey mail-out.

2.4 Survey Design and Development

The survey (see Appendix A) was developed by the PI to cover three broad areas: attitude, consent and communication regarding universal tumor screening. Specifically, we wanted to measure patients' attitudes towards a provincial tumor screening program, their desire to take part, whether they saw the need for informed consent for such testing, and their willingness to talk with family

members about tumor testing results. With permission from the author, some questions were adapted from a survey conducted in the US examining patient perspectives on the benefits and barriers of universal screening (Hunter et al., 2015). As the current literature is sparse on patient perspectives, this will allow some comparison of our findings with another patient population.

The survey consisted of 32 questions. The items were mostly close-ended questions with response options on Likert scales (strongly disagree-strongly agree), yes/no items, and items with multiple response options (e.g., besides you, who else in your family has had cancer?). A 'not sure' or 'neither agree nor disagree' option was included in most questions to account for a neutral response. One open-ended question was included to allow patients to describe any comments/suggestions they had about tumor screening.

The survey was divided into three sections; 1) Knowledge and understanding; 2) Attitude and opinions about screening, including the need for and preferred form of informed consent; and 3) Personal, demographic and family history information. Varying numbers and types of questions were included in each section.

In the first section, participants were asked about their prior knowledge about inherited forms of colon cancer and about universal tumor screening (items 1 and 3). Participants were asked about their self-perceived risk of developing CRC based on family history (item 2). These questions were included to explore

knowledge about LS and universal screening among patients who have had colon cancer in NL, and to identify any association between risk perception and attitude towards the screening test.

The second section of the survey consisted of twenty-two items. Items 4 to 12 were attitudinal items that explored participants' attitudes towards having their tumor tested for LS. Components included perceptions of the benefits and risks of tumor testing (e.g., identifying high-risk families and worries about insurance, respectively). The responses were on 5-point Likert scales, with 1 being strongly disagree to 5 strongly agree. Some items were negatively worded to address the potential barriers of tumor testing. They included questions about financial barriers (e.g., "I would not take a tumor screening test it if I had to pay for it."), social barriers (e.g., "I am concerned about any discrimination I could face based on the test result.") and the way a tumor testing program might be offered (e.g., "People should not have their tumors screened if they don't ask for the test."). Another key item asked about the willingness of the participant to undergo the screening test ("If a tumor screening program for Lynch Syndrome were to be offered in Newfoundland and Labrador, how willing you might be to have your tumor screened?"). Items 14, 15, and 18 were designed to evaluate the self-perceived likelihood of communicating with family members and healthcare professionals (e.g., "Would you be willing to discuss your test result with any of your doctors or

other healthcare providers to guide your future care or treatment?" or "I would talk to my family members about the results of a tumor screening test done on my tumor."). One question in this section asked the participants if they would need help from a healthcare professional to discuss the results of a screening test with their family members. This item was included to address the potential need for resource allocation if establishing a screening program was undertaken in the province (e.g., the need for meeting with genetic counselors or training primary care physicians or surgeons in facilitating communication with the family about tumor testing). Item 17, ("I understand the implications for my family members of a tumor screening test on my tumor.") was developed to explore any associations among willingness to have one's tumor screened, overall attitude, and understanding the implications the test has for family members of the participant.

The perspectives of patients regarding the need for, and preferred form of, informed consent for a screening program were probed in items 19, 20, and 23. Items 20 and 23 asked about the timing and type of consent if needed. In the last few items in the second section, participants were asked about their views on how a screening program could be run (e.g., when a health care professional should talk to the patients (item 22) or if and when educational materials should be provided (items 24 and 25)). Participants were asked who they thought should talk to the patients about screening tests in a multiple option question (item 21). The options

ranged from family doctor to genetic counselor, but an option to check “anyone above” was also included.

The third and final section of the survey consisted of demographic items (e.g., education level, marital status and number of children). Two items were included to learn about participants’ family history of cancer and colon cancer in particular. In case of a positive family history, participants were given the option to check the relationship with the affected family member (parent, children, spouse, sibling or others). This provided data to explore the relationships between positive family history and attitude towards screening tests and communication. The questionnaire concluded with the open-ended question asking for the participants’ comments and the option to participate in a prize draw (a $500 gift card).

Initial drafts of the survey cover letter and full survey were presented first to the patient partner who reviewed it for language, flow and level of respondent burden. Small revisions were made following his review and the survey was provided to the larger project team (consisting of an epidemiologist, gastroenterologist, and gynecological oncologist) for review. This interdisciplinary review process helped refine the questionnaire to best suit the study objectives, while minimizing medical jargon and respondent burden. The feedback from the patient partner was particularly beneficial in providing a critical patient perspective, resulting in rewording some items for better readability.

Five demographic variables related to the eligible patients were extracted from the tumor registry by the Manager of the provincial cancer registry. They included date of birth, sex, date of diagnosis, stage of tumor at diagnosis and first three digits of postal code. The first three variables were extracted to obtain the age, sex, and year of diagnosis of the participants in order to explore if these were related to the survey responses. Staging of patients was based on The American Joint Committee on Cancer (AJCC) staging criteria, 7th edition (Edge & Compton, 2010). This was extracted to examine associations and relationships among tumor stage and survey content areas. The first three digits of postal code was used to classify participants as urban or rural. The first character denotes the province (example: A for Newfoundland and Labrador). Second character which is numerical, denotes if the area is urban or rural. If the second character in the postal code was '0', it was considered to be rural. If it was any other digit between one and nine it represented an urban area (Du Plessis & Statistics Canada, 2002). A data file containing the case ID of the eligible patients and the five variables were given to the research team by the Cancer Center. The file contained no patient names or other identifying information.

2.5 Survey Administration

A postal survey was chosen for several reasons, including: 1) a potential to reach a large sample size, making postal surveys more cost- and time-effective than telephone and personal interviews; 2) a large number of participants from rural areas and relatively older participants (often less likely to complete electronic or web-based surveys); and finally, 3) a postal survey is relatively easy to administer and allows respondents the freedom to complete at their convenience.

Eligible patients were assigned a case ID by the Cancer Centre starting from 0001. This case ID was used henceforth for tracking the response and for linking the participant to clinical and demographic variables in the tumor registry needed for data collection and analysis. All participants were sent a survey packet to their mailing address given in the registry. Survey packets consisted of the survey booklet, an introduction letter from the cancer center containing the research team's information, and a postage-paid return envelope addressed to the research team.

The survey booklets were also numbered serially from LS-0001 onwards to link back to the participant case ID and contained a cover letter followed by the questionnaire. The cover letter was signed by the research team and outlined the purpose of the study and provided instructions to complete the survey. It contained elements of consent, including the information that taking part in the study was

voluntary, respondents' care would not be affected by survey participation, and withdrawal from the study could be accomplished by either mailing the unfilled survey back or by contacting the research team directly. Telephone numbers, email addresses and mailing addresses of the research team were provided for this purpose. A copy of the cover letter is provided in Appendix B.

The introduction letter from the Cancer Centre was addressed directly to the participant from the Manager of the Cancer Center. The letter outlined the purpose of the study, how the participant was selected and information about the researchers. The letter also informed respondents that the participation in the survey was voluntary and confidential. A copy of the introduction letter is given in Appendix C.

To preserve participant anonymity, the research team assembled the packets including the survey booklet and postage-paid return envelope without having the patients' identifying information. They were inserted into custom-made mailing envelopes with same serial number as the survey. The prepared packets were provided to the Cancer Centre, who inserted the personalized introduction letter and addressed the outer envelopes according to the case ID and serial number on the envelope. The first survey mail-out was on May 29th, 2017.

A second mail-out was administered six weeks later to any participants who did not respond to the first mailing. Case IDs of undelivered surveys and that of

participants who declined participation by contacting the research team were removed from the reminder mail-out. The second round of mailing was administered in the same multi-step process as the first round and was mailed July 20th, 2017.

2.6 Strategies to increase response rate

Several measures recommended to increase response rate (Edwards, 2002) were taken as resources permitted. A monetary incentive was provided in the form of a prize draw. All participants were asked if they wanted their name to be included in prize draw at the end of the study. The winning respondent received a $500 gift card, mailed from the Manager of the Cancer Centre. The mailing envelope and the return envelope contained logos of both the Cancer Centre and Memorial University to emphasize institutional support of this research. The introduction letter from the cancer centre was addressed directly to the participant to establish a personal connection. A postage-paid, addressed return envelope was included in the packet for convenience. A follow-up was made in the form of a reminder mail out, also including the survey booklet and return envelope. The surveys themselves were printed in a large, reader-friendly font in the form of a booklet. Additionally, the booklet was printed in pink colour as some research has shown an increase in survey response rates based on this colour (Etter, 2002).

2.7 Data Collection

The returned surveys arrived directly to the research team. The electronic data set containing the case ID and the five variables was merged with the survey data file. All data collection, storage and analysis were done using SPSS statistical software package, version 23.0 for windows (IBM, 2015). The information from the survey was manually entered into this electronic file by linking the case ID. The entered data were double-checked to ensure accuracy and to reduce errors. Separate variables were created for items with multiple response options to capture all information. For example, item 29 (Has anybody in your family ever had had cancer?) was followed by item 30 (If yes, mark x to all that apply). For item 30, separate variables were created for parent, children, spouse, sibling and others, and responses entered 1 or 0 for yes and no, respectively. This allowed the full capture of family cancer history. Any responses to the options "others, please specify" for items was entered separately. Depending on the responses, additional response categories were added to certain questions. For example, several respondents wrote in "at the time of diagnosis" for item 22. In that case a new category "at the time of diagnosis" was created to capture the information. Any comments and suggestions given by the respondent were entered to the data file verbatim. A second electronic file was kept for tracking the returned and unreturned case IDs. This was also

checked again at the end of the data collection to ensure accuracy. Finally, all surveys returned on or before August 31st, 2017 were included in the analysis.

Several steps were taken to ensure patient confidentiality, data privacy and security. De-identification of the participant list by assigning a random case ID was done by the Cancer Center to make the personal information confidential and not accessible to those outside the patients' circle of care. No contact or identifiable personal information was entered to the electronic data file. Surveys were tracked only using the case ID. Returned surveys were handled directly by the research team. Survey booklets were stored in the office of the PI under lock and key. Data entry and analyses was completed using encrypted computers with password protection.

2.8 Data Analysis

The collected information was double-checked for errors and discrepancies. An alpha level of 0.05 was considered significant. The data analysis was carried out in a series of steps as outlined below.

In the first step, survey response rates were determined, and responders and non-responders were compared on available demographic information provided by the cancer registry. Responders and non-responders were compared using chi square

tests and independent t-tests as appropriate to look for any significant differences between them.

The second step consisted of the descriptive analysis of the responses. The descriptive statistics of all variables were examined. Frequency distribution was used for categorical variables while means and standard deviations were provided for continuous variables. The 5-point Likert type responses were considered as continuous for this purpose. The negatively worded questions (items 6, 7, 9,10 and 11) were reverse coded to reflect higher scores for favourable/positive response towards universal tumor screening for LS. For several items, analysis was limited to descriptive statistics due to the nature of the study. To our knowledge, however, the current study represents the first survey ever conducted in the province about universal tumor screening. As such, simple descriptive analyses can provide valuable initial information for organizers of such a screening program.

In the next step, items measuring similar themes were pooled together to create scales. The internal consistency of the scales was measured using Chronbach's alpha. The mean scores of the scales created were used for all further analyses. Several bivariate analyses were done to examine the associations between various survey items, attitude and communication scores, outcome variables and demographic variables using appropriate statistical tests. Willingness to undergo screening (item 13) and the participant's thoughts on need for informed consent

(item 19) were considered as the outcome variables. The last step of data analyses was the multivariate analyses of outcome variables with other survey items and demographics. All variables with significant associations in the bivariate analyses were included in the regression model. Multivariate regression analyses explored the variables and its relationships to attitude, communication, willingness and consent protocol regarding universal screening of Lynch Syndrome.

CHAPTER 3

RESULTS

Survey results are presented in two sections. The first section consists of descriptive statistics for the survey as whole and for each item. For several items, the analysis is limited to descriptive statistics because of the nature of the study. In the second section, scales are described, and several bivariate and multivariate analyses are presented that explore the associations among survey items, outcome variables and various clinical and demographic factors.

3.1 Descriptive statistics

This section includes the response rates for the survey followed by the demographic characteristics of all eligible participants from the cancer registry. Survey respondents are compared with non-responders to assess if they are similar and representative of the eligible population. This is followed by the demographic and clinical characteristics of the responders (participants).

3.1.1 Response rates

There were 1155 patients diagnosed with CRC from 2014 to 2016 in the Provincial Cancer registry. Of these, 698 patients were eligible for the study after mortality clearance from the Newfoundland and Labrador Centre for Health Information (NLCHI). The survey packets were mailed to all 698 eligible patients. Thirty were undeliverable and were returned to the cancer center, due to incorrect or incomplete mailing addresses. A number of eligible participants explicitly declined participation either by sending back unanswered surveys (n=19) or by informing the research team through telephone calls (n=8). We received 318 completed surveys, giving an effective response rate of 47.6% (318/668). The response flowchart is given in Figure 3.1.

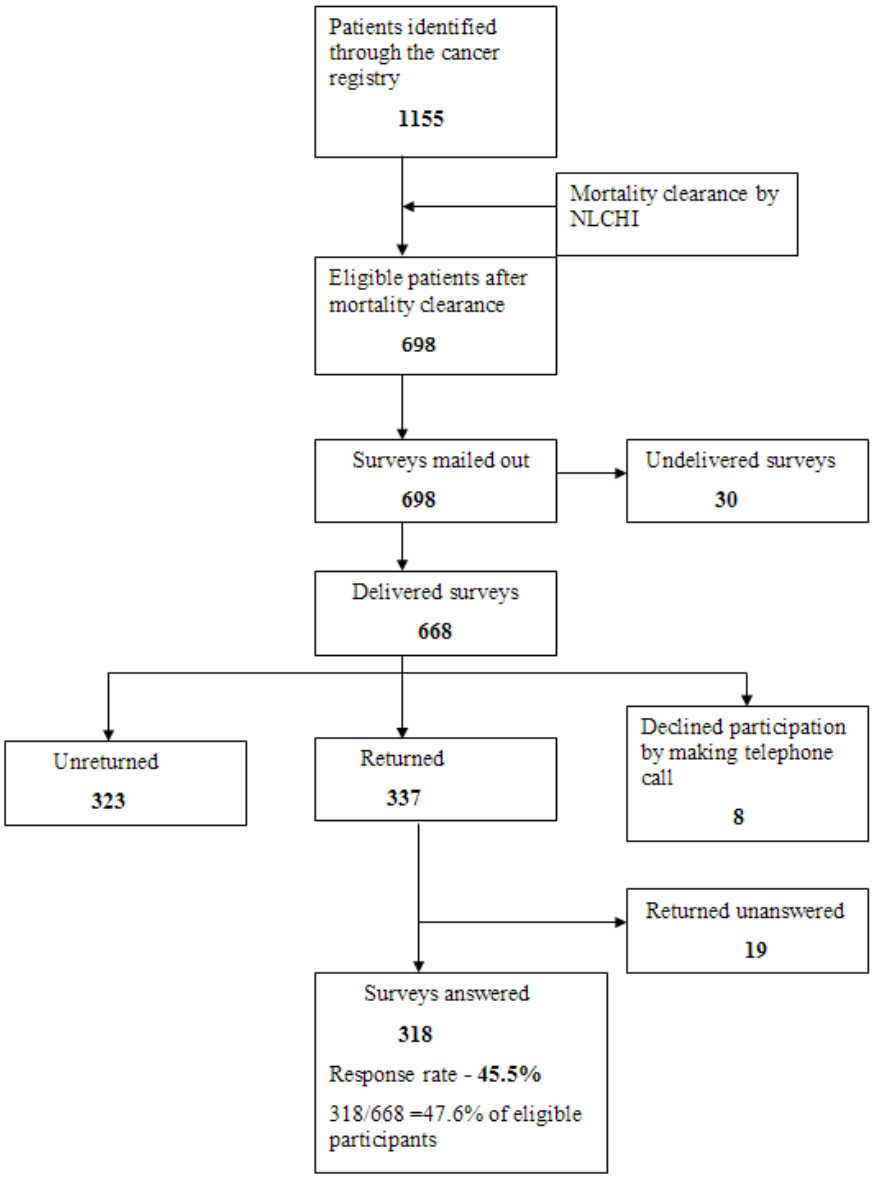

Figure 3.1. Flowchart showing the survey participants and response rate.

The demographic characteristics of the 698 patients are given in Table 3.1. The eligible patients were 56.6% male and 43.4% female. Their mean age was 70, ranging from 34-99 years. A little over half of the patients were residing in rural areas (52.4%) and 313 (45%) were diagnosed in 2016. Information on stage of tumor was not recorded in the cancer registry for 315 (45.1%) of the patients.

Table 3.1. Characteristics of the eligible patients (N=698)

Variable	Categories	N (%)
Sex	Male	395 (56.6%)
	Female	303 (43.4%)
Age	Mean age (SD)	70.5 (10.6)
	Range	34-99
Year of Diagnosis	2014	116 (16.6)
	2015	269 (38.5)
	2016	313 (44.8)
Stage of Tumor [a,b]	I	71 (10.2)
	IIA	122 (17.5)
	IIB	10 (1.4)
	IIC	9 (1.3)
	IIIA	18 (2.6)
	IIIB	101 (14.5)
	IIIC	22 (3.2)
	IVA	21 (3.0)
	IVB	8 (1.1)
	UNK[c]	1 (0.1)
Area	Rural	366 (52.4)
	Urban	332 (47.6)

SD: Standard Deviation

[a] information regarding the stage of tumor was missing for 315 eligible participants.

[b] the stage of tumor is based on American Joint committee on cancer 7th edition (Edge & Compton, 2010)

[c] UNK- Unknown

Survey responders and non-responders were compared to explore any differences among available demographic and clinical variables (Table 3.2). No significant differences were observed in sex, area of residence, year of diagnosis and stage of tumor between the two groups. Patients who responded to the survey were younger than patients who did not, as determined by independent sample t-test (Mean difference =- 2.51; t (694.7) = -3.15; $p<0.05$).

Table 3.2. Comparison of responders and non-responders of the survey.

Variable	Responders	Non-responders	Test
Age	Mean = 69.1	Mean = 71.6	Mean difference =-2.51 (t=-3.15; p<0.05)
Sex	Females 44.3%	Females 42.6%	Chi square 0.206; p -.650
Area of residence	Rural 52.8%	Rural 52.1%	Chi square .036; p- .849
Year of diagnosis	2014- 17.6%	2014- 15.7%	Chi square .0448; p- .799
Stage of tumor*	Stage I – 10.3%	Stage I – 10%	Chi square 7.036; p- .722

*Stage of tumor information missing for 45.1% individuals. 7 cells (31.8%) have expected counts less than 5; Chi square test not valid.

The demographic characteristics of the responders are given in Table 3.3. The mean age of the responders was 69, (SD = 9.7; range 43-94); 55.7% were male. Among the participants, 168 (52.8%) were living in rural areas and 150 (47.2%) in urban areas. The highest level of education for 51% of respondents was a high school certificate or lower, whereas only 18 (5.7%) participants had reported an education level higher than a bachelor's degree. Most of the participants were married or living with a partner (71%) and had children (mean number of children 2; SD 1.6, range 0-10).

The clinical characteristics and family history information of the responders are given in Table 3.4. Among them, 44.7% (n=142) were diagnosed in 2016. Information on stage of tumor was not recorded in the cancer registry for 141 (44.3%) of the patients.

Table 3.3. Demographic Characteristics of the participants (N= 318)

Variable	Categories	N (%)
Sex	Male	177 (55.7)
	Female	141 (44.3)
Age	Mean age (SD)	69 (9.7)
	Range	43- 94
Area of residence	Rural	168 (52.8)
	Urban	150 (47.2)
Highest level of Education [a]	High School certificate or lower	162 (50.9)
	Trade school/non-university or some university	119 (37.4)
	Bachelor's degree or higher	28(8.8)
Current marital status [b]	Single	18 (5.7)
	Married or living with a partner	227 (71.4)
	Divorced/separated	19 (6.0)
	Widowed	46 (14.5)
Number of children [c]	None	18 (5.7)
	1-3	218(68.6)
	3-5	55 (17.3)
	>5	17 (5.3)

[a] Information regarding the highest level of education was missing for 9 participants.
[b] Information regarding the marital status was missing for 8 participants.
[c] Information regarding the number of children was missing for 10 participants
SD: Standard Deviation

Table 3.4. Clinical characteristics and family history of the participants (N=318)

Variable	Categories		N (%)
Year of Diagnosis	2014		56 (17.6)
	2015		120 (37.7)
	2016		142 (44.7)
Stage of Tumor [a,b]	I		33 (10.4)
	IIA		50 (15.7)
	IIB		4 (1.3)
	IIC		4 (1.3)
	IIIA		9 (2.8)
	IIIB		51 (16.0)
	IIIC		11 (3.5)
	IVA		13 (4.1)
	IVB		2 (0.6)
Family History of Cancer (self-reported)	Yes 267 (85.9%)	Parent	134 (42.1)
		Children	25 (8.1)
		Spouse	47 (15.2)
		Sibling	139 (45.0)
		Others	93 (30.0)
	No 44 (14.1%)		
Family History of colon cancer (self-reported)	Yes 137 (44.3%)	Parent	43 (13.9)
		Children	9 (2.9)
		Spouse	12 (3.9)
		Sibling	55 (17.8)
		Others	57 (18.4)

	No 172 (55.7%)

[a] based on American Joint Committee on Cancer (AJCC) guidelines, 7th Edition (Edge & Compton, 2010).

[b.] Information on stage of tumor is missing for 44.3% of the participants.

3.2 Descriptive statistics of survey items

This section details the descriptive statistics of the participants' responses to the survey items. The section is organized based on the objective of the questions in the survey**.** Most participants completed the entire survey, but some surveys were missing data, ranging from 0 to 3.8% of items. Some participants left groups of questions unanswered. It is plausible that pages might have been stuck together while turning sheets in those cases. Descriptive statistics of each subsection are described in the following sections.

3.2.1 Knowledge

Participants had generally little knowledge about inherited forms of colon cancer and universal tumor screening. Around 30% of the participants had never heard about inherited forms of colon cancer, whereas only 9% had heard a fair amount or more. While most of the participants (83.1%) had

never heard of universal tumor screening for Lynch Syndrome prior to this survey, only four participants (1.25%) had heard a fair amount or more. Many participants did not agree with the statement “I have always suspected I would get cancer, because it runs in my family” (221/318; 69.5%). Table 3.5 shows the descriptive statistics of items related to knowledge and risk perception.

Table 3.5. Survey Responses regarding Knowledge and risk perception

Question	Mean response	SD	Missing (%)	Response values frequency (%) 1 least positive, 5 most positive				
				1	2	3	4	5
Before today, how much had you heard about genetic or inherited forms of colon cancer?	2.09	0.971	5 (1.6)	92 (29.4)	135 (43.1)	58 (18.5)	21 (6.7)	7 (2.2)
I have always suspected I would get cancer, because it runs in my family.	2.72	1.195	6 (1.9)	60 (19.2)	77 (24.2)	84 (26.9)	71 (22.8)	20 (6.4)
Before today, how much had you heard about 'Universal tumor screening for Lynch Syndrome'?	1.23	0.593	6 (1.9)	261 (83.7)	35 (11.2)	12 (3.8)	3 (0.9)	1 (0.3)

SD: Standard Deviation

3.2.2 Attitude towards universal screening

Attitude towards universal screening among participants was clearly positive. The majority (259; 81.4%) of participants indicated they would be willing to have their tumor screened if a screening program were offered in NL. Among the participants, 89% agreed that universal tumor screening would be useful for high risk individuals, and 87% believed their family could benefit from this test. Most of the participants agreed that the result of a tumor screening test would help them plan their future (77%) and felt that the test should be available for anyone who has had colon cancer and wishes to have information about his/her inherited risk (92%). Only 27 % of the participants said they would not take a tumor test if they had to pay for it, and 37% were worried that the testing would affect their ability to get health or life insurance in the future. A small portion of the participants agreed to the statement that people should not have their tumors screened if they didn't ask for it (18%), whereas 10% of the participants did not want to know any genetic risks they might have. Twenty one percent of them were concerned about any discrimination they could face based on the test result. These results are summarized in Table 3.6.

Table 3.6: Descriptive frequencies of survey responses about attitude towards universal screening.

Item	Mean response	SD	Missing (%)	Response values frequency (%) 1 least positive, 5 most positive				
				1	2	3	4	5
Universal tumor screening of colon cancer tumors would be useful for identifying high risk individuals.	4.3	0.782	7 (2.2)	6 (1.9)	2 (0.6)	20 (6.4)	147 (47.3)	136 (43.7)
My family could benefit from this test.	4.29	0.795	5 (1.6)	4 (1.3)	5 (1.6)	27 (8.6)	136 (43.5)	141 (45.0)
I would not take a tumor screening test it if I had to pay for it. *	3.25	1.26	10 (3.1)	35 (11.4)	51 (16.6)	84 (27.3)	79 (25.6)	59 (18.6)
People should not have their tumors screened if they don't ask for the test.*	3.72	1.149	9 (2.8)	13 (4.2)	45 (14.6)	47 (15.2)	116 (37.5)	88 (28.5)
The result of a tumor screening test could help me plan my future.	3.96	0.888	9 (2.8)	8 (2.6)	11 (3.6)	46 (14.9)	163 (52.8)	81 (26.2)
I would be worried that universal tumor screening would affect my ability to get health or life insurance in the future. *	2.93	1.11	11 (3.5)	29 (9.4)	88 (28.7)	92 (30.0)	71 (23.1)	27 (8.8)
I am concerned about any discrimination I could face based on the test result. *	3.5	1.1	11 (3.5)	12 (3.9)	57 (18.6)	60 (19.5)	123 (40.1)	55 (17.9)
I do not want to know about any genetic risks I might have. *	3.98	1.02	7 (2.2)	11 (3.5)	22 (7.1)	33 (10.6)	140 (45.0)	105 (33.8)

The test should be available to anyone who has had colon cancer and wishes to have information about his/her risk of inherited forms of colon cancer.	4.36	0.806	5 (1.6)	6 (1.9)	7 (2.2)	8 (2.6)	138 (44.1)	154 (49.2)
If a tumor screening program for Lynch Syndrome were to be offered in Newfoundland and Labrador, how willing you might be to have your tumor screened?	4.24	0.789	6 (1.9)	1 (0.3)	5 (1.6)	47 (15.1)	123 (39.4)	136 (43.6)

SD: Standard Deviation

* : These items were reversely coded to reflect a positive attitude towards universal screening

3.2.3 Communication with health care professionals and family members

Overall, participants were positive about communicating their results with healthcare professionals and family members. Nearly all were willing to discuss their test result with doctors and other healthcare professionals to guide future treatment (n=299; 94%). When asked if they would need help from a healthcare professional to discuss the results with their family, 195 patients (61.3%) agreed that they would. A vast majority of the participants (n=300; 94.3%) indicated they would talk to their family members about the test results. Among the participants, 242 (76.2%) said they understood the implications a screening test could have on their family and most of them (288; 90.5%) agreed that they would encourage their family members to learn more about the implications as well. The descriptive frequencies are given in Table 3.7.

Table 3.7: Descriptive frequencies of survey responses about communication.

Question	Mean response	SD	Missing (%)	Response values frequency (%) 1 least positive, 5 most positive				
				1	2	3	4	5
Would you be willing to discuss your test result with any of your doctors or other health care providers to guide your future care or treatment?	4.41	.582	6 (1.9)	0	1 (0.3)	12 (3.8)	157 (50.3)	142 (45.5)
I would talk to my family members about the results of a tumor screening test done on my tumor.	4.4	.576	6 (1.9)	0	1 (0.3)	11 (3.5)	161 (51.6)	139 (43.7)
I would need help from a healthcare professional to discuss the results of a screening test with my family members.	3.55	1.053	8 (2.5)	10 (3.2)	53 (17.1)	52 (16.8)	145 (46.8)	50 (16.1)
I understand the implications for my family members of a tumor screening test on my tumor.	3.88	.763	10 (3.1)	4 (1.3)	12 (3.9)	50 (16.2)	193 (62.7)	49 (15.9)
I would encourage my family members to learn more about the implications of a tumor screening test done on my tumor.	4.21	.706	8 (2.5)	5 (1.6)	2 (0.6)	15 (4.8)	188 (60.6)	100 (32.3)

Would you be willing to discuss your test result with any of your doctors or other health care providers to guide your future care or treatment?	4.41	.582	6 (1.9)	0	1 (0.3)	12 (3.8)	157 (50.3)	142 (45.5)
I would talk to my family members about the results of a tumor screening test done on my tumor.	4.4	.576	6 (1.9)	0	1 (0.3)	11 (3.5)	161 (51.6)	139 (43.7)
I would need help from a healthcare professional to discuss the results of a screening test with my family members.	3.55	1.053	8 (2.5)	10 (3.2)	53 (17.1)	52 (16.8)	145 (46.8)	50 (16.1)

SD: Standard Deviation

3.2.4 Need for and form of informed consent

Participants' perspectives regarding the need for, and preferred form of, informed consent were more variable than their attitudes towards tumor testing. While a large number (62.6%) were in favour of consent being obtained for universal tumor screening, a quarter of the respondents did not think consent was necessary. Ten percent of the participants were unsure about the need for consent. Most of the participants (63%) thought that the consent can be taken at the same time as the surgical consent, but 20% were not sure about the timing. More than half of the participants preferred a written consent (51.6%), whereas 21 patients (6.77) indicated they wanted both verbal and written consent. Eleven percent of the responders were unsure about the type of consent. The distribution of responses for the items related to need and form of consent is given in Figure 3.2.

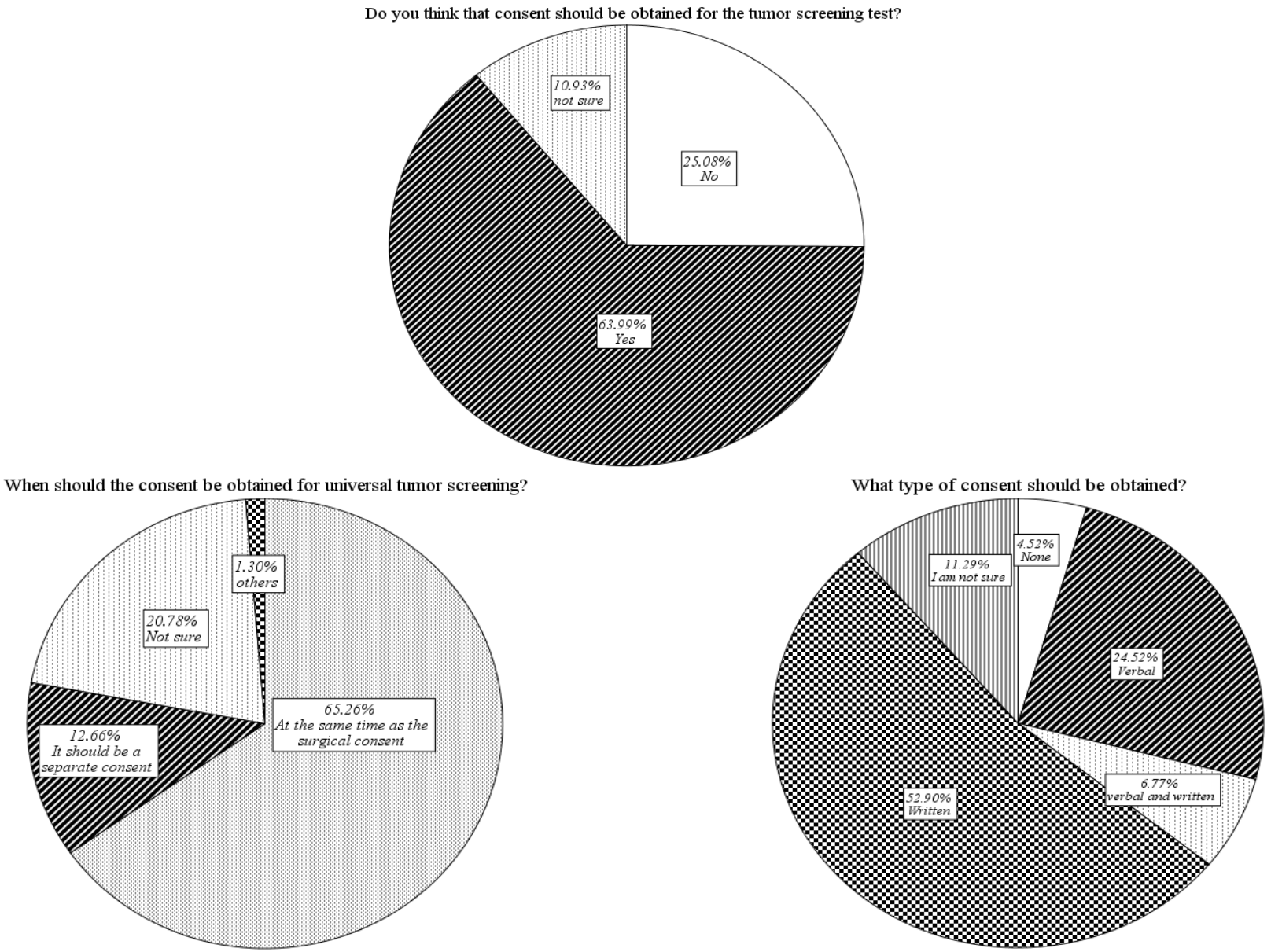

Figure 3.2. Pie charts showing the distribution of responses for items related to consent.

3.2.5 Informing and educating patients

When asked about who should talk to patients about universal screening (item 21), participants wanted to be informed, but they expressed no clear preference for which healthcare professional should be responsible for these discussions. The preferences ranged from genetic counselor (19.5%), oncologist (34.3%), family doctor (40.3%), surgeon (45.3%), or any one of these professionals (52.5%). A bar graph showing this distribution is given in Figure 3.3.

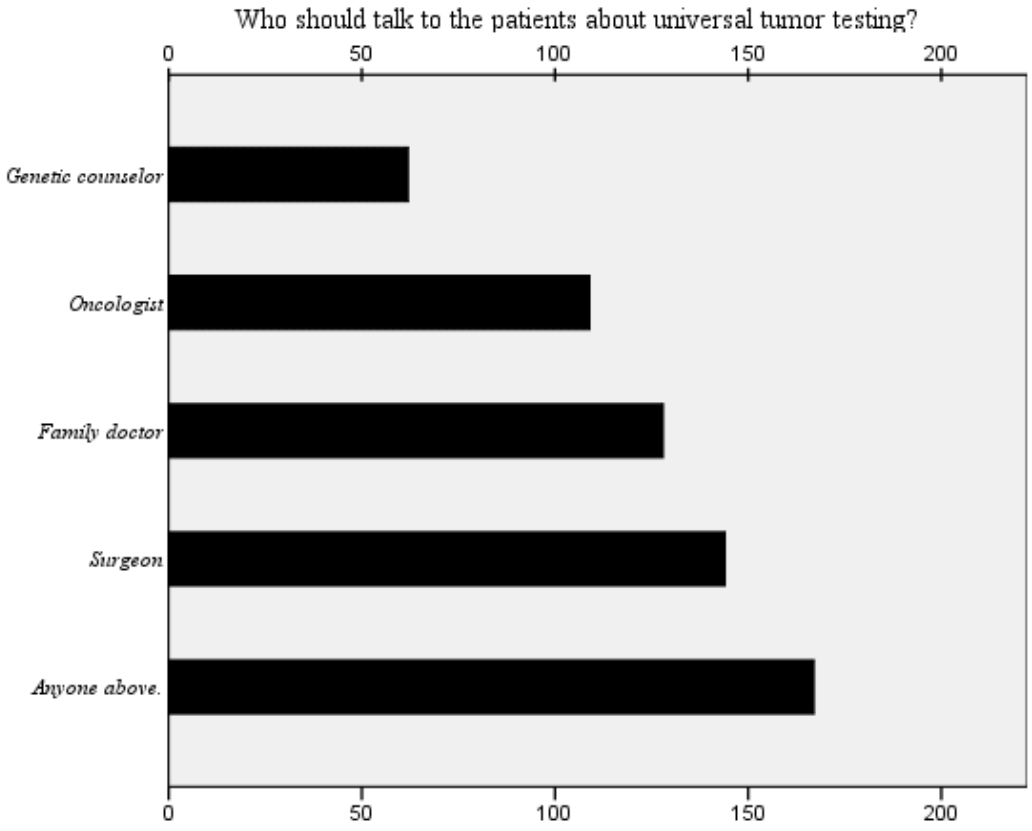

Figure 3.3. Bar chart showing the distribution of responses to item 21.

Most of the study participants (59.1%) were of the opinion that patients should be informed about tumor testing when they first receive the diagnosis. Almost all participants (91.5%) agreed that they needed written educational materials about universal screening and the risk of inherited colon cancer. While over half of them said the educational materials should be provided before the day of surgery, open comments on the survey revealed a small minority who preferred materials at the time of diagnosis. One participant noted they "would like to see more educational material displayed -maybe in Dr's waiting room". Participants' responses on items related to informing and educating patients are given in Figure 3.4.

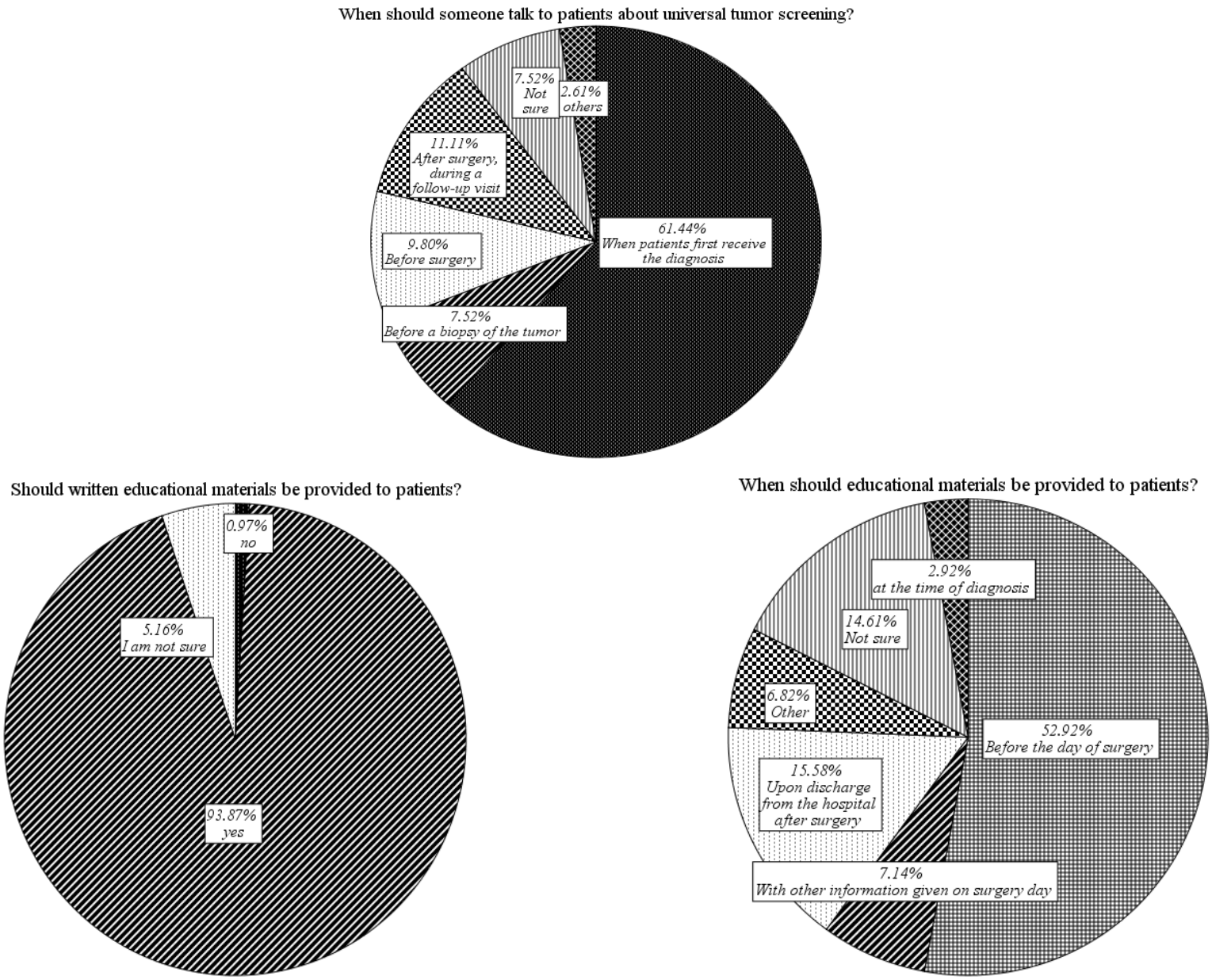

Figure 3.4. Pie charts showing the distribution of survey responses related to informing and educating patients.

3.2.6 Comments and suggestions

An open-ended question was given at the end of the survey questionnaire for the participants to leave any comments or suggestions about tumor testing. Sixty-one people provided comments, which were positive. The following comments were typical:

- "Very happy to hear about it. Should be done in my opinion."
- "I hope that this screening testing will be available soon for my children and grandchildren."
- "I feel this testing is very important for myself and my family. I have two grown sons and siblings that may benefit from this testing."
- "I think this is important, a screening would obviously be pre-emptive for the next generation's ability to seek timely testing such as colonoscopy, etc."
- "I do feel some cancers are hereditary, so if this can help my family or other patients, go for it."
- "This testing should be standard procedure. My question is why is it not?"

One participant indicated he/she was, “very concerned about insurance implications; my medical info should remain confidential.” Overall however, participants were very supportive of tumor testing and thought it would be beneficial to themselves and their family.

3.2.7 Section Summary

The descriptive statistics indicated that participants are willing to undergo screening, have a favourable attitude towards it, and are willing to communicate about the test results with their families and healthcare professionals. Patients also think they should be informed about the test at the earliest occasion and require educational materials about universal screening. The majority of participants prefer a written consent for universal screening for LS, taken at the same time as surgical consent.

3.3 Inferential analyses

This section presents inferential statistics performed on survey data. First, the creation of scales from survey items is described. Secondly, several bivariate and multivariate analyses are presented that explore the associations and relationships between two or more variables.

3.3.1 Creation of scales

Several items in the survey measured the attitude of the participants towards universal screening for Lynch Syndrome. These nine items were summed, and the average taken to create an attitude scale named ATT. The internal consistency of the scale was adequate (Chronbach's α- 0.631). The mean score of the scale was 3.8 (SD=0.5), showing a positive attitude towards screening by the participants.

Similarly, items from the questionnaire pertaining to communication were summed and the average taken to create the communication scale (COMM). When items 14, 15, 16 and 18 were included in the internal consistency analysis, the scale had a low Chronbach's alpha of 0.525.

Further examination revealed that item 16 had a low item-total correlation (0.144) and was removed. Thus, the final COMM scale was created with three items, namely 14, 15 and 18, with a good internal consistency (Chronbach's α -.703). The mean score of COMM scale was 4.34 (SD 0.49). Item 16 was included as a separate item in the subsequent analyses. High scores on COMM scale indicate more communication with family members and healthcare professionals. Table 3.8 shows the properties of both ATT and COMM scales.

Table 3.8 Properties of ATT and COMM scales.

Scale	Items included	Mean score (S.D)	Range	Chronbach's α
ATT	4, 5, 8, 12 6*, 7*, 9*, 10*, 11*	3.8 (0.5)	2.56 - 5.0	0.631
COMM	14, 15, 18	4.34 (0.49)	2.33 – 5.0	0.703

ATT: Attitude scale
COMM: Communication scale
*These items were reversely coded to reflect a positive attitude towards universal screening.
SD: Standard Deviation

3.3.2 Bivariate and multivariate analyses

The section begins with a correlational analysis of key survey items. First, the scales (ATT and COMM) were correlated with each other, with other survey items and with demographic variables. Second, the associations of the two outcome variables (willingness and consent) with other survey items, demographic variables and the scales were explored using the appropriate statistical tests.

3.3.2. Analysis of the scales (ATT and COMM)

A positive correlation was observed between attitude (ATT) and the communication (COMM) scales, indicating that the more positive attitude participants have towards universal screening, the more likely they are to communicate with healthcare providers and family members ($r=0.492$; $p<0.01$). Higher scores on the ATT and COMM scales were positively correlated with an increased willingness to undergo screening. However, the need for informed consent was not significantly correlated with either attitude towards tumor testing or willingness to communicate about it. Prior knowledge about inherited forms of colon cancer and universal screening

was associated with a higher score on COMM ($p<0.05$), but not on ATT. Participants with higher levels of knowledge were more likely to indicate willingness to communicate with family and healthcare professionals about tumor testing. Participants with a higher risk perception had a less positive attitude towards screening test ($r= -.141$; $p<0.05$), but no correlation was observed with the COMM scale ($r=0.006$, p-NS). The correlation matrix of ATT and COMM with the other survey items is given in Table 3.9.

Table 3.9. Correlational analyses of ATT, COMM scales with other survey items.

	ATT [a]	COMM [b]	Willingness.	Need for consent	Prior knowledge about inherited colon cancers	Prior knowledge about universal screening.	Cancer risk perception	Understanding implications for family.	Need for help from HCP [c]
ATT [a]	1								
COMM [b]	.492**	1							
Willingness	.381**	.581**	1						
Need for consent.	-.024	.045	.051	1					
Prior knowledge about inherited colon cancers	.056	.153**	.105	.001	1		.		

Prior knowledge about universal screening.	.032	.119*	.055	.057	.419**	1			
Cancer risk perception.	-.141*	.006	-.011	-.004	.205**	.181**	1		
Understanding implications for family.	.199	.352	.235	.030	.119	-.035	.009	1	
Need for help from HCP [c].	-.031	.144	.057	.109	-.018	-.003	.154	.119	1

[a] Attitude scale
[b] Communication scale
[c] Healthcare professional
** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

Bivariate analyses of ATT and COMM with demographic and clinical variables were conducted separately to explore any significant associations. Age was negatively correlated with both ATT and COMM. Younger participants were observed to have a higher score in the attitude scale ($r=-.117$; $p<0.01$), as well as in the communication scale ($r=-.134$; $p<0.01$). Thus, younger participants had more positive attitudes towards tumor testing and were more likely to communicate with family members and healthcare professionals about it. Independent sample t tests were conducted to compare the ATT and COMM scores across dichotomous variables such as sex, place of residence, family history of cancer, and family history of colon cancer. Among these, participants residing in urban areas (Mean= 4.43, SD= .480) were found to have higher COMM scores than those from rural areas (Mean= 4.26, SD= .497). This difference was statistically significant; $t(307) = 2.93$, $p=.004$. One-way ANOVA tests showed that COMM scores were different across the levels of education of the participants. Participants with higher levels of education were found to score higher in COMM score, showing greater intentions to communicate their test results, $F(2,302) =9.68$, $p<0.01$. However, no difference was observed in the ATT scores across place of

residence or level of education. Family histories of cancer in general or colon cancer in particular were not associated with attitude or communication scores. The results of bivariate analyses of ATT and COMM with demographic and clinical variables are given in Table 3.10 and Table 3.11 respectively.

Table 3.10. Bivariate analyses of ATT with demographic and clinical variables.

Variable		ATT		
		Mean (SD)	Test statistic (df)	Sig
Age			r=-.117*	.046
Sex	Male	3.80 (.510)	t (291) =.946	.345
	Female	3.85 (.502)		
Area of residence	Rural	3.821 (.476)	t (291) = .177	.860
	Urban	3.832 (.539)		
Family history of Cancer	No	3.785 (.567)	t (289) = .585	.559
	Yes	3.836 (.497)		
Family history of colon cancer	No	3.855 (.539)	t (287) =.864	.389
	Yes	3.803 (.464)		
Level of education	Highschool certificate or lower	3.79 (.503)	F (2, 287) = 1.342	.263
	Trade school/some university	3.84 (.526)		
	Bachelor's degree or higher	3.96 (.438)		

Marital status	Single	3.77 (.599)	F (3,286) = 1.149	.330
	Divorced/separated	3.96 (.505)		
	Widowed	3.72 (.545)		
	Married/Living with a partner	3.83 (.485)		
Number of children			r=.013	.825
Year of diagnosis			r= -.030	.609
Stage of tumor [a]	I	3.90 (.486)	F (8,154) = .479	.870
	IIA	3.78 (.503)		
	IIB	3.77 (.192)		
	IIC	3.61 (.584)		
	IIIA	3.89 (.319)		
	IIIB	3.76 (.448)		
	IIIC	3.80 (.538)		
	IVA	3.82 (.493)		
	IV B	4.22 (00)		

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).
SD: Standard Deviation
df: Degrees of freedom
[a] Information on stage of tumor was missing for 141 (44.3%) patients.

Table 3.11. Bivariate analyses of COMM with demographic and clinical variables.

Variable		ATT		
		Mean (SD)	Test statistic (df)	Sig
Age			r=-.134*	.018
Sex	Male	4.321 (.469)	t (307) =.851	.396
	Female	4.370 (.526)		
Area of residence	Rural	4.266 (.497)	t (307) =2.93	.004
	Urban	4.429 (.480)		
Family history of Cancer	No	4.21 (.453)	t (304) =1.788	.075
	Yes	4.362 (.50)		
Family history of colon cancer	No	4.303 (.510)	t (302) =1.881	.061
	Yes	4.410 (.464)		
Level of education	Highschool certificate or lower	4.23 (.483)	F (2,302) = 9.68**	.000
	Trade school/some university	4.44 (.493)		
	Bachelor's degree or higher	4.55 (.435)		

Marital status	Single	4.333 (.5480	F (3,301) =1.745	.158
	Divorced/separated	4.574 (.468)		
	Widowed	4.260 (.557)		
	Married/Living with a partner	4.33 (.477)		
Number of children			r=-.026	.648
Year of diagnosis			r=-.022	.699
Stage of tumor [a]	I	4.40 (.470)	F (8, 162) = 1.369	.214
	IIA	4.35 (.511)		
	IIB	4.89 (.192)		
	IIC	4.50 (.430)		
	IIIA	4.37 (.611)		
	IIIB	4.32 (.424)		
	IIIC	4.27 (.327)		
	IVA	4.10 (.550)		
	IV B	4.833 (.235)		

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).
SD: Standard Deviation
df: Degrees of freedom
[a] Information on stage of tumor was missing for 141 (44.3%) patients.

Prior knowledge about inherited colon cancer or universal screening was not correlated with any clinical or demographic variables, whereas people with a positive family history of colon cancer were more likely to know about inherited forms of colon cancer ($p<0.05$). This risk perception was significantly correlated with their knowledge about inherited colon cancer and universal screening ($p<0.01$).

3.3.3. Willingness to undergo screening.

The outcome variable willingness describes the participants' willingness to undergo a universal tumor screening test if it were offered in our province. Bivariate analysis of willingness with other variables including the ATT and COMM scales, other survey items, and clinico-demographic variables was done. As mentioned earlier, ATT and COMM scores were positively correlated with willingness. Higher scores on the ATT scale were associated with a greater willingness to undergo screening ($r=0.381$, $p<0.01$). Similarly, a high score on the COMM scale was associated with increased willingness to undergo screening ($r=0.581$, $p<0.01$). Patients' willingness to get their tumor tested for LS was not related to their prior knowledge about inherited forms of

colon cancer and universal screening. Likewise, their cancer risk perception was not found to influence willingness to participate in the screening program. Patients' agreement with the statement "I understand the implications of a tumor screening test on my family," was positively correlated with their willingness to undergo screening ($r=0.235$, $p<0.01$). The results of the correlation of willingness with scales as well as survey items are given in Table 3.12.

Table 3.12. Correlational analyses of willingness with the ATT, COMM scores and other survey items.

	Willingness.	ATT [a]	COMM [b]	Prior knowledge about inherited colon cancers	Prior knowledge about universal screening.	Cancer risk perception.	Understanding implications for family.	Need for help from HCP [c].
Willingness.	1							
ATT [a]	.381**	1						
COMM [b]	.581**	.492**	1					
Prior knowledge about inherited colon cancers	.105	.056	.153**	1				
Prior knowledge about universal screening.	.055	.032	.119*	.419**	1			
Cancer risk perception.	-.011	-.141*	.006	.205**	.181**	1		
Understanding implications for family.	.235	.199	.352	.119	-.035	.009	1	

Need for help from HCP [c].	.057	-.031	.144	-.018	-.003	.154	.119	1

[a] Attitude scale
[b] Communication scale
[c] Healthcare professional
** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

The outcome ‘willingness’ was examined for any correlations with clinical and demographic variables. Age was found to be negatively correlated with willingness. Younger people were more willing to undergo universal screening ($r = -.215$; $p<0.01$). The willingness to undergo tumor screening was different between participants who reported a positive family history of colon cancer and others, $t(305) = 2.92$; $p<0.01$. A significant weak correlation between number of children and willingness was also observed ($r=-.137$, $p<0.05$). No significant differences in willingness to undergo tumor screening was observed across variables like sex, place of residence, level of education and marital status of the participant. The results of bivariate analysis of willingness with clinical and demographic variables are given in Table 3.13.

Table 3.13. Bivariate analyses of willingness with clinical and demographic variables.

Variable		Willingness		
		Mean (SD)	Test statistic (df)	Sig
Age			r=-.117*	.046
Sex	Male	4.20 (.816)	t (310) =.1.104	.271
	Female	4.30 (.751)		
Area of residence	Rural	4.20 (.782)	t (310) = 1.143	.254
	Urban	4.30 (.795)		
Family history of Cancer	No	4.05 (.861)	t (307) = 1.866	.063
	Yes	4.28 (.768)		
Family history of colon cancer	No	4.14 (.840)	t (305) = 2.92**	.004
	Yes	4.40 (.682)		
Level of education	Highschool certificate or lower	4.17 (.752)	F (2, 304) = 2.381	.094
	Trade school/some university	4.38 (.751)		
	Bachelor's degree or higher	4.29 (.937)		

Marital status	Single	4.17 (.707)	F (3,304) = 2.253	.082
	Divorced/separated	4.53 (.772)		
	Widowed	4.02 (.856)		
	Married/Living with a partner	4.28 (.770)		
Number of children			r=-.137*	.017
Year of diagnosis			r=.089	.115
Stage of tumor [a]	I	4.16 (.884)	F (8,165) = 1.867	.068
	IIA	4.26 (.777)		
	IIB	5.0 (.00)		
	IIC	4.00 (.816)		
	IIIA	4.67 (.50)		
	IIIB	4.20 (.782)		
	IIIC	3.82 (.874)		
	IVA	3.77 (.927)		
	IV B	5.00 (.00)		

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).
SD; Standard Deviation
df: Degrees of freedom
[a] Information on stage of tumor was missing for 141 (44.3%) patients.

Variables found to be significantly associated with participants' willingness to undergo universal screening in the bivariate analyses, namely age, family history of colon cancer, number of children, understanding of implications, and the two scales measuring patients' attitude and communication were included in the multivariate analysis. A multivariate regression model was developed using Generalized Linear Models, adding and removing variables using the mixed selection method. There was homoscedasticity and no evidence of multicollinearity. The assumption of normality was met, as assessed by a Q-Q plot. The final regression model included age, ATT score, COMM score and family history of CRC with all four variables added significantly to the model ($p<0.05$). Age was weakly, albeit significantly associated with willingness to undergo screening (OR-0.992, 0.98-0.999). A higher score on the ATT scale was associated with an increased willingness to undergo screening (OR- 1.21. 1.02-1.43). The more likely patients are to communicate with healthcare professionals and family members, the more willing they are to have their tumors screened (OR- 2.14, 1.8-2.5). A positive family history of CRC, however, slightly lowers their inclination to get screened for LS, when age, attitude and communication are considered (OR-0.858, 0.74-0.93). The parameter estimates of the final regression model are given in Table 3.14.

Table 3.14. Willingness to undergo screening by age, ATT score, COMM score and family history of CRC.

Variable	Sig.	OR	95% CI	
			Lower	Upper
Intercept	.069	2.38	.935	6.086
COMM	.000	2.14	1.805	2.553
ATT	.022	1.21	1.028	1.438
[Family history of colon cancer=0]	.041	.858	.740	.994
[Family history of colon cancer=1]	.	1	.	.
Age	.027	.992	.984	.999

3.3.4 Need for consent

Item 19, need for consent before universal screening, was considered as an outcome variable and was tested for associations with the ATT and COMM scales, as well as other survey items, willingness to undergo tumor screening and clinico-demographic variables. The outcome was binomial, grouping participants who answered yes to '1' and those who answered no or unsure to '0'. Categorical and continuous variables were included in the bivariate analysis using Chi square tests and students t test as appropriate.

The need for consent was not associated with participants' attitude or communication scores, as evidenced by non-significant test results with the ATT and COMM scales. The need for consent was not associated with the willingness of the participant to undergo screening or their understanding of the implications of the tumor screening test on their family members. Neither prior knowledge about tumor testing, nor risk perception, were associated with opinions about consent. The results of correlational analyses of the need for consent with the scales, willingness and other survey items are given in Table 3.15.

Table 3.15. Bivariate analyses of need for consent with ATT, COMM scales, willingness and other survey items.

Variable	Consent (1=yes)		Consent (0=others)				
	Mean	SD	Mean	SD	t	df	Sig.
Willingness.	4.27	0.765	4.19	0.837	-.890	307	.374
ATT	3.82	0.45	3.84	0.538	.402	289	.688
COMM	4.364	0.481	4.318	0.514	-.780	305	.436
Prior knowledge about inherited colon cancers	2.098	1.007	2.098	0.910	-.024	308	.981
Prior knowledge about universal screening.	1.257	0.652	1.187	0.475	-.997	308	.320
Cancer risk perception.	2.730	1.192	2.741	1.198	.071	307	.943
Understanding implications for family.	3.903	0.788	3.855	0.698	-.525	305	.600
Need for help from healthcare professional to communicate with family	3.64	1.038	3.41	1.064	-1.924	306	.055

SD: Standard Deviation
df: Degrees of freedom

Among the clinical and demographic variables, place of residence and level of education of the participants were associated with a difference in consent outcome. People living in urban areas were more likely to think a separate consent was required for tumor testing (Chi square = 5. 86; $p<0.05$). Similarly, patients with higher education were more likely to require consent (Chi square = 10.5: $p<0.01$). Age, sex and family history of colon cancer were not significantly associated with patients' need for consent. No other clinical and demographic variables were significantly associated with the consent outcome. The results of the bivariate analyses exploring need for consent and various clinical and demographic outcomes are given in Table 3.16.

Table 3.16. Bivariate analysis of need for consent with clinical and demographic variables.

Variable		Need for consent (1= yes; 0=others)
Age	t test (df)	t (309) = 1.345
	Sig.	.180
Sex	Chi square	1.106
	Sig.	.293
Place of residence	Chi square	5.86 *
	Sig.	.016
Level of education	Chi square	10.50**
	Sig.	.005
Marital status	Chi square	.932
	Sig.	.334
Number of children	t test(df)	t (303) =1.91
	Sig.	.057
Year of diagnosis	Chi square	1.228
	Sig.	.541
Stage of tumor [a]	Chi square	6.231
	Sig.	.717
Family history of cancer	Chi square	2.046
	Sig.	.153
Family history of colon cancer	Chi square	.011
	Sig.	.915

** Association is significant at the 0.01 level.
* Association is significant at the 0.05 level.

[a] Information on stage of tumor was missing for 43.4% of the participants. Nine cells have expected count less than 5, results not valid.

A binomial logistic regression model was fitted to examine the effects of place of residence, level of education and attitude on the need for consent outcome. Binomial logistic regression model was fitted with need for consent (1= yes, 0= others) as the outcome variable. It was found that place of residence and level of education were the factors determining need for consent. People with bachelor's degree or higher were 5.9 times more likely to prefer consent compared to those with high school level education or lower ($p<0.05$). Similarly, patients with lower than a bachelor's degree were 6.9 times less likely to think they need informed consent than those with a bachelor's degree or higher ($p<0.05$). Patients living in urban areas were 1.7 times more likely to think a separate consent was required than those in rural areas ($p<0.05$). Factors such as age, sex and attitude were not predictive of the participants' preference for consent. The Parameter estimates are given in Table 3.17.

Table 3.17. Regression parameters of need for consent by place of residence and level of education.

Variable		Sig.	OR	95% CI	
				Lower	Upper
Rural		.042	1.707	1.019	2.861
Urban	.	.	1	.	.
High school certificate or lower		.019	5.958	1.337	26.548
Trade school/non-university program/some university		.012	6.892	1.537	30.907
Bachelor's degree or higher.	.	.	1	.	.

3.4 Chapter summary

The support and positive attitude of the participants towards universal tumor screening was evident from the analyses presented in this chapter. The multivariate regression analysis showed that irrespective of age or clinical characteristics, participants were favourable towards universal screening for LS. The information obtained regarding opinion on consent protocols and the education needs of patients will provide critical information to develop a screening program in Newfoundland and Labrador. A deeper understanding of the implications of the results of this study is detailed in the next chapter.

CHAPTER 4

DISCUSSION

This chapter begins with a discussion of the study sample, followed by a discussion of the survey results. The strengths and limitations of the study are described. The chapter concludes with a review of the implications of this research and suggestions for future studies.

4.1 Introduction

Colorectal cancer (CRC) is a leading cause of mortality and morbidity in Canada. Approximately 3-5% of CRC is due to Lynch Syndrome (LS), making it the most common type of familial colon cancer. Newfoundland and Labrador (NL) has the highest incidence of CRC and the highest rate of CRC death in Canada (Public Health Agency of Canada, 2015). Moreover, NL has the highest frequency of familial colon cancer in the world (Green et al., 2007; Woods et al., 2005). In this province, identifying individuals at risk of having LS is therefore particularly important. Identification of high-risk individuals by conventional family history

criteria can be ineffective due to low reliability; that is, a significant number of high-risk individuals are missed (Berg et al., 2009). Universal tumor screening for LS for all newly diagnosed CRC patients has been recommended by several international groups and guidelines and is now standard of care in the US and elsewhere (Berg et al., 2009; Bonis et al., 2007; Giardiello et al., 2014; Provenzale et al., 2016; Weissman et al., 2012). However, access to universal tumor screening is variable across Canada. Understanding the perspectives of eligible patients regarding attitudes towards tumor screening and their willingness to take part in screening will be critical to the successful implementation and conduct of a universal screening program. This study explored the perspectives of patients with colon cancer in NL towards universal tumor screening for LS. In particular, their attitude towards a screening program, willingness to participate, thoughts on communication with both family members and healthcare professionals, and their beliefs on the type of informed consent needed for tumor screening (or indeed, whether it was needed at all). The project was conceived directly in response to local discussion about the feasibility of establishing a tumor screening program in NL.

4.2 Sample and representativeness

The study response rate was 47%. This response rate is consistent with other research utilizing postal surveys with patients with colon cancer specifically, and cancer generally (Asch, Jedrziewski, & Christakis, 1997; Hornik Robert, Fraze Taressa, & Kelly Bridget, 2010). The response rate is higher than surveys of similar populations in the US (Hornik Robert et al., 2010; Smith et al., 2007). The good response rate may be indicative of the interest local patients have on the topic and helped ensure an adequate sample size for analyses.

Survey respondents were representative of the target population across all demographic variables, except age. The mean age of the respondents was slightly lower than the non-respondents, consistent with the available literature (Hornik Robert et al., 2010; Smith et al., 2007). This could be due to an increased difficulty in completing the survey because of the morbidity associated with a cancer diagnosis and advancing age, or that younger individuals are more interested in participating in the survey. We note, however, that the difference in age was minor (roughly 71 years versus 69 years).

The male-female ratio, as well as the rural-urban ratio of the participants, were comparable to the target population. Regarding level of education, over half of the participants in this study had a high school certificate or lower. In general, those

with higher education levels are more likely to respond to surveys than those with lower levels of education (Curtin, Presser, & Singer, 2000). For example, a similar survey study in the US exploring CRC patients' beliefs about universal screening reported that most participants were highly educated (Hunter et al., 2015). However, the range of education levels represented in our sample corresponds to the level of education of the average Newfoundland resident (Etchegary et al., 2013). We believe this has helped ensure a more representative sample from the population.

The majority of the participants had a positive family history of cancer. This finding was unsurprising and corresponds to the high prevalence of cancer in the province (Public Health Agency of Canada, 2015). Less than half of the respondents reported a positive family history of colon cancer specifically, also consistent with other Newfoundland studies (Green et al., 2007). In all, survey respondents were representative of patients in Newfoundland with colon cancer, and there were no important differences between respondents and non-respondents.

4.3 Prior knowledge and risk perception

Study participants had low levels of knowledge regarding inherited forms of colon cancer and universal screening. This finding is consistent with the existing

literature (Etchegary et al., 2013; Manne S. et al., 2007). The knowledge levels of participants with CRC were lower than those of patients with known LS mutations. This was expected as patients with known LS would have received detailed genetic counselling and therefore more likely to be familiar with inherited forms of colon cancer (Etchegary et al., 2009; Hunter et al., 2015). Our study population included all patients with CRC, irrespective of family history or known mutations, as this would be the target population for a universal screening program. Additionally, our participants were not highly educated, with most of them having a high school certificate or lower. The findings of this study demonstrate low knowledge levels among the general population and the need for awareness among the general public if a tumor screening program were to be implemented. Thus, there is a critical need for the development of patient-centered educational materials about universal tumor screening.

Study findings revealed low perceived risk of developing colon cancer among the participants. Risk perception was significantly correlated with family history of cancer and level of education. Participants with a positive family history of cancer reported a higher risk perception, whereas those with a higher level of education reported a lower risk perception. Level of perceived risk was consistent with other studies (Croyle & Lerman, 1993; Hunter et al., 2015), but is lower than that found in the literature related to Lynch syndrome risk perception and genetic testing

(Watkins et al., 2011). Studies suggest that knowledge about genetic cancer is associated with an increased risk perception (Seven, 2017). The lower education level, in addition to low levels of prior knowledge of inherited cancer in our sample, could help explain the lowered risk perception observed in our study. While NL has a high incidence of familial cancers, (Green et al., 2007) low knowledge levels observed in this study suggest the need for better education and the need for more awareness about Lynch Syndrome in the province. It is interesting to note that even with low risk perception and low knowledge levels, surveyed patients were highly willing to undergo screening and had a positive attitude towards it.

4.4 Patient attitude and willingness to undergo screening.

Attitude of the patients and their willingness to participate in a tumor screening program are both critical to identifying individuals at risk of having Lynch syndrome (LS) (Daudelin, Lehoux, Abelson, & Denis, 2010; Etchegary, 2014). Our study results suggest that patients with colon cancer in Newfoundland and Labrador (NL) have a positive attitude towards universal screening and are willing to have their tumors screened if such a program were to be offered in the province. Patients agreed with the potential benefits of the program. Specifically, they agreed

that their family could benefit from such a screening test, and that the results could help them plan their future. They also agreed that a screening program for LS would be beneficial to high risk individuals and should be available to anyone who has had colon cancer. These findings are consistent with the results of the handful of studies to report patients' attitudes towards universal tumor screening (Hunter et al., 2015; Manne S. et al., 2007) and reflects the overall positive attitude towards genetic screening tests (Etchegary et al., 2009; Etchegary, 2014; Kessler et al., 2005; Meisel et al., 2013; Scuffham, McInerny-Leo, Ng, & Mellick, 2013). Of note, the majority of the participants did not consider paying for the test as a barrier, in contrast to the US study (Hunter et al., 2015). Similarly, only a small percentage of participants noted concerns about health or life insurance. While this finding was consistent with existing evidence, concerns about health and life insurance implications of a screening test are valid concerns for some patients as evidenced in studies conducted across Canada and elsewhere (Esplen et al., 2001; Lerman, 1994). The relatively low concerns about barriers to tumor screening observed in this sample is likely the result of Canada's Universal health care system and its extensive coverage. Research confirms that Canadian patients are not generally as worried about insurance or the cost of medical care compared to their counterparts in other parts of the western world (Blendon, Leitman, Morrison, & Donelan, 1990; Ridic, Gleason, & Ridic, 2012). Our findings on other barriers

such as ‘people should not have their tumors screened if they don’t ask for it’ and ‘I do not want know about any genetic risks I might have’ are consistent with similar studies (Hunter et al., 2015; Manne S. et al., 2007). We found that patients with a higher risk perception had a less positive attitude towards screening. This finding was also in line with those found in the literature (Manne S. et al., 2007). It is possible some patients would have a fatalistic attitude towards cancer risk, believing that nothing can be done to change the risk and therefore not seeing value in a possible risk-reducing or preventative measure (Claassen et al., 2010; McClure, 2002). The potential relationship between fatalistic attitudes and behavioural modification after the identification of a genetic risk has been studied with inconclusive results. Some studies found that patients see genetic risk information as uncontrollable and are therefore less likely to engage in screening or preventative behaviors (Senior, Marteau, & Peters, 1999). Others have found limited /little evidence as to its impact on risk reducing behaviour (Collins, Wright, & Marteau, 2011; Marteau et al., 2004; Wright, 2006). In our study, the correlation between risk perception and unwillingness to undergo the screening test could be due to fatalistic attitudes or that some patients may simply fear knowing their genetic status (Croyle & Lerman, 1993; Hunt, Davison, Emslie, & Ford, 2000).

An overwhelming majority of the participants were willing to have their tumors screened if a universal screening program were available in NL. This finding is

consistent with existing literature; patients are generally willing to undergo screening tests and hold a positive attitude (Hall et al., 2014; Kessler et al., 2005; Knight et al., 2015; Manne S. et al., 2007; Meisel et al., 2013; Scuffham et al., 2013). Unsurprisingly, patients with a more positive attitude towards screening were more willing to undergo screening themselves, which is again consistent with the findings of other studies (Cameron & Muller, 2009; Etchegary, 2014; Meisel et al., 2013; Scuffham et al., 2013). However, a positive attitude does not necessarily translate into increased uptake (Cameron & Muller, 2009). As such, we have no way of knowing if the positive attitudes observed in this study would actually translate into positive tumor screening uptake. However, the favourable attitude of patients who have had colon cancer is a necessary first step in the creation of a local tumor screening program.

The results of this study indicate that younger patients had a slightly more favourable attitude towards screening and were more willing to undergo screening themselves. This trend has been observed in studies examining the factors associated with MSI testing specifically, and genetic testing in general (Etchegary, Green, Parfrey, Street, & Pullman, 2015; Shaikh, Handorf, Meyer, Hall, & Esnaola, 2017). This could be due to the extra burden an additional test would bring on elderly patients, and suggests the need for more patient education about the importance of tumor screening, not only for self, but also other family members

(Hall, 2010). In our study, family history of cancer had no correlation with the patients' attitude. It was found that patients with a positive family history specifically of CRC, however, were more willing to undergo screening. While not a strong correlation, this finding is consistent with the literature (Karlitz et al., 2015; Kinney et al., 2000). It is interesting to note that in the study by Hunter et al., the lack of family history of CRC was the most common reason given by the participants to refuse screening (Hunter et al., 2015). The relatively weak associations of age and family history of cancer with willingness to undergo tumor screening could be a reflection of the lack of variability in the outcome variable: a sizable majority of respondents indicated their intention to participate in a tumor screening program.

We found that patients who were willing to undergo screening were also more likely to communicate their results with family members and healthcare professionals. Willingness to communicate test results is also a key factor in the success of a tumor screening program. The findings related to communication are discussed in the following section.

4.5 Communication

It was clear from our study that patients with a favourable attitude and willingness to undergo screening were more likely to communicate their results with family members and healthcare professionals. This finding is consistent with the other studies in the literature (Esplen et al., 2001; Graves et al., 2014; J. Hunter et al., 2017; Katz et al., 2017; Leenen et al., 2016; Pentz et al., 2005; Stoffel et al., 2008). Patients who had prior knowledge about Lynch Syndrome and universal screening, and those of a younger age, with higher education levels, and an urban residence were more inclined to communicate their results. Graves et al. studied the psychological, communication, and behavioral outcomes following an offer to learn MMR results among patients in a Colon Cancer Family registry. They examined the participants' views on communication of their MMR test result with family members. Most of the participants, whilst having a higher risk perception, had disclosed their test results with their family members and healthcare professionals. Those with a family history of CRC and prior knowledge were more likely to discuss this with their doctor (Graves et al., 2014). In a qualitative study of HNPCC families, Pentz et al. similarly found that HNPCC families supported the idea of communication with family members about their genetic risk, namely to facilitate early screening among at risk individuals. They also found that while the probands were the main informants,

healthcare professionals also played an important role in the dissemination of the information to the family members (Pentz et al., 2005). In our survey, more than half of the participants thought that they would need help from a healthcare professional in communicating to their family about the results of the screening test. This finding is also consistent with other studies (Kass, Sugarman, Faden, & Schoch-Spana, 1993) and highlights the critical need for trained healthcare professionals in a tumor screening program, or at least for the development of educational resources for use by healthcare professionals involved in tumor screening programs.

Stoeffel et al. found no demographic factors to be associated with communication in a study among patients who fulfilled family history criteria for LS and had undergone genetic testing (Stoffel et al., 2008). In the current study, participants had low prior knowledge and had never been screened for LS mutations. Even so, the clear majority of participants expressed an intention to communicate their results with family members and healthcare professionals. Study findings suggest that educational initiatives about the value of tumor testing for families or communication support may be needed for particular subgroups of the population, such as older patients, those living in rural areas or those with lower levels of education. The findings highlight clear expectations of patients for the role of healthcare professionals in helping them communicate with family

members and suggest resources that would be necessary in developing a tumor screening program for our province.

There are several identified barriers to communication with family as well. They include factors such as pre-existing relationship dynamics within the family, uncertainty of the risk, and varied understanding of the implication of the genetic risk on the relatives (Forrest et al., 2003). Healthcare professionals and genetic counselors need to be cognizant of these barriers from the patient perspective so that effective communication with the at-risk relatives can be established. Several studies have explored various approaches to facilitate communication with family members regarding a genetic risk. One of them is providing the patients with printed informational materials and subsequent follow up support (Gorrie, Archibald, Ioannou, Curnow, & McClaren, 2018). A 'family mediated approach' in which the communication methods to the family members are discussed with the patients during genetic counseling following diagnosis, and a printed informational letter for the relatives provided to the patients, has also been found to be satisfactory and effective by patients in the Netherlands (Leenen et al., 2016). Another strategy that has been proposed is a telephone-based, two-step approach, in which patient education and support are given through telephone calls from counselors, along with printed informational sheets for healthcare providers and patients themselves (Graves et al., 2014). These strategies, coupled with the

findings and insights from our study, could help formulate counseling and communication policies that would benefit the patients and aide them in communicating their results to family members and relatives. This, in turn, could facilitate genetic screening of the relatives, frequent cancer screening tests to detect early cancer if needed, and eventual lowering of the mortality and morbidity due to Lynch Syndrome.

4.6 Need and preferred form of consent.

A key aim of the current research was to explore patients' perspective on the need for (and preferred form of) informed consent for tumor testing. Informed consent involves educating the patients about the risks, benefits and alternatives to the procedure or test prior to the test, thereby enabling them to make informed decisions about their health; it also has ethical and legal ramifications (Annas, 1977; Faden, 1986). Explicit informed consent is required prior to colon cancer screening procedures, including colonoscopy. However, there is no similar mandate of consent requirement in testing biopsy samples or resected tissue samples (Feld, 2002). The consent model often used in this situation is of implied consent. That is, testing takes place unless patients explicitly decline. Genetic tests require explicit informed consent because of their implications in the patient's, as

well as their families', health and future (Feld, 2002). There are no universally-accepted guidelines for consent protocols of universal screening for LS and it is the subject of debate in the literature (Beamer et al., 2011; Shipman et al., 2013). MSI testing can be considered a genetic test, and as such, the EGAPP Working Group (EWG) suggests the use of informed consent prior to MSI testing, whilst noting the contrasting views from the literature (Berg et al., 2009). IHC testing is not viewed as 'genetic testing' and thus, informed consent is not a requirement (Berg et al., 2009). Some authors disagree, suggesting IHC testing has more in common with genetic tests because of the information the test provides (Chubak et al., 2011). Chubak et al. conclude that explicit informed consent is not required for MSI testing because the testing does not affect patients in "potential harmful ways" that would necessitate an informed consent. From a medical and public health ethics point of view, debate exists about protecting patient autonomy for the patients who test positive and the fear of causing unnecessary stress and anxiety for the patients who test negative. The need for, and form of, informed consent for the cascade screening of family members of patients who test positive has largely not been addressed. Furthermore, resources, personnel and time needed for building consent protocols and obtaining them are also of significant concern (Bombard et al., 2017; Zeps, Iacopetta, Schofield, George, & Goldblatt, 2007). To date, the consent protocols regarding these screening tests are not well established and are widely

debated (Bombard et al., 2017; Chubak et al., 2011; Janet & Marc, 2011; Shipman et al., 2013).

Given the reflexive nature of tumour screening and the significance of cascade testing of the family members which would significantly impact the success of the screening program, the need for consent and the consent protocol for universal screening, we suggest that patient views on consent protocols are a critical piece of information in the planning of a universal tumor screening program.

Patient perspectives on consent models for tumor screening have not been researched extensively, and this study aimed to contribute to filling that gap. Contrary to most current practice, our results indicate that the majority of patients believed an informed consent was required for universal screening. This finding is consistent with the few other studies that have examined patient perspectives on consent in this context (Ormond et al., 2007; Wolf & Schorling, 2000). The finding is in contrast to the perspectives of many healthcare providers on informed consent for tumor screening. For example, none of the 29 National Cancer Institute–designated cancer centers that participated in a survey exploring Lynch Syndrome screening practices using MSI or IHC required an informed consent from the patients (Beamer et al., 2011). Several other studies have also suggested that a consent is not necessary for screening for Lynch Syndrome (Gaff, Rogers, & Frayling, 2007; Janet & Marc, 2011). Bombard et al. found that healthcare

professionals in Canada did not see the need for obtaining consent for screening for LS in a qualitative study, but did agree with giving patients the choice of opting out of further confirmatory mutation testing (Bombard et al., 2017). In the current study, highly educated patients were more likely to believe informed consent is required before a universal screening test. This result is consistent with the existing evidence: namely, that educated patients prefer to be in control of their health and to participate in decision making (Degner & Sloan, 1992). In contrast, it has been observed in a UK study that people with low education levels were more likely to expect to be asked for explicit consent (Riordan et al., 2015). We found that the belief on the need for informed consent was not associated with the attitude towards the screening test or willingness to undergo screening. These findings are also in agreement with the existing evidence (Degner & Sloan, 1992; Riordan et al., 2015). This, coupled with the highly positive attitude of the participants towards tumor screening, highlights the interest of the patients in understanding their genetic risk and their desire for active participation in decision making about tumor screening. Our findings suggest that patients prefer a written informed consent taken at the same time as surgical consent. These findings have immense practical value in the implementation of the screening program, but they also raise serious practical and logistical concerns regarding the content of consent materials and the role of healthcare professionals in gaining consent, particularly in the

existing climate that tends towards non-requirement of informed consent in screening for LS. Serious thought will need to be taken by decision makers responsible for planning tumor screening programs about consent protocols that are acceptable to patients. In the light of present findings of patient preference for consent, an opt-out strategy could be a practical suggestion Even though there is some difference of opinion among healthcare providers whether an opt-out option be provided before or after the screening test, it is generally agreed upon that seeking such a consent could be appropriate considering the minimal constraints on resources for its implementation (Bombard et al., 2017).

4.7 Informing and educating patients

Expert guidance on implementing universal tumor screening programs for Lynch syndrome (LS) suggests that educating patients and families is a crucial step (Berg et al., 2009; Forrest et al., 2003; Provenzale et al., 2016). In the current study, participants wanted to be informed about screening for LS at the time of diagnosis, by almost any healthcare professional. Most often, patients indicated their surgeons or primary care physicians could talk to them about universal screening for LS. Given the scarcity of genetic counsellors and long wait times for counselling services in NL, this finding has practical implications (Parfrey et al.,

2017). There is evidence suggesting the public expect their primary care physician to know about genetics and to communicate potential genetic risks (Feero, 2008; Miller et al., 2010). Pre-test counselling/ discussion with the patients could be undertaken by trained nurses, surgeons, or family doctors, thereby utilizing scarce counseling resources wisely. The CanIMPACT (Canadian Team to Improve Community-Based Cancer Care along the Continuum) study found that Primary Care Physicians (PCP) understand their role and express interest in genomics and personalized medicine. However, only 53% of the participating PCPs were knowledgeable about genetic testing for CRC (Carroll et al., 2016). Strategies to increase awareness and knowledge about genetic services and genomics and collaboration with genetic counselors and geneticists should be incorporated in optimizing the role of PCPs in universal screening. Similarly, surgeons also play a role in communicating and educating the patients. As they are the first healthcare providers patients often see after their initial diagnosis, the burden of providing adequate information on Lynch Syndrome, screening and its implications could fall with surgeons. It has been found that healthcare providers hold a favourable attitude towards universal screening. HCPs also understand the importance of patient education at an early stage as well as creating awareness in the community (Bombard et al., 2017). Resource allocation for training other healthcare professionals on tumor screening for LS and informing patients is an important

issue that needs to be addressed by policy and decision makers. (Rahimzadeh & Bartlett, 2014; Watson, Shickle, Qureshi, Emery, & Austoker, 1999).

We found that patients prefer educational materials to be provided about universal tumor screening and LS prior to screening tests. Educating patients and creating awareness is agreed upon by healthcare professionals and policy makers (Beamer et al., 2011; Bombard et al., 2017; Manne S. et al., 2007), but as of yet, no common set of guidelines or materials are universally accepted and used. EGAPP guidelines recommend providing educational materials for all CRC patients, as well as their relatives (Berg et al., 2009). The low levels of prior knowledge and awareness in the current study population stresses the importance of informing and educating patients. Several studies have underscored the importance and effectiveness of educational materials in LS screening, which range from educating and enabling the patients themselves, to communication with and educating the family members (Dilzell, Kingham, Ormond, & Ladabaum, 2014). Such facilitation of communication with the aid of educational materials could be useful in cascade screening of the family members resulting in early identification and subsequent preventative measures (Dilzell et al., 2014). Programs such as the Lynch Syndrome Educational Workshop (LSEW) and Lynch Syndrome Patient Advocacy Network (LSPAN) support group have been found to be satisfactory by patients. The participating patients expressed preference for topics including

family communication, genetic testing decisions, and support groups (Corines et al., 2017). Our findings, together with the existing knowledge, could help in formulating program guidelines, namely the development of educational materials and training programs for healthcare professionals who might be involved in tumor screening programs.

This is the first study conducted in the province about patients' attitudes towards universal tumor testing in the context of LS. Given the high rate of familial colon cancer in the province, and the growing endorsement of universal tumor testing as an effective strategy for identifying high-risk individuals, study results provide invaluable information for the healthcare professionals and policy makers who are discussing this possibility locally. Our results are consistent with the studies conducted in the US and elsewhere (Hunter et al., 2015; J. Hunter et al., 2017; Manne S. et al., 2007) and reveal the importance of understanding patient perspectives on tumor screening.

4.8 Limitations of the study

There are a few limitations to consider in this study. The questionnaire developed by the research team was not pilot tested. However, it was reviewed by our patient partner for the flow of items, readability, length and content. Changes were made

based on his review, as well as the review by a gastroenterologist and gynaecologic oncologist, both of whom have worked with families affected by LS. Despite the lack of pilot testing, no research has been conducted in this area in the province and the study's key objective was to obtain patient perspectives, which we believe was achieved. While adequate, the internal consistency of the attitude scale (as measured by Chronbach's alpha) was low. Further, while we created attitude and communication scales for purposes of analysis, these were not subject to formal scale validation. Given the pilot nature of this work, and the need to collect patient opinion data before any tumor testing program started in the province, we believe the results have descriptive value. However, we recommend formal scale validation in future work should similar scales be used. The eligible participants from the cancer registry included patients diagnosed from 2014-2016, which excludes the views of patients diagnosed before or after that period. The research team had no control over the potential population, as the Cancer Centre decided these were the years to be included. While we have no reason to believe that attitude or willingness would be different if patients were diagnosed in other years, we cannot rule out the possibility. Our study did not have an age limit set for the eligibility criteria. The mean age of participants was around 70, and this could affect generalizability of the results. However, with recent studies suggesting all newly diagnosed CRC patients undergo screening irrespective of age, we think our

eligibility criteria were inclusive and more representative of the stakeholder population in our province. The current study also did not include the perspectives of family members; however, a positive tumor screening test has notable implications for relatives. Their perspectives are also critically important, and we suggest future research explore the opinions of this population. Lynch syndrome (LS) is associated with a higher incidence of cancer in extra colonic sites, including the endometrium for which universal screening is recommended. In this current study, the perspectives of endometrial cancer patients are not explored. Future studies might also explore the attitudes of these patients with LS-associated, extra colonic malignancies. All surveys are liable to non-response bias which occurs when the responders and non-responders differ in certain ways including socio-demographic factors, behaviour and attitude. Those who have responded to the survey could have had more favourable attitudes than the non-responders, thereby overestimating our findings and lowering the external validity of the study. Non-response bias is different from volunteer bias, in which the people who volunteered to participate in the survey (completed the survey) systematically differed from the population. It is possible that people who participated in the survey had more favourable attitudes than the target population. The sequencing of survey items (e.g., “People should not have their tumours screened if they don’t ask for the test”, before items on the need for informed consent in the

questionnaire) could have primed the participants about expectations for consent, thereby affecting response to the consent items. We cannot rule out this possibility and it is a limitation of the study. We also excluded the patients who died prior to the survey. It is possible that these patients (prior to death) and/or their families, could hold extreme views about the benefits/risks of tumor screening that would not be representative of the rest of the group. Finally, the extreme lack of variability in the outcome variable (willingness to take part in a tumor screening program) could have skewed the results and reduced the validity of the results. We note however, that planners of a tumor screening program in the province would need this key information on interest from the general public.

4.9 Strengths of the study

This is the first study of its kind exploring the perspectives of patients towards universal screening for LS in the province. To our knowledge, there are no published studies in Canada about patient views. This is the main strength of the current study, addressing the existing knowledge gap in this area and providing important patient perspectives that should be helpful in planning a tumor screening program in the province. While limited in years, the inclusion of all patients from the cancer registry diagnosed during the specified time period helped to avoid

sampling bias. One of the strengths of this survey is the good response rate, which highlights the interest of the population in this topic. We undertook several steps to increase the response rate including reminder mail outs, a personalized cover letter, a prize draw, and including postage-paid return envelopes with the survey booklet. The high response rate, combined with the low number of missing responses, contributed to the quality of the data. Finally, the range of education level in our sample was variable and represented the provincial distribution fairly well. Survey studies in genetics very often contain highly educated samples. Our sample better reflected the patients who would be offered tumor testing, thus increasing the generalizability of our results.

In this era of patient autonomy and personalized medicine, the role of public engagement in research is inimitable (Etchegary & Wilson, 2013).This study involves the patients who are the key stakeholders, on two levels, namely patient participation and patient engagement. Firstly, this study provides strong descriptive answers from patients regarding the practical aspects of the development and implementation of a universal screening program. Specifically, when tumor screening should be discussed with patients, who should have that discussion with patients, what kinds of consent protocols might need to be in place, and what kind of educational materials would need to be developed. Secondly, this study engaged a patient partner, a person who brought his expertise and experience as a colon

cancer survivor. He was involved with the research team from the beginning stages of the study. He helped to review the survey and provided valuable input to ensure the survey quality and dissemination. He is eager to be involved in the future steps as well, including dissemination of results to patients and providers. This aspect of patient engagement is one of the main strengths of this study.

4.10 Implications of the research

This thesis is part of a larger project, exploring the perspectives of three key stakeholder groups about a universal screening program for Lynch Syndrome (LS). The other phases address the attitudes of pathologists and genetic counsellors across Canada. As stated earlier, Newfoundland and Labrador (NL) has the highest incidence of familial colon cancer in the world (Green et al., 2007). Despite universal tumor screening being recommended by several international organizations and governments, such a program is lacking in NL. However, the research team is aware of discussion locally and pending funding, there is a willingness to develop such a program for the province. The findings of this study have real world implications in implementing a universal screening program for LS in NL**.** Our findings on patients' desire for informed consent could provide insight into developing educational materials and consent protocols in the province. In a

province with a significant rural population and few genetics healthcare professionals, involving primary care physicians and surgeons in discussions with patients about Lynch syndrome would also have implications for resource allocation. We acknowledge the deficiencies in resources and budgetary constraints in implementing a screening program in the province. However, we suggest these considerations for decision makers as a starting point based on the results of this study: a) Building awareness of familial colon cancer including LS, its prevalence in the province and its wider implications; b) A deeper understanding of universal tumour screening and its significance in the province given the prevalence of CRC and familial colon cancer in NL; c) Devising program guidelines based on stakeholder perspectives (patients, healthcare providers, genetic counselors) obtained from the findings of the current study as well as those exploring perspectives of other stakeholders; d) Considering the low knowledge levels among the participants about LS and screening, we would suggest developing detailed patient educational materials that could be made available in various ways including doctors' office, online, etc.; e) Developing and implementing policy guidelines and consent protocols considering perspectives of patients and other stakeholders.

The study also attempts to fills a knowledge gap in addressing the perspectives of patients regarding attitudes towards universal screening, contributing to the

academic discourse. However, further research can be done to validate the survey and use it to explore the perspectives of stakeholders in other parts of the country. Future studies focusing on the perspectives of the family members of colon cancer patients, and on that of patients with LS-associated extracolonic cancers need to be undertaken.

We plan to disseminate the findings of the study by conducting workshops across the province, helping to raise awareness about Lynch syndrome and tumor screening. Frequent cancer screening and other preventative measures for the patients and their families will help lower the mortality and morbidity associated with Lynch Syndrome.

4.11 Conclusion

Universal screening for LS using MSI or IHC testing of all newly diagnosed CRC patients is beneficial in early identification of at-risk individuals. Identification is necessary to allow appropriate cancer screening/ surveillance and preventative risk-reducing measures for this high-risk population. Our study found that CRC patients have a favourable attitude towards universal tumor screening for LS and are willing to have their tumors screened if such a program were available. Their perspectives on informed consent, the provision of educational materials and the potential requirement of help from healthcare professionals could help planners of a screening program for LS for the province and hopefully optimize the screening rates. A universal tumor screening program could ultimately help reduce the high mortality and morbidity of familial colon cancer in the province. Further research by exploring the perspectives of genetic counselors, pathologists and family members of the patients would be beneficial in expanding the knowledge base and identifying key concerns.

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Appendix A

Survey Questionnaire

This survey has three sections. The first section is about your knowledge and understanding of a hereditary form of colon cancer, known as Lynch Syndrome. The second part is about your attitude and opinions about screening for this genetic form of colon cancer, and the last section consists of a few questions about yourself. Please feel free to ignore any question you do not want to answer. There are no right or wrong answers here. We are only interested to know what you think about this screening test. We thank you for your time and appreciate your efforts.

SECTION 1

1. Before today, how much had you heard about genetic or inherited forms of colon cancer?

Please indicate your answer from the following.

- ☐ I had never heard about it
- ☐ I had heard a little
- ☐ I had heard some details, but not a lot
- ☐ I had heard a fair amount about it
- ☐ I had heard a lot

For question 2, please indicate how much you agree with the following statement.

2. I have always suspected I would get cancer, because it runs in my family.

Please indicate your answer in score from 1 to 5, 1 being strongly disagree to 5 being strongly agree.

- ☐ 1. Strongly disagree
- ☐ 2. Disagree
- ☐ 3. Neither agree nor disagree
- ☐ 4. Agree
- ☐ 5. Strongly agree

When a patient with colon cancer undergoes surgery as part of their treatment, their colon cancer tumor is tested in the lab to help identify the stage of cancer. This is routinely done. Another test can also be done on the tumor to find out if a patient is at risk for a genetic form of colon cancer called Lynch syndrome. This is sometimes called 'Universal tumor screening'. If that test is abnormal, further testing can be done, including a blood test to check for genetic risk of Lynch syndrome. At this time, universal tumor screening is not routinely done in Newfoundland and Labrador.

3. Before today, how much had you heard about 'Universal tumor screening for Lynch Syndrome'?

Please indicate your answer from the following.

- ☐ I had never heard about it
- ☐ I had heard a little
- ☐ I had heard some details, but not a lot
- ☐ I had heard a fair amount about it
- ☐ I had heard a lot

SECTION 2

For questions 4-12 please indicate how much you agree with each statement.

4. Universal tumor screening of colon cancer tumors would be useful for identifying high risk individuals.

Please indicate your answer in score from 1 to 5, 1 being strongly disagree to 5 being strongly agree.

- ☐ 1. Strongly disagree
- ☐ 2. Disagree
- ☐ 3. Neither agree nor disagree
- ☐ 4. Agree
- ☐ 5. Strongly agree

5. My family could benefit from this test.

Please indicate your answer in score from 1 to 5, 1 being strongly disagree to 5 being strongly agree.

- ☐ 1. Strongly disagree
- ☐ 2. Disagree
- ☐ 3. Neither agree nor disagree
- ☐ 4. Agree
- ☐ 5. Strongly agree

6. I would not take a tumor screening test it if I had to pay for it.

Please indicate your answer in score from 1 to 5, 1 being strongly disagree to 5 being strongly agree.

- ☐ 1. Strongly disagree
- ☐ 2. Disagree
- ☐ 3. Neither agree nor disagree
- ☐ 4. Agree
- ☐ 5. Strongly agree

7. People should not have their tumors screened if they don't ask for the test.

Please indicate your answer in score from 1 to 5, 1 being strongly disagree to 5 being strongly agree.

- ☐ 1. Strongly disagree
- ☐ 2. Disagree
- ☐ 3. Neither agree nor disagree
- ☐ 4. Agree
- ☐ 5. Strongly agree

8. The result of a tumor screening test could help me plan my future.

Please indicate your answer in score from 1 to 5, 1 being strongly disagree to 5 being strongly agree.

- ☐ 1. Strongly disagree
- ☐ 2. Disagree
- ☐ 3. Neither agree nor disagree
- ☐ 4. Agree
- ☐ 5. Strongly agree

9. The result of a tumor screening test could help me plan my future.

Please indicate your answer in score from 1 to 5, 1 being strongly disagree to 5 being strongly agree.

- □ 1. Strongly disagree
- □ 2. Disagree
- □ 3. Neither agree nor disagree
- □ 4. Agree
- □ 5. Strongly agree

10. I am concerned about any discrimination I could face based on the test result.

Please indicate your answer in score from 1 to 5, 1 being strongly disagree to 5 being strongly agree.

- □ 1. Strongly disagree
- □ 2. Disagree
- □ 3. Neither agree nor disagree
- □ 4. Agree
- □ 5. Strongly agree

11. I do not want to know about any genetic risks I might have.

Please indicate your answer in score from 1 to 5, 1 being strongly disagree to 5 being strongly agree.

- □ 1. Strongly disagree
- □ 2. Disagree
- □ 3. Neither agree nor disagree
- □ 4. Agree
- □ 5. Strongly agree

12. The test should be available to anyone who has had colon cancer and wishes to have information about his/her risk of inherited forms of colon cancer.

Please indicate your answer in score from 1 to 5, 1 being strongly disagree to 5 being strongly agree.

- ☐ 1. Strongly disagree
- ☐ 2. Disagree
- ☐ 3. Neither agree nor disagree
- ☐ 4. Agree
- ☐ 5. Strongly agree

13. If a tumor screening program for Lynch Syndrome were to be offered in Newfoundland and Labrador, how willing you might be to have your tumor screened?

Please indicate your answer in a score from 1 to 5, 1 being "definitely not willing" to 5 being "Definitely willing"

- ☐ 1. Definitely not willing
- ☐ 2. Not willing
- ☐ 3. Not sure
- ☐ 4. Willing
- ☐ 5. Definitely willing

14. Would you be willing to discuss your test result with any of your doctors or other health care providers to guide your future care or treatment?

Please indicate your answer in a score from 1 to 5, 1 being "definitely not willing" to 5 being "Definitely willing"

- ☐ 1. Definitely not willing
- ☐ 2. Not willing
- ☐ 3. Not sure
- ☐ 4. Willing
- ☐ 5. Definitely willing

For the following questions 15-18, please indicate how much you agree with each statement.

15. I would talk to my family members about the results of a tumor screening test done on my tumor.

Please indicate your answer in score from 1 to 5, 1 being strongly disagree to 5 being strongly agree

- ☐ 1. Strongly disagree
- ☐ 2. Disagree
- ☐ 3. Neither agree nor disagree
- ☐ 4. Agree
- ☐ 5. Strongly agree

16. I would need help from a healthcare professional to discuss the results of a screening test with my family members.

Please indicate your answer in score from 1 to 5, 1 being strongly disagree to 5 being strongly agree

- ☐ 1. Strongly disagree
- ☐ 2. Disagree
- ☐ 3. Neither agree nor disagree
- ☐ 4. Agree
- ☐ 5. Strongly agree

17. I understand the implications for my family members of a tumor screening test on my tumor.

Please indicate your answer in score from 1 to 5, 1 being strongly disagree to 5 being strongly agree

- ☐ 1. Strongly disagree
- ☐ 2. Disagree
- ☐ 3. Neither agree nor disagree
- ☐ 4. Agree
- ☐ 5. Strongly agree

18. I would encourage my family members to learn more about the implications of a tumor screening test done on my tumor.

Please indicate your answer in score from 1 to 5, 1 being strongly disagree to 5 being strongly agree

- 1. Strongly disagree
- 2. Disagree
- 3. Neither agree nor disagree
- 4. Agree
- 5. Strongly agree

When patients with colon cancer are advised to have surgery by their doctor, their consent is needed to allow surgery to happen. This consent also includes testing a tumor sample for the stage of colon cancer. Screening a colon cancer tumor to find out if a patient is at risk for genetic or inherited form of colon cancer is a similar test that can be done using the tumor sample.

19. Do you think that consent should be obtained for the tumor screening test to identify patients who might be at increased risk for inherited colon cancer?

- Yes, I would want to know what tests are being conducted on my tumor.
- No, a consent is not required to test my tumor for risk for inherited colon cancer.
- I am not sure.

20. If informed consent is taken for tumor screening to identify patients at risk for inherited colon cancer, when do you think this consent should be taken from patients?

- At the same time as the surgical consent
- It should be a separate consent
- Others, please explain: _____
- I am not sure

21. Who do you think should talk to patients about this tumor screening test? Please select all that apply:

- My Family doctor
- My Surgeon

- ☐ My oncologist
- ☐ A genetic counselor
- ☐ Anyone above, as long as I am told about it
- ☐ I am not sure

22. When do you think someone should talk to patients about tumor testing for inherited colon cancer?

- ☐ When patients first receive the diagnosis of colon cancer
- ☐ Before a biopsy of the tumor is taken
- ☐ Before surgery
- ☐ After surgery, during a follow-up visit
- ☐ Others, please explain:_____
- ☐ I am not sure

23. What type of consent should be obtained for the tumor screening test to identify patients who might be at increased risk for inherited colon cancer?

- ☐ Verbal
- ☐ Written
- ☐ None
- ☐ I am not sure

24. Do you think written educational materials should be provided to patients about screening their tumors for increased risk of inherited colon cancer?

- ☐ Yes
- ☐ No
- ☐ I am not sure

25. When do you think educational materials should be provided to patients?

- ☐ Before the day of surgery
- ☐ With other information given to patients on the day of surgery
- ☐ Upon discharge from the hospital after surgery
- ☐ Other, please explain: _____
- ☐ I am not sure

SECTION 3

26. What is the highest level of education you have completed?

- ☐ Did not complete high school
- ☐ High school certificate
- ☐ Trade school or non-university post-secondary program
- ☐ Some university
- ☐ Bachelor's degree
- ☐ Higher than a Bachelor's degree
- ☐ Other, please specify _____

27. What is your current marital status?

- ☐ Single
- ☐ Married or living with a partner
- ☐ Divorced or separated
- ☐ Widowed

28. How many children do you have? If none, enter zero.

_____

29. Has anybody in your family ever had cancer? (Other than yourself)

- ☐ Yes
- ☐ No

30. If yes, please mark an 'x' next to all that apply.

- ☐ Parent
- ☐ Children
- ☐ Spouse
- ☐ Sibling
- ☐ Others

31. Has anybody in your family ever had colon cancer? (Other than yourself)

- ☐ Yes
- ☐ No

32. If yes, please mark an 'x' next to all that apply.

- ☐ Parent
- ☐ Children
- ☐ Spouse
- ☐ Sibling
- ☐ Others

Please feel free to provide us with any other comments or suggestions about tumor testing for inherited forms of colon cancer.

_____
_____

_____
_____

_____
_____

Would you like your name to be entered into the prize draw for a $500 gift card?

- ☐ **Yes, please**
- ☐ **No thanks**

Thank you for your time!

Appendix B

Copy of the cover letter

Hello!

You are invited to take part in a research study called **Universal tumor screening for Lynch syndrome: Perspectives of patients regarding benefits and barriers**. The study involves filling out one survey that is included with this letter.

You are being invited to take part in this study as a person who has had colon cancer. Researchers from Memorial University would like to study what patients think about screening colon cancer tumors for signs of a genetic condition called Lynch syndrome. This kind of screening is being done in other parts of Canada, but not yet in our province. We believe that patients' opinions about colon cancer tumor screening would be helpful if a tumor screening program was ever started in Newfoundland and Labrador.

Filling out this survey is voluntary, and you are free to leave out any question you do not wish to answer. If you are not interested in taking part, please feel free to ignore the survey. If you do not wish to receive reminder mail-outs about the survey, please send us back the blank survey in the postage paid envelope provided and we will remove your name from the mailing list. You can also call us on the phone number **709-864-6605** to opt out of the survey.Taking part in this survey will not affect any healthcare you or your family receives. There are no names attached to the survey, so no one will know your answers. Your name will never be reported in any papers or reports prepared from the survey. The data we collect for this study will be stored for 5 years. Should you wish to withdraw from the study at any time, any survey data you have provided will be removed from the data set and destroyed.

Participants who wish can have their name entered in a prize draw for a $500 gift card. This will take place at the end of the study and the prize will be mailed to the winning participant. At the end of the survey, simply check "yes" and your name will be entered in the prize draw.

Filling out the survey should only take 15-20 minutes. Please send it back in the postage paid envelope provided. If you have any questions or concerns about the study or would like more information, please feel free to contact the lead researcher, Ms. Anusree Subramonian or her supervisor Dr. Holly Etchegary directly:

Dr. Holly Etchegary, Assistant Professor, Faculty of Medicine
Patient Engagement Lead
Phone: 709-864-6605; Email: holly.etchegary@med.mun.ca

Anusree Subramonian,
MSc Clinical Epidemiology (c),
Faculty of Medicine
Memorial University of Newfoundland
Email: as7273@mun.ca

Or you can talk to someone who is not involved with the study at all, but can advise you on your rights as a participant in a research study. This person can be reached through:

Ethics Office at 709-777-6974
Email at info@hrea.ca

This study has been reviewed and given ethics approval by the Newfoundland and Labrador Health Research Ethics Board.

We thank you for taking the time to give us your thoughts and opinions about colon cancer tumor screening.

Sincerely,

Holly Etchegary and Anusree Subramonian, on behalf of the research team

Appendix C

Copy of the introduction letter

Date

Dear

A research study is being conducted by Memorial University, "Universal tumor screening for Lynch syndrome: Perspectives of patients regarding benefits and barriers." This study will survey patients who have had colon cancer. Based on the study's eligibility criteria, your name and contact information was selected from the Cancer Registry. The study involves filling out one survey that is included with this letter. Your study participation is completely voluntary and confidential.

Lynch syndrome is a genetic form of colon cancer. People who have Lynch syndrome are at high risk for colon and several other kinds of cancers. Researchers believe it is important to identify these patients so that early screening of them and their family members can be started. There is a screening test for Lynch syndrome that can be done on a colon cancer tumor. If that test is abnormal, further testing can be done, including a blood test to check for genetic risk of Lynch syndrome.

Researchers are interested in what people who have had colon cancer think about testing a colon cancer tumor for genetic forms of cancer. This kind of tumor testing is being done in other places in Canada. The researchers believe that patients' opinions about testing a colon cancer tumor for genetic forms of cancer would be helpful if a tumor testing program was ever started in Newfoundland and Labrador.

If you are interested in taking part, simply complete the survey and send it back to the researcher in the enclosed envelope. If you do not wish to take part in the study or believe you have received this letter in error, please contact the lead study researcher directly. Her name is Holly Etchegary, and she can be reached at 709-864-6605 or by email at holly.etchegary@med.mun.ca. Holly is a researcher at the Faculty of Medicine, Memorial University. She is happy to remove your name from the list or to answer any questions you may have about the study.

Thank you for taking the time to consider taking part in the study.

Best regards,

Susan Ryan, Manager Cancer and Cytology Registry