# Colorectal Cancer Screening in Manitoba: Analysis of Factors Associated With Program Participation and Outcomes

By

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# ABSTRACT

## Introduction

Fecal-based (FT) colorectal cancer (CRC) screening is designed to prevent cancer or diagnose it early when it is most amenable to treatment. This study assessed the socio-demographic and clinical factors associated with participation and outcomes of a population-based provincial CRC screening program.

## Methods

This retrospective cohort study included individuals age 50-74 who were eligible to participate in Manitoba's CRC screening program from 2007-2014. Sociodemographic factor and clinical variable subgroup analyses were performed using multivariable logistic regression.

## Results

118,096 screening FTs were completed, and 3081 follow-up colonoscopies were completed. On multivariable analysis, screening participation is associated with age, sex, deprivation index, and geography. Age and sex were associated with identifying advanced neoplasia and non-advanced adenomas on colonoscopy.

## Conclusions

Our study suggests CRC screening participation and outcomes are associated with specific sociodemographic and clinical factors. Through identification of disparities and barriers to participation, access, or timely investigations, we can inform and direct future program initiatives.

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# INTRODUCTION

## BACKGROUND

Colorectal cancer (CRC) is a common and deadly disease. It is the third most commonly diagnosed cancer and the second leading cause of cancer-related death in the Western world.[1] In 2019, an estimated 860 men and women in Manitoba will be diagnosed with CRC, and 360 individuals will die of their disease.[2]

CRC is, however, potentially preventable. The vast majority of colorectal cancers are believed to arise from adenomatous polyps in a multistep process called the "adenoma-carcinoma sequence".[3] In this model, a series of genetic alterations occur to transform a benign adenomatous polyp to a dysplastic polyp and then into invasive cancer. This transformation generally occurs over a period of many years. Removing polyps when they are still in the early, benign stages may interrupt this sequence, thus affording a means to prevent CRC.[4]

Once CRC develops, it is still potentially curable, especially if it is diagnosed and treated in its early stages. Survival rates for CRC depend on the stage of the disease. The 5-year survival rate is 93% for individuals with stage I colon cancer, but drops to 82% and 58% for individuals with stage II and III disease, respectively.[5] The 5-year survival for stage IV colon cancer is dismal at 8%. Early-stage diagnosis and treatment of CRC are clearly associated with improved prognosis. However, early-stage CRC can be difficult to diagnose as individuals are often completely asymptomatic despite harbouring invasive disease.

## COLORECTAL CANCER SCREENING

CRC screening programs are designed to prevent CRC (by identifying and removing polyps before they become cancerous) or diagnose it early in its course when it is most amenable to treatment. The two most commonly used CRC screening programs throughout the world are fecal occult blood tests and colonoscopy. While debate continues over which program is most effective at reducing cancer, ultimately both the quality of a program and a patient's willingness to adhere to all steps of the CRC screening program determines its overall effectiveness.[6]

The fecal occult blood test (FT) and colonoscopy programs take very different approaches to screening – FT programs are initially non-invasive, multi-step programs, while colonoscopy programs are a single step but involve a more invasive procedure. Positive FT should be followed by colonoscopy and a negative FT should be followed by repeat annual or biannual testing. Completion of the recommended follow up tests after a positive FT is critical to the overall effectiveness of any FT program.[6]

A large body of literature on CRC screening developed from randomized controlled trials (RCTs) in the 1990s has found that CRC screening programs using FT are associated with a 15 to 30% reduction in CRC mortality compared with unscreened control participants.[7–9] Mortality reduction is primarily achieved by detecting and treating CRC at an early, curable stage. There is also modest reduction in CRC incidence (17 to 20%), which contributes to mortality reduction through detection and removal of polyps.[8,9] A meta-analysis that included four randomized controlled trials involving over 320,000 participants showed a 16% reduction in the relative risk of CRC mortality with FT screening, and a 25% risk reduction when adjusted for those who

attended at least one round of CRC screening.[10]

Despite the benefits shown in these studies, the applicability of findings to individual populations and contexts outside of clinical trials requires constant evaluation, as numerous behavioural, cultural, programmatic and health systems-related factors can affect the success of screening programs.[11,12]

## CURRENT CRC SCREENING GUIDELINES

In 2004, the Canadian Association of Gastroenterology (CAG) and the Canadian Digestive Health Foundation (CDHF) established the current Canadian guidelines for colon cancer screening. Recommendations are based on patients with average risk of developing CRC, which constitutes the majority of the Canadian population.[13] These were most recently updated in 2016 when the Canadian Task Force on Preventative Health Care published their recommendations for colorectal cancer screening in 2016.[14]

Colon cancer is uncommon below the age of 50 years. The probability of developing cancer in the next 10 years is 1:125 in the 50 to 59 year old age group and 1:50 in the age 60 to 69 year old age group, compared with 1:1000 in the 30 to 39 age group.[15] As such, most authorities recommend screening be offered to individuals age 50 years and older, if they are of average risk. Although the relative benefits of screening appear similar for both older (60–74 years) and younger (50–59 years) individuals, the absolute benefits of screening are larger for the former because of the higher incidence of colorectal cancer.[14]

Currently in Canada, individuals over the age of 50 years with a negative family history should undergo screening with one of the following strategies:

1. Fecal occult blood testing (FT) every two years – with guaiac-based or immunochemical-based FT
2. Flexible sigmoidoscopy every 10 years[14]

While the recommendation to not screen adults aged 75 years and older for CRC still stands, compared to previous guidelines, it is now recommended to not use colonoscopy as a screening test for CRC.[14] Of course, these recommendations do not apply to adults aged 50 years and older who are at high risk for colorectal cancer. They do not apply to those with previous CRC or polyps, inflammatory bowel disease, signs or symptoms of CRC, history of CRC in one or more first-degree relatives, or adults with hereditary syndromes predisposing to CRC (e.g., familial adenomatous polyposis, Lynch syndrome).[14]

At present, there is no evidence-based approach to screening of high-risk patients in Canada – guidelines are based on consensus agreements. Cancer Care Ontario's (CCO) Colon Cancer Check (CCC) recommends individuals who are at high risk based on family history criteria should be screened with colonoscopy beginning at age 40 or 50, or 10 years prior to the age at diagnosis of their affect family member, whichever occurs first and depending on the specific family history CRC profile.[16] These recommendations were based on the Canadian Association of Gastroenterology Clinical Practice Guidelines for CRC screening released in 2018.[17] FT does not have adequate sensitivity for those at higher risk, and a screening program for CRC must

consider the resources needed for endoscopic screening of high-risk patients.[13] Symptomatic individuals should not be considered "screening" candidates. They require an appropriate diagnostic work up, as directed by their specific symptoms. Asymptomatic individuals at average risk below the age of 50 years are significantly less likely to develop colon cancer, and thus screening in this population is not currently recommended in Canada.

## FECAL OCCULT BLOOD TESTING

Screening programs in Canada use either a guaiac-based fecal occult blood test (gFT) as the primary screening test or an immunochemical FT (FIT). The gFT involves collecting stool samples on three separate days, which are then sent to a lab for testing. Most screening programs define an abnormal result as one or more positive windows on a gFT card. If the test result is abnormal and blood in the stool is identified, follow-up with a diagnostic colonoscopy is recommended. Although most people who have blood in their stool do not have CRC, a colonoscopy is required for all abnormal tests to confirm or exclude a cancer. If no blood is found in the stool, the test result is normal, and patients should re-screen using the FT every two years in Canada.[16,18], or at 1- to 3- year intervals as per the US Preventative Services Task Force.[6] If a quantitative FIT is used, which detects human hemoglobin in stool, a positive test is defined as a result above a predetermined threshold/cut off level.[18]

Current guidelines suggest a preference for the Hemoccult SENSA gFT test, or a FIT test.[6] Hemoccult SENSA has replaced Hemoccult II because of its improved sensitivity to detect CRC. Based on three diagnostic accuracy studies, Hemoccult SENSA (three samples) sensitivity

ranged from 61.5 to 79.4%.[19] The specificity was reported as low as 86.7 %.[19] The Cochrane Colorectal Cancer Group update on CRC screening using Hemoccult testing reported an overall reduction in CRC mortality with the use of FT screening of 16%.[10] Compared with gFT, FIT testing has greater sensitivity with similar specificity, and neither test appears to have direct substantial harms, except for harms due to follow-up investigations and therapy.[14]

The effectiveness of both FIT and gFT depends on patients' adherence to several steps of the stool-based CRC screening program: (1) successful completion of the initial stool tests, (2) undergoing diagnostic colonoscopy if the test is positive, and (3) having repeat stool testing every two years if the test is negative.[6] Studies have shown rates of patient adherence to a first round of testing are 60% to 80%, and that patients are significantly more likely to complete a stool blood testing program compared to a screening program exclusively based on periodic colonoscopy.[20,21]

## COLORECTAL CANCER SCREENING IN CANADA / MANITOBA

As of 2016, all 10 provinces in Canada have implemented or were in the process of implementing organized colorectal cancer screening programs.[22] CancerCare Manitoba, with funding from Manitoba Health, introduced a centrally administered, province-wide CRC screening program (ColonCheck) in 2007. The continued goal of the program is to reduce the number of Manitobans dying from CRC.[23]

Since its introduction, more than 400,000 individuals have been offered screening, making it one of the largest CRC screening programs in the country. In 2011 and 2012, 25.4% of individuals invited to participate in ColonCheck completed a program FT, and only 50.1% of the eligible Manitoba population were considered up-to-date for CRC screening (FT, colonoscopy, or flexible sigmoidoscopy).[23]

A recent paper by Major et al. and members of the Canadian Partnership Against Cancer (CPAC) presented the combined early results of FT screening from five provincial programs (for which Manitoba contributed almost one-third of the cases).[24] The study reported an average Canadian participation rate of only 16.1%.[24] While this number is difficult to interpret because the population to whom screening was made available does vary by province, participation rates varied widely within and between the existing organized programs across the country, and none of the programs met the participation target of ≥ 60% set by CPAC in 2011.[22]

Large scale CRC screening programs in Canada face unique challenges related to geographically dispersed populations, limited access to health care for many non-urban residents, and limited endoscopic capacity within publicly-funded health care systems. Participation rates from other population-based CRC screening programs elsewhere in the world range from 45 to 60%.[21,25–28] While direct comparisons between different populations and systems of care are difficult to make, the CPAC finding as well as our provincial results strongly suggest the need for further, more detailed evaluation.

## ACCESS TO HEALTH CARE IN CANADA

Health care in Canada is a universal health care system guided by the provisions of the Canada Health Act of 1984.[29] All Canadian citizens and permanent residents are eligible for the public health insurance delivered by each individual Provincial Ministry of Health. Ideally, all Canadians receive the same level of care, however regional, social and economic disparities have been well described, and their underlying etiologies are often complex.

Cancer treatment can be especially complex, requiring high quality, multidisciplinary and often multimodal care, and ensuring such care is standardized across and within each province is paramount. Barriers to equitable care can be numerous and complex, and can occur throughout all stages of cancer treatment, from screening and diagnosis to specialist treatment and follow up surveillance. Any barrier to health care, at any point along a clinical pathway, can have a significant impact on both individual and population health outcomes.

Resource distribution and treatment wait times frequently pose an ongoing challenge for equitable care in Canada given our geographically dispersed population, combined with our universal health care model. Delays in scheduled care or long waits for required care continue to be an issue.[30] For many conditions, including CRC, the opportunity to intervene clinically or surgically can be brief, and missing that opportunity can dramatically change an individuals' outcome.

Addressing any urban/rural divide is often the first place that draws the attention of policy makers in Canada. However, the social, economic, and psychological effects associated with

illness, hospitalization, and long wait times are well described, and may themselves affect health outcomes as much or more than a patient's geographic residence.[31] The Canadian federal government recognized these concerns, and in 2004 the Wait Times Reduction Fund was created.[31] Over the subsequent six years, the fund was to invest $4.5 billion to establish benchmarks for health care areas of high priority – including cancer treatment. Manitoba received $155 million, with the funds intended for jurisdictional priorities such as expanding facilities, recruitment of more health care professionals, and resource allocation.[30] Although eliminating disparities in access to health care is a difficult and ongoing process, the identification of key problems, such as wait times, allows for vital interventions to be implemented.

## QUALITY INDICATORS FOR COLORECTAL CANCER SCREENING

The Canadian Partnership Against Cancer (CPAC) convened the National Colorectal Cancer Screening Network (NCCSN) in 2007 as a national platform for the exchange of knowledge to support the colorectal cancer screening community, to help improve the patient experience with CRC screening, and to leverage expertise and make evidence-based recommendations to the cancer control system. The NCCSN's primary aim is to improve participation and enhance the quality of CRC screening in Canada.[32] A set of quality indicators for CRC screening in Canada was initially developed in 2009 for reporting at the national level, and included quality indicators in five domains: coverage, follow-up, quality of screening, detection and disease extent at diagnosis.[32] Subsequent work by the NCCSN in 2011 resulted in the development of targets for six of the indicators. In 2013, the Partnership released a revised version of the report Quality

determinants and indicators for measuring colorectal cancer screening program performance in Canada, which included new and revised quality determinants and indicators included in this report.[32] Appendix A describes the 13 quality indicators and associated targets for quality colorectal cancer screening programs.

Every CRC screening program's effectiveness depends on appropriate follow-up of positive and negative tests. For positive results, all screening programs inevitably depend on the performance of high-quality colonoscopy. Previously cited elements that define high-quality colonoscopy include completeness of the examination or ability to intubate the cecum, documentation of the quality of bowel preparation, adequate adenoma detection rates, and appropriate follow-up recommendations.[6,33] Studies have shown that following a positive fecal occult blood test, approximately 70% to 90% of patients undergo the recommended follow-up colonoscopy.[8,21] In Canada between 2009 and 2011, 45% of individuals participating in program-based CRC screening underwent colonoscopy within 60 days and 81% within 180 days following an abnormal FT.[34] Previously reported rates of colonoscopy compliance in Manitoba were 91% in 2012, with 78.6% attending their colonoscopy within 180 days of their abnormal FT result.[23]

The 2012 Canadian Community Health Survey estimated that only 55% of those aged 50 to 74 years were up-to-date with CRC screening.[35] While the rates in Manitoba are the highest across the country, the most recent report from CPAC indicates that, based on surveys, 67.4% of asymptomatic Manitobans are up to date with CRC screening, which still does not meet the set target.[32,35] Screening will not be effective for those patients who do not undergo follow-up colonoscopy because polyps or early-stage CRC are not detected. The importance of adherence

to the full screening program in order for it to improve health outcomes cannot be overstated. As a quality measure, treating physicians should monitor patients' adherence to the full CRC screening program, including biennial re-screening.

## TRENDS IN SEX AND AGE VARIATION IN CRC SCREENING

Multiple studies have shown that CRC is more common in men.[27,36–38] Canadian males are more likely to develop colorectal cancer than females, with 1 in 14 men expected to develop CRC during their lifetime.[39] Comparatively, the lifetime risk of CRC for women in Canada is 1 in 16.[39] In Canada, CRC incidence rates for both males and females are highest in Newfoundland and Labrador. For females, the second highest rates were observed in Nova Scotia, while the second highest rates among males were seen in Manitoba.[39] The 2013 study by the Colorectal Cancer Screening Monitoring Program Performance Working Group and CPAC found that screening participation was higher in women (18.1%) than in men (14.2%).[24] The positivity rate was significantly higher in men (5.9%) than in women (3.4%), and accordingly, the PPV for adenomas was also higher in men than women (54.3% vs. 37.7%)

Age is one of the strongest risk factors for CRC. The population in Canada is aging, and as a result a greater proportion of Canadians are at increased risk of developing CRC simply by the fact they are living longer.[1,6,40] Fortunately, it appears with increased age comes increased engagement with screening programs. The same 2013 study of CRC screening across Canada reported that participation increased from 13.4% in the 50–54 age group to 21% in the 70–74 age group.[24] The rate of abnormal FTs (the "positivity rate" – see Appendix A) also increased with

age to 5.7% in the 70–74 year old age group from 3.4% in the 50–54 year old age group. The Positive Predictive Value (PPV) for adenomas (see Methods section for definition) showed a steady increase with age, from 35.1% in the 50-54 year old age group to 53.0% in the 70–74 age group.[24]

The most recent report from CancerCare Manitoba, which reviewed the ColonCheck screening program between 2011 and 2012, reported that women were more likely to successfully complete an FT than men (28.1% of invited women compared to 22.5% of invited men).[23] In accordance with the CPAC study in 2013, the participation rate in Manitoba also increased with age, with 19.4% of invited 50-54 year-olds successfully completing an FT compared to 36.5% of invited 70-74 year olds.[23] The positivity rate similarly increased with age, with 3.1% of 50-54 year-olds receiving a positive test result compared to 4.3% of 70-74 year olds.[23]

## TRENDS IN GEOGRAPHIC IMPOSITIONS IN CRC SCREENING

Previous studies have reported barriers to CRC screening at multiple levels, including patient level factors, program level factors, and contextual factors, including geographic location and proximity to cancer resources.[41] It makes some logical sense that geography can have an impact on an individual's health outcomes. Differences in cancer mortality rates may correlate with differences in incidence due to regional variations in modifiable risk factors, as well as differences in access to cancer services, such as screening, diagnosis, treatment and follow-up.[42] Disparities in infrastructure and physician distribution across the urban/rural divide can create barriers to accessing health care, especially cancer care resources which are often centralised into

urban areas. Unfortunately for Canada's rural and remote populations, despite national efforts to improve access and provide equitable care, it has been repeatedly shown that cancer outcomes in rural and remote communities are worse that those seen within urban centres.[42,43]

In the United States, there is significant regional variation in risk of CRC. The high-risk states in the central Midwest have an incidence of 41.7 to 48.9 cases per 100,000 age-adjusted population, which is much higher than low-risk states (incidence 32.5-37.5 cases per 100,000 age-adjusted population.[6] A cross sectional analysis of data collected from 1998 to 2005 by the Centers for Disease Control's Behavioral Risk Factor Surveillance Study showed that the up-to-date screening rate for colon cancer was 54% in urban areas, 48% in rural areas, and was the lowest at 45% in remote rural areas.[44] A case-control analysis of almost forty years of SEER-Medicare database files on CRC patients by Liang and colleagues in 2016 also identified small rural residence to be strongly associated with increased CRC incidence (OR 1.50) and mortality (OR 1.35) when compared with urban residence.[45] These differences were entirely explained by a lower endoscopic screening rate in rural areas, despite a slight increase in rural FT use, coupled with a decrease in urban FT use.[45] The disparity in incidence and mortality between rural and urban regions did decline after coverage was extended to FT and sigmoidoscopy in 1998, but the differences did not improve appreciably after 2001, when coverage had also extended to colonoscopy.[45]

Torabi and colleagues identified regional variations in CRC mortality in Manitoba and widening SES gap in CRC mortality between income groups in their 2014 population study of all Manitobans who died from CRC between 1985 and 2009.[43] While investigating the geographical

variation and small geographical area level factors associated with CRC mortality, they identified the mortality rate ratio (MRR) of southeast (MMR=1.31, 95% CI 1.12-1.54) and southcentral (MRR=1.62, 95% CI 1.35-1.92) regions of Manitoba had higher CRC mortality rates than suburban Winnipeg (MRR 1.0).[43] According to CancerCare Manitoba, in 2012 the median wait time from FT to colonoscopy was 10.3 weeks for patients residing in Winnipeg, compared with 12.3 weeks for those residing outside of the province's main urban centre.[23]

It has been hypothesized that regional variation may be due to different patient factors (lifestyle factors and co-morbidities) as well as management patterns and clinical experience in regional hospitals. It has previously been shown that rural and remote patients with locally advanced CRC are less likely to receive chemotherapy, which may be another reason for poorer outcomes seen in rural and remote populations.[46] Differences in access to follow-up care after initial treatment by place of residence may be another explanation. The persistence of worse survival outcomes seen among patients from remote areas with CRC suggests the inequalities in access to care, and/or the quality of care in rural and remote areas may be at the root of the cause of regional differences in stage at diagnosis. Further exploring geographical variations in CRC mortality and predictors of CRC mortality could help develop specific risk-tailored approaches for CRC screening programs.

## TRENDS IN SOCIOECONOMIC VARIATIONS IN CRC SCREENING

Lower socioeconomic status (SES) is a well-known barrier to any cancer screening. For colorectal cancer, there is extensive literature to support the claim that patients from lower SES

have lower rates of CRC screening.[47,48] There is also evidence of a dose-response relationship in the rates of endoscopy or FT testing in the US according to levels of education and income.[48] Rates of CRC screening decreased as levels of education and income also decreased, and no significant differences were seen after adjusting for age and sex.[48] This relationship and the resultant screening uptake disparity was found to persist over time, even though FT is both relatively inexpensive and fully reimbursed by Medicare services.[48]

In England, the Bowel Cancer Screening Program, operated by the publicly-funded NHS since 2006, does not pose any financial costs to participants. Despite this fact, there were clear differences in CRC screening uptake among the first 2.1 million participants. Screening uptake was the highest (61%) in the least socially and economically deprived areas, whereas uptake was the lowest (35%) in the most disadvantaged areas.[49] Persistence of these disparities suggests that additional factors contribute to the differences observed in economically disadvantaged populations. While direct causes are unclear, low social supports, competing life demands, cultural differences, literacy, patients' mistrust of physicians, and poor patient-physician communication have all been implicated in contributing to the disparities in cancer screening participation.[7,48,50,51] While SES alone may be a strong determinant of survival, there is also a complex interaction between SES and ethnicity.[52] Similar to other factors associated with treatment disparities, ethnic populations may also be more vulnerable to the negative effects of lower SES.[51]

## TRENDS IN ETHNIC VARIATIONS IN CRC SCREENING

Ethnic disparities exist along each stage of the colon cancer pathway, from screening participation to survival outcomes. It has been widely reported that ethnic minorities have been found to have lower CRC screening uptake.[51,53,54] This is apparent across multiple ethnic groups including African Americans[53,55], Asians[51], and North American Indigenous populations, including Canadian First Nations, and the Inuit and Metis peoples.[51]

A 2009 study assessing CRC screening patterns among US Medicare enrollees found for each year during the 2000 to 2005 study period, non-Caucasian enrollees had significantly lower rates of FT, recent endoscopy, and endoscopy within the last 5 years when compared with their Caucasian counterparts.[48] Similarly, in association with ethnic minority status, immigrant populations are also less likely to receive screening. A study in 2013 comparing US-born citizens to non-citizens who participated in the California Health Interview Survey demonstrated that 67% of citizens, vs 46% of non-citizens had participated in CRC screening.[51]

Multiple factors have been implicated in contributing to low CRC screening rates and delays to diagnosis. While poor health literacy and a lack of knowledge around CRC, and poor awareness of the importance of screening are central, the fear of procedural discomfort, the anxiety of waiting for results, and the general mistrust of healthcare professionals have all been reported in the literature as reasons why marginalized populations do not engage in CRC screening.[51] The disparities in survival outcomes appear to be more strongly influenced by tumor stage at presentation rather than by treatment, suggesting a failure of early diagnosis in these higher risk populations. Previous studies have even highlighted that racial disparities in CRC outcomes may

be more strongly related to differences in health-care utilization rather than differences in tumor biology.[52,56]

## TRENDS IN CRC INCIDENCE AND MORTALITY

From the mid-1980s until the mid-1990s, overall incidence rates for CRC in Canada declined for both sexes, though the decrease was more prominent amongst females.[42] Incidence rates then rose again through 2000, followed by a second decline thereafter as western countries began implementing CRC screening programs.[42] Although CRC incidence overall has been on the general decline for several decades due to changing patterns in risk factors and the uptake of screening, this largely reflects the rates seen in older adults and masks trends in the younger age groups.[42]

The most recent annual percent change (APC) in age-standardized mortality rates (ASMR), by sex, show that in Canada the mortality rates for CRC have declined significantly for both males (-2.3% per year) and females (-1.7% per year), between 1984 and 2015. Part of this decline may be driven by the overall decrease in incidence due to increased patient awareness and lifestyle modification, but it is likely that a significant portion of the decline in mortality is due to initiation and advancements in screening and improvements in treatment.[42,57]

Incidence rates can change for a variety of reasons. Increases can be seen with increased awareness of a disease and health care engagement, or improved detection techniques. Incidence decreases are seen with the introduction of prevention strategies and improvement of risk factors,

and with the introduction of screening programs that detect disease in the pre-malignant state. The current annual decline in CRC incidence rates in Canada appears confined to the older adult population, as the rates are unfortunately increasing among young adults under the age of 50 years in both Canada and the United States.[39,57]

Modeling has suggested that half of the decrease in CRC incidence and mortality since the 1980s can be attributed to screening.[57] However, not all groups have benefitted equally from screening, prevention and treatment, and sociodemographic factors and socioeconomic status have been reported to influence CRC outcomes.[54,58,59] In Canada, the mortality rate from CRC declined significantly between 2003 and 2012 for both males (2.3% per year) and females (2.0% per year).[42,57] Given that organized screening in Canada began in the latter half of that time period, the decline in mortality rates was more likely driven by improvements in diagnosis and treatment, rather than the introduction of CRC screening programs.

A large case-control study by Liang and colleagues analysing four decades of SEER data on temporal trends in CRC incidence and mortality identified that individuals who are male, older, rural residents, ethnic minorities or immigrants, or those who have lower socioeconomic status are more likely to be diagnosed with and die from CRC.[45] Geographic inequalities have persisted over the four decades, whereas racial and socioeconomic disparities have worsened over the same time period.[45]

# SOCIOECONOMIC AND CLINICAL FACTORS AFFECTING CRC INCIDENCE AND MORTALITY

Across the globe, the majority of CRCs continue to occur in industrialized countries, however, incidence rates are rising in developing nations as they increasingly adopt a more Western lifestyle.[60] Migration studies have also demonstrated a greater lifetime incidence of CRC among immigrants who have moved to industrialized nations with a higher burden of CRC compared to those residents who remain in their native, low-incidence countries. Findings such as this highlight the impact of environmental influences on colorectal carcinogenesis.[60] CRC has been linked to many environmental risk factors, including obesity, physical inactivity, consumption of red and processed meat, and smoking and alcohol intake.[28,61] Physical activity has also been shown to be associated with a reduction in CRC incidence and mortality.[43,60]

## Socioeconomic Status

Although absolute CRC incidence and mortality rates have decreased across the board since the 1990s,[42,55] after 1998 an inverse relationship between SES and mortality across racial/ethnic groups has been reported.[45,58,59] Historically, areas with higher SES have been associated with increased rates of CRC mortality.[62] However, higher income and education level became protective against mortality after 1998 and 2002, respectively. Liang et al identified in their 2016 paper that the trend reversals for mortality occurred earlier than for incidence, suggesting that perhaps socioeconomically advantaged groups benefit first from advances in treatment and then later from greater access to screening.[45] In Canada, higher colorectal cancer mortality rates have been seen in areas of lower income despite universal access to healthcare.[43]

## Diabetes

There has been increasing evidence to suggest that diabetes mellitus (DM) is associated with increased cancer incidence and mortality. Several mechanisms involved in DM, including the increased cell proliferation and decreased apoptosis, may promote carcinogenesis. A systematic review and meta-analysis from the Netherlands in 2013 assessed the association between DM and cancer incidence and cancer-specific mortality in patients with breast and colorectal carcinoma. The overall Hazard Ratio (HR) for CRC incidence was 1.38 and the overall HR was 1.30 for CRC-specific mortality in patients with DM compared to those without, suggesting that diabetes is a considerable risk factor for developing and succumbing to CRC.[63]

## Body Mass Index (BMI)

Case-control and prospective studies have consistently associated excess body weight with an increased risk of colon cancer.[6,60,64] A meta-analysis was completed in 2009 by Ning et al. assessing 56 case-control and cohort studies, conducted among 7,213,335 individuals including 93,812 cases of CRC.[64] In that analysis, when compared to patients with BMI < 23.0, there was a 14% increased risk of colorectal cancer for patients with a BMI of 23.0 –24.9; 19% for a BMI of 25.0 –27.4; 24% for BMI of 27.5–29.9; and a 41% increased risk of CRC for BMI of > 30.0. The association was stronger for men than for women and for the colon than for the rectum. Controls for various other lifestyle factors did not appreciably alter the findings for BMI or body circumference measures.[64]

## Aspirin or Anti-Platelet Therapy

In the 1980s and 1990s, several case-control studies, and later some prospective cohort studies, consistently associated aspirin use with a lower risk of CRC and adenomas.[60] A 2009 meta-analysis of four randomized, placebo-controlled trials of aspirin found that aspirin users had pooled risk ratio of 0.83 (95% CI, 0.72–0.96) for any adenomas and 0.72 (95% CI, 0.57–0.90) for advanced adenomas.[65] These studies and others clearly established that aspirin and COX-2 selective inhibitors reduce the risk of colorectal neoplasia.[66–72] However, it is also well known that regular use of aspirin and oral anticoagulants is associated with gastrointestinal bleeding.[73] Consequently, the routine use of such medications is not recommended for prevention of CRC in the general population due to concern about their associated toxicities. There are, however, specific populations in which the potential benefit associated with their use may outweigh the risks.

# SUMMARY, HYPOTHESIS AND OBJECTIVES

CRC screening programs are designed to prevent cancer or to diagnose it early in its course when it is most amenable to treatment. Most provinces in Canada have launched population-wide, fecal-based CRC screening programs. However, these programs have led to challenges about how to proceed with follow-up testing for individuals with abnormal results given the large number of individuals with abnormal results and limited endoscopy capacity within a publicly-funded health care system. In Manitoba, we have the ability to link our ColonCheck registry with provincial health administrative databases, which enables us to analyze the sociodemographic and health-related factors associated with CRC screening participation and outcomes. Understanding these factors and identifying any barriers to participation or follow up investigations may provide opportunities for program improvement through more targeted interventions.

The objectives of this Master's thesis are to assess socio-demographic and clinical factors associated with the performance and outcomes of an organized, population-based CRC screening program. Specifically,

1. To assess the socio-demographic and clinical factors associated with participation and retention within a population-based CRC screening program

2. To assess the socio-demographic and clinical factors associated with finding
    a) any adenomas (non-advanced adenomas),
    b) advanced adenomas, and/or

c) CRC

among individuals who undergo colonoscopy following an abnormal ColonCheck FT result.

# METHODS

## STUDY DESIGN

This is a population-based retrospective analysis of all individuals who were invited to participate in the ColonCheck screening program from 2007 to 2014. At the point of data analysis, more than 400,000 individuals had been offered CRC screening through the ColonCheck program, and over 127,000 screening fecal occult blood tests (FTs) were completed by eligible Manitobans during the study period. FT kits were mailed to eligible individuals through the ColonCheck program, and they were also distributed through primary care providers, in collaboration with the BreastCheck program, and at community events. Over 3000 colonoscopies were completed through the program over the study time period.

## ETHICS APPROVAL

Ethics approval was obtained from the Health Information Privacy Committee (HIPC) for access to health information held by the government of Manitoba, including the Manitoba Health database, the Manitoba Cancer Registry, the ColonCheck registry, and the ColonCheck Patient Assessment Form. Ethics approval was obtained from the University Manitoba Health Research Ethics Board (HREB) for access to patient charts for review purposes. Approval was also obtained from the Research Resources Impact Committee (RRIC) for the purpose of access to CancerCare Manitoba charts.

## STUDY POPULATION

The ColonCheck program was established in 2007. ColonCheck invited individuals 50 to 74 years of age who have not had an FT in the previous 2 years, a colonoscopy in the previous 5 years, or a previous CRC diagnosis, to participate in the program. Eligible individuals were sent a notification letter stating that they would be receiving a test kit in the mail shortly. Individuals who do not wish to be sent a kit could inform the program by telephone or e-mail. Three weeks later, participants who have not contacted the program were sent a 3-sample guaiac-based FT (Hemoccult II SENSA; Beckman Coulter, Brea, CA, USA) kit by mail. Individuals with a normal FT result were recalled for screening every two years and were sent a FT kit with their recall letter. Individuals with abnormal FT results were contacted by telephone and mail and were referred for colonoscopy.

ColonCheck arranged colonoscopy assessment and appointments for individuals who receive health services in the city of Winnipeg (if agreed upon by the individual's primary care provider [PCP]). ColonCheck also had agreements with the other regional health authorities (RHAs) for individuals who receive health services outside of Winnipeg. ColonCheck communicated directly with designated hospitals in each RHA and the hospital scheduled the colonoscopy appointment. When screening participants provided information about their health care providers, their providers were also sent the FT results and colonoscopy referral information.

# DEFINITIONS

## Adenoma, Advanced Adenoma, Colorectal Cancer

A colon adenoma is defined as a benign epithelial tumour or polyp arising from the bowel wall. Adenomas or adenomatous polyps can be pedunculated (polypoid) or sessile (flat) and can have different degrees of dysplasia or different histologic characteristics (i.e., tubular, tubulovillous, and villous). Although there is some variation in the exact definition of advanced adenomas, in concordance with the definition promoted by CPAC and Cancer Care Ontario, our study defined an "advanced" adenoma as any adenoma with:

i) Size ≥ 1 cm,

ii) High grade dysplasia,

iii) Villous component > 20-25%, or

iv) Sessile serrated shape with any dysplasia.[16]

- Advanced adenomas are also benign tumors, but with an increased likelihood for progression to malignancy.
- A CRC is defined as malignant tumour with invasion through the muscularis mucosa of the bowel lining into the submucosa.[19]
- Colorectal cancer that were not adenocarcinomas were excluded from our analysis

## Adenoma Detection Rate

The number of individuals who had an abnormal FT who attended colonoscopy and had an outcome of adenoma, divided by the number of individuals who had a successful FT

### Advanced Adenoma / Colorectal Cancer Detection Rate

The number of individuals who had an abnormal FT who attended colonoscopy and had an outcome of advanced adenoma or CRC, divided by the number of individuals who had a successful FT

### Positive Predictive Value

The number of individuals who had an abnormal FT with a subsequent pathology sample from attending colonoscopy and had an outcome of adenoma, advanced adenoma or CRC, divided by the number of individuals who had an abnormal FT and had a complete colonoscopy

### Resource Utilization Band

Participant co-morbidity was measured by the Resource Utilization Band (RUB), a simplified co-morbidity category that measures overall morbidity burden. It is calculated using the Johns Hopkins Adjusted Clinical Group (ACG) System software.[74] RUB is based on age, sex, physician claims, and hospital discharges in the year prior to diagnosis, and it is a validated measure of comorbidity based on health care resource utilization rather than specific diagnosis.

The RUB includes six categories: Non-users; Healthy user/no morbidity; Low morbidity; Moderate morbidity; High morbidity; Very high morbidity. We grouped the RUB categories into three groups for analysis purposes, due to small numbers in the higher comorbidity categories: (1) No use, healthy users, or no data; (2) Low morbidity; and (3) moderate, high and very high morbidity.

### Number Positive Windows

The number of positive windows refers to the number of positive windows showing "positive" on a 3-sample Hemoccult II SENSA test. Each guaiac-based fecal occult blood test assesses stool samples over 3 consecutive days, with 2 windows sampled on each day, for a total number of 6 windows for one complete test. We grouped number of positive windows into 3 groups due to smaller numbers in the 3-6 positive windows categories: (1) 1 positive window, (2) 2 positive windows, (3) 3-6 positive windows.

## DATABASES

The sources utilized for accrual of administrative data for this study included the ColonCheck Registry, the ColonCheck Patient Assessment Form (PAF) and Colonoscopy Procedure Report (CPR), the Manitoba Cancer Registry (MCR), the Manitoba Health Medical Claims (MHMC) database, Hospital Separations Abstracts (HSA), and Statistics Canada census 2006 data.

### ColonCheck Registry

ColonCheck maintains a prospective, population-based registry of all Manitobans 50 to 74 years of age. The registry is updated monthly with demographic and vital statistics information from the Manitoba Health Population Registry (including age, sex, and postal code), as well as the dates of previous FTs, colonoscopy, and flexible sigmoidoscopy tests from the MHMC database. The ColonCheck Registry includes the dates and outcomes of program FTs, follow-up colonoscopy information, pathology information, and final outcomes. The ColonCheck registry is also updated with CRC information (date of diagnosis, stage, International Classification of

Diseases for Oncology (ICD-O) morphology code and ICD-O topography code) from the MCR each month.

ColonCheck organizes colonoscopies for patients with abnormal FTs if their primary care provider is agreeable. For patients who reside in Winnipeg, a nurse practitioner performs a pre-colonoscopy assessment and completes a detailed Patient Assessment Form (Appendix B). This form includes data on symptoms, medical history, medications, family history, and body mass index. To date, approximately 1,700 individuals have been assessed by the ColonCheck nurse practitioner. For patients who undergo a colonoscopy, the endoscopist also completes a Colonoscopy Procedure Report (Appendix C). Both paper-based PAFs and CPRs were used to abstract data about symptoms, medical history, procedure findings, outcomes, and recommendations.

### The Manitoba Cancer Registry

CancerCare Manitoba is the provincial institution responsible for data collection, management and treatment of all cancer patients within the province of Manitoba. The Manitoba Cancer Registry (MCR), which began in 1937, is maintained by CancerCare Manitoba, and has been a population-based database since 1956. The MCR receives reports on all cases of cancer diagnosed in Manitoba, irrespective of whether patients receive treatment at CCMB. The MCR provides detailed tumor-specific information to capture or verify the histologic diagnosis and stage at the time of diagnosis for patients with CRC regardless of participation in the Colon Check program.

The North American Association of Central Cancer Registries, Inc. is an international organization that promotes the establishment of standards for cancer registration. It compiles annual reports of cancer incidence and mortality statistics for both Canada and the United States, and provides assessment of data quality and completeness of case ascertainment.[75] The Manitoba Cancer Registry has among the highest levels of completeness across Canada, with a completeness of case ascertainment of 101.6% in 2016.[75]

### Manitoba Health Medical Claims Database and Hospital Separation Abstracts

The Manitoba Health and Medical Claims database (MHMC) and Hospital Separation Abstracts (HSAs) provide information on patient-specific contacts with the health care system in Manitoba. Maintained by Manitoba Health, the databases contain information about consultations and services provided to individuals after an abnormal FT and colonoscopy both in and out of hospital, including information about the provider, location, type, and date of services rendered.

The HSAs provide admission dates, discharge dates, and information on diagnoses, procedures, and complications of treatment. Diagnosis information was based on the International Statistical Classification of Diseases and Related Health Problems, 10$^{th}$ Revision (ICD-10) and the International Classification of Diseases for Oncology (ICD-O, 3$^{rd}$ Edition) coding.[76] The Medical Claims database and Hospital Separations Abstracts were used to determine co-morbidity based on RUB.

### Statistics Canada

Statistics Canada 2006 Census Data was used to assess socio-economic status (SES) based on the deprivation index. There are four versions: one for Canada as a whole, one for each Canadian region (Atlantic, Québec, Ontario, the Prairies, and British Columbia); one for the three largest metropolitan areas (Toronto, Vancouver and Montreal), and one for certain geographic areas defined on an urban-rural gradient, each created using data from each dissemination area.

First described in 1988 in the book "Health and Deprivation: Inequality in the North" by Peter Townsend, the deprivation index embodies two forms of deprivation: material and social. Material deprivation refers to the lack of the goods and conveniences that are part of modern life; social deprivation refers to the fragility of the social network, from the family to the community. The deprivation index in this analysis combines socio-economic indicators including no high school diploma; employment; income; being widowed, separated or divorced; living alone; and being in a lone-parent family. Each deprivation quintile represents 20% of the population, from the most privileged (Quintile 1) to the most deprived (Quintile 5).

## DATA LINKING

The administrative information received through the ColonCheck Registry and the MCR for each patient was linked to the other administrative databases maintained by Manitoba Health. Since 1984, every resident in Manitoba has been assigned a unique Personal Health Identification Number (PHIN) by Manitoba Health and Healthy Living. To protect patient confidentiality, the data linkages in this study were performed via a scrambled PHIN using an anonymized version

of each database.

## DATA ANALYSIS

Appendix D lists the program's performance measures and their definitions. Using Statistical Analysis System (SAS) software, multivariate analyses will be used to assess the associations of socio-demographic and clinical factors with performance measures. The performance measures assessed for associations with participation, retention, and colonoscopy adenoma and CRC detection rate were limited to age, sex, SES status, and geographic region within the province, as we did not have access to specific health-related data for non-responders and those who undergo colonoscopies outside of ColonCheck. As there is a strong correlation between education level and income level, to avoid multi-collinearity, we chose to use only deprivation quintile in our final models in our statistical analysis.

Through the MHMC and HSA we were able to access data on colonoscopies (number, dates) arranged outside of ColonCheck. For the subset of patients assessed for colonoscopies through the ColonCheck program, a greater number of clinical factors (including BMI, Family history of CRC, prior colonoscopy history, resource utilization band (RUB), patient home medications, number of positive windows on FT, and presence of symptoms) have been included in our multivariate analyses, with more specific outcomes.

# RESULTS

During the study period, a total of 118,096 fecal occult blood tests (FTs) were completed. 3,876 abnormal (positive) results were identified, for a FT abnormal rate of 3.47%. Of those abnormal FT outcomes, 3,081 resulted in a complete colonoscopy (79.5%). Of the 3,081 colonoscopies completed during our study period, there were 2,930 colonoscopies with complete data available to be included in our analysis. Demographic and clinical descriptive characteristics of the included patients are shown in Table 1.

From 2011 to 2014, there were 1198 patients who underwent their colonoscopy through the ColonCheck Program, and thus had a Patient Assessment Form (PAF) completed at the time of their colonoscopy. 1182 (98.7%) of these colonoscopies had complete PAF data available for our analysis.

Table 1 – Descriptive Characteristics of Individuals who had an abnormal fecal occult blood test (FT) and underwent follow up colonoscopy

| DESCRIPTIVE CHARACTERISTICS | n | % |
|---|---|---|
| Number of Invitations Sent (2007-2014) | 400,132 | - |
| Number of Completed FTs | 118,096 | 29.51 |
| Number of Incomplete FTs | 282,036 | 70.49 |
| **FT Outcomes** | | |
| Negative (normal) | 107,835 | 38.23 |
| Positive (abnormal) | 3,876 | 3.47 |
| Inadequate / indeterminate[a] | 6,385 | 2.26 |
| **Total Positive FT with Complete Colonoscopy** | 3,081 | 79.49[b] |
| Scopes within 180 days | 2,685 | 87.15 |
| Scopes with complete data | 2,930 | 95.10[c] |
| **Sex** | | |
| Female | 1,256 | 42.87 |
| Male | 1,674 | 57.13 |
| **Age** | | |
| 50-59 | 1,326 | 45.26 |
| 60-69 | 1,143 | 39.01 |
| 70-74 | 461 | 15.73 |
| **Geography** | | |
| Urban | 1,897 | 64.74 |
| Rural South | 971 | 33.14 |
| Rural North | 62 | 2.12 |
| **Deprivation Quintile** | | |
| 1 (least deprived) | 555 | 18.94 |
| 2 | 592 | 20.20 |
| 3 | 644 | 21.98 |
| 4 | 574 | 19.59 |
| 5 (most deprived) | 565 | 19.28 |
| **Screen Type** | | |
| First screen | 2,190 | 74.74 |
| Second Screen | 740 | 25.26 |
| **RUB** | | |
| 0 (no data / non-users) | 1,838 | 62.73 |
| 1 (healthy users) | 228 | 7.78 |
| 2 (low users) | 363 | 12.39 |
| 3 (moderate/high/very high users) | 501 | 17.10 |
| **Scopes with Patient Assessment Form (PAF) data** | | |
| 2011-2012 | 550 | 45.91 |
| 2013-2014 | 648 | 54.09 |
| Total PAF scopes | 1,198 | |
| Total with complete PAF data | 1,182 | 98.66 |
| **PAF Scopes - Outcomes** | | |
| No Pre-cancerous lesion identified | 663 | 56.09 |
| Non-Advanced Adenoma | 266 | 22.50 |
| Advanced Adenoma + Cancer | 253 | 21.40 |

***Notes:*** Number (%) unless otherwise stated. BMI - Body mass index. RUB - Resource utilization band (see text for description of categories). PAF – Patient Assessment Form; [a] see Appendix D for definition and target for indeterminant results. [b] percent total colonoscopies resulting from the 3876 positive FT results; [c] percent total colonoscopies with a complete data set, from total 2930.

# SCREENING PARTICIPATION AND RETENTION

## PARTICIPATION

Table 2. FT Participation Frequencies

| Time Period | Eligible Population | Unsuccessful FT | Successful FT | PARTICIPATION Rate (%) |
|---|---|---|---|---|
| 2007-2008 | 202,887 | 198,816 | 4,071 | 2.01 |
| 2009-2010 | 210,090 | 184,932 | 25,158 | 11.97 |
| 2011-2012 | 245,453 | 196,609 | 48,844 | 19.90 |
| 2013-2014 | 237,248 | 188,176 | 49,072 | 20.68 |
| | | | | |
| **2007-2014** | 895,678 | 768,533 | 127,145 | 14.20 |
| | | | | |
| **2007-2010** | 412,977 | 383,748 | 29,229 | 7.08 |
| **2011-2014** | 482,701 | 384,785 | 97,916 | 20.29 |

Overall, 29,229 individuals successfully completed FTs between 2007 and 2010, and 97,916 individuals successfully completed FTs between 2011 and 2014.

Participation for the first 4-year period after screening program initiation was 7.1% (2007-2010). This increased to 20.3% for the second 4-year period from 2011-2014 (Table 2). The mean age of participants at the mid-point of the time period was 59 years (Table 3).

Table 3. Participation Frequencies of total eligible population from 2007-2014 by FT Result

| | Unsuccessful FT n (%) | Successful FT n (%) | P value |
|---|---|---|---|
| n (total) = 895,678 | n = 768,533 | n = 127,145 | |
| **Age at midpoint of time period (mean (SD))** | 59 (6.71) | 60 (7.18) | <0.0001 |
| **Age at midpoint of time period (median (IQR))** | 58 (53 - 64) | 59 (54 - 66) | <0.0001 |
| **Median age at midpoint of time period (min-max))** | 58 (50 - 74) | 59 (48 - 75) | <0.0001 |
| **Sex (n (%))** | | | <0.0001 |
| Female | 370636 (48.23) | 72895 (57.33) | |
| Male | 397897 (51.77) | 54250 (42.67) | |
| **Deprivation Quintile (n (%))** | | | <0.0001 |
| DQ1 - Least deprived | 122085 (17.10) | 26304 (21.74) | |
| DQ2 | 133053 (18.64) | 26132 (21.59) | |
| DQ3 | 147334 (20.64) | 25812 (21.33) | |
| DQ4 | 152118 (21.31) | 23402 (19.34) | |
| DQ5 - Most deprived | 159402 (22.33) | 19369 (16.00) | |
| **urban/rural (n (%))** | | | <0.0001 |
| Rural North | 42475 (5.53) | 3097 (2.44) | |
| Rural South | 299670 (38.99) | 47048 (37.00) | |
| Urban | 426388 (55.48) | 77000 (60.56) | |
| **time period (n (%))** | | | <0.0001 |
| 2007-2008 | 198816 (25.87) | 4071 (3.20) | |
| 2009-2010 | 184932 (24.06) | 25158 (19.79) | |
| 2011-2012 | 196609 (25.58) | 48844 (38.42) | |
| 2013-2014 | 188176 (24.49) | 49072 (38.60) | |

Notes: SD – Standard Deviation; IQR – Inter-quartile Range; FT – Fecal Occult Blood Test.

Total successful FT participation from 2007 to 2014 was 16.43% for female patients (72 895 out of 443,531 eligible individuals), and 12.0% for male patients (54,250 out of 452,147 eligible individuals) (Table 3).

As deprivation increased within the population, participation decreased (Table 3). In the least deprived quintile, DQ1, 17.73% of eligible individuals successfully completed an FT (26,304 out of 148,389). This decreased sequentially through the quintiles, dropping to 16.42% in DQ2

(26,132 out of 159,185), 14.91% in DQ3 (25,812 out of 173,146), 13.33% in DQ4 (23,402 out of 175,520), down to 10.83% in the most deprived quintile, DQ5 (19,369 out of 178,771).

Participation for those living in an urban community in Manitoba was 15.30% (77,000 out of 503,388). This compared to 13.57% participation for those living in a rural south region (47,048 out of 346,718), and 6.79% participation for those living in the rural north regions of Manitoba (3097 out of 45,572) (Table 3).

Table 4. Participation Frequencies – Eligible population from 2007-2014 by Time Period of Invitations Sent

| **TIME PERIOD** | **2007-2008** | **2009-2010** | **2011-2012** | **2013-2014** | **P value** |
|---|---|---|---|---|---|
| n (total) = 895,678 | n = 202,887 | n = 210,090 | n = 245,453 | n = 237,248 | |
| **age at midpoint of time period (mean (SD))** | 59 (6.72) | 59 (6.79) | 59 (6.80) | 59 (6.82) | < 0.0001 |
| **age at midpoint of time period (median (IQR))** | 58 (53 - 64) | 58 (53 - 64) | 58 (53 - 64) | 58 (53 - 65) | < 0.0001 |
| **Median age at midpoint of time period (min-max)** | 58 (49 - 75) | 58 (49 - 75) | 58 (48 - 75) | 58 (49 - 75) | < 0.0001 |
| **Sex** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | < 0.0001 |
| Female | 99772 (49.18) | 103797 (49.41) | 121747 (49.60) | 118215 (49.83) | |
| Male | 103115 (50.82) | 106293 (50.59) | 123706 (50.40) | 119033 (50.17) | |
| **Deprivation Quintile** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | < 0.0001 |
| DQ1 | 32004 (16.87) | 33340 (17.01) | 42406 (18.50) | 40639 (18.47) | |
| DQ2 | 35208 (18.56) | 36730 (18.74) | 44334 (19.34) | 42913 (19.50) | |
| DQ3 | 40150 (21.17) | 41598 (21.22) | 46723 (20.38) | 44675 (20.30) | |
| DQ4 | 40642 (21.43) | 41571 (21.20) | 47616 (20.77) | 45691 (20.77) | |
| DQ5 | 41671 (21.97) | 42811 (21.84) | 48181 (21.02) | 46108 (20.96) | |
| **Geography – Urban vs Rural** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | < 0.0001 |
| Urban | 111672 (55.04) | 116046 (55.24) | 142761 (58.16) | 132909 (56.02) | |
| Rural South | 80942 (39.90) | 83149 (39.58) | 91045 (37.09) | 91582 (38.60) | |
| Rural North | 10273 (5.06) | 10895 (5.19) | 11647 (4.75) | 12757 (5.38) | |
| **FT** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | < 0.0001 |
| not successful FT | 198816 (97.99) | 184932 (88.03) | 196609 (80.10) | 188176 (79.32) | |
| successful FT | 4071 (2.01) | 25158 (11.97) | 48844 (19.90) | 49072 (20.68) | |

Notes: SD – Standard Deviation; IQR – Inter-quartile Range; DQ – Deprivation Quintile; FT – Fecal Occult Blood Test.

Table 5. Multivariable Analysis for Participation

| VARIABLE | 2007 - 2010 | | | 2011-2014 | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | P Value | OR | 95% CI | P Value |
| **Sex** | | | | | | |
| Female (ref) | 1.000 | | | 1.000 | | |
| Male | 0.645 | 0.6277 - 0.6619 | <.0001 | 0.723 | 0.7102 - 0.7358 | <.0001 |
| **Geography** | | | | | | |
| Urban (ref) | 1.000 | | | 1.000 | | |
| Rural South | 0.846 | 0.8227 - 0.8704 | <.0001 | 1.008 | 0.9889 - 1.0277 | 0.4084 |
| Rural North | 0.085 | 0.0691 - 0.1039 | <.0001 | 0.785 | 0.7423 - 0.8293 | <.0001 |
| **MB Deprivation Quintile** | | | | | | |
| DQ1 (ref) | 1.000 | | | | | |
| DQ2 | 0.953 | 0.9145 - 0.9922 | 0.0196 | 0.909 | 0.8845 - 0.9335 | 0.0196 |
| DQ3 | 0.955 | 0.9169 - 0.9937 | 0.0233 | 0.789 | 0.7661 - 0.8100 | 0.0233 |
| DQ4 | 0.761 | 0.7290 - 0.7944 | <.0001 | 0.731 | 0.7105 - 0.7517 | <.0001 |
| DQ5 | 0.594 | 0.5683 - 0.6208 | <.0001 | 0.578 | 0.5615 - 0.5950 | <.0001 |
| **2009/10 vs 2007/08** | 6.112 | 5.9368 - 6.2930 | <.0001 | | | |
| **2013/14 vs 2011/12** | | | | 0.909 | 0.9012 - 0.9177 | <.0001 |

Notes: OR – Odds Ratio; CI – Confidence Interval; DQ – Deprivation Quintile.

On multivariable analysis, being male (OR 0.72, 95% CI 0.71-0.74), increased deprivation (OR Q5 vs. Q1 0.58, 95% CI 0.56-0.60) and living in a northern rural residence compared with an urban area (OR 0.78, 95% CI 0.74-0.83) were associated with statistically significantly decreased odds of participation (Table 5).

On multivariable regression, the effect of age on participation was non-linear and so the results for age are presented graphically as probabilities instead of with odds ratios. Age 55 was associated with a dip in participation across the entire study period (Figures 1 and 2).

Figure 1. Probability of Screening FT vs Age (from invitations sent between 2007-2010)

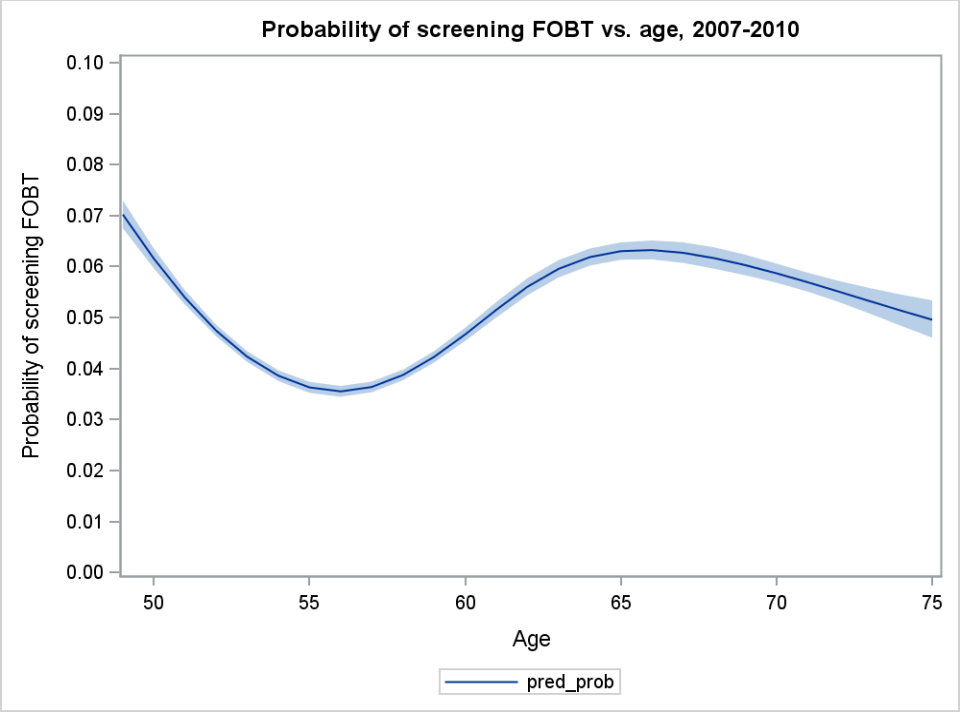
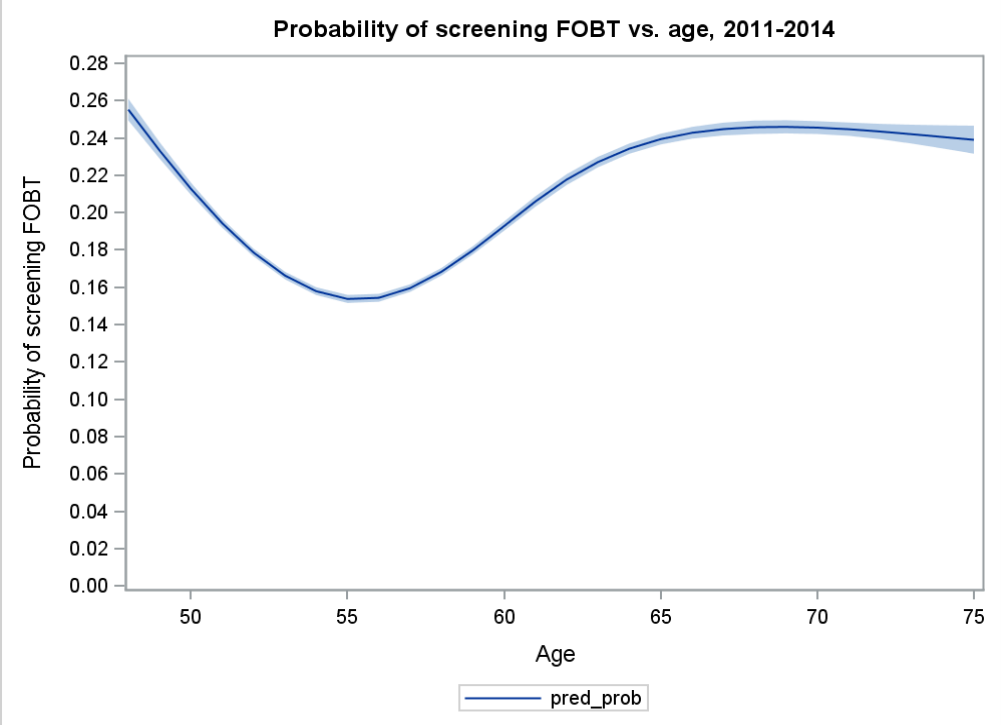



Figure 2. Probability of Screening FT vs Age (from invitations sent between 2011-2014)



**RETENTION**

Table 6. FT Retention Frequencies

| Time Period | Normal Index FT | No retention FT | Retention of FT | Retention Rate (%) |
|---|---|---|---|---|
| 2007-2008 | 1,934 | 818 | 1,116 | 57.70 |
| 2009-2010 | 14,080 | 4,922 | 9,159 | 65.05 |
| **2007-2010** | 16,014 | 5,740 | 10,275 | 64.16 |

The retention frequencies in Table 6 outline the rates of individuals who were retained in the ColonCheck screening program following their participation in the previous cycle. Of those who participated in the 2007-2008 screening program, 57.7% were retained, and of those who participated in FT screening in the 2009-2010 cycle, 65.1% were retained in the program.

Table 7. Retention Frequencies by FT Result

| Normal Index FT | No Retention of FT | Retention of FT | P value |
|---|---|---|---|
| | n = 5740 | n = 10,274 | |
| **Age at index FT (mean (SD))** | 59 (6.39) | 60 (6.54) | <0.0001 |
| **Age at index FT (median (IQR))** | 58 (53 - 63) | 60 (54 - 65) | <0.0001 |
| **Age at index FT (min-max))** | 58 (50 - 72) | 60 (50 - 72) | <0.0001 |
| **Sex (n (%))** | | | 0.748 |
| Female | 3463 (60.33) | 6225 (60.59) | |
| Male | 2277 (39.67) | 4049 (39.41) | |
| **Deprivation Quintile (n (%))** | | | 0.2331 |
| DQ1 - Least deprived | 959 (17.26) | 1655 (16.49) | |
| DQ2 | 1094 (19.69) | 2033 (20.26) | |
| DQ3 | 1425 (25.65) | 2706 (26.96) | |
| DQ4 | 1127 (20.28) | 1953 (19.46) | |
| DQ5 - Most deprived | 951 (17.12) | 1689 (16.83) | |
| **Urban vs. Rural (n (%))** | | | 0.1916 |
| Rural North | 27 (0.47) | 30 (0.29) | |
| Rural South | 2516 (43.83) | 4509 (43.89) | |
| Urban | 3197 (55.70) | 5735 (55.82) | |
| **Time Period (n (%))** | | | <0.0001 |
| 2007-2008 participants | 818 (14.25) | 1116 (10.86) | |
| 2009-2010 participants | 4922 (85.75) | 9158 (89.14) | |

Notes: SD – Standard Deviation; IQR – Inter-quartile Range; FT – Fecal Occult Blood Test;

Table 8. Retention by Time Period

| TIME PERIOD | 2007-2008 | 2009-2010 | P value |
|---|---|---|---|
| | n = 1934 | n = 14,080 | |
| **age at index FT (mean (SD))** | 60 (6.22) | 59 (6.55) | 0.0317 |
| **age at index FT (median (IQR))** | 59 (54 - 65) | 59 (54 - 65) | 0.1204 |
| **age at index FT (min-max))** | 59 (50 - 72) | 59 (50 - 72) | 0.1204 |
| **Sex – n (%)** | | | <0.0001 |
| Female | 1263 (65.31) | 8425 (59.84) | |
| Male | 671 (34.69) | 5655 (40.16) | |
| **Deprivation Quintile – n (%)** | | | <0.0001 |
| DQ1 - Least deprived | 263 (13.90) | 2351 (17.16) | |
| DQ2 | 312 (16.49) | 2815 (20.55) | |
| DQ3 | 532 (28.12) | 3599 (26.27) | |
| DQ4 | 465 (24.58) | 2615 (19.09) | |
| DQ5 - Most deprived | 320 (16.91) | 2320 (16.93) | |
| **Urban vs. Rural – n (%)** | | | <0.0001 |
| Rural North + South | 1116 (57.70) | 5966 (42.37) | |
| Urban | 818 (42.30) | 8114 (57.63) | |
| **FT Retention – n (%)** | | | <0.0001 |
| No Retention of FT | 818 (42.30) | 4922 (34.96) | |
| Retention of FT | 1116 (57.70) | 9158 (65.04) | |

Notes: Rural North and Rural South regions were combined for statistical analysis due to small numbers; SD – Standard Deviation; IQR – Inter-quartile Range; FT – Fecal Occult Blood Test.

Table 9. Multivariable Analysis for Retention of FT Participants

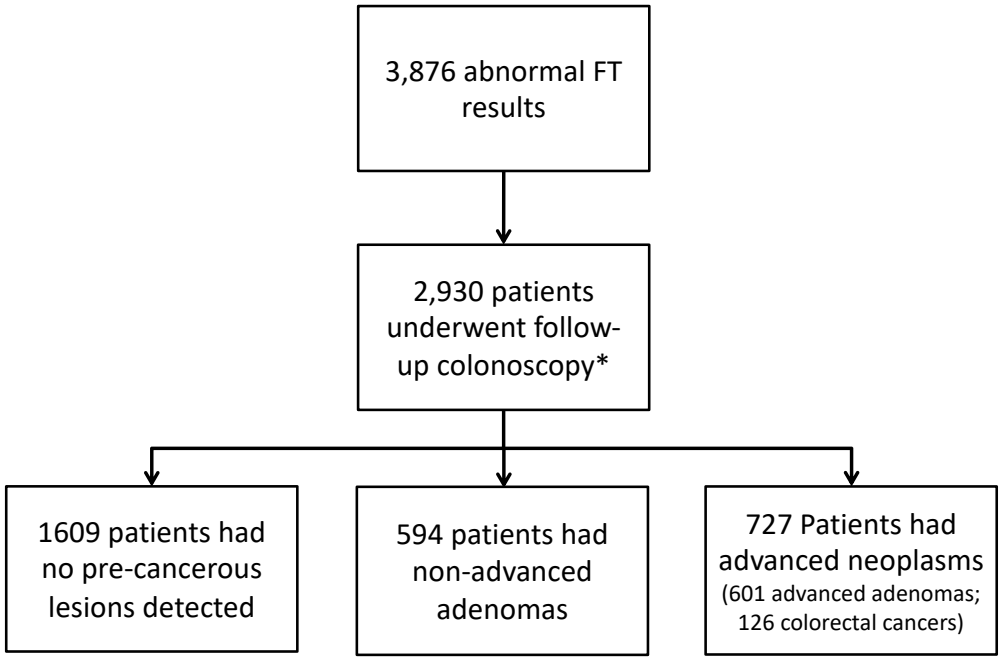
| VARIABLE | 2007 - 2010 | | |
|---|---|---|---|
| | OR | 95% CI | P Value |
| **Age** – at index FT (ref) | 1.000 | | < 0.0001 |
| at index FT, 1 yr | 1.031 | 1.0255 - 1.0362 | |
| at index FT, 5 yrs | 1.164 | 1.1343 - 1.1946 | |
| at index FT, 10 yrs | 1.355 | 1.2867 - 1.4270 | |
| **Sex** | | | |
| F (ref) | 1.000 | | |
| M | 0.989 | 0.9243 - 1.0588 | 0.7547 |
| **Geography** | | | |
| Urban (ref) | 1.000 | | |
| Rural South | 0.976 | 0.9090 - 1.0481 | 0.5056 |
| Rural North | 0.771 | 0.4282 - 1.3883 | 0.3861 |
| **Deprivation Quintile** | | | |
| DQ1 (ref) | 1.000 | | |
| DQ2 | 1.063 | 0.9518 - 1.1867 | 0.2793 |
| DQ3 | 1.069 | 0.9595 - 1.1913 | 0.2257 |
| DQ4 | 0.992 | 0.8861 - 1.1095 | 0.8820 |
| DQ5 (most deprived) | 1.000 | 0.8896 - 1.1241 | 0.9998 |
| **2009/10 vs 2007/08** | 1.436 | 1.3061 - 1.5781 | < 0.0001 |

Notes: OR – Odds Ratio; CI – Confidence Interval; DQ – Deprivation Quintile.

On multivariable analysis, increasing age from the time of index FT was the only variable associated with a statistically significantly increased odds of retention (OR 1.03 (CI 1.03–1.04) at 1 year from first FT; OR 1.16 (95% CI 1.13– 1.19) at 5 years from first FT, and OR 1.36 (95% CI 1.29–1.43) at 10 years from first FT) (Table 9).

## PROVINCIAL COHORT – ADVANCED NEOPLASIA AND NON-ADVANCED ADENOMA DETECTION RATES

Figure 3. Summary of follow-up colonoscopies and outcomes of patients with abnormal fecal-occult blood test (FT) results (2007-2014)




**Colonoscopy within 6 months. Colonoscopies were arranged by: (1) a patient's primary care provider or (2) ColonCheck also had agreements with the other regional health authorities (RHAs) for individuals who received health services outside of Winnipeg; ColonCheck communicated directly with designated hospitals in each RHA and the hospital scheduled the colonoscopy appointment for these patients.*
*NB: The number of abnormal FTs is a test-based result, while the number of colonoscopies is an individual, patient-based result.*

During the study period, there were 118,096 FTs completed, with 3876 abnormal results recorded. In total, 2930 colonoscopies were completed within 6 months of an abnormal FT result (Figure 3). 1609 patients had no precancerous lesions identified, 594 patients had non-advanced neoplasms identified, and 727 patients had advanced neoplasms identified (601 advanced adenomas and 126 cancers).

The PPV for any adenoma was 40.8% (Table 10). For advanced adenomas the PPV was 20.5% and 4.3% for CRC, for a combined PPV for advanced neoplasms of 24.8% (Table 10).

Table 10. All Colonoscopy Outcomes

| **Outcomes** | **n** | **%** |
|---|---|---|
| No Pre-cancerous lesion identified | 1,609 | 54.91 |
| Non-Advanced Adenoma | 594 | 20.27 |
| Advanced Adenoma | 601 | 20.51 |
| Cancer | 126 | 4.30 |
| *Any Adenoma* | *1195* | *40.78* |
| *Adv Adenoma + Cancer* | *727* | *24.81* |
| Total | 2,930 | |

Table 11. All Colonoscopy Outcomes by Sex

| **Outcomes** | **FEMALE (n)** | **PPV (female)** | **MALE (n)** | **PPV (male)** |
|---|---|---|---|---|
| No Pre-cancerous lesion identified | 779 | | 830 | |
| Non-Advanced Adenoma | 213 | 16.96 | 381 | 22.76 |
| Advanced Adenoma | 210 | 16.72 | 391 | 23.36 |
| Cancer | 54 | 4.299 | 72 | 4.301 |
| *Any Adenoma* | *423* | *33.68* | *772* | *46.12* |
| *Advanced Adenoma + CRC* | *264* | *21.02* | *463* | *27.66* |
| Total | 1256 | | 1674 | |

Notes: PPV – Positive Predictive Value; CRC – colorectal cancer.

When assessing detection rates between sexes, the PPV for any adenoma for females was 33.7%, vs 46.1% for males. For advanced neoplasms, the PPV was 21.0% for females, vs 27.7% for males (Table 11).

Table 12. All Colonoscopy Outcomes by Age

| **Outcome** | **Age 50-59** | **PPV (50-59yrs)** | **Age 60-69** | **PPV (60-69yrs)** | **Age 70-74** | **PPV (70-74yrs)** |
|---|---|---|---|---|---|---|
| No Pre-cancerous lesion | 816 | 61.54 | 590 | 51.62 | 203 | 44.03 |
| Non-Advanced Adenoma | 266 | 20.06 | 243 | 21.26 | 85 | 18.44 |
| Advanced Adenoma | 222 | 16.74 | 245 | 21.43 | 134 | 29.07 |
| Cancer | 22 | **1.66** | 65 | **5.69** | 39 | **8.46** |
| *Any Adenoma* | *488* | ***36.80*** | *488* | ***42.69*** | *219* | ***47.51*** |
| *Advanced adenoma + CRC* | *244* | ***18.40*** | *310* | ***27.12*** | *173* | ***37.53*** |
| Total | 1326 | | 1143 | | 461 | |

Notes: PPV – Positive Predictive Value (%); CRC – Colorectal Cancer; yrs – years.

When separating patients by age, there were significant differences across age groups (Table 12). For non-advanced adenomas, the PPVs for age 50-59, 60-69 and 70-74 were 36.8%, 42.7%, and 47.5% respectively. For advanced neoplasms, the PPV for age 50-59, 60-69 and 70-74 were 18.4%, 27.1% and 37.5% respectively. When looking specifically at colorectal cancer detection, the PPV for identifying a CRC with a positive FT result was 1.7%, 5.7%, and 8.5% for ages 50-59, 60-69 and 70-74 respectively.

## MULTIVARIABLE ANALYSIS – FULL PROVINCIAL COHORT

Table 13. Multivariable Analysis of Clinical Factors Associated with Adenoma or Advanced Neoplasms Identified on Colonoscopy

| | ADENOMA | | | ADVANCED ADENOMA + CRC | | |
|---|---|---|---|---|---|---|
| **VARIABLE** | **OR** | **95% CI** | **P Value** | **OR** | **95% CI** | **P Value** |
| **Age** | | | | | | |
| By 5-year split | 1.095 | 1.024 - 1.170 | | 1.355 | 1.272 - 1.444 | |
| By 10-year split | 1.198 | 1.048 - 1.370 | 0.0081 | 1.837 | 1.618 - 2.085 | < 0.0001 |
| **Sex** | | | | | | |
| Female (ref) | 1.000 | - | - | 1.000 | - | - |
| Male | 1.706 | 1.403 - 2.074 | < 0.0001 | 1.694 | 1.410 - 2.037 | < 0.0001 |
| **Geography** | | | | | | |
| Urban (ref) | 1.000 | - | | 1.000 | - | - |
| Rural | 0.981 | 0.796 - 1.208 | 0.8537 | 1.202 | 0.990 - 1.459 | 0.0635 |
| **Screen Type** | | | | | | |
| 1st Screen (ref) | 1.000 | - | | 1.000 | - | - |
| 2nd Screen | 1.167 | 0.941 - 1.448 | 0.1589 | 0.792 | 0.640 - 0.979 | 0.0313 |
| **Deprivation Quintile** | | | | | | |
| DQ1 (ref) | 1.000 | - | - | 1.000 | - | - |
| DQ2 | 1.102 | 0.809 - 1.502 | 0.5384 | 0.915 | 0.689 - 1.215 | 0.5402 |
| DQ3 | 1.105 | 0.742 - 1.388 | 0.9266 | 0.821 | 0.615 - 1.094 | 0.1776 |
| DQ4 | 1.100 | 0.800 - 1.513 | 0.5574 | 1.012 | 0.758 - 1.350 | 0.9361 |
| DQ5 (most deprived) | 1.270 | 0.933 - 1.728 | 0.1288 | 0.728 | 0.539 - 0.984 | 0.0387 |
| **RUB** | | | | | | |
| 0 (ref) | 1.000 | - | - | 1.000 | - | - |
| 1 | 1.180 | 0.828 - 1.683 | 0.3593 | 0.840 | 0.591 - 1.195 | 0.3322 |
| 2 | 1.192 | 0.889 - 1.599 | 0.2407 | 1.063 | 0.806 - 1.403 | 0.6645 |
| 3 | 1.199 | 0.928 - 1.549 | 0.1660 | 0.877 | 0.683 - 1.127 | 0.3063 |

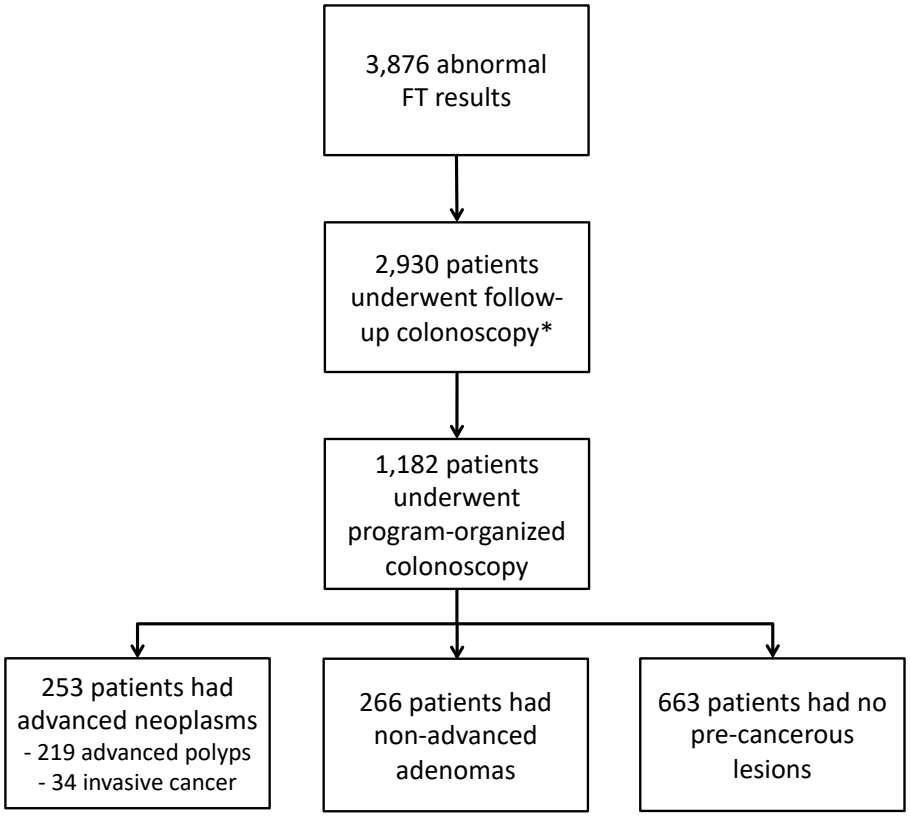
Notes: OR – Odds Ratio; CI – Confidence Interval; DQ – Deprivation Quintile; RUB = *Resource Utilization Band* – simplified morbidity category that measures overall morbidity burden. 0 = Non-users; (1) = Healthy Users; (2) = Low Morbidity; (3) = Moderate + High + Very High.

After adjusting for all variables, older age (OR 1.84, 95% CI 1.62-2.08) and male sex (OR 1.69, 95% CI 1.41-2.04) were associated with higher odds of identifying advanced neoplasms and colorectal cancer (Table 13). Older age (OR 1.20, 95% CI 1.05-1.37) and male sex (OR 1.71, 95% CI 1.40-2.07) were also associated with higher odds of identifying non-advanced neoplasms.

Age and sex were consistently found to be statistically significant across all three pathology subtypes analyzed (Table 13). Geography and Deprivation Index were not found to be statistically significant sociodemographic factors affecting the odds of identifying pathology on colonoscopy. However, for Geography, there was a near statistically significant increased odds of identifying, advanced adenomas or cancer for those in rural residences compared to urban. For Deprivation, there was a clear trend towards increased odds of identifying non-advanced adenomas on colonoscopy as deprivation increased, however there was no definite trend seen with respect to the odds of identifying advanced adenomas or colorectal cancers and deprivation quintile.

## PATIENT ASSESSMENT FORM SUBGROUP – ADVANCED NEOPLASIA AND NON-ADVANCED ADENOMA DETECTION RATES

Figure 4. Summary of follow-up colonoscopies and outcomes of patients with abnormal fecal-occult blood test (FT) results (2007-2014).




**Colonoscopy within 6 months – patients may have undergone colonoscopy at another later time.*
*NB: The number of abnormal FTs is a test-based result, while the number of colonoscopies is an individual, patient-based result.*

During the study period, 2930 colonoscopies were completed within 6 months of an abnormal FT result, 1182 (40.3%) of these patients underwent program-organised follow up colonoscopies, with completion of the Patient Assessment Form (PAF) (Figure 4).

Table 14. All Colonoscopy Outcomes for patients with a PAF

| **Outcomes** | **n** | **%** |
|---|---|---|
| No pre-cancerous lesions | 663 | 56.09 |
| Non-advanced Adenomas | 266 | 22.50 |
| Advanced adenomas / cancer | 253 | 21.40 |
| Total | 1182 | |

The PPV for non-advanced adenomas was 22.5% (95% CI, 20.1% to 24.9%). The PPV for advanced neoplasms was 21.4% (95% CI, 19.1% to 23.7%). The PPV for CRC was 2.9% (95% CI, 1.9% to 3.8%) (Table 14).

Table 15. Characteristics of individuals for individuals who had an abnormal fecal-occult blood test result and underwent program-organized follow up colonoscopy with PAF (n = 1,182).

| | Total | No pre-cancerous lesions (n = 663) | No pre-cancer lesions (%) | Non-Advanced Adenoma (n = 266) | Adenoma (%) | Advanced adenoma / Cancer (n = 253) | Advanced Adenoma / Cancer (%) |
|---|---|---|---|---|---|---|---|
| **Anti-platelet Drug**[a] | | | | | | | |
| Aspirin | 280 | 154 | 34.52 | 68 | 5.75 | 58 | 4.91 |
| No aspirin | 902 | 509 | 21.57 | 198 | 16.75 | 195 | 16.50 |
| **Bleeding** | | | | | | | |
| No | 700 | 408 | 34.52 | 171 | 14.47 | 121 | 10.24 |
| Yes | 482 | 255 | 21.57 | 95 | 8.04 | 132 | 11.17 |
| **BMI** | | | | | | | |
| Underweight/Healthy | 318 | 182 | 15.40 | 84 | 7.11 | 52 | 4.40 |
| Overweight | 440 | 267 | 22.59 | 82 | 6.94 | 91 | 7.70 |
| Obese | 424 | 214 | 18.10 | 100 | 8.46 | 110 | 9.31 |
| **CRC Family History** | | | | | | | |
| Not selected | 1032 | 589 | 49.83 | 225 | 19.04 | 218 | 18.44 |
| Selected | 150 | 74 | 6.26 | 41 | 3.47 | 35 | 2.96 |
| **Sex** | | | | | | | |
| Female | 500 | 319 | 26.99 | 95 | 8.04 | 86 | 7.28 |
| Male | 682 | 344 | 29.10 | 171 | 14.47 | 167 | 14.13 |
| **Number of Positive Windows on FT** | | | | | | | |
| 1 | 400 | 223 | 18.87 | 97 | 8.21 | 80 | 6.77 |
| 2 | 471 | 284 | 24.03 | 114 | 9.64 | 73 | 6.18 |
| 3 or more | 311 | 156 | 13.20 | 55 | 4.65 | 100 | 8.46 |
| **History of Prior Scope** | | | | | | | |
| Scope within 10 yrs | 162 | 102 | 8.63 | 35 | 2.96 | 25 | 2.12 |
| No prior scope / >10yrs | 1020 | 561 | 47.46 | 231 | 19.54 | 228 | 19.29 |
| **RUB** | | | | | | | |
| 0 | 721 | 422 | 35.70 | 154 | 13.03 | 145 | 12.27 |
| 1 | 121 | 67 | 5.67 | 31 | 2.62 | 23 | 1.95 |
| 2 | 157 | 81 | 6.85 | 36 | 3.05 | 40 | 3.38 |
| 3 | 183 | 93 | 7.87 | 45 | 3.81 | 45 | 3.81 |

***Notes:*** Number (%) unless otherwise stated. PAF – Patient Assessment Form; BMI - Body mass index. CRC – colorectal cancer; FT – fecal occult blood test; RUB - Resource utilization band (simplified morbidity category that measures overall morbidity burden. 0 = No data or non-users; (1) = Healthy Users; (2) = Low Morbidity; (3) = Moderate + High + Very High). [a] See Appendix E for medications included as Aspirin.

Table 15 lists the demographic and clinical characteristics of the PAF subgroup patients. The mean time interval between the date of receipt of the abnormal FT results and colonoscopy was 73 days (median = 58 days). The demographics of the patients who underwent program-organized colonoscopies were not significantly different from those patients who underwent colonoscopies arranged outside of the ColonCheck screening program (see Table 1).

## MULTIVARIABLE ANALYSIS – PAF DATA SUBGROUP

Table 16. Multivariable Analysis of Clinical Factors Associated with Adenomas or Advanced Neoplasms Identified on Colonoscopy – PAF Data

| VARIABLE | ADENOMA | | | ADVANCED ADENOMA + CRC | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | P Value | OR | 95% CI | P Value |
| **Age** | | | | | | |
| By 5 year split | 1.210 | 1.077 - 1.340 | 0.0010 | 1.588 | 1.414 - 1.782 | <0.0001 |
| By 10 year split | 1.444 | 1.161 - 1.795 | | 2.520 | 2.000 - 3.176 | |
| **Sex** | | | | | | |
| Female (ref) | 1.000 | | | 1.000 | | |
| Male | 1.836 | 1.357 - 2.484 | <0.0001 | 1.892 | 1.369 - 2.615 | 0.0001 |
| **Anti-platelet Drug** | | | | | | |
| No Aspirin (ref) | 1.000 | | | 1.000 | | |
| Aspirin | 0.882 | 0.616 - 1.264 | 0.4947 | 0.594 | 0.405 - 0.870 | 0.0075 |
| **Bleeding Symptoms** | | | | | | |
| No (ref) | 1.000 | | | 1.000 | | |
| Yes | 0.899 | 0.662 - 1.221 | 0.4971 | 1.848 | 1.350 - 2.532 | 0.0001 |
| **BMI** | | | | | | |
| Underweight/healthy (ref) | 1.000 | | | 1.000 | | |
| Overweight | 0.615 | 0.426 - 0.889 | 0.0097 | 1.058 | 0.699 - 1.602 | 0.7904 |
| Obese | 0.953 | 0.662 - 1.373 | 0.7961 | 1.704 | 1.127 - 2.575 | 0.0114 |
| **CRC Family History** | | | | | | |
| Not selected (ref) | 1.000 | | | 1.000 | | |
| Selected | 1.604 | 1.048 - 2.452 | 0.0294 | 1.473 | 0.923 - 2.350 | 0.1046 |
| **Number Positive Windows** | | | | | | |
| 1 (ref) | 1.000 | | | 1.000 | | |
| 2 | 0.921 | 0.662 - 1.282 | 0.6261 | 0.741 | 0.506 - 1.085 | 0.1235 |
| 3 or more | 0.775 | 0.521 - 1.152 | 0.2074 | 1.635 | 1.118 - 2.390 | 0.0112 |
| **Prior Scope History** | | | | | | |
| Scope within 10 yrs (ref) | 1.000 | | | 1.000 | | |
| No prior scope/ > 10 yrs | 1.461 | 0.944 - 2.261 | 0.0891 | 2.464 | 1.494 - 4.063 | 0.0004 |
| **RUB** | | | | | | |
| 0 (ref) | 1.000 | | | 1.000 | | |
| 1 | 1.242 | 0.771 - 1.999 | 0.3734 | 0.823 | 0.479 - 1.413 | 0.4803 |
| 2 | 1.235 | 0.789 - 1.933 | 0.3559 | 1.236 | 0.782 - 1.952 | 0.3647 |
| 3 | 1.349 | 0.884 - 2.059 | 0.1654 | 1.126 | 0.772 - 1.755 | 0.6019 |

***Notes:*** Number (%) unless otherwise stated. OR – Odds Ratio; CI – Confidence Interval; BMI - Body mass index. CRC – colorectal cancer; RUB - Resource utilization band (simplified morbidity category that measures overall morbidity burden. 0 = No data or non-users; (1) = Healthy Users; (2) = Low Morbidity; (3) = Moderate + High + Very High).

After adjustment, older age, male sex, and family history of CRC were associated with increased odds of identifying non-advanced adenomas on colonoscopy. (Table 16). Having an overweight

BMI (> 25 to ≤ 30) was significantly associated with decreased odds of findings of non-advanced adenomas.

After adjustment, older age, male sex, reporting bleeding symptoms, BMI > 30, > 3 positive windows on FT, and no prior history of colonoscopy or > 10 years since last colonoscopy were associated with increased odds of finding advanced neoplasms on colonoscopy (Table 16).

The use of anti-platelet medication, including aspirin and non-aspirin agents, was associated with a statistically significant decreased odds of finding advanced neoplasms (Table 16).

When the multivariable analysis excluded patient reports of bleeding symptoms at the time of their colonoscopy, the results remained the same, with the same factors showing statistical significance for increased or decreased odds of identifying advanced or non-advanced neoplasms (Table 17).

Table 17. Multivariable Analysis of Clinical Factors Associated with Adenomas or Advanced Neoplasms Identified on Colonoscopy – PAF Data – minus "bleeding"

| VARIABLE | ADENOMA | | | ADVANCED ADENOMA + CRC | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | P Value | OR | 95% CI | P Value |
| **Age** | | | | | | |
| By 5 year split | 1.206 | 1.082 - 1.344 | 0.0007 | 1.557 | 1.390 - 1.745 | < 0.0001 |
| By 10 year split | 1.454 | 1.170 - 1.807 | | 2.425 | 1.932 - 3.045 | |
| **Sex** | | | | | | |
| F (ref) | 1.000 | | | | | |
| M | 1.824 | 1.349 - 2.467 | <0.0001 | 1.975 | 1.433 - 2.722 | < 0.0001 |
| **Anti-platelet Drug** | | | | | | |
| No Aspirin (ref) | 1.000 | | | 1.000 | | |
| Aspirin | 0.882 | 0.616 - 1.262 | 0.4917 | 0.594 | 0.406 - 0.869 | 0.0072 |
| **BMI** | | | | | | |
| Underweight/healthy (ref) | 1.000 | | | 1.000 | | |
| Overweight | 0.612 | 0.424 - 0.884 | 0.0089 | 1.094 | 0.725 - 1.652 | 0.6686 |
| Obese | 0.951 | 0.660 - 1.370 | 0.7878 | 1.722 | 1.142 - 2.595 | 0.0094 |
| **CRC Family History** | | | | | | |
| Not selected (ref) | 1.000 | | | 1.000 | | |
| Selected | 1.595 | 1.043 - 2.440 | 0.0312 | 1.484 | 0.934 - 2.360 | 0.0948 |
| **Number Positive Windows** | | | | | | |
| 1 (ref) | 1.000 | | | 1.000 | | |
| 2 | 0.923 | 0.663 - 1.284 | 0.6632 | 0.737 | 0.504 - 1.077 | 0.1144 |
| 3 or more | 0.773 | 0.520 - 1.150 | 0.2036 | 1.660 | 1.138 - 2.421 | 0.0085 |
| **Prior Scope History** | | | | | | |
| Scope within 10 yrs (ref) | 1.000 | | | 1.000 | | |
| No prior scope/ > 10 yrs | 1.482 | 0.959 - 2.288 | 0.0762 | 2.265 | 1.380 - 3.717 | 0.0012 |
| **RUB** | | | | | | |
| 0 (ref) | 1.000 | | | 1.000 | | |
| 1 | 1.235 | 0.767 - 1.987 | 0.3854 | 0.837 | 0.490 - 1.432 | 0.5163 |
| 2 | 1.212 | 0.777 - 1.892 | 0.3698 | 1.339 | 0.851 - 2.107 | 0.2073 |
| 3 | 1.343 | 0.880 - 2.049 | 0.1710 | 1.154 | 0.742 - 1.794 | 0.5255 |

***Notes:*** Number (%) unless otherwise stated. OR – Odds Ratio; CI – Confidence Interval; BMI - Body mass index. CRC – colorectal cancer; RUB – Resource utilization band (simplified morbidity category that measures overall morbidity burden. 0 = No data or non-users; (1) = Healthy Users; (2) = Low Morbidity; (3) = Moderate + High + Very High)

# DISCUSSION

In 2019, CRC stands as the second most common cause of cancer cases and deaths in Manitoba, and our publicly-funded health care system is obliged to focus many of its resources towards the care and management of patients diagnosed with the disease. The central tenet of Canadian health care policy, outlined in the 1984 Canada Health Act, is to "protect, promote and restore the physical and mental well-being of residents of Canada and to facilitate reasonable access to health services without financial or other barriers."[29] The purpose of this Master's thesis was to analyze Manitoba's provincial colorectal cancer screening program in an effort to identify sociodemographic and/or clinical factors associated with the patients who have participated in the CRC screening program and to analyze the outcomes so that barriers to participation or treatment may be identified. Identifying patterns within our population will allow for opportunities for program improvement through more targeted interventions.

The results of this study show that participation within the Manitoba provincial colorectal screening program is associated with age, sex, deprivation index, and location of residence. Research shows that about 50% of colorectal cancers diagnosed today are detected at a later stage (stage III or IV).[42] Given the strong connection between stage at diagnosis and survival for colorectal cancer, increased participation in colorectal cancer screening programs in Canada will help to diagnose more patients earlier, and help further reduce colorectal cancer mortality rates in the near future.[42,77,78]

With regards to outcomes after participation in screening and subsequently having abnormal results requiring colonoscopy, we found that age and sex were most consistently associated with findings of advanced neoplasms and non-advanced adenomas. Geography and Deprivation Index were not found to be statistically significant sociodemographic factors affecting the odds of identifying advanced neoplasms or non-advanced adenomas, reinforcing the idea that their importance in improving CRC outcomes lies at the level of participation and retention. An understanding of the variables associated with adverse outcomes has the potential to help expedite the diagnosis and treatment of more urgent cases in our health care system where resources are limited.

Population screening by design embraces a heterogeneous group of individuals. It is important to know what variables affect participation and other key indicators of the performance of a screening program, as this will influence the interpretation of such indicators. In addition, knowledge of how population variables affect the performance of a screening program can inform methods of delivering the program.[12] This study has endeavoured to provide valuable information for programs attempting to reduce the burden of colorectal cancer in Manitoba. Through identification of disparities and potential barriers to participation, access, or timely investigations, we can inform and direct future program initiatives to reduce barriers.

## PARTICIPATION IN COLORECTAL CANCER SCREENING

In the last 20 years since its prevention potential was recognized, screening for CRC has undergone a paradigm shift. It has progressed from parochial ad hoc opportunistic activities, led

by clinical champions, to a structured, organized public health priority tailored to specific health-care environments in population-based settings.[79] So how does the Manitoba experience compare with other organized colorectal cancer screening programs? Results from the English Bowel Cancer Screening Program (BCSP), launched in 2006 and reported by Logan and colleagues in 2011, showed a FT participation rate of 52% after the first 1.08 million tests.[37] Finland rolled out their screening program in 2004 with phased implementation, and reported a FT participation rate in 2008 of 70.8%.[80] The Scottish pilot screening program reported participation rates of 55%, 53% and 55.3% over the first three rounds respectively.[12] While direct comparisons between different populations and systems of care are difficult to make, there is an obvious difference between participation in the programs and countries listed above and that seen in Manitoba and Ontario.

One of the main markers of success of a screening program and therefore its ability to reduce CRC mortality is achieving high participation in the program. Many Canadian provinces have been struggling to explain why their CRC screening program participation rates continue to sit far below the CPAC target of ≥ 60%.[34] Manitoba is by no means the only province where screening rates lag behind the CPAC target. In a program similar to that in Manitoba, Rabeneck and colleagues reported in 2014 on the Cancer Care Ontario (CCO) ColonCancerCheck (CCC) program performance since its initiation.[38] Their analysis revealed that of the 2,612,382 persons in the target population who were eligible for screening, only 29.8% (95% CI, 29.7%–29.9%) completed a screening FT between 2010 and 2011. In their 2013 paper, Major and colleagues outlined that five of the provincial screening programs in place at the time (British Columbia, Saskatchewan, Manitoba, Prince Edward Island, and Nova Scotia) were reporting an average

participation rate of 16.1%.[24] Our study reports a participation rate for Manitoba's ColonCheck program from 2011-2014 of 20.3% ($p < 0.0001$). Our results also outline a steady improvement over the years since the program was introduced as a pilot program back in 2007. Nevertheless, despite the annual improvements seen, participation continues to be well below the CPAC target of $\geq 60\%$.[34]

Some important differences may explain the lower rates seen in the Manitoba and Ontario programs in comparison to these European studies, but the most critical is the clinical environment into which they were introduced. The European programs were launched into communities where there was virtually no (or very limited) opportunistic CRC screening being performed at the time.[38] In Ontario, well before the population-wide CCC program was launched in 2008, Vinden et al demonstrated an increase in colonoscopy use between 1996-2001, confirming that opportunistic screening was on the rise.[81] The 2014 analysis of the CCC program performance since its inception reported that 53.2% of the eligible population in Ontario was considered up to date with CRC screening.[38] In Manitoba, a similar CCMB analysis on the ColonCheck program reported that 45.2% of Manitobans in 2009-2010 and 50.1% in 2011-2012 were up to date with their CRC screening.[23] Moss and colleagues stated that "in a setting where opportunistic screening has been taking place for some time, the uptake and performance of an organized program may differ markedly from those in a setting where no such screening has been taking place."[21] This reasoning can certainly explain, to some extent, why Canadian participation rates are lower than those seen in other publicly funded health care systems. In comparison to the European studies, the lower uptake rates in Ontario and Manitoba, where opportunistic screening colonoscopy was widely available prior to the implementation of

population wide screening, could be explained simply by the fact that a larger portion of the eligible population was already up to date with CRC screening by these ad hoc methods, and thus less likely to participate in a screening program.

Another reason to explain the lower participation rates achieved was first posited by the Australian Bowel Cancer Screening Pilot Program analysis in 2005. They suggested that the higher rates of participation in the UK Pilot program and other major international RCTs reported were the result of adjusting for the exclusion of people in the target age group who were judged "unsuitable" for screening, largely due to participation in CRC screening through other avenues.[28] Had the entire eligible population been included, the rates were likely comparable to the Australian Pilot Rates, where no such exclusions were made.[28] If true, this may also explain the lower rates similarly seen across Canadian screening programs, and it is certainly supported by the much higher rates of eligible individuals being up to date with their CRC screening compared to provincial screening program participation rates. Many experts even argue that the percentage of eligible population that is overdue for screening is a more appropriate measure of the extent of screening as it better describes the unmet need for a given population.[38]

**SEX**

There is extensive literature showing that participation rates for CRC screening programs is significantly higher in females than it is in males. Our results of a significantly decreased odds of participation for males compared with females (OR 0.72, 95% CI 0.71-0.74) aligns with results previously reported in Manitoba and across Canada, as well with results seen in multiple other

publicly-funded health care systems.[21,23,24,27,28,37] Both the Scotland Pilot program in 2010 and the English UKCCSP pilot in 2012 showed consistency in the trend for higher uptake in females across three rounds of CRC screening program roll out.[21,27] The CPAC results presented by Major et al in 2013, which are perhaps the most analogous representation to trends seen in Manitoba, reported an almost 4% difference in participation between males (14.2%) and females (18.1%) across the Canadian programs reporting their results. Even in programs such as the one launched in Finland in 2004 where uptake rates were significantly higher than other screening programs (70.8% participation), there still seems to be a significant gender bias towards higher uptake in females (78.1% vs 63.3%). Conversely, a systematic review in 2016 reported on 77 studies worldwide and found that female sex was in fact a barrier to adherence to CRC screening.[82]

A higher uptake of CRC screening in women is not unexpected given that other cancer screening programs have been available to the female population for some time. Experience with screening programs for breast and cervical cancer may translate into a greater willingness to participate in CRC screening as the idea of screening programs for early detections of cancer is more familiar to them. There is also an abundance of evidence suggesting men are less likely than women to seek health advice or make use of medical services.[12,77] While the sex differences in participation have been recognized across CRC screening programs worldwide, recent data suggest that this difference diminishes as age increases over 70 years,[37,83] and as programs become more established.[21,27] The disappearance of differences in participation between sexes as patients get older will be discussed in more detail later, however, the narrowing of sex differences as a

screening program matures is likely due in part to a selection effect, since participation in successive screening depends heavily on previous participation.[84]

**AGE**

The effect of age on participation was non-linear, and age 55 was associated with a dip in participation, consistent across all years of the program's operation. In a 2015 analysis of CRC screening in Manitoba, Singh and colleagues also identified lower rates of CRC screening among individuals aged 50-55.[35] Other studies have also reported this trend in the past.[35,85] The underlying reasons for an increased willingness for older age groups to engage with colorectal screening are not clear, but we speculate that more free time and increasing concern with health matters generally may contribute.[12]

It has previously been thought that the younger age group may be less appropriate to target due lower rates of CRC incidence and mortality when compared with older age groups, and stratified analyses of FT clinical trials have not shown the same benefits of CRC screening in the younger age groups.[9,35,86] However, the decline in CRC incidence rates may be confined to older adults as rates are reportedly increasing among adults younger than 50 years of age in both Canada and the US.[42,87] This new trend showcases the significance of ensuring the younger populations are aware of colorectal cancer screening, and the additional focus on improving adherence to screening uptake at age 50 is of critical importance to lowering the incidence of CRC among Canada's younger patients.

Through this study's analysis and identification of the patterns in our Manitoban population, we can direct future screening information delivery to better serve our younger patients. By alerting the public and primary care providers that patients who fall within this age group may be less likely to participate and may not be up to date with their CRC screening, we have to ability to focus efforts to find ways to motivate these individuals and improve participation. The long-term health and economic benefits of CRC prevention through improved screening participation will be far greater, with broader ranging health benefits, in contrast to simply expanding the screening age guidelines.

## GEOGRAPHY

In comparison to other publicly-funded health care systems, large scale CRC screening programs in Canada face unique challenges related to geographically dispersed populations, and more limited access to health care for many non-urban residents. Significantly geographically smaller countries with publicly-funded systems, such as the United Kingdom and Finland where less of the population resides in a rural or remote region, have reported higher rates of participation – 61.8 % in the UKCCSP[21], and 70.8% in Finland.[80]

The Australian screening program has reported higher participation rates than any of the Canadian programs, however, while also having to deal with a small population spread over vast geographic distances. The Bowel Cancer Australia screening pilot program in 2005 reported participation rates of 45.4%. Their pilot study was rolled out across three sites; two urban cities (Melbourne and Adelaide), and one rural town (McKay in northern Queensland). Interestingly,

the participation rate in the more rural Mackay (57.5%) was significantly higher than the participation in the two urban centers Adelaide (46.3%) and Melbourne (39.9%).[28] While direct comparisons of participation rates within a pilot rollout to that of a population wide screening program are not straightforward, the differences in participation uptake between rural and urban populations in Australia show an inverse urban-rural divide when compared to our provincial results.

This variation highlights that it is possible to attain high participation rates in rural and remote communities. When we look specifically at the early years (2007-2010) of the ColonCheck program, compared to the 2011-2014 data, we can see a marked improvement in the Rural South population's participation. Increasing from OR 0.85 (95% CI, 0.82 – 0.87) to 1.01 (95% CI, 0.99 – 1.03), the performance of the rural south exceeded that of their Urban counterparts. So why does Manitoba struggle to mobilize its northern population? This data suggests that reasons for non-participation extend beyond the geographic distance to an urban centre and its health care resources.

**DEPRIVATION**

The notion that deprivation adversely affects participation in screening programs has been well documented, through analysis of screening for both breast and cervical screening.[88–90] Socioeconomic deprivation has previously been shown to affect participation in FT-based colorectal cancer screening.[45,46,50] Given this history, the striking decrease in uptake of colorectal screening with increasing deprivation observed in our study, OR 0.91 (95% CI 0.884 –

0.934) for the 2nd least deprived quintile, down to 0.58 (95% CI 0.562 – 0.595) in the most deprived quintile, is therefore not entirely surprising. This pattern is in keeping with trends seen in the Scottish pilot and the English pilot analyses,[21,25] and has also been demonstrated previously for both FT screening and flexible sigmoidoscopy screening.[91,92]

Logan and colleagues reported in 2011, after the first million tests in the UK BCSP had been performed, that as expected, uptake was highest in the least deprived areas at 61.4% in the top quintile, and lowest in the most deprived areas, with 41.7% overall participation in the bottom quintile.[37] A review of the initial roll-out of the first 2.6 million invitations from 2006 and 2009 indicated overall screening uptake of 54% with an independent effect of deprivation: 35% in the most deprived to 61% in the least deprived area-based quintile.[50] While uptake was generally lower in areas with greater deprivation, the spread across deprivation quintiles in different regions in the UK was quite variable. Uptake in the North-East region was 3-5% higher for each income quintile, and in contrast, uptake was substantially lower throughout the London region for each quintile.[37] This regional variation was also seen in our study, however we identified differences between our two rural populations, both of which are overall more materially deprived regions of the province, in comparison to the Urban cohort. Learning why the Rural South population differs so dramatically to the Rural North population will be integral to moving the screening program forward for our non-urban participants.

A recent cross-sectional study of screening across Canada identified not only large differences in uptake of screening between the provinces, but also identified significant differences across socioeconomic lines. The prevalence of up-to-date CRC screening among individuals age 50–74

in 2012 was 55.2%, ranging from 41.3% in the territories to 67.2% in the province of Manitoba.[35] Individuals in the highest income groups were more likely than those in lower-income groups to be up to date with CRC screening, even in provinces with well-established population-based screening programs.[35]

Reducing socioeconomic inequalities in cancer mortality is a priority not just in Canada, but also worldwide. Screening is a major component of global efforts to prevent cancers or bring forward diagnoses to earlier, more treatable stages. However, our results show that in Manitoba (and the rest of Canada) where screening with FT incurs no financial cost to the individual, uptake still declines with increasing socioeconomic deprivation. This pattern aligns with trends seen in other socialist health care systems.[37,89]

Proposed explanations for decreased participation in screening in more deprived populations include factors such as stress, low social support, and competing life demands.[49,50] These factors can be difficult to address through screening programs and coordinating efforts at the front line with a patient's general practitioner may help to elucidate strategies to better help the more economically deprived individuals eligible for screening. Differences in health literacy may also play a key role in screening uptake because information is delivered largely through mailed written communications. The reasons, however, are likely to be multiple, and are clearly not just related to income level. Explanations for the lower uptake remain to be definitively established but may involve problems with undelivered mail, immigrant populations or populations with non-English speaking backgrounds and overall decreased use of healthcare resources. Poor screening participation and the relationship to socioeconomic deprivation are a largely unmet

challenge in research.[49] Action to promote equality of CRC screening uptake is needed to avoid widening inequalities in CRC mortality.

### Health Literacy and Screening

There is good evidence that health literacy declines with increasing socioeconomic deprivation.[93] The Public Health Agency of Canada defines health literacy as "the ability to access, comprehend, evaluate and communicate information as a way to promote, maintain and improve health in a variety of settings across the life-course."[94] The 2003 International Adult Literacy and Skills Survey (IALSS) found that a significant proportion of adults in Canada have low levels of literacy. Statistics Canada considers Level 3 to be the minimum level of proficiency required to "meet the demands of modern life, independently and reliably in an industrialized nation", and the IALSS estimates that among Canadians aged 16 to 65, up to 50% score below level 3 in terms of health literacy.[94] If low health literacy is associated with perceived confidence to participate in screening[50], the fact that a significant proportion of individuals eligible for screening may not understand *why* we perform CRC screening, it may affect their likelihood of participating in a screening program.

Health literacy is a particular problem for the CCMB screening programs which rely heavily on printed information delivered by mail, including the ColonCheck program. Our findings suggest that the tailoring of information delivery might be useful to improve participation. An opportunity in communities that have more deprived and possibly greater poor-literacy groups is to supplement mailed information with direct contact with health professionals, or amongst health professionals and community leaders. The results of our study illustrate the difficulty of

addressing inequality in screening uptake within an organized program, but also highlight the importance of continuing to investigate new strategies to improve participation among these under-served groups.

### CONCLUSIONS ON PARTICIPATION PERFORMANCE MEASURES

It is notable that the lower participation trends seen with CRC screening are similarly seen in both the breast and cervical cancer screening programs in Manitoba.[95,96] While participation in CRC screening overall was lower than for breast or cervical cancer screening, the same demographic factors, including male sex, increasing age, socioeconomic deprivation have been associated with poor uptake across these programs, and in other jurisdictions[97]. As women who complete breast and cervical are more likely to also complete bowel screening, interventions at the time of these procedures to also encourage bowel screening participation can be explored.

## RETENTION IN COLORECTAL CANCER SCREENING

Most tests for population-based screening for cancer rely on repeat participation by individuals for optimal public health outcomes. Randomized controlled trials have shown that regular, repeated screening with gFT reduces colorectal cancer (CRC) mortality by up to 25% among participants in a screening program.[10,98,99] Because of the lower sensitivity of Hemoccult II Sensa test used in the Manitoba ColonCheck program (combined carcinoma and polyp sensitivity is 71.2%, and specificity is 87.5%), repeated participation is extremely important for the effectiveness of stool guaiac-based CRC screening.[100]

Uptake of the first repeat screening invitation was 86.6% in a recent study of the NHS BCSP.[83] Previous participation was strongly associated with retention in the subsequent rounds of screening invitations. As the uptake results from the third round demonstrate, among previous responders screening uptake was the highest to date at 94.5%.[101] High repeat uptake rates were also reported in a Spanish CRC screening pilot program (87%)[102], an Australian pilot program (80%)[44], and a Dutch pilot program (85%)[103]. These findings confirm screening history is a strong predictor of subsequent response to invitations for screening.

Retention in the 2009/2010 cycle of the 2007/2008 cycle participants was 57.7%, and the subsequent cycle in 2011/2012 showed an increase to 65.0% retention of the 2009/2010 participants. With only two cycles of retention reported thus far in the ColonCheck program, results show statistically significant improvement ($p < 0.0001$). As our screening program becomes more established, we expect there to be continued increase in retention. ColonCheck plans to continue to follow their program participation and to monitor for changes in retention. Future assessment of retention figures will endeavour to guide changes in the screening program needed to continue to reduce risks from colon cancer.

## COLORECTAL CANCER SCREENING OUTCOMES: ADVANCED NEOPLASIA AND ADENOMAS

During our study period, there were 118,096 FTs completed, with 3876 abnormal results recorded. From those abnormal FTs, 2930 colonoscopies were performed, including 1182

patients who underwent a program completed colonoscopy with an accompanying Patient Assessment Form. 1609 patients had no precancerous lesions identified, 594 patients had non-advanced neoplasms identified, and 601 advanced adenomas and 126 cancers were identified.

From the full cohort of colonoscopies, the PPV for any adenoma was 40.8%, which exceeds the national benchmark for adenoma detection rate with screening guaiac-based FT (gFT) is ≥ 35%.[22] The PPV for non-advanced adenomas was 20.3%. For advanced adenomas the PPV was 20.5% and 4.3% for CRC, for a combined PPV for advanced neoplasms of 24.8%. In comparison, the data from the colonoscopies completed with the additional PAF information yielded a PPV for non-advanced adenomas of 22.5% (95% CI 20.1–24.9%), and the PPV for advanced neoplasms was 21.4% (95% CI 19.1–23.7%). The total PPV for any adenoma was 43.9%, and the PPV for CRC was 2.9% (95% CI 1.9–3.8%).

Our findings also show, however, that for an individual with an abnormal FT result, the PPV for significant findings can vary substantially based on a number of risk factors. Specifically, for the full cohort of patients with a complete colonoscopy, after adjusting for all variables, older age and male sex were associated with higher odds of identifying advanced neoplasms and colorectal cancer. Older age and male sex were also associated with higher odds of identifying non-advanced neoplasms. Age and sex were consistently found to be statistically significant across all three pathology subtypes analyzed (CRCs, advanced adenomas, non-advanced adenomas). Geography and Deprivation were not found to be statistically significant sociodemographic factors affecting the odds of identifying advanced neoplasia or non-advanced adenomas.

For the PAF data cohort, after adjustment, older age, male sex, reporting some bleeding symptoms, BMI > 30, ≥ 3 positive windows on stool guaiac test, and no prior history of colonoscopy or > 10 years since last colonoscopy were associated with increased odds of finding advanced neoplasms on colonoscopy. The use of ASA-containing agents was associated with a statistically significant decreased odds of finding advanced neoplasms. Older age, male sex, and family history of CRC were associated with increased odds of identifying non-advanced adenomas on colonoscopy, and having an overweight BMI (> 25 to ≤ 30) was associated with a significantly decreased odds of findings of non-advanced adenomas. When the multivariable analysis excluded patient reports of bleeding symptoms at the time of their colonoscopy, the results remained the same, with the same factors showing statistical significance for increased or decreased odds of identifying advanced or non-advanced neoplasms.

An understanding of the variables associated with significant clinical outcomes has the potential help to expedite diagnosis and treatment of more urgent cases in publicly funded health care systems where diagnostic testing resources are limited. Of the variables listed above, most screening programs record and maintain data on age, sex, and possibly the number of positive windows on FTs. The other symptom or medical history variables were available to us only because a ColonCheck program nurse contacted individual patients with abnormal FT results for consideration of a program organized colonoscopy.

**SEX**

In line with our results, previous studies have also shown a significant association between male sex and findings of advanced neoplasms during colonoscopy after abnormal gFT results. In the Scottish Bowel Screening Programme study (SBoSP), the PPV for significant neoplasia was 48.4% in men and 29.5% in women.[36] The English Bowel Cancer Screening Program (BCSP) reported very similar results after their first one million tests. CRCs and higher risk adenomas were found in 11.6% and 43% of men and 7.8% and 29% of women investigated, respectively.[37] As previously stated, our results showed a PPV for advanced neoplasms was 27.7% for males and 21.0% for females. For non-advanced adenomas, the PPV was 46.1% and 33.7% for males and females respectively. The reason for the consistency across multiple jurisdictions is likely related to multiple factors, however the most significant impact likely relates to differences in CRC incidence between males and females.

The American Cancer Society publish cancer statistics annually, and have consistently found men to have a higher age standardized incidence of CRC than women.[1] The 2018 Cancer Facts report estimated a lifetime probability of developing CRC for a male to be 4.5% (1 in 22), in comparison to the 4.2% lifetime risk for a female (1 in 24).[1] This difference is born out even further when looking at specific age groups. For those age 50-59, the probability for males of developing invasive cancer is 0.7%, vs 0.5% for females. For those age 60-69, it rises to 1.2% vs 0.8% for males and female respectively. Finally, for those age 70 and older, the probability of developing CRC is 3.4% (1 in 29) for males, and 3.1% (1 in 32) for females.[1]

The Canadian Cancer Society 2019 Canadian cancer statistics reported age-standardized incidence rates (ASIR) for CRC to be 71.7 cases per 100,000 people for males and 50.9 cases per 100,000 for females.[42] The probability of dying from CRC was 3.1% for males (1 in 32) compared to 2.7% (1 in 37) for females.[42] Incidence rates for colorectal cancer in Canada were stable for males and females from 1996 to 2000, and then they declined moderately from 2000 to 2011 (-0.5% in males and females).[42] Since 2011, CRC incidence rates have declined more sharply in males (-2.2%) and females (-1.9%), however, across all types of cancer, cancer is still more commonly diagnosed in males compared to females, except for breast and thyroid cancers.[42]

A number of biological and behavioural factors have been hypothesized to increase the vulnerability of men to developing CRC.[104–106] Men are more likely to smoke, consume more alcohol, have a diet higher in red meat, all of which are common associations with CRC development.[77] Men also have a greater predisposition to higher levels of visceral fat, which is associated with an increased risk of CRC.[107–109] While sex differences in adenoma and carcinoma rates most likely reflect the epidemiology trends seen generally in CRC, it may also reflect screening factors as well. The female sex is known to be more associated with hypermethylation, microsatellite instability, BRAF V600E mutation, and CpG island methylator phenotype (CIMP)-high, which are more likely to result in the sessile serrated polyps (SSP),[77,110,111] which may be more likely to be missed on colonoscopy. Lesions in the proximal colon are also more commonly seen in female patients, and these lesions are also the ones more likely to be missed.[77]

In contrast to all of these studies, however, our study included multiple additional patient level risk factors that have been associated with the development of adenomas, advanced adenomas, and CRC, including family history, prior scope history, BMI, and antiplatelet medications, which were not adjusted for in these other studies. Even when adjusting for these additional variables, male sex was independently associated with a statistically significant increased odds of finding advanced neoplasms (OR 1.89) and non-advanced adenomas (OR 1.84) on colonoscopy after an abnormal FT. Further research could focus on why incidence and mortality rates continue to remain higher in the male population, however it will be even more important to try and identify how much the difference is due to modifiable risk factors. Gaining a better understanding of the modifiable risk factors in CRC outcomes, will allow screening providers to design changes to a program that benefit each sex individually, at all points along the CRC diagnosis pathway.

**AGE**

When separating patients by age, there were significant differences across age groups, with a clear association between age and the likelihood of identifying adenomatous neoplasms at colonoscopy. For advanced neoplasms, the PPV for age 50-59 years, 60-69 and 70-74 were 18.4%, 27.1% and 37.5% respectively. When looking specifically at colorectal cancer detection, the PPV for identifying a CRC after a positive FT result was 1.7%, 5.7% and 8.5% for ages 50-59, 60-69 and 70-74 respectively. Multiple, large studies have previously demonstrated an association between age and findings of colorectal neoplasms on colonoscopy in individuals with abnormal gFT results. Our PPV results for colorectal neoplasms and the trends seen with differences in age are consistent with results from Ontario, Scotland, and England.[36–38]

In 2014, Rabeneck et al. reported the early performance results from Ontario's province-wide colorectal cancer screening program which was launched in 2008. Results showed a PPV for CRC of 7.4% for patients between 70-74 years of age, compared to 2.0% for patients between 50-54 years of age.[38] In Scotland, the Scottish Bowel Screening Programme (SBoSP) was introduced in a staged manner across Scotland beginning in 2007, and was introduced into the NHS Greater Glasgow and Clyde region in April 2009. After two years of FTs, Mansouri et al. found a PPV for CRC of 11.9% in patients ≥ 65 years of age, compared to 5.3% in patients ≤ 55 years of age ($p < 0.001$).[36]

The goals of CRC screening programs are not just early detection of CRCs, but also CRC prevention. This is why the PPV for adenomas and advanced adenomas is as important as early identification of cancers. Our findings of an association between older age and adenomas and advanced neoplasms on colonoscopy are consistent with findings from large studies from across Canada, France, and Scotland.[24,36,112] In the previously mentioned 2013 analysis by Major and colleagues, which collected the results from the first round of CRC screening for British Columbia, Saskatchewan, Manitoba, Prince Edward Island, and Nova Scotia, the PPV for adenoma steadily increased with age, from 35.1% in the 50-54 age group to 53.0% in the 70-74 age group.[24] A population-based study in 2015 on behalf of the French colorectal cancer screening program identified the PPV for detection of advanced neoplasia increased with age.[112] The PPV for males age 50-54 was 19.9% vs 28.4% for males age 70-74. For females the PPV for advanced adenomas was 11.5% and 17.5% for the same age groups respectively. The SBoSP reported the PPV for significant neoplasia (significant polyp or cancer) found at colonoscopy

increased with increasing age, from 30.2% in patients ≤ 55 years of age compared to 45.6% in patients ≥ 65 years of age ($p < 0.001$).[36]

In contrast to all of these studies, however, our study included multiple additional patient level risk factors that have been associated with the development of polyps and CRC, including family history, which were not adjusted for in these other studies. Even when adjusting for these additional variables, age was independently associated with an increased odds of finding advanced neoplasms on colonoscopy after an abnormal FT (OR 1.84 for advanced neoplasms and OR 1.20 for non-advanced adenomas). Even as research suggests that individuals aged 70–74 have the highest rates of up to date CRC screening (65.3%),[35] older patients are clearly at a significantly increased risk for pathology. The consistency and magnitude of these findings should therefore impart more concern on practitioners who come across abnormal FT results in older patients.

**SCREEN TYPE**

To our knowledge, this is the first study to report on the PPV with repeat screening. While many studies have reported on the consistency in screening uptake or participation with repeat cycles of screening as well as decreased colon cancer positivity rates with repeat cycles of screening,[21,27,113,114] there have been no studies showing the effect of return screening on the PPV of adenoma or cancer detection at the time of colonoscopy following a positive FT. Our results show a statistically significant decreased odds of identifying advanced adenomas or colon cancer with a second round of screening (OR 0.79, $p = 0.0313$), even when adjusting for other variables.

These results align with the extensive literature reporting global risk reduction of CRC screening on mortality. If the first participation in CRC screening identifies pathology, once they return back into the screening population, individuals may be more inclined to return for repeat screening so that any new pathology may again be identified earlier and more advanced disease again prevented. If an initial FT leads to a colonoscopy that then identifies non-advanced lesions, subsequent colonoscopies have a greater potential to identify fewer advanced lesions, as lesions were identified and dealt with on prior cycles of screening, furthering the argument for greater risk reduction with each cycle of screening participation. Showcasing a result like decreased odds of identifying advanced neoplasia in the colon and rectum with repeat rounds of screening is a powerful message that can be conveyed to screening-eligible individuals to reinforce the reasons and benefits associated with CRC screening.

## GEOGRAPHY

The literature overwhelmingly suggests that a significant proportion of the decline in incidence and mortality since the 1980s can be attributed to screening.[57] However, not all groups have benefitted equally from the improvements made with regards to disease prevention and treatment. While sociodemographic factors such as race, ethnicity, socioeconomic status and deprivation level are known to influence CRC outcomes,[48,58,59,115] the role of geographic factors in CRC is less well understood. The largest analysis by Liang and colleagues, conducted in 2016, was a case-control study using the 1973-2010 Surveillance, Epidemiology, and End Results (SEER) and Medicare linked database. They analyzed over 1 million records, including 336,321

CRC cases and identified that compared to urban residence, small rural residence was strongly associated with increased CRC incidence (OR 1.50, 95% CI: 1.43-1.57) and mortality (OR 1.35, 95% CI: 1.26-1.45) in 1973-1997, but the associations diminished by 2007-2010 (OR 1.09, 95% CI: 1.04-1.15 for incidence; OR 1.10, 95% CI: 1.01-1.20 for mortality).[45]

There are numerous clinical environmental and lifestyle factors that are associated with an increased risk of CRC that may be more prevalent in our rural inhabitants, and thus may contribute to geographic differences in pathology identified on colonoscopy. While these factors may not confer an increase in risk as substantial as others factors such as family history, genetics, and inflammatory bowel disease, they undoubtedly have some impact on CRC outcomes.

Diabetes mellitus and insulin resistance, obesity, and increased alcohol intake are all risk factors for CRC.[116–118] These characteristics are all more prevalent in our rural populations in Canada,[119–121] and may therefore contribute to the increase odds of identifying high risk pathology on colonoscopy following a positive FT result. A meta-analysis of 14 studies estimated that the risk of colon cancer among diabetics was approximately 38% higher than in non-diabetics (relative risk [RR] 1.38, 95% CI 1.26-1.51), and the risk of rectal cancer was 20% higher (RR 1.20, 95% CI 1.09-1.31).[116] The association between diabetes and CRC remains even when the analyses are limited to studies that control for smoking, obesity, and physical inactivity. A systematic review and meta-analysis of data from 13 studies reported that weight gain in the early adulthood and midlife years was associated with a modest but significant increase in the risk of CRC (hazard ratio [HR] 1.23, 95% CI 1.14-1.34).[117] An association between increased alcohol consumption and increased CRC risk has been observed in several

studies. A meta-analysis of 27 cohort and 34 case-control studies concluded that, compared with never drinkers, there was a significant increase in risk of CRC for those with moderate (two to three drinks per day) alcohol intake (RR 1.21, 95% CI 1.13-1.28) and heavy (≥ 4 drinks per day) alcohol intake (RR 1.52, 95% CI 1.27-1.81).[118]

Many of these associations have been seen consistently in observational studies, and these three risk factors are present in higher numbers in our rural populations in Canada, in particular, in the northern and indigenous populations.[119–122] While these risk factors independently increase the risk for CRC, they likely also influence pathology outcomes as they relate to geographic differences. The relationship between geographic factors and CRC outcomes may also evolve with differences in screening patterns.

As screening plays such an integral role in CRC outcomes, we hypothesized that geographic factors which influence access to screening – specifically rural and remote residence and therefore ease of access to health care resources – would affect screening participation, retention and colonoscopy uptake, and would therefore subsequently affect pathology outcomes. There was no statistically significant association identified between geography and participation, although our study showed a trend towards increased odds of identifying advanced neoplasia for individuals living in a rural location compared to their urban counterparts. These findings suggest that smaller and more rural communities may particularly benefit from targeted interventions for screening and treatment of CRC.

## DEPRIVATION

Socioeconomic deprivation has previously been shown to affect participation in FT-based colorectal cancer screening.[45,46,50] Socioeconomic and regional inequalities in overall survival from CRC have been observed in studies from around the world, despite many countries having universal health care.[62,91,123,124] Beckman and colleagues reported on sociodemographic disparities and colorectal cancer outcomes in South Australia in 2016. Patients from the most socioeconomically advantaged areas had significantly better outcomes than those from the least advantaged areas (HR =0.75, 95 % 0.62-0.91).[46] The case control study by Liang and colleagues in 2016, analyzing nearly 4 decades of data from a nationally representative sample in the US (using the SEER and Medicare linked database) identified higher income and higher education level to be protective against mortality after 1998 and 2002, respectively. They also reported that while inequalities relating to the geographic location and rurality of screened individuals have remained stable for decades, racial and socioeconomic disparities have actually worsened over time.[45]

Conversely, the Scottish Bowel Screening Program reported in 2013 that while individuals who are deprived are less likely to participate in screening and less likely to undergo colonoscopy, they were also less likely to have cancer identified as a result of a positive test. Though the highest test positivity rates were found in the most deprived individuals, being less deprived was actually associated with a higher PPV for cancer (10.5% least deprived vs 7.8% most deprived, p= 0.003).[36] Our findings of a statistically significant decreased odds of identifying advanced colorectal neoplasms in the most deprived income quintile is consistent with the Scottish study

(OR 0.73, p = 0.0387), but in contrast to many other studies evaluating the effects of deprivation on CRC outcomes.

It is interesting that while those who were more deprived were less likely to participate in our study (OR 0.58 for the most deprived income quintile), our study did not show a consistent pattern with respect to changes in deprivation levels and odds of identifying pathology at the time of colonoscopy. Our study did identify a trend towards increased odds of identifying non-advanced adenomas with increasing deprivation, but the results were neither statistically significant nor consistent. Understanding the sociodemographic effects on different CRC screening program performance measures is important because unequal access across groups runs the risk of creating new or widening current health inequalities. Our results suggest that strategies aimed at improving the CRC outcomes of more deprived individuals through CRC screening should be directed at all stages of the screening process and not just uptake of the screening test.

## ANALYSIS OF ASSOCIATED VARIABLES FOR THE PATIENT ASSESSMENT FORM (PAF) SUBGROUP

### ASA CONTAINING ANTI-PLATELET AGENTS

Whether antiplatelet agents effect the PPV of FT remains open to debate.[125] Most CRC develop from adenomas, and trials have shown that aspirin and cyclo-oxygenase-2 enzyme (COX-2) inhibitors reduce the risk of recurrence by about 20%.[65–72] Prevention with COX-2 inhibitors is

not practicable because of an increased risk of vascular events, but long-term use of low-dose aspirin is feasible and does appear to decrease the incidence of colon cancer.[126,127] Rothwell and colleagues published in the Lancet in 2010 the results of their follow up of five randomized control trials that analyzed the effect of aspirin on the risk of CRC through long term follow up during and after the trials. They established that taking aspirin reduced the 20-year risk of developing colon cancer (incidence HR 0.76, 95% CI 0.60-0.96, P = 0.02), and there was no increase in benefit at doses of aspirin greater than 75 mg daily, with an absolute reduction of 1.76 % (0.61–2.91; p = 0·001) in 20-year risk of CRC mortality.[127]

While antiplatelet therapy has been shown to be beneficial, it is also possible that these medications increase the false-positive rate of FT for neoplasia by inducing or revealing other, non-neoplastic sources of GI blood loss. Our finding of a statistically significant decreased odds (OR 0.59) of advanced neoplasms in patients on antiplatelet medication, including aspirin and non-aspirin agents, is consistent with previous studies, and a comparably sized and designed study by Sawhney et al. using data from the Minneapolis Veterans Affairs Medical Center.[128] There are, however, other much smaller studies that show no significant difference in PPV in patients on aspirin.[129] Some authors have recommended stopping anti-platelet agents 1-3 days prior to and during gFT testing[7,128], but there is currently no consensus and there remains a paucity of evidence on whether or not stopping these medications would reduce false positive results. Currently, the only medication that ColonCheck (and other gFT screening programs) requires patients to stop is Vitamin C. Of note, we did not separately include anti-coagulants because the number of users of these agents was too low to allow meaningful analysis.

## NUMBER OF POSITIVE WINDOWS

Most gFT administrations for screening purposes require two windows or slides being tested on stool samples over three consecutive days (6 windows in total for assessment). Consistent with many other programs, in our screening practice, when any one of these windows is positive, the test is considered abnormal. Our study found that FT results with ≥ 3 positive windows were associated with an increased odds of finding advanced neoplasms on colonoscopy (OR 1.66, p = 0.0085). Three or more positive windows implies abnormal results on at least two different days. This is consistent with prior studies examining the effects of the predictive role of more positive windows.[8,130,131] Interestingly, there was no association between number of positive windows and non-advanced adenomas, suggesting that small or lower risk polyps are unlikely to be a cause of occult bleeding.

The same pattern was seen for patients with bleeding symptoms – those with bleeding symptoms had higher odds of advanced adenoma, but not non-advanced adenomas (OR 1.64, p = 0.0112). As previously mentioned at the beginning of the discussion, when the multivariable analysis excluded patient reports of bleeding symptoms at the time of their colonoscopy, the results remained the same, with the same variables showing statistical significance. While those with bleeding symptoms would not be considered for "average risk" screening, these findings reflect the realities of province-wide screening, when individual symptoms are often not known prior to completing screening FTs. Moreover, in our specialty practices, we still occasionally see patients with bleeding symptoms in which lab-based FT has been ordered or completed prior to referral. Our findings confirm that this practice should be discouraged as it may waste resources and time. Patients with bleeding symptoms in this age group should be directly referred for endoscopy.

**BMI**

Obesity is a major independent risk factor thought to increase the risk of CRC by 60% and CRC mortality up to 90%.[132–135] Obese men and those with very high BMI have the greatest risk of developing a CRC and dying as a result of their CRC.[133–135] Potential links between excess adiposity and CRC include hormonal effects of insulin, changes in gut microflora, and higher levels systemic inflammation[136,137], though suboptimal screening rates likely also contribute. In 2017, Seibert and colleagues reported on the disparities in CRC screening among obese adults in the US, analyzed through the National Health Interview Survey. They found that obese class III men (BMI ≥ 40), compared with normal-weight men, were significantly less likely to be adherent to screening guidelines (38.7% vs 55.8%, Adjusted OR 0.35), less likely to have undergone an endoscopic test (36.7% vs 53.0%, Adjusted OR 0.37), and displayed a trend toward lower FT use (4.2% vs 8.9%, Adjusted OR 0.42)[138] Among women, there was no significant difference in the odds of guideline adherence and use of different screening modalities across all BMI classes of obese or overweight women.[138]

Despite overwhelming evidence that screening reduces CRC mortality,[14,19,22,40] only 55% of eligible Canadians and less than two thirds of eligible US adults were up to date with CRC screening in 2012.[35,57] Several studies have shown that obese adults participate less in cancer screening than their normal BMI counterparts[139–143], while other studies and systematic reviews have not shown any BMI-related differences in CRC screening.[144–147] Conversely, some studies have even observed an increase in screening among obese subgroups.[148–150] These mixed results in the literature may reflect multiple variables, including differences in screening modalities

used, inconsistencies with BMI categories, and smaller study sample sizes that are less representative.

Our study found that for BMI > 30 there is an increased odds of identifying advanced neoplasms on colonoscopy (OR 1.72, p = 0.0094). We also identified that individuals with a BMI > 25 and < 30 had a decreased odds of identifying non-advanced adenomas on colonoscopy (OR 0.61, p = 0.0089), which further suggests the complex interplay of both biologic and behavioural factors in CRC outcomes. Understanding causal mechanisms by which obesity drives cancer initiation and progression is essential for the development of therapy tailored to our obese cancer patients. Unfortunately, the mechanisms contributing to higher cancer incidence and mortality in the obese patient are not clear. Various mechanisms have been proposed for different the progression of difference types of cancer in the obese population, but they appear to relate to the global impact of obesity on systemic levels of inflammation.[151] Other pathophysiological hypotheses for the relationship between obesity and increased cancer risk may include alterations in sex hormone metabolism, insulin and insulin-like growth factor levels, and adipokine pathways.[152]

As the obesity epidemic continues to evolve, screening will be increasingly important in helping reduce preventable CRC morbidity and death in these individuals. Despite CRC screening barriers being reasonably clearly established for the general population[47,57,153], studies on BMI-related barriers are limited[140], and none have investigated obesity-specific reasons for non-adherence to screening on a large scale. Identifying reasons for non-adherence, especially among high-risk subgroups such as the obese, is essential for determining strategies to help promote screening participation and improve overall uptake.

**SCOPE HISTORY**

Similar to the decreased odds of identifying advanced neoplasia with subsequent rounds of CRC screening and repeat participation, the greatly increased odds of identifying advanced neoplasia in those with no prior history of colonoscopy or more than 10 years since colonoscopy (OR 2.26, p = 0.0004) is another variable that highlights the impact of non-participation in CRC screening. While many of the variables assessed in our study, such as age, sex, deprivation and geographic location have been previously and consistently identified as factors that leave patients at increased risk of identifying advanced pathologies at the time of investigation, our study is the first to show results pertaining to an individuals' screening history.

Many patients who come through population-based screening programs are not completely naïve to CRC screening. In Manitoba we know that while participation in the ColonCheck screening program sits at 20.3% for our 2011-2014 analysis, in 2012 it was reported that over two thirds of the eligible population (67.2%) is considered up to date with their bowel cancer screening.[35] Many patients who come to participate in CRC screening programs have previously had signs or symptoms that resulted in investigation with flexible sigmoidoscopy (FS) or colonoscopy. In the same paper by Singh and colleagues, using data obtained from the 2012 Canadian Community Health Survey, they reported that 51.7% of Manitobans had a FT completed within the last 2 years, and 33.4% had undergone FS or colonoscopy within 10 years.[35]

Our study's results of an increased odds (OR 2.46) of identifying more advanced pathology with a positive FT in individuals who have no history of previous colonoscopy investigation, or no

exposure in over 10 years, reinforces the literature and the known risk reduction in CRC mortality seen with any form of CRC screening, regardless of how it arrived at. While our study and its results pertain specifically to population-based screening programs and their outcomes, CRC screening and positive FTs lead to endoscopic evaluation, which leads to earlier diagnoses, which leads to overall risk reduction. By providing eligible individuals with concrete numbers of how a lack of CRC screening in the past can greatly impact the odds of identifying advanced pathology when participants return with a positive FT, screening program administrators may find another means of convincing the public of the great importance of bowel cancer screening and further encourage participation.

## STRENGTHS AND LIMITATIONS

The strengths of this study include a relatively large sample size, and the detailed, prospective collection of more specific data than what might be gathered from population-based databases. Our study is one of the largest screened cohorts in Canada ever to be analyzed, and the cohort is heterogeneous and representative of the broader Canadian population. This study controlled for multiple clinically relevant risk factors associated with colonic neoplasia that have not been included in previous studies, reducing the risks of confounding. However, it is possible that there are missing variables that could be responsible for some degree of the relationships identified in our analysis. The PAF subgroup analyzed in this study allowed us to include data on specific and important clinical risk factors like BMI, medications, history of previous bowel screening and family CRC history that might otherwise be inaccessible in a larger population-based series.

Several notable limitations require discussion, however. First, although the data was prospectively collected, they were retrospectively analyzed, with inherent limitations commonly associated with retrospective analyses, including selection bias. Second, incomplete data and/or errors in data entry or coding is another concern inherent to research using administrative health data. However, the Manitoba Cancer Registry has previously been demonstrated to be among the highest quality administrative databases.[30,154] Third, in rural and northern Manitoba, data on FTs performed outside of ColonCheck may not be completely accounted for in Medical Claims data. To account for this, future plans to analyze CRC incidence, stage at diagnosis, mortality, cancer-specific survival and overall survival will compare cohorts with respect to participation in ColonCheck specifically rather than to participation in any CRC screening at all.

Finally, the sample who underwent program organized colonoscopies represent a proportion of the colonoscopies completed following a positive ColonCheck FT – a majority of the population in the province who underwent ColonCheck screening had their follow up colonoscopies performed elsewhere. There were also a number of patients referred for program organized colonoscopies who did not follow through with the procedure, and the reasons for this are not entirely known. The reasons that some primary care providers (PCP) were not agreeable to their patients undergoing program organized colonoscopies are also unknown. This highlights a possible future area of investigation, to elucidate reasons for why PCP may not be sending their patients through the ColonCheck program for their diagnostic colonoscopy and seem to prefer referring their patients on to a specific endoscopist. A systematic patient-related bias against the

program is also unlikely, but further investigation into patient preferences could also be of benefit.

In light of the above limitations, the use of administrative databases to assess the sociodemographic factors of colorectal cancer screening is essential. This research is important with respect to its implications for Manitoba's health care system, for both primary and specialist care practitioners, and for the general public. This thesis represents the largest analysis of population level data on the performance of the ColonCheck bowel cancer screening program since its inception and provides insight into the areas of success, and those performance areas that can be improved. Though there are differences between Manitoba's gFT based program and other immunohistochemistry FT screening programs across the country, recommendations for Manitoba's program can be extrapolated to the other Canadian programs, and to other publicly funded health care systems around that world that also struggle with resource management concerns.

## FUTURE DIRECTIONS

For CRC screening by FT to be effective in the general population, a balance between sensitivity and specificity must be achieved. Guaiac based FTs remain the only stool-based screening test with evidence from randomized controlled trials confirming CRC screening reduces CRC-related mortality. Many regions are now piloting or implementing fecal immunohistochemistry testing

(FIT)-based screening programs. FIT appears to have improved sensitivity and participation rates over gFT, albeit with increased costs.[155]

The current number of organized and completely rolled out FIT-based programs is increasing world-wide, and a newer economic analysis of FIT screening in England using data directly comparing FIT with gFT in the NHS BSCP suggest that FIT is highly cost-effective at all thresholds considered when starting screening at age 60 years.[156] Further analysis is needed to estimate economic outcomes for screening across all age cohorts simultaneously, but many publicly funded systems are moving towards FIT-based screening programs.

In Canada, more than half of the population resides in provinces with gFT-based testing (Ontario has just launched their provincial FIT-based screening, but gFT remains part of its screening program.[157] Overall, colonoscopy uptake within 180 days of an abnormal FT remains below target across all jurisdictions, and varies widely across provinces (Canadian target: ≥ 85% within 180 days).[24] To achieve their maximum efficacy, organized CRC screening programs have to make every effort to encourage all individuals with an abnormal FT to pursue follow-up colonoscopy. Colonoscopy uptake may improve as capacity is increased with screening program expansion and with implementation of follow-up strategies.

Access to timely follow-up testing for program participants with abnormal FT results is an integral part of CRC screening programs. Singh et al. previously found that diagnostic delays from endoscopy wait times were the main contributor to the overall wait time to CRC treatment in a Canadian population.[158] For patients with abnormal FT results, multiple groups have

proposed 90% of patients undergoing colonoscopies within 60 days as a national benchmark.[14,22] However, not a single province in Canada meets this benchmark.[24,157] All seven reporting provinces in a recent national environmental scan had wait times for colonoscopy follow up after abnormal FT results substantially exceeding the target benchmark.[157] Furthermore, compared to previous studies[159], more recent studies show that endoscopy wait times for people with abnormal FTs are not improving.[160,161] Canadian CRC screening programs are consequently implored to develop strategies that can help select higher risk patients to undergo endoscopy more urgently or develop tiered benchmarks based on risk in order to improve resource utilization and reduce wait times that may delay CRC diagnosis. Age might be the most important and straightforward factor to focus on, as its association with advanced neoplasms has been most consistent in the literature, and again reinforced by our results.

# SUMMARY AND CONCLUSIONS

The results of the present study show that age, sex and socioeconomic deprivation have a significant impact throughout the colorectal cancer screening pathway. Participation is further impacted by geographic location of participants. After adjustment, older age, male sex, reporting bleeding symptoms, BMI > 30, > 3 positive windows on FT, and no prior history of colonoscopy or > 10 years since last colonoscopy were all associated with increased odds of finding advanced neoplasms on colonoscopy.

# RECOMMENDATIONS

**1) Focus public health efforts to improve CRC screening participation**

a. Currently about 50% of colorectal cancers are detected at a late stage (stage III or IV).[42] Given the strong connection between stage at diagnosis and survival for colorectal cancer,[77,78] increased participation in CRC screening programs in Manitoba and the rest of Canada may help further reduce colorectal cancer mortality rates in the near future.

b. Participation rates have been shown to markedly improve as a screening program matures.[162] Prospective analysis of the ongoing performance of the ColonCheck program will help to further shape the program and allow for continued CRC risk reduction.

c. High positivity rates challenge the available colonoscopy resource, but improvements in neoplasia detection are still achievable within this limited resource[162]

d. Special attention those in rural and remote geographic locations as this subset of eligible participants is known have less update and to be at increased risk of worse CRC-related outcomes.

2) **Monitor ColonCheck Retention Patterns**

a. As the ColonCheck screening program becomes more established, we expect there to be continued increase in retention. Future assessment of retention numbers will help guide changes in the screening program required to retain engagement and participation in the program.

3) **Risk stratify patients with positive FTs, and prioritize patients for follow up colonoscopy based on tiered triage of patients** based on:

a. Age – older patients prioritized for colonoscopy before younger patients (OR 1.83 for advanced neoplasms)

4) **Encourage PCPs to refer their patients with positive FTs to undergo ColonCheck program colonoscopies.**

a. Continue collection of associated clinical factors through continued use of the Patient Assessment Form

b. Identification of risk factors for advanced neoplasms from PAF data can help to risk stratify patients in our resource limited health care system.

i. Older age (OR 2.52)

ii. Male sex (OR 1.89)

iii. Reporting bleeding symptoms (OR 1.85)

iv. BMI > 30 (OR 1.70)

v. ≥ 3 positive windows on FT (OR. 1.64)

vi. No prior history of colonoscopy or > 10 years since last colonoscopy (OR 2.46)

One of the proposed strengths of population-based CRC screening programs is wider and more equitable coverage of the eligible population. Our results suggest that such programs have not yet narrowed the sociodemographic disparities in CRC screening. Socioeconomic and regional disparities in CRC screening participation and outcomes remain evident in Manitoba, despite having a universal health care system. Of particular concern is if decreased participation translates into worse outcomes and poorer survival for patients from deprived areas with potentially curable CRC. Reasons for these disparities require further exploration to identify factors that can be addressed to improve outcomes.

Although the overall mortality rate continues to decline in Canada, the number of cancer related deaths continues to increase due to the growth and aging of the Canadian population.[42] This has major implications for health policy and resource planning in our publicly funded health care system. The age, sex and deprivation disparities in CRC screening rates are concerning, especially as it has been reported that incidence and mortality are increasing in younger patients[39,57], and widening disparities in CRC mortality have been seen with increasing deprivation levels.[43,163]

Our results, and those of previous studies, suggest that people who are at a greater risk for CRC-related mortality and therefore would benefit the most from CRC screening are frequently the individuals who are less likely to receive CRC screening. We must target these specific subgroups of eligible individuals for CRC screening program efforts. Improving early detection and treatment for people diagnosed with colorectal cancer and improving supports for people living with cancer and beyond their cancer treatment continues to be of the utmost importance.

# APPENDICES

## APPENDIX A – COLORECTAL CANCER SCREENING QUALITY INDICATOR DEFINITIONS

CANADIAN PARTNERSHIP AGAINST CANCER
COLORECTAL CANCER SCREENING IN CANADA MONITORING & EVALUATION OF QUALITY INDICATORS
RESULTS REPORT JANUARY 2013 – DECEMBER 2014

### COLORECTAL CANCER SCREENING QUALITY INDICATOR DEFINITIONS

| INDICATOR DEFINITION & TARGET | CALCULATION |
|---|---|
| **PARTICIPATION** | |
| **Participation Rate**<br>**Definition:** The percentage of the target population that successfully completed at least one FT in the program within the measurement timeframe of 30 months<br>***Target:*** *≥60% of the target population within the specified period* | **Numerator:** Number of individuals who successfully completed at least one FT in the program within a 30-month period<br>**Denominator:** Number of individuals to whom the program was available in a defined 24-month period (Jan 1, 2013, to Dec 31, 2014) |
| **Fecal Test Utilization**<br>**Definition:** The percentage of the target population that completed at least one FT, either programmatic or non-programmatic, within the measurement timeframe<br>***Target:*** *Not yet determined* | **Numerator:** Number of individuals within the target population with at least one FT within the measurement timeframe (programmatic or non-programmatic)<br>**Denominator:** Number of individuals in the target population within the measurement timeframe (2013, 2014) |
| **Retention Rate**<br>**Definition:** The percentage of the target population aged 50 to 72 years of age rescreened within 30 months after a normal FT in the measurement timeframe<br>***Target:*** *Not yet determined* | **Numerator:** Number of individuals with successful FTs in the measurement timeframe who had at least one subsequent successful FT in the program within 30 months<br>**Denominator:** Number of individuals aged 50–72 with normal FT results within the measurement timeframe (Jan 1, 2011 – Dec 31, 2012) |
| **ENTRY-LEVEL SCREENING TEST** | |
| **Fecal Test Inadequacy Rate**<br>**Definition:** The percentage of individuals whose FT was inadequate and who have not repeated the test to get a successful FT result within the measurement timeframe<br>***Target:*** *≤5% of all FTs* | **Numerator:** Number of individuals having an inadequate FT who have not repeated the test to obtain a successful FT laboratory result within the measurement timeframe<br>**Denominator:** Number of individuals having a FT within the measurement timeframe (Jan 1, 2013 – Dec 31, 2014) |

| INDICATOR DEFINITION & TARGET | CALCULATION |
|---|---|
| **Positivity Rate**<br><br>**Definition:** The percentage of individuals with an abnormal FT result in the measurement timeframe<br><br>***Target:*** *Not yet determined* | **Numerator:** Number of individuals with an abnormal FT result<br><br>**Denominator:** Number of individuals having had at least one successful FT processed by a laboratory within the measurement timeframe (Jan 1, 2013 – Dec 31, 2014) |
| **FOLLOW-UP COLONOSCOPY** | |
| **Follow-up Colonoscopy Uptake Rate**<br><br>**Definition:** The percentage of individuals who had a follow-up colonoscopy performed within 180 days of an abnormal FT result in the measurement timeframe<br><br>***Target:*** *≥85%* | **Numerator:** Number of individuals who had a follow-up colonoscopy performed within 180 days of an abnormal FT result<br><br>**Denominator:** Number of individuals with an abnormal FT lab result within the measurement timeframe (Jan 1, 2013 – Dec 31, 2014) |
| **Wait Time to Follow-up Colonoscopy**<br><br>**Definition:** The time from an abnormal FT result to follow-up colonoscopy<br><br>***Target:*** *≥90% within 60 days of an abnormal FT result* | Median and 90th percentile number of calendar days from an abnormal FT result in the measure timeframe (Jan 1, 2013 – Dec 31, 2014) to a follow-up colonoscopy within within 180 days |
| **DIAGNOSIS AND INITIATION OF TREATMENT** | |
| **Positive Predictive Value (PPV) for Adenoma**<br><br>**Definition: a)** Percentage of individuals with an abnormal FT in whom one or more adenomas were confirmed by pathology<br><br>**b)** Percentage of individuals with an abnormal FT who also completed a follow-up colonoscopy (within 180 days of the FT) in whom one or more adenomas were confirmed by pathology<br><br>***Target:*** *≥50% for FTi ≥35% for FTg* | **Numerator:** Number of individuals with one or more adenoma (excluding invasive CRC) on pathology from colonoscopy within 180 days of an abnormal FT result obtained within the measurement timeframe<br><br>**Denominator: a)** Number of individuals with an abnormal FT within the measurement timeframe (Jan 1, 2013 – Dec 31, 2014)<br><br>**b)** Number of individuals with an abnormal FT within the measurement timeframe (Jan 1, 2013 – Dec 31, 2014) who had a follow-up colonoscopy within 180 days |
| **Wait Time from Follow-up Colonoscopy to Definitive Pathological Diagnosis**<br><br>**Definition:** Time from a follow-up colonoscopy to definitive pathological diagnosis<br><br>***Target:*** *Not yet determined* | Median and 90th percentile number of calendar days between colonoscopy (within 180 days of the abnormal FT) and definitive pathological diagnosis |
| **COLORECTAL CANCER SCREENING PROGRAM OUTCOMES** | |
| **Program Adenoma Detection Rate**<br><br>**Definition:** The number of individuals per 1,000 screened with one or more adenomas confirmed by pathology from a follow-up colonoscopy performed within 180 days of an abnormal FT result in the measurement timeframe<br><br>***Target:*** *Not yet determined* | **Numerator:** Number of individuals with one or more adenomas confirmed by pathology from a follow-up colonoscopy performed within 180 days of an abnormal FT result obtained within the measurement timeframe<br><br>**Denominator:** Number of individuals having had at least one successful FT processed by a laboratory within the measurement timeframe (Jan 1, 2013 – Dec 31, 2014) |

| INDICATOR DEFINITION & TARGET | CALCULATION |
|---|---|
| **Program Invasive Colorectal Cancer Detection Rate**<br><br>**Definition:** The number of individuals per 1,000 screened with invasive CRC confirmed by pathology from a follow-up colonoscopy performed within 180 days of an abnormal FT result in the measurement timeframe<br><br>***Target:*** *≥2 CRCs per 1,000 people screened* | **Numerator:** Number of individuals with invasive CRC on pathology from a follow-up colonoscopy performed within 180 days of the date of an abnormal FT result obtained within the measurement timeframe<br><br>Invasive CRC in ICD-10 includes C18.0, C18.2-C18.9, C19, C20, C26.0 with behaviour 3, but the following histology types excluded: colon lymphoma, sarcoma and carcinoid<br><br>Group stages were classified using American Joint Committee on Cancer (AJCC) 7th edition<br><br>**Denominator:** Number of individuals having had at least one successful FT processed by a laboratory within the measurement timeframe (Jan 1, 2013 – Dec 31, 2014) |
| **Invasive Colorectal Cancer Stage Distribution**<br><br>**Definition:** The distribution of screen-detected invasive CRC by TNM stage<br><br>***Target:*** *Not yet determined* | **Numerator:** Number of individuals with invasive CRC Stage I, II, III or IV; unknown stage; and unstaged diagnosed by the screening program from a follow-up colonoscopy within 180 days after an abnormal FT result within the measurement timeframe<br><br>Invasive CRC in ICD-10 includes C18.0, C18.2-C18.9, C19, C20, C26.0 with behaviour 3, but the following histology types excluded: colon lymphoma, sarcoma and carcinoid<br><br>Group stages were classified using American Joint Committee on Cancer (AJCC) 7th edition<br><br>**Denominator:** Number of individuals with invasive CRC (including of unknown stage) confirmed by pathology at follow-up colonoscopy within 180 days after an abnormal FT result within the measurement timeframe (Jan 1, 2013 – Dec 31, 2014) |
| **Interval Colorectal Cancer**<br><br>**Definition:** The number of individuals per 1,000 screened who were subsequently diagnosed with CRC within 24 months of a negative result for CRC in the measurement timeframe<br><br>***Target:*** *Not yet determined* | **Numerator:** Number of individuals subsequently diagnosed with CRC within 24 months of an FT result that was negative for CRC in the measurement timeframe<br><br>Invasive CRC in ICD-10 includes C18.0, C18.2-C18.9, C19, C20, C26.0 with behaviour 3, but the following histology types excluded: colon lymphoma, sarcoma and carcinoid<br><br>**Denominator:** Number of individuals with FT screening result negative for CRC in the measurement timeframe (Jan 1, 2011 – Dec 31, 2012) |

FT = fecal test; PPV = positive predictive value; FTg = guaiac fecal test; FTi = immunochemical fecal test; CRC = colorectal cancer; TNM = tumour, node, metastases

# APPENDIX B – ColonCheck PATIENT ASSESSMENT FORM

Sections and Key Questions

1. Name and DOB

2. Physical Exam
    a. Height, Weight, BMI
    b. Blood Pressure, Heart Rate, Oxygen Saturations
    c. Cardiovascular, Respiratory, and Abdominal Exams

3. Medical History

4. Gastrointestinal History
    a. BM frequency
    b. Change in Bowel Habits
    c. Diarrhea
    d. Diverticulitis
    e. Constipation
    f. Bleeding
    g. Urgency/straining
    h. Abdominal or perianal pain
    i. Weight Loss
    j. Upper GI symptoms – nausea, acid reflux

5. Alerts for Colonoscopy
    a. Anti-coagulation (Warfarin)
    b. Anti-platelet agent
    c. ASA Class ≥ III
    d. Congestive Heart Failure
    e. Coronary Heart Stent
    f. New York Heart Classification ≥ III
    g. Defibrillator or Pacemaker
    h. Valve replacement or valvular heart disease
    i. Clotting abnormality
    j. Iron tablets
    k. Diabetic requiring insulin or oral medications
    l. Renal insufficient / dialysis
    m. Liver disease
    n. Glaucoma
    o. Splenomegaly
    p. Allergies
    q. Obstructive Sleep Apnea / BiPAP or CPAP machine use

6. Decision / Outcome
    a. Medically fit, ok to book colonoscopy
    b. Needs further assessment by endoscopist prior to scope
7. Actions (pre-procedure)
8. Transportation home for day of colonoscopy
    a. Name and contact details

# APPENDIX C – ColonCheck COLONOSCOPY REPORTING FORM

Sections and Key Questions

## Colonoscopy Reporting Form

1. Name, DOB, PHIN,
2. Procedure Date, Endoscopist, PCP
3. Insertion Depth
    a. TI, Cecum, Ascending Colon, Transverse Colon, Descending Colon, Sigmoid, Rectum, Other
4. Withdrawal Time
5. Boston Bowel Prep Scale
6. Specimen Taken
    a. Yes / No
        i. Type, Location, Size, Completeness of Removal
7. Unplanned Events
    a. None
    b. Bleeding, perforation, early termination, etc.
8. Findings
    a. Normal colonoscopy, polyps, possible cancer, diverticula, inflammation, hemorrhoids, etc.
9. Further Tests required
    a. Barium enema, CT Colonography, Repeat Colonoscopy
10. Clinical Impression
11. Endoscopist Signature

## Post Colonoscopy Screening Recommendations

a) Negative result – screening recommendation
    a. ColonCheck recommendation – based on CCMB ColonCheck Screening Guidelines
    b. Endoscopist recommendation

b) Positive result – follow up recommendations – based on CCMB ColonCheck Screening Guidelines
    a. ColonCheck recommendation – based on CCMB ColonCheck Screening Guidelines
    b. Endoscopist recommendation

c) Other

# APPENDIX D – PROGRAM PERFORMANCE MEASURES

| Measure | Definition | ColonCheck Results* (2011-2012) | Target** (if applicable) |
|---|---|---|---|
| Participation rate (%) | Percentage of the invited Manitoba population (50-74 years) who successfully completed a ColonCheck FT | 25.4% | ≥ 60% |
| Inadequate or indeterminate rate (%) | Percentage of individuals who return tests that yield inadequate results | 2.2% | ≤ 5% |
| Abnormal rate (%) | Percentage of individuals with an abnormal FT | 3.4% | No target |
| Retention rate (%) | Percentage of individuals rescreened within 2 years after a normal FT | 54.3% | No target |
| Colonoscopy compliance rate (%) | Percentage of patients with positive FTs who undergo colonoscopy | 78.6% within 180 days; 90.9% with no end date | ≥ 85%, within 180 days |
| Wait time to follow-up colonoscopy (% within time frame) | Time from an abnormal FT to a follow-up colonoscopy completed within 180 days of the FT | ≥ 90% within 140 days | ≥ 90% within 60 days |
| Wait time from colonoscopy to final diagnosis (% within time frame) | Time from a follow-up colonoscopy (that occurred within 180 days of the FT) to a pathological diagnosis | ≥ 90% within 22 days | No target |
| Detection rates for advanced adenomas or CRC | Number of advanced adenomas or invasive CRC detected for every 1,000 individuals screened who have a colonoscopy following an abnormal FT result | 6.8 per 1,000 (advanced adenoma), 1.4 per 1,000 (invasive CRC) | Target ≥ 2 per 1,000 screened for CRC |
| Positive predictive value (PPV) of abnormal FT (%) for adenomas, advanced adenomas or CRC | Likelihood of patients with abnormal FT to have (A) any adenomas, (B) advanced adenoma, or (C) CRC | 39.8% (any adenoma), 20.8% (advanced adenoma), 5.1% (invasive CRC) | Target ≥ 35% for adenomas, |
| Interval CRC | Number of individuals diagnosed with invasive CRC within 24 after a normal FT per 10,000 person-years | NA | No target |

Sources: *ColonCheck. Colorectal cancer screening in Manitoba, 2011-2012 Report. Winnipeg, MB: ColonCheck, CancerCare Manitoba, 2013.
**Canadian Partnership Against Cancer: Quality Determinants and Indicators for Measuring Colorectal Cancer Screening Program Performance in Canada. Toronto, ON: The Partnership, 2012.

## APPENDIX E – ANTIPLATELET DRUGS INCLUDED AS ASPIRIN

- 'ACETYLSALICYLIC ACID'
- 'AGGRENOX'
- 'ANACIN'
- 'ASA'
- 'ASPIRIN'
- 'ENTROPHEN'
- 'NOVASEN'

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