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Community Fecal Immunotesting for Colorectal Cancer Screening

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Community Fecal Immunotesting for Colorectal Cancer Screening

by

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A THESIS

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Abstract

Community fecal immunochemical testing screening programs are important for detecting early disease and are a common way of promoting colorectal cancer screening by primary care physicians.

Fecal Immunochemical testing has advantages to the patient as well as to clinical laboratories, but screening rates remain low across Canada and may be associated with sociodemographic factors.

This research assesses the operational test characteristics of a FIT pilot program in Calgary, Alberta. Data from a new community-based screening program were also used to test associations of screening rate with sociodemographic variables.

The performance of FIT in this clinical setting was very good for detecting carcinoma, but marginal for detection of colonic adenomas. There was also significant geographic variation in screening rates in Calgary. These are associated with a number of sociodemographic factors.

Preface

This preface lists the publications by the author of this thesis which include the materials and ideas presented in the thesis.

1. Crouse, A., et al., *Sociodemographic correlates of fecal immunotesting for colorectal cancer screening*. Clin Biochem, 2015. 48(3): p. 105-9.
2. Crouse A, de Koning L, Sadrzadeh H, Naugler C. *Sensitivity and specificity of community fecal immunotesting screening for colorectal carcinoma in a high risk Canadian population*. Archives of Pathology and Laboratory Medicine, 2015.
3. Crouse A, de Koning L, Sadrzadeh H, Naugler C. *Test characteristic of community fecal immunotesting for colorectal carcinoma in Calgary, Alberta*. Poster presentation, CAP-ACP Conference, 13 July 2014.
4. Crouse A, Sadrzadeh H, de Koning L, Naugler C. *Sociodemographic factors affecting fecal immunotesting for colorectal cancer screening*. Poster presentation, University of Pathology, Department of Pathology and Laboratory Medicine Annual Residents' & Graduate Students' Research Day, 07 November 2014.

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Dedication

To mom and dad, thank you for your endless encouragement and support. I would not be where I am today without you.

To my brother, thank you for raising the bar high and making me constantly strive towards achieving my goals.

Table of Contents

Abstract.....	ii
Preface.....	iii
This preface lists the publications by the author of this thesis which include the materials and ideas presented in the thesis.	iii
Acknowledgements.....	iv
Dedication.....	v
Table of Contents.....	vi
List of Tables.....	viii
List of Figures and Illustrations.....	ix
CHAPTER ONE: OBJECTIVES.....	1
1.1 Objectives.....	1
1.1.1 Test Utilization.....	1
1.2 Sociodemographic Factors.....	2
1.2.1 Sensitivity and Specificity of FIT.....	4
1.3 Significance.....	5
1.4 Thesis Structure.....	5
CHAPTER TWO: INTRODUCTION.....	7
2.1 Background.....	7
2.2 Colorectal Cancer.....	8
2.2.1 Dysplasia.....	8
2.2.2 Colorectal Polyps.....	9
2.3 Colorectal Screening.....	10
2.3.1 Family History of Colorectal Carcinoma.....	11
2.4 Colorectal Carcinoma Screening.....	12
2.4.1 Colonoscopy and Sigmoidoscopy.....	15
2.4.2 Non-Invasive Screening Methods.....	16
2.4.2.1 Guaiac Fecal Occult Blood Screening.....	16
2.4.2.2 Fecal Immunochemical Testing.....	17
2.4.2.3 Barium Enema.....	19
2.4.2.4 Computerized Tomography Colonography (CTC).....	20
2.4.2.5 Stool DNA Testing.....	20
2.5 Community Screening Programs.....	21
CHAPTER THREE: SENSITIVITY & SPECIFICITY.....	26
3.1 Introduction.....	26
3.2 Methods.....	28
3.3 Results.....	29
3.4 Discussion.....	40
3.5 Conclusion.....	41
CHAPTER FOUR: SOCIODEMOGRAPHICS.....	43
4.1 Introduction.....	43
4.2 Methods.....	44

4.3 Results.....	54
4.4 Discussion.....	60
CHAPTER FIVE: CONCLUSIONS AND FUTURE RESEARCH	64
5.1 Conclusions.....	64
5.2 Future Research	67

List of Tables

Table 1 Status of provincial colorectal community screening program [23, 66].....	22
Table 2 Canadian provinces, fecal occult blood invitation methods as of 2013 [66].....	24
Table 3 Characteristics of study subjects.....	30
Table 4 Test characteristics of a community-based trial of FIT testing. Sensitivity and specificity refer to the commonly used cut-off of 75ng/mL for all neoplasia (colorectal carcinoma and colonic adenoma). AUC=Receiver operator characteristic area under the curve.....	34
Table 5 Cross tabulation of results. A positive biopsy includes carcinoma and any adenoma subtype. Fecal immunochemical test positivity is defined as a quantitative value >75ng/mL.	35
Table 6 Clinical history of all patients included for analysis with both FIT screening and colonoscopy.....	36
Table 7 Histologic diagnoses from 457 patients undergoing colonoscopy. The total is greater than 457 as some individuals had multiple diagnoses.	37
Table 8 Comparative PPV for all neoplasia (carcinoma and adenomas) in related studies.	39
Table 9 Sociodemographic variables and FIT screening rates in Calgary, Alberta.....	57

List of Figures and Illustrations

Figure 1 Mathematical calculation of sensitivity, specificity, PPV, and NPV [48].	14
Figure 2 Study flow diagram.	31
Figure 3 Receiver operator curves for a community trial of FIT in Calgary, Alberta. Area under the curve was 0.79 (95% CI 0.71-0.87) for colorectal carcinoma and 0.60 (95% CI 0.54-0.65) for colonic adenomas.	32
Figure 4 Box and whisker plot showing a scatter of results from positive FIT and colonoscopy.	38
Figure 5 ArcGIS hot spot analysis of census Canada for Income in the city of Calgary, Alberta.	46
Figure 6 ArcGIS hot spot analysis of census Canada for Education in the city of Calgary, Alberta.	47
Figure 7 ArcGIS hot spot analysis of census Canada for Aboriginal First Nation in the city of Calgary, Alberta.	48
Figure 8 ArcGIS hot spot analysis of census Canada for Aboriginal Metis in the city of Calgary, Alberta.	49
Figure 9 ArcGIS hot spot analysis of census Canada for Recent Immigrant in the city of Calgary, Alberta.	50
Figure 10 ArcGIS hot spot analysis of census Canada for Visible Minority Black in the city of Calgary, Alberta.	51
Figure 11 ArcGIS hot spot analysis of census Canada for Visible Minority Chinese in the city of Calgary, Alberta.	52
Figure 12 Study flow diagram.	54
Figure 13 ArcGIS hot spot analysis of FIT screening rates in the city of Calgary, Alberta.	55
Figure 14 ArcGIS hot spot analysis of FIT screening rates in the city of Calgary, Alberta.	58
Figure 15 ArcGIS hot spot analysis of FIT screening rates in the city of Calgary, Alberta.	59

List of Symbols, Abbreviations and Nomenclature

Symbols	Definition
CRC	Colorectal Cancer
FIT	Fecal Immunochemical Testing
gFOBT	Guaiac Fecal Occult Blood Testing
ROC	Receiver Operators Characteristic
AUC	Area Under the Curve
CI	Confidence Interval
CTC	Computerized Tomography Colonoscopy
IBD	Inflammatory Bowel Disease
HNPCC	Hereditary Nonpolyposis Colorectal Cancer
FAP	Familial Adenomatous Polyposis
PPV	Positive Predictive Value
NPV	Negative Predictive Value
CLS	Calgary Laboratory Services
LIS	Laboratory Information System
CPG	Colorectal Cancer Screening Clinical Practice Guidelines
GIS	Geographic Information System

Chapter One: **Objectives**

1.1 Objectives

The objective of this thesis is to examine the utilization of colorectal cancer (CRC) screening within Calgary, Alberta. Calgary is the only major city in North America with testing provided by a single laboratory. This provides a unique opportunity to study the effects of utilization management interventions within an entire city. While many laboratory tests are being over utilized and are increasing the cost of provincial health care, Fecal Immunochemical Testing (FIT) screening is currently under-utilized and could help reduce costs by identifying patients who do not need a colonoscopy [1].

1.1.1 Test Utilization

Alberta Health Services has recently established a provincial laboratory utilization office to study utilization trends in Alberta and to make recommendations to improve more appropriate utilization of lab tests. Having utilization data on different sociodemographic groups is important to determine the diverse utilization initiatives. The main objective is to recognize which forms of screening are being used to detect CRC and to determine the sociodemographic factors associated with them.

1.2 Sociodemographic Factors

Although the reason behind under screening is unknown, it is believed that a lack of awareness about screening programs is one of the main reasons [2]. By looking at certain sociodemographic factors it may be determined what can be done to improve screening rates. The following sociodemographic factors will be examined for their correlations with FIT screening in Calgary, Alberta:

- *Age:* Individuals between the ages of 50 and 74 years are eligible for CRC screening. Even though screening is recommended and endorsed by the Canadian Association of Gastroenterology, many individuals in this age category are not being screened [3]. Individuals with underlying health problems who tend to see their primary care physician on a regular basis have a higher chance of being screened for CRC [4]. Screening awareness tends to be higher among these individuals as they have a closer relationship with their primary care physicians [2].
- *Gender:* Unlike other cancer screening tests, both sexes are candidates for CRC screening. As with age, it has been noted that females tend to have a closer relationship with their primary care physicians [2]. Due to this, their awareness of screening may be higher [5], increasing their chances of getting screened. Studies indicated that females in Ontario are more likely to be screened over males, likely due to their closer relationship with their primary care physician and being more compliant to the advice [4, 6].

- *Education level:* It is believed that patients with higher education levels are more likely to be screened for CRC. These individuals are more likely to be aware of the disease and the prevention that screening can provide [7]. They may also be more likely to have employment that provides health care coverage for any further screening or health care treatment that may be needed if tests come back positive [8].
- *Income:* Individuals with higher income in the United States are more likely to be screened for CRC because of cost to patients [8, 9]. Screening in Canada is free; by looking at individual's income it may be possible to determine whether this is even a barrier in Canada. This may not be a factor within Canada, although Canadian studies have included income as a possible factor concerning CRC screening. It has been indicated that those with a higher income were at increased odds of receiving CRC screening.
- *Location:* Certain neighbourhoods have better access to primary care, including CRC screening facilities [10]. Individuals located further away from primary care physicians and screening centers may not have the same opportunity for screening, as they may have a more difficult time finding a family physician [11, 12]. This directly affects getting screened in areas such as Alberta, where screening kits are given to patients directly from their family physicians [2, 13, 14].
- *Race/Ethnicity:* Race and ethnicity can have a direct affect from other factors that can include education, location and income. Immigrants and those with lower education or income tend to live in the same areas.[15] This can be due to lower

income and possible language barriers [16]. These individuals may also not have access to family physicians or health care and tend to use walk-in clinics [11]. This again can directly affect their knowledge of screening or how to get screened. Studies have indicated that visible minorities have the lowest percentage of CRC screening rates [12, 16, 17].

By looking at factors associated with utilization of FIT, it may be possible to see who is actually being screened and which areas of Calgary are following CRC screening guidelines and programs.

1.2.1 Sensitivity and Specificity of FIT

This will examine the sensitivity and specificity of FIT screening and describe the test characteristics of a FIT pilot program. By comparing FIT results with corresponding biopsy results, Receiver Operator Characteristics (ROC) curves can be created to show the overall predictive strength of biopsy-proven neoplasias, as ROC curves plot all sensitivity and specificity at as many possible cut points. This can show how accurate FIT is at detecting colonic adenomas and colorectal carcinomas. The area under the curve (AUC) determines the diagnostic power of the test. Several studies in Europe evaluated FIT cut points using ROC curves, which are compared to the data in this thesis. It is hypothesised that FIT will detect higher grade and carcinomas more often, compared to low grade and small polyps.

1.3 Significance

Mapping sociodemographic variables of a FIT pilot screening program will give a snapshot of which individuals and groups within Calgary are participating in the screening program. Having data on the relative utilization of tests among different sociodemographic groups is important to determine both the affect of future utilization management initiatives among different groups and also to determine which groups education initiatives would be best directed.

This study will provide valuable new information on laboratory test utilization within Calgary. It will help to inform the best practices regarding testing protocols and compliance, as the highest sensitivity and specificity of FIT should be used. The information obtained will be of direct interest to laboratory medicine practitioners, researchers, and policy makers in Alberta and other jurisdictions.

1.4 Thesis Structure

The structure of this thesis follows the thesis manuscript format. The thesis is structured as follows:

Chapter one lays out the main points focused of the thesis and the possible significance behind the research.

Chapter two consists of background information on colorectal cancer, the types of colonic polyps, and screening methods for polyps and CRC. This chapter also includes an introduction to Canadian CRC screening programs, as this thesis is focused around community CRC screening programs.

Chapter three focuses on the sensitivity and specificity of FIT screening and the predictive ability for colorectal carcinoma and colonic adenomas.

Chapter four looks at the first six months of a community screening program. This will look at the sociodemographic factors associated with screening rates and which of these groups are participating in the screening program.

Chapter five is the final conclusion of the thesis, including possible future research ideas.

Chapter Two: **Introduction**

2.1 Background

Colorectal cancer is the third most common type of cancer diagnosed in Canada, and is the leading cause of cancer-related deaths, despite major improvements in treatment. CRC is considered 90% curable with early detection and an effective population based screening program can decrease CRC mortality [18-20]. Numerous screening test have been developed including guaiac fecal occult blood testing (gFOBT), FIT screening, sigmoidoscopy, colonoscopy, barium enema, and digital rectal examinations such as CT colonoscopy (CTC) [14, 21, 22]. Screening methods have improved over time, but there are still those who are not taking advantage of the simple non-invasive procedures that are available. Even the most routine forms of screening for CRC are being under-utilized [3]. This will be shown throughout the thesis, by focusing on the utilization of FIT.

The Canadian Association of Gastroenterology has supported provinces to create organized screening programs to increase CRC screening. This varies widely across Canada depending on the region and the fact that as CRC screening methods advance, screening guidelines change [3, 23, 24]. There are advantages and disadvantages to all screening types. Regardless of screening methodology, a key factor in designing screening programs is the determination of optimal cut off points to maximize sensitivity and specificity.

2.2 Colorectal Cancer

Colorectal cancer is a cancer that starts in the colon or rectum. They can be referred to separately as colon cancer or rectal cancer, but have many features in common. Colonic polyps are considered as any mass that protrudes into the lumen of the colon. These polyps are classified histologically into different types of lesions [25]. Although some forms of polyps (e.g. hyperplastic and inflammatory polyps) are entirely benign, adenomas are considered to be dysplastic lesions and can progress to invasive carcinoma over a number of years

2.2.1 Dysplasia

Dysplasia is graded by the degree that epithelial growth is disturbed. Adenomatous polyps may harbour either low or high grade dysplasia. Low grade or mild dysplasia is histologically characterised by tubules that are lined with epithelium from top to bottom. Their architecture features are not disrupted, but there is an excess of mitotic figures, the nuclei are enlarged, elongated, hyperchromatic, and have normal orientation. Severe or high grade dysplasia is commonly referred to as “carcinoma in situ” and “intramucosal carcinoma”. There are structural alterations in these types of polyps that include budding and branching of tubules, back to back arrangement of glands, and cribriform growth of epithelial cells displayed in clusters. Large and irregular nuclei are also present with scalloped membranes and increased nuclear to cytoplasm ratio [26], but there is no involvement in the muscularis mucosa [27].

2.2.2 Colorectal Polyps

Between 70 to 90% of polyps are classified as adenomatous polyps, which can be either pedunculated or sessile. Polyps can vary in shape and size, with different types being more at risk for developing into CRC [28]. Non-precancerous polyps are normally smaller in size and increase in amount with older age [25]. These types of polyps are classified as normal, inflammatory, and hyperplastic polyps. Masses found in the colon that are non-neoplastic are usually pseudo polyps or false polyps. They are the beginning of inflammation or ulceration that develops into raised areas of inflamed tissue that resemble a polyp [29]. Inflammatory polyps are found in patients with inflammatory bowel disease (IBD), Crohn's disease, and ulcerative colitis and tend to arise secondary to these diseases due to a reaction to chronic inflammation within the colon [25, 29].

It is pre-cancerous polyps that have a higher chance of developing into cancer over a period of time. These types of polyps are considered adenomatous polyps of benign neoplastic epithelium with the potential for malignancy [27] and consist of villous adenomas, tubulovillous adenomas, and sessile serrated adenomas [26, 27, 30-33]. These polyps are considered a family of diseases with different precursor lesions and different end stage carcinomas and prognoses [34]. Adenomas are the most common neoplastic polyps and are precursor lesions for the majority of CRC [26, 31].

Polyp shapes normally come in two separate forms. Tubular polyps are pedunculated, mushroom shaped growths of tissue attached to the surface of the mucous membrane by long thin stalks. Villous adenomatous polyps are similar, but have broader bases and tend to be larger [30]. Sessile polyps do not have stalks and are flat. They sit on the surface of the mucous membrane and are harder to detect by screening methods

compared to pedunculated polyps [26, 34]. There is a greater risk of potential malignancy, with larger polyps. [30, 34].

Sessile serrated adenomas are increasingly being recognized as a higher risk lesion [35]. Up to 35% of carcinomas arise from serrated pathways that develop from sessile serrated adenomas [34]. Serrated polyps were originally classified as hyperplastic polyps until 2005 due to their architectural features overlapping with hyperplastic polyps [36]. It was then realized there was a histologic assessment that revealed they had a high potential of not being benign [31, 36, 37]. Sessile serrated adenomas appear flat or sessile and can be slightly elevated. They have a soft, smooth surface and sometimes irregular borders that is often covered with mucus, giving them a yellow or pale appearance. Due to the fact that they are small, flat, or only slightly elevated they have a potential to be missed during screening. The yellow-pale appearance also makes them harder to see during a colonoscopy [26, 31, 34, 35, 37, 38].

2.3 Colorectal Screening

The purpose of CRC screening is to discover and identify precancerous polyps before they progress to carcinoma without having to undergo invasive procedures. Due to the fact that CRC is progressive over time, it is imperative that it is caught during the early stages. Average risk people are to be screened, not to diagnose a disease, but to identify those in a high risk group. This limits the number of people who are invited for more expensive, invasive follow up procedures. Those in the average risk group do not have a family history of CRC. They also have no prior diagnosis of Inflammatory Bowel Disease (IBD), adenomas, colonic polyps, and any previous colon or rectal surgery.

These patients should start screening once they reach age 50 [39]. Individuals at high-risk are classified as having a family history of CRC. They are at a higher risk if they have a sibling or parent affected by CRC and have been diagnosed at an earlier age than 50 [40].

2.3.1 Family History of Colorectal Carcinoma

There are also a small number of individuals who carry an inherited gene mutation. This increases the risk for CRC are classified as familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC) [41]. Genetic testing is used to identify those who carry the gene mutation, making them at a higher risk for developing CRC than the general public [25, 30, 37, 39]. These people along with individuals who have a personal history of adenomatous polyps, IBD, or previous resection of colon should start screening at an earlier age [42].

Inherited CRC accounts for 15-30% of all CRC cases. There are several variations to FAP with slightly different clinical syndromes, but the majority have a APC gene mutation [43]. These patients are prone to develop large amounts of polyps throughout the colon and gastrointestinal tract, beginning in early life. By the age of 40, almost all patients with FAP will develop CRC [30]. Although, FAP contributes to a smaller percentage of CRC cases, it is more likely to develop into CRC [43, 44].

Hereditary nonpolyposis colorectal cancer is another variation of inherited gene mutation involving CRC. To identify those with HNPCC, clinical criteria are looked at through the Amsterdam criteria. This requires a thorough family history and genetic testing that follows the “3-2-1” rule. Having three relatives confirmed of having CRC, at

least two successive generations involved, and at least one of these cancers diagnosed before age 50 [45]. Once HNPCC has been identified, regular surveillance can be started, as there is an 80% risk of developing CRC. The average age of being diagnosed with CRC is also much earlier [30, 43, 44].

2.4 Colorectal Carcinoma Screening

Screening can help detect early stages of a disease and can improve prognosis [14]. People of lower income, lower education, with no health insurance, and are foreign born are less likely to be screened for CRC, as they may not have the information or finances or do not have access to a primary care physician due to geography, that is needed for screening programs [46]. Data on trends in utilization among different sociodemographic groups is important to determine the affect of utilization management of screening [47]. This can give a more clear idea if these factors are influencing individuals who are participating in community based screening programs.

In a perfect world, a laboratory test would never be positive in a patient who is disease free and would never be negative in a patient who has a disease. Unfortunately, this is not the case with many laboratory tests, including FIT. When evaluating a screening method it is important to examine the sensitivity and specificity of a test. Sensitivity is the ability of a test to correctly identify patients with a disease. A test with 100% sensitivity will correctly identify all patients with the disease [48]. Specificity is the ability of a test to correctly identify patients without a disease. A test with 100% specificity will correctly identify all patients without a disease. Both sensitivity and specificity can be calculated with the use of true and false positive and negatives. A test

with a high sensitivity and low specificity will result in many patients who are disease free to be told they possibly have the disease with further investigation needed. A test that is low in sensitivity and high in specificity would be needed to rule out false positives [48].

Positive and negative predictive values are also useful in determining if a patient has a disease or not. Positive predictive value (PPV) can answer the question of how likely a patient has a disease given that the test is positive. While negative predictive values (NPV) can answer the question of how likely a patient does not have the disease given that the test result is negative. These are dependent on the population being tested and are influenced by the prevalence of the disease in that population [48]. Figure 1 shows the mathematical calculations for sensitivity, specificity, PPV, and NPV.

		True class		Measures
		Positive	Negative	
Predicted class	Positive	True positive <i>TP</i>	False positive <i>FP</i>	Positive predictive value (PPV) $\frac{TP}{TP+FP}$
	Negative	False negative <i>FN</i>	True negative <i>TN</i>	Negative predictive value (NPV) $\frac{TN}{FN+TN}$
Measures		Sensitivity $\frac{TP}{TP+FN}$	Specificity $\frac{TN}{FP+TN}$	Accuracy $\frac{TP+TN}{TP+FP+FN+TN}$

Figure 1 Mathematical calculation of sensitivity, specificity, PPV, and NPV [48].

Since FIT has a high sensitivity and specificity, it is used by many regions as the main screening method. While CRC screening is publically funded in Canada, lower sociodemographic status may nevertheless be associated with lower rates of screening. This may be due to lower income, lower education, a lack of a family physician, and being foreign born, as language may be a barrier. This can decrease the likelihood of CRC screening as patients may simply not be aware of the screening program [4] [46]. Data on utilization among different sociodemographic groups is important to determine the affect of utilization management of CRC screening [47]. This can give a better idea

of what is influencing certain individuals in participating in community based screening programs.

Knowledge of colorectal cancer, the types of polyps and other forms of screening are also helpful in understanding why screening is important. This can give the population a foundation to understand the necessity of screening programs across Canada.

2.4.1 Colonoscopy and Sigmoidoscopy

Screening for the average population is used before patients present with symptoms, insuring they did not have early signs of CRC. This is associated with diseases with a high morbidity or mortality with people in certain risk groups. Screening can help detect early stages of a disease and can improve prognosis with treatment [14]. The type of screening performed for early diagnoses has changed over the years. The “gold standard” for screening is considered a colonoscopy, as it can visualize the entire colon. It is able to detect neoplastic lesions and has the advantage of removing adenomas and taking biopsies throughout the colon during the initial scope. Other tests performed need the confirmation of a colonoscopy or for possible removal of tissue [49]. Sigmoidoscopy shares the same basic procedure as a colonoscopy with the limitation of only being able to visualize the distal colon. Visualization of the left side of the colon is achieved through sigmoidoscopy, any polyps or cancer on the right side would be missed. Due to cost and wait-time, it is impossible to provide all individuals with colonoscopies as the main form of screening [1].

2.4.2 Non-Invasive Screening Methods

Some screening methods use the detection of occult blood in stool to determine the possibility of cancer cells. Cancers tend to bleed more than normal mucosa and the amount of blood present can be determined by the size of a polyp or the stage of cancer. Tests such as gFOBT and FIT are screening methods that detect blood in stool and are non-invasive, often being done at home [50] .

2.4.2.1 Guaiac Fecal Occult Blood Screening

Guaiac fecal occult blood was the first occult blood screening method used to screen for CRC, beginning in the 1970's. Early findings supported the benefits of FOBT as a screening tool for early stages of CRC. More became known about this form of screening in the early 1980's with the use of Hemoccult II kits [22]. Patients collect three consecutive bowel movements at home. All three samples are necessary to improve the sensitivity of the test. Patients follow a three day dietary restriction, avoiding red meats and certain fruits and vegetables. These can create a false positive reaction if present in the stool, as gFOBT cannot differentiate between human and animal hemoglobin [51] [52]. They are also to avoid certain medications such as aspirin and anti-inflammatory drugs for seven days prior [53]. These are gastric irritants that can cause occult gastrointestinal bleeding. The gFOBT detects blood in the stool through a chemical reaction. It is a guaiac based test to detect the blood through pseudoperoxidase activities of hemoglobin [14]. The gFOBT tests are read by a trained laboratory technician using the naked eye to interpret the results [54]. When the first outreach screening program was created within Canada, FOBT was the test of choice [23].

2.4.2.2 Fecal Immunochemical Testing

More recently, in the last decade, FIT testing began to replace gFOBT within outreach programs. Fecal Immunochemical Testing is also a screening test that detects occult blood in the stool. This test is performed at home, essentially the same way as gFOBT. Fecal Immunochemical Testing is considered easier to perform due to the fact that there are fewer restrictions for the patient [51]. There are no food or drug restrictions as this test is less likely to react to bleeding from the digestive tract and only one sample is needed [14]. Another advantage of FIT is that it is specific for human blood, which is why there are no dietary restrictions. It is able to distinguish between human hemoglobin and animal hemoglobin[55] [51].

Depending on the brand, FIT samples are analysed by automated systems in the laboratory. By using an automated system a numerical result is provided, allowing for a customized cut-off in hemoglobin concentration that can be set to define a positive test [54]. Fecal Immunochemical Testing has shown an increased sensitivity for detecting neoplasms compared to gFOBT, but specificity is reduced compared to gFOBT [51, 56]. The sensitivity for advanced neoplasms have been reported to be higher for FITs compared to gFOBT, at commonly used cut-offs for test positivity [55, 57]. The Brenner et al study indicated that their three consecutive FIT tests showed better diagnostic performance than gFOBT. This included indicators for sensitivity, specificity, positive predictive values, and negative predictive values. FIT was also able to detect a larger proportion of neoplasms and advanced neoplasms with different sets of cut offs [55].

As mentioned, sensitivity is increased with FIT and specificity is increased with gFOBT. Factors can influence sensitivity and specificity for each test. Tests for gFOBT

can be stored at room temperature for a couple of days before testing is performed. This preserves the stability of the hemoglobin, if it is present. The sensitivity of guaiac based tests is increased if the test slide is rehydrated with drops of water before adding the hydrogen peroxide reagent. The trade off to doing so reduces the specificity. Patients are also required to sample three consecutive bowel movements because the sensitivity increases with the number of samples tested. These factors and the dependence of the patient following restrictions before performing the test all rely on the sensitivity and specificity of any false positive results [53]. This not the same for FIT, as changes in temperature can possibly result in a degradation of hemoglobin in the sampling solution [51].

As with gFOBT, there are things to rely on with FIT testing in order to achieve high sensitivity and sensitivity. FIT devices use a range of sampling methods and can differ with regards to hemoglobin stability, reporting hemoglobin concentrations in different ways. The volume of feces and buffer used can vary, making the comparison of test characteristics difficult. There can also be a lack of consistency in units when it comes to reporting hemoglobin concentrations, depending on the device and units used. Quantitative FIT tests use more automated devices for testing. This form of testing has a cut off for hemoglobin concentrations. Cut off units for tests are unique to each device. Many facilities use the manufacturers suggested cut off concentrations, but several newer FIT tests allow adjustment of cut off values of fecal hemoglobin that is required to generate a positive result. Simple comparison is impossible with this, but a standardized system can create an appropriate method for screening with FIT [58, 59]. With these

variables being considered for each occult blood test, studies have shown that overall FIT is a better screening source [50, 51, 55].

Although gFOBT and FIT are the most popular screening methods, there are other forms of screening that are being developed. This consists of test such as, barium enema, stool DNA testing and Computerized Tomography Colonography (CTC) [60-62], but are not as widely used to date.

2.4.2.3 Barium Enema

Barium enema is an evaluation of the colon by coating the surface of the mucosa with barium sulphate, a chalky liquid, to distend the colon. A flexible tube is inserted into the rectum and the colon is partially filled with barium. As the barium spreads through the colon, air is then pumped in to expand the colon. X-rays are used to detect any abnormal areas [14]. Retained barium will outline any lesions of the mucosa located within the colon. This form of testing is slightly more difficult and expensive, but is better at locating mucosal lesions and polyps. Barium enema is safer than a sigmoidoscopy or colonoscopy, but small polyps can be missed and doctors are unable to remove polyps or biopsy during the procedure. This leads to having a scoping procedure performed if any polyps are found, the same as any occult blood testing [13].

2.4.2.4 Computerized Tomography Colonography (CTC)

This is a new advanced form of CT scan of the colon and rectum using two and three-dimensional imaging to identify polyps and other abnormalities. This less invasive form of screening could be an alternative to colonoscopy [63]. This exam requires the same bowel preparation as barium enema testing and endoscopes, with air or carbon dioxide inserted into the colon with the use of a catheter, then imaging of the colon[14]. However, one major disadvantage of this test is that patients must undergo colonoscopy if CTC is positive [63]. This test is also very new; sensitivity and specificity are not fully understood. Studies to date vary, with CTC accuracy being higher with larger lesions. The quality of CTC depends on correct bowel preparation, adequate inflation of the colon, and the proper technique used for imaging [14, 60, 61, 63]

2.4.2.5 Stool DNA Testing

One of the newest forms of screening is stool DNA testing, which involves DNA sequencing or genotyping of DNA from shed CRC cells in stool. Since CRC cannot be detected by a blood test, as other DNA tests can, cells from CRC or polyps that contain gene mutations can be detected using DNA testing [14]. In this procedure, there are no dietary restrictions and only a single whole stool sample is needed for collection. Also, mutated genes responsible for neoplastic transformation are only present in precancerous and cancerous lesions [18].

In this procedure, DNA is harvested from colon cells and replicated to provide material for analysis for genetic alterations associated with cancer or precancerous changes. If abnormalities are detected, colonoscopy is preformed [18]. Stool DNA

testing has not be thoroughly evaluated for screening. Studies that have recently been performed showed that specificity is higher than sensitivity for detecting advanced adenomas [62]. Imperiale et al [64] showed improvements in detecting carcinomas compared to FIT, with higher sensitivity and lower specificity [64]. However, DNA testing is more expensive than fecal screening kits [14, 18, 62].

2.5 Community Screening Programs

As previously mentioned, non-invasive screening tests for colorectal carcinoma include FOBT and FIT [18]. Screening programs based on these tests are not only important for detecting early disease [13, 14, 65], but may also be efficiently promoted by primary care physicians [22]. This type of clinical guideline can transmit knowledge regarding the best practice of screening options and can be given to patients by their primary care physician [3]. Studies by Strumpf et al have indicated that although there are guidelines in place for many of the provinces of Canada, they are not being followed and remain unknown to many individuals. Fifty eight percent of Canadians over the age 50 had never had fecal occult blood tests as of 2010 [3].

Canadian Association of Gastroenterology has published guidelines followed in each province across Canada. The majority use FIT or are considering a pilot program of FIT community screening programs, listed in Table 1 [23]. Alberta has recently rolled out a FIT community screening program in November 2013. Data from this new pilot program in Alberta will be used in part of this research.

Table 1 Status of provincial colorectal community screening program [23, 66].

Province	Primary Screening Test	Comments
Northwest Territories	N/A	No organized program
Yukon	N/A	No organized program
Nunavut	N/A	No organized program
Newfoundland & Labrador	FIT	Planning screening program
New Brunswick	FIT	Planning screening program
Prince Edward Island	FIT	Province wide screening program
Nova Scotia	FIT	Province wide screening program
Quebec	FIT	Phased rollout of screening program
Ontario	gFOBT	Province wide screening program
Manitoba	gFOBT	Phased rollout of screening program
Saskatchewan	FIT	Phased rollout of screening program
Alberta	FIT	Phased rollout of screening program
British Columbia	FIT	Phased rollout of screening program

Even with guidelines and community screening programs, there are differences in screening available across Canada as of March 2013. Alberta, Ontario, Nova Scotia, and Prince Edward Island are the only provinces that have 100% availability for CRC screening for their entire population of the province. The remainder of the provinces vary in range, with Manitoba having organized programs for between 50-99% of their population. Saskatchewan and Newfoundland and Labrador are even lower with 10-49% CRC screening available for their provinces. British Columbia only provides 1-9% and Quebec and New Brunswick with 0% available. The most northern provinces, Yukon, Northwest Territories, and Nunavut have no organized screening programs for their provinces [66].

A more recent update shown above indicates Canadian provinces from 2013. Table 2 lists provinces that use either physician requested programs and mail invitation screening [66].

Table 2 Canadian provinces, fecal occult blood invitation methods as of 2013 [66].

	Physician	Self-referral	Self-referral (pharmacy)	Mailed invitation letter	Mailed fecal test
NU	No organized program	No organized program	No organized program	No organized program	No organized program
NT	No organized program	No organized program	No organized program	No organized program	No organized program
YK	No organized program	No organized program	No organized program	No organized program	No organized program
BC	✓			✓	
AB	✓			✓ future plan	
SK				✓ primary method	✓ 1 month after letter
MB	✓	✓		✓ primary method	✓ 3 weeks after letter or on request
ON	✓ Primary method			✓	
QC	✓			✓ plan for 2014	Pick-up kit at hospital/community laboratory
NB				✓	✓
NS				✓	✓ 2 weeks after letter
PE	✓		✓	✓	Mail fecal test on request
NL	✓	✓			Kits mailed weekly to participants

Many studies have indicated that physician recommendation for CRC screening plays a critical role with patients getting screened [3, 24, 67-70]. Zarychanski et al stated, even though screening rates are low in all provinces, patients that are in contact with their family physicians are associated with an increased likelihood of being screened for CRC [24] and physician promotion of CRC screening can help spread the word for all organized screening programs [71]. This reinforces the importance for family physicians to be up to date with all screening guidelines; this includes introducing CRC screening education in the residency curriculum [72]. The more education and the earlier it is introduced for both patients and physicians, the less bias that may be used, as many physicians are using the screening guidelines selectively [70]. Klabunde et al also stated that many physicians are overusing and recommending colonoscopy over fecal screening programs [73].

Some provinces eliminated the need for a family physician and mail CRC screening kits directly to all eligible patients. This option was created to increase screening in a cost effective manner, bypassing physicians who lack a system of supporting CRC screening [74]. Mailed invitations linked with a physician letter or recommendation had a 6% increase in participation, according to Tinmouth et al [69]. This was also true when only a letter recommending they obtain a kit from their family physician was sent. This approach helped with avoiding waste of sending a screening kit to a patient that was not used [69].

Chapter Three: **Sensitivity & Specificity**

3.1 Introduction

Non-invasive screening tests for colorectal carcinoma include forms of screening that detect occult blood in stool to determine the possibility of cancer cells. This form of screening using gFOBT and FIT [18], is used on average risk people to catch any polyps or adenomas in the early stages. Screening programs based on these tests are not only important for detecting early disease (2-4), but can be efficiently promoted by primary care physicians (5). Recent research, however, has indicated that FIT testing is more sensitive compared to guaiac based testing [50, 52, 57, 75], as well as being more convenient for patients (6-10). There is also the added benefits that FIT only involves one or two stool samples and there are no dietary or medication restrictions before testing [76, 77].

Organized community screening programs are an ideal way to endorse FIT testing. Since colorectal cancer is progressive over time, it is imperative that it is caught during the early stages [14]. By screening the general population, it can help recognize those individuals with colonic adenomas [65] and it is a way to increase the amount of screening within Canada, especially with family physicians promoting screening programs [22].

Other advantages of FIT include advantages to clinical laboratories including the potential for automation and the ability to customize the cut-off level to define a positive test [54, 55, 57, 78-81]. Fecal immunochemical testing samples are analysed by automated systems in the laboratory. By using an automated system a numerical result is

provided, allowing for a customized cut-off in hemoglobin concentration that can be set to define a positive test [54, 57]. Sensitivity relates to the tests ability to identify positive rates of a test. This is the opposite for specificity, which measures the proportion of actual negatives that are correctly identified as being negative [79]. Fecal immunochemical testing has shown an increased sensitivity for detecting neoplasms compared to gFOBT which only gives a positive or negative result [77, 80]. This gives an advantage of setting a cut-off value within particular populations to obtain optimal sensitivities and specificities [80, 81]. This can eliminate patients who do not need a colonoscopy; a FIT screening program may be more cost effective than colonoscopy-based screening [1, 57].

Despite numerous reported advantages of FIT as a screening modality, there are few community-based program evaluations and no published studies from Western Canada describing the characteristics of FIT testing (e.g. sensitivity, specificity, positive predictive value) and therefore no data on which to evaluate existing and planned screening programs. The purpose of this study is to provide an opportunity to determine the positivity of FIT and the accuracy of the cut off levels in a FIT trial in Calgary, Alberta, Canada. Receiver Operator Characteristics curves will illustrate the trade-offs of each cut-off value, providing the highest sensitivity and specificity. By focusing on Calgary, Alberta, we can assess whether FIT can determine a predictor of colorectal carcinoma and colonic adenomas within one Canadian community setting. This can be done by comparing FIT results with subsequent biopsy results to produce ROC curves for FIT testing.

3.2 Methods

This research was approved by the University of Calgary Conjoint Research Ethics Board (ID 13-0376) prior to the start of data collection.

Data for this study was obtained from a trial of community FIT screening using the FOBT-CHEK Sampling Bottle (Polymedco Inc, NY) FIT testing platform performed in Calgary, Alberta between April 2011 and May 2012. FIT collection kits were distributed directly to patients by participating family physicians and primary care physicians. Samples were returned to Calgary Laboratory Services (CLS) for testing. Calgary Laboratory Services is the sole provider of laboratory services to Calgary and surrounding areas (catchment population of 1.4 million persons). In the vast majority of cases two paired FIT test collections were collected on consecutive days. Where two kits were collected, the higher of the two values was used for analysis. For each FIT result laboratory information system was searched for colon biopsy reports signed out in the one-year period following the FIT result. Biopsy reports were searched, which were signed out in the one year period for each patient following the verification date of the FIT result and results from each test were matched. All patient information was de-identified prior to further analyses.

Biopsy results were classified as colonic adenoma and colorectal carcinoma. Non-neoplastic biopsies were not included and consisted of normal mucosa, inflammatory, and hyperplastic polyps. Colonic adenomas included sessile serrated adenoma, villous adenoma, tubulovillous adenoma and tubular adenomas. For individuals with more than one biopsy, the most advanced lesion only was considered.

For example, if a patient had both a carcinoma and a tubular adenoma, they were coded as a carcinoma.

Receiver Operator Characteristics curves were then constructed for FIT quantitative values and colonic adenoma and colorectal carcinoma. In addition to the overall analysis, subgroup analysis was performed for females and males and for ages greater than and less than the mean age of 62. Areas under the curve values were calculated for each ROC curve to determine the overall predicative strength of the associations. An AUC value of 0.8 is considered a strong predictor and a range between 0.5-0.6 is generally considered to represent a weak or non-predictor [82]. Positive predictive values (PPV) were also calculated. Statistical analyses were performed using SPSS for Macintosh version 21 (IBM SPSS Inc).

3.3 Results

The operational pilot of FIT at our institution ran between April 2011 and May 2012. A total of 457 patients who underwent both FIT and colon biopsies; occurring within a year after the FIT test and were included in the analysis. Characteristics of patients and histology results are summarized in Table 3 and a flow diagram of the patient's eligibility and results are shown in (Figure 2).

Table 3 Characteristics of study subjects.

Characteristic	Number
Females	201
Mean age females (range)	49 (34-83)
Males	256
Mean age males (range)	51 (33-84)
FIT result range	0 – 981
Individuals with carcinoma as most serious lesion	35
Individuals with adenoma as most serious lesion*	209

* Includes: sessile serrated adenoma, villous adenoma, tubulovillous adenoma, tubular adenoma

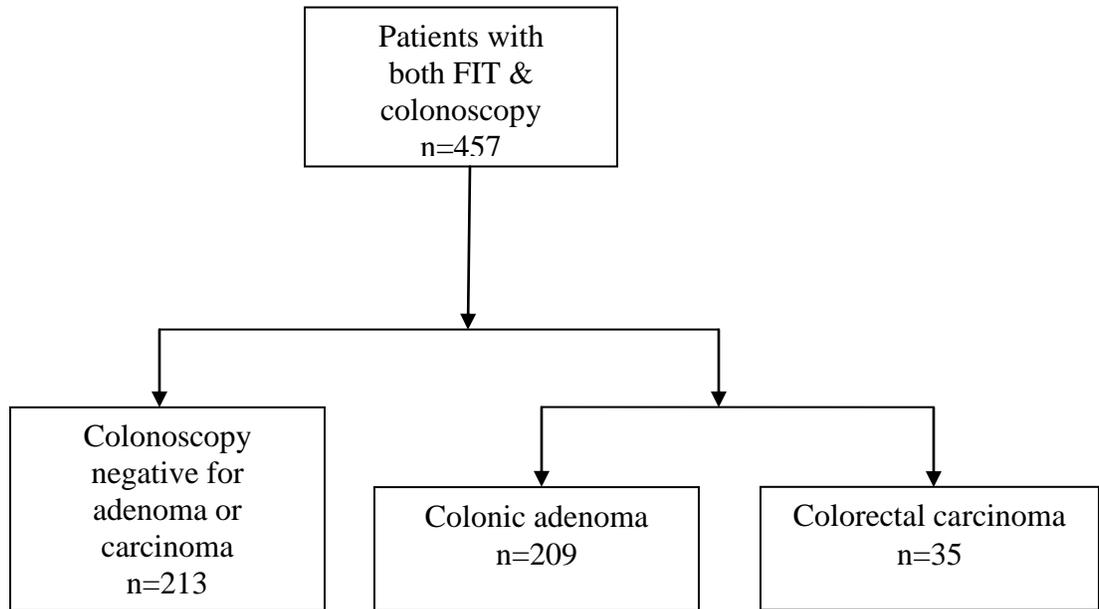


Figure 2 Study flow diagram.

Of these patients, 256 were male with a mean age of 51 and 201 were female with a mean age of 49. The FIT test results ranged from 0-981. Higher numbers indicate higher hemoglobin levels in the kit tested [57]. Of the biopsy results, 418 were diagnosed as negative and 35 were positive for carcinoma. Of the patients negative for carcinoma, 209 were classified as harbouring colonic adenomas.

Figure 3 illustrates the ROC curve for FIT test result and colonic adenoma and carcinoma. The predictive ability for carcinoma was very good with an AUC of 0.79 (95% CI 0.71-0.87). In contrast to carcinoma, the predictive ability for colonic adenoma was poor with an AUC of 0.60 (95% CI 0.54-0.65).

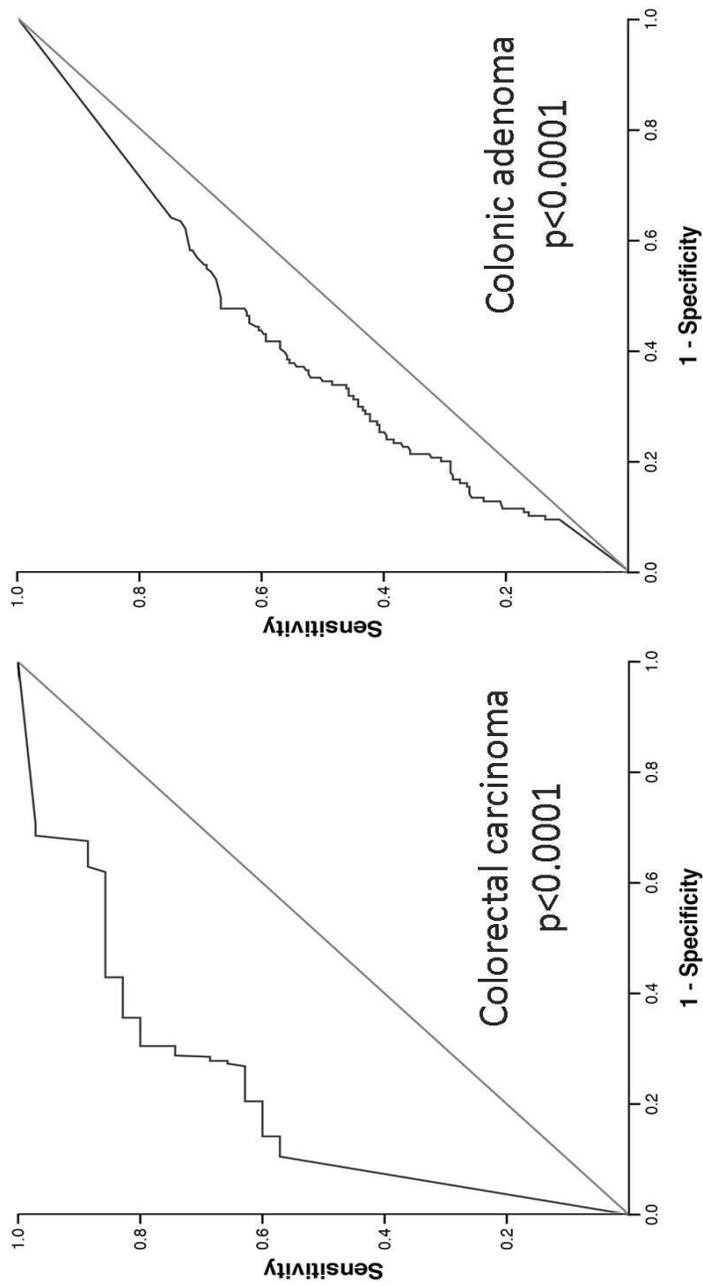


Figure 3 Receiver operator curves for a community trail of FIT in Calgary, Alberta. Area under the curve was 0.79 (95% CI 0.71-0.87) for colorectal carcinoma and 0.60 (95% CI 0.54-0.65) for colonic adenomas.

Table 4 indicates the sensitivities and specificities for FIT using the current cut-off level of 75ng/mL, at CLS. Cross tabulations were calculated from positive and negative FIT tests and biopsies and are shown in Table 5. The cross tabulation revealed an overall 53% PPV, for all neoplasia.

Table 4 Test characteristics of a community-based trial of FIT testing. Sensitivity and specificity refer to the commonly used cut-off of 75ng/mL for all neoplasia (colorectal carcinoma and colonic adenoma). AUC=Receiver operator characteristic area under the curve.

Lesion	Sensitivity	Specificity	AUC (95% CI)	P value
Tubular adenoma	36.4%	62.2%	0.49 (0.41-0.54)	.470
Advanced adenoma*	49.5%	62.7%	0.57 (0.50-0.64)	.052
Carcinoma	82.9%	60.0%	0.79 (0.71-0.87)	< .001
Tubular adenoma males only	38.1%	56.8%	0.45(0.36-0.54)	.245
Advanced adenoma males only	51.6%	58.6%	0.53(0.44-0.62)	.525
Carcinoma males only	83.3%	66.0%	0.78 (0.66-0.91)	.001
Tubular adenoma females only	34.5%	69.9%	0.52(0.42-0.62)	.681
Advanced adenoma females only	44.8%	68.1%	0.63(0.52-0.74)	.026
Carcinoma females only	82.6%	65.9%	0.81(0.70-0.91)	<.001
Tubular adenoma age > 62	40.0%	55.0%	0.44(0.35-0.53)	.202
Advanced adenoma age > 62	46.5%	56.9%	0.51(0.41-0.62)	.773
Carcinoma age > 62	75.0%	56.2%	0.75(0.64-0.86)	<.001
Tubular adenoma age < 62	32.7%	70.7%	0.51(0.42-0.61)	.798
Advanced adenoma age < 62	50.0%	69.4%	0.60(0.51-0.70)	.034
Carcinoma age < 62	100%	64.8%	0.85(0.78-0.93)	<.001

* Includes: sessile serrated adenoma, villous adenoma, tubulovillous adenoma, and any high grade dysplasia

Table 5 Cross tabulation of results. A positive biopsy includes carcinoma and any adenoma subtype. Fecal immunochemical test positivity is defined as a quantitative value >75ng/mL.

		Biopsy	
		Positive	Negative
FIT	Positive	183	63
	Negative	122	89

Although the majority of patients that underwent colonoscopy did so for routine screening or because FIT positive screening results, there were patients who were FIT negative who also had colonoscopy. Table 6 shows the indications for colonoscopy even with a negative FIT result.

Table 6 Clinical history of all patients included for analysis with both FIT screening and colonoscopy.

Clinical History	Number of Patients
Routine Screening	159
FIT Positive	104
No History	76
GI Symptoms*	51
Family History	30
History of Prior Polyps	24
History of Prior Cancer	14
Iron Deficiency Anemia	7

*GI Symptoms include change in bowel habits, abdominal pain, and rectal bleeding

*The total is greater than 457 patients as some individuals fit into more than one category

The histologic diagnosis for all 457 patients who underwent a colonoscopy is found in Table 7.

Table 7 Histologic diagnoses from 457 patients undergoing colonoscopy. The total is greater than 457 as some individuals had multiple diagnoses.

Patients Diagnoses	Number Positive
Carcinoma	35
Sessile Serrated Adenoma	45
Tubulovillous Adenoma	80
Villous Adenoma	10
Tubular Adenoma	436
Hyperplastic Polyp	180
Inflammatory Polyp or Colitis	63
No Pathologic Diagnosis	130

Many patients had more than one polyp found during colonoscopy and had multiple diagnoses. Figure 4 shows the diagnoses of positive FIT patients and the range of associated quantitative FIT results.

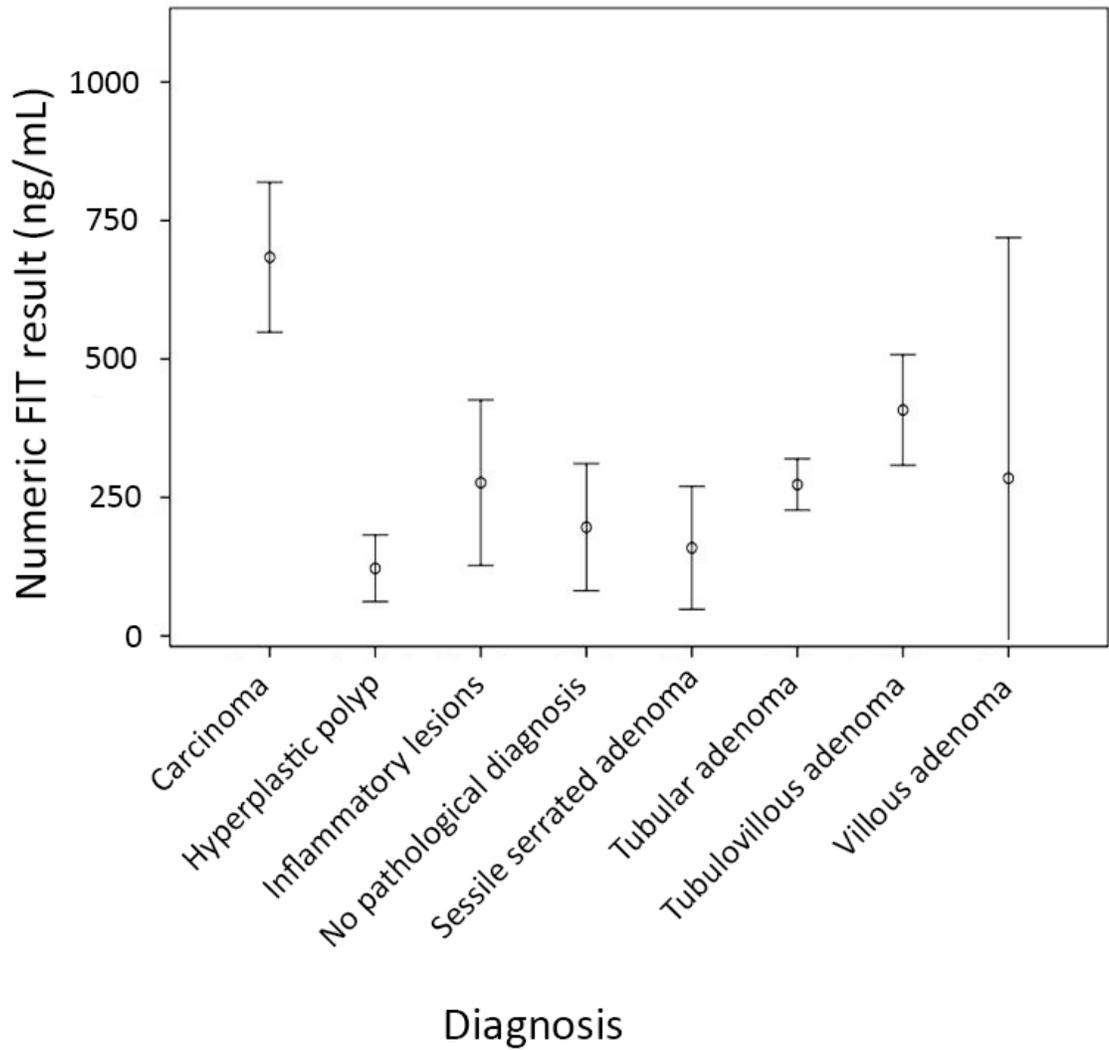


Figure 4 Box and whisker plot showing a scatter of results from positive FIT and colonoscopy.

Positive Predictive Values showed a 53% for all neoplasia. This is similar to other studies and has been broken down in Table 8. Each study included a mix of symptomatic and asymptomatic patients who received both FIT testing and colonoscopy. The PPV for our study is lower than Zubero et al., which tested two different brands of FIT and had a PPV of 62.4% and 58.9% [83]. Other studies indicates a lower PPV, Randell et al, another Canadian study demonstrated a 40% PPV [84]. This illustrates that our PPVs are consistent with other FIT and colonoscopy results

Table 8 Comparative PPV for all neoplasia (carcinoma and adenomas) in related studies.

Study	Population Tested	PPV for All Neoplasia	Brand of FIT
Crouse et al [85]	Symptomatic patients & high risk patients scheduled for colonoscopy	53%	FOBT-CHEK (Polymedco Inc, NY)
Zubero et al [83]	Patients scheduled for colonoscopy after a positive FIT test result	62.4%	OC-Sensor (Eiken Chemical Co, Japan)
Zubero et al [83]	Patients scheduled for colonoscopy after a positive FIT test result	58.9%	FOB Gold (Sentinel Diagnostics, Italy)
Randell et al [84]	Symptomatic patients & high risk patients scheduled for colonoscopy	40%	Hemp Techt NS-Plus (Alfresa Pharma, Japan)
Oono et al [86]	Recruited CRC symptomatic patients with a range of colorectal disorders	33.7%	Auto iFOBT (Alfresa, Pharma, Japan)
Levi et al [87]	Asymptomatic patients, symptomatic & high risk patients referred from a clinic, treating physician, or for elective colonoscopy	43.9%	OC-MICRO (Eiken Chemical Co, Japan)

3.4 Discussion

In this paper, it reports the test characteristics from a FIT community screening program in Calgary, Alberta. This is the first time this information has been reported from a Canadian Western province. The ROC curve for FIT test results and colorectal carcinoma showed good predictive ability with an AUC of 0.79 (95% CI 0.71-0.87). However, the predictive ability for colonic adenomas was not as strong, with an AUC of 0.60 (95% CI 0.54-0.65). The predictive ability was also better for males and for older individuals.

Several studies in Europe and Israel have shown higher sensitivities for FIT as compared to FOBT [50, 75]. Reported sensitivities in these studies have ranged from 40.5% to 94% [52, 75, 87]. Our results are likely more reflective of the expectations for a community-based program. We report AUCs for carcinoma of 0.75 to 0.85 which are considerably lower than those reported by Tao et al [88] who reported AUCs for the three quantitative tests of 0.90 to 0.92. However, it is important to add that the high AUCs reported from Tao et al [88] were not from a community based population. Another study by Haug et al [89] reported AUCs of 0.60 to 0.71 but is not directly comparable with our results because of their inclusion of certain types of adenoma along with colorectal carcinoma.

One potential weakness of the study was the time difference between patients receiving their FIT testing and the time when the biopsy was taken. Indeed, in some cases, there was up to a year between when the FIT was reported and the colonoscopy was performed, which could allow for the possible interval progression of any lesions that were present at the time of FIT testing. The latter, represents a more real-world

situation, where due to different reasons such as type of health system wait times or patient related factors, colonoscopy may not be available immediately after a FIT is reported. A second weakness of the study is that secondary data was used, and were unable to control for the presence or absence of symptoms which may prompted FIT testing or a colonoscopy in the first place. Lastly, as patients were studied who had undergone both FIT and colonoscopy; these sample was doubtless enriched for symptomatic and/or high risk subjects. It should be noted, however that this is a general limitation of observation studies employing an invasive or potentially harmful gold standard.

3.5 Conclusion

In conclusion, the results show generally poorer performance for FIT than previous studies and also indicate that while FIT is sensitive for carcinoma, it was less so for precursor lesions. The poor predictive ability for these colorectal carcinoma precursors suggests that reliance on screening by FIT testing alone will miss early lesions, which would have been detected by primary screening with colonoscopy. Based on these results, physicians should not consider FIT equivalent to colonoscopy for detecting precursor lesions.

Chapter three of this thesis has been published in a peer-reviewed publication and presented as a poster presentation at Toronto, Ontario at the Annual Meeting of the Canadian Association of Pathologists (CAP-ACP):

- Crouse A, de Koning L, Sadrzadeh H, Naugler C. *Sensitivity and specificity of community fecal immumotesting screening for colorectal carcinoma in a high risk Canadian population.* Archives of Pathology and Laboratory Medicine, 2015
- Crouse A, de Koning L, Sadrzadeh H, Naugler C. *Test characteristic of community fecal immunotesting for colorectal carcinoma in Calgary, Alberta.* Poster presentation CAP-ACP Conference, 13 July 2014.

Chapter Four: **Sociodemographics**

4.1 Introduction

Colorectal cancer community FIT screening programs are important for detecting early disease [13, 14, 90] and can be very effective when promoted by family physicians [3, 5, 67, 68, 73]. Despite this, screening rates across Canada have been consistently low [71]. This is true even with recent endorsement by the Canadian Association of Gastroenterology of CRC screening guidelines [6]. Alberta, Canada introduced a new FIT screening program through family physicians in November 2013 [6, 91]. This is offered to all individuals aged 50-74 years, free of cost and only through family physicians. As this is a new program in Alberta, there is no data to evaluate participation rates.

The reasons for low participations are unclear, however sociodemographic factors such as minority ethnicity, education, income, sex, and age are associated with CRC screening rates [91-93]. These associations may be related to poor health care knowledge, physician bias towards screening programs, language barriers, and reduced access to health care among certain sociodemographic groups [11, 22, 90, 94-96] . Organized screening programs have the potential to increase participation [91], but without knowing which factors are associated with under utilization of CRC screening [97], little can be done to boost screening rates.

By determining which sociodemographic variables and barriers are associated with under screening for CRC, it is hoped that efforts can be made to promote screening

to the appropriate groups. In this manuscript this issue is addressed by examining the sociodemographic factors associated with screening rates in Calgary, Alberta.

4.2 Methods

This research was approved by the University of Calgary Conjoint Research Ethics Board (ID 13-0376) prior to the start of data collection.

Geographic Information System (GIS) are computer-based integrated systems designed to analyze data using geographical and spatial coordinates. Geographic information systems can combine statistical analysis of data with geographic analysis that can be visually displayed through maps. Other studies within Calgary, Alberta have used this method of analysis [12, 98, 99] and will be included within this methodology as Calgary, Alberta has highly stratified neighbourhoods that can be compared to Census Canada data.

Data on a community FIT screening program was obtained from the LIS of CLS for the first six and a half months of this program (November 18, 2013 to May 31, 2014). CLS is the sole provider of laboratory services to Calgary and surrounding areas (catchment population of 1.4 million persons). This date range was chosen as Alberta's new Colorectal Cancer Screening Clinical Practice Guidelines (CPG) were introduced in November 2013, introducing FIT screening for patients between the ages 50-74 years.

FIT collection kits are distributed to patients only through primary care physicians. Each patient was screened using one CRC screening kit. Samples were returned to CLS for testing on an automated analyzer, OC-Sensor Diana, with a positive cut off value of 75 ng/mL. All test results reported by CLS (and therefore all patients

receiving screening) were extracted into an excel file. Only individuals residing within the City of Calgary were included in the analysis. In cases where more than one test result existed per patient, the first test result was chosen for analysis and the others were removed from the dataset. Only patients included in the Alberta clinical practice screening guidelines (i.e. between the ages of 50 and 74) were included in the analyses.

Along with test results, month of testing, patient provincial health number, age, and sex were also extracted from CLS's LIS. Provincial health care numbers were then used to obtain each patient's postal code from an Alberta Health Services database. Postal codes were then used to assign individuals to Census Canada census dissemination areas. Following this linkage, all identifying information was removed from the dataset.

To graphically illustrate variations in FIT screening rates, hot spot analysis maps were produced using ArcGIS software v.9.3. The software uses the Getis-Ord G_i^* statistic [100], producing z-scores that identify statistically significant hot (increased screening) and cold (decreased screening) spots, depending on the standard deviations of the data from the mean in specific census dissemination areas.

Screening effort was then determined for each of the census dissemination areas by summing the number of patients tested in each age group (50-54, 55-59, 60-64, 65-69, 70-74) and sex cohort and dividing this by the number of individuals in that age and sex cohort present in that census dissemination area in the 2011 Canada census. That provided FIT screening rates for each census dissemination area. All FIT screening rates were compared to the following census Canada maps shown in Figures 5-11.

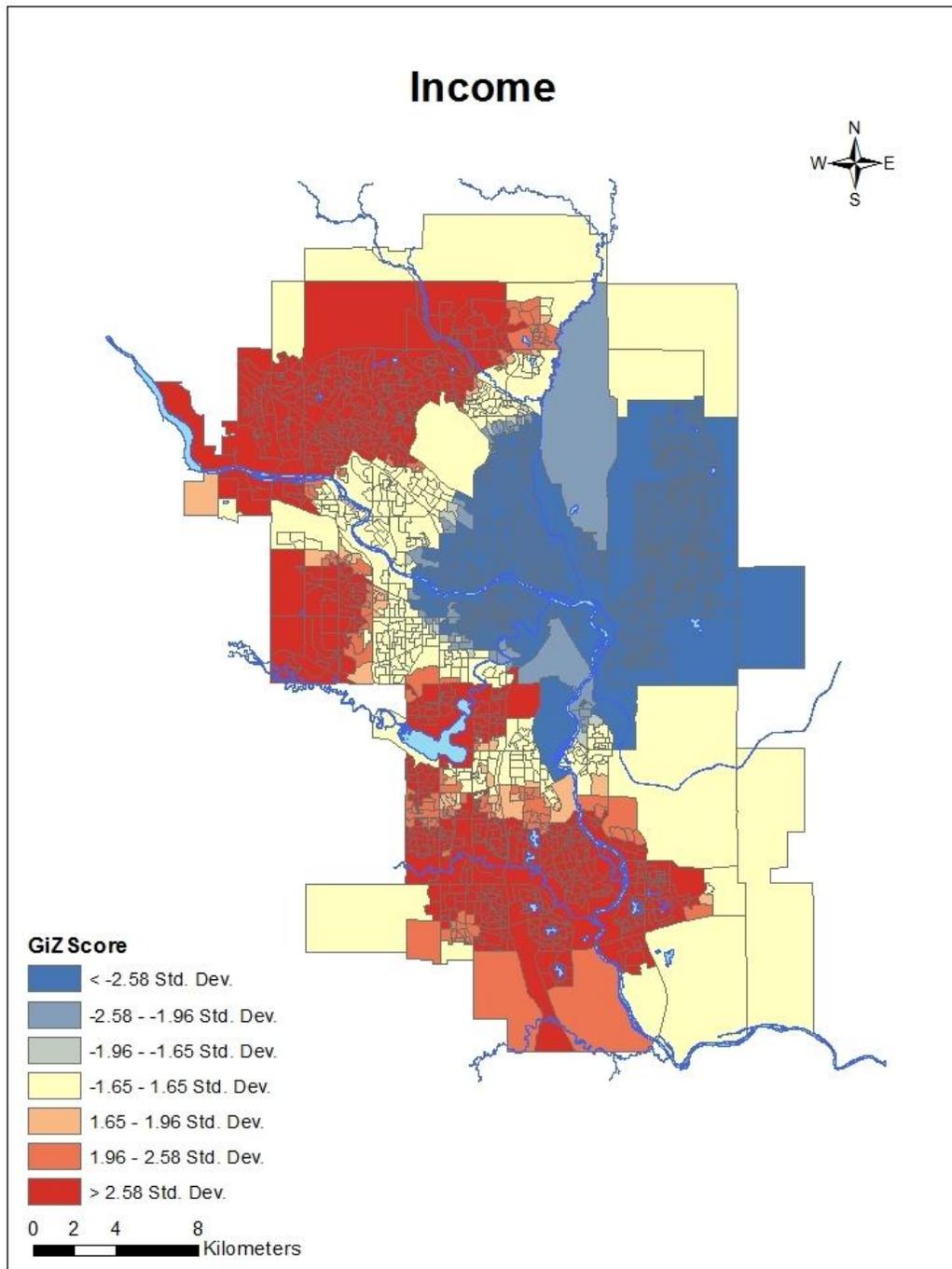


Figure 5 ArcGIS hot spot analysis of census Canada for Income in the city of Calgary, Alberta.

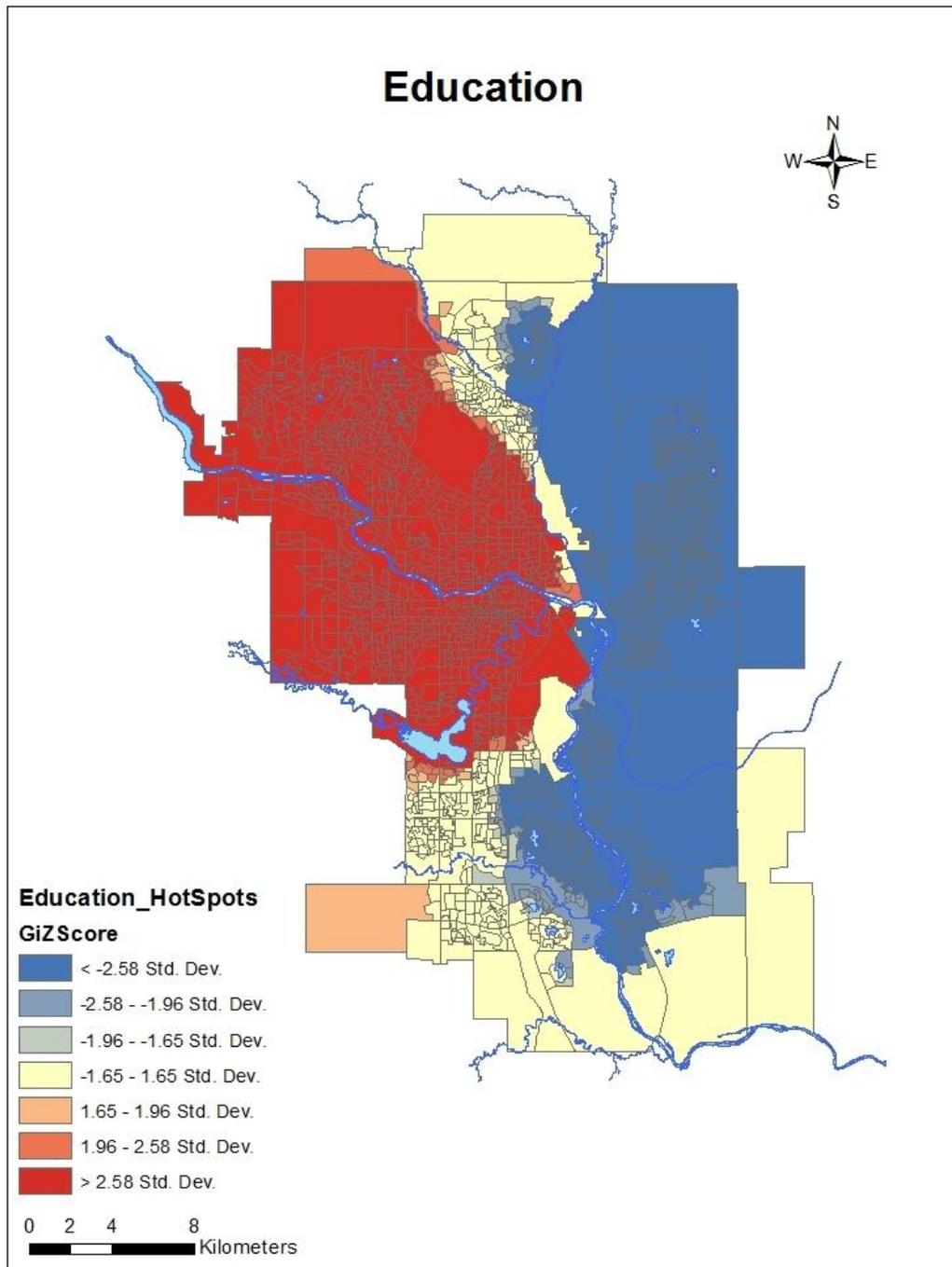


Figure 6 ArcGIS hot spot analysis of census Canada for Education in the city of Calgary, Alberta.

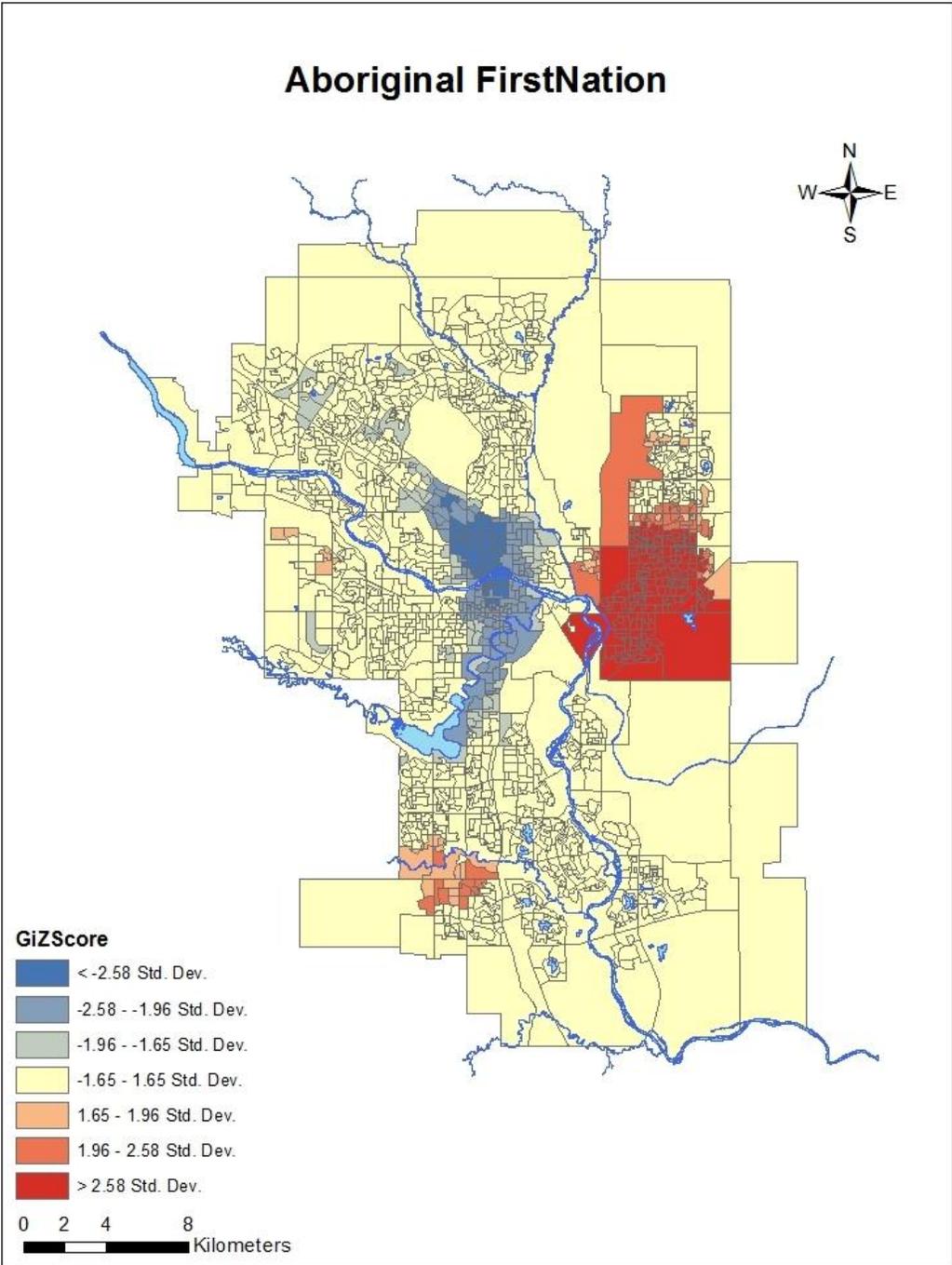


Figure 7 ArcGIS hot spot analysis of census Canada for Aboriginal First Nation in the city of Calgary, Alberta.

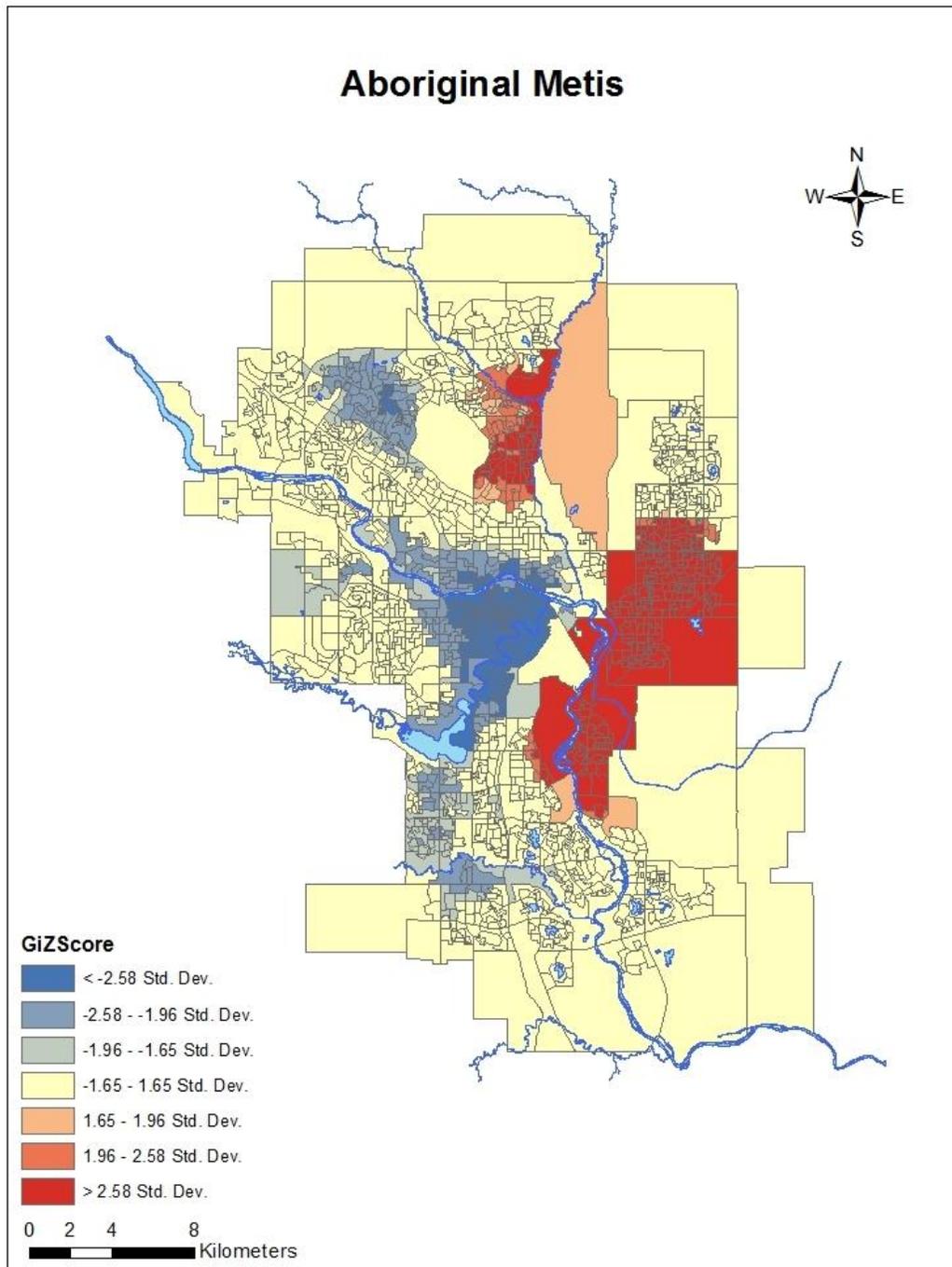


Figure 8 ArcGIS hot spot analysis of census Canada for Aboriginal Metis in the city of Calgary, Alberta.

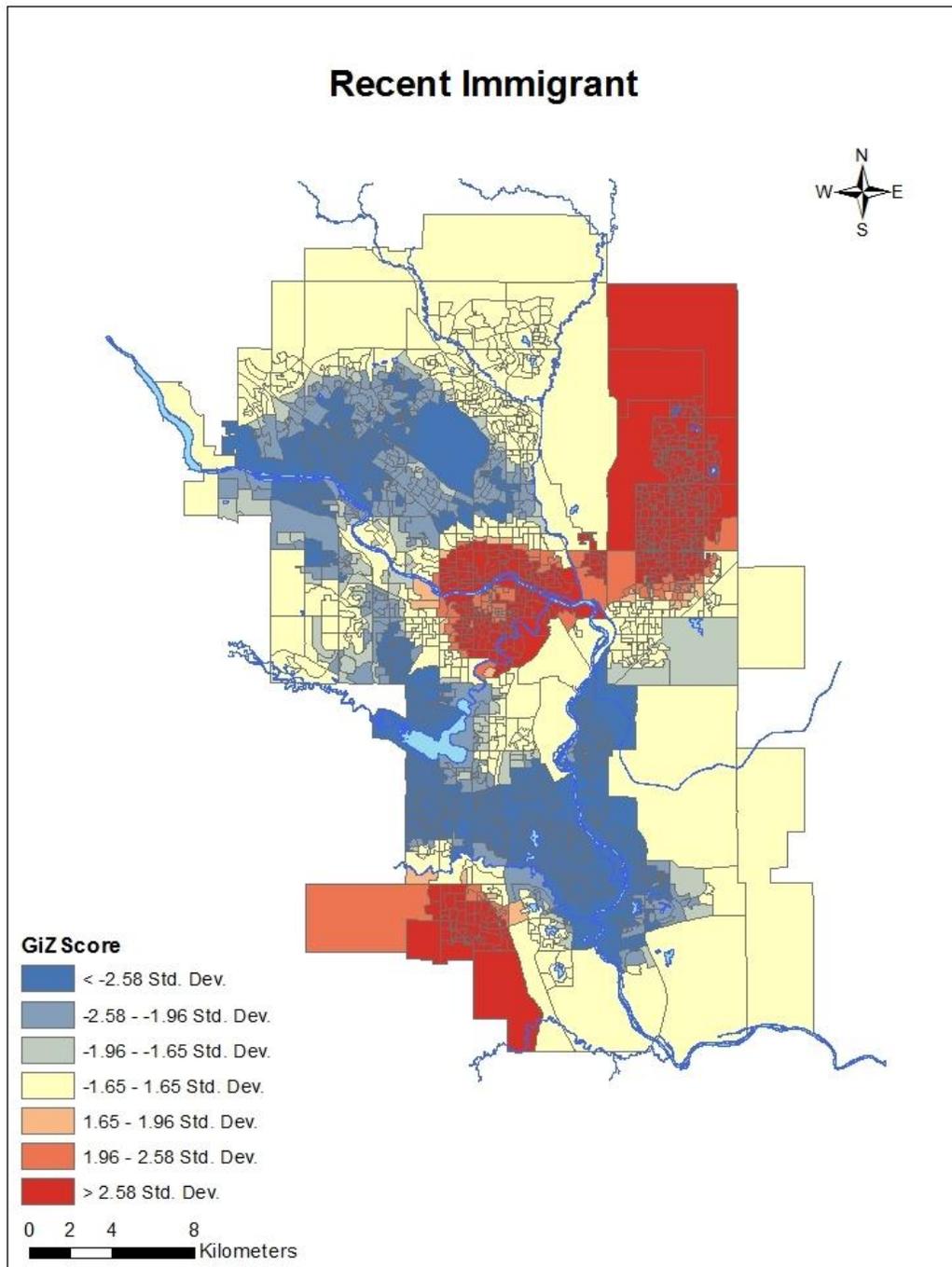


Figure 9 ArcGIS hot spot analysis of census Canada for Recent Immigrant in the city of Calgary, Alberta.

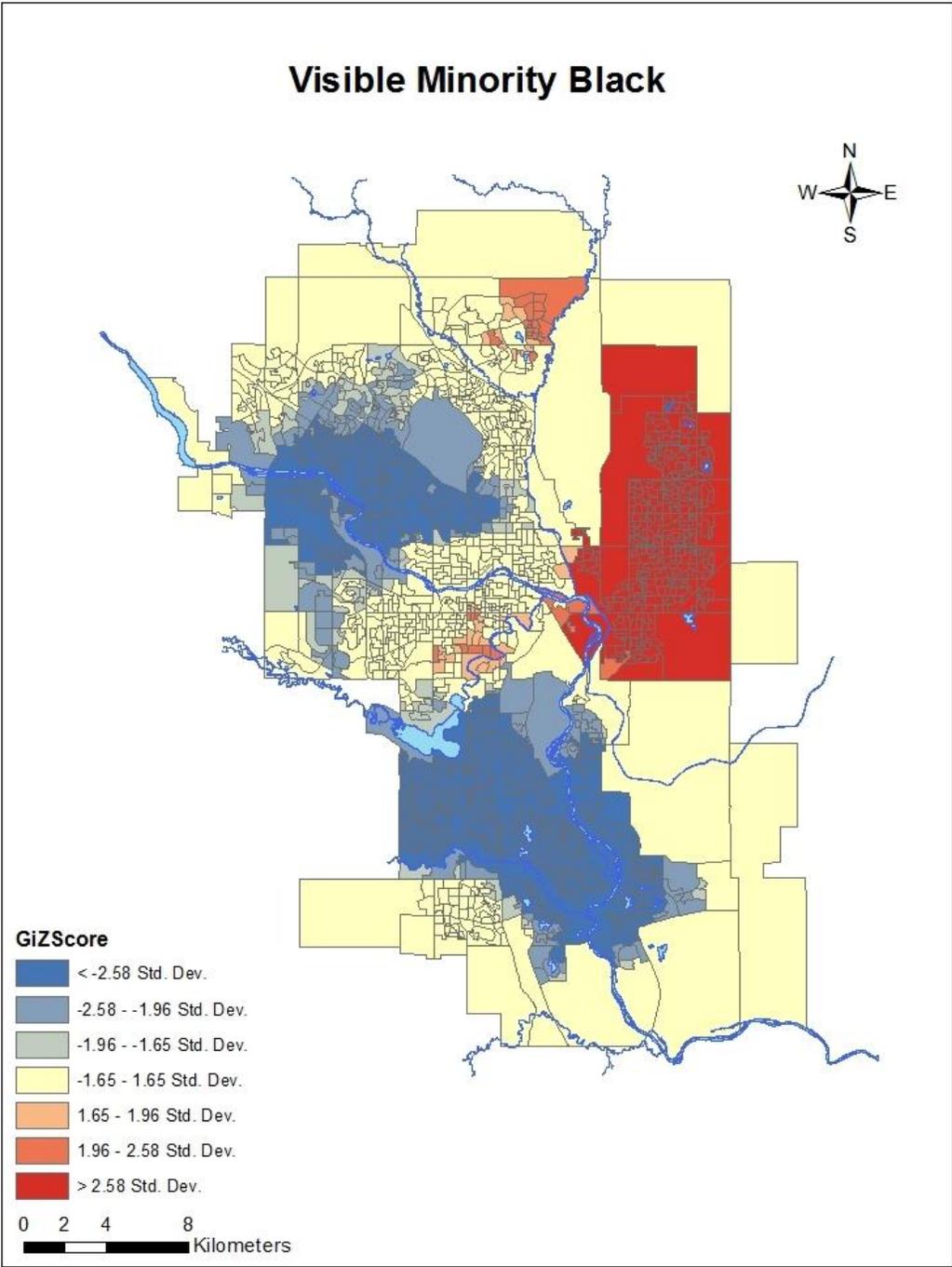


Figure 10 ArcGIS hot spot analysis of census Canada for Visible Minority Black in the city of Calgary, Alberta.

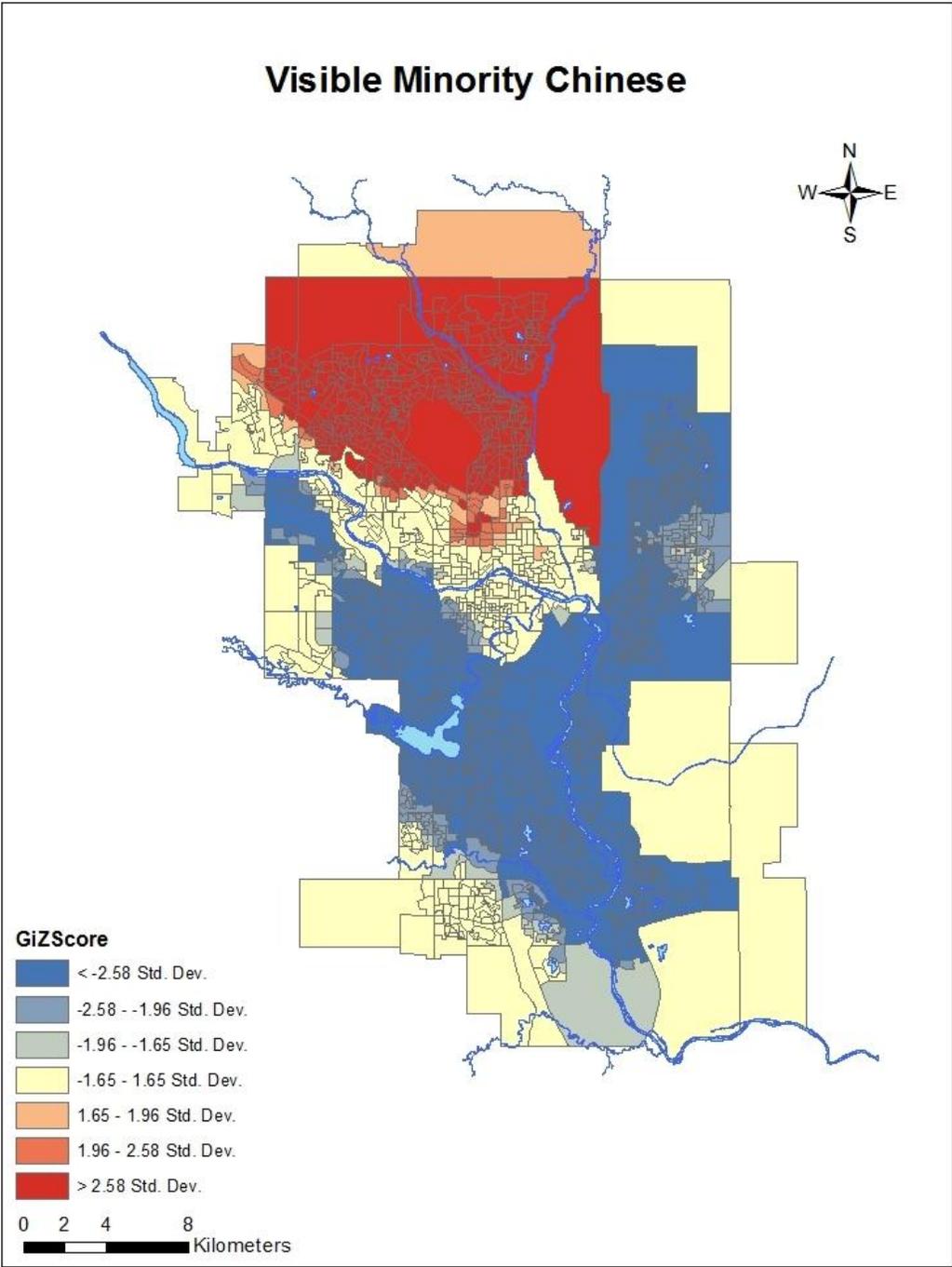


Figure 11 ArcGIS hot spot analysis of census Canada for Visible Minority Chinese in the city of Calgary, Alberta.

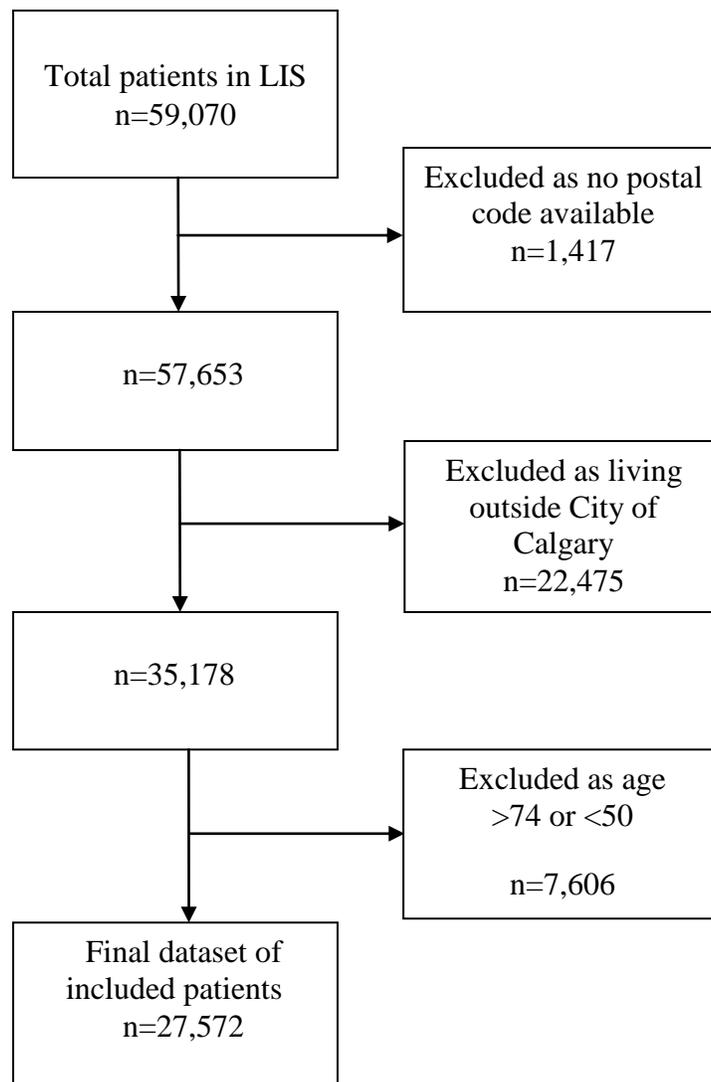
In addition to the individual level variables of age and sex, sociodemographic variables were inferred at the level of census dissemination area from the 2011 Canada census. Group level sociodemographic variables considered included: recent immigration status (immigrated within the last five years), Aboriginal First Nations, Aboriginal Metis, Census Canada defined visible minority status “Chinese”, visible minority status “Black”, education level, and median household income. Chinese and Black ethnic groups were chosen for analysis as they were the largest minority groups within Calgary.

Statistical inference regarding sociodemographic variables associated with testing rate was performed using the generalized estimating equations (to account for the hierarchical nature of the data) version of Poisson regression in SAS v.9.2. Coefficients for all models were considered statistically significant if their associated P values were <0.05. The statistical significance of each variable was assessed independently with categorical variable (age group and sex) held constant at an arbitrary reference state, sociodemographic variables held constant as the absence of that variable and the sole continuous variable (median household income) reported as the significance of each increase in income of \$100,000 CDN. Visible minority groups were referenced to all other ethnic groups not included in this model. Finally, the differences in screening rates associated with individual sociodemographic variables are reported as relative risk (RR) for the independent contribution of that variable to the analysis.

4.3 Results

Data on 59,070 FIT results were available in our LIS, of which 27,572 results met our inclusion criteria shown in Figure 12.

Figure 12 Study flow diagram.



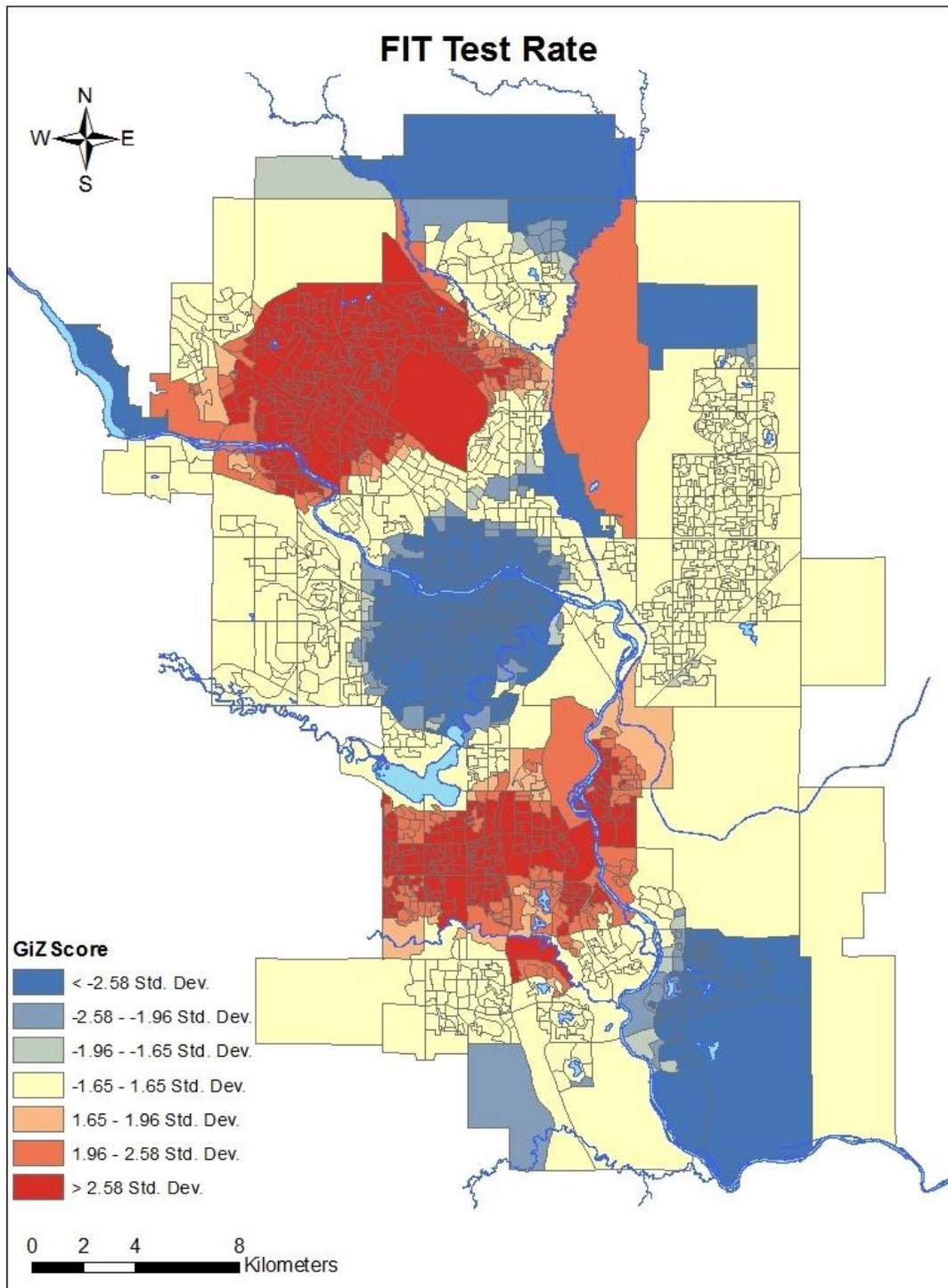


Figure 13 ArcGIS hot spot analysis of FIT screening rates in the city of Calgary, Alberta.

The ArgGIS hot spot analysis illustrates significant differences in screening rates throughout the city (Figure 13). Fecal immunochemical screening rates varied among neighbourhoods from a low of 0.2% to a high of 25.8% in the first 6.5 months of the screening program. Using a cut off of 75ng/mL to define a positive test, the positivity rate for the period covered in this study was 9%. The mean screening rate during this period was 2.8%. Table 9 shows the sociodemographic variables associated with FIT screening rates. There were multiple inequities in screening rates associated with sociodemographic groups. Specifically, recent immigrants (RR=0.18, P=<.0001), Aboriginal First Nations (RR=0.39, P=0.01), Aboriginal Metis (RR=0.14, P=0.0003), visible minority “Black” (RR=0.35, P=0.0002), and those with a university education (RR=0.65, P=<.0001) were less likely to be screened, compared to all other age groups. Visible minority “Chinese” (RR=1.72, P=<.0001), however had a higher screening rate. Interestingly, any increase of household income by \$100,000 was not significantly associated with screening rate (P=0.08). The age group of 70-74 was the least likely to be screened. Screening rates increased with each younger age cohort. Overall, females had a slightly lower rate of screening than males (RR=0.95, P=<.0001). Screening rates for males and females are shown in ArgGIS hot spot analysis maps (Figures 14 and 15).

Table 9 Sociodemographic variables and FIT screening rates in Calgary, Alberta.

Sociodemographic Variable	Parameter Estimate	95% Confidence Limits		P Value	Relative Risk
Female	-0.05	-0.07	-0.03	<.0001	0.95
Age group 50-54	0.55	0.51	0.60	<.0001	1.74
Age group 55-59	0.43	0.39	0.48	<.0001	1.54
Age group 60-64	0.32	0.28	0.36	<.0001	1.38
Age group 65-69	0.23	0.19	0.27	<.0001	1.25
Recent Immigrant	-1.69	-2.15	-1.23	<.0001	0.18
Aboriginal First Nation	-0.93	-1.65	-0.22	0.01	0.39
Aboriginal Metis	-1.95	-3.01	-0.90	0.0003	0.14
Visible Minority Chinese	0.54	0.27	0.80	<.0001	1.72
Visible Minority Black	-1.04	-1.59	-0.49	0.0002	0.35
University Education	-0.44	-0.65	-0.22	<.0001	0.65
Median Household Income (\$100,000 CDN)	-0.61	-1.28	0.06	0.08	

*Males were used as reference for females. Age group 70-74 years were used as reference for all other age groups. All other ethnic groups, not used in the model, were used as reference for those groups included for analysis.

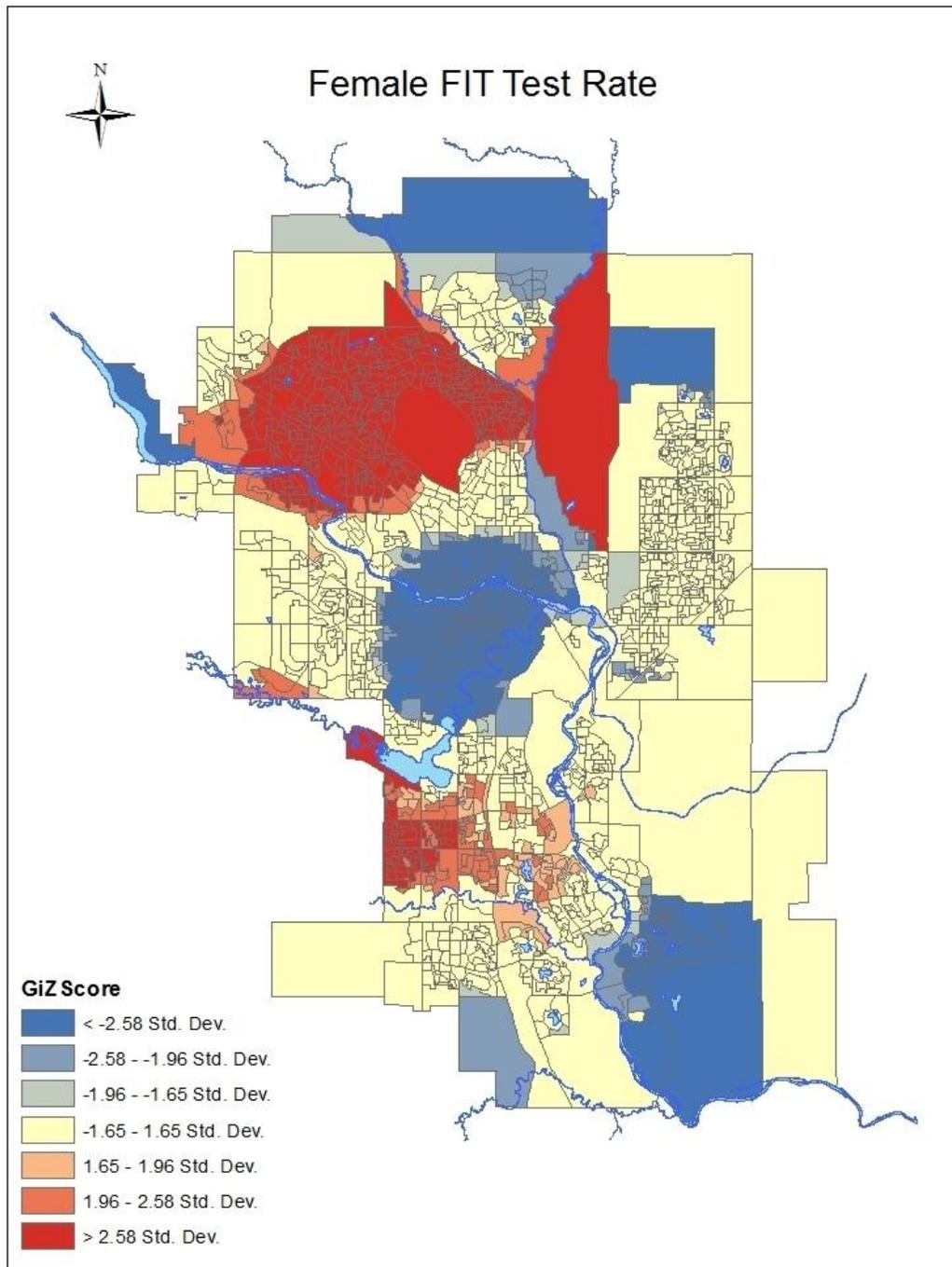


Figure 14 ArcGIS hot spot analysis of FIT screening rates in the city of Calgary, Alberta.

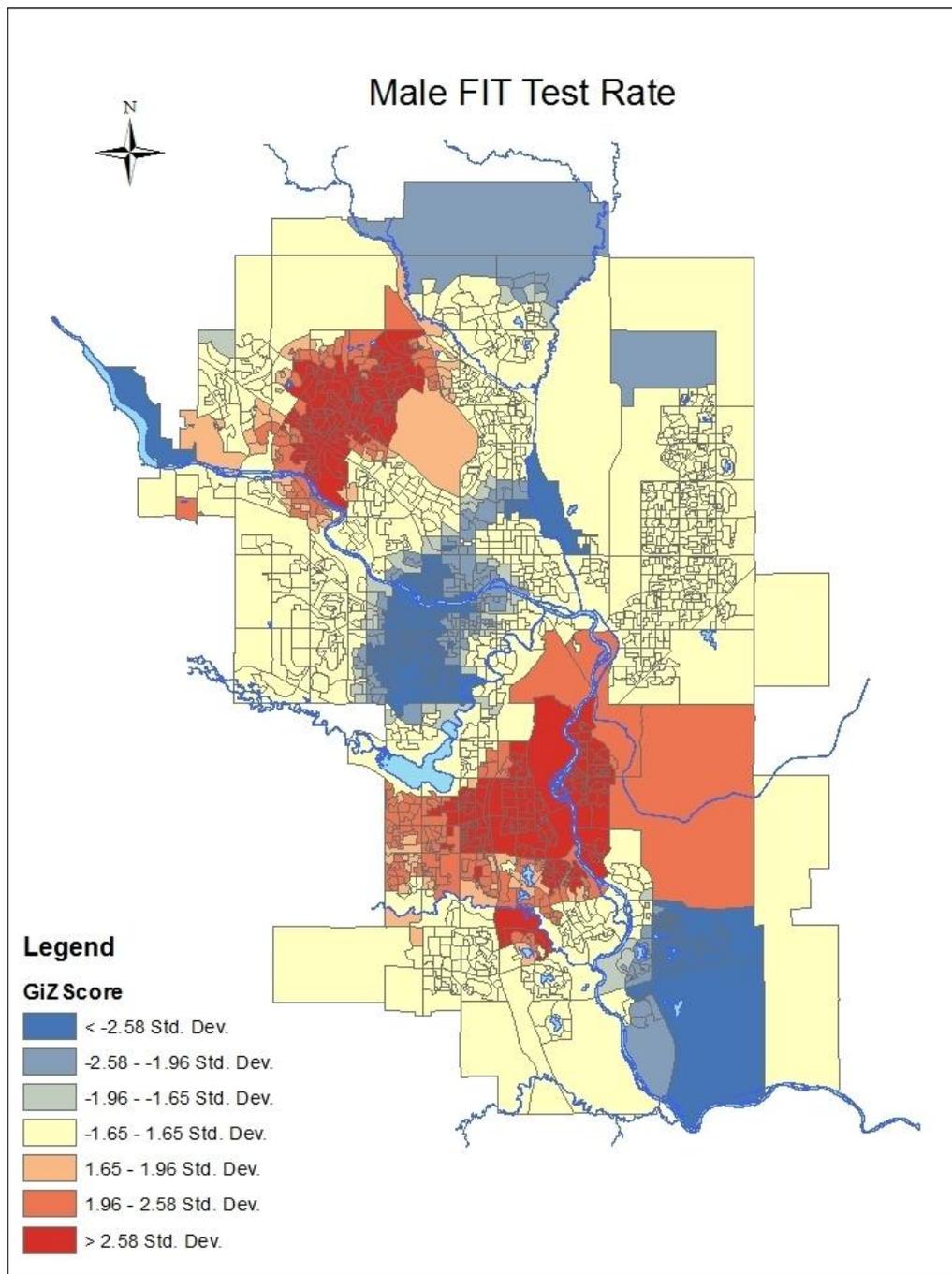


Figure 15 ArcGIS hot spot analysis of FIT screening rates in the city of Calgary, Alberta.

4.4 Discussion

Community CRC screening programs are still relatively new in Canada, with all provinces having organized programs, but none of the three territories, having one in place [6, 66, 97]. Accordingly, Canadians are more aware of screening for other cancers, with men 2.7 times more likely to be up to date with Prostate Specific Antigen (PSA) testing and women 2.4 times more likely to be up to date with breast and cervical cancer screening [3, 6], even though CRC has a higher fatality rate for both sexes [101]. There are also differences among provinces, with some conducting mailed invitation letters and FIT tests to patient homes, while others have physician based referral screening programs, such as those in Alberta and Ontario [4, 6, 11, 90, 97, 101, 102].

Sociodemographic variables are also believed to play a role in which individuals are being screened. In this study, there were marked differences in FIT screening rates among sociodemographic groups. In contrast to previous reports which found a correlation between higher socioeconomic status and higher education associated with higher screening rates [4, 5, 10, 15, 91, 92, 97, 102, 103], this study indicated a reverse correlation with higher education associated with lower screening rates (Table 1). It is believed that this unexpected association may be due to individuals with higher education bypassing FIT screening and accessing colonoscopy as a primary screening modality. This is a topic for further study in our population.

The ethnic differences observed may be due in part to decreased access to primary care physicians among certain groups. Indeed, studies have found that recent immigrants tend to use walk in clinics for health care services when first moving to Canada [11, 104]. Also, the use of walk in clinics for groups such as recent immigrants can have the

complication of language barriers, making it hard for groups to understand the importance of CRC screening [94, 95]. This finding is consistent with an older United States study which found that blacks were less likely to be screened for CRC [27].

Also observed were age and sex differences in screening rates with higher participation rates among men and younger individuals. Again the reasons for this are unclear but may be influenced by barriers such as a lack of patient awareness, lack of physician recommendation, lack of confidence in the screening program, and a negative connotation for handling stool specimens [6, 16, 67, 68, 91, 93, 97, 102]. Lower FIT screening rates in older individuals may be due to a physician's belief that as patient's get older, a more appropriate diagnostic tool is colonoscopy [105] due to the higher risk in older patients [32].

Previous studies examining sociodemographic correlates of laboratory testing for vitamin D [12] and PSA [30] in Calgary also reported similar sociodemographic associations with testing rates. Therefore the trends observed in this study may be representative of broader inequities in health care access within the city.

Some strengths of this study were that it was a community-based program. This allows all eligible individuals to be screened by FIT with no cost and it has the potential to increase participation of CRC screening [91]. The study also had a large sample size and as CLS performs all of the FIT analyses for the city, our dataset showed a complete picture of screening effort for Calgary. There were also several weaknesses within the study. Firstly, as in a number of other programs, FIT kits were given to patients directly by their physicians [22, 73, 96, 106]. Therefore, it is unknown if the results we report are due to variation in access to primary care physicians. Individuals without a family

physician may not be aware of the FIT screening program [96, 107] or may be unable to access the screening kits. Secondly, for patients who have a family physician, it is unknown if there is any physician bias in terms of who is being referred for screening [91, 93, 106]. Although, all individuals are to be screened between the ages 50-74 years, not all physicians may be following these guidelines [67, 68, 73, 107]. It was also difficult to identify individuals who were being tested due to symptoms or were at higher risk due to family history. The attempt to control for was done by only including individuals between the recommended ages, as many individuals with a family history of CRC begin the screening process before 50 or receive colonoscopy as their main screening source [37, 39, 108], but a small proportion of individuals may have been high risk patients. Thirdly, it cannot be accounted for patients who are not compliant with completing screening kits after their physicians recommend screening [67, 68, 93, 109]. Lastly, a potential limitation is the time lag between the 2011 census data and the start of the FIT screening in 2013. As census Canada only comes out every five years, it is difficult to exactly align census data with new data testing programs. This has also been a limitation in previous published works [99]. In the context in this study however, it is important to note the areas of Calgary undergoing the greatest demographic change are at the periphery of the city, where new neighbourhoods are constantly being built. These tend to coincide with under testing in our analysis; the expected interval population growth would mean that the associations we describe maybe even more pronounced than the results we suggest.

Further work could include following this population over time to assess long term changes in screening. For example, Honein-AbouHaidar et al [91] reported an

increase in screening after the initial release of their screening program, with a slight decline afterwards.

In conclusion, the results show that there are marked differences in FIT screening rates among sociodemographic groups at the start of a new community screening program in Calgary, Alberta.

Chapter four of this thesis has been published in a peer-reviewed publication and presented as a poster presentation at the University of Pathology, Department of Pathology and Laboratory Medicine Annual Residents' & Graduate Students' Research Day.

- Crouse, A., et al., *Sociodemographic correlates of fecal immunotesting for colorectal cancer screening*. Clin Biochem, 2015. 48(3): p. 105-9.
- Crouse A, Sadrzadeh H, de Koning L, Naugler C. *Sociodemographic factors affecting fecal immunotesting for colorectal cancer screening*. Poster presentation, University of Pathology, Department of Pathology and Laboratory Medicine Annual Residents' & Graduate Students' Research Day, 07 Nov 2014.

Chapter Five: **Conclusions and Future Research**

5.1 Conclusions

This study focused on a community screening program for CRC, looking at the forms of screening and the sensitivity and specificity for an accurate FIT screening test. The sociodemographic factors that can affect who are participating in this type of screening program were also looked at. Colorectal cancer is one of the most common cancers in Canada. With the current guidelines in place for CRC screening, the implications for screening can create a more favourable prognosis through the detection of CRC at an earlier stage [20]. With low screening rates across Canada, the possibility of diagnosing more patients with CRC at an earlier stage is less likely.

With the use of operational characteristics of a FIT screening program, a sense of what makes a good CRC screening test was better understood. By evaluating the screening method to find the optimal sensitivity and specificity of a test, patients can correctly be identified as having a disease or not having a disease. Sensitivity is the ability of a test to correctly identify patients with a disease and specificity being the opposite, with the ability of a test to correctly identify patients without a disease [48]. The use of a ROC curve allowed the demonstration of ideal sensitivities and specificities with CLS cut off of 75ng/mL for FIT screening. The ROC curves showed that FIT was a sensitive indicator for colorectal carcinomas, but less so for precursor colonic adenomas. By breaking down the sensitivities and specificities even further into advanced adenoma (including sessile serrated adenoma, villous adenoma, and tubulovillous adenoma) and carcinoma as well as comparing males and females greater than or equal to and less than

the mean age of 62, a clearer view of test performance emerged. The sensitivities and specificities from these groups clearly illustrate that FIT screening is most sensitive for carcinomas. It was slightly higher for males compared to females, but was the highest for individuals over the mean age of 62 with 100% sensitivity. The PPV of this study was also similar to other studies [83, 84, 86, 87], with a PPV of 53%. Overall, this shows that screening with FIT alone can miss early lesions, which could possibly be detected through screening with colonoscopy. These results indicate that FIT screening cannot be considered equivalent to colonoscopy for detecting colonic adenomas.

By moving the knowledge of what makes an ideal screening test into an operational pilot program within Calgary, Alberta, a visual representation through geomapping can show some of the inequalities of a screening program. Colorectal screening is being underutilized throughout all of Canada [6, 71] and a better understanding of why this is the case is needed before anything can be done to boost these rates [97]. The reason behind low screening rates is not known, but previous research has shown this can be due to sociodemographic factors such as minority ethnicity, education, income, sex, and age [91-93]. These factors can have a direct correlation with poor health care knowledge, physician bias towards screening programs, language barriers, and reduced access to health care among certain sociodemographic groups [11, 22, 90, 94-96] By looking at sociodemographic factors throughout Calgary and mapping these finding with the use of geomapping, I showed that there are many differences in FIT screening rates among many different sociodemographic groups within the first six months of the new community screening program.

Of the sociodemographic factors looked at in this study, there were a number of factors that were statistically significant. By looking at the relative risk for the significant factors, a better sense of who was not participating in the screening program was determined. Groups such as recent immigrants and those who were Black were less likely to be screened. Those who were Chinese were more likely to get screened over other groups. Most surprising was that household income did not have an influence on screening rates and those with a university education were being under screened. It was believed that these factors would be positively correlated with each other; with individuals having a higher education, having a higher income. These individuals were believed to have more knowledge of possible screening programs as they may be more likely to have family physicians. This may be due to the fact that these individuals are bypassing the screening process altogether and accessing colonoscopy as their primary screening tool, as this is the gold standard for CRC screening.

5.2 Future Research

From the operational characteristics and the operation of a pilot FIT screening program, some inequalities were identified. Firstly, it is important to note that FIT is a screening test for cancer, not for colonic neoplasia. It is hard to determine if the general population know what they are actually being screened for with FIT. Many may think it is more geared towards finding adenomas, not cancer. This is not a topic that can be answered from this study, but could be addressed with further research through surveys asking patients and physicians what they believe FIT screening is directed towards. If the general population knew specifically what they are being screened for, they may be more apt to participate.

Secondly, there may be a bias of who is being screened for CRC. This is a concept brought about when looking at sociodemographic factors and whether patients have access to a primary care physician and whether those physicians have a procedure in place in recommending CRC screening to their patients. As the pilot screening program in Alberta is distributed through primary care physicians, patients need to be in contact with a physician to receive screening kits and possibly know about the screening program. Even patients regularly visiting their family physician may not be participating in the screening program, depending on their physician's belief in the screening program and whether they are following the screening guidelines. Some physicians could even be bypassing the FIT screening program altogether, opting for colonoscopy as their screening method. Sociodemographic factors of individuals having colonoscopy over FIT screening may also give more insight of which individuals are opting for colonoscopy as their primary screening choice.

Any bias towards FIT screening by physicians could possibly be eliminated by mailing invitation screening kits. This would eliminate the need for eligible patients to get the screening kits from their family physician, as a kit would be directly mailed to their home. A comparison among provinces with physician based programs and mailed based programs could be useful in showing if one was more compliant over the other. Unfortunately, there is no data on provinces with mail invitation screening programs. A study in a province with this type of screening program would help facilitate this type of future research. Previous studies in the United States have shown that patients are most compliant to screening when they are mailed a screening kit and the screening is recommended by their physician, even mailed invitation letters from their physicians have helped patients pursue CRC screening [67, 93, 110].

Lastly, the implications of having FIT as the primary screening method for CRC has to be considered. Fecal immunochemical testing is a good indicator for carcinoma, but is much less sensitive for adenomas. This may have implications for the future epidemiology of CRC and may alter future referral patterns.

This research can be taken further than these two future areas of research. This research has shown that there are many sociodemographic factors throughout all of Calgary that are being under screened. The next obvious step would be developing interventions targeting underserved populations that are not getting FIT screening community screening programs.

As CRC screening programs evolve, data from testing laboratories can be used to study the potential impact on long term CRC epidemiology.

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