The Effect of Sociodemographic and Health System Factors on the Association Between Multimorbidity and Colorectal Cancer Survival

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

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Abstract

Objectives: This thesis aimed to assess the effect of multimorbidity (MMB) on colorectal cancer (CRC) patients' survival and explored whether sociodemographic and health system factors affected this relationship or not. This thesis also describes the complexity of CRC patients through the description of condition combinations and related health services use.

Methods: A retrospective cohort study was conducted using administrative data from the Institute for Clinical Evaluative Sciences (ICES). The population was adult Ontario residents who were diagnosed with CRC between 2003 and 2013 and were followed until March 31, 2018. The exposure of interest, MMB, was defined as having one or more of 17 common conditions in addition to CRC and categorized (1, 2, 3, 4 or more). Conditions diagnosed prior to or within 30 days of CRC diagnosis were included. Survival analyses were performed using Cox proportional hazards regression to assess the association between MMB and CRC patients' survival. To investigate additional factors associated with CRC patients' survival, Cox models were adjusted for sociodemographic (age, sex, income, ethnicity, and rurality) and health system factors (primary care models (PCMs), continuity of care (COC), and primary care (PC) visits) as well as cancer stage.

Results: Among the 67,520 adult Ontario residents diagnosed with CRC, most (83.1%) had MMB. Overall, the most prevalent comorbid condition was hypertension (58%), followed by osteoarthritis (35.4%), diabetes (23.7%), anxiety (22.9%), and chronic coronary syndrome (17.7%). Multiple combinations of conditions were identified, and an increase in the number of condition combinations was observed as the level of MMB (i.e. the number of additional conditions) increased. Compared to CRC patients without MMB, those who had 3 conditions or 4 or more conditions prior to cancer diagnosis had a greater risk of mortality. The risk of death

was 1.06 times (aHR 1.06, 95% CI: 1.02-1.10) greater for CRC patients with 3 comorbidities, and 1.30 times (aHR 1.30, 95% CI: 1.25-1.35) greater for CRC patients with 4 or more comorbidities, compared to those with CRC only. Patients with regular PC visits had a lower risk of death than those with 1 or fewer PC visits per person-years. CRC patients with 2 to 3 PC visits per person-years had the lowest risk of death and were 61% less likely to die than those with 1 or fewer PC visits. Compared to patients with high COC (1.00), those with low COC (<0.50) had a 7% greater risk of death (aHR 1.07, 95% CI: 1.04-1.10). A slightly higher risk of death was observed for patients rostered in capitated and capitated + primary care models, who were 7% and 5% more likely to die than patients in non-capitated models, respectively (aHR 1.07, 95% CI: 1.04-1.10; aHR 1.05, 95% CI: 1.01-1.09).

Conclusions: MMB is prevalent among CRC patients in Ontario. Many conditions exist alongside CRC, and each combination of conditions has a unique impact on survival. COC and health services factors such as capitation may also affect outcomes for people with CRC and MMB.

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List of Abbreviations

aHR – Adjusted Hazard Ratio

CRC – Colorectal Cancer

CI – Confidence Interval

COC – Continuity of Care

DAD – Discharge Abstract Database

HR – Hazard Ratio

ICES – Institute for Clinical Evaluative Sciences

IDAVE – ICES Data & Analytic Virtual Environment

MMB – Multimorbidity

NACRS – National Ambulatory Care Reporting System

OCR – Ontario Cancer Registry

OHIP – Ontario Health Insurance Plan

ON-Marg – Ontario Marginalization Index

PC – Primary Care

PCM – Primary Care Model

Ref. – Reference Category

RPDB – Registered Persons Database

Overview of Thesis Content

This thesis is organized into six chapters. The first chapter provides a general introduction to the study topics; colorectal cancer, multimorbidity, cancer survival, and a brief discussion of the healthcare systems and services relevant to cancer patients with multimorbidity. The second chapter is the literature review, which synthesizes what is known about the study topic and identifies current knowledge gaps. The third chapter provides an overview of the thesis methodology, which includes the study objectives and hypotheses, thesis approach, conceptual framework, and ethical considerations. The fourth chapter provides the methods used to address each of the study objectives. The fifth chapter presents the results obtained through the analyses. The sixth chapter is a summary of the study findings, their epidemiological implications, and future research directions as well as the strengths and limitations of the design.

Chapter 1: Introduction

Colorectal cancer (CRC) is the third most common cancer in the world (Bray et al., 2018) after lung and breast cancers, and the second most common cancer in Canada after lung cancer (Canadian Cancer Statistics Advisory Committee, 2018). According to Statistics Canada, it is also the third most common cancer in the Province of Ontario (Government of Canada, 2018b). In 2017, there were 7,645 new cases of CRC and its age-standardized incidence rate was 50.2 per 100,000 (Government of Canada, 2018b). Although the mortality rate for CRC has decreased in recent years, likely due to improvements in cancer screening and treatment, it remains the second leading cause of cancer death in Ontario after lung cancer (Cancer Care Ontario, 2018). There were 3,030 deaths attributed to CRC in 2013 with an age-standardized mortality rate of 21.6 per 100,000 (Cancer Care Ontario, 2018).

Both the incidence of cancer and the prevalence of chronic conditions rise with age (Sarfati et al., 2016; Wu et al., 2015). As individuals aged 50 and older have a greater risk of CRC and represent 90% of new cases (PDQ Screening and Prevention Editorial Board, 2018), cancer is often diagnosed amidst other conditions (Sarfati et al., 2016; Wu et al., 2015). Multimorbidity (MMB) is defined as the co-existence of multiple conditions in an individual (Smith et al., 2012). MMB is common in cancer patients for several reasons; cancer and chronic conditions have shared risk factors, certain chronic conditions or their treatments may cause cancer and physiological pathways between cancer and chronic conditions exist (Sarfati et al., 2016). MMB can include two conditions other than cancer, however it is likely that cancer and another condition will co-exist. Furthermore, the term multimorbidity regards all conditions as equal importance, with no condition taking precedent over the others (Radner et al., 2014). The concept of multimorbidity is more patient-centered and broader than comorbidity alone as it recognizes that conditions can potentially interact and may be related physiologically (Radner et

al., 2014). Comorbidity refers to an additional condition that exists alongside an index condition (in this case, CRC) (Valderas et al., 2009). Additional conditions can impact cancer diagnosis, treatments and outcomes. Cancer patients with comorbidities are less likely to receive standard treatments, are more likely to experience adverse drug interactions and are more likely to have poorer outcomes than patients with cancer only (Sarfati et al., 2016; Søgaard et al., 2013). Several studies have reported that approximately one-third of CRC patients have at least one other condition (Cuthbert et al., 2018; Edwards et al., 2014; Ostenfeld et al., 2013) and have shown that comorbidity negatively impacts survival (Erichsen et al., 2013; Gross et al., 2006; Iversen et al., 2009).

While it is recognized that multimorbidity makes cancer care more complex, the current healthcare system is not equipped to meet the needs of these individuals. The term "complex" acknowledges that patients not only has multiple health conditions but also recognizes that other factors such as socioeconomic status, access to health care, mental health and immigration status have an impact on overall health (Manning & Gagnon, 2017). Complexity also refers to the care needs of patients with multimorbidity. Care for patients with multimorbidity is complex for many reasons, including the involvement of multiple providers and sites of care, clinical guidelines with a single disease focus, and the management of conditions with multiple medications (Boyd & Fortin, 2010). Therefore, complexity in this study refers to the patient, their broader health situation, and their care needs.

Cancer patients with comorbidity require care from siloed healthcare systems such as oncology and primary care to manage the competing demands of their conditions. In addition, healthcare services are organized and delivered with a single-disease focus (Doessing & Burau, 2015). As such, these patients are more vulnerable to fragmented care (Doessing & Burau, 2015)

and are at risk of poorer quality of life and outcomes (Sarfati et al., 2016). Similarly, evidence to inform cancer care guidelines is largely based on the management of single conditions, as those with MMB are generally excluded from clinical trials (Mazza & Mitchell, 2017). Patient-centered approaches to healthcare present an opportunity to move away from a single-disease focus and include patients in decisions about their care (Entwistle & Watt, 2013). The Ontario Medical Association (2010) defines patient-centered care as follows: "A patient-centered care system is one where patients can move freely along a care pathway without regard to which physician, other health-care provider, institution or community resource they need at that moment in time. The system is one that considers the individual needs of patients and treats them with respect and dignity" (p.34). Moreover, patient-centered care prioritizes the needs of the patient over the needs of service providers (Entwistle & Watt, 2013). Care is planned and delivered with the patient as an equal partner, rather than through a one-size-fits-all model (Entwistle & Watt, 2013).

Further research is needed to understand how patient factors and comorbid conditions impact outcomes for cancer patients, as these are necessary considerations for patient-centered care. While studies have established that comorbidity adversely impacts cancer survival, research on specific conditions and combinations of conditions is limited. The majority of the current research is based on comorbidity indices or condition counts that assess overall burden but that do not consider clinically relevant conditions or disease combinations. Describing condition combinations may provide opportunities to target care management to better meet the needs of particular patient groups while identifying areas for further research. Similarly, assessing the impact of specific health system factors is essential to health system reform and policies that will benefit patient-centered care for complex cancer patients. The purpose of this study, therefore, is

to examine CRC patients' complexity and to determine if sociodemographic and health system factors have an effect on the association between MMB and CRC patients' survival or not.

Chapter 2: Literature Review

This study aims to assess the effect of MMB on CRC patients' survival and to explore whether sociodemographic and health system factors affect this relationship or not. Therefore, the existing literature was searched for relevant studies pertaining to MMB and outcomes among cancer patients, particularly those with CRC. Moreover, the current body of literature was carefully reviewed for peer-reviewed publications and reports about MMB in CRC patients, and the impacts of MMB, sociodemographic, and health system factors on outcomes in CRC patients. For example, PubMed was searched using relevant keywords and MESH terms such as (((((((comorbidity) OR "Comorbidity"[Mesh]) OR comorbid*)) OR (((Multimorbidity) OR "Multimorbidity"[Mesh]) OR multimorbid*))) AND (("colorectal cancer") OR "Colorectal Neoplasms"[Mesh]))) AND ((survival) OR mortality).

The literature retrieved during these searches is described below.

2.1 Colorectal Cancer

Cancer is a complex disease characterized by the abnormal division and growth of cells (Canadian Cancer Statistics Advisory Committee, 2019). This disease presents a huge burden on the health of Canadians and the healthcare system as a whole. As the leading cause of death nationally, cancer accounts for nearly 30% of Canadian deaths (Canadian Cancer Statistics Advisory Committee, 2019). Cancer is also the leading cause of premature death in the country, meaning that those who die from cancer are younger than the average age of death from other causes (Canadian Cancer Statistics Advisory Committee, 2019).

Cancers are classified based on the primary cancer site. CRC includes cancerous growths of the colon and rectum (Canadian Cancer Society, 2017). As these organs are composed of the same tissues and do not have a definite border they are often grouped (Canadian Cancer Society, 2017). Generally, CRC begins with a benign (non-cancerous) growth called adenomatous polyps

(adenomas) that can later develop into a malignancy (cancer) (Public Health Agency of Canada, 2017). Cancer can spread to other sites in the body. This is referred to as metastasis, meaning a secondary malignant growth away from the primary cancer site (Canadian Cancer Society, 2017).

Globally, CRC is the third most commonly diagnosed cancer (Bray et al., 2018; World Health Organization, 2018). Among women, CRC has the second highest incidence after breast cancer and among males, it is ranked third preceded only by lung and prostate cancers (Bray et al., 2018; Favoriti et al., 2016). Roughly 1 in 10 cancer deaths were attributed to CRC in 2018 around the world (Bray et al., 2018). In Canada, CRC represented the third most commonly diagnosed cancer after lung and breast cancers, and the second leading cause of cancer death after lung cancer in 2019 (Canadian Cancer Statistics Advisory Committee, 2019). Nationally, CRC is the second and third most common cause of cancer death in men and women respectively (Canadian Cancer Statistics Advisory Committee, 2019). Among Ontarians, CRC was the second most frequently diagnosed cancer and the second highest cause of cancer death in 2018 (Cancer Care Ontario, 2018). More males than females were diagnosed with CRC with an age-standardized incidence rate of 86.2 per 100,000 and 60.4 per 100,000 respectively (Cancer Care Ontario, 2018). Likewise, mortality was higher in males than females with an age-standardized rate of 20.4 per 100,000 for men and 16.8 per 100,000 for women (Cancer Care Ontario, 2018).

2.1.1 Risk Factors

There are several modifiable and non-modifiable risk factors associated with the development of CRC. The most notable factor is age, as the risk of CRC increases progressively between age 40 and 50, and then sharply after 50 years (Haggar & Boushey, 2009). Although 90% of individuals diagnosed with CRC are aged 50 and older, in recent years the incidence rate

has risen for young adults (Haggar & Boushey, 2009). The risk of CRC is greater among those with a first-degree relative (parent, sibling, child) with a history of CRC (American Cancer Society, 2018; Canadian Cancer Society, 2017; Haggar & Boushey, 2009; National Cancer Institute, 2018), and is doubled for those with a family member diagnosed before the age of 55 (National Cancer Institute, 2018). Although the majority of those with CRC have no family history, approximately 1 in 3 have a relative with the condition (American Cancer Society, 2018). Having a personal history of adenomas (Amersi et al., 2005) or a history of breast, endometrial, or ovarian cancer (Schoen et al., 1994) increases the risk of CRC. Similarly, individuals with inflammatory bowel disease (IBD) such as ulcerative colitis and Crohn's disease have a greater risk (Janout & Kollárová, 2001; Laukoetter et al., 2011). IBD can increase the risk of CRC between 4 to 20-fold (Janout & Kollárová, 2001). As inflammation in the colon can lead to abnormal cell growth, these individuals should be screened sooner and more frequently (American Cancer Society, 2018). Likewise, people with Type II diabetes are at an increased risk of CRC and could benefit from early screening (Berster & Göke, 2008; Canadian Cancer Society, 2017). Approximately 5% of CRCs diagnoses occur in people with inherited syndromes such as Lynch syndrome (hereditary non-polyposis CRC, or HNPCC) and familial adenomatous polyposis (FAP) (American Cancer Society, 2018; Canadian Cancer Society, 2017; Haggar & Boushey, 2009; National Cancer Institute, 2018).

Lifestyle-related risk factors such as physical inactivity, being overweight or obese, consuming diets high in red or processed meats, smoking and moderate-to-heavy alcohol use are strongly linked to CRC (Canadian Cancer Society, 2017). Globally, physical inactivity accounts for roughly 10% of the burden of disease from colon cancer (Lee et al., 2012). In a systematic review and meta-analysis conducted by Wang et al. (2017), physically active individuals had a

23% lower risk of CRC and a 27% lower risk of advanced CRC respectively when compared to inactive individuals (Wang et al., 2020). Together, physical inactivity and obesity account for approximately one third of CRCs (Haggar & Boushey, 2009). Obesity, as measured with body mass index (BMI), is associated with colon and rectal cancers (Ma et al., 2013). The risk of CRC associated with obesity (measured by BMI) is stronger in males than in females and is greater for colon cancer than for rectal cancer (Jochem & Leitzmann, 2016). Likewise, incremental increases of 5kg/m^2 in BMI are associated with colon cancer in men and women respectively (RR=1.24, 95%CI: 1.20-1.28; RR=1.09, 95%CI:1.05-1.13) and with rectal cancer (RR=1.09, 95%CI:1.06-1.12) in men (Renehan et al., 2008). The relationship between CRC and obesity remains when obesity is measured with waist circumference (WC) (RR=1.42, 95%CI: 1.30-1.55) and with waist-to-hip ratio (WHR) (RR=1.39, 95%CI: 1.25-1.53) (Dong et al., 2017). A review of meta-analyses by Aykan (2015) suggests that the consumption of red and processed meats increases the risk of CRC by 20 to 30% (Aykan, 2015). The quantity and frequency of consumption of red and processed meats influence the risk of CRC (Baena & Salinas, 2015). For instance, consuming approximately 100g/day of red meat and 50g/day of processed meat increases the risk of CRC (World Cancer Research Fund, 2017). Eating red meat more than once daily can increase the risk of both colon (RR=1.37, 95%CI: 1.09-1.71) and rectal (RR=1.43, 95%CI: 1.24-1.64) cancers (Smolińska & Paluszkiewicz, 2010). Likewise, meat preparation can have an impact on the production of carcinogens with the intake of grilled and barbecued red meat presenting an increased risk of cancer (Punnen et al., 2011). This is particularly true when cooked well-done (Punnen et al., 2011). Smoking is also a known risk factor for CRC (Liang et al., 2009). Those who currently or formerly smoked are significantly more likely to develop CRC compared to nonsmokers (Liang et al., 2009). The risk of CRC is increased by 18% for

those who have smoked compared to those who have never smoked (RR=1.18, 95%CI: 1.11-1.25) (Botteri et al., 2008). Botteri et al. (2008) observed a statistically significant dose-response relationship for increasing pack-years and cigarettes per day (Botteri et al., 2008). For every 10 cigarettes per day, the risk of CRC increased by 7.8% (95%CI:5.7%-10.0%) and for every 10 pack-years the risk of CRC increased by 4.4% (95%CI:1.7%-7.2%) (Botteri et al., 2008). Alcohol consumption is a risk factor for CRC (Bagnardi et al., 2015). Compared to non-drinkers and occasional drinkers, moderate and heavy drinkers had a 17% (RR=1.17, 95%CI:1.11-1.24) and 44% (RR=1.44, 95%CI:1.25-1.65) increase in risk of CRC respectively (Bagnardi et al., 2015). A time-dependant relationship between alcoholism and risk of CRC exists (Lin et al., 2020). Those with a longer history of alcoholism have a greater likelihood of developing CRC (Lin et al., 2020). For instance, the likelihood of developing CRC is 1.9 times greater for alcoholism >1 year (Odds Ratio (OR)=1.875, 95%CI: 1.788-1.967) whereas the likelihood of developing CRC is 2.7 times greater for alcoholism >5 years (OR=2.662, 95%CI: 2.498-2.835) (Lin et al., 2020).

2.1.2 Colorectal Cancer Treatment

CRC treatments include surgery, chemotherapy, radiation therapy and targeted therapy. Treatment options depend largely on the tumour location and cancer stage (Jackson et al., 2007), as well as patient preference and overall health (Canadian Cancer Society, 2019). A patients overall health and preferences are important considerations from a patient-centered perspective. Surgery is the main treatment for CRC (Abraham et al., 2004; Jackson et al., 2007; Kuipers et al., 2015). This can range from local excision for early stage tumours (Jackson et al., 2007; Simmonds et al., 2000) to resection at advanced stage (Konyalian et al., 2007). Local excision removes abnormal intestinal tissue only (Abraham et al., 2004) while bowel resection involves

the removal of part of the intestine and nearby lymph nodes (Ikematsu et al., 2013). In some cases, bowel resection may be followed by colostomy or ileostomy; surgical procedures used to prevent bowel obstruction or anastomosis leakage (Tilney et al., 2007). Chemotherapy includes the anticancer medications used to control or cure growing cancers (Canadian Cancer Society, 2019). Adjuvant chemotherapy can be used following surgery as a secondary treatment or to prevent recurrence (Mitry et al., 2016), particularly for stage II or III CRC (Ayanian et al., 2003; Binefa et al., 2014). For stage IV CRC, surgical resection as a primary curative treatment is not possible in 75 to 90% of patients (Cook et al., 2005). As such, advanced or recurrent CRC is typically treated with chemotherapy (Ikeguchi et al., 2011). Radiation therapy kills cancer cells with high-energy beams (Cancer Care Ontario, 2017a). This can be used to shrink tumour size prior to surgery, or can be used to target tumour cells left over after surgery (Cancer Care Ontario, 2017a). In some cases, chemoradiation, a combination of chemotherapy and radiation may be applied (Canadian Cancer Society, 2019). Neoadjuvant chemoradiation (chemoradiation before surgery) is mostly used for stage II or III rectal cancer patients (Ayanian et al., 2003; Binefa et al., 2014). There are few instances where chemoradiation is used following surgery, however, it may be used for some rectal cancers (Binefa et al., 2014). Targeted therapy medications are mostly given alongside chemotherapy for advanced CRC (Ayanian et al., 2003; Ohhara et al., 2016), particularly if it has metastasized to the liver or lungs (Canadian Cancer Society, 2019).

2.1.3 Colorectal Cancer Survival

Overall, the 5-year net survival rate (i.e. the percentage of individuals who will live at least five years after cancer diagnosis) is 65% for CRC patients (Canadian Cancer Statistics Advisory Committee, 2019). However, survival rates vary based on numerous factors, especially

cancer stage (Boyle & Langman, 2000; Maringe et al., 2013). The extent of cancer in the body is described by cancer staging that encompasses the amount of cancer in the body, the location it was first diagnosed, the size of the tumour and whether it has spread to other sites (Canadian Cancer Society, 2020b; National Cancer Institute, 2015). Most cancers are assigned an overall stage from 0 to IV, with 0 representing the least advanced, and IV representing the most advanced stage (Canadian Cancer Society, 2020b). Stage 0 indicates in situ carcinoma (precancerous change), stage I indicates a small localized tumour, stage II and III are indicative of a large tumour that has spread beyond the organ to tissue in close proximity and in stage IV the cancer has metastasized to distant body parts (Canadian Cancer Society, 2020b). When CRC is diagnosed at early stage, treatment and management of the condition are likely to be more successful (Marley & Nan, 2016). If CRC is diagnosed at localized stage, the 5-year survival rate is around 90% (Canadian Cancer Society, 2020a). Meanwhile, the 5-year survival rate is only 13% if cancer has metastasized to distant body parts (Canadian Cancer Society, 2020a). As stage at diagnosis is strongly associated with survival, early detection can improve outcomes (Canadian Cancer Statistics Advisory Committee, 2019). Participation in cancer screening programs could reduce mortality rates among CRC patients (Canadian Cancer Statistics Advisory Committee, 2019). However, despite the availability of widespread screening across most of Canada, approximately 50% of CRCs are diagnosed at late stage (III or IV) (Canadian Cancer Statistics Advisory Committee, 2019).

Sociodemographic factors also contribute to CRC survival rates. Age is particularly important as survival rates for most cancers decrease with advancing age at diagnosis (Canadian Cancer Statistics Advisory Committee, 2019). For CRC specifically, prior research has shown that survival is greater among young adults than those of older age, even after adjusting for

disease, patient and treatment factors (McKay et al., 2014). Survival estimates among CRC patients aged 15 to 69 years are constant at 68%, then decline with increasing age (Canadian Cancer Statistics Advisory Committee, 2017). For colon cancer specifically, the median decline in 5-year net-survival between the 15-to-44 and 75-to-84 age groups is 10 percentage points (73% to 63%), while that of rectal cancer patients is 15 percentage points (73% to 58%) (Government of Canada, 2018a). As 93% of people diagnosed with CRC are aged 50 or older, the Canadian Cancer Society recommends regular screening every two years for average-risk adults aged 50 to 74 years (Canadian Cancer Society, 2020c; Canadian Task Force on Preventive Health Care, 2016). High-risk adults, such as those with hereditary syndromes, should be screened more frequently and sooner (Patel & Ahnen, 2018). While the incidence of CRC has decreased for older adults, an upward trend has been noted for younger adults (aged 50 and under) (Patel & Ahnen, 2018).

Differences in mortality have also been noted between sexes. More men than women are diagnosed with and die from CRC nationally (Canadian Cancer Statistics Advisory Committee, 2019). In Canada, roughly 5,200 men and 4,400 women died from CRC in 2019 (Canadian Cancer Statistics Advisory Committee, 2019). Likewise, the lifetime probability of dying from cancer is 26% for males and 23% for females (Canadian Cancer Statistics Advisory Committee, 2019). Reasons for differences in cancer survival between sexes among CRC patients are not well understood. Possible reasons that women are more likely to survive longer than men include lower prevalence of comorbidity, earlier stage at diagnosis, and better resistance to disease (Sant et al., 2009). Hendifar et al. (2009) reported that female hormones, particularly estrogen, may play an important role in the development and pathogenesis of CRC (Hendifar et al., 2009). More specifically, younger women with metastatic CRC had greater survival than younger men,

whereas survival among older adults was comparable between sexes (Hendifar et al., 2009). This finding may partially be attributed to menopausal status (Hendifar et al., 2009). Other potential explanations for this difference include greater exposure to carcinogens among males (i.e. through cigarette smoking or exposures at work), and women's propensity to seek medical care more than men (Ellison, 2016). Women's engagement in health-promoting behaviours (i.e. cancer screening) could lead to diagnosis at an earlier cancer stage and better prognosis (Ellison, 2016).

Indigenous people of Canada (including First Nations, Inuit, and Metis) experience health disparities, and generally have poorer health than the general population (Towle et al., 2006). These disparities are multifactorial, and result from factors such as racism, colonialism, disparities in the social determinants of health, and intergenerational trauma from historial oppression and residential school experiences (Adelson, 2005; Greenwood et al., 2015; Malcolm King et al., 2009). Additionally, Indigenous peoples face important barriers accessing health care due to a lack of health services in remote communities (Gunn, 2017). Ethnic and racial differences in cancer survival have been noted between First Nation and Non-Aboriginal adults in Canada for the majority of the most common cancers (Withrow et al., 2017). For CRC specifically, a significant disparity in 5-year survival between First Nations adults and their Non-Aboriginal peers was reported (Excess Mortality Rate Ratio (EMRR): 1.52; 95%CI 1.81-4.21) with minimal change after adjusting for income and rurality (Withrow et al., 2017). Differences in cancer survival may be partially explained by tumour size, stage at diagnosis, as well as patient, and health care system factors (Withrow et al., 2017). However, First Nation ethnicity was not associated with CRC stage at diagnosis in a prior Canadian study (Decker et al., 2016). Psychosocial factors such as social support, stigma and the associated delays in care-seeking

behaviour can contribute to ethnic disparities in cancer survival (Withrow et al., 2017). Other factors related to ethnicity and those constructed through systemic racism, such as the prevalence of comorbidities, quality of nutrition and general health are associated with differences in survival between ethnic groups (Withrow et al., 2017). Systemic racism within the healthcare system contributes to the widespread heath disparities and to the poorer outcomes experienced by indigenous peoples in Canada (Gunn, 2017). Differences in healthcare system factors such as treatment (Hill et al., 2010; Valery et al., 2006) and screening uptake (Decker et al., 2016; Withrow et al., 2014) between indigenous and non-indigenous adults have been reported in multiple studies. Additionally, poor communication between service providers and indigenous patients could contribute to differences in cancer survival (Jacklin et al., 2017; Towle et al., 2006).

Lower socioeconomic status (SES) is associated with worse survival among patients with colon and rectal cancer (Aarts et al., 2010; Booth et al., 2010). A review by Aarts et al (2010) reported worse 5-year relative survival rates for low SES compared to high SES CRC patients (RRs = 0.5 to 0.9) (Aarts et al., 2010). Similarly, they found that low SES patients consistently had a greater risk of dying in the first 5-years following CRC diagnosis when compared to high SES patients (Hazard Ratio (HR)=1.1 to 1.8) (Aarts et al., 2010). Booth et al. (2010) divided the Ontario population into quintiles (Q1-Q5) based on community median household income reports with Q1 representing the poorest community (Booth et al., 2010). Substantial gradients in 5-year overall survival (OS) and 3-year cancer-specific survival (CSS) were noted across Q1 and Q5 for colon (8% OS, $p<0.001$; 3% CSS, $p=0.02$) and for rectal cancers (9% OS, $p<0.001$; 4% CSS, $p=0.096$) (Booth et al., 2010). Thus, despite access to universal healthcare, disparities in survival exist between socioeconomic groups (Booth et al., 2010).

Rurality of residence can also impact cancer survival in many ways. Travel requirements for patients from rural communities can complicate cancer care and treatments (Stranges et al., 2010). Patients residing in rural areas are less likely to receive recommended cancer screening than those residing in urban areas (Liff et al., 1991). Chow et al (2015) reported that rural residence was associated with later stage at diagnosis, inadequate lymphadenectomy, lower likelihood of receiving chemotherapy, and worse cancer-specific mortality among American colon cancer patients (Chow et al., 2015). Similarly, Bosma et al. (2018) found that Canadian colon cancer patients residing in rural areas as defined using residential postal codes had lower overall survival (OS) compared to those in urban areas (HR: 1.1, 95%CI 1.0-1.2) (Bosma et al., 2018). Thus, survival disparities between rural and urban colon cancer patients persist even in the context of universal healthcare (Bosma et al., 2018). While most studies report survival disparities between rural and urban patients, others indicate similar mortality rates. Pong et al. (2009) explored rural-urban disparities in health among Canadians. For all cancers combined, rural areas had lower mortality rates compared to urban areas (Pong et al., 2009). However, similar mortality rates were reported for CRC patients from rural and urban areas (Pong et al., 2009). These findings were consistent across age groups and between sexes (Pong et al., 2009).

2.2 Multimorbidity and Cancer

The coexistence of multiple chronic conditions in an individual, also known as multimorbidity (MMB), is a public health priority in many countries including in Canada (Navickas et al., 2016). Roughly 90% of the primary care population aged 65 and older are affected by multimorbidity (Navickas et al., 2016). In a Canadian study, Fortin et al. (2005) found that 90% of patients in family practice had more than one chronic condition and that more than half of all patients had 5 or more conditions (Fortin, 2005). Among these patients, common

conditions included hypertension, hyperlipidemia, and rheumatologic disease (Fortin, 2005). In Ontario, the prevalence of multimorbidity was roughly 24% in 2009, nearly double the prevalence reported in 2003 (Koné Pefoyo et al., 2015). Among this cohort, the most prevalent conditions were osteoarthritis and other arthritis, hypertension, asthma, depression, diabetes, and cancer (Koné Pefoyo et al., 2015).

Multimorbidity is the "norm rather than the exception" among CRC patients (Gross et al., 2006). While it is known that multimorbidity is common among cancer patients, the prevalence of multimorbidity differs based on the cancer and comorbidity type, as well as the measure used to assess comorbidity and the study population (Sarfati et al., 2016). For instance, in a review conducted by Lee et al. (2011) the prevalence of comorbidity among cancer patients ranged from 0.4% to 90% (Lee et al., 2011). Among cancer patients in Ontario, Kone et al. (2015) found that the prevalence of multimorbidity was over 70% in 2009 (Koné Pefoyo et al., 2015). For CRC specifically, evidence suggests that more than half of these individuals have at least one comorbid condition (Boakye et al., 2018). Prior studies have reported that diabetes, chronic obstructive pulmonary disease (COPD), and congestive heart failure (CHF) are common comorbid conditions among CRC patients (Gross et al., 2006).

Chronic conditions and CRC co-exist for many reasons. For instance, both regularly occur among older adults (Jørgensen et al., 2012; Koroukian et al., 2016; Wedding et al., 2007). Additionally, risk factors for CRC such as smoking, poor diet, physical inactivity, obesity, and moderate-to-heavy alcohol consumption are associated with an increased risk of most chronic conditions (Riley et al., 2016). Certain chronic conditions including diabetes mellitus are causally associated with an increased risk of CRC (Chang & Ulrich, 2003; Larsson et al., 2005). However, in some cases, the relationship between comorbidity and cancer can be protective

(Sarfati et al., 2016). For example, arthritis is often treated with nonsteroidal anti-inflammatory drugs which are associated with a reduced risk of CRC (Din et al., 2010; Flossmann & Rothwell, 2007). Physiological pathways may partially explain the relationship between cancer and certain chronic conditions (Sarfati et al., 2016). For instance, neurodegenerative disorders (such as Alzheimer's and Parkinson's disease) have an inverse relationship with cancer (Roe et al., 2010; West et al., 2005). The inhibition of cell growth, repair and replication that occurs with neurodegenerative disorders might be responsible for this relationship (Behrens et al., 2009).

Certain sociodemographic factors are associated with chronic conditions and with multimorbidity. Notably, female sex, older age, and decreasing household income have been described across studies (Agborsangaya et al., 2012). Marengoni et al. (2008) found that older age, female sex, and lower education independently increased the risk of multimorbidity by more than 50% (Marengoni et al., 2008). Likewise, Fortin et al. (2010) reported that more women than men in the general population had multimorbidity (Fortin et al., 2010). A higher prevalence of multimorbidity was also reported among those in advanced age groups (Fortin et al., 2010). Likewise, comorbidity tends to be most prevalent among those living in poverty or living with higher levels of deprivation as well as within minority racial/ethnic groups (Sarfati et al., 2016).

2.3 Multimorbidity and Cancer Survival

Multimorbidity among cancer patients has been associated with poorer physical and mental wellbeing, greater levels of frailty, decreased quality of life and poorer survival compared to cancer patients without additional conditions (Sarfati et al., 2016). This section will describe the impact of multimorbidity on various aspects of cancer care and survival.

2.3.1 Impact of Multimorbidity on Cancer Diagnosis

Cancer diagnosis can be affected in one of two ways. Patients with chronic conditions are likely to have frequent contact with the healthcare system (Sarfati et al., 2016; Søgaard et al., 2013). Thus, they may have more chances to be screened for cancer or to have cancer symptoms recognized, which could lead to earlier diagnosis (Sarfati et al., 2016; Søgaard et al., 2013). However, other conditions may distract patients and healthcare providers from cancer (Sarfati et al., 2016) or could mask cancer symptoms (Søgaard et al., 2013) which could delay diagnosis. The impact of comorbid conditions on the time to cancer diagnosis depends on the particular conditions present, and their severity (Sarfati et al., 2016; Søgaard et al., 2013). Conditions with competing demands and those that are plausible alternatives for symptoms are especially likely to prolong time to diagnosis (Mounce et al., 2017). For colon cancer patients, research has shown that dementia, alcohol consumption and major depression are associated with later-stage at diagnosis (Søgaard et al., 2013). Likewise, a prolonged diagnostic interval is common for CRC patients with more conditions (Mounce et al., 2017). The impact of comorbidity on stage at diagnosis varies based on whether or not conditions are controlled (Siddiqui et al., 2008). For example, Siddiqui et al. (2008) found that controlled type II diabetes mellitus was not associated with stage at diagnosis for CRC, whereas uncontrolled type II diabetes mellitus was associated with later stage at diagnosis (Siddiqui et al., 2008). Differences in timing of diagnosis also depend on the particular cancer type, as well as the organization and funding of health services (Sarfati et al., 2016). For CRC and other screen-detected cancers, earlier cancer diagnosis is likely when widespread and funded screening programs are available (Sarfati et al., 2016). However, despite the availability of screening programs across most of Canada (Canadian Partnership Against Cancer, 2018), nearly 50% of CRCs are diagnosed at late stage (III or IV) (Canadian Cancer Statistics Advisory Committee, 2018). This has implications for CRC patients,

as treatment with curative intent is not feasible at stage IV (Corkum et al., 2012), and survival is reduced with diagnostic delay (Mounce et al., 2017).

2.3.2 Impact of Multimorbidity on Cancer Treatment

Cancer patients with comorbidity are less likely to receive treatment with curative intent and generally have lower treatment uptake than those with cancer only (Chen et al., 2012). In particular, many studies indicate that comorbidity decreases the likelihood of surgical management for cancer. For instance, Janssen-Heijnen et al. (2007) reported that CRC patients with COPD, cardiovascular diseases, or diabetes had lower resection rates than patients without these conditions (Janssen-Heijnen et al., 2007). Similarly, resection rates were lower for CRC patients with 2 or more comorbidities compared to patients with CRC only (Janssen-Heijnen et al., 2007). Iversen et al. (2009) found that 83.8% of colon cancer patients with Charlson Comorbidity Index (CCI) score 0 had resection, while 77.7% of patients with CCI score 1-2 and 63.2% of patients with CCI score ≥3 had surgery (Iversen et al., 2009). Likewise, resection rates for rectal cancer patients dropped from 73.9% for those with CCI score 0 to 66.3% and 52.9% for patients with CCI score 1-2 and CCI score ≥3 respectively (Iversen et al., 2009).

Additionally, those with comorbidity are less likely to receive or to complete adjuvant chemotherapy and are more likely to be administered lower dosages (Søgaard et al., 2013). For example, Gross et al. (2007) reported that receipt of adjuvant chemotherapy for CRC patients decreased with additional conditions (Gross et al., 2007). Sixty-nine percent of CRC patients with no other conditions received adjuvant chemotherapy, compared to 55.4% with 1-2 conditions and 38.6% with ≥3 conditions (Gross et al., 2007). They examined individual conditions and found that CHF negatively impacted receipt of adjuvant chemotherapy, while COPD and diabetes did not (Gross et al., 2007). Adjuvant chemotherapy was found to be

beneficial for CRC patients that had these conditions (Gross et al., 2007). Moreover, the particular conditions that co-exist with cancer can affect treatments and outcomes differently (Gross et al., 2007). Other studies have reported that the presence of comorbidity prolongs the time from cancer detection to surgical resection, or to the start of chemotherapy or radiation (Søgaard et al., 2013). Although most studies report lower likelihood of treatment for cancer patients with multimorbidity, fewer studies indicate overtreatment for CRC patients (Sarfati et al., 2016). The risk of undertreatment can result in lower response and cure rates (Ritchie et al., 2011).

Regardless, treatment decisions for cancer patients with multimorbidity are inconsistent and rarely follow clinical guidelines (Stairmand et al., 2015). Moreover, clinical practice guidelines for complex cancer patients are unclear as those with multiple chronic conditions are often excluded from clinical trials (Mazza & Mitchell, 2017). Additionally, siloed healthcare systems such as oncolocy and primary care contribute to inefficiency. Possible concerns regarding treatment effectiveness and tolerance to treatments could partially explain more conservative treatment approaches (Stairmand et al., 2015). Likewise, practitioners may decide it is unreasonable to subject patients with an increased risk of side-effects or limited life expectancy to treatments (Lemmens et al., 2005). Refusal of treatments by the patients themselves is another possibility (El Shayeb, 2011).

Evidence surrounding treatment complications for cancer patients with comorbidity is mixed. The impact of comorbidity on treatment tolerance and outcomes depends on the specific conditions and their severity, as well as the particular treatment (Sarfati et al., 2016). Research has shown that comorbidity can negatively impact the quality of surgical care for cancer patients and their post-surgical outcomes (Sarfati et al., 2016). One study of colon cancer patients found

that comorbidity score >2 was significantly associated with more postoperative complications and increased duration of stay in intensive care after surgery (Rieker et al., 2002). Comparably, Kennedy et al. (2011) found that colon cancer patients with COPD who underwent surgical resection were more likely to experience 30-day post-operative complications (OR=1.84, 95%CI: 1.49-2.27), compared to those without the condition (Kennedy et al., 2011). They also reported that colon cancer patients with comorbidity had higher 30-day post-operative mortality rates than those without comorbidity (Kennedy et al., 2011).

However, other studies suggest that cancer patients with comorbidity are not more likely to experience treatment complications. For instance, LoConte et al. (2009) found that comorbidity was not predictive of dose-limiting toxicity among patients with various cancer types in an RCT for phase 1 chemotherapy (LoConte et al., 2010). Correspondingly, most research indicates that treatments positively impact survival for cancer patients. Lemmens et al. (2005) reported that among elderly CRC patients, comorbidity influenced uptake of chemotherapy in stage III colon cancer patients and adjuvant radiotherapy in rectal cancer patients (Lemmens et al., 2005). Elderly patients with comorbidity had worse survival than those without comorbidity (Lemmens et al., 2005). Likewise, Gross et al. (2007) found that adjuvant chemotherapy benefitted the survival of older stage III CRC patients with comorbidity, yet reported lower likelihood to receive treatment for these patients compared to those with no comorbidity (Gross et al., 2007).

2.3.3 Polypharmacy Among Cancer Patients with Multimorbidity

Cancer patients living with multimorbidity are often exposed to polypharmacy (Masnoon et al., 2017). Polypharmacy can be defined as the concurrent use of multiple medications by one individual (Masnoon et al., 2017). Although necessary to manage co-existing conditions,

treatment with multiple medications can predispose these individuals to adverse drug interactions. Rodrigues et al. (2016) conducted a systematic review on drug-drug interactions and adverse drug reactions among older adults exposed to polypharmacy (Rodrigues & de Oliveira, 2016). Over 40% of older adults use ≥5 different medications concomitantly, and roughly 12% use ≥10 (Rodrigues & de Oliveira, 2016). Reason et al. (2012) reported that 27% of individuals aged 65 and older regularly took 5 or more medications (Reason et al., 2012). Roughly 12% of those taking 5 or more medications had experienced side effects that necessitated medical care compared to only 5% for those taking 1 or 2 medications (Reason et al., 2012). Karuturi et al. (2018) explored the impact of potentially inappropriate medication use on adverse outcomes for cancer patients (Karuturi et al., 2018). Among CRC patients, adverse outcomes (including ER visits, hospitalizations, and death) were associated with taking ≥5 medications, older age, female sex, and higher comorbidity (Karuturi et al., 2018).

2.4 Patient-Centered Care

This section will describe patient-centered care in relation to the healthcare system and health services as well as the benefits of patient-centered care for patients with MMB and cancer. Patient-centered approaches contribute to positive health outcomes for these patient groups and should be considered in the delivery of healthcare for complex cancer patients. Similarly, health system factors can be modified to facilitate patient-centered care which can subsequently improve health outcomes for complex cancer patients. It should be noted that this thesis utilizes Canadian data and takes place in the context of the Canadian healthcare system, which is if not unique but very specific, and thus evidence presented will be focused on Canadian healthcare.

Patient-centered care is the delivery of healthcare that is holistically aligned with the patients' values, needs, and personal priorities (Baker, 2001). Patients are empowered to actively

participate in decisions about their care as part of a therapeutic alliance with their healthcare provider (Constand et al., 2014). The patient-centered care approach acknowledges the need to shift focus from single diseases toward the whole person experiencing illness in the context of their lives (Barry & Edgman-Levitan, 2012). The whole person includes the biological, social, psychological, and spiritual components of the individual (McCormack, 2003). Patients must be listened to, informed, respected, and included in their care (Epstein & Street, 2011). Eight principles are central to patient-centered care: respect for the patient's values, preferences, and expressed needs; coordination and integration of care; information and education; physical comfort; emotional support and alleviation of fear and anxiety; involvement of family and friends, as appropriate; continuity and transition; and access to care (Barry & Edgman-Levitan, 2012; Morgan & Yoder, 2012).

Patient-centered care is recognized as a measure of health care quality and has been associated with positive health outcomes (Singh et al., 2018). In a primary care setting, patient and family involvement in decision-making has been associated with reduced pain and discomfort, faster physical recovery and improved emotional wellbeing (Stewart et al., 2000). Patient-centered care has been shown to correlate with a patients' ability to maintain their personal health and adhere to treatment regimens (Smith et al., 2013). Among patients with chronic conditions, patient-centered care has been positively associated with treatment adherence, patient satisfaction, physical health outcomes and quality of life and wellbeing (Michie et al., 2003). For instance, Roumie et al. (2011) reported that patient-centered care was associated with antihypertensive medication adherence in patients with hypertension (Roumie et al., 2011). Similarly, patient-centered care was found to be a predictor of long-term adherence to recommended tamoxifen medication use in breast cancer patients (Kahn et al., 2007). In general

practice, patient-centered care significantly improved patient-provider communication, wellbeing and satisfaction in patients with newly diagnosed diabetes (Kinmonth et al., 1998). Comparably, perceived autonomy was found to be positively associated with patient trust, satisfaction, and mental health-related quality of life in patients with Type II diabetes (Lee & Lin, 2010). Patients with musculoskeletal chronic pain and fibromyalgia who received patient-centered care had greater improvements in psychological distress (anxiety) and in the number of tender points compared to those receiving usual care from their family physician (Alamo et al., 2002). Additionally, positive trends were reported for pain intensity (Alamo et al., 2002). Among cancer patients, patient-centered care has been associated with improved self-representation, optimism, and a sense of wellbeing (Radwin et al., 2009). Patient-centered care has been positively associated with satisfaction and the physical and social well-being of patients with multimorbidity (Kuipers et al., 2019).

Although patient-centered care has been described as a core healthcare aim in Canada, the need for care coordination is a global issue and patients commonly experience challenges navigating the healthcare system (Beaulieu, 2013; Misra et al., 2020; Smith et al., 2013). Patients with multimorbidity are especially vulnerable to fragmented care as they have multiple conditions and complex needs yet receive care in a single disease oriented healthcare system (Boyd & Fortin, 2010). Cancer patients with multimorbidity, in particular, require services from many providers, including oncology, primary care, and other specialties to manage all of their conditions (Lee et al., 2016). Additionally, clinical guidelines are largely focused on the management of single conditions and may not be applicable to patients with multimorbidity (Boyd & Fortin, 2010). Patient-centered care presents an opportunity to improve the experiences and outcomes of cancer patients with multimorbidity.

This study will help elucidate the value of patient-centered care by exploring the impact of sociodemographic and health system factors on the association between multimorbidity and CRC survival. The involvement of multiple providers can be expected in the care of a single patient with multimorbidity. This has implications for continuity of care (COC), an important component of patient-centered care. COC has been shown to improve patient outcomes but has yet to be investigated in this context. Health system factors, such as primary care models, should be considered in the case of multimorbidity as they can be altered to facilitate patient-centered care. For instance, health care provider arrangements and physician payments that encourage the management of patients with multimorbidity and that favour interdisciplinary collaboration merit attention. Conversely, payment systems that reinforce a single condition focus could be problematic. Examining sociodemographic factors and co-existing conditions presents an opportunity to better target care for high-risk patient groups.

2.5 Primary Care Models in Ontario

This section will present the role of primary care in the Canadian healthcare system and will describe the evolution of Ontario's primary care models. Organizational components will be presented following the description of funding arrangements for each model.

Primary care serves as the patient's initial point of contact with the healthcare system and the site of continuing care as the patient accesses necessary health services (Walters et al., 1994). The scope of primary care includes health promotion and disease prevention, health maintenance, counselling, patient education as well as the diagnosis and treatment of acute and chronic illnesses (Walters et al., 1994). High quality primary care consists of the initial point of access for all health needs and includes care that is comprehensive, coordinated, and person-focused (rather than disease-focused) (Muldoon et al., 2006). Central elements of primary care

include first-contact care; responsibility for patients over time; comprehensive care that meets the patients' healthcare needs; and coordination of care across conditions, healthcare professionals, and settings (Berenson et al., 2008).

Historically, primary care in Ontario was mainly delivered by physicians who practiced independently and were reimbursed through fee-for-service (FFS) billings (Hutchison & Glazier, 2013). Efforts to improve access to and the quality of primary care through health system reform have been underway since 2000 (Hutchison et al., 2011). Since this time, primary care models encouraging group-based practices with requirements for patient enrollment have been introduced (Hutchison & Glazier, 2013). Patient enrollment, or rostering, is an agreement that involves the patient voluntarily committing to consult the same physician (or group of physicians) for all non-emergency health needs in exchange for access to one-to-one correspondence with the practice (Sweetman & Buckley, 2014). Physicians practicing in the new primary care models are compensated through blends of fee-for-service, capitation, salary and targeted payments for providing priority services (Hutchison et al., 2011). Capitation refers to a single payment for the provision of a specified basket of services to a patient over a fixed time period (Sweetman & Buckley, 2014). Capitation payments do not vary based on the number of services provided (Sweetman & Buckley, 2014). Blended models commonly include a FFS component that covers services that fall outside of the capitated basket (Sweetman & Buckley, 2014). Pay-for-performance incentives and bonuses may be included for preventative care services and chronic condition management (Sweetman & Buckley, 2014). Physicians enrolled in either of the blended capitation models (FHO, FHN) are held accountable for providing care to their rostered patients and are penalized with the loss of access bonus payments if their patients receive primary care from other practices (Glazier et al., 2012).

Accountability can be defined as the mechanisms that hold an individual responsible for their actions. Primary care models and funding arrangements are associated with accountability agreements based on pre-defined goals and objectives (Wooder et al., 2011). One example of this would be the goal of expanding access to primary care by introducing after-hours premiums as part of physician compensation. While these efforts create a foundation for accountability, alone they are insufficient to ensure providers are held responsible for their actions. Moreover, accountability requires ongoing-monitoring, measurement and at times corrective actions. Currently, there is no consistent strategy or approach to ensure that the primary care system is held accountable for performing towards its goals. Similarly, no consistent or timely approach is in place to ensure corrective action or remediation is applied when accountability requirements are left unmet (Wooder et al., 2011).

Ontario's primary care models were developed with the "patient-centered medical home" in mind, which includes the following principles: a personal physician, a physician-directed team, whole-person orientation, coordination of care, quality and safety, and enhanced access (Ferrante et al., 2010; Rosser et al., 2010). The patient-centered medical home is a concept which aims to optimize the core attributes of primary care through changes to practice organization and reimbursement systems (Stange et al., 2010). As of 2012, 75% of the provinces population and 75% of primary care physicians were enrolled in Ontario's new primary care models (Marchildon & Hutchison, 2016a). By this time, substantial improvements could be noted such as extended hours of care, establishing primary care infrastructure including electronic medical records, a greater pool of primary care providers, provision of formerly undersupplied targeted services, and further integration and interprofessional primary care (Marchildon & Hutchison, 2016a). Ontario's primary care models are described below in Table 1.

Fee-For-Service (FFS)

FFS is the traditional compensation method in Ontario (McLeod et al., 2016). Physicians bill the provincial government based on a set schedule of fees for each service they provide. Providers are not required to roster patients, a feature commonly associated with capitation and blended capitation models (McLeod et al., 2016; Wooder, 2011). Patients seek care for medical issues when necessary (Sweetman & Buckley, 2014). No single provider or provider group is responsible for the patient or the provision of preventative services and chronic condition management (Sweetman & Buckley, 2014). FFS does not include requirements for after-hours services or group based practice (Wooder, 2011)

Enhanced Fee-For-Service

In enhanced FFS models, physicians are primarily compensated through FFS billing (McLeod et al., 2016). Bonus payments, incentives and premiums are paid for patient enrolment, after-hour services, chronic disease management and preventative care. Physicians receive monthly comprehensive care capitation payments for enrolled patients. Enhanced FFS models include the Comprehensive Care Model for solo physicians and the Family Health Group (FHG) for three or more physicians (McLeod et al., 2016).

Comprehensive Care Model

The Comprehensive Care Model includes physicians who operate independently (Hutchison & Glazier, 2013). Physicians are mainly compensated on a FFS basis. Patient rostering is required and encouraged through incentives and bonuses. Care is provided during regular office hours and after-hours at least once weekly (Hutchison & Glazier, 2013).

Family Health Group (FHG)

The Family Health Group was introduced in 2003 (Glazier et al., 2012). Groups of three or more physicians offer services during regular office hours and after-hours services. Physicians are mainly compensated on a fee-for-service basis. A monthly comprehensive care fee is paid for each patient rostered (Glazier et al., 2012). To improve access to and the quality of care, this model features premiums for extended hours, bonuses for chronic condition management and incentives for patient enrollment (Kantarevic et al., 2011). Out of all the new primary care models, the FHG is the most popular compensation model for primary care physicians and is often the first model physicians join when transitioning from traditional FFS (Kantarevic et al., 2011).

Blended Capitation Models

Blended capitation models include at least three physicians who are primarily compensated through capitation fees (McLeod et al., 2016). Capitation payments are determined by patient enrollment (rostering) based on the age and sex of each patient and do not consider socioeconomic or health status (Collier, 2009). Moreover, physicians are not compensated more for the care they provide to sicker patients or those with serious mental illness than those who are healthier. Other services are paid on a FFS basis. Additional bonuses and premiums are paid for services including chronic disease management, preventative care, prenatal care and home visits for enrolled patients as well as hospital visits, obstetrical care and palliative care for all patients. Monthly comprehensive care capitation payments are included for patient enrollment. Both the Family Health Network (FHN) and the Family Health Organization (FHO) models are considered blended capitation models (McLeod et al., 2016).

Family Health Network (FHN)

The Family Health Network (FHN) was introduced in Ontario in 2001 (Glazier et al., 2012). This blended reimbursement model includes three or more physicians who are primarily reimbursed through capitation, blended with FFS payments and incentives. Capitation payments are age-sex based but are not adjusted for health care needs or social disparities. Bonus payments are available for patient enrolment (rostering), after-hours services, chronic disease management and certain preventative health care efforts. A monthly comprehensive care fee is paid for each patient rostered (Glazier et al., 2012).

Family Health Organization (FHO)

The Family Health Organization (FHO**)**, a combination of two pre-existing models the Health Service Network and the Primary Care Network, was introduced in 2005 (Hutchison & Glazier, 2013). Like the FHN model, the FHO model includes age-sex based capitation payments that are not adjusted for health care needs and social disparities (Glazier et al., 2012). The FHO model has similar provisions to the FHN model but includes more services and a greater capitation component (Glazier et al., 2012).

Blended Salary Models

Blended Salary Models include physicians who receive most of their income from salary (Hutchison & Glazier, 2013). Physicians practicing as part of a Family Health Team with community or mixed governance may be compensated through a blended salary model. Salary is determined by the number of patients enrolled. Benefits and bonuses are available (Hutchison & Glazier, 2013).

Salaried Models

Community Health Centres (CHCs)

CHCs are community governed primary health care organizations that have existed in Ontario for over 40 years (Glazier et al., 2012). Interprofessional teams deliver services with a focus on health promotion and disease prevention (Government of Ontario, 2019). All health professionals are compensated through salaried arrangements (Glazier et al., 2012). CHCs generally include physicians, nurse practitioners, nurses, social workers, health promoters, community health workers and may include chiropodists, nutritionists or dietitians (Government of Ontario, 2019). These organizations aim to improve access to primary care services in underserved, low income, and isolated areas in Ontario (Hurley et al., 2011). Salaried models are well suited for providers serving smaller populations and those serving high risk and vulnerable populations as capitation and FFS models would otherwise undercompensate physicians for their efforts (Wranik & Durier-Copp, 2010). For this reason salary based models have been considered as a means to increase physicians recruitment and retention in rural and remote areas. Physicians may find salary based models attractive as they offer a stable income. Howeover, concerns have been raised around physician productivity. Salary models are costly and may motivate physicians to spend more time with each patient limiting access to care for a larger patient population (Wranik & Durier-Copp, 2010).

Family Health Teams (FHTs)

FHTs are interdisciplinary team models that were introduced in Ontario in 2005 (Hutchison & Glazier, 2013). Of all the models, the FHT is considered the Ontario governments "flagship initiative in primary care renewal" as it enables service providers such as physicians, nurses and practitioners to work alongside allied health professionals including social workers, psychologists, dieticians, and pharmacists to better meet the needs of patients (Marchildon & Hutchison, 2016a). Moreover, patients can receive a multitude of necessary services under one

roof (Hurley et al., 2011). All FHTs provide the following services: health assessments, diagnosis and treatment, primary reproductive care, primary mental health care, primary palliative care, patient education, preventative care, and telephone health advisory service (available 24 hours a day, 7 days per week) (Government of Ontario, 2009). Certain FHTs deliver specialist services including diagnostic services, health promotion programs, chronic disease management, and rehabilitation services (Government of Ontario, 2009). FHTs that do not provide all of these services can facilitate service coordination and system navigation based on the patient population and community they serve (Government of Ontario, 2009). FHTs are planned with the care team, the patient population, and the community in mind (Hurley et al., 2011). FHTs are not physician-payment models (Glazier et al., 2012). Physicians practicing as part of a FHT are paid through either a blended capitation (FHNs or FHOs) or a blended salary model (Glazier et al., 2012) and allied health providers are salaried (Marchildon & Hutchison, 2016a). Physicians who operate on a FFS basis and those who are part of FHGs are unable to join a FHT (Glazier et al., 2012).

Specialized Models

Specialized models, such as the Rural-Northern Physician Group Agreement (RNPGA) model, have been created to target specific populations and geographic areas in the provicne of Ontario (Government of Ontario, 2017).

Rural-Northern Physician Group Agreement (RNPGA)

The Rural-Northern Physician Group Agreement model includes 1 to 7 physicians practicing in rural communities with a limited number of physicians (Government of Ontario, 2017). Primary care services are provided to all residents of a community. Physicians are

compensated with a base payment as well as overhead payments, locum coverage, premiums and bonuses (Government of Ontario, 2017).

Table 1. Overview of Ontario's predominate primary care models *(Glazier et al., 2012)*

	Model Characteristics				
	Remuneration	Patient Enrolment	Group size (physicians)	Interdisciplinary team members	After-hours requirement
Family Health Group	Blended fee-for-service	Yes	At least 3	Limited	Yes
Family Health Organization	Blended capitation	Yes	At least 3	Limited	Yes
Family Health Team	Blended capitation or blended salary	Yes	At least 3	Yes	Yes
Family Health Network	Blended capitation	Yes	At least 3	Limited	Yes
Comprehensive Care Model	Blended fee-for-service	Yes	Solo	No	Optional
Community Health Centre	Salary	No	None	Yes	Yes
Rural and Northern Health Group	Blended salary	Optional	Solo	No	Yes

A Comparison of Ontario's Primary Care Models

This section will discuss the pros and cons of components central to Ontario's primary care models based on the current literature and assess how they may impact service provision and patients' outcomes.

Fee-for-service (FFS) models reward physicians based on the number of health services they perform (Glazier et al., 2019). Moreover, FFS creates an incentive to provide a large quantity of services (Glazier et al., 2019). A greater quantity of care is appropriate in some circumstances, however, instances of 'supplier-induced demand' (i.e., physicians providing more care than necessary) are not uncommon when compensation is linked to services provided (Rudmik et al., 2014). That is, FFS physicians may be more inclined to consider patient wants and satisfaction in an effort to retain patients and therefore provide more services (Sorbero et al., 2003). High-cost and low-cost patients (i.e., patients who cost the system more or less in care charges) are treated equally in a FFS system (i.e. no incentive to care for one over the other), as opposed to capitation or salary systems (Rudmik et al., 2014). Moreover, FFS remuneration can benefit the healthcare system through patient satisfaction, increase physician productivity, and may reduce preferential selection of low risk patients (i.e. cream skimming) (Rudmik et al., 2014). While FFS is well understood and somewhat modifiable (fee schedules), there are clear drawbacks to this payment method (Glazier et al., 2019). FFS could motivate an inappropriate increase in service provision and subsequently raise healthcare costs (Rudmik et al., 2014). Traditional FFS physician payments deterred collaboration between physicians, provided few incentives for health promotion and disease prevention, offered little after-hours care, and tended to encourage an oversupply of services, prompting a shift towards alternative models of care (Marchildon & Hutchison, 2016a; Sweetman & Buckley, 2014).

In contrast, capitation-based models provide physicians with a single payment for each patient enrolled in their practice over a period of time (Rudmik et al., 2014). Moreover, capitation creates an incentive to increase the number of patients seen by a practice, but does not reward providers for the number of services (i.e., there is a disincentive to see patients more than

needed) (Rudmik et al., 2014). However, capitation models only work when accountability metrics are in place to keep practices from collecting patients without actually providing care. Enrollment provides physicians with greater access to patient information and can benefit patient outcomes through continuity of care (Chechulin, 2014). Additionally, enrolling physicians are well-positioned to guide their patients towards the most appropriate care (Chechulin, 2014). This can lead to more efficient health service use, redirecting non-urgent care away from emergency departments and walk-in clinics toward primary care (Chechulin, 2014).

One downfall of Ontario's capitation models is that physicians attracted to these models may serve healthier, low-cost patients (Marchildon & Hutchison, 2016a). Motivation to take on healthy patients and minimize the number of unhealthy patients can lead practices to reject (i.e. cream-skimming) and refer out (i.e. dumping) high needs patients (Rudmik et al., 2014). Capitated practices and providers might be inclined to serve socially advantaged populations and those with fewer healthcare needs (Marchildon & Hutchison, 2016a). Capitated payments are adjusted for age and sex only. Equity concerns have been raised as socioeconomic status is not considered, a serious limitation as morbidity burden and healthcare needs are associated with lower socioeconomic status (Sibley & Glazier, 2012). A cross-sectional study by Glazier et al. (2012) found that low-income neighbourhoods were underrepresented in Ontario's capitated models (Glazier et al., 2012). Capitated models (FHOs, FHNs, and FHTs) also served less newcomers to Canada, and encompassed individuals with fewer chronic conditions and lower morbidity and comorbidity (Glazier et al., 2012). Conversely, Rudoler et al. (2015) did not find that capitated physicians reduced the amount of care provided to high-cost patients with greater morbidity (Rudoler et al., 2015). Moreover, physicians practicing in capitated models are overcompensated for low complexity patients, and undercompensated for more complex patients

(Sibley & Glazier, 2012). Capitation could be beneficial as it controls costs while avoiding supplier-induced demand (i.e. oversupply of services) (Rudmik et al., 2014). However, capitation based remuneration could result in lower continuity of care and reduce productivity (Rudmik et al., 2014).

Salary is a remuneration method that is fixed over a period of time (Rudmik et al., 2014). The payment does not depend on the number of patients or the number of services provided (Rudmik et al., 2014). Salary is better suited to recruit and retain physicians in underserved regions with smaller populations than FFS and capitation (Wranik & Durier-Copp, 2010). Moreover, FFS and capitation would insufficiently compensate physicians for their efforts (Wranik & Durier-Copp, 2010). Salary-based physician remuneration can increase the appropriateness of care and improve quality of care through increased focus on disease prevention, health promotion, and greater collaboration between health professionals (Gosden et al., 2003). However, salary could reduce productivity and the provision of necessary care as income is stable regardless of services performed (Rudmik et al., 2014) and may be comparable to FFS models in terms of preventative care practices or self-help promotion (Gillett et al., 2001; Hibbard et al., 2001).

Pay-for-performance incentives are sometimes provided to physicians for achieving certain clinical targets (McDonald & Roland, 2009). These payments can be beneficial, however, there is a risk that incentivized services will be prioritized over those without incentives (Rudmik et al., 2014). Similarly, pay-for-performance can negatively impact the patient-provider relationship as physicians may feel resentful toward patients who do not comply with their advice (McDonald & Roland, 2009). However, Doran et al. (2011) did not find that pay-for-performance negatively impacted the delivery of non-incentivized services (Doran et al., 2011).

Blended remuneration reaps the benefits of various remuneration methods while minimizing their drawbacks (Rudmik et al., 2014). FFS combined with capitation provides physicians with income for each service they provide while simultaneously collecting a small fee for patient enrollment. Capitation combined with FFS allows physicians to earn income to cover pre-defined services delivered to each patient in their practice while receiving FFS payments for other services. Salary mixed with FFS allows physicians to collect fixed fee for their practice with additional payments for a percentage of FFS billings. Capitation with FFS could increase health promotion and disease prevention while maintaining productivity and equal access for patients. Salary blended with FFS could benefit underserved areas through physician recruitment while maintaining productivity (Rudmik et al., 2014). However, further research is needed to determine the implications of combined models on health outcomes for cancer patients and those with MMB.

2.6 Coordination and Integration of Care

Patients with multimorbidity generally require care from multiple organizations to manage all of their conditions (Doessing & Burau, 2015). Thus, successful care delivered often depends on collaboration between organizations that operate independently. Efficient collaboration is essential as no single provider can manage such complex patients alone (Doessing & Burau, 2015).

Integration has recently been conceptualized as “the process of combining social and health services through alignment of financial, administrative, and clinical management incentives and modalities with the clinical practices of the multidisciplinary team in charge of their health and social care” (Vedel et al., 2011). Integrated care refers to the management and delivery of health services to ensure patients receive seamlessly connected health promotion,

disease prevention, diagnosis, treatment, disease management, rehabilitation, and palliative care across the care continuum (Huitema et al., 2018). For complex patients in particular, integrated health systems have been promoted as an efficient way to improve access, quality and continuity of services (Valentijn et al., 2013). Integration can be established at the macro (system integration), the meso (organizational and professional integration) and the micro (clinical integration) levels (Valentijn et al., 2013). At the macro level, system integration can improve the provision of continuous, comprehensive, and coordinated services throughout the care continuum (Valentijn et al., 2013). This can be achieved through vertical integration (i.e. across sectors, bringing together primary and secondary care services) and horizonal integration (i.e. through cross-sectorial collaboration) (Frcgp et al., 2008). Both vertical and horizontal integration are needed to overcome health system fragmentation (Nolte & McKee, 2008). Moreover, efficient health systems require partnership between organizational and professional boundaries (Valentijn et al., 2013). Organizational integration concerns the seamless delivery of health services (Delnoij et al., 2002), professional integration refers to collaboration among providers within and across organizations (Kodner, 2009), and clinical integration involves coherence in the delivery of services to an individual patient (Delnoij et al., 2002).

Examples of integrated care systems have been cited throughout the literature. Of interest, the Improving Mood -Promoting Access to Collaborative Treatment (IMPACT) intervention in the United States includes elements of evidence-based chronic condition models and has been shown to effectively serve primary care patients with diverse sociodemographic and clinical characteristics (Unützer et al., 2002). Patients with depression who were included in the intervention had significantly lower depression severity, higher rates of treatment response and higher rates of complete recovery from depression (Unützer et al., 2002). Patients also had

reportedly lower health-related functional impairments and greater overall quality of life (Unützer et al., 2002). These results highlight the need for interdisciplinary collaboration among team members with clearly defined roles, the benefits of integrating psychiatrists or psychologists into primary care, and the importance of personalizing treatment plans in accordance with patient preferences (Unützer et al., 2002). Another model of interest, the Spoke-Hub-and-Node (SHN) model of care designed to integrate care for people with heart failure has been promoted for complex patients (Huitema et al., 2018) has been implemented in Canada. The SHN represents an organization of care that collaborates with the primary care sector, community-based multidisciplinary teams, and specialists (Huitema et al., 2018). Patient risk and complexity guide this systems-based approach with care management involving a range of health professionals working together (Huitema et al., 2018). Key features of this approach originate from the Chronic Care Model (CCM) (Huitema et al., 2018). The CCM is one of the most highly regarded integrated care approaches for patients with chronic conditions. Designed to improve health outcomes through patient-centered and evidence-based care, the CCM brings together the following elements: community resources, health care organization, self-management support, delivery system design, decision support, and clinical information systems (Coleman et al., 2009). Overall, evidence suggests that redesigning care around the CCM elements improves the quality of care and patient outcomes (Coleman et al., 2009).

Funding arrangements can act as a barrier to the delivery of integrated, patient-centered care (Doessing & Burau, 2015). Providing bundled funding rather than FFS models has been suggested as a way to encourage collaboration between care environments and within multidisciplinary teams (Huitema et al., 2018). In Ontario, FHTs and CHCs provide primary care in a multidisciplinary setting with physicians and allied health professionals working as a team

(Gocan et al., 2014). CHCs are developed to meet community needs and focus on providing care to those with barriers to health (Government of Ontario, 2015). Moreover, CHCs offer a range of health promotion and disease prevention services with a focus on the social determinants of health (Government of Ontario, 2015). However, evidence suggests that only moderate levels of collaboration between multidisciplinary providers have been attained in CHCs in practice (Government of Ontario, 2015). FHTs were developed to provide patient-centered care, increase access to a variety of health professionals, assist with health system navigation, and offer more preventative care services and chronic care management (Gocan et al., 2014). Positive outcomes have been associated FHTs in prior research (Gocan et al., 2014), however not all studies have found that FHTs perform better than other primary care models (Glazier et al., 2015).

2.7 Continuity of Care

Continuity of care (COC) can be conceptualized as the way an individual patient experiences integration of services and coordination between providers over time (Haggerty, 2003). Continuity is experienced when a patient receives ongoing care from a single provider (or providers) that is connected, coherent, and consistent with the patients' healthcare needs and personal circumstances (Haggerty, 2012; Maarsingh et al., 2016). Three components of COC are commonly described; management, informational, and relational continuity (Freeman et al., 2001; Haggerty, 2003).

Management continuity refers to communication and coordination between providers within teams and across institutions and the delivery of care in a timely and orderly manner to achieve health goals (Freeman et al., 2001; Haggerty, 2012). Informational continuity covers the availability of necessary information at the point of care (Freeman et al., 2001; Haggerty, 2012). Information about prior health events and regarding a patient's preferences, values, and context

can promote the delivery of services that are responsive to the patients' needs (Haggerty, 2003). In primary care, relational continuity described as patient-centered care over time, is highly valued (Haggerty, 2012; Maarsingh et al., 2016; Starfield, 1998). Relational continuity concerns the therapeutic relationship between a patient and one or more providers that bridges episodes of care (Freeman et al., 2001; Maarsingh et al., 2016). Patients experience continuity most directly through relationships based on partnership and trust with trustworthy providers (Freeman et al., 2001; Haggerty, 2012).

Many measures can be used to evaluate the association between COC and health care utilization and patient outcomes (Health Quality Ontario, 2013). Measures generally focus on one component of COC, either management, informational, or relational continuity (Health Quality Ontario, 2013). For relational continuity in particular, common indices assess the following: (1) duration (the length of time with a particular provider), (2) density (the number of visits with the same provider over a defined period of time), (3) dispersion (the number of visits with different providers), and (4) sequence (the order in which visits with different providers occur) (Health Quality Ontario, 2013). The two most commonly used indices are the Usual Provider of Care (UPC) index and the Continuity of Care Index (COCI) (Jee & Cabana, 2006). The UPC index measures density of care while the COCI focuses on the dispersion of care and accounts for density of care (Jee & Cabana, 2006). Another measure of COC, the Sequential Continuity (SECON) index, captures the order in which providers are visited (Jee & Cabana, 2006). High COC with the SECON index occurs when the patient sees the same provider repeatedly for an episode of care and then another provider for the next episode of care as opposed to visits back and forth between different providers (Health Quality Ontario, 2013). The COCI has been used to evaluate the association between COC and outcomes among patients with

multimorbidity in other studies (Gruneir et al., 2016; Mondor et al., 2017). As the UPC index assesses visits with an index provider only and penalizes patients with chronic conditions who seek specialty care with other health care providers, the COCI is better suited for this study (Jee & Cabana, 2006), because it measures the dispersion and concentration of care. The COCI can account for both primary care and specialist visits (Health Quality Ontario, 2013), an important consideration as patients with multimorbidity require care from many providers including specialists.

COC has been associated with positive health outcomes in cancer patients. Fenton et al. (2008) explored whether continuity with the same physician was beneficial for CRC screening (Fenton et al., 2008). Patients with higher COC were more likely to receive fecal occult blood testing than patients with lower COC (28.9% vs. 26.8%, $p<0.001$) (Fenton et al., 2008). COC with a family physician was associated with a decreased likelihood of visiting the emergency department (OR=0.59, 95%CI: 0.52-0.66) and the hospital (OR=0.51, 95%CI: 0.46-0.57) in the last two weeks of life and a decreased likelihood of hospital death (OR=0.61, 95%CI: 0.55-0.68) in cancer patients (Almaawiy et al., 2014). Comparably, higher oncology COC in the post-treatment phase was associated with a lower likelihood of hospitalization (OR=0.78, 95%CI: 0.71-0.85) and emergency department use (OR=0.88, 95%CI: 0.82-0.95) in breast cancer patients (Chen et al., 2019). Likewise, patients with higher primary care provider COC were less likely to be hospitalized (OR=0.77, 95%CI: 0.70-0.85) or to utilize the emergency department (OR=0.75, 95%CI: 0.68-0.82) (Chen et al., 2019). Greater COC has been associated with patients supportive care needs in the areas of health care information and psychological needs being met (Husain et al., 2013). Higher experienced continuity was predictive of lower future needs for supportive care in a cancer care study (King et al., 2008). Fragmented cancer care,

defined as care received across multiple hospitals, has been associated with increased time-to-treatment and worse overall survival among patients with liver cancer (Hester et al., 2019). Conversely, COC has been associated with lower mortality in the surgical setting (Ryoo et al., 2009). Patients who were readmitted to the same hospital following resection for gastric cancer had a lower risk of death within 1 year (RR=0.693, 95%CI: 0.687-0.697) (Ryoo et al., 2009). Comparably, readmission to the same hospital and surgeon has been associated with decreased mortality among CRC patients (Justiniano et al., 2017). Patients with another surgeon had a 2-times greater risk of mortality (RR=2.40, 95%CI: 2.01-2.85) and those readmitted to another hospital with another surgeon had a 3 times greater risk of mortality (RR=3.14, 95%CI: 2.53-3.84) compared to those with the same hospital and surgeon (Justiniano et al., 2017).

Gruneir et al. (2016) found that the likelihood of hospitalization rises with increasing multimorbidity (Gruneir et al., 2016). However, the effect of multimorbidity on hospitalization was reduced with greater COC (Gruneir et al., 2016). COC has been associated with the early diagnosis of chronic conditions (Koopman et al., 2003), decreased hospitalizations (Gill, 1998), reduced emergency department (ED) use (Gill, 2000), and improved quality of care (Parchman et al., 2002). Koopman et al. (2003) found an association between continuity of care and the early diagnosis of diabetes mellitus (Koopman et al., 2003). Patients with a usual provider of care had 70% less unrecognized diabetes compared to patients with no usual site or provider of care (OR=0.30, 95%CI: 0.10-0.95) (Koopman et al., 2003). Gill et al. (1998) reported a significant association between COC and decreased future likelihood of hospitalization (Gill, 1998). For patients with chronic conditions (angina, asthma, grand mal seizures, other convulsions, COPD, CHF, diabetes mellitus, hypoglycemia, hypertension) provider COC was associated with lower likelihood of hospitalization (OR=0.54, 95%CI: 0.34-0.88) (Gill, 1998). Similarly, Gill et al.

(2000) found an association between provider COC and the number of hospital ED visits (Gill, 2000). COC was associated with a significantly lower likelihood of multiple ED visits among patients with stable (OR=0.86, 95% CI: 0.81-0.91) and unstable chronic conditions (OR=0.89, 95% CI: 0.82-0.96) (Gill, 2000). Furthermore, COC has been associated with improved quality of care among patients with diabetes (Parchman & Burge, 2002) and with reductions in resource utilization and costs for patients receiving outpatient treatment for chronic conditions (Parchman & Burge, 2002). Among older patients with diabetes, those with higher COC had lower rates of death than those with lower COC (8.6% vs 18.5%) (Worrall & Knight, 2011). Similarly, patients with no or weak usual sources of care had an increased risk of mortality following AMI (Spatz et al., 2014).

Chapter 3: Thesis Overview & Methodology

A review of the literature suggests that MMB is common among CRC patients. Similarly, studies have shown that MMB negatively impacts CRC patients' survival, however research examining the impact of specific conditions and condition combinations is limited. While it is known that patients with MMB are vulnerable to fragmented care, there is a paucity of research assessing the impact of specific health system factors on outcomes in this patient group. This thesis aimed to address these gaps in the literature. Understanding the effects of patient factors and comorbid conditions on survival in CRC patients can provide opportunities to target care management to better meet the needs of particular patient groups. Assessing the impact of specific health system factors will provide the evidence needed to inform health system reform and policies that will benefit patient-centered care for complex cancer patients.

3.1 Objectives

The aim of this study was to examine CRC patients' complexity and determine if sociodemographic and health system factors have an effect on the association between multimorbidity and CRC patients' survival.

The following specific objectives were examined to assess this overarching research aim:

1) To describe the complexity of CRC patients (through the prevalence of each condition and of each multimorbidity level, and the description of disease combinations);
2) To evaluate the association between multimorbidity and CRC patients' survival;
3) To evaluate if sociodemographic and health system factors influence the relationship between multimorbidity and CRC patients' survival.

3.2 Approach to Thesis

I used a quantitative research approach with population-based administrative data to address the overarching aim and specific objectives in this study.

The conceptual framework for this study is the Andersen's Behavioural Model for Health Services Use which has been widely used in health services research (Andersen, 1995). The model was introduced to assist with understanding health service utilization, and was designed to define and measure equitable access to health care (Andersen, 1995). Further development has led to the emerging model, which exemplifies the complex nature of health services use, and incorporates individual and contextual factors that influence utilization and that subsequently influence health outcomes (Andersen, 1995).

According to Andersen's Behavioural Model, an individual's use of health services is a function of three dynamics: predisposing factors, factors that enable and impede utilization, and need (Andersen, 1995). Predisposing factors refer to the characteristics which are intrinsic to the individual, prior to the development of illness. This would include demographic factors (age and sex), social structure (education, occupation, and ethnicity), and health beliefs (attitudes, values, and knowledge about health and health services) which contribute to an individual's propensity to seek care. Enabling factors are resources (such as income, health insurance, primary care model, and regular source of care), which must be available for health service use to occur. Moreover, services must not only be accessible, but individuals must know how to, and have the means to access these services. Finally, both perceived need (an individual's view of their own health) and evaluated need (professional judgement of an individual's health status) are important. Perceived need provides an understanding of care-seeking behaviour and adherence to

medical regimen, while evaluated need relates to the kind and amount of treatment received after consultation with a health care provider (Andersen, 1995).

This model was used to further understand the effect of sociodemographic and health system factors on the association between multimorbidity and CRC patients' survival. This conceptual framework was used to guide our research as health services use may impact the health status and survival of CRC patients. As described in Figure 1, the outcome of interest (survival) is determined by predisposing characteristics, enabling resources, need for health care utilization and the use of health services. We assessed how sociodemographic factors such as age, sex, ethnicity, income, and rurality (conceptualized as predisposing characteristics and enabling resources) and health system factors such as primary care models, primary care visits and continuity of care (included as enabling resources and proxies for health service use) impact survival among CRC patients of various cancer stages with comorbidities (need for service).

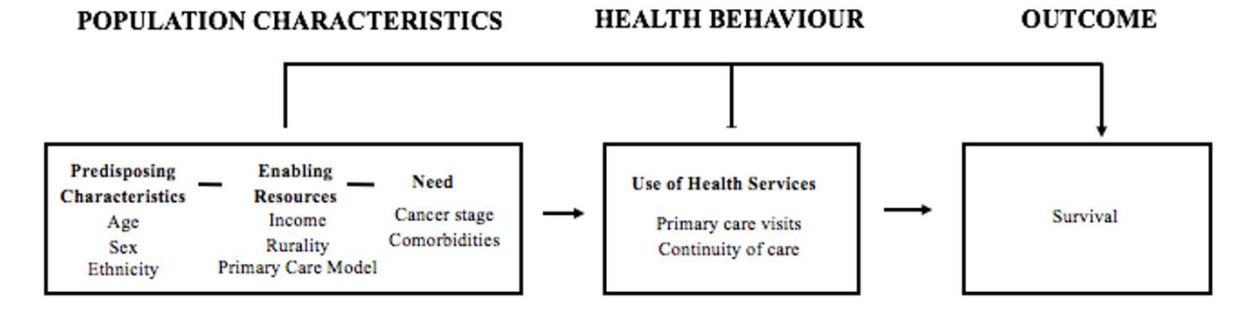


Figure 1. *Adapted Andersen's Model for Health Services Use*

3.3 Hypotheses

Hypothesis #1: *MMB has an impact on CRC patients' survival and this impact is influenced by sociodemographic factors, health system factors, and cancer stage.*

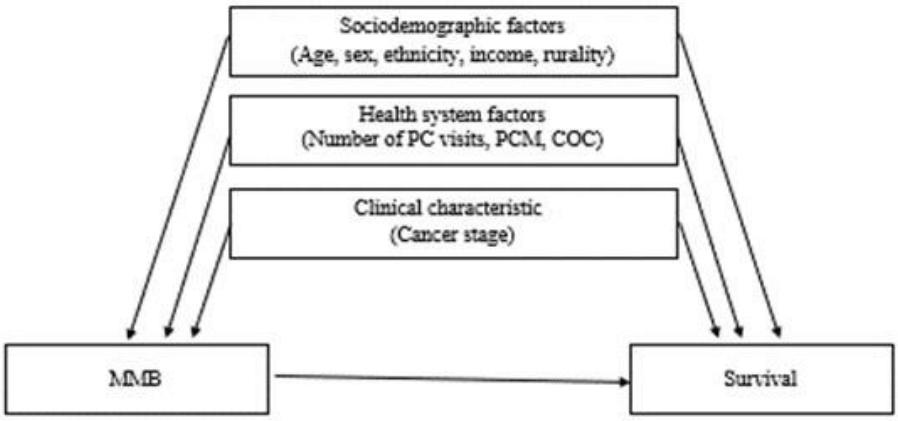


Figure 2. *Hypothesis #1: MMB has an impact on CRC patients' survival and this impact is influenced by sociodemographic factors, health system factors, and cancer stage*

Hypothesis #2: *The impact of MMB on CRC patients' survival is modified by health system factors, after controlling for sociodemographic factors and cancer stage.*

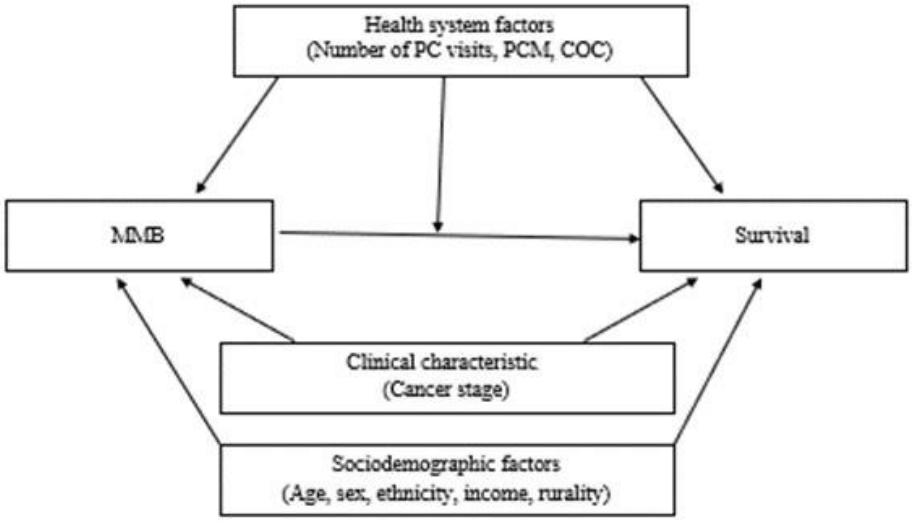


Figure 3. Hypothesis #2: The impact of MMB on CRC patients' survival is modified by health system factors, after controlling for sociodemographic factors and cancer stage.

3.4 Study Setting

This study was conducted in Ontario, the largest province in Canada. The population includes more than 13 million people (Government of Canada, 2017). The Canadian healthcare system is publicly funded and administered through provincial and territorial insurance plans (Health Canada, 2016). These plans are guided by the standards outlined in the Canada Health Act (Brian Hutchison et al., 2011; Health Canada, 2016). This system, informally known as Medicare, provides Canadian residents with universal health coverage (Health Canada, 2016). Thus, Ontario residents receive coverage for the costs of necessary care, which includes services provided by hospitals and physicians (Health Canada, 2016).

3.5 Data Sources

Population-based administrative data from the Institute for Clinical Evaluative Sciences (ICES) were used to address the overarching aim and specific objectives. Participants were identified from linked healthcare databases housed at the ICES that contain information on all Ontario residents, and recent immigrants following a three-month waiting period, who are eligible for provincial health coverage. An ICES key number (IKN) is used to anonymously link the data to ensure the privacy of all information. Databases include information on health services utilization, disease registries, and demographic characteristics. The specific databases used for this study were the Client Agency Program Enrolment (CAPE), Discharge Abstract Database (DAD), ICES Physician Database (IPDB), National Ambulatory Care Reporting System (NACRS), Ontario Cancer Registry (OCR), Ontario Health Insurance Plan (OHIP) claims, Ontario Marginalization Index (ON-Marg), and the Registered Persons Database (RPDB).

The Client Agency Program Enrolment (CAPE) includes data about patients registered with one of Ontario's primary care organizations (Institute for Clinical Evaluative Sciences (ICES), 2020). The database provides information about a patient's association with a particular physician or primary care organization. The CAPE captures information on patient enrollment with a primary care model (PCM) and includes the PCM type (ICES, 2020). In this study, the CAPE was used to identify patients enrolled in a PCM.

The Discharge Abstract Database (DAD) contains administrative, clinical, and demographic data on hospitalizations (Government of Canada, 2018c). In particular, the DAD includes data from hospital discharges (inpatient acute, chronic, rehabilitation) and day surgery interventions in Canada (Juurlink et al., 2006). In this study, the DAD was used to identify chronic conditions, and their date of diagnosis.

The ICES Physician Database (IPDB) captures information from the Ontario Health Insurance Plan (OHIP) database, the OHIP Corporate Provider Database (CPDB), and the Ontario Physician Human Resource Data Centre (OPHRDC) database (ICES, 2020). The IPDB contains data on physician demographics, specialty type, certification, and practice location (ICES, 2020). This database was used for the COC variable included in this study.

The National Ambulatory Care Reporting System (NACRS) collects data on ambulatory care in hospital and community-based settings across Canada (Government of Canada, 2018c). The NACRS includes data from emergency departments, day surgery interventions, and outpatient and community-based clinics (Government of Canada, 2018c). In this study, the NACRS was used to identify chronic conditions, and their date of diagnosis.

The Ontario Cancer Registry (OCR) contains information on all Ontario residents with a cancer diagnosis. Cancer cases are captured following the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) standards and rules for histology and primary cancer coding (Cancer Care Ontario, 2017c). Data in the registry are collected from a wide range of sources such as hospital admissions and discharges, pathology reports, consultation and treatment records from regional cancer centres or hospitals, and death certificates (Cancer Care Ontario, 2017b). The OCR was used to identify the cancer type, date of diagnosis, cancer stage, and date of death for patients included in this study. Cancer stage data was only available for a limited number of cases.

The Ontario Health Insurance Plan (OHIP) claims database contains information from physician claims from inpatient, outpatient, and long-term care facilities in Ontario. Provincial health coverage covers the costs related to medically necessary services including appointments with a family physician, and to some other health care providers, walk-in clinic visits, emergency department visits, medical tests, and surgery (Government of Ontario, 2020a). The OHIP claims database captures physician and patient data for each claim, such as the diagnosis, the service provided, and the date of the service (Tu et al., 2013). In this study, the OHIP claims database was used to determine the number of PC visits, inform the COC variable, and to identify chronic conditions and their date of diagnosis.

The Ontario Marginalization Index (ON-Marg) is a measure of deprivation based on four distinct dimensions of marginalization: residential instability, material deprivation, dependency, and ethnic concentration (Matheson et al., 2012). Ethnic concentration quintiles, representing the percentage of recent immigrants (relocated to Canada in the last 5 years of the census) and the percentage of visible minorities (self-identified), were considered in this study. Higher ethnic

concentration values represent a greater proportion of recent immigrants and visible minorities (Matheson et al., 2012).

The Registered Persons Database (RPDB) contains demographic information for individuals registered through the Ontario Health Insurance Plan (OHIP) and those eligible for the Ontario Drug Program (Government of Ontario, 2020b). In this study, the RPDB was used to determine a patients age, sex, income quintile, rurality, and vital status. The Rurality Index of Ontario (RIO), a scale that indicates a community's degree of rurality based on factors such as community population and access to health services, was used to identify rurality. The RIO ranges from 0 to 100, in which scores of 0-39 are considered rural, and scores of 40 or more are considered urban (Kralj, 2009).

A summary of databased and variables used in this study is provided in Table 1.

Table 1. *ICES databases and variables used in this study*

Database	Description	Variables
Client Agency Program Enrollment (CAPE)	Captures information on patient enrolment with specific practitioners or groups. Includes primary care models.	Primary care models
Discharge Abstract Database (DAD)	Provides information on hospitalizations in Ontario.	Chronic conditions based on ICD codes, date of diagnosis

	Includes admissions, length of stay and discharges.	
ICES Physician Database (IPDB)	Contains information on all Ontario physicians. Includes physician characteristics and specialty type.	Physician specialty for COC
National Ambulatory Care Reporting System (NACRS)	Captures information on outpatient visits to hospital and community-based ambulatory care. Includes day surgery, outpatient clinics, and emergency departments.	Chronic conditions based on ICD codes, date of diagnosis
Ontario Cancer Registry (OCR)	Provides information on all Ontario residents with newly diagnosed cancer. Includes date of diagnosis, site of primary cancer and cancer deaths.	Date of diagnosis, age at diagnosis, primary cancer site, cancer stage, date of death
Ontario Health Insurance Plan (OHIP) claims database	Captures information on claims paid for by OHIP.	Chronic conditions based on ICD codes, date of diagnosis,

	Includes service provided, date and associated diagnosis.	number of PC visits, number of visits for COC
Ontario Marginalization Index (ON-Marg)	Information about deprivation and marginalization from residential instability, material deprivation, dependency, and ethnic concentration.	Ethnic concentration quintile
Registered Persons Database (RPDB)	Contains demographic information for all individuals who have ever had a valid Ontario health card number. Includes age, sex, neighbourhood income and residence.	Sex, income quintile, rurality, date of death

3.6 Ethical Considerations

This study was part of a larger research project titled "Supporting complex cancer patients with multimorbidity navigate efficiently between health care and cancer care systems". Ethics approval from the ICES and through the Lakehead University Research Ethics Board was obtained for the larger project and for this thesis (see Appendix A). All researchers completed the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans – Course on

Research Ethics (TCPS 2: CORE). All the data are secured at the ICES and were accessible to researchers with valid ICES user credentials only. Data were accessed and analysed through the ICES Data and Analytic Services Environment (IDAVE) a secure virtual server to ensure information was protected at all times. Direct personal identifiers were not included in the data and only aggregate results approved by ICES were released for use outside of the IDAVE interface.

Chapter 4: Methods

4.1 Study Design & Population

A population-based retrospective cohort study was conducted with linked administrative data from the Institute for Clinical Evaluative Sciences (ICES). All Ontario residents, aged 18 to 105 years, diagnosed with CRC between April 1, 2003 and March 31, 2013 (index date) who were eligible for provincial health coverage were included, and followed until March 31, 2018. This time period was selected to fit within the scope of a larger project on complex cancer patients. Patients with a date of death recorded in the same month as their cancer diagnosis, or who had an invalid health card number, were excluded. Health card numbers are required by the ICES to accurately assign the confidential ICES number (IKN) that is used to link data across sets. All Ontario residents including recent immigrants following an initial three month waiting period are eligible for provincial health coverage and would therefore have a health card number.

4.2 Study Measures

Exposure Assessment

The exposure of interest in this study is MMB. The degree of MMB was defined as having one or more of the following chronic conditions: acute myocardial infarction (AMI), anxiety, asthma, cardiac arrythmia, chronic coronary syndrome (CCS), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), dementia, diabetes mellitus, hypertension, mood disorders (including depression), osteoarthritis, osteoporosis, renal failure, rheumatoid arthritis, stroke, and other mental health conditions (including substance use disorder; psychotic disorder; stress reaction, specifically post traumatic stress disorder (PTSD), and personality disorder) in addition to CRC. Conditions diagnosed prior to or within 30 days of CRC diagnosis were included. These conditions have been chosen due to their clinical relevance and burden (Kone Pefoyo et al., 2015). For instance, diabetes, COPD, and CHF were prevalent

among CRC patients in prior studies (Gross et al., 2006). MMB was measured with specific conditions and with MMB levels which were created by categorizing the number of conditions (1, 2, 3, 4 or more conditions) in addition to CRC. Patients with CRC only (i.e., those with no comorbidities) were treated as the reference group in the analyses. The top 10 condition combinations by level of MMB were identified. Condition combinations included grouping of commonly co-occurring conditions, based on co-occurring conditions observed for each individual. Some conditions, including AMI, asthma, CHF, COPD, hypertension and diabetes, have been defined in validated ICES cohorts, while the others are identified in a similar manner, based on a single diagnosis in acute care or two diagnoses in physician records over a two-year period (Koné Pefoyo et al., 2015).

Outcome Assessment

In survival analysis, the outcome of interest is the time to event, and incomplete data is censored. The outcome of interest in this study is the time from CRC diagnosis to death, or until March 31, 2018 if the individual is still alive. In this case, those who were lost to follow-up or who did not die at the end of the study period were censored. Censoring data at the end of the study indicates that the patient survived at least as long as the duration of the study.

Covariates

Sociodemographic factors in this study include age, sex, income level, ethnic concentration, and rurality. As identified through the literature, sociodemographic factors such as age, sex, income level, ethnic concentration, and rurality could potentially impact CRC patients' survival. To further understand the impact of sociodemographic factors on the association

between MMB and CRC patients' survival, these covariates were selected (see table 1 in chapter 3 for variable description).

Health system factors in this study include continuity of care (COC), primary care models (PCM), and primary care (PC) visits. COC with physicians, PCMs, and PC visits are all health system factors that can modified to better meet patient needs and improve patient outcomes. Health system factors examined in other settings, such as hospital admissions and readmissions and emergency department use were not assessed in this study. Prior studies have shown that PC use and COC are associated with a reduction in the rate of avoidable hospitalizations and emergency department visits among cancer patients and those with multimorbidity (Burge et al., 2003; Gill, 2000; Glazier et al., 2008). Similarly, ED visits are often used as an indicator of access to primary care (Glazier et al., 2012; McCusker et al., 2003), which can be improved through PCMs with patient enrollment and extended hours of care. Patient-centered approaches to care in particular contribute to quality of care and to improved outcomes for patient. Therefore, this set of health system factors were selected as they can be altered to facilitate patient-centered care and benefit the quality of care and outcomes of complex cancer patients.

COC can be conceptualized as the way an individual patient experiences integration of services and coordination between providers over time (Haggerty, 2003). Patients with MMB often require care from multiple places and providers and thus risk fragmented care which could potentially impact their survival (Haggerty, 2003). Moreover, COC was selected as a covariate to further understand how health system factors impact the relationship between multimorbidity and CRC patients' survival. The Bice-Boxerman Continuity of Care Index (COCI) was used to measure COC in our study. The COCI is an expression of the dispersion of visits across different

providers, ranging from 0 (no continuity, all visits to different providers) to 1 (high continuity, all visits to one physician).

Primary care (PC) visits were included as a proxy of health services use. This was used to measure the volume of visits during follow up to account for potential patients' needs. To account for the number of people in the study, and the amount of time each person spent in the study, the number of PC visits per person-years were measured and included in the analyses.

Primary Care Models (PCMs) were defined as follows: non-capitated models including non-rostered models, and those compensating physicians through FFS payments; capitated models such as the Family Health Networks (FHN) and Family Health Organizations (FHO) that operate through age-sex adjusted capitation payments; and capitated + models including the Family Health Teams (FHT) that offer incentives for interdisciplinary care in addition to capitation payments. PCMs should be considered in the context of MMB as changes to primary care organization and funding can be made to better meet patient needs. Alternate arrangements, including changes to physician payments and access to interdisciplinary care, could benefit patient-centered care and outcomes for complex cancer patients.

Cancer stage at diagnosis was considered as a clinical/needs factor. As previously described, stage at diagnosis is an important prognostic factor for CRC patients' and thus plays a crucial role in determining survival.

4.3 Analyses

The study population characteristics were described overall, and according to vital status (alive vs. deceased). Measures of central tendency were reported for continuous variables and the frequency/percentage was reported for categorical variables. Bivariate analyses were used to

assess the association between each covariate and death. Chi-square test was used for categorical variables and ANOVA was used for continuous variables.

Objective #1: To describe the complexity of CRC patients.

The complexity of CRC patients was described through the prevalence of each condition, and of each MMB level, as well as through the description of observed condition combinations. Condition combinations included grouping of commonly co-occurring conditions, based on co-occurring conditions observed for each individual. First, the percentage of each condition and the percentage of MMB level were determined. Next, the top 10 combinations for CRC patients within each level of MMB were identified, and the prevalence was reported. For each level of MMB, the prevalence of each combination was determined by dividing the number of CRC patients in that combination by the number of CRC patients in that level. MMB levels were defined with five categories representing patients with CRC as well as 1, 2, 3, or 4 or more conditions. For patients with CRC and one condition, the prevalence of each condition was reported. Next, the top 10 most prevalent pairs, triads, and quartets of observed combinations were reported for patients with two other conditions, three other conditions, and four other conditions, respectively. We identified combinations of chronic conditions through observation of unordered combinations, meaning that all patients with the same conditions were included in a combination, regardless of the order in which conditions were diagnosed.

Objective #2: To evaluate the association between MMB and CRC patients' survival.

The average survival by condition combination and by MMB level were described. Kaplan-Meier survival analyses and log-rank tests were performed with MMB as the exposure and survival as the outcome. Next, Cox proportional hazard regression was used to evaluate the

crude association between MMB and CRC survival by estimating unadjusted hazard ratios (HRs) and 95% confidence intervals (CIs). Additionally, the impact of MMB on the risk of death was reported with HRs and 95% CIs.

Objective #3: To evaluate if sociodemographic and health system factors influence the relationship between MMB and CRC patients' survival.

Cox proportional hazard models were performed to evaluate the adjusted impact of MMB on CRC patients' survival. Covarites included in the multivariate model tested for proportionality graphically using LLS (log(-log(S(t))) vs. log(t)) curves and with the Schoenfeld residuals test. A multivariate model was fitted to evaluate the impact of MMB on CRC patients' survival, adjusting for cancer stage and sociodemographic characteristics (age at diagnosis, sex, income quintile, ethnic concentration quintile, and rurality), as well as health system factors (COC, PCMs, and PC visits). Additional analyses were performed to test for effect modification. Effect modification occurs when the magnitude of effect of a predictor variable on an outcome variable differs based on a third variable. In this case, the effect of MMB on CRC patients' survival might be different for patients based on the level of COC and might vary based on the PCM in which a patient is enrolled. Tests for interaction were performed to investigate each of these potential effect modifications. The impact of MMB on the risk of death was reported with adjusted HRs and 95% CIs.

Statistical Software

All statistical analyses were performed with SAS version 9.4.

Chapter 5: Results

5.1 Description of the study population and crude associations with mortality

The study included 67,520 Ontario residents, aged 18 or more, who survived at least one month following colorectal cancer (CRC) diagnosis. Patients were predominately older, with an average age of 68.5 years. The cohort included more males than females and fewer patients from rural areas. More patients belonged to non-capitated primary care models (PCMs) (70.1%) than to capitated, capitated + or other models. The distribution of patients across PCMs was similar to that reported in the general population of Ontario (Glazier et al., 2012). A large proportion of the study population received high continuity of care (COC), as the median score was 0.75, and nearly 30% of patients had the maximum score of COC=1. Other studies have reported high median COC scores among adult Ontario residents with at least one chronic condition (Chau et al., 2021) and those with cancer (Almaawiy et al., 2014). About 38% of patients had quarterly visits (4 to 7 visits per year) with a primary care (PC) provider. Most patients experienced multimorbidity (MMB), as 83.1% of CRC patients had at least one condition at the time of cancer diagnosis. Of the 17 chronic conditions included in the study, the most prevalent condition was hypertension which affected more than half (58%) of all CRC patients. Other conditions such as osteoarthritis, diabetes, anxiety, and chronic coronary syndrome (CCS) accounted for the next most prevalent conditions. The prevalence of each additional condition is listed in Appendix B. On average, patients survived 6.1 years after cancer diagnosis. More than half of the cohort (54.1%) died by the study endpoint. The proportion of deceased patients increased with the number of chronic conditions, from around 45% for patients with no previous comorbidity to nearly 70% for patients with 4 or more comorbidities. The study population who survived until March 31, 2018 was followed on average 9.4 years (± 2.8 years), and up to 15

years. As shown in Table 1, sociodemographic characteristics, health system factors and cancer stage were associated with mortality.

Table 1. *Cohort characteristics, overall and according to vital status (CRC patients aged ≥ 18 years, who survived at least one month following cancer diagnosis)*

Variable	Total N (%)[†]	Deceased N (%)[‡]	P-value[a]
All	67,520 (100)	36,528 (54.1)	
Age at diagnosis (years)			
<60	16,462 (24.4)	5,858 (35.6)	<0.0001
60 to 69	16,896 (25.0)	7,302 (43.2)	
70 to 79	19,526 (28.9)	11,551 (59.2)	
80+	14,636 (21.7)	11,817 (80.7)	
Sex			
Male	36,607 (54.2)	20,065 (54.8)	<0.0001
Female	30,913 (45.8)	16,463 (53.3)	
Number of comorbid conditions (prior to cancer)			
0	11,407 (16.9)	5,092 (44.6)	<0.0001
1	15,865 (23.5)	7,383 (46.5)	
2	15,279 (22.6)	7,937 (52.0)	
3	10,926 (16.2)	6,299 (57.7)	
4 or more	14,043 (20.8)	9,817 (69.9)	
Cancer stage			
I	9,215 (13.7)	2,766 (30.0)	<0.0001
II	12,313 (18.2)	5,320 (43.2)	
III	13,720 (20.3)	6,937 (50.6)	
IV	8,911 (13.2)	8,193 (91.9)	
Unknown	23,361 (34.6)	13,312 (57.0)	
Ethnic concentration quintile			
Q1	15,169 (22.8)	8,709 (57.4)	<0.0001
Q2	14,354 (21.5)	8,056 (56.1)	
Q3	12,802 (19.2)	6,918 (54.0)	
Q4	12,261 (18.4)	6,429 (52.4)	
Q5	12,033 (18.1)	5,862 (48.7)	

Neighborhood income quintile			
Q1	12,852 (19.1)	7,514 (58.5)	<0.0001
Q2	13,926 (20.7)	7,733 (55.5)	
Q3	13,449 (20.0)	7,208 (53.6)	
Q4	13,546 (20.2)	7,079 (52.3)	
Q5	13,449 (20.0)	6,828 (50.8)	
Rural			
No	56,953 (84.5)	30,580 (53.7)	<0.0001
Yes	10,490 (15.5)	5,908 (56.3)	
Number of primary care visits (per person-years)			
0 to 1	5,691 (8.4)	3,794 (66.7)	<0.0001
2 to 3	12,026 (17.8)	4,394 (36.5)	
4 to 7	25,464 (37.7)	11,392 (44.7)	
8 to 12	14,179 (21.0)	9,054 (63.9)	
13 or more	10,169 (15.1)	7,894 (77.7)	
Primary care practice model*			
Non-capitated	47,323 (70.1)	26,381 (55.7)	<0.0001
Capitated	11,357 (16.8)	5,800 (51.1)	
Capitated +	7,949 (11.8)	3,872 (48.7)	
Other	891 (1.3)	475 (53.3)	
Continuity of care			
High (1.00)	19,348 (28.7)	9,956 (51.5)	<0.0001
Medium (0.50-0.99)	28,441 (42.1)	15,917 (56.0)	
Low (<0.50)	19,731 (29.2)	10,655 (54.0)	
Time since cancer diagnosis in years (maximum follow-up date: March 31, 2018)			
Mean (SD)	6.10 (4.25)	3.28 (3.09)	<0.0001
Median (IQR)	6.00 (7.36)	2.29 (4.09)	

[a] Calculated by t-test, ANOVA, or chi-square as appropriate.
† Column percentages, ‡ Row percentages
* Primary care models of interest were the CCM, the FHG and non-rostered models (non-capitated models), the FHN and the FHO (capitated models), and the FHT (capitated+). All other models were included as part of the "other" category.

5.2 Crude impact of MMB on CRC patients' survival

As displayed in Figure 1a, CRC patients' survival varied significantly ($p<0.0001$) according to the level of MMB. Patients with no comorbidity and those with one comorbidity

had the greatest survival probability whereas patients with ≥4 comorbidities had the poorest. Survival probability for patients with one comorbidity surpassed that of patients with CRC only until the study mid-point. After this point, survival was better for patients with CRC only, likely due to newly developed conditions. The survival curves were also stratified by cancer stage and the trend remained the same. Patients with MMB continued to have poorer survival than those with CRC only, and survival was poorest for those with more conditions. While survival continued to vary significantly ($p<0.0001$) for each cancer stage, the differences in survival probability between patients with and without MMB were less pronounced among those with Stage IV CRC as all patients had low survival probability (Figure 1b to 1e).

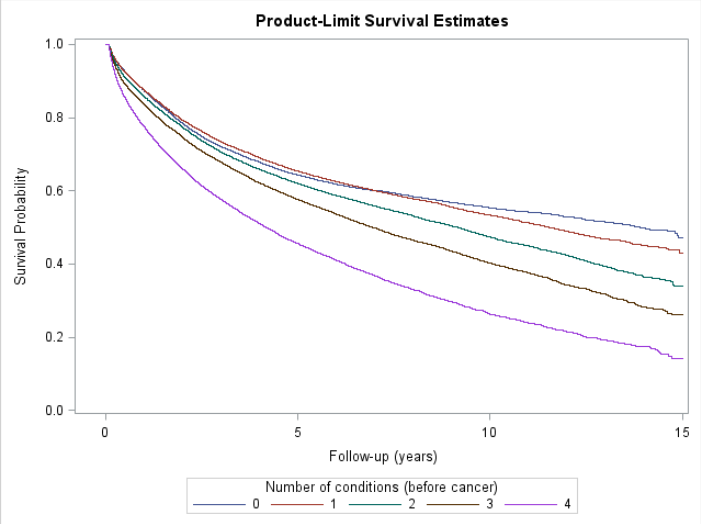
Kaplan-Meier survival analyses were also performed to examine the probability of death among CRC patients' according to health system factors, namely PC visits, PCMs, and COC (results not shown). Patients who had 2 to 3 PC visits per person-years had the greatest survival probability, followed by those with 4 to 7 PC visits per-person years. CRC patients with 0 to 1 visit per person-years had the lowest survival probability until the 5-year point. After this time, patients with 13 or more visits per year had the poorest survival probability. Patients with high COC consistently had the highest survival probability. However, patients with low COC only had the lowest survival probability until the study mid-point. Patients with medium COC had relatively poorer survival probability after this point. Finally, survival probability was not significantly different between PCMs.

Kaplan-Meier curves were created to examine the combined effect of MMB and each of the health system factors. The survival probability shown in these models stemmed largely from the effect of MMB rather than the combined effect of these variables (see Appendix C). The only

exception was noticed for CRC patients with 0 to 1 PC visits, as those with CRC only had a much better survival probability than those with MMB.

Figure 1: *Survival probability after colorectal cancer diagnosis by degree of multimorbidity, overall and by cancer stage*

Figure 1a: Overall



P-value <0.0001 with log-rank test

Figure 1a: *Survival probability after colorectal cancer diagnosis by degree of multimorbidity*

Figure 1b: Stage I

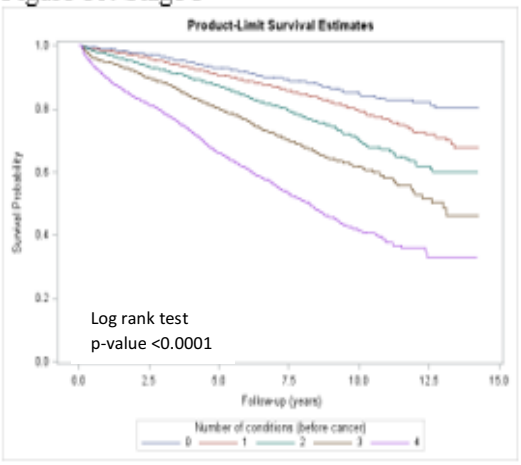


Figure 1c: Stage II

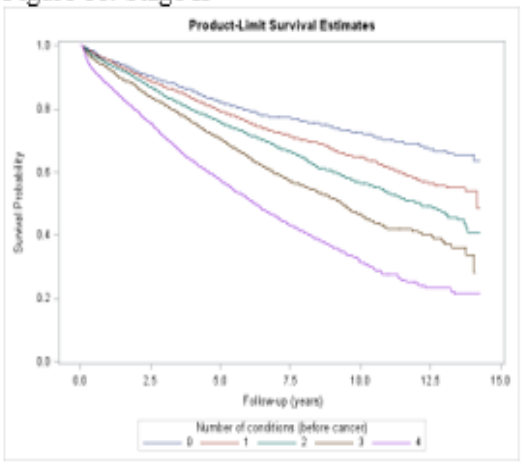


Figure 1d: Stage III

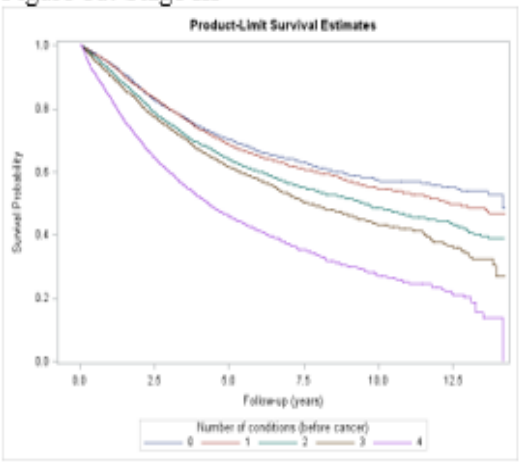


Figure 1e: Stage IV

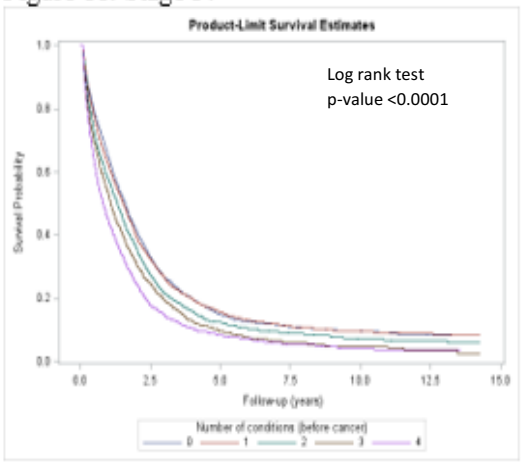


Figure 1b-d*: Survival probability after colorectal cancer diagnosis by degree of multimorbidity and cancer stage*

5.3 Adjusted impact of MMB on CRC patients' survival

Cox Proportional Hazard Regression was performed to examine the adjusted impact of MMB on CRC patients' survival. Covariates included in the multivariate model were tested for proportionality graphically using LLS (log(-log(S(t))) vs. log(t)) curves and with the Schoenfeld residuals test. The LLS curves appeared parallel for all variables, except for cancer stage which seemed to violate the proportionality assumption. For all variables except for cancer stage, the proportional hazard assumption was supported by a non-significant relationship between the Schoenfeld residuals and time. Cancer stage is one of the most important factors used to

determine a patients' prognosis. As such, we chose to include cancer stage in the model given that through stratification, it would not be possible to estimate its effect. This may lead to some over- or under-estimation as we are using an average rather than time-varying effect, and we have interpreted these findings with caution.

First, univariate models were fitted to separately examine the unadjusted impact of MMB and each health system factor on CRC patients' survival for comparison with the adjusted model. As shown in Table 2, MMB, COC, and PC visits were significantly associated with CRC patients' survival, while PCMs were not. A clear gradient was observed between MMB levels, with higher levels associated with worse survival. At any point during the study period a patient with one comorbidity was 5% more likely to die (HR 1.05, 95% CI: 1.02-1.09) than a patient with CRC only, whereas a patient with ≥4 comorbidities was 210% more likely to die (HR 2.10, 95% CI: 2.03-2.17). However, after controlling for cancer stage, age at diagnosis, sex, rurality, ethnicity, and income, the impact of MMB level became less important in the fully adjusted model. It was only significant for those with 3 and 4+ conditions respectively, who were 6 and 30% more likely to die, reflecting the role of appropriate care management, and the influence condition severity. In the multivariates model, CRC patients with low COC had a significantly lower survival than those with high COC, however the results for medium COC were not significant. Patients with regular PC visits had a lower risk of death than those with 1 or fewer PC visits per year. All patients with a greater number of visits had better survival than those with 0-1 visit, though survival somewhat decreased with increasing visits. Moreover, compared to patients with 1 or fewer annual visits, the risk of death for patients with 2 to 3 visits dropped by 61% (aHR 0.39 95% CI: 0.37-0.41) whereas the risk of death for patients with 13 or more visits only dropped by 13% (aHR 0.87, 95% CI: 0.84-0.91). It seems that having a reasonably regular

follow-up (2 to 7 visits) reduces the risk of death for CRC patients but those without a PC provider and those requiring too many visits are likely not appropriately managed, or have more severe status, thus a higher rate of death. For PCMs, members of capitated and capitated + models had a 7% and a 5% greater risk of death than non capitated, respectively (aHR: 1.07, 95% CI: 1.04-1.10; aHR: 1.05 95% CI: 1.01-1.09). Other factors such as cancer stage, age at diagnosis, sex, ethnicity, and income had a significant effect on CRC patients' survival.

Table 2. *Crude and adjusted impact of MMB on CRC patients' survival (CRC patients aged ≥ 18 years, who survived at least one month following cancer diagnosis)*

Variable	Crude HR (95% CI)	Adjusted HR (95% CI)
Number of comorbid conditions (prior to cancer)		
0	ref.	ref.
1	1.05 (1.02-1.09)	0.96 (0.93-1.00)
2	1.24 (1.20-1.28)	1.00 (0.96-1.03)
3	1.48 (1.42-1.53)	1.06 (1.02-1.10)
≥4	2.10 (2.03-2.17)	1.30 (1.25-1.35)
Primary care visits (per person-years)		
0 to 1	ref.	ref.
2 to 3	0.32 (0.31-0.33)	0.39 (0.37-0.41)
4 to 7	0.40 (0.39-0.41)	0.45 (0.44-0.47)
8 to 12	0.68 (0.66-0.71)	0.67 (0.64-0.69)
13 or more	1.03 (0.99-1.07)	0.87 (0.84-0.91)
Primary care model		
Non-capitated	ref.	ref.
Capitated	1.00 (0.97-1.03)	1.07 (1.04-1.10)
Capitated +	0.97 (0.94-1.01)	1.05 (1.01-1.09)
Other	1.03 (0.94-1.13)	1.00 (0.90-1.09)
Continuity of care		
High	ref.	ref.
Medium	1.13 (1.10-1.16)	0.97 (0.95-1.00)
Low	1.11 (1.08-1.14)	1.07 (1.04-1.10)
Stage		
I		ref.
II		1.45 (1.38-1.52)
III		2.07 (1.98-2.17)
IV		9.13 (8.73-9.54)

	Unknown		2.16 (2.07-2.25)
Age at diagnosis (years)			
	<60		ref.
	60-69		1.26 (1.21-1.30)
	70-79		1.91 (1.85-1.98)
	80+		3.53 (3.41-3.65)
Sex			
	Male		ref.
	Female		0.89 (0.87-0.91)
Rural			
	No		ref.
	Yes		1.04 (1.00-1.07)
Ethnic quintile			
	Q1		1.23 (1.18-1.27)
	Q2		1.21 (1.17-1.26)
	Q3		1.16 (1.12-1.20)
	Q4		1.12 (1.08-1.16)
	Q5		ref.
Income quintile			
	Q1		1.21 (1.17-1.25)
	Q2		1.10 (1.07-1.14)
	Q3		1.08 (1.04-1.12)
	Q4		1.04 (1.00-1.07)
	Q5		ref.

5.4 Description of CRC patients' complexity through condition combinations and impact on mortality

Another way to explore the impact of MMB is to examine patient complexity through the description of condition combinations, and associations with survival. Table 3 shows the top ten most common condition combinations for each level of MMB. There were multiple combinations of conditions. Among CRC patients with one other condition, the top ten conditions accounted for roughly 98% of the population in that level of MMB. Conversely, only 14% of CRC patients with four or more conditions were captured by the top ten quartets. An

increase in the number of condition combinations was observed as the level of MMB increased. There were 112 combinations of conditions observed among patients with two comorbidities, compared to 3230 combinations among patients with four comorbidities.

Of the top ten conditions for CRC patients with 1 comorbidity those with COPD had the worst mortality rate (69.8%), followed by those with diabetes (50.4%) and those with hypertension (50.3%). Other conditions not represented in the top ten had poorer mortality rates, such as AMI, dementia, CHF, and renal failure. Among CRC patients with 2 comorbidities, the risk of death was especially high for patients with COPD and hypertension, those with arrythmia and hypertension, as well as those with CCS and hypertension based on the top ten most common condition combinations. Combinations which included both CCS and hypertension seemed to represent the most lethal combinations for CRC patients with 3 or 4 or more comorbidities. For instance, 64.3% of patients with arrythmia, CCS, and hypertension died, which was the highest risk of death among the top ten most frequent combinations.

Table 3. *Top ten frequent combinations of co-occurring chronic conditions among CRC patients, by level of MMB and associated crude mortality rate (CRC patients aged ≥ 18 years, who survived at least one month following cancer diagnosis)*

MMB level	Combinations	Total N (%)	Deceased N (%)
No condition prior to CRC diagnosis		11,407 (100)	5,092 (44.6)
1 condition (n=15,865 – 17 conditions in total)	Hypertension	6,896 (43.5)	3,469 (50.3)
	Osteoarthritis	2,995 (18.9)	1,173 (39.2)
	Anxiety	2,204 (13.9)	872 (39.6)
	Diabetes	1,267 (8.0)	639 (50.4)
	Asthma	664 (4.2)	251 (37.8)
	Osteoporosis	428 (2.7)	169 (39.5)
	Coronary Syn.	405 (2.6)	196 (48.4)

	COPD	278 (1.8)	194 (69.8)
	Mental Health	205 (1.3)	97 (47.3)
	Arrythmia	186 (1.2)	85 (45.7)
	Dementia	73 (0.5)	N/A*
	Stroke	70 (0.4)	43 (61.4)
	CHF	65 (0.4)	50 (76.9)
	Rheumatoid Arthritis	49 (0.3)	26 (53.1)
	Renal Failure	41 (0.3)	31 (75.6)
	Mood disorders	32 (0.2)	13 (40.6)
	AMI	7 (0.1)	7 (100)
2 conditions (n=15,279 – 112 combinations in total)	Hypertension, Osteoarthritis	3,210 (21.0)	1,625 (50.6)
	Diabetes, Hypertension	2,652 (17.4)	1,444 (54.4)
	Hypertension, Anxiety	1,497 (9.8)	711 (47.5)
	Osteoarthritis, Anxiety	1,094 (7.2)	397 (36.3)
	Coronary Syn., Hypertension	981 (6.4)	554 (56.5)
	Diabetes, Osteoarthritis	463 (3.0)	222 (47.9)
	Asthma, Hypertension	418 (2.7)	211 (50.5)
	Hypertension, Osteoporosis	347 (2.3)	167 (48.1)
	Arrythmia, Hypertension	335 (2.2)	202 (60.3)
	COPD, Hypertension	280 (1.8)	214 (76.4)
3 conditions (n=10,926 – 364 combinations in total)	Diabetes, Hypertension, Osteoarthritis	1,232 (11.3)	635 (51.5)
	Hypertension, Osteoarthritis, Anxiety	1,060 (9.7)	498 (47.0)
	Coronary Syn., Hypertension, Osteoarthritis	636 (5.8)	347 (54.6)
	Coronary Syn., Diabetes, Hypertension	581 (5.3)	351 (60.4)
	Diabetes, Hypertension, Anxiety	488 (4.5)	249 (51.0)
	Asthma, Hypertension, Osteoarthritis	309 (2.8)	139 (45.0)

	Hypertension, Osteoarthritis, Osteoporosis	302 (2.8)	153 (50.7)
	Arrythmia, Hypertension, Osteoarthritis	240 (2.2)	139 (57.9)
	Coronary Syn., Hypertension, Anxiety	212 (1.9)	125 (59.0)
	Arrythmia, Coronary Syn., Hypertension	182 (1.7)	117 (64.3)
4 conditions (n=14,043 – 3230 combinations in total)	Diabetes, Hypertension, Osteoarthritis, Anxiety	404 (2.9)	192 (47.5)
	Coronary Syn., Diabetes, Hypertension, Osteoarthritis	327 (2.3)	179 (54.7)
	Coronary Syn., Hypertension, Osteoarthritis, Anxiety	215 (1.5)	123 (57.2)
	Asthma, Diabetes, Hypertension, Osteoarthritis	155 (1.1)	79 (51.0)
	Asthma, Hypertension, Osteoarthritis, Anxiety	152 (1.1)	63 (41.4)
	Arrythmia, Coronary Syn., Hypertension, Osteoarthritis	145 (1.0)	83 (57.2)
	Asthma, COPD, Hypertension, Osteoarthritis	138 (1.0)	102 (73.9)
	Hypertension, Osteoarthritis, Osteoporosis, Anxiety	135 (1.0)	71 (52.6)
	Arrythmia, CHF, Coronary Syn., Hypertension	128 (0.9)	106 (82.8)
	CHF, Coronary Syn., Diabetes, Hypertension	120 (0.9)	96 (80.0)

*<6 still alive (not reportable).

5.5 Effect of condition combinations on CRC patients' survival

Cox Proportional Hazard Regression was also performed to examine the adjusted impact of condition combinations on CRC patients' survival. As shown in Table 4, the impact of condition combinations on CRC patients' survival changed after controlling for cancer stage, age at diagnosis, sex, rurality, ethnicity, income, PC visits, PCMs, and COC. Survival differences

were noted not only between levels of MMB, but also within each level depending on the specific conditions that co-existed before cancer diagnosis.

Of the top ten conditions among CRC patients with 1 comorbidity, those with COPD or other mental health conditions had the worse survival, respectively 56% and 26% greater compared to those with CRC only. However, the top ten conditions did not represent the most lethal conditions in this patient group. For instance, patients with AMI and those with renal failure were 149% and 108% more likely to die respectively than those without comorbidity. Similarly, patients with dementia, CHF, and stoke, were more significantly more likely to die than those with CRC only.

For patients with two comorbidities, those with COPD and hypertension had the greatest risk of death and had a 64% greater risk of death than those with CRC alone. Patients with hypertension and diabetes had the next poorest survival and were 8% more likely to die than those without comorbidity. Patients with other combinations not represented in the top ten had a 1.17 times greater likelihood of death than those with CRC only.

Of the top ten combinations for patients with 3 comorbidities, the combination of CCS, diabetes, and hypertension was the most lethal. Compared to those with no other conditions, patients in this group were 1.14 times more likely to die. Patients with combinations outside of the top ten conditions were 31% more likely to die than those with CRC only. Likely, the most lethal combinations of conditions are not represented in the top ten condition combinations for this group.

At the highest MMB level (4 or more comorbidities), the likelihood of death was 63% greater for those with CHF, CCS, diabetes, and hypertension; 48% greater for those with

arrythmia, CHF, CCS, and hypertension; and 36% greater for patients with asthma, COPD, hypertension, and osteoarthritis.

On another hand, some conditions or combinations of conditions showed a lower risk of death than those who had no condition prior to CRC, regardless of the level of MMB. These combinations often included osteoarthritis, hypertension, and osteoporosis.

Table 4. *Crude and adjusted impact of MMB combinations on CRC patients' survival (CRC patients aged ≥ 18 years, who survived at least one month following cancer diagnosis)*

Combinations	Crude HR (95% CI)	Adjusted HR (95% CI)*
No condition prior to CRC	ref	ref
1 Condition		
Hypertension	1.15 (1.10-1.20)	0.95 (0.91-0.99)**
Osteoarthritis	0.85 (0.80-0.91)	0.84 (0.79-0.89)**
Anxiety	0.86 (0.80-0.93)	0.98 (0.91-1.05)
Diabetes	1.20 (1.11-1.30)	1.11 (1.02-1.21)**
Asthma	0.80 (0.71-0.91)	0.90 (0.79-1.02)
Osteoporosis	0.83 (0.72-0.97)	0.80 (0.69-0.94)**
Coronary Syndrome	1.06 (0.92-1.22)	0.85 (0.74-0.98)**
COPD	2.05 (1.78-2.37)	1.56 (1.35-1.80)**
Other Mental Health	1.16 (0.95-1.42)	1.26 (1.03-1.54)**
Arrythmia	1.00 (0.80-1.23)	0.91 (0.73-1.13)
Dementia	3.63 (2.85-4.61)	1.83 (1.43-2.34)**
Stroke	1.71 (1.27-2.31)	1.37 (1.01-1.86)**
CHF	2.42 (1.83-3.19)	1.46 (1.10-1.94)**
Rheumatoid Arthritis	1.30 (0.89-1.91)	1.22 (0.83-1.79)

Renal Failure	2.62 (1.84-3.73)	2.08 (1.45-2.98)**
Mood disorders	0.86 (0.50-1.48)	1.11 (0.64-1.91)
AMI	4.22 (2.01-8.86)	2.49 (1.19-5.22)**
2 Conditions		
Hypertension, Osteoarthritis	1.17 (1.11-1.24)	0.92 (0.87-0.97)**
Diabetes, Hypertension	1.30 (1.22-1.38)	1.08 (1.02-1.15)**
Hypertension, Anxiety	1.09 (1.01-1.18)	0.95 (0.87-1.02)
Osteoarthritis, Anxiety	0.81 (0.73-0.90)	0.89 (0.80-0.99)**
Coronary Syndrome, Hypertension	1.35 (1.23-1.47)	0.98 (0.89-1.07)
Diabetes, Osteoarthritis	1.14 (1.00-1.30)	1.06 (0.93-1.21)
Asthma, Hypertension	1.11 (0.97-1.28)	0.96 (0.83-1.10)
Hypertension, Osteoporosis	1.08 (0.92-1.25)	0.84 (0.72-0.98)**
Arrythmia, Hypertension	1.48 (1.29-1.70)	1.12 (0.97-1.29)
COPD, Hypertension	2.49 (2.18-2.86)	1.64 (1.43-1.88)**
Other with two conditions	1.37 (1.31-1.44)	1.17 (1.11-1.23)**
3 Conditions		
Diabetes, Hypertension, Osteoarthritis	1.26 (1.16-1.37)	0.99 (0.91-1.07)
Hypertension, Osteoarthritis, Anxiety	1.11 (1.01-1.21)	0.98 (0.89-1.07)
Coronary Syndrome, Hypertension, Osteoarthritis	1.33 (1.19-1.48)	0.97 (0.87-1.08)
Coronary Syndrome, Diabetes, Hypertension	1.44 (1.29-1.60)	1.14 (1.02-1.27)**
Diabetes, Hypertension, Anxiety	1.23 (1.08-1.40)	1.11 (0.98-1.27)

Asthma, Hypertension, Osteoarthritis	1.02 (0.86-1.21)	0.87 (0.73-1.03)
Hypertension, Osteoarthritis, Osteoporosis	1.23 (1.04-1.44)	0.89 (0.75-1.04)
Arrythmia, Hypertension, Osteoarthritis	1.48 (1.25-1.76)	0.91 (0.77-1.08)
Coronary Syndrome, Hypertension, Anxiety	1.38 (1.16-1.65)	0.98 (0.82-1.18)
Arrythmia, Coronary Syndrome, Hypertension	1.69 (1.40-2.02)	1.16 (0.96-1.39)
Other with 3 conditions	1.70 (1.63-1.78)	1.31 (1.25-1.37)**
4 Conditions		
Diabetes, Hypertension, Osteoarthritis, Anxiety	1.17 (1.01-1.35)	1.09 (0.94-1.26)
Coronary Syndrome, Diabetes, Hypertension, Osteoarthritis	1.33 (1.15-1.54)	1.01 (0.87-1.18)
Coronary Syndrome, Hypertension, Osteoarthritis, Anxiety	1.47 (1.23-1.75)	1.14 (0.95-1.36)
Asthma, Diabetes, Hypertension, Osteoarthritis	1.28 (1.02-1.60)	1.13 (0.90-1.41)
Asthma, Hypertension, Osteoarthritis, Anxiety	0.93 (0.73-1.19)	0.90 (0.70-1.15)
Arrythmia, Coronary Syndrome, Hypertension, Osteoarthritis	1.45 (1.17-1.80)	0.92 (0.74-1.14)
Asthma, COPD, Hypertension, Osteoarthritis	2.19 (1.80-2.67)	1.36 (1.12-1.66)**
Hypertension, Osteoarthritis, Osteoporosis, Anxiety	1.30 (1.03-1.65)	0.87 (0.69-1.10)
Arrythmia, CHF, Coronary Syndrome, Hypertension	2.58 (2.13-3.12)	1.48 (1.22-1.80)**

CHF, Coronary Syndrome, Diabetes, Hypertension	2.37 (1.94-2.91)	1.63 (1.33-2.00)**
Other with 4 or more conditions	2.23 (2.15-2.31)	1.57 (1.51-1.63)**

*adjusted for stage, age at diagnosis, sex, rurality, ethnicity, income, COC, PCMs and PC visits
**flag for significance

Chapter 6: Discussion

This study assessed the effect of multimorbidity (MMB) on colorectal cancer (CRC) patients' survival considering the role of sociodemographic factors (conceptualized as predisposing characteristics) and health system factors (included as enabling resources and proxies for health service use). The effects of MMB were examined according to levels of MMB prior to cancer diagnosis, defined as 0, 1, 2, 3, 4 or more conditions, as well as through condition combinations. The findings showed differences in survival between levels of MMB as hypothesized, and also showed substantial variations within each level depending on the specific conditions that co-existed before CRC diagnosis.

We found that MMB was prevalent, as 83.1% of the study population had at least one other condition. Other studies have reported prevalence rates of MMB among CRC patients ranging from 14% to 70% (Morris et al., 2011; Sarfati et al., 2009) which differed based on the study population, the conditions considered and the measures used to assess comorbidity. Another Canadian study in the Province of Alberta found that roughly one third of CRC patients had MMB (Cuthbert et al., 2018).

Similar to some prior studies, the most common condition was hypertension (Sarfati et al., 2009; van Leersum et al., 2013) which occurred among more than half (58%) of the study cohort. Other conditions such as osteoarthritis, diabetes, chronic coronary syndrome (CCS), and anxiety were common. Roughly 35% of CRC patients in our study had osteoarthritis, and about 24% had diabetes. Comparably, Kenzik et al. (2016) found that musculoskeletal conditions, such as arthritis, were commonly diagnosed prior to CRC. Patients with CRC also had a high prevalence of diabetes and other metabolic conditions in other studies (Hahn et al., 2018; Kenzik et al., 2016; Sarfati et al., 2009; van Leersum et al., 2013). In our study, about 18% of the cohort had CCS. Cardiovascular conditions, such as CCS, are among the most prevalent concomitant

conditions in CRC patients (De Marco et al., 2000; Hawkes et al., 2011). Across the literature the prevalence of anxiety in CRC patients ranges largely from 1.0% to 47.2% (Tavoli et al., 2007; Zhang & Cooper, 2010). The wide-range likely reflects the different measures used to identify anxiety. In our study, the prevalence falls within this range with around 22% of patients having anxiety.

The study results showed that MMB negatively impacts survival for CRC patients, which is consistent with the findings of past cohort studies and across a diversity of study settings. A meta-analysis conducted by Boakye et al. (2018) found that CRC patients with mild/moderate and severe comorbidity had 1.41 times and 2.03 times higher risk of overall mortality respectively, compared to CRC patients without comorbidity. Mild/moderate comorbidity was defined as a Charlson Comorbidity Index (CCI) score of 1-2, and severe comorbidity was defined as a CCI score ≥ 3. All studies included in the meta-analysis adjusted for at least age and cancer stage. The crude HRs from our study more closely resemble these findings than those from the adjusted model that are lower. Also, we assessed multiple levels of MMB.

We found that the risk of death increased with the number of comorbidities and ranged from a 1.05 times greater risk of mortality for those with 1 comorbidity, to a 2.10 times greater risk for those with 4 or more conditions compared to those with CRC only. After adjusting for cancer stage, sociodemographic characteristics (age, sex, income, ethnicity, rurality), and health system factors (PCMs, COC, PC visits) the results for patients with 1 or 2 comorbidities were not significantly different from those of patients with no comorbidity. Patients with CRC and 3 comorbidities continued to have a greater risk of death than those with CRC only, however the risk dropped from 48% to only 6% in the adjusted model. For those with 4 or more comorbidities the risk dropped from 110% to 30% greater than those with no prior conditions at CRC

diagnosis. While higher levels of MMB remain a risk factor, these findings likely reflect the confounding role of appropriate care management, and the influence condition severity. Moreover, it is likely that care management for CRC takes precedence over lower level MMB, however higher complexity is still an issue. As we only examined the top 10 combinations for each level of MMB, there may be other combinations of conditions that are more lethal, as evidenced in the HRs for those grouped as "other" in each MMB level.

A handful of prior studies have identified commonly co-occurring condition combinations among CRC patients, and have explored the impact of these combinations on patient outcomes (Cuthbert et al., 2018; Gross et al., 2006; Hahn et al., 2018; Kenzik et al., 2016). We found that disease combinations including both hypertension and diabetes were especially common. For instance, these conditions comprised the second most prevalent combination among CRC patients with two other conditions, and grouped together with osteoarthritis, and with osteoarthritis and anxiety, to form the most prevalent combinations in CRC patients with 3 conditions, and with 4 or more conditions, respectively. Similarly, Kenzik et al (2016) identified clusters of self-reported chronic conditions using exploratory factor analysis and reported that 30% of their cohort belonged to the metabolic cohort representing both diabetes and hypertension .

Our study results show that the combinations of conditions that impact survival in CRC patients are diverse, and often difficult to predict. For example, many combinations of conditions that included both diabetes and hypertension were detrimental, while others did not have a significant impact on survival. One explanation for this variation includes the severity of co-existing conditions (Sarfati et al., 2016). For example, if these conditions are combined with

more severe conditions, such as CCS, survival will likely be poorer than a combination including osteoarthritis.

We found that combinations including cardiovascular conditions (including CCS, and CHF) alone, cardiovascular conditions with respiratory conditions (such as COPD), and cardiovascular conditions combined with diabetes, faired the worst. While CHF and COPD were relatively uncommon in our study, they were often represented among the most lethal groups. Comparably, Hahn et al. (2018) identified four distinct comorbidity profiles using latent class analysis and found that the class representing the fewest patients had the poorest survival. Common conditions in this class were diabetes, renal disease, COPD, CHF, MI, and other vascular conditions (Hahn et al., 2018). Another study by Cuthbert et al. (2018) categorized patients into mutually exclusive comorbidity groups and found that patients with cardiovascular disease and diabetes had poor survival (Cuthbert et al., 2018). These findings allow clinicans to keep a watchful eye for co-occuring conditions that heighten patient risk. Gross et al. (2006) examined the effect of specific chronic conditions on mortality among older CRC patients. They obtained aHRs for each condition and calculated the population attributable risk (PAR) for each estimate. The PAR represents the proportion of deaths that could be attributed to a particular condition and can be calculated as a risk difference between those exposed and unexposed to a condition or cluster of interest. The HR on the other hand can be used to indicate the risk of death for a condition or combination of conditions taking into account other factors, such as the effect of other conditions or combinations of conditions, that contribute to mortality. Conditions with the highest HRs were chronic renal failure, liver disease, and dementia, while the conditions with the greatest PARs were CHF, COPD, and diabetes mellitus (Gross et al., 2006). As we estimated HRs only, our results reflect the risk of death for CRC patients with particular

condition combinations, rather than the risk difference observed between those exposed or unexposed that condition or combination. Condition management must also be considered. For example, if a condition like diabetes is well controlled, it will likely be less fatal (Vigneri et al., 2009). Our study did not estimate diabetes control due to the lack of indicators for glycemic control in our dataset. It is also possible that patients with well-managed pre-existing conditions have more positive health behaviours in general, and more frequent contact with the healthcare system, contributing to better outcomes. We found that CRC patients with certain conditions or combinations of conditions had a lower risk of death than those who had no condition prior to CRC. Among CRC patients with one comorbidity these conditions included hypertension, osteoarthritis, osteoporosis, and coronary syndrome. Similarly, patients with CRC and two comorbidities including hypertension and osteoarthritis, osteoarthritis and anxiety, or hypertension and osteoporosis had a lower risk of death than those with CRC only. It is possible that these findings reflect the impact of condition severity and the role of appropriate treatment and management of these chronic conditions. However, it is not possible to determine with certainty based on our results.

A key aspect of this research was to assess the impact of specific health system factors, namely primary care models (PCMs), continuity of care (COC), and primary care (PC) visits, and how this may influence the association between MMB and CRC patients' survival. After testing for interaction, we did not find that PCMs or COC modified the effect of MMB on CRC patients' survival, so we rather evaluated the confounding effect and individual role of these factors. We found that patients rostered in capitated and capitated + models had poorer survival than those in non-capitated models. Findings for other PCMs were not significant. In non-capitated models, patient enrollment is not a requirement, and physicians are compensated on a

FFS basis (i.e. for the number of services they provide) (Glazier et al., 2019). In capitated models, patient enrollment is a requirement, and physicians are compensated with a single payment for each patient they enroll (Rudmik et al., 2014). Prior studies have examined the impact of Ontario's PCMs on outcomes among patients with MMB, and in the general population. Gruneir et al. (2016) found that patients with MMB who were members of capitated and non-capitated PCMs were less likely to have outcomes such as hospitalizations, and 30-day readmissions, than those in capitated + models, and did not find that PCMs modified the impact of MMB on hospitalizations (Gruneir et al., 2016). Similarly, Glazier et al. (2012) found that capitated and team-based models were associated with higher than expected ED visits (Glazier et al., 2012).

Overall, our study and some others found that patient enrolment in capitated and capitated + PCMs were associated with worse outcomes. Potential reasons for these findings include the possibility of higher quantity of services provided in the non-capitated models, which could benefit the management of chronic conditions and therefore reduce mortality. Another reason could be the lack of patient enrollment with FFS, which may motivate physicians to improve patient satisfaction in an effort to retain patients as seen in other settings. Forsberg et al. (2001) found that physicians were more aware of patient satisfaction when receiving FFS remuneration (Forsberg et al., 2001). Similarly, Sorbero et al. (2003) reported that patients with stable chronic conditions were 36% more likely to switch from capitation-based providers than similar patients with FFS providers (Sorbero et al., 2003). Additionally, PCMs differ greatly based on their components, such as their facilitation of care coordination, access to interdisciplinary care, and their funding arrangements. PCMs compensating physicians on a FFS basis have been criticized for prioritizing the quantity of services which has raised concerns over

supplier-induced demand meaning that physicians provide more services than necessary (Rudmik et al., 2014). However, it seems that these models may be well suited for complex cancer patients who have high-needs and may require more frequent encounters with the healthcare system. Conversely, capitated models create an incentive to increase the number of patients seen by a practice (Rudmik et al., 2014), and have raised concerns over cream-skimming, in which providers may preferentially select patients with lower health needs (Marchildon & Hutchison, 2016b). Equity concerns have also been brought forward, as capitation payments adjust for age and sex only, omitting socioeconomic status (Sibley & Glazier, 2012). Moreover, primary care providers in capitated PCMs may be less motivated to regularly see patients as their payments do not depend on the number of services provided and may be less inclined to serve high-needs patients, which could contribute to our findings. Additionally, Ontario's capitation based primary care models lack accountability mechanisms to keep providers from collecting patients without actually providing services.

We grouped PCMs based on funding arrangements and considered the role of interdisciplinary care. Examining specific factors central to these models rather than considering PCMs in their entirety may provide further insight into the poorer outcome observed in capitated and capitated + models compared to non-capitated models in our study. The characteristics of PCMs vary greatly even between models with similar funding arrangements. Therefore, it is difficult to determine whether the funding arrangement themselves or other organizational components explain our findings. Regardless, there seems to be a mismatch between the funding arrangements and organizational characteristics of Ontario's PCMs and the desired results from these models.

Health system role was also assessed through a proxy of care coordination, namely the continuity of care (COC) index. We found that CRC patients who had low COC were more likely to die than those with high COC. Thus, our findings and that of others suggests that having most visits with one provider, who can oversee that care needs are met, that is a better continuity in the care provision, is particularly important for complex cancer patients (Husain et al., 2013). Primary care providers in particular may be well-positioned to facilitate care coordination, communicate with specialists, and ensure that chronic conditions are well-managed. Other studies, including a systematic review by Pereira Gray et al. (2018), have found that mortality is significantly reduced with increased COC (Pereira Gray et al., 2018). Among CRC patients specifically, Justiniano et al. (2017) reported poorer mortality for patients who did not have surgeon and hospital COC after surgery (Justiniano et al., 2017). Several studies have shown that COC prevents adverse outcomes such as hospitalizations, emergency department visits, drug interactions, and mortality, among patients with MMB (Bayliss et al., 2015; Cheng & Chen, 2014; Gruneir et al., 2016; Weir et al., 2016). While we cannot determine why COC was associated with reduced mortality in our study, the differences between types of COC provide some insight. We used a proxy of relational continuity to measure COC in our study. Relational continuity refers to a personal relationship between a physician and patient that persists over time. As relational continuity could foster an environment of trust, and subsequently improve patient adherence to recommended treatments, it is possible that this mechanism could partially explain our findings (Menec et al., 2006). However, it should be noted that reaching perfect COC in a diverse population of complex cancer patients is unlikely. Complex patients often require care from providers of many specialties, and high COC could demonstrate inadequate access to specialty care for some patients (Bayliss et al., 2015). Therefore, it is important for healthcare

providers to make efforts to increase continuity of care while still encouraging patients to see specialists when necessary. Furthermore, to reduce the risks associated with the inclusion of multiple providers in the care of a single patient, efforts should be made to support care coordination and communication between providers.

Our study found that CRC patients who had regular PC visits had better survival than those with 1 or fewer visits per year. Given the important role primary care physicians play in managing chronic conditions and the high prevalence of MMB in our study, this is not surprising. Cancer patients with greater primary care use prior to diagnosis may benefit from screening tests and earlier diagnosis contributing to better outcomes. Ferrante et al. (2011) examined PC visits prior to CRC diagnosis, and found that patients with 5 to 10 PC visits had lower mortality than those with 0 to 1 PC visits (Ferrante et al., 2011). Another study by Earle and Neville (2004) reported that cancer survivors followed exclusively by an oncologist were less likely to receive preventative care, and care in accordance with clinical guidelines for non-cancer chronic conditions, than those receiving care from both an oncologist and primary care physician (Earle & Neville, 2004). Thus, complex cancer patients can benefit from primary care across the cancer care continuum, that goes beyond the specialized management of cancer and includes care of co-occurring conditions.

6.1 Strengths and Limitations

Results should be interpreted in the context of the following strengths and limitations. This section will first describe the study strengths followed by the limitations.

6.1.1 Strengths

A major strength of this study is the use of health administrative databases accessible through ICES. This large network of databases provides information on individuals with MMB

at the population level and over time. As the study includes all adult Ontarians with CRC, selection bias is minimized and we can confidently generalize our findings to residents of this province, who use provincial health services covered by the OHIP. While many retrospective studies are subject to recall bias, the use of routinely collected administrative data rather than self-reported data avoids this issue in our study. Furthermore, the retrospective design and the length of follow-up period (at least 5-years) ensures that a large group of CRC patients could be identified and that long-term survival for these patients could be assessed. The large sample size allows us to detect small differences in estimates and provides sufficient power to analyze condition combinations and to conduct stratified analyses. ICES core databases, such as the OCR, are frequently updated and commonly used for health services research. Finally, the linkability of the datasets through DAS (Data and Analytic Services) allows us to include basic characteristics as covariates in the study. As such, we were able to control for many potential confounders, contributing to the internal validity of our study.

6.1.2 Limitations

Among the limitations of this study, the use of a retrospective cohort limits the covariates included. As the administrative data were not collected specifically to answer our research question, potential confounders such as smoking, alcohol use and nutrition factors such as meat consumption, all identified as lifestyle-related risk factors for CRC, are unavailable and could not be considered. Treatment and quality of care aspects were also not included in our models. As there is no gold standard approach to assess comorbidity, we chose to measure multimorbidity based on the presence of 17 common chronic conditions. While these conditions are clinically relevant, CRC patients could have other conditions that were unaccounted for in our study. Thus, our study might underestimate the real prevalence of multimorbidity.

Furthermore, we chose to assess multimorbidity using an intent to treat approach, and identified conditions diagnosed prior to, or within 30 days of CRC diagnosis. This could also contribute to an underestimation of multimorbidity in our study. It should be noted that the combinations we identified are the most prevalent combinations of conditions, and that these combinations do not necessarily represent the most lethal combinations. As data on members of First Nations reserves and settlements were not available, the results of this study cannot be generalized to this group or to others facing barriers to access the heath system. It should be noted that while we did control for ethnic concentration quintiles, this measure was used as a proxy rather than an exact measure, as complete data on immigration status and ethnicity was not available. Our study is further limited by the lack of measure for deprivation which may have impacted survival for CRC patients. However, income contributes to capture some of the deprivation variation. Other aspects of the ON-Marg index were not included for parsimony purpose and considering that they have some limitations. Additionally, the variables used to measure ethnicity and income in our study were area based rather than individual based variables and thus our findings may be subject to ecological fallacy. Ecological fallacy is a misinterpretation of data that occurs when group level data is used to make inferences about individuals. Details about individuals might be missed in aggregate data sets, and therefore these findings should be interpreted with caution. This study examines all-cause mortality and not disease specific mortality. However, as it is difficult to determine with certainty whether CRC, cancer complications, or comorbidities are the true cause of death, this measure is still useful and sufficient to answer our research questions. Finally, misclassification bias could limit our findings. Misclassification bias might occur if diagnostic codes are improperly assigned to the conditions under study. For instance, if a condition is wrongfully classed as another condition, the findings would not reflect the real

prevalence of multimorbidity. The most probable misclassification bias would be non-differential, pulling the estimated effect toward the null and a decreasing the observed association. Multiple statistical tests were conducted in the analyses for condition combinations and therefore the issue of multiple comparisons must be considered. When multiple comparisons are conducted simultaneously, there is a greater chance that significant results will reflect random associations. However, most statistically significant combinations consistently included the same conditions, and thus it is unlikely that these results reflect false positives. Additionally, this study examined a limited set of health system indicators. For instance, continuity of care is only one component of quality of care which can improve the care management and outcomes of complex cancer patients. Future studies should also examine polypharmacy, and health system factors not included in this study such as hospital admissions and readmission, as well as emergency department use.

6.2 Conclusion/Implications

This study showed that MMB negatively impacts survival for CRC patients. Findings showed that survival was different between MMB levels, and also within MMB levels based on the specific conditions that co-existed before CRC diagnosis. There are several important implications of these findings. First, this study highlights the importance of considering cancer in the context of other chronic conditions, as MMB can substantially impact survival. Although there is no gold standard for measuring MMB, our findings along with those of prior studies, demonstrate that examining specific conditions and condition combinations as opposed to simple condition counts alone is important. Our study underscores the benefits of primary care in improving health outcomes for complex cancer patients and emphasizes the need for appropriate access to primary care. We found that CRC patients with higher COC and more frequent PC

visits had better survival than patients with lower COC and those with 1 or fewer PC visits per year. These findings likely reflect the importance of ongoing chronic condition management in primary care following cancer diagnosis. Without care coordination between primary care providers and oncologists complex cancer patients may experience inadequate care as cancer care may take precedent over other health issues and risk poorer outcomes. Complex cancer patients should receive coordinated care for their cancer and ongoing care for pre-existing chronic conditions. Efforts should be made to improve COC, especially for patients requiring care for multiple chronic conditions from numerous providers. After examining the role of PCMs, we found that CRC patients in capitated and capitated + PCMs had poorer survival than those in non-capitated models. Our study, as well as some others, have found that patients enrolled in capitated models have worse outcomes than those in non-capitated models. These findings have several policy implications. As we were unable to determine which components of the PCMs led to these differences, future studies should investigate specific components of PCMs, such as their facilitation of care coordination, access to interdisciplinary care, and their funding arrangements, to further understand how these models impact patient outcomes. Future studies should further examine condition combinations among CRC patients, and investigate how MMB affects nonfatal health outcomes, including functional status, and quality of life, for cancer patients.

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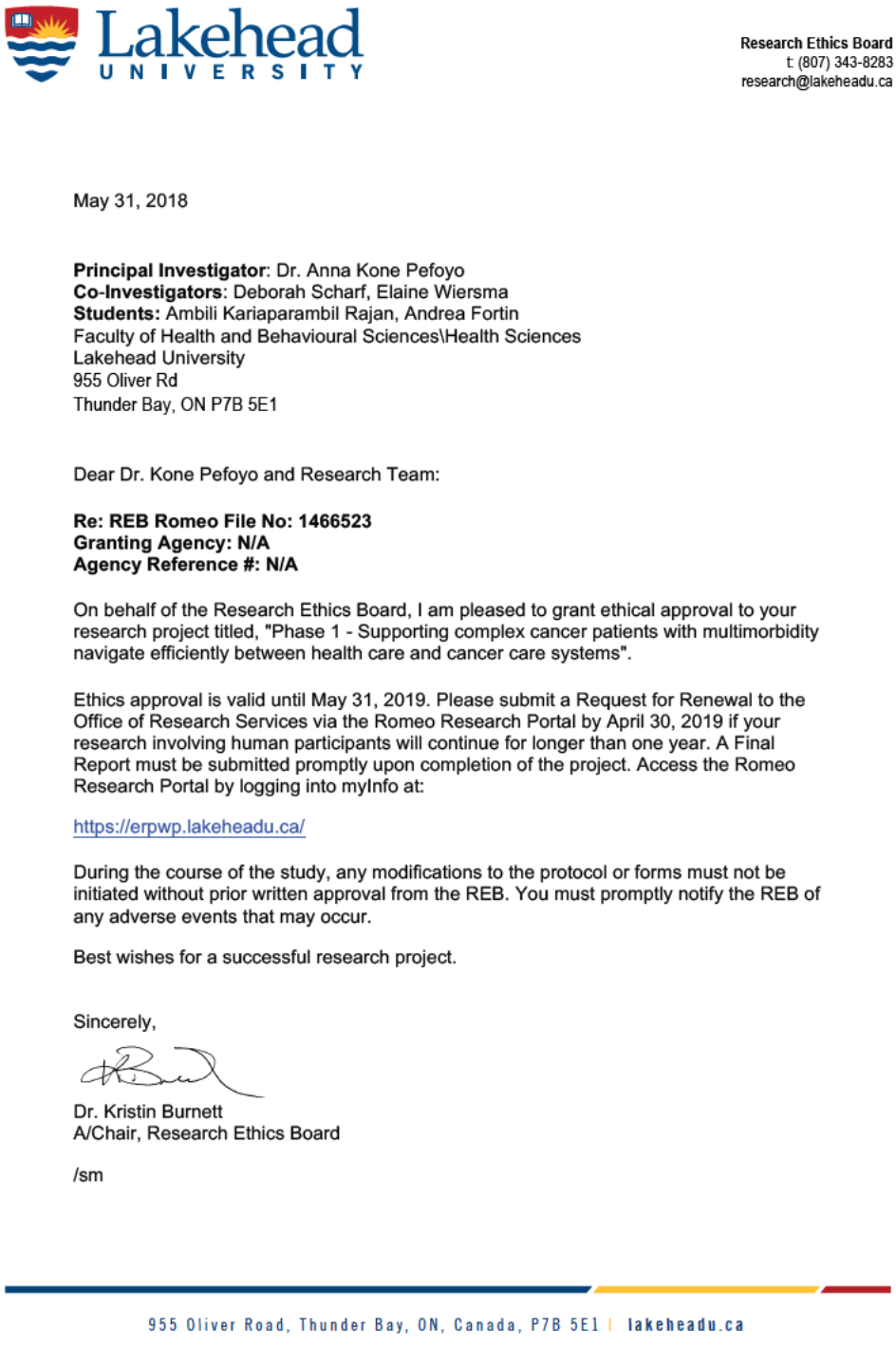
Appendix A

Figure 1: Ethics Approval



Lakehead UNIVERSITY

Research Ethics Board
t: (807) 343-8283
research@lakeheadu.ca

May 31, 2018

Principal Investigator: Dr. Anna Kone Pefoyo
Co-Investigators: Deborah Scharf, Elaine Wiersma
Students: Ambili Kariaparambil Rajan, Andrea Fortin
Faculty of Health and Behavioural Sciences\Health Sciences
Lakehead University
955 Oliver Rd
Thunder Bay, ON P7B 5E1

Dear Dr. Kone Pefoyo and Research Team:

Re: REB Romeo File No: 1466523
Granting Agency: N/A
Agency Reference #: N/A

On behalf of the Research Ethics Board, I am pleased to grant ethical approval to your research project titled, "Phase 1 - Supporting complex cancer patients with multimorbidity navigate efficiently between health care and cancer care systems".

Ethics approval is valid until May 31, 2019. Please submit a Request for Renewal to the Office of Research Services via the Romeo Research Portal by April 30, 2019 if your research involving human participants will continue for longer than one year. A Final Report must be submitted promptly upon completion of the project. Access the Romeo Research Portal by logging into myInfo at:

https://erpwp.lakeheadu.ca/

During the course of the study, any modifications to the protocol or forms must not be initiated without prior written approval from the REB. You must promptly notify the REB of any adverse events that may occur.

Best wishes for a successful research project.

Sincerely,

Dr. Kristin Burnett
A/Chair, Research Ethics Board

/sm

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Research Ethics Board
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October 14, 2020

Dr. Anna Kone Pefoyo
Andrea Fortin
Department of Health Sciences
Lakehead University

VIA Email: akonepe@lakeheadu.ca, and afortin2@lakeheadu.ca

RE: Secondary use of non-identifiable data – Research Ethics Board exemption

Dear Dr. Kone Pefoyo and Ms. Fortin:

Thank you for providing the Lakehead University Research Ethics Board information regarding your project titled, "Effect of Sociodemographic & Health System Factors on the Association Between Multimorbidity & Colorectal Cancer Survival". You intend to conduct a secondary analysis of anonymized ICES data.

Your use of the data meets the criteria of the Tri-Council Policy Statement 2 (TCPS 2), Chapter 2, Article 2.4, exemption from Research Ethics Board review as it involves secondary use of anonymous data and there is no opportunity of re-identification of this data through your analysis.

"REB review is not required for research that relies exclusively on secondary use of anonymous information, or anonymous human biological materials, so long as the process of data linkage or recording or dissemination of results does not generate identifiable information."

~TCPS 2, Chapter 2, Article 2.4

If the above process related to your project changes, please contact the Research Ethics Board. On behalf of the Lakehead University Research Ethics Board, I wish you success with your research study.

Sincerely,

Dr. Kristin Burnett
Chair, Research Ethics Board

/sw

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Appendix B

Table 1*: ICD Codes and Prevalence of Chronic Conditions*

Condition	ICD 9/OHIP	ICD 10	Prevalence (%)
AMI	410	I21	1,805 (2.7)
Anxiety	300	F40-F42, F93	15,468 (22.9)
Arthritis – Osteoarthritis	715	M15-M19	23,934 (35.4)
Arthritis – Rheumatoid	714	M05-M06	1,360 (2.0)
Asthma	493	J45, J46	7,308 (10.8)
Cardiac Arrhythmia	427.3 (DAD) / 427 (OHIP)	I48.0, I48.1	5,943 (8.8)
CHF	428	I500, I501, I509	5,703 (8.5)
COPD	491, 492, 496	J41, J42, J43, J44	5,974 (8.9)
Coronary Syndrome (excluding AMI)	411-414	I20, I22-I25	11,943 (17.7)
Dementia	290, 331 (OHIP) / 046.1, 290.0, 290.1, 290.2, 290.3, 290.4, 294, 331.0, 331.1, 331.5, F331.82 (DAD)	F00, F01, F02, F03, G30	2,190 (3.2)
Diabetes	250	E10, E11, E13, E14	16,021 (23.7)
Hypertension	401, 402, 403, 404, 405	I10, I11, I12, I13, I15	39,180 (58.0)
Mood Disorder (includes major depressive disorder)	296, 309, 311	F30-F34 (excl. F34.0), F38, F39, F43.1, F43.2, F43.8, F44, F45.0, F45.1, F45.2, F48, F53.0, F68.0, F99	1,090 (1.6)
Osteoporosis	733	M81, M82	3,652 (5.4)
Other Mental Health (personality disorder, psychotic disorder, stress reaction (specifically PTSD), substance use disorder)	291, 292, 295, 297, 298, 299, 301, 302, 303, 304, 305, 306, 307, 313, 314, 315, 319	F04, F050, F058, F059, F060, F061, F062, F063, F064, F07, F08, F10, F11, F12, F13, F14, F15, F16, F17, F18, F19, F20, F21, F22, F23, F24, F25, F26, F27, F28, F29, F340, F35, F36, F37, F430, F439, F453, F454, F458, F46,	2,289 (3.4)

		F47, F49, F50, F51, F52, F531, F538, F539, F54, F55, F56, F57, F58, F59, F60, F61, F62, F63, F64, F65, F66, F67, F681, F688, F69, F70, F71, F72, F73, F74, F75, F76, F77, F78, F79, F80, F81, F82, F83, F84, F85, F86, F87, F88, F89, F90, F91, F92, F931, F932, F933, F938, F939, F94, F95, F96, F97, F98	
Renal Failure	403,404,584,585,586,v451	N17, N18, N19, T82.4, Z49.2, Z99.2	2,634 (3.9)
Stroke	430, 431, 432, 434, 436	I60-I64	2,373 (3.5)

Appendix C

Figure 1: *Combined effect of MMB and COC on CRC patients' survival*

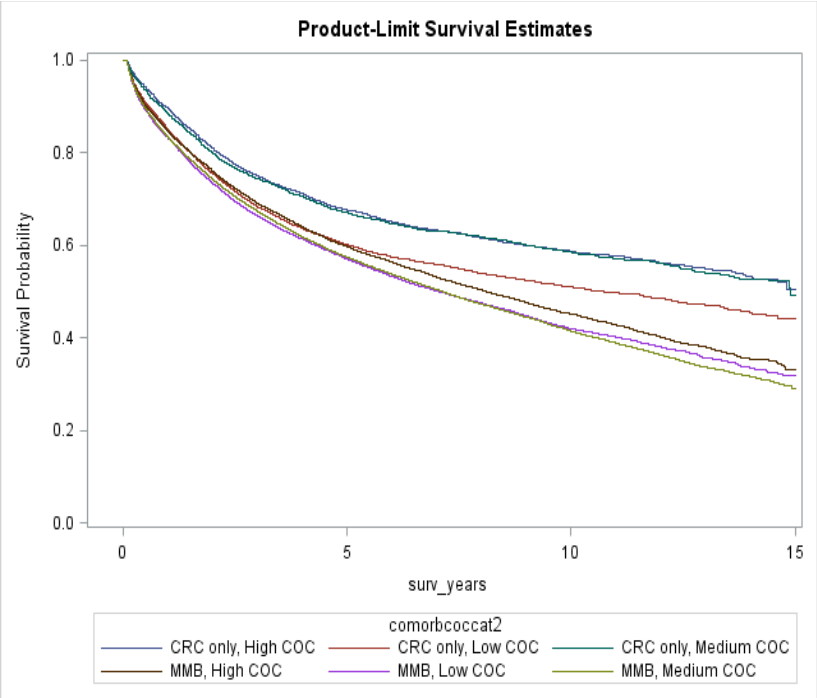

Figure 2: *Combined effect of MMB and PCMs on CRC patients' survival*