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The Impact of Rural-Urban Residency on Colorectal Cancer Screening, Stage at Diagnosis and Treatment in the Privately Insured Population

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THE IMPACT OF RURAL-URBAN RESIDENCY ON COLORECTAL CANCER SCREENING, STAGE AT DIAGNOSIS AND TREATMENT IN THE PRIVATELY INSURED POPULATION

by

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Mesnad Alyabsi, Ph.D.

University of Nebraska, 2018

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Colorectal Cancer (CRC) is the third most common and leading cause of cancer death in the United States. Although CRC screening can prevent and detect CRC at an early stage, about 35% of Americans are not screened. Despite the recent increase in screening, people with lower SES and those who live in rural areas have lowest screening. In rural areas, a common obstacle for screening is the long trips for health services which is associated with advanced CRC.

Moreover, surgery is a substantial part of CRC treatment since stages I-III and some metastatic CRC (mCRC) patients are treated with surgery. Up to 25% of patients who undergo surgery get readmitted to the hospital due to several factors which costs $300 million annually. Prior studies showed some variations in CRC treatment between rural and urban patients.

The purpose of this study was to assess the association between rural-urban status and CRC screening, stage at diagnosis and the receipt of CRC surgery. There were three specific aims: 1) To assess the impact of rurality on CRC screening, 2) To assess the impact of travel time on the stage of CRC diagnosis, and 3) To evaluate rural-urban differences in healthcare utilization.

We conducted analyses using data from Blue Cross Blue Shield of Nebraska (BCBSNE) between 2012 and 2016. For Aim 1, the study population included BCBSNE members aged 50-64 years with average-risk CRC. For Aim2, the study population included BCBSNE members aged 50-

64 years with average-risk CRC. For Aim 3, the study population consisted of CRC patients between the ages of 19-65 years old who had CRC surgery during the study period.

Claims data were used to ascertain the CRC screening, diagnosis, receipt of surgery and hospital readmission using ICD and CPT codes. Rural-urban status was based on the Rural-Urban Commuting Area Codes and travel time between the residence and the provider facility was calculated using Google Map. For Aim 1, prevalence rates for FOBT and colonoscopy were calculated and compared using X^2-test. Univariate and multivariate logistic regression analyses were performed to assess the relationship between the independent variables and CRC screening test. For Aim 2, we used Wilcoxon rank-sum tests for continuous variables and X^2-tests for categorical variables and we adjusted for covariates using logistic regression. For Aim 3, Readmission and surgery status were estimated using multivariate logistic regression.

There was no significant difference between rural and rural residents in colonoscopy use. However, after adjustment, rural residents were 47% more likely to use FOBT. Patients who do not use preventive services were 2.80 more likely to present with mCRC and urban residents were 3.50 times more likely to receive mCRC. The fact that 12% of our population presents with mCRC suggests some non-compliance with screening guidelines. Therefore, we recommend removing barriers that prevent rural patients from receiving screening colonoscopy and thus increase early detection of CRC. Until these obstacles have been lessened, screening with more convenient tests is encouraged. The use of mailed FOBT test is easy and more accessible.

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LIST OF ABBREVIATIONS

CRC	Colorectal Cancer
PCPs	Primary Care Physicians
FOBT	Fecal Occult Blood Test
FIT	Fecal Immunochemical Test
CDC	Center for Disease Control and Prevention
LAR	Low Anterior Resection
APR	Abdominoperineal Resection
CI	Confidence Intervals
OR	Odds Ratio
ICD	International Classification of Diseases
CPT	Current Procedural Terminology
BCBSNE	Blue Cross Blue Shield of Nebraska
NHA	Nebraska Hospital Association
RUCA	Rural Urban Commuting Area Codes
MAR	Missing at Random
SCV	Systematic Component of Variation
NCDB	National Cancer Data Base

SES	Socioeconomic Status
IOM	Institute of Medicine
NHTS	National Household Travel Survey
BRFSS	Behavioral Risk Factor Surveillance System
SSS	Sphincter Sparing Surgery
HSA	Health Service Area
PTR	Primary Tumor Resection
FOLCape	Folinic Acid-Fluorouracil-Capecitabine
FOLFOX	Folinic Acid-Fluorouracil-Oxaliplatin
NCCN	National Comprehensive Cancer Network
EUS	Endoscopic Ultrasonography
TNM	Tumor, Node, and Metastases
AJCC	American Joint Committee on Cancer
FS	Flexible Sigmoidoscopy
MRC	Magnetic Resonance Colonography
CTC	Computed Tomographic Colonography
DCBE	Double Contrast Barium Enema
DNA MMR	DNA Mismatch Repair Gene
USPSTF	U.S. Preventive Services Task Force

APC	Adenomatous Polyposis Coli
HNPCC	Hereditary Nonpolyposis CRC
FAP	Familial Adenomatous Polyposis
IBDs	Inflammatory Bowel Diseases
PAHs	Polycyclic Aromatic Hydrocarbons
HSA	Heterocyclic Amines
SEER	Surveillance, Epidemiology, and End Results
NSQIP	National Surgical Quality Improvement Program
UHC	University Health System Consortium
NHIS	National Health Interview Survey
CEA	Carcinoembryonic Antigen
ECOG	Eastern Cooperative Oncology Group

CHAPTER 1: INTRODUCTION

Epidemiology of Colorectal Cancer in the US

Burden of Colorectal Cancer

Colorectal cancer (CRC) is a malignant tumor of the large intestine or rectum. It is the third most common cancer in the US preceded by lung and breast cancers in women and lung and prostate cancers in men.[1] CRC is also the third leading cause of cancer deaths in the US.[2] According to the Surveillance, Epidemiology, and End Results (SEER), in 2017 there will be 135,430 new cases of CRC and 50,260 deaths from CRC.[3] The total annual cost of care for CRC is projected to increase between 2010 and 2020, from $6.0 billion to $7.2 billion for the diagnosis, from $4.0 billion to $4.9 billion for the treatment and from $4.3 billion to $5.3 billion for the end-of-life care.[4]

Overall, the lifetime risk of developing CRC is about 1 in 21 for men and 1 in 23 for women.[5,6] As shown in Figure 1, since 1975, the risk of developing CRC has varied by gender, with males having consistently higher incidence rates than females, possibly due to higher prevalence of the risk factors such as physical inactivity and limited consumption of fruits and vegetables.[6-9]

CRC Incidence

For both males and females, the incidence rate has steadily declined between 1975 and 2013 from 68.45 per 100,000 to 42.90 per 100,000 among males and from 53.66 per 100,000 to 32.42 per 100,000 among females.[5] According to Figure 2, the incidence rates declined among all groups with Whites and Blacks had the largest decline.[5] Before 1985, Whites had higher incidence rates than Blacks, but the trends started to reverse in 1985 when rates for both Whites and Blacks started declining. This decline was sharpest among Whites—a decrease from 67.2 per 100,000 in

1985 to 36.0 per 100,000 in 2013, compared with Blacks – from 64.1 per 100,000 to 46.3 per 100,000.[10] The decline occurred with a corresponding increase in colonoscopy screening among the Medicare population.[11,12]

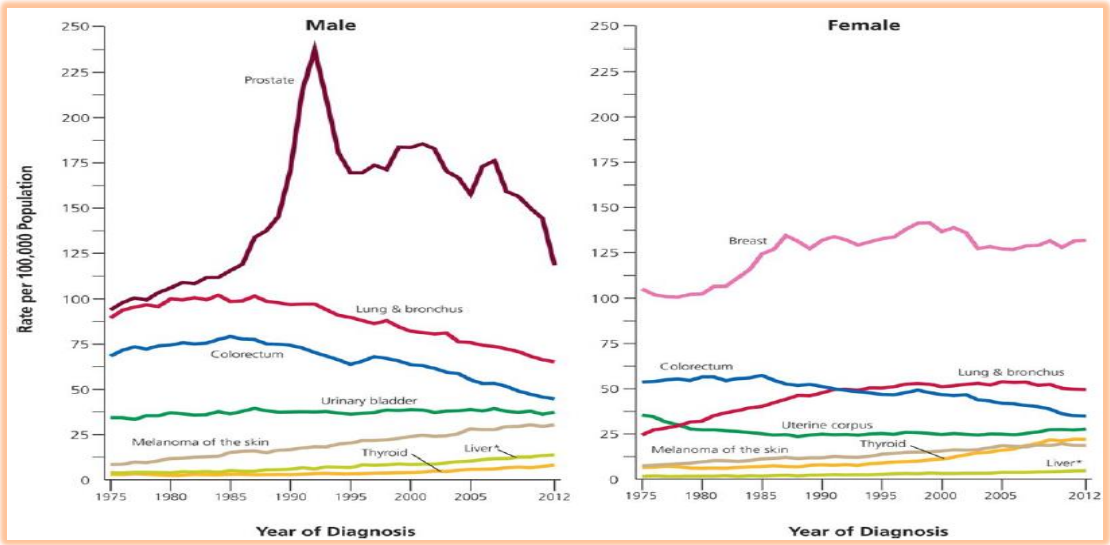

Figure 1. Trends in Age-Adjusted Incidence Rates for Selected Sites by Gender, United States, 1975 to 2012[6]

CRC Mortality

Mortality data showed overall consistent declining trends for both Blacks and Whites with a steeper declining curve among Whites.[2] Starting in 1988, Whites had declining death rates – from 25.1 per 100,000 to 14.1 per 100,000, while Blacks showed less decline – from 29.2 per 100,000 to 19.3 per 100,000. The rapid decline in death rates among Whites occurred due to an increase in early detection and increasing polypectomy rates.[2] Other races have had lower mortality rates including Hispanics and Asian/Pacific Islanders.

As shown in Figure 3, the time trend of death rate has a distinct pattern by gender. The death rate among males peaked around 1945 with a rate of 36.0 per 100,000 and remained steady until around 1985 when the rate started to decrease gradually to 17.34 per 100,000 by 2012;

among females the peak was also around 1940, but afterwards the rate immediately declined consistently to reach 12.12 per 100,000 by 2012.[6] Declines in both incidence and death rates of CRC have been attributed to the decline in the prevalence of risk factors and the increased screening.[2,6,13] Recently, the sharp decline in the mortality rate of CRC (1990-2012) is due to increases in colonoscopy screening rates.[2,14]

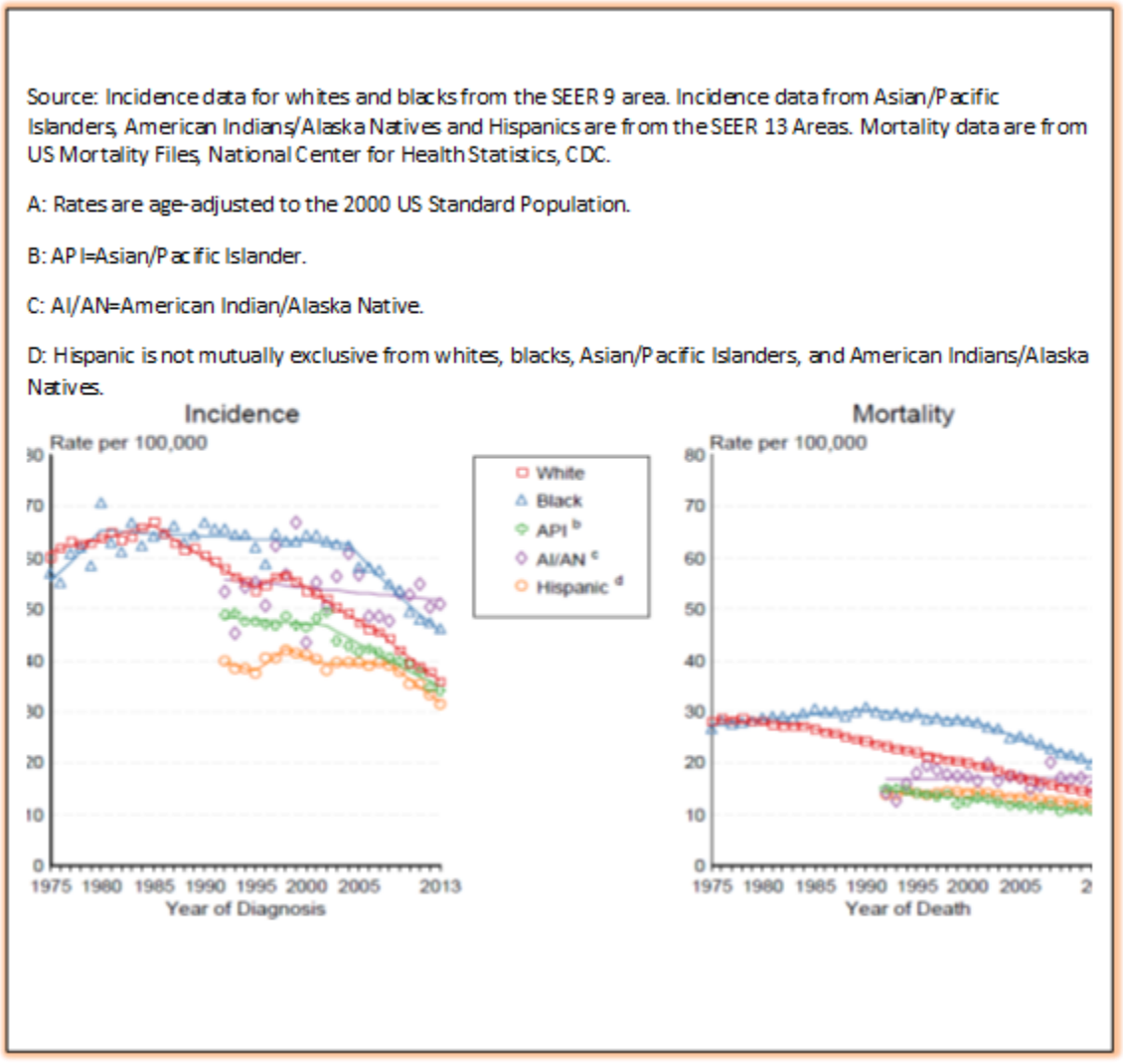

Figure 2. Trends in Age-Adjusted Incidence and Death Rates for Colorectal Cancer by Race, United States, 1975 to 2013[10]

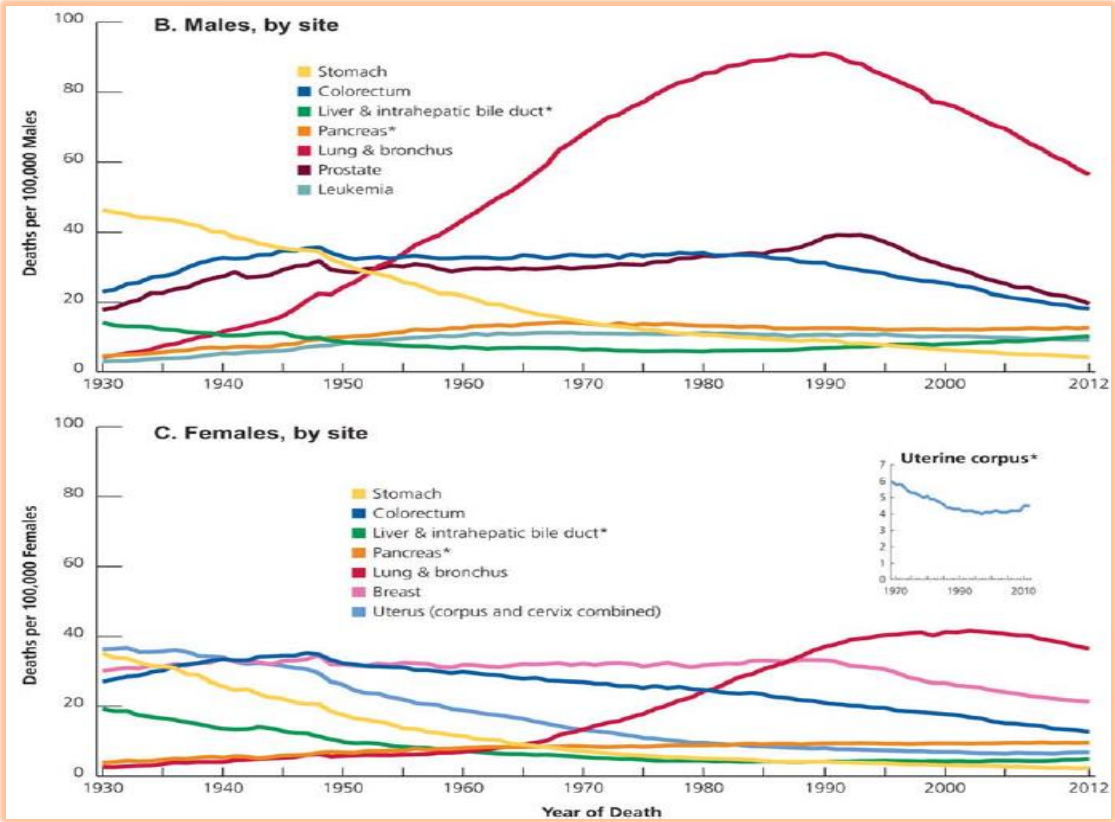

Figure 3. Trends in Age-Adjusted Death Rates for Selected Sites by Gender, United States, 1930 to 2012[6]

CRC Incidence and Mortality Rates by Age Group

Like most other cancers, incidence and death rates of CRC increase with age. Overall, 90% of new cases and 94% of deaths occur in individuals 50 years and older;[2,15] in fact, the incidence rate of CRC is more than 15 times higher in adults 50 years and older than those between 20 and 49 years. While the CRC death rate has declined in both older and younger age groups, the decline was greater for those 65 years and older than those between 50 and 64 years old.[15,16] Specifically, more than 70% of the decline in death is among individuals 65 years and older.[2] This pattern might be partly explained by higher CRC screening rates among individuals 65 years and older.[16] In July 2001 the Congress enacted a law to entitle Medicare beneficiaries who are at average risk of

developing CRC to colonoscopy screening every ten years.[11,12] By 2005, 47% of people 65 years and older had been screened compared to only 33% of those 50-64 years of age.[12]

CRC Incidence and Mortality Rates by Geographic Location

Incidence and death rates of CRC vary by geographic location.[14,17] Overall, the age-adjusted incidence rates are highest in the Midwest and lowest in the Northeast. For instance, the lowest rate was in District of Columbia while the highest was in Kentucky.[17] As shown in Figure 4, CRC mortality rates are highest in the South and Midwest in both White and Black men and women.[14] In the northeast regions, where mortality rates have decreased, there has been an increased utilization of CRC screening tests. Other factors that have contributed to such regional variations include access to screening and treatment facilities, which is also influenced by regional differences in socioeconomic status.[17-19] Therefore, the need for a study that assesses the distribution of screening utilization while controlling for socioeconomic status is warranted.

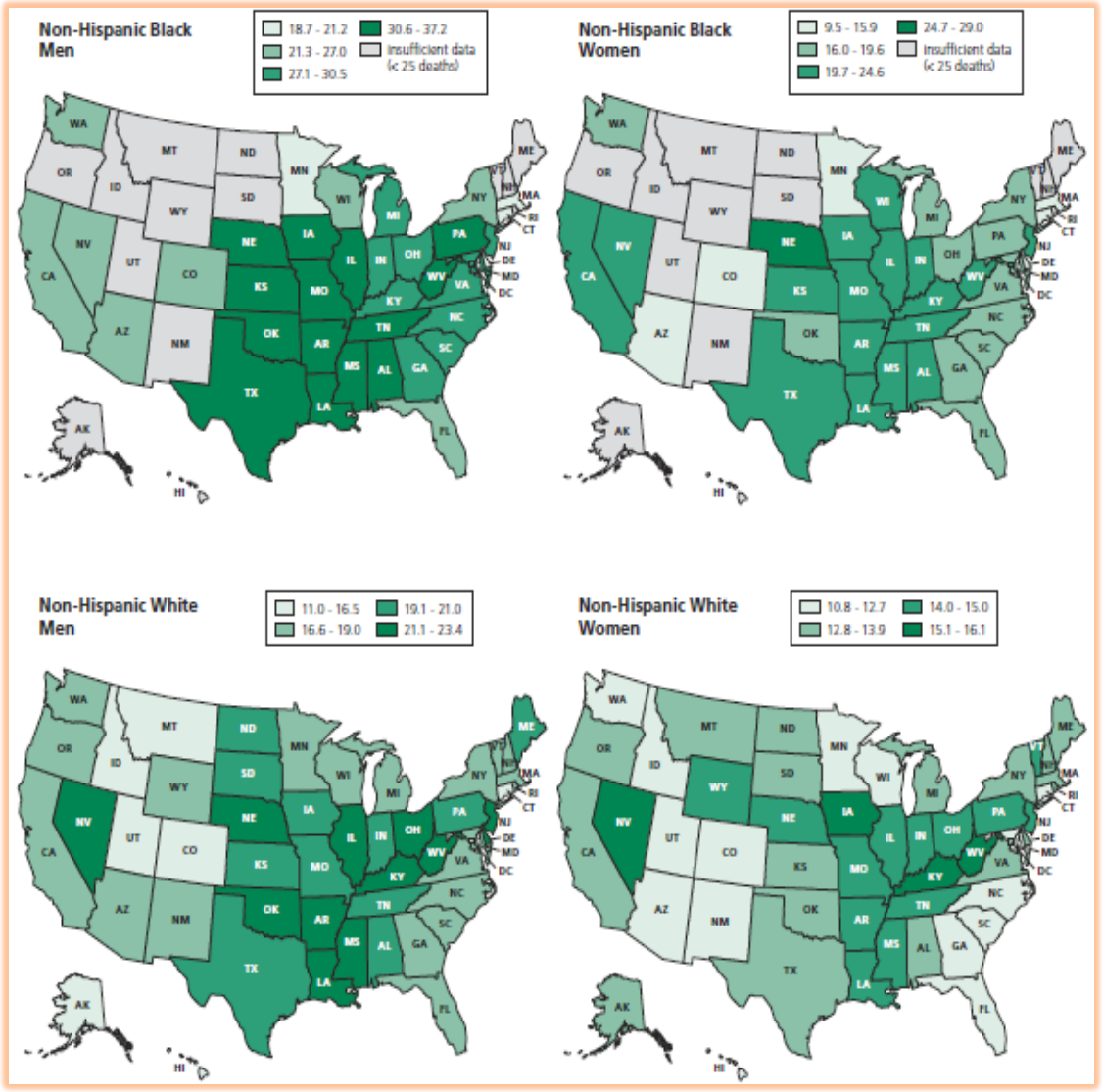

Figure 4. Colorectal Cancer Death Rates by State, 2006-2010[17]

Risk and Protective Factors for Colorectal Cancer

Overview

Factors that increase the risk of CRC are older age (≥65 years old), meat consumption, alcohol intake, smoking, and obesity, while factors that reduce the risk are consumption of fruit

and vegetables, physical activity, aspirin intake and consumptions of other nutrients (e.g., fiber and dairy products).[20,21] In this section, these factors are discussed in details.

Average Risk Population

Average risk population is individuals who are at least 50 years old, with no personal history of CRC or adenomatous polyps, no personal history of inflammatory bowel disease, no family history of CRC or polyps or a known family history of a hereditary CRC syndrome such as familial adenomatous polyps or Lynch syndrome.[22]

Age

The mechanism behind the increasing incidence rate of CRC with age is related to the aging process.[23] In a normal colorectal epithelial cell, hypermethylation (i.e., an addition of methyl groups) of tumor suppressor genes is associated with increased cell proliferation and differentiation, a characteristic that precedes the development of cancer. The hyperproliferation (i.e., increase in cell divisions) accumulates over time and manifests at an older age. Additionally, as explained below, tumorigenesis involves genetic alterations that take decades to manifest into CRC which also explains the role of age as a potential CRC risk factor.

In the U.S., the risk of CRC increases with age regardless of gender or race.[6] However, recent incidence rate trends show that the disease is increasing among people younger than 50 years of age and slightly decreasing among those 50 years and older. Of the various types of CRC, proximal colon cancer, or a tumor located in the right and transverse colon, increases with age from 26-27% in the youngest age group (younger than 50 years) to 49-56% (80 years and older).[2] In addition, people younger than 50 years of age had the lowest annual percentage changes in incidence rates of proximal colon cancer between 2001 and 2010 (-0.2%) compared to the older age groups (ages 50-64 years: -2.8% and ages ≥65 years:-2.7%). On the other hand, rectal cancer

is more common among younger individuals. While only 1 in 5 rectal cancer patients 80 years and older presents with the disease, 2 in 5 rectal cancer patients younger than 50 years present with the disease.

Dietary Factors

Increased fruit and vegetable consumption has been associated with lower risk of CRC.[20,21] Vegetables contain substances with antioxidant properties such as carotenoids and ascorbate as well as bioactive compounds such as flavonoids.[21] Another component of vegetable is folic acid, which is also available as a nutritional supplement. Folic acid is a water-soluble vitamin B, which plays a vital role in the transfer of one-carbon during biosynthesis of purines and thymidylate during DNA synthesis.[24] Folate is also an intracellular coenzyme (5, 10-Methylenetetrahydrofolate) that is needed during the conversion of deoxyuridylate to thymidylate which is oxidized to 10-formyltetrahydrofolate for purine synthesis. Due to its role in DNA synthesis and stability, folate reduces DNA damage and protects against CRC development.[20,25]

Similarly, calcium intake and dairy food might lower risk of CRC through a reduction in cell proliferation. Multivitamin supplements, non-steroidal anti-inflammatory drugs, and hormone replacement therapy contribute to the reduction of CRC as well.[21] The anticarcinogenic properties of these compounds reflect their preventive effect, which has been found in studies such as the Health Professional Study, the Nurses' Health Study and the Seventh Adventists Study.[26,27]

In contrast, increased consumption of red and processed meat is associated with an increased risk of CRC.[20] Heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) are chemicals produced when meat is cooked at high temperature or directly over open flame.[28] HCAs are produced as a result of the reaction between amino acids, sugars, and creatine at a high

temperature. PAHs are produced when fat from meat drips into the fire and form flames; these flames contain PAHs, which remain on the surface of the meat.[28] The Nurses' Health Study found a 2.5-fold increase in risk among women who consumed meat frequently compared to women who rarely ate meat. Likewise, the Male Health Professional Study showed that men with 5 or more servings per week of meat had a statistically significant higher risk of CRC.[29]

Obesity

A large geographic variation in CRC incidence rates reported in migration studies suggests the roles of different lifestyle factors such as obesity, which plays a significant role in the etiology of CRC. Previous studies suggested that obese individuals are up to 60% more likely to develop CRC compared with normal weight individuals.[30] The association is stronger among colon cancer patients when compared with rectal cancer patients. Additionally, the risk tends to be higher among obese men compared with obese women.[31]

Cigarette Smoking, Alcohol Intake, and Other Factors

Tobacco smoking is associated with both an increase in incidence and mortality of CRC.[32] Compared to non-smokers, smokers are 2-3 times more likely to develop premalignant adenoma.[33] Likewise, daily alcohol intake is linked to an increase of about 40-70% in the risk of CRC occurrence.[34,35] Together, alcohol and smoking might act in synergy to increase CRC risk. Moreover, insulin and insulin-like growth factors contribute to the regulation of human growth and development and thus promote cell proliferation and angiogenesis while preventing apoptosis in the colon. Finally, individuals diagnosed with type-2 diabetes, those who are physically inactive, and those who are overweight have higher risk of CRC.[36]

High-Risk Population

High-risk population is individuals who had a personal history of CRC or adenomatous polyps, personal history of inflammatory bowel disease, family history of CRC or polyps or a known family history of a hereditary CRC syndrome such as familial adenomatous polyps or Lynch syndrome.[22]

Personal History of Inflammatory Bowel Disease

Individuals with diseases that cause long-term inflammation of the colon are at increased risk of CRC.[37] The two Inflammatory Bowel Diseases (IBDs) associated with the development of CRC are Crohn's disease and ulcerative colitis. While Crohn's disease affects the bowel wall, ulcerative colitis involves inflammation of the bowel mucosa.[38] Regardless of one's age, people diagnosed with IBDs, have 4-20 fold the risk of CRC development compared with those without IBDs.[39]

Personal History of Adenomatous Polyps

Almost all CRCs develop from precursor benign polyps, primarily adenomatous polyps.[40,41] Adenomatous polyps that are large (>1cm), with high-grade dysplasia and with villous features are more likely, if not removed, to develop into CRC within 5-10 years.[42] In the average US population, the lifetime risk of developing adenomatous polyps is 19%.[38] CRC is a largely preventable disease since colonoscopy with polypectomy is associated with up to 76% reduction of the occurrence of CRC[43] and a 53% decrease in CRC mortality.[44]

Family History of Colorectal Cancer or Adenomatous Polyps and Inherited Genetic Risk

Approximately one in five individuals diagnosed with CRC have at least one family member with adenomatous polyps or CRC.[38,45] Those with first-degree relatives, who were diagnosed with adenomatous polyps or CRC, are more likely than those with non-first-degree

relatives to develop the disease. Both environmental, as well as genetic factors, contribute to the occurrence of CRC among family members with a history of polyps and CRC. Furthermore, CRC due to inherited genetic risk occurs in 5-10% of the CRC patients. The two common inherited conditions are Familial Adenomatous Polyposis (FAP) and Hereditary Nonpolyposis CRC (HNPCC). Both will be explained in details in the pathogenesis section below.

Pathogenesis of Colorectal Cancer

CRC Pathways and Tumorigenesis

Fearon and Vogelstein were among the first to describe colorectal tumorigenesis, or the process of cancer formation, by defining the stages of disease development.[46] They proposed a genetic model of colorectal tumorigenesis or the adenoma-carcinoma pathway for the occurrence of CRC (Figure 5). Fearon and Vogelstein showed four distinctive genetic alterations that are pertinent to CRC; the mutations of ras gene (i.e., activation of oncogene) and the deletion of chromosomes 5q, 17p, and 18q (i.e., inactivation of tumor suppressor genes). These alterations accumulate over time, and the percentage of alterations tends to increase from approximately 25% during early adenomas to 49% in intermediate adenomas. Over 90% of carcinomas have two or more alterations. Although these stages can occur in any order, Figure 5 illustrates the most typical order of CRC tumorigenesis as it consistently occurs in populations with different race and ethnicity, and in various geographic locations.[20,46]

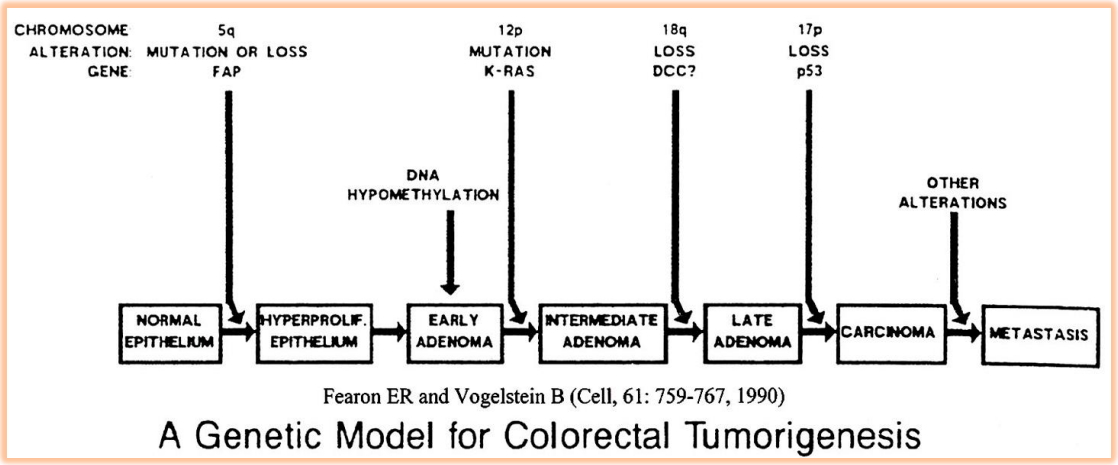

Figure 5. Genetic Model Of Colorectal Tumorigenesis[46]

During the early stage of tumorigenesis, the Adenomatous Polyposis Coli (APC) gene, which is located in chromosome 5q, undergoes germline or somatic mutation. This loss or silencing of the APC gene results in the change of the normal epithelium into the hyperproliferative epithelium. For the development of early adenoma (i.e., adenoma with a size of ≤ 1cm), an additional clonal expansion is implicated and results in DNA-hypo-methylated adenomas. Further mutations in the K-ras gene result in an intermediate adenoma (i.e., > 1cm) but without the foci for carcinoma. Further gene mutation or loss on chromosome 18q or tumor suppresser gene P53 will subsequently lead to late adenoma (i.e., > 1cm) with the carcinoma foci. Eventual accumulating loss of the tumor suppressor gene leads to carcinoma and then metastasis.

CRC is a heterogeneous disease, with four distinct molecular pathways that lead to CRC, as described by Potter et al. (Figure 6).[20] The first is the adenoma-carcinoma sequence, where the APC gene is mutated. The second is the Lynch syndrome pathway, where the DNA mismatch repair gene is lost either through inherited or acquired mutation or methylation. The third is the dysplasia-carcinoma sequence, where CRC develops through ulcerative colitis (no APC mutation or polyp formation). Fourth and final is the hypermethylation silencing of the estrogen receptor

genes, which is more common in sporadic CRC. These different pathways have an impact on disease progression, screening, and treatment. The US Preventive Services Task Force (USPSTF) guidelines suggest that high-risk groups such as those diagnosed with Lynch syndrome or FAP should be screened at an early age, which typically occurs ten years earlier than the general population.[47,48]

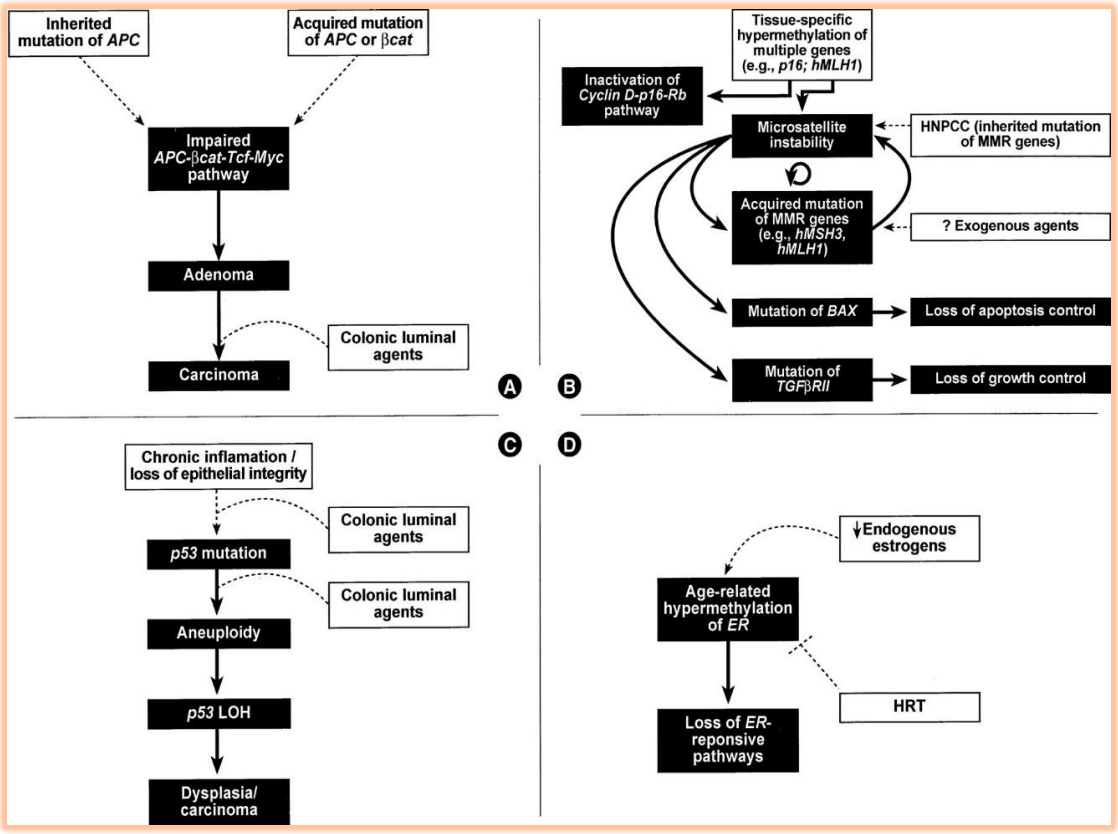

Figure 6. Colorectal Cancer Pathways[20]

CRC tumorigenesis consists of three main stages: initiation, progression, and transformation (Figure 7).[49,50] At the initiation stage, some normal colon stem cells will outgrow adjacent cells due to various stimuli (genetic or environmental). Because of this increased abnormal cell growth, normal cells become hyperplastic (i.e., tissue growth due to excessive proliferation while maintaining the same cell structure as normal cells); with more proliferation,

hyperplastic cells become dysplastic cells (i.e., a premalignant tissue characterized by an increased cell number with nuclear abnormalities) (Figure 7). During the progression stage, dysplastic cells will undergo additional genetic events that will result in the development of abnormal growth in the lining of the colon; this abnormal yet benign tumor is called a polyp and is considered an early adenoma. It takes several years during the last stage, the transformation stage before advanced adenoma develops. If the advanced adenoma or polyp is not removed it will lead to a malignant tumor.[51]

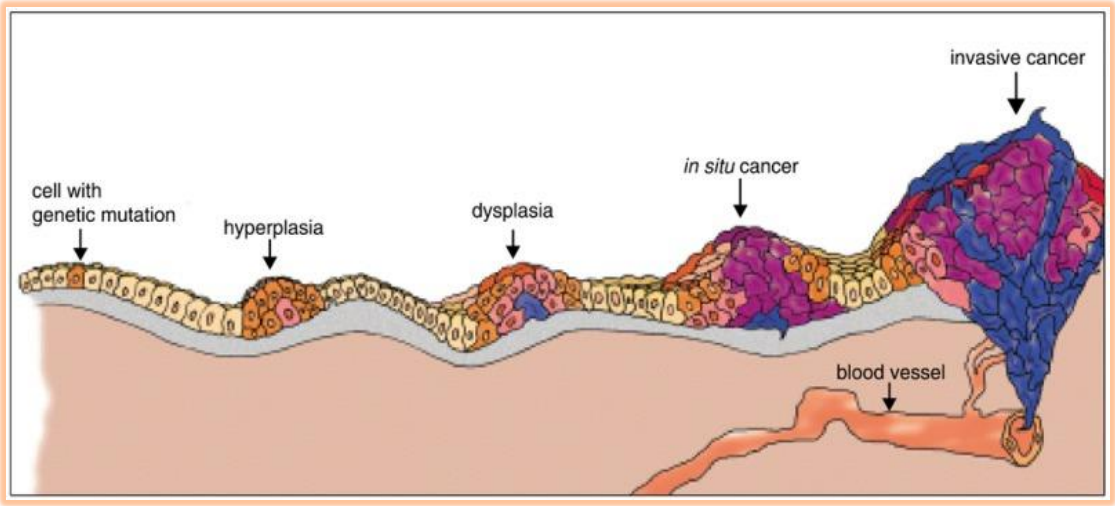

Figure 7. The Sequences from Normal to Cancer Tissue[52]

Classification of CRC

Based on personal and family history, CRC is classified into syndromic and sporadic. Approximately 15-30% of CRC is syndromic or hereditary and occurs in persons with first- or second-degree relatives who have had CRC.[45,53] The two most common syndromic CRC cancers, which are associated with increased risk of CRC occurrence, are FAP and HNPCC (i.e., Lynch Syndrome). On the other hand, sporadic CRC, which accounts for 70-85% of CRC cases, occurs among average-risk persons with no genetic risk factors. Somatic CRC develops due to somatic mutations over the course of the lifespan through the exposure to environmental and lifestyle

risk factors. The rate of disease progression is higher in syndromic than in sporadic CRC. For instance, the likelihood of developing adenoma among individuals with a defect in the DNA mismatch repair gene (DNA MMR), an inherited mutated gene among patients with Lynch syndrome, is not different from the general population. However, once the adenoma has developed, progression to carcinoma is faster than the progression among sporadic CRC patients due to the irreparable damage caused by DNA MMR defect.[20]

CRC Screening

The Available Screening Tests

CRC screening is recommended for average-risk individuals (i.e., no history of CRC, polyps or inflammatory bowel disease) starting at age 50.[48,54] CRC screening tests include three stool-based tests, four imaging tests, and two endoscopy tests. The stool tests are gFOBT, FIT and fecal DNA test. The imaging tests are double-contrast barium enema (DCBE), computed tomographic colonography (CTC), magnetic resonance colonography (MRC) and capsule endoscopy.[47] The endoscopy tests are flexible sigmoidoscopy (FS) and colonoscopy. The most commonly used tests in the US are colonoscopy, FS, FIT, and high-sensitivity gFOBT.[55,56] The current National Comprehensive Cancer Network (NCCN) guidelines recommend the following screening methods and frequency: annual high sensitivity guaiac-based fecal occult blood test (gFOBT) or fecal immunochemical test (FIT); FS every five years with stool blood tests (FOBT or FIT); and colonoscopy every ten years.[43,48,57]

Effectiveness of Screening Tests

CRC screening tests can be classified according to their effectiveness in detecting adenomatous polyps, and CRC.[43] While FS, colonoscopy, DCBE, and CTC can detect both

adenomatous polyps and cancer, gFOBT, FIT, and stool DNA test with high sensitivity can only detect cancer. Tests that are effective in detecting both are more invasive, require bowel preparation, associated with more complications (e.g., perforation and bleeding) and are costly.[43,47]

CRC screening can prevent cancer with the use of polypectomy and can detect CRC at an early stage.[43] The National Polyp Study found that polypectomy could decrease up to 76% of CRC incidence.[58] Subsequent studies corroborated such findings but with a lesser reduction in CRC incidence.[59,60] The National Polyp study also estimated a reduction of 53% in CRC deaths due to polypectomy.[44] Many other studies have found decreased mortality with screening.[47] Taken together, evidence suggests a reduction in both incidence and mortality rates with CRC screening. It should be noted, however, that the effectiveness of screening using colonoscopy varies between specialties.[61-64] Non-gastroenterologists are significantly less likely to detect and remove polyps compared with gastroenterologists. Specifically, general surgeons are 20% less likely, and internists are 7% less likely to detect and remove polyps compared with gastroenterologists.[61] This study, however, relied on physician's specialty without considering the training level on colonoscopy use. Nonetheless, failure to detect polyps, a precursor lesion of CRC, undermines the main purpose of screening using colonoscopy, which is to prevent CRC through polypectomy.

Diagnosis

Clinical Diagnosis

CRC is diagnosed histologically through biopsy taken during endoscopy.[65] Because 2%-4% of patients present with synchronous tumors, complete colonoscopy or CT colonography must be performed to detect additional tumors. Other approaches (flexible sigmoidoscopy plus barium

enema or CT colonography) might be alternative options for patients with contraindication for colonoscopy (e.g., those with high comorbidities). For rectal cancer, because the treatment is based on the exact location of the tumor, the use of endoscopic ultrasonography (EUS) is necessary to for an accurate diagnosis and staging. A meta-analysis of the diagnostic accuracy of the EUS test shows that EUS is accurate for measuring T staging of rectal cancer.[66]

CRC Staging

According to the 2016 staging manual of the American Joint Committee on Cancer (AJCC), the staging for CRC is based on Tumor, Node, and Metastases (TNM) categories.[67] T1 tumors involve the submucosa, T2 tumors involve muscularis propria, T3 tumors penetrate through muscularis propria, T4a tumors penetrate through the surface of visceral peritoneum, and T4b tumors invade or are adherent to other organs. The classification of lymph node involvement includes tumors with one positive lymph node (N1a), 2-3 positive lymph nodes (N1b), 4-6 lymph nodes (N2a) and ≥7 lymph nodes (N2b). Metastatic tumors include metastases to one organ (M1a), metastases to multiple distant organs (M1b) and peritoneal carcinomatosis with or without blood-borne metastases to visceral organs (M1c).

Treatment

Colon Cancer

According to the NCCN guidelines, for non-metastatic colon cancer cases, the primary treatment depends on tumor resectability and the presence of colon obstruction by a tumor.[67] For a resectable non-obstructing tumor, colectomy with en bloc (i.e., cancer adherent to other organs) removal of regional lymph nodes is indicated. A resectable tumor that is blocking the colon is treated according to the patient's condition, which might include a one-stage colectomy

with en block removal of regional nodes, resection with diversion, or diversion or stent and then colectomy. However, if the tumor is unresectable, systemic therapy (e.g., chemotherapy or biologics) is indicated with the objective of shrinking the tumor to make the tumor more operable.

The three primary organs for metastasis for CRC are liver, lung and abdomen/peritoneal cavity. Tumors metastasized to the liver, the lung, or both are approached similarly. For those with resectable primary tumor and resectable metastases of liver or lung or both, patients are treated with staged or simultaneous resection. For patients with unresectable metastases, the systemic treatment is the only option even if the primary tumor is not obstructed. Among the most recommended systemic therapy are Folinic Acid-Fluorouracil-Oxaliplatin (FOLFOX) and Folinic Acid-Fluorouracil-Capecitabine (FOLCape). Finally, patients with peritoneal metastases have shorter survival compared with those without peritoneal metastases, and the goal of the treatment of most cases is palliative rather than curative .[67]

Rectal Cancer

Rectal cancer patients are treated according to the clinical stage at diagnosis.[68] Those diagnosed with early stage rectal cancer are primarily treated with surgical resection, usually done by local excision.[67] However, patients who present with a locally advanced disease are more likely to receive neoadjuvant (i.e., before surgery) chemoradiotherapy followed by an appropriate surgical treatment. The primary goal of the chemoradiotherapy is to increase tumor resectability by downsizing the initial tumor. In contrasts to early-stage tumors, treatment of advanced stage tumors is through radical excision (i.e., excision of the rectum and mesorectum).

There are several rectal cancer surgeries depending on tumor characteristics such as location and size. Among the surgical approaches that have been used are transanal excision, transanal endoscopic microsurgery, transanal minimal invasive surgery, transabdominal

resection, and sphincter-sparing surgery. In contrast to colon cancer, rectal cancer is usually treated with neoadjuvant therapy of chemoradiation. For early stages, chemoradiation is for those with T3-4 tumors that are node negative but where the tumor has penetrated the muscle wall. In stage-III, neoadjuvant chemoradiation is recommended for all tumors, and adjuvant chemotherapy is indicated in both stages II and III.

Metastatic Colorectal Cancer

Treatment

Twenty percent of CRC patients are diagnosed with metastatic CRC.[2] With the objective of planning the treatment, clinicians usually investigate whether the tumor is resectable and whether patients present with symptoms at the time of diagnosis.[67] If the tumor is unresectable, patients are either treated with neoadjuvant therapy with the goal of making the tumor more operable or are treated with systemic therapy. However, if the tumor is resectable in both primary and metastatic sites, it is curable. Unfortunately, only 10%-20% of metastatic CRC patients are curable.[67,69]

For curable tumors, there are three common approaches for the treatment of mCRC.[70,71] First, in the conventional staged approach, the primary tumor is resected first followed by chemotherapy for 3-6 months then the metastatic tumor is resected in a second surgery. The second approach, the liver-first approach, was introduced in 2008. This approach is limited to asymptomatic patients. It is a staged approach where the metastatic tumor is resected first followed by resection of the primary tumor. In this approach, neoadjuvant and adjuvant therapies are used as well. The third one is called the synchronous approach (simultaneous approach). In this approach, both the primary and metastatic tumors are resected during the same procedure.

For incurable tumors, if patients present with a symptomatic tumor, primary tumor resection (PTR) is indicated. The current NCCN guidelines recommend PTR among metastatic CRC patients with symptomatic disease (e.g., obstruction, bleeding).[67] However, for asymptomatic patients, there is no treatment consensus. Proponents of PTR among asymptomatic cases advocate surgical intervention because of its potential in preventing symptoms of the unresected primary tumor. However, some argue against doing so because the surgery can result in unecessary morbidity and mortality.[72-74]

Effectiveness of Metastatic CRC Treatment

Among asymptomatic patients, two studies used SEER data to investigate utilization of PTR.[72,75] Cook et al. compared the characteristics and survival of metastatic CRC patients who underwent PTR with those treated with non-PTR between 1988 and 2000, while Hu et al. investigated the trends of PTR use from 1988 to 2010 when new systemic therapies (chemotherapeutic and targeted agents) were introduced to the market. Both studies found a reduction in PTR use over time, with a major decrease starting in 2001 at the time of introduction of new systemic therapies. During the same period, there were also increased survival rates among these patients, but it is unclear if this increase was due to higher use of systemic therapies or because surgeons are reluctant to operate on asymptomatic patients. Authors were not able to differentiate symptomatic patients form asymptomatic ones. Because the symptomatic status (symptomatic versus asymptomatic) is not captured in the data, the increased use of PTR might be due to selection bias. This bias could contribute to the decreased rate of PTR because it is unknown if the reduction was due to a decrease in PTR among asymptomatic patients or due to an increase in systemic therapy.

An additional study by Xu et al.[76] using SEER data tried to circumvent the limitation of the previous two studies. They used the improved methodology of instrumental variable analysis to account for unmeasured confounding by linking Health Service Area (HSA) to the county where PTR took place. The authors reported better survival among the PTR group. They also looked at the impact of place of residence and found consistent improved overall and cancer-specific survival in the PTR group among patients in both metropolitan and non-metropolitan counties. Moreover, when Shapiro et al. investigated the same period using SEER data, they found gender, geographic region, insurance status, tumor location, tumor grade and Carcinoembryonic Antigen (CEA) level to be independent predictors of PTR. For instance, insured patients were 35% more likely to undergo PTR compared with uninsured patients.

A more recent review study[74] investigated the differences in patient outcomes among metastatic patients who were treated with PTR followed by chemotherapy versus those with only primary chemotherapy. Overall, authors found better survival with PTR, although the two approaches were comparable. Specifically, among patients with primary chemotherapy, 3%-40% presented with complications of the unresectable primary tumor with onsets that varied between 3-12 months. The most common complications included obstruction, perforation, hemorrhage, and pain. On the other hand, complications among patients who underwent PTR were wound infection, anastomotic leaks, urinary tract infection and ileus which required subsequent surgical intervention in 3%-11% of cases. In addition, postoperative mortality ranges from 2%-5% with a single study reporting an estimate of 29%. Lastly, factors that are more likely to predict overall survival among reviewed studies were the extent of hepatic involvement, Eastern Cooperative Oncology Group (ECOG) performance status ≥2, as well as metastatic dissemination to at least two distant sites compared to disease confined to one organ

Sphincter-Sparing Surgery

Surgery Types and Effectiveness

The two primary rectal cancer surgeries are Sphincter-Sparing Surgery (SSS) with intestinal continuity (also known as low anterior resection or LAR) and sphincter scarifying surgery with permanent colostomy (also known as abdominoperineal resection or APR).[77] Not all rectal cancer patients are candidates for SSS. In general, the lower the tumor (i.e., the lower third of the rectum), the more difficult it is to resect while maintaining safe margins and therefore the less likely that SSS in indicated. Nonetheless, the ultimate decision is individualized. With a better definition of the clear safe margin for resection, the advancement in surgical technique and the development of staplers, patients with tumors at the lower third can be treated without sacrificing the sphincter.[78,79]

Both SSS (LAR) and APR aim at reducing the local recurrence by ensuring tumor-free margins in the resected specimen. The most significant predictor of increased local recurrence and reduced survival is the tumor circumferential margin that is defined as the shortest distance between the mesorectal fascia and rectal tumor. Using histological samples, studies that compared LAR and APR showed higher positive margin from APR compared to LAR (SSS).[80] Given the importance of sphincter-sparing, while maintaining bowel continuity, it is essential that patients receive SSS if indicated. Maintaining bowel continuity via SSS has a positive impact on patient's quality of life.[81-83] However, not all patients who are candidates for SSS receive the surgery depending on tumor, patient and surgeon’s factors.

Current Knowledge about Colorectal Cancer in the Rural Health Literature

Colorectal Cancer Screening by Geographic Location

While CRC screening rates increased between 2000 and 2008, the increase in the prevalence of CRC screening among people with lower SES and those who live in rural areas have been relatively small.[84,85] A study showed that rural residents are more likely to perceive that early detection of CRC is helpful compared with their urban counterparts; however, rural residents are less likely to receive screening for CRC.[55] Using the national Behavioral Risk Factor Surveillance System (BRFSS) data, Cole et al. assessed CRC screening uptake by geographic location between 1998 to 2005.[86] They found that the more rural the place of residence was, the less likely an individual would get screened. The findings were also corroborated by other studies that used state-level data.[87,88] Additionally, as shown in Figure 8 below, the northeast and some of the northern regions have the highest rates of CRC screening while the Midwest regions have the lowest rates.

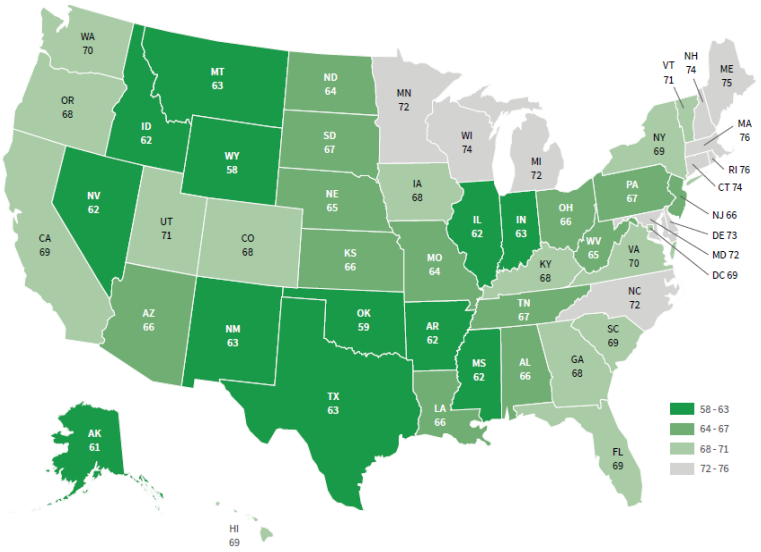

Figure 8. Colorectal Cancer Screening (%), in Adults 50 Years and Older, BRFSS 2014[2]

Note: The estimates do not distinguish between examinations for screening and diagnosis. Screening tests included a fecal occult blood test within the past year or sigmoidoscopy within the past five years or colonoscopy within the past 10 years.

Travel Time and Stage at Colorectal Cancer Diagnosis

According to the National Household Travel Survey (NHTS), 41% of trips in the US traveled by rural residents for medical or dental services were longer than 30 minutes while only 25% of trips traveled by urban residents were longer than 30 minutes.[89] Traveling is especially burdensome for cancer screening, with distance to a screening facility as a significant barrier for rural patients.[88,90-98] This barrier is exacerbated in rural areas where primary care provider density is low, in particular among the younger adults and people with a lower SES.[99] Rural populations overall are more likely to have unstaged cancers, and if staged disease, it tends to present as advanced CRC.[100]

Rural-Urban Status and Colorectal Cancer Care and Outcomes

Surgery is a significant part of CRC treatment since stages I-III and some metastatic patients are treated through surgery.[67] Post-surgery, about 25% of patients who are operated on

need to get readmitted to the hospital due to factors that are not fully understood.[101] Excessive readmissions following CRC surgery are estimated to cost $300 million annually.[102] To contain these unnecessary costs, the Affordable Care Act includes the provision called the Hospital Readmission Reduction Program that penalizes hospitals for readmission after surgery.[101,103] In 2015, the penalty was 3% reduction in payments for all Medicare admissions during a given year.[104]

Suspected factors that contribute to excess readmission can be classified into surgical and non-surgical. Surgery-related factors consist of preoperative (e.g., surgical approach, procedure-urgency, comorbidities, obesity, the severity of illness, and indication), perioperative (e.g., operating time and stoma creation and immunosuppression use) and postoperative factors (e.g.. length of stay, complications, non-home discharge, blood transfusion, postoperative steroids). Non-surgical factors are geographic location, age, gender, race, SES and hospital's patient volume.[101,102]

Several studies have been conducted in the northern and southern part of the US. A multi-institution study conducted in northern Minnesota, northwest Wisconsin, and the western portion of Michigan's Upper Peninsula, showed variations in CRC treatment between rural and urban patients and in general indicated that rural patients are at a disadvantage.[105] Another study from the state of Georgia found no differences in surgical receipts by geographic location.[106] However, several studies lacked information about travel time to cancer care, hospital case volume, SES, patient's comorbidities and complications.

Research Gaps

Previous research on CRC shows that screening decreases incidence and mortality rates by detecting polyps or tumors at an early stage. Additionally, prior studies found that longer travel distance to screening facilities to be associated with late stage of diagnosis and delayed or no surgical treatment. Previous research was limited to self-reported surveys or focused on older adults (e.g., Medicare beneficiaries). Our study was designed to evaluate CRC screening uptake among a younger cohort of a privately insured population in a rural state; no previous work studied the characteristics of the younger CRC patients among the BCBSNE population. The younger working-age population included in this study are more likely than older population to have a busy schedule and less motivated to travel to colonoscopy facility to get screened and therefore more likely to be diagnosed with metastatic CRC. Therefore, this younger population is an ideal population.

Additionally, no prior studies assessed the CRC surgery use and outcome among this population. Specifically, none of the previous studies assessed the association between rurality and 30-day hospital readmission among CRC patients who are privately-insured in a rural state. Only one study assessed 30-day hospital readmission using privately insured data but was not focused on CRC patients and, unlike our study, was not examining the impact of rurality on hospital readmission.

Moreover, the association between rurality and the receipt of mCRC is not well characterized. For instance, four published studies evaluated the surgery uptake among patient with mCRC by geography. However, none of the studies assessed the impact of rurality. Instead, the studies either reported the geographic location of the SEER registry where cases have arisen (e.g., Northeast, South, etc.) or measured rurality at the county level. Further, none of these

studies assessed such relationship among the privately insured population. Although previous research found that in urban areas the odds of undergoing SSS is 1.4 times the odds of surgery in rural areas, it is not clear if such relationship sustains in a privately insured population who reside in a rural state.

Furthermore, prior research shows that the majority of SSS were conducted in urban areas even after adjusting for hospital surgery volume.[107,108] This suggests that other reasons could elucidate the differences between rural and urban population. For instance, higher income level and the availability of private insurance were associated with higher SSS uptake. It is unclear, however, if patient's rurality status would have an impact on the receipt of SSS among the privately insured population in a rural state. To fill the gaps in the literature, this study had the following aims and related hypotheses:

Specific Aims

Aim1: To assess the impact of rural residence on CRC screening among 50-64 years old in a privately insured population.

H1a: Colonoscopy rate is lower in the rural population compared to the urban population.

H1b: FOBT screening rate is higher in the rural population compared to the urban population.

H2: The urban population has higher PCP visits than the rural population.

H3: Patients with a higher number of PCP visits are more likely to receive CRC screening.

Aim2: To assess the impact of travel time on the stage of CRC at diagnosis among 50-64 years old in a privately insured population.

H1: Shorter travel time to a colonoscopy facility is associated with a non-metastatic diagnosis of CRC.

Aim3: To evaluate rural-urban differences in healthcare utilization among CRC patients.

H1: Urban CRC patients who undergo surgery are more likely to have lower readmission and emergency department visits.

H2: Among patients with metastatic CRC, the proportion who undergo surgery is higher among the urban population compared with the rural population.

H3: Among rectal cancer patients, the proportion who undergo sphincter-preserving surgery is higher among the urban population compared with the rural population.

Scope of the Study

Our study is a retrospective cohort study conducted among privately insured adults residing in Nebraska. This unique population was rarely included in previous CRC studies. The study is limited to individuals who are 50-64 years old. It is also limited to the period from January 2012 to June 2016. The Institutional Review Board at the University of Nebraska Medical Center approved the study.

Summary

CRC is the third most common cancer in the US and the third leading cause of cancer deaths. Although CRC can be prevented or detected at early stages when the treatment results in high survival rates, a large proportion of individuals are not screened. Specifically, the prevalence of CRC screening among the rural population and those with lower SES have been less than the urban population. Among the factors that contributed to lower screening is the distance to the screening or treatment facilities and this is especially burdensome for the rural patients. Some

previous studies found that longer travel distance to screening facilities to be associated with late stage of diagnosis and delayed or no surgical treatment. Additionally, hospital readmission rate has been shown to be higher among low volume centers which exist primarily in the rural areas. The study is significant because it is designed to characterize this privately-insured population for the first time. It is also designed to uncover differences between the rural and the urban populations in the receipt of CRC screening, the impact of travel time on stage at diagnosis, the differences in hospital readmission and the receipt of mCRC and SSS among a privately insured population. In addition to directing future research questions, our findings will have clinical and public health implications. For instance, if the rural population is less likely to receive indicated CRC surgery, this might reflect unawareness or disagreement with existing treatment guidelines.

CHAPTER 2: REVIEW OF THE LITERATURE

Definition and Characteristics of the Rural Population

There are 60 million adults in the US (20% of the US population) living in rural areas.[109,110] Unlike urban communities, rural communities have lower population density, higher non-working population such as elderly and children, more unemployed or underemployed who are less likely to be insured.[109] Prior research showed that rural population and those with lower socioeconomic status were less likely to undergo screening, less likely to receive treatment and at an increased risk of death following CRC diagnosis.[85-88,106,111-113]

The most widely used definitions of rural and urban populations are established by three government agencies: The U.S. Census Bureau, the Office of Management and Budget, and the Economic Research Service of the U.S. Department of Agriculture (USDA) (Table 1).[114] The U.S. Census Bureau relies on total population or population density within a census tract to designate an area into rural or urban.[109,115] There are three classes of areas: An Urbanized Area (UA), an Urban Cluster (UC) and rural. UA has a population density of 50,000 or more people. The characteristic of the UA is that it has a core (at least one contiguous census block groups) with a total land area fewer than two square miles, might contain adjacent territory with at least 500 people per square mile and include a population of at minimum 50,000 people. UC is similar to UA, but it contains a population less than 50,000 and at least 2,500 people. Any other territory, population, and housing units located outside the UA and UC areas are considered rural areas.

Unlike the U.S. Census Bureau definition, the office of Management and Budget classifies counties as metropolitan and nonmetropolitan areas.[109,115] Metropolitan areas are core counties with at least one urbanized area and outlying counties with economic ties to the core county as

measured by work commute. The outlying counties are considered part of the metropolitan area if 25% of workers commute to the urbanized area or if at least 25% of employment in the county consists of workers coming from the urbanized area. Furthermore, the nonmetropolitan counties are located outside the metropolitan areas and are divided into micropolitan (i.e., any nonmetro county with a cluster of the urban area more than or equals 10,000 people) and noncore counties.

The USDA has two definitions that are measured at the county level: The Rural-Urban Continuum Code and the Urban Influence Code.[116] The Rural-Urban continuum code classifies metropolitan counties by the population size of their metropolitan area and nonmetropolitan counties by the extent of urbanization and proximity to a metropolitan area. Counties are grouped based on their classification by the Office of Management and Budget (metro and nonmetro) then subdivided into three metropolitan and six nonmetropolitan classes. Unlike the Rural-Urban Continuum Code, the Urban Influence Code subdivides the metropolitan area into two metropolitan groups based on their size. It also subdivides the nonmetropolitan area into ten nonmetropolitan groups based on their proximity to the metropolitan area, and the nonmetropolitan-noncore counties into seven groups based on their proximity to metropolitan or micropolitan areas and if they have their town of more than 2,500 people.

The Rural-Urban Commuting Areas (RUCAs) was developed by University of Washington with help from the Economic Research Service of the USDA.[117] This classification uses the U.S. Census Bureau's UA and UC definitions supplemented with information on work commute. The classification assigns metropolitan, micropolitan, small town and rural commuting areas with numbers between 1 and 10. These numbers are subdivided into 21 secondary codes based on commuting flows. Although the original RUCA classification was based on census tract, it uses the ZIP code as its geographic unit.

Table 1: Characteristics and Classifications of the Rural-Urban Areas[114-116]

Classification	Geographic Unit Used	Pros	Cons
U.S. Census Bureau: Urban and Rural Areas	Census Tract	• Census is the smallest and most accurate geographic unit. • Reduces the problem of under-bounding or overabounding that is associated with county-based classifications.	• Definition based on census can be hard to implement because such small geographic unit is not commonly used by payers. • No stable across census years.
U.S. Office of Management and Budget (OMB): Metropolitan and Nonmetropolitan areas	County	• County boundaries represent political jurisdictions and considered stable over time.	• County size differ across the U.S., and larger counties contain both rural and urban areas (over- and under-bounding)
Economic Research Service, USDA: The Urban Influence Code	County	• Because it differentiates counties with several small towns from those with one or two large towns for grouping nonmetropolitan counties, it is better than RUCA for suggesting a level of locally available services. Proximity to metropolitan areas indicates the degree of economic integration with	• County size differs across the U.S., and larger counties contain both rural and urban areas. • Does not differentiate metropolitan counties as well as does RUCA.

		metropolitan counties.	
Economic Research Service, USDA: The Rural-Urban Continuum Code	County	County boundaries represent political jurisdictions and considered stable over time.	County size differs across the U.S., and larger counties contain both rural and urban areas.
RUCA	Census tract/ZIP code approximation	• ZIP code areas are easy to implement with programs that are dependent on provider or beneficiary address. • Structuring of the codes allows for multiple levels of generalization- from 2 (rural-urban) to 33.	• ZIP codes are unstable and can change from year to year. • No stable across census years.

No matter what definition one uses, the chosen definition will somehow over- or under-represent urban or rural areas. The definition that dichotomizes areas (metropolitan and nonmetropolitan or rural and urban) will ignore any gradations in nonmetropolitan areas. For instance, the use of OMB definition will ignore proximity to metropolitan areas and thus underestimate the level of locally available services. However, the use of dichotomy is easier especially if the urban reflects the urbanest areas and the rural reflects the most rural areas.[110]

According to Hart and colleagues,[109] there are three points that researchers should consider when embarking on a project: the purpose of the study, the availability of data and the suitability and availability of definition. The primary purpose of our study is to measure travel time between members and providers. Because current study is not an interventional study (e.g., allocating resources or programs to areas that are not part of large urban or rural areas), using

RUCA as a dichotomy is appropriate. Regarding data availability, we have access to ZIP code provided by BCBSNE, which is more suitable for RUCA definition. The use of this definition is also consistent with previous studies, which make results comparable.[86,87,118]

Roles of Primary Care Providers in Colorectal Cancer Screening

The Institute of Medicine (IOM) defines primary care as "the provision of integrated, accessible health care services by clinicians who are accountable for addressing a large majority of personal health care needs, developing a sustained partnership with patients, and practicing in the context of family and community."[119] This definition emphasizes the important attributes of primary care such as the accessibility to health services, the sustained relationship between the healthcare provider and the patient and the integrated care to provide a referral to a specialist when needed. Primary care practice ensures the availability of a usual source of care, which is a well-established factor associated with an increased uptake of CRC screening.[120-125]

Primary care providers (PCPs) include general practitioners or family medicine, internists and general pediatricians.[125] A PCP is the patient's first contact with the healthcare system, and the preventive services are often initiated through primary care. In case of CRC prevention and control, the roles of a PCP include discussion and recommendation regarding screening, performing non-invasive screening (e.g., FOBT), and referring patients to specialists (e.g., gastroenterologists, general surgeons or colorectal surgeons) who can perform an endoscopic screening test.[43]

Previous research demonstrates favorable CRC outcomes associated with PCP visits. For example, improved outcomes such as a lower incidence of late-stage CRC and a higher survival are proportional to the supply of PCPs.[19,126-128] For each 10% increase in the supply of PCPs measured by the number of PCPs per 100,000 people, the odds of late stage diagnosis of CRC is

reduced by 5%.[128] In particular, non-metropolitan areas with high level of PCPs supply is associated with less late-stage CRC.[19] In contrast, each 10% increase in the supply of specialists such as gastroenterologists, general surgeons or colorectal surgeons is associated with 5% increase in late-stage CRC diagnosis. This could be because of the nature of the relationship between PCPs and patients, which tends to be longer and covers patients' overall health, as opposed to the limited contact between specialists and patients.[129]

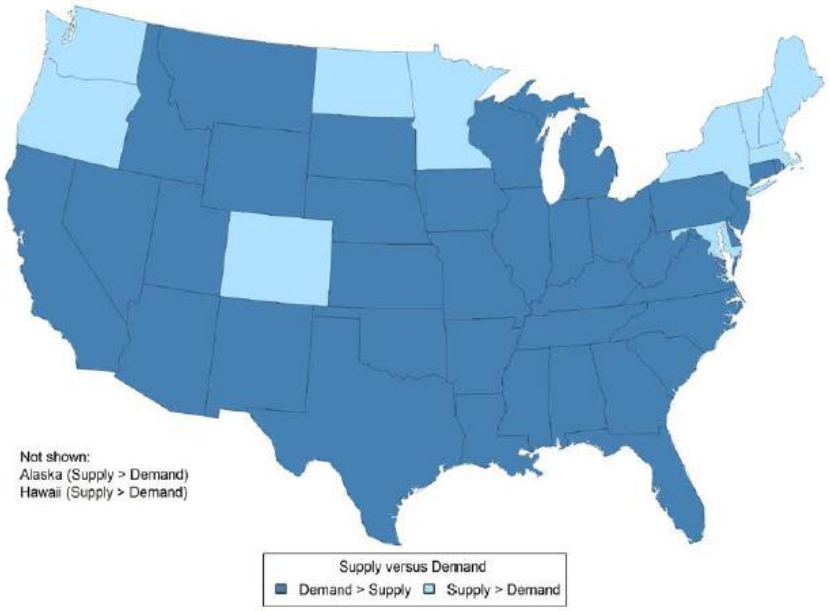

Figure 9. Primary Care Physician Supply versus Demand, by State, 2025[128]

Roles of Geography in Colorectal Cancer Screening Use

There are many factors associated with the use of CRC screening including race, socioeconomic status, health insurance coverage, availability of a usual source of care, communication with provider, level of knowledge about CRC screening, rural residence and geographic access to screening facilities.[85,130-132] An analysis of Behavioral Risk Factor Surveillance System (BRFSS) data indicated that rural residents are 17% less likely to be up-to-date on overall

CRC screening compared with urban residents.[86] Moreover, compared to the urban and the rural residents, the remote rural (often termed as "frontier") residents are the least likely to receive CRC screening.[86] Limited use of CRC screening among the rural and the frontier community can be explained by the lack of access to screening facilities, the differences in individuals' preference for the screening tests (e.g., individuals tend to prefer non-invasive tests such as FOBT) and the differences in provider's recommendations (e.g., providers recommend colonoscopy, which is recommended once every 10 years, for individuals who are less likely to comply with the annual tests).

A recent study in Nebraska found similar disparities in CRC screening.[113] Hughes and his colleagues used the Health Belief Model to elucidate factors that contribute to a lower CRC screening, especially in rural Nebraska. The study found significant differences between the rural and the urban populations regarding their beliefs about CRC screening. For example, rural respondents perceived that they are less able to prevent themselves from getting CRC compared with the urban respondents. Also, there were significant differences concerning access to care, with rural residents tend to be less likely to identify a regular source of care. Having a usual source of care is a well-established reason for increased screening uptake.[85] Interestingly, 35% of the rural residents reported that CRC screening cost too much while only 18% of the urban residents reported that the cost was too high. This view was held even though the majority of survey respondents were insured.

One possible reason that rural residents are less likely to undergo CRC screening is the long distances they need to travel to the nearest colonoscopy facility as well as the lack of public transportation.[87,88,113] On average, rural patients travel 30 minutes longer for medical or dental care compared with their urban counterparts.[89] An analysis of the Utah BRFSS data shows that

among individuals at high risk of CRC (defined as those with a history of CRC, polyps or inflammatory bowel disease) individuals who traveled less than 10 minutes was significantly more likely to receive colonoscopy compared to those who traveled 20 minutes or longer. It should be noted, however, that the study did not find a significant association between the median travel time to the nearest colonoscopy facility and CRC screening use.[88]

Long-distance travel may be especially burdensome for CRC screening. Endoscopic screenings such as colonoscopy come with some logistical challenges such as the need for taking time off from work and the need for somebody to accompany the patient to the procedure. Although screening colonoscopy usually takes half an hour, as the patient needs to be sedated, the procedure requires the patient to take at least a day off from work or other usual activities. Also, because of sedation, the patient needs somebody to drive him or her back home after the procedure. Additionally, the unpleasant experience of bowel preparation before the procedure may be problematic for patients who live in the rural areas and need to travel long distance.

Impact of Travel Time on Stage at Colorectal Cancer Diagnosis

As mentioned earlier, an analysis of national BRFSS data and a survey study conducted in Nebraska suggest that rural residents are less likely to use CRC screening compared to urban residents and that longer travel time to a colonoscopy facility may be associated with less likelihood of colonoscopy screening.[86,87,113] Furthermore, the literature suggests that rural residents are more likely to be diagnosed with late-stage CRC compared to urban residents. However, because of lack of research, the relationship between the travel time and the stage at diagnosis is not very well understood. To our knowledge, there are only two published population-based studies that examined the stage at diagnosis.[118,133]

Charlton and colleagues used the Iowa SEER Cancer Registry that is linked with the Medicare claims database to assess both the impact of rural-urban status as well as travel time to colonoscopy facility on the stage of CRC diagnosis.[118] In this Medicare sample, 69% were diagnosed with late-stage CRC. There was no significant association between rural-urban status or travel time and stage at diagnosis. Authors speculated that this insignificant finding might be due to the high accessibility to healthcare services in the state of Iowa since there is at least one hospital in each county. They also explained that travel time might become less of an issue when the PCP refers the patient to a gastroenterologist whom the patient is familiar with. Another possible explanation of the insignificant findings is that those at retirement age might not consider travel time as a barrier to CRC screening.

The second study was conducted by Massarweh and colleagues using the National Cancer Data Base (NCDB).[133] The authors examined factors associated with metastatic colon cancer diagnosis. In this study, where half of the patients were younger than 69 years old, authors found that 50% of their population were diagnosed with late-stage CRC. In the multivariate analysis, the authors reported a dose-response relationship between age and likelihood of metastatic colon cancer diagnosis where those younger than 60 years had the lowest odds of metastatic colon cancer diagnosis. They also showed that men were more likely to be diagnosed with metastatic CRC compared with women and those who were underinsured or with Medicare or Medicaid insurance were more likely to be diagnosed with metastatic CRC compared to those who were privately insured. Additionally, unlike the study from Iowa mentioned above, Massarweh et al. found a significant association between rural-urban status as well as travel distance and diagnosis of metastatic colon cancer. Those who lived in urban areas and those who lived in rural areas were 4% and 8% more likely to be diagnosed with metastatic colon cancer, respectively, compared

to those who live in metropolitan areas. Additionally, compared to those who traveled a short distance (<12.5 miles), those who traveled an intermediate distance (12.5-49.9 miles) and those who traveled a long distance (≥50 miles) were 18% less likely to be diagnosed with metastatic colon cancer.

Rural-Urban Differences in Receipt of Colorectal Cancer Surgery among Patients with Metastatic Colorectal Cancer

Twenty percent of CRC patients are diagnosed with metastatic CRC. While 10%-20% of metastatic CRC cases are curable[2,67,69] CRC surgery among resectable metastatic CRC patients is a complex procedure and requires a multidisciplinary team to ensure safe and effective operation. Several prior studies found a positive association between the hospital surgery volume and clinical outcomes, which led many to advocate centralization of care (i.e., concentrate complex surgeries at high-volume hospitals). Toward that end and to ensure high-quality procedures, there has been an increase in the centralization of complex cancer surgery including ones for CRC.[134] However, despite the benefit of centralization, travel barriers undermine the beneficial effect of centralization especially among the rural population,[134-136] regardless of one's insurance status.[137,138]

There is a paucity of research that investigates the association between rural-urban status and surgery uptake among patients diagnosed with metastatic CRC. Four published studies assessed geographic location as a covariate in multivariable analyses.[72,73,76,139] These studies found that while patients in the northeast are less likely to undergo PTR those who reside in the south are more likely to receive PTR. Further, 71.8% of those who live in the metro counties and 58.3% of those who live in the nonmetro counties have received PTR. However, these studies focused

on incurable metastatic CRC where the focus of the papers was on the PTR as opposed to synchronous or staged-resection of all metastatic tumors for curative purpose.

Regional Variations in the CRC surgeries

The provision of CRC surgeries varies by the geographic location and the availability of surgical centers with adequate surgery volume.[134,135,140] Depending on the procedure type, the volume of surgery can widely vary by region which leads to the different distance traveled by patients to the treatment center. For instance, the distance traveled for esophageal cancer procedure ranges between 4.4 and 30.7 miles, for pancreatic cancer procedure between 3.0 and 18.0 miles, for colon procedure between 1.9 and 9.3 miles and rectum procedure between 2.2 and 9.9 miles. While the distance traveled to low-volume hospitals is usually shorter, the distance traveled to the high-volume hospitals is longer. For hospitals with very high volume, the distance traveled for esophageal cancer procedure ranges between 13.4 and 57.5 miles, for pancreatic cancer procedure between 9.6 and 43.3 miles, for colon procedure between 2.9 and 11.9 and rectum procedure between 4.8 and 24.5 miles. The differences in the provision of surgery according to the procedures' volume resulted in regional variations depending on procedure type.

The Regional Variation model classifies factors associated with regional variations into clinical and environmental factors.[141] Examples of clinical factors include the physician's decision to refer the patient to a surgeon or the surgeon's belief about the indication for the surgery. Furthermore, examples of the environmental factors are technology diffusion, the supply of surgeons and financial incentives. Clinical factors reflect differences in disease incidence rates such that the higher the incidence of the disease the higher the observed volume for a given operation.[134,135] Further, regional differences are a reflection of variations in the use of cancer detection methods such as screening, which subsequently leads to more or fewer surgeries.[13] For

instance, an ecological study of prostate cancer found that Seattle, which had a higher screening rate than Connecticut, had a higher rate of prostatectomy use than Connecticut.[142]

Additionally, regional variations in CRC surgery is a result of differences in the availability of diagnostic testing. Since colonoscopy is the primary diagnostic test for CRC, both the availability of colonoscopy as well as the accessibility to a facility where colonoscopy is provided are essential to ensure timely tumor detection and, if indicated, surgical resection. Timely detection of tumors varies according to ones' travel distance,[133] disadvantaging rural residents.[89]

Physician's referral pattern is another reason that contributes to regional variations in CRC surgery. Depending on the type of surgery, physicians have different opinions on whether to operate and on the need to refer the patient to a high-volume hospital where the likelihood of a better outcome is higher.[141] For example, variation in volume is measured using Systematic Component of Variation (SCV), where high SCV scores indicate large geographic variations and low SCV scores reflect low variations. Whereas prostatectomy has a very high score of 13.5, colectomy has low SCV score of 3.5 which reflects the consensus in clinical evidence that surgery is the treatment of choice for colon cancer patients.[141] In other words, patient's preferences are less likely to influence treatment in colectomy but contribute significantly to prostatectomy (where the patient has to balance the psychological benefits of tumor removal and survival after surgery versus the risk of sexual dysfunction and permanent urinary incontinence from surgery). Unlike prostatectomy where there are significant variations between low and high-volume areas, colectomy is less likely to vary,[143] and therefore referral is less likely to impact surgical uptake.

The supply of surgeons also contributes to the regional variations in CRC surgery. Since 1970, the supply of general surgeons has been steadily decreasing mainly because of the increased surgical sub-specialization, the aging of surgeons and the lack of training.[144] For

example, during the past 25 years there was a 26% reduction in the number of general surgeons.[145] Regions with the least supply is the rural areas where 56% of the rural counties have no general surgeons.[146] Moreover, general surgeons lack advanced training, for example in laparoscopic and endoscopic techniques, which are predominant in rural hospitals.[145]

Factors Associated with Sphincter-Sparing Surgery (SSS)

There has been an increase utilization of SSS between the years 1988 (35.4%) and 2006 (60.5%).[107,108] Many factors determine who receive the SSS including patient, surgeon or hospital factors. In general, studies found that those who are male, of older age, Blacks, with Medicaid insurance or those who live in a lower-income ZIP code were less likely to receive the surgery. Additionally, high-volume hospitals located in urban areas were associated with a higher use of SSS compared to hospitals located in rural areas.

Age is a significant predictor of SSS use where almost all previous studies found that the use of surgery significantly decreases with age.[107,108,147] Among those who are younger than 60 years of age, the likelihood of receiving the surgery is 21% higher compared with those who are 60 years or older [OR: 1.21 (95% CI: 1.13, 1.29)].[107,108] The differences in SSS use by age is due to the less aggressive treatment with aging (including any surgical intervention) and the lower likelihood of survival among elderly who underwent surgery.[147] For instance, after adjustment for sex, race and tumor characteristics such as grade and stage, increased age is significantly associated with an increased likelihood of dying from rectal cancer. The magnitude of the likelihood of dying is higher among those 70 years and older [RR: 1.31 (95% CI: 1.25, 1.36)] compared with patients 69 years and younger [RR: 1.10 (95% CI: 1.05, 1.15)].[147]

There are also racial disparities in the receipt of SSS, which have been reported in previous studies.[107,148] After adjusting for stage and patients' characteristics, a study using the SEER

database found that Blacks were 42% more likely to receive sphincter sacrificing procedure. Additionally, Ricciardi and colleagues noted a decline in SSS use among Blacks; the authors speculated that the decline might be due to geographic segregations where Blacks are less likely to see a physician who is sufficiently competent to operate.[149]

While only 11% of patients who live in the rural areas receive SSS, the majority of patients who underwent SSS live in urban areas.[108] In urban hospitals, where the volume of SSS is higher than rural hospitals, the odds of undergoing SSS is 1.4 times the odds of receiving surgery in rural hospitals [OR: 1.38 (95% CI: 1.26, 1.52)], even after adjusting for variations in SSS volumes between the rural and the urban hospitals, which indicates that other factors might explain variations between the rural and the urban areas.[108] Other speculated factors include higher income level as well as the availability of private insurance, both of which are associated with the increased uptake of SSS.[107] However, It is unknown if patients in rural areas will differ from those who live in urban areas in the rate of SSS uptake especially among a privately insured population.

Factors Associated with Colorectal Cancer Surgical Outcomes

Compared with the urban residents, the rural population tends to be older, with a lower income and with a lower level of education.[101,150,151] These characteristics have been found to be associated with lower CRC surgery rates or poor outcomes.[101,102,139,151] In addition to these differences, the rural population has more geographic barriers to cancer care especially sophisticated surgical therapy.[152,153] This lower level of access to surgical care contributes to the worse surgical outcomes that have been experienced by the rural residents such as higher mortality, surgery-related complications and hospital readmission.[150,154] For instance, the rural population is more likely to undergo cancer surgery as a result of a non-elective hospital admission.[150]

Many factors contribute to the increase in hospital readmission after colorectal surgery, including older age, male gender, Black race, lower income, lower education, being unmarried, lack of insurance, higher deprivation score, and lower SES. In general, previous studies of CRC surgeries found that the older the patients, the more likely that they were readmitted after the index surgery.[155-159] Compared to the individuals who were 50 to 64 years of age, those who were 65 and older were more likely to readmit. The odds of readmission increase proportionally with age.[159,160] Those who were more likely to get readmitted within 30 days after CRC surgery tended to have increased odds of one-year mortality compared to those who were not, and this pattern in mortality increased with age.[160,161] Moreover, mortality among older age groups (>80 years) compared with younger age group (<50 years) was higher in the rural hospitals [OR: 5.74 (95% CI: 3.45, 9.54)] compared to the urban hospitals [OR: 4.32 (95% CI: 3.81, 4.90)].

In addition to the association between age and hospital readmission, gender and race were found to predict hospital readmission. Most studies found that male patients were more likely to be readmitted compared to female.[102,155,159,161,162] For instance, Greenblatt et al. using SEER-Medicare database found that males were 20% more likely to be readmitted to the hospital within 30 days of CRC surgery, and 21% more likely to die within one year.[161] One of the hypothesized reasons is that males tend to have longer hospital stay compared with females.[155] Additionally, Blacks were 17% more likely to be readmitted compared to Whites.[155]

Moreover, clinical factors such as higher comorbidities, the use of immunosuppressant or steroids and obesity are associated with a higher likelihood of readmission.[156,163-167] There are consistent findings between the association of comorbidity and readmission, a relationship which increases with the increased level of comorbidities. For instance, one study that used claims database reported a 13% increase in the hospital readmission rate as the severity of illness level

increased from 0 to 3, and a 29% increases in readmission as the severity of illness level increased from 0 to 4. Likewise, Schneider and colleagues found that those with Charlson Comorbidity Index (CCI) of 3 or higher were 27% more likely to be readmitted compared to those with a comorbidity score lower than 3.[159]

Although readmission rates vary between 9%-25%, these variations reflect differences in perioperative factors. Specifically, readmission is higher among patients diagnosed with IBD, those admitted urgently, those with longer operation time, patients with complications and those discharged to nursing homes.

Summary

In this chapter, we defined the rural population, identified different classification systems for the rural and the urban populations including the pros and cons of each system and explained the characteristics of the rural population. We found that using RUCA system is more appropriate for the current study. We also defined PCPs and identified their role in the CRC screening process and the benefits (e.g., early detection of CRC or referral to specialists) associated with having a usual source of care. We then elucidated factors associated with CRC screening rates according to geography and stated that previous research found that rural residents are 17% less likely to be up to date in CRC screening. Some of the potential reasons for such lower screening rate is that rural patients are less likely to identify a usual source of care and more likely to travel long distances to receive care. Further, we evaluated the current literature on CRC stage at diagnosis between the rural and the urban populations and especially the effect of travel time. Although many studies have found that the rural population is less likely to get screened and more likely to get diagnosed at a later stage, the evidence is controversial about the impact of travel time on the stage of CRC diagnosis. These inconsistent findings are due to different study populations and

different sources of data. Moreover, there is a paucity of research about CRC treatment differences between the rural and the urban populations who are privately insured, especially the surgery use among those diagnosed with metastatic CRC and the SSS among rectal cancer patients.

This study is designed to fill these gaps in the literature. Unlike previous studies, our study characterizes the CRC screening among the privately insured population who live in a rural state. It also sheds light on the impact of travel time on CRC stage at diagnosis using working-age population, which we believe has never been studied. This population is unique because unlike other population (e.g., Medicare), the younger working population has busy schedules and are therefore less inclined to travel to colonoscopy facility to get screened and thus are more likely to present with metastatic CRC.

CHAPTER 3: RESEARCH METHODS

Overview

The current study is a retrospective cohort study using claims data from the state of Nebraska. The primary data used in this study were BlueCross BlueShield of Nebraska (BCBSNE), supplemented by information from the Rural-Urban Commuting Area Codes Data (RUCA), Health Professions Tracking Service (HPTS) and Google Map. The outcome variables were CRC screening use, stage at diagnosis of CRC, hospital readmission and emergency department visit following CRC surgery, CRC surgery use among patients diagnosed with metastatic CRC, and sphincter-sparing surgery utilization among rectal cancer patients. The exposure variables included rural-urban residence, travel time, and travel distance. The main analyses were X^2-tests, Wald test, and multivariate logistic regressions.

Data Sources

BlueCross BlueShield of Nebraska

BCBSNE is the largest private health insurance company in Nebraska serving over 700,000 people.[168] The claims file, which contains 72,160,334 visits, includes services that occurred between January 1, 2012, and June 30, 2016, and were paid through September 15, 2016. These services consisted of verified claims from inpatient, professional and outpatient facilities. The data were limited to the providers and members who lived in Nebraska during the time the service was provided.

The member file, which contains 920,227 visits, includes all members who were active between January 1, 2012, and June 30, 2016. The file also contains member's demographic

information such as age, gender, member- and provider-5-digit ZIP codes. BCBSNE also captures members' beginning and ending date of coverage. Diagnosis and procedural codes for the relevant inpatient, outpatient, and professional claims are all available as well.

To assess sample representativeness, the proportion of the BCBS members residing in each regional health department district was compared to that of the Nebraska population (Appendix D). The proportions were similar except for Dakota County Health Department (0.35% for BCBS vs. 1.15% for state population) and for West Central District Health Department (0.23% for BCBS vs. 2.16% for state population).

The Rural-Urban Commuting Area Codes Data

RUCA is a publicly available data published by the University of Washington.[169] It is a classification scheme that is based on census tract and uses the standard Bureau of Census Urbanized Area and Urban Cluster definition in combination with work commuting information to characterize all of the census tracts regarding their rural and urban status and their relationship.

RUCA codes are based on the same concepts utilized by the Office of Management and Budget (OMB) to define county-level metropolitan and micropolitan areas. The RUCA codes used the same criteria by OMB by categorizing the U.S. census tracts using measures of population density, urbanization, and daily commuting.[116] The latest RUCA codes are based on the 2010 decennial census and the 2006-2010 American Community Survey.

There are ten primary and 21 secondary codes in RUCA. The primary codes consist of whole numbers (1-10) that represent metropolitan, micropolitan, small town, and rural commuting areas based on size and direction of largest commuting flows. The secondary codes subdivide the ten codes based on secondary commuting flows. Therefore, the classification

satisfies various needs by allowing users to choose their preferred definitions. For the current study, we used "Categorization C" to dichotomize the area of residence into rural and urban. We used this categorization because other categorization would break the sample into subgroups that are too small.

Google Maps Data

Commercial websites such as Google offer accurate driving directions between places. Open-source programming language (i.e., developed by the referenced authors) that is available on SAS was used to make repeated calls to Google to obtain travel time information for any number of locations.[170] Subsequently, the program was tested by the same authors using a nationally representative sample that covers 66,000 locations in the fifty states, the District of Columbia and Puerto Rico.[171] The authors suggest that the SAS code could change to reflect the occasional changes in Google web site structure. For example, if Google map changes its URL, the same change must be reflected in the FILENAME statement in SAS (Please see below for FILENAME method).

In this study, we utilized publicly available Google Maps to calculate travel time as well as travel distance. We calculated travel time by measuring time in minutes between the geographic centroid of each member ZIP code of residence and the provider ZIP code at the time of service. Travel time calculations were made via repeated calls to the Google Maps Web page using SAS FILENAME URL method in SAS.[171] The method has a high correlation with straight-line distance (r^2=0.96) but with superior travel time estimate. When both members and providers had the same ZIP code (i.e., artificial zero bias), we conducted a sensitivity analysis to assess the impact of small variations of travel time (1-, 10-, and 20-minutes) on the metastatic stage at diagnosis.[172] There were no changes in the proportion of metastatic CRC with the changes in travel time.

Health Professions Tracking Service (HPTS)

The HPTS is Nebraska's healthcare workforce monitoring systems since 1995.[173] It collects information about health care providers practicing in Nebraska. The collected information includes profession, license type, primary specialty, training, expertise, languages spoken fluently, retirement plans, practice setting and arrangements for all practice site locations, the ZIP code and county of practice location. The list of professionals is updated periodically to reflect active practitioners in Nebraska.

We used HPTS data to measure access to PCP. The measure is based on the provider-to-population ratio and calculated by dividing the total number of actively practicing PCPs (i.e., medical or osteopathic physician who specializes in general practice, internal medicine or family practice) in each ZIP code by the total population of each ZIP code.[110]

Study Samples

There were two samples for Aim 1 (Sample-1 and Sample-2; Figures 10 and 11 below). The objective of using Sample-1 was to assess the annual use of FOBT or colonoscopy. The eligibility criteria for Sample-1 were BCBSNE members aged 50-64 years old during the year and with average-risk CRC. The cut-off age of 50 was used because this age is considered the average-risk age for the development of CRC according to the USPSTF guideline.[48] We excluded members who were 65 years and older because of their supplemental Medicare insurance. That is, these members have additional coverage through Medicare, and therefore some of their procedures are not captured in BCBSNE. We also excluded members with high risk of development of CRC during each year.

As shown in Figure 10, we first identified the 765,868 members in BCBSNE who have any membership coverage between January 1st, 2012 and June 30th, 2016. We excluded members who

have duplicate enrollment records, overlap in the coverage periods or gaps in enrollment more than 31 days.[174] These exclusions, though not part of eligibility criteria, were necessary to prepare data for final analysis. Among the 688,299 members with no lapse in coverage of more than 31 days, we excluded 546,703 individuals who were outside of the age group of interest. Next, we excluded 36,448 high-risk members defined as members who had a personal history of CRC or adenomatous polyps or a personal history of inflammatory bowel disease. We were unable to exclude members with a family history of CRC or polyps or a known family history of a hereditary CRC syndrome such as familial adenomatous polyps or Lynch syndrome because these members are not captured in the data. A total of 105,148 members met the eligibility criteria for Aim 1 Sample-1. Finally, we looked at every single year and identified members who have coverage for the entire year. Some members have coverage for more than one year.

Moreover, the objective of using Sample-2 was to assess the association between rural-urban status and the CRC screening use (Figure 11). We limited our cohort to members who were continuously-enrolled during the 2013-2015 period (319,245). We did so to ensure the temporality between the covariates and the outcome. That is, we want to ensure that the CRC screening tests occur after PCP visits. We further limited the sample to the age groups 50-64 years old and members with average risk CRC (78,891). Finally, we excluded members with no records (the only available variables for these members was their IDs). A total of 58,774 members met the eligibility criteria for Aim 1 Sample-2.

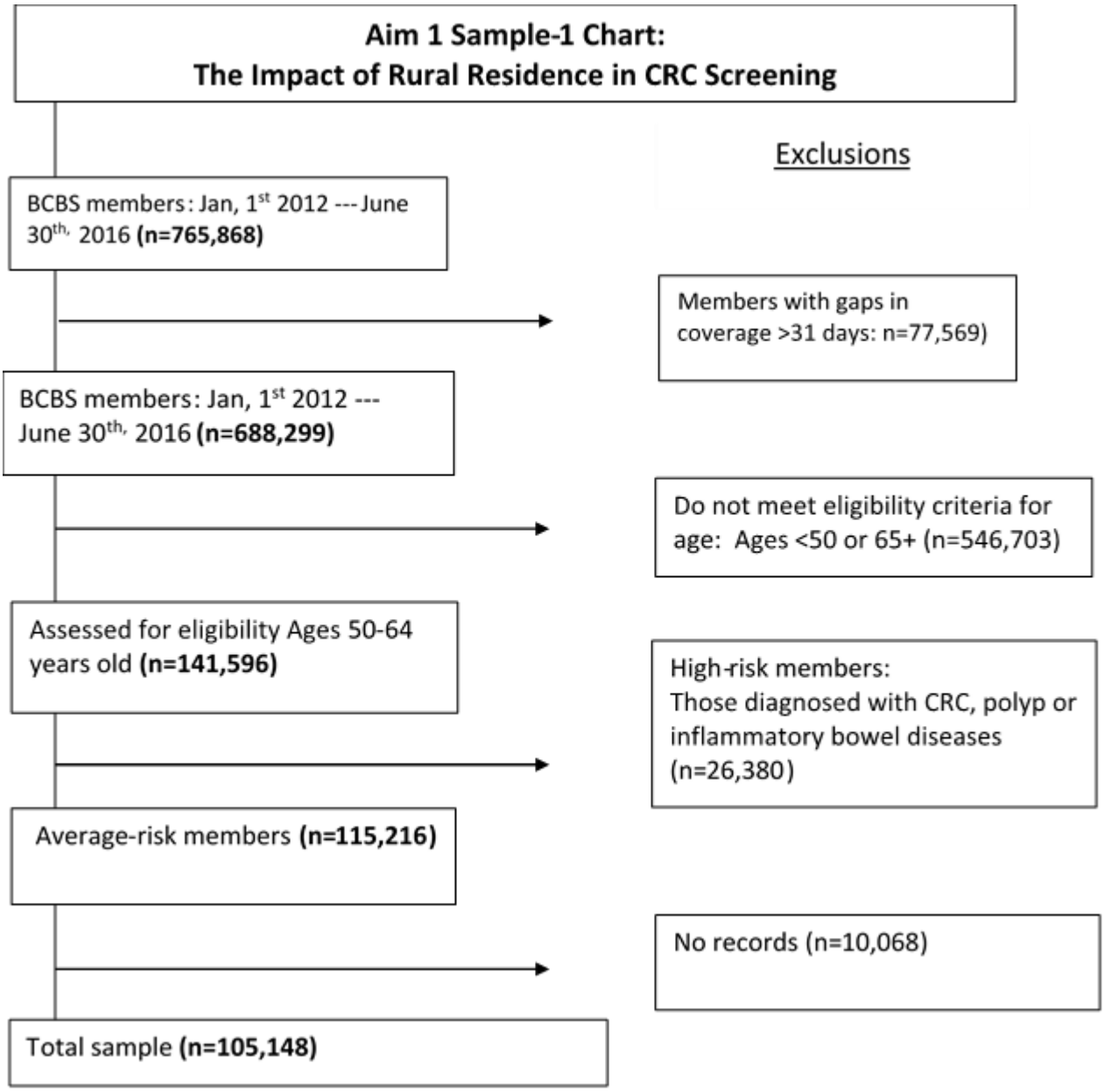

Figure 10. Aim 1 Sample-1 Selection Flow Chart

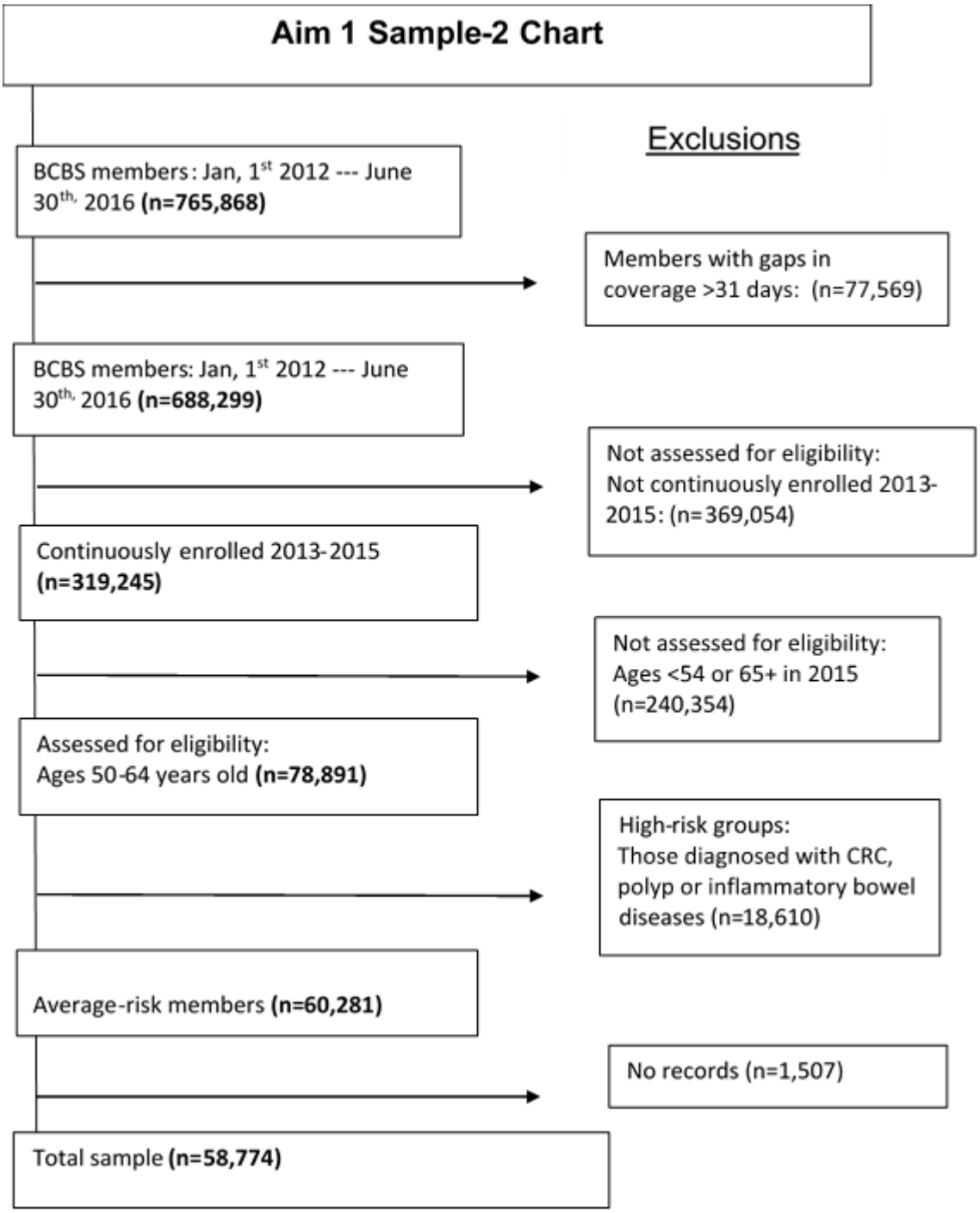

Figure 11. Aim 1 Sample-2 Selection Flow Chart

For Aim 2, the study sample consisted of members aged 50-64 years old with no history of cancer (Figure 12). Out of the 688,299 members, we excluded a total of 546,703 members who were younger than 50 years because they are not recommended for screening. We excluded members who were older than 65 years of age because the BCBSNE data likely did not contain claims for all their health services that may have been covered under Medicare. We also excluded 140,771 people with no diagnosis of CRC. Further, we excluded 149 members with no inpatient claims or fewer than two outpatient claims for CRC because they did not meet our CRC diagnosis definition. We also limited our sample to those with 6-month continuous enrollment before CRC diagnosis and those with no prior cancers. We chose the six months cut-off time to ensure that the identified cases are incident and not prevalent cases.[175]

We conducted sensitivity analysis, that is guided by publications from Setoguchi and colleagues,[175] Song and colleagues,[176] Paramore and colleagues,[177] and Rao and colleagues.[178] These definitions have high agreement with cases reported in the cancer registry in the date of the first diagnosis. All definitions reported by the authors resulted in high specificity and good sensitivity for identifying incident cases. Given that CRC is a rare outcome and in order to improve statistical efficiency, we chose the definition that resulted in high sensitivity. Accordingly, we assumed that those who met the definition of at least one inpatient or at least two outpatient claims of CRC and who have no CRC cancer within six months prior to first CRC diagnosis to be diagnosed with CRC (see Appendix C).

For the travel time analysis, we limited our analysis to members who had colonoscopy claims during the four months prior to CRC diagnosis. We conducted a sensitivity analysis to assess the impact of different continuous enrollment periods (4, 6, 9, 12, 18 and 24 months) on percentages of colonoscopy use and on whether the identified cases were incident not prevalent

cases. A total of 204 members met the eligibility criteria and used in the calculation of travel time (Figure 12).

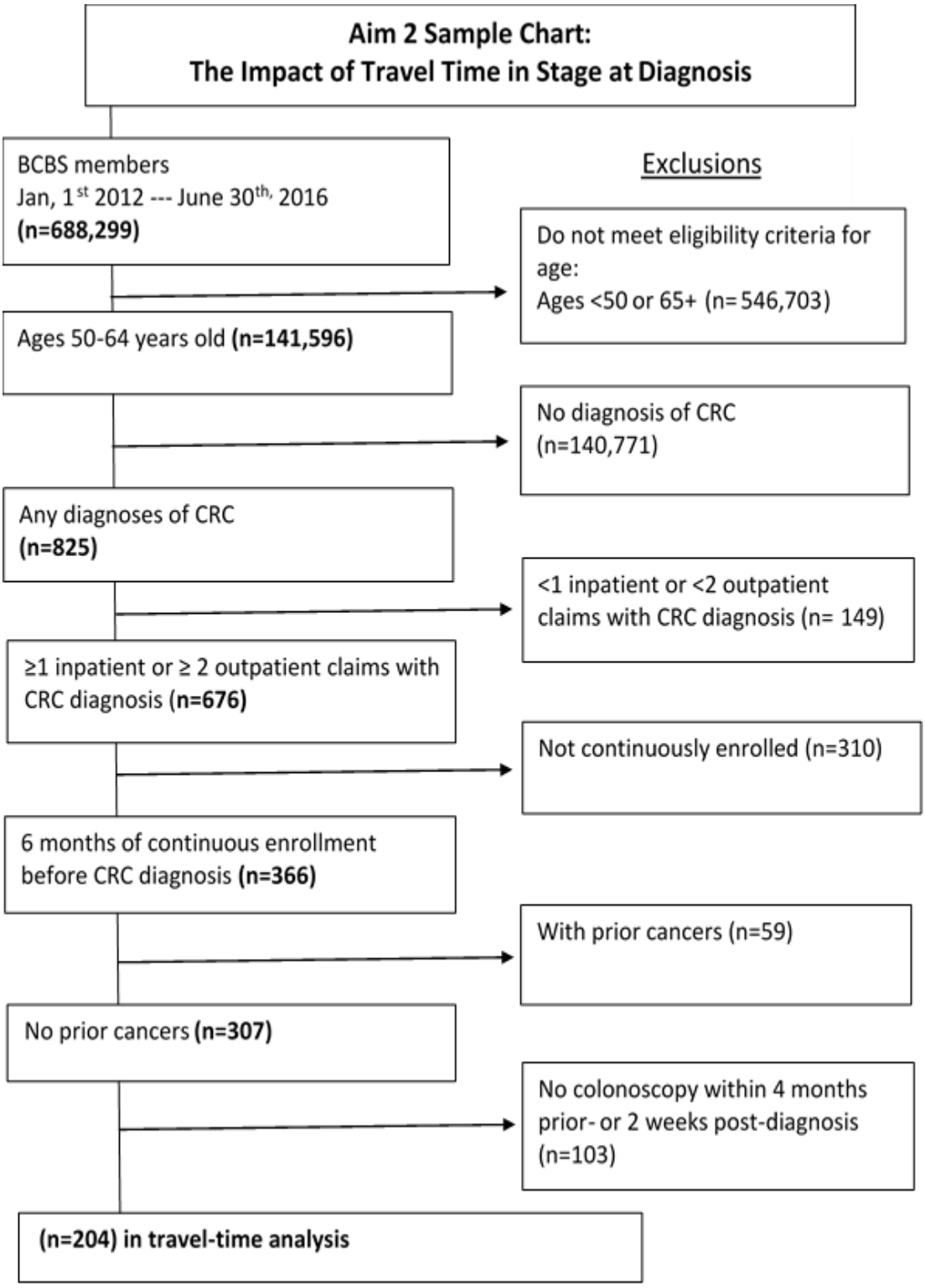

Figure 12. Aim 2 Eligibility Criteria

For Aim 3, Hypotheses 1-3, the study sample consisted of CRC patients between the ages of 19-65 years old (Figures 13-15). Of the 688,299 members, we excluded the following: 255,934 who were younger than 19 years or 65 years or older, and 431,290 with no CRC diagnosis. For Hypothesis 1, the following additional exclusion criteria were applied: no inpatient claims or fewer than two outpatient claims or those who were not continuously enrolled for six months before CRC diagnosis (n=147), no surgery claims (n=284), and no admission or discharge dates (n=72). A total of 315 members met the eligibility criteria (Figure 13).

For Hypothesis 2, the following additional criteria were applied: no inpatient claims or fewer than two outpatient claims or those who were not continuously enrolled for 6 months prior to CRC diagnosis (n=147), no metastatic stage at diagnosis for CRC (n=487), no inpatient claim or fewer than two outpatient claims for mCRC (n=23), and diagnosed with other primary cancers (n=92). A total of 69 members met the eligibility criteria (Figure 14).

For Hypothesis 3, the following additional criteria were applied: no diagnosis of rectal cancer (n=431,863), diagnosed with anal cancer (n=121), no inpatient claims or fewer than two outpatient claims (n=136) and no rectal cancer surgery (n=155). A total of 90 members met the eligibility criteria (Figure 15).

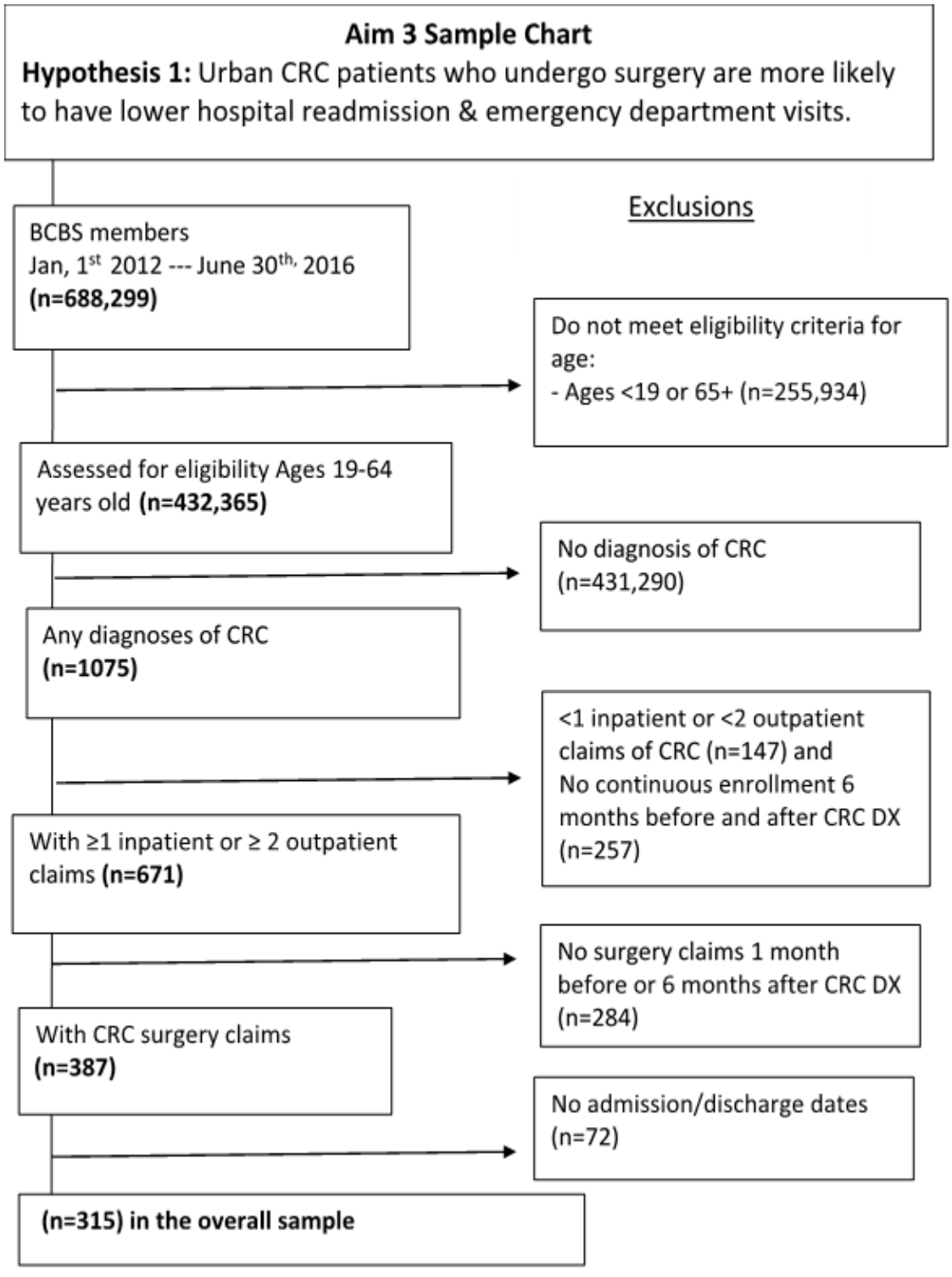

Figure 13. Aim 3-Hypothesis 1 Eligibility Criteria

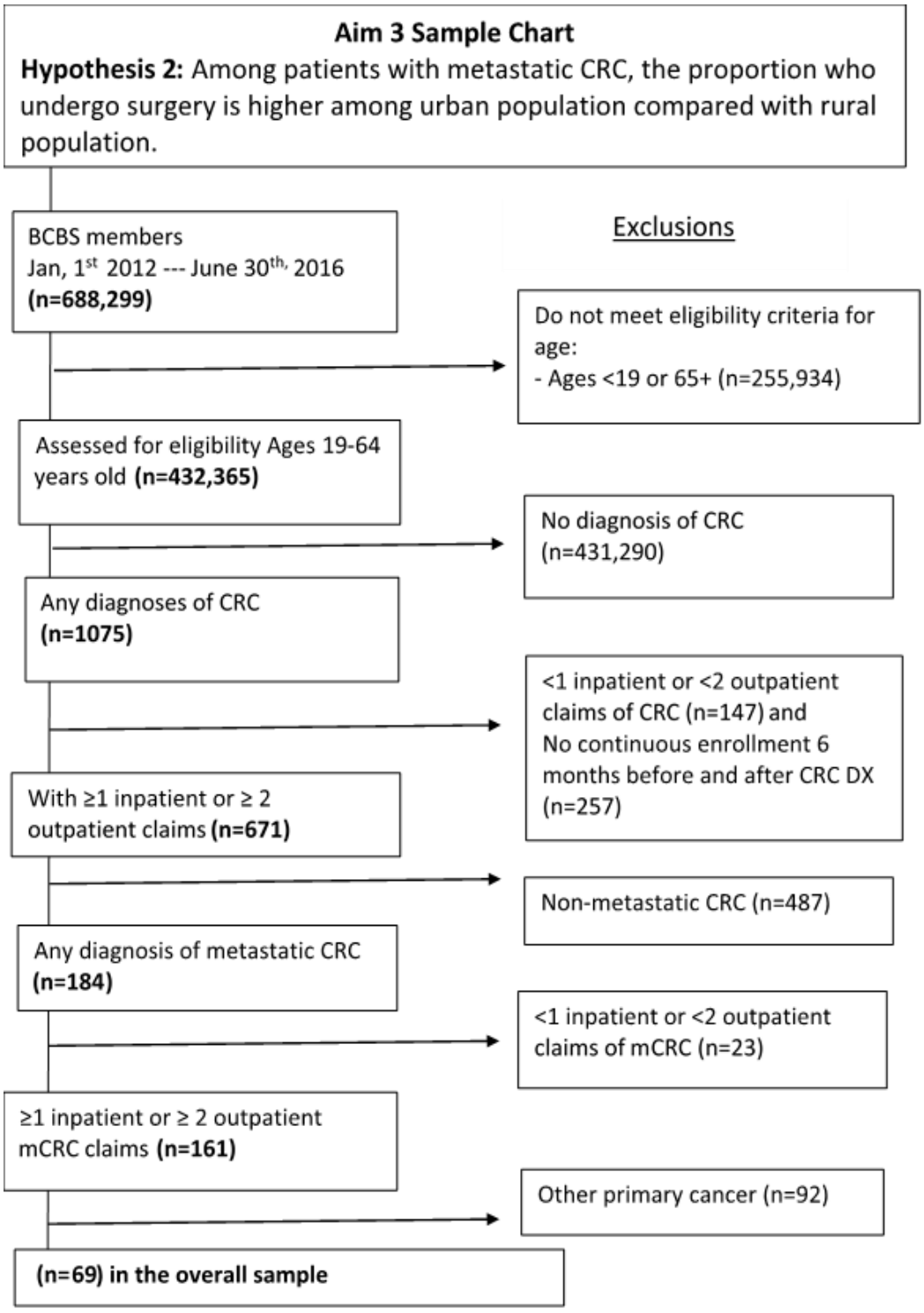

Figure 14. Aim 3-Hypothesis 2 Eligibility Criteria

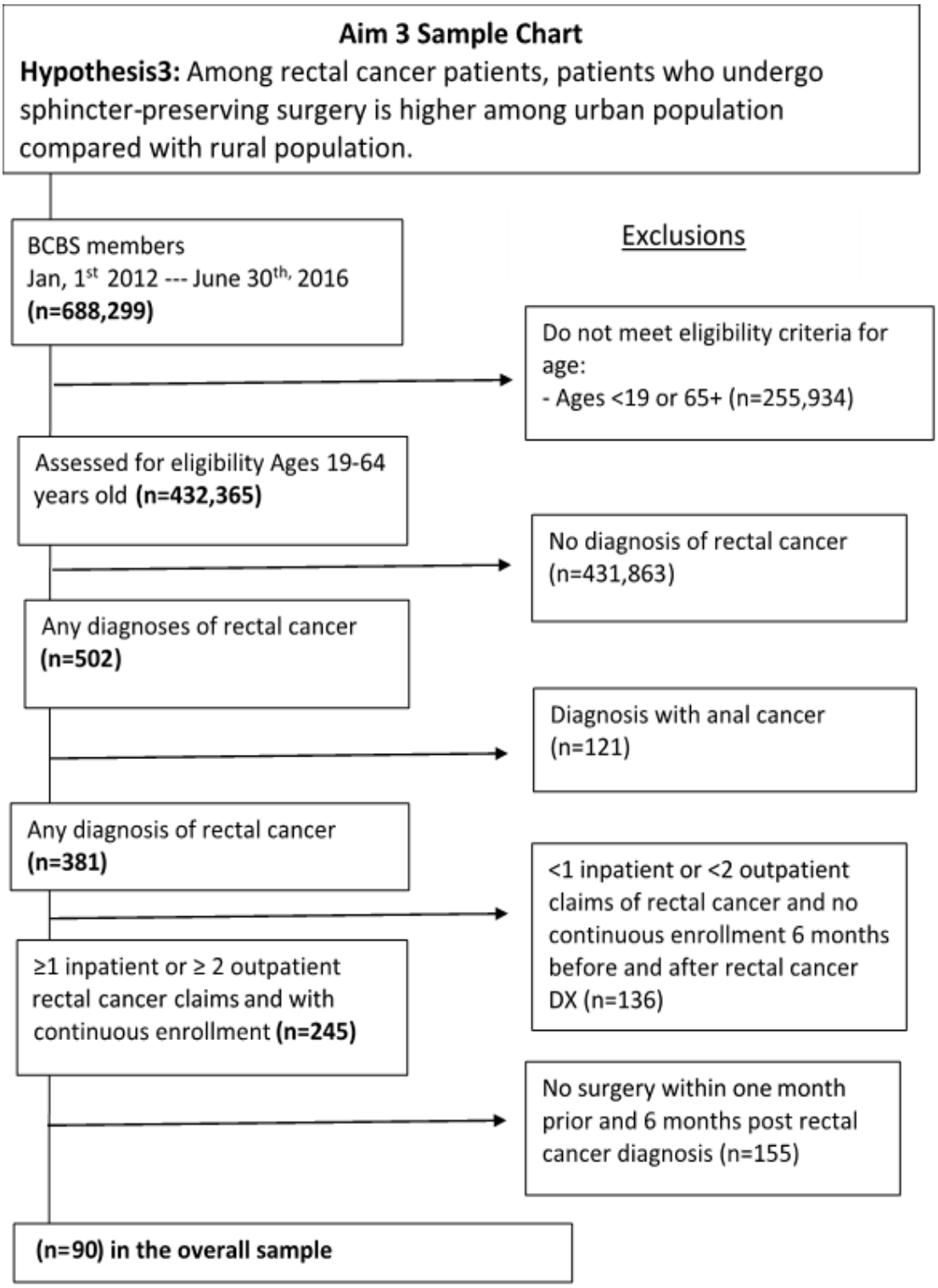

Figure 15. Aim 3-Hypothesis 3 Eligibility Criteria

Key Variables and Measures

Table 1 summarizes select key variables and measures. In the following, assumptions and definitions for the key variables and measures are described.

Coverage Dates, Service Dates and Age at Diagnosis

To identify the coverage period, variables called "beginning date of coverage" and "ending date of coverage" were identified from the BCBSNE enrollment files. These variables were used during the data preparation step when we removed duplicate records and corrected the coverage periods (e.g., by removing overlap coverage). For beginning and ending dates of service, the first and last dates of service by a recognized medical practitioner during the study period (1/1/12-6/30/16) were used to identify services related to the research questions (e.g., CRC diagnosis). Age at diagnosis was identified using the age when the first CRC diagnosis was reported within the six months continuous enrollment provided.

CRC Risk, Diagnosis and Staging

Claims data were used to identify individuals who had ICD codes for the malignant neoplasm of colon or rectum (excluding anal cancer). For the specific codes used, see Appendix B. Individuals were considered to be diagnosed with CRC if they had at least one inpatient claim or at least two outpatient claims for CRC diagnosis during the study period (2012-2016). ICD codes are based on codes used in a similar study by several authors[118,133,175] (Appendix B3). Note that given that the BCBSNE did not provide CRC diagnosis variable, we had to make assumptions to develop an operational definition of CRC diagnosis. These assumptions were guided by publications from Setoguchi and colleagues,[175] Song and colleagues,[176] Paramore and colleagues,[177] and Rao and colleagues.[178] For instance, we applied the definitions suggested by Setoguchi and colleagues to define incident CRC in administrative data. These definitions have

high agreement with cases reported in cancer registry in the date of the first diagnosis. All definitions reported by the authors resulted in high specificity (99.62%-98.51%) and good sensitivity (67.25%-88.02%) for identifying incident cases. Given that CRC is a rare outcome and in order to improve statistical efficiency, we chose the definition that resulted in a high sensitivity. Accordingly, we assumed that those who met the definition of at least one inpatient or at least two outpatient claims of CRC to be diagnosed with CRC. Based on a study by Gupta et al. who used claims data to study CRC, high-risk groups was operationally defined as those who have previous CRC diagnosis, polyps diagnosis or inflammatory bowel disease.[179]

Given that BCBSNE does not have a variable to identify stage at diagnosis, we reviewed the literature and consulted with the surgeon about measuring CRC stage at diagnosis. Several publications have used secondary malignant CRC as a surrogate for metastatic CRC[176,177] and metastatic breast cancer.[178] Thus, we assumed that patients who were diagnosed with secondary metastatic neoplasm, according to Appendix B4, would have been diagnosed with metastatic CRC. In this study, the CRC staging was dichotomized into metastases versus non-metastatic CRC. Metastasis was defined as the occurrence of at least one inpatient claim or at least two outpatient claims for metastatic CRC codes (Appendix C) within 30 days before CRC diagnosis or any time after CRC diagnosis. These codes have also been used elsewhere.[177]

CRC Screening

In order to define the purpose of colonoscopy (i.e., Screening versus Diagnostic or Surveillance), we identified the pertinent ICD and CPT codes. Members were classified as having a diagnostic colonoscopy if they received claims indicating CRC symptoms such as blood in stool, rectal bleeding or abdominal pain four months prior to colonoscopy (see Appendix X for specific codes used). To be classified as having surveillance colonoscopy, members should not have claims

associated with potential CRC symptoms but should have diagnoses indicating a history of a condition that merits more frequent CRC surveillance such as polyps or IBD. Members who did not meet the diagnostic or surveillance criteria above were classified as having a screening colonoscopy (see Appendix B1, B2, and B5 for specific codes used).

We assessed members who received colonoscopy within four months prior- or two weeks post-diagnosis of CRC to determine if the purpose of colonoscopy was screening, surveillance or diagnostic (Appendix C6). We conducted sensitivity analysis for periods between three and six months prior- and between two weeks and six months post-diagnosis. But this sensitivity analysis resulted in fewer additional colposcopies identified. For instance, restricting to six months of continuous enrollment before diagnosis resulted in 210 cases, four months resulted in 204 cases and three months resulted in 200 cases. Likewise, restricting continuous enrollment for a post-diagnosis period of 14 days resulted in 22 cases, 30 days to 25 cases, 60 or 90 days to 31 cases, 120 days to 35 cases and 180 days to 44 cases. We decided to choose four months prior- or two weeks post-diagnosis of CRC because of the fewer cases identified by extending the time.

CRC Surgery and Readmission

Receipt of CRC surgery was defined as the endoscopic removal of polyps (polypectomy), local excision, resection of the primary tumor with or without stoma creation among patients with six months continuous enrollment before CRC diagnosis and six months continuous enrollment after CRC diagnosis. The one year of continuous enrollment was chosen to ensure that we are not missing surgeries conducted after systemic therapy according to guidelines (i.e., surgery after neoadjuvant therapy).[67] For the codes used to identify surgeries, see Appendix B7 and B8. These codes were used after consultation with the surgeon and after meeting with the trained coder. Additionally, these codes were guided by previous publications.[101,102,155,161,180] After applying these

codes, we found that the rate of CRC surgery is lower than what has been reported in the literature.[101] To fully understand the lower rates of CRC surgery, we conducted a sensitivity analysis. Please refer to Appendix C for the detailed explanation and results of the sensitivity analysis.

Finally, the 30-day readmission was defined as the number of patients who were discharged from hospital and readmitted within 30 days divided by the number of all people who were discharged. The same definition has been used in a previous publication.[181] Operationally, we used the inpatient records and the two variables created by BCBSNE (admission date and discharge date) to measure hospital readmission. For the codes used to determine the readmission, see Appendix B.

Classification of Rural-Urban Status

According to RUCA developer,[117] a total of 33 codes can be used to categorize geographic population. A researcher can collapse these codes into categories that fit his or her research objectives. For instance, one can choose categories from the table below. Consistent with the relevant literature, we used Categorization 'C.' Since the current study is limited to a sample of Nebraska residents, we used RUCA Nebraska file.

Measurement of Travel Time to Screening Facility

For the measurement of travel distance and travel time, we used Google Maps as well as BSBSNE's provided member's 5- digit ZIP codes and providers' 5- digit ZIP codes. Many previous studies defined distance as the straight-line distance between locations using coordinates or latitude and longitude. Although the straight-line distance is useful,[171] a greater precision can be achieved using actual road distance when the driving distance is estimated using Google Maps.

Using the centroid of ZIP code, we calculated the travel time between members and providers. Accordingly, travel time is defined as the time in minutes between the ZIP codes' centroid for participants and the ZIP codes' centroid for providers. There are three main steps for the calculation of travel distance: 1) identification of distances between a single ZIP code and all ZIP codes in Nebraska,[170] 2) combining all calculated distances, and 3) merging distance for the study sample.

To operationalize travel time, we used the date of the first claim of index colonoscopy to identify both participants as well as provider addresses. We measured travel time as a continuous variable and reported the mean and median. When both members and providers have the same ZIP code, we conducted a sensitivity analysis to assess the impact of small variations of travel time (1-, 10-, and 20-minutes) on the metastatic stage at diagnosis.

PCP Access and Preventive Service Use

The PCP access was defined as the provider-to-population ratios which highlight gaps in service availability and delivery.[110] It was calculated by dividing the total number of actively practicing PCPs in each ZIP code by the total population of each ZIP code.

Preventive service use was defined as any health services such as checkups or counseling to prevent illness or to detect illness at an early stage when treatment is more viable.[182] For the codes used for to identify preventive services, see Appendix B6. These codes have been used in previous study.[183]

Primary Care Physician Visits

Primary care physician visits were measured using the number of visit in a calendar year to a general practitioner, an internist or family practitioner. For Sample-1 of Aim 1, we looked at

the number of PCP visits during a calendar year. For Sample-2 of Aim 1, we looked at the number of visits during a two-year period (2013-2014).

Enhanced Charlson Comorbidity Index

Enhanced Charlson Comorbidity Index was developed by Charlson et al. to determine the burden of disease and case mix.[184] Researchers use the index to account for comorbidities in the regression models. To apply the index to administrative data, other authors modified the comorbidity index and validated its use.[185,186] In 2011, Quan et al. updated the index that was validated for use in administrative data by adjusting the weights of comorbidities.[187]

Table 2. Description of select key variable and measures

Variable / Measure	Data Source and Operational Definition
Beginning date of coverage	BCBS enrollment file. The first date of BCBSNE coverage.
Ending date of coverage	BCBS enrollment file. The last date of BCBSNE coverage.
Beginning date of service	BCBS enrollment file. The first date of service by a recognized medical practitioner during the data period 1/1/12-6/30/16. The calendar year of service derived from date of service.
Ending date of service	BCBS enrollment file. The last date of service by a recognized medical practitioner during the data period 1/1/12-6/30/16. The calendar year of service derived from the end date of service.
Age at diagnosis	BCBS enrollment file. Member's age at the time of CRC diagnosis
Receipt of FOBT	BCBS claims file. Having at least one paid claim for FOBT conducted during the specified calendar year.
Receipt of screening colonoscopy	BCBS claims file. Having at least one paid claim for non-diagnostic and non-surveillance colonoscopy conducted during the calendar year.
Receipt of diagnostic colonoscopy	BCBS claims file. Having at least one paid claim for diagnostic colonoscopy (i.e., symptoms such as rectal bleeding) conducted during the calendar year.
Receipt of surveillance colonoscopy	BCBS claims file. Having at least one paid claim for surveillance colonoscopy (i.e., among high-risk individuals with a history of CRC, polyps or IBD) conducted during the calendar year.
High-risk individuals	BCBS claims file. Having a history of CRC, polyps or IBD.
CRC diagnosis	BCBS claims file. Having at least one inpatient or at least two outpatient claims of CRC diagnosis during the specified continuous enrollment.
Metastatic stage of CRC	BCBS claims file. Having at least one inpatient or at least two outpatient claims of metastatic CRC diagnosis within 30 days before

	CRC diagnosis or any time after CRC diagnosis during the specified continuous enrollment.
Receipt of CRC surgery	BSBS claims file. Having at least one claim for CRC surgery during specified continuous enrollment with BCBSNE.
ER visit	Emergency department visit within 30 days after CRC surgery.
30-day readmission	The number of patients who were discharged from hospital and readmitted within 30 days divided by the number of all people who were discharged.
Rural-urban status of member's residence	BCBS enrollment file. Based on RUCA classification system, individuals who lived within the ZIP codes that were designated as a rural area by RUCA were classified as rural residents, and the remaining were classified as urban residents.
Travel time to receive health care	BCBS denominator and claims files. A straight-line travel time between the geographic centroid of member ZIP code and the provider ZIP code at the time of service calculated by Google Map.
PCP access	2016 HPTS data and 2010 US Census data. The number of actively practicing PCPs per population in a given zip code.
PCP visits	Primary care physician visits are computed using the number of visit in a calendar year to a general practitioner, an internist or family practitioner. For Sample-2 of Aim 1, we looked at the number of visits during a two years period (2013-2014).
Preventive service use	Preventive services are any health services such as checkups or counseling to prevent illness or to detect illness at an early stage when treatment is more viable.
Enhanced Charlson comorbidity index	A method developed by Charlson et al. and is used to determine comorbidities or the burden of disease and case mix. Quan et al. updated the index that is used in administrative data by adjusting the weights for comorbidities. For Aim 1, we included cancer diagnosis as part of the measurements of CCI, however; we excluded cancer diagnosis from the calculation in Aim 3 where all study populations were diagnosed with CRC.

Missing Data

For Aim 1, there were six observations with missing value for the rural-urban status. For Aim 2, the only missing variable was "access to primary care physician" (26% missing). We did not use access to PCP in our analyses. This variable was created using the HPTS data because it is not available in the BCBSNE data. To circumvent the problem of missing data, we imputed the value of the missing variable. Because there was an association between other covariates and stage at

diagnosis, we assumed that "access to primary care physician" is Missing At Random (MAR). Therefore, multiple imputations using the SAS procedure PROC MI was used. The imputation consisted of three phases: the imputation phase where we ran a total of 10 imputations; the analysis phase where logistic regression was used to calculate parameter estimates and odds ratios; and the pooling phase where the parameter estimates from analysis phases were pooled. Finally, for Aim 3, there were no missing variables.

Statistical Analyses

We used SAS statistical software version 9.4 (SAS Institute Inc. Cary, NC) to conduct all analyses. All tests were 2-tailed with α level of 0.05.

Aim 1

The first aim was to assess the impact of rural residence on CRC screening. The first part of the analysis was to estimate the annual prevalence rates for FOBT and colonoscopy. The numerator was the number of members with at least one paid claim for the specified screening test during the specific year. The denominator was the number of members eligible for screening during the specific year. To compare the rates between urban and rural members, we used X^2-test. The same test was used to assess the CRC screening use across years as displayed in Figure1.

The second part of the analysis was to assess the association between rural-urban status and FOBT or colonoscopy use. We estimated the unadjusted odds ratios using univariate logistic regression. The variables used in the univariate models are age, gender, rural-urban status, PCP visit in 2013-2014 and CCI. Predictor variables with p-value <0.25 were included in the multivariate model. We assessed if the association between rural-urban status and the use of FOBT was modified by assessing the interaction. We found that there were interactions between

rural-urban status and age, gender and PCP visits. Likewise, there was an interaction between rural-urban status and age when we assessed the colonoscopy use. We reported the stratified results by each of the effect modifiers.

Aim 2

We used Wilcoxon rank-sum tests for continuous variables and X^2-tests for categorical variables. We also used univariate analysis to compare metastatic versus non-metastatic CRC diagnosis using univariate logistic regression. In the univariate analysis, we made comparisons by age, gender, rural-urban status, use of colonoscopy within four months prior to CRC diagnosis and travel time. Wald tests were used to assess predictors' significance. We checked interaction between travel time and age, gender, rural-urban status, use of colonoscopy within four months prior to CRC diagnosis and there was no interaction.

We used the fractional polynomial method (PROC LOESS) to examine any non-linear relationship between the log odds of metastatic diagnosis and continuous variables. We inspected the curves of the predictors against the dichotomous response and used the likelihood ratio test for improvement in fit against the assumed linear relationship. Lastly, we conducted a multivariate logistic regression analysis to assess the relationship between travel time and metastatic CRC diagnosis adjusting for all variables. Univariate logistic regression analyses were conducted to assess the association between the predictor variables (age, gender, rural-urban status, use of preventive services, colonoscopy type, and PCP access) and the metastatic CRC. Predictor variables with p-value <0.25 were included in the multivariate logistic model. Multivariate logistic regression was built to adjust for the confounding variables using the step-wise method. There was no interaction between travel-time and predictors. We used PROC LOGISTIC in SAS statistical software.

Aim 3

We used descriptive analysis to compare the demographic and clinical characteristics between the rural and the urban populations. For the significance tests, we used X^2-test for categorical variables and t-test for continuous variables. Hospital readmission was defined as re-hospitalization within 30 days of the index hospitalization. Patients with any hospitalization after the index surgery were identified using inpatient CRC claims. These patients were then classified according to their time of inpatient visits after the index surgery into hospitalization within 30 days versus more than 30 days. For the univariate analysis, we used logistic regression model to compare the readmitted patients versus the non-readmitted, and patients who received surgery from those who did not receive the surgery among all variables; Wald tests were the test of significance. We also estimated the unadjusted odds ratios using univariate logistic regression models for the rural residence among those readmitted versus none and those received surgery versus no surgery. Readmission and surgery status were estimated using multivariate logistic regression.

Univariate analyses were performed between hospital readmission and clinical and demographic variables. Logistic regression was conducted to assess the association between rural-urban status and hospital readmission after adjustment for the following independent variables: surgery approach, the presence of intestinal obstruction or perforation and CCI. These independent variables were based on previous knowledge of the association between rural-urban status and readmission or were with p-value <0.25. The variables include age, gender, travel-time, LOS, tumor location, site of surgery and stoma creation. There were no interactions between rural-urban status and independent variables.

Receipt of surgery among metastatic CRC patients was calculated by measuring the proportion of CRC patients who were in the rural and the urban population and comparing them for the receipt of surgery. Receipt of rectal surgery is measured by calculating the proportion of rectal cancer patients who are in the rural and urban areas and comparing them for the receipt of surgery. For Hypothesis 2 (the relationship between rural-urban status and the use of surgery among patient diagnosed with metastatic CRC), univariate analyses were conducted to assess the relationship between the predictor variables and the use of surgery among patients diagnosed with metastatic CRC. These variables are age, gender, rural-urban status, CCI, travel-time, primary tumor site, site of metastasis, number of metastatic sites and access to PCP services. Predictor variables with p-value <0.25 were included in the multivariate model. Multivariate logistic regressions were built to adjust for the confounding variables using the step-wise method. We also assessed the interaction between rural-urban status and all predictors and found no interaction. For Hypothesis 3 (the relationship between rural-urban status and the use of surgery among patient diagnosed with rectal cancer), univariate analyses were assessed between rural-urban status and the use of SSS in patients diagnosed with rectal cancer.

Sample Size Calculation

Because some of the analyses were underpowered, a post hoc sample size calculation was conducted (Table 3). The travel time sample size calculation was based on findings from the current study: the median travel time of 19 minutes, and those who live closer to the facility to be less likely to be diagnosed with metastatic CRC (15%). The estimated sample size was calculated using the PROC POWER in SAS. It was found that for a comparison of two independent binomial proportions using Pearson's X^2-test statistic with X^2 approximation with a two-sided

significance level of 0.05, a sample size of 175 per group has an approximate power of 0.79 when the proportions are 0.15 and 0.27.

Table 3: Power Analysis

Power analysis for varying proportions of subjects who live >19 minutes from colonoscopy facility, assuming 0.15 metastatic CRC in subjects who live ≤19 minutes, α=0.05		
Power	Proportion of metastatic CRC in subjects live >19 minutes of colonoscopy facility	Sample size per group
0.23	0.20	173
0.31	0.21	176
0.40	0.22	179
0.48	0.23	176
0.56	0.24	173
0.65	0.25	176
0.72	0.26	174
0.80	0.27	175
0.84	0.28	173

Summary

The current study is a retrospective cohort study of a privately insured population from Nebraska. The overall study population comprised of members who met the eligibility criteria as described in Figures 10-15 between the years of 2012 and 2016. The main exposures were rural-urban status and travel time. The main outcomes were screening use, stage at CRC diagnosis, hospital readmission and emergency department visits, surgery use among patients diagnosed with metastatic CRC and sphincter-sparing surgery use among patients diagnosed with rectal cancer. The statistical analyses used in this study were logistic regression, and all analyses were conducted using SAS.

CHAPTER 4: RESEARCH FINDINGS

Aim 1: The Prevalence of Colorectal Cancer Screening by Rural and Urban Status in Nebraska

Members Eligible for Colorectal Cancer Screening by Demographic Characteristics

As shown in Figure 10 (Aim 1 Study Sample Selection Chart), a total of 105,148 individuals met the eligibility criteria for this aim: aged 50-64 years, active members of BCBSNE during the study period (2012-2016), and are of average risk of developing CRC. Table 4 compares the characteristics of rural and urban members. Despite the statistically significant differences between the rural and urban populations, the two populations share similar characteristics. For instance, the majority of the two populations visit the PCP (82% and 83%).

Table 4: BCBSNE Members Eligible for Colorectal Cancer Screening by Rural/Urban Residence (N=105,148).

Characteristics	Rural (n=52,469)	Urban (n=52,673)	*P-value*
Age			
50-54	18365 (35.0)	18977 (36.0)	0.002
55-59	17702 (34.0)	17476 (33.0)	
60-64	16402 (31.0)	16220 (31.0)	
Gender			
Female	27847 (53.0)	29172 (55.0)	<.0001
Male	24622 (47.0)	23501 (45.0)	
PCPs visits			
Yes	42870 (82.0)	43497 (83.0)	0.0002
No	9599 (18.0)	9176 (17.0)	
CCI			
0	35739 (68.0)	35546 (67.0)	0.0004
1	9319 (18.0)	9235 (18.0)	
≥2	7411 (14.0)	7892 (15.0)	

Rural, urban status: 6 observations with missing values

Annual FOBT Use

Table 5 shows the annual FOBT use. During the period 2012-2016, the annual number of members eligible for CRC screening fluctuated between 67,821 in the year 2012 to 79,544 in the year 2014. In all years except in 2016, the number of eligible members was larger for rural compared to urban areas. Overall, there was a small but significant decrease in the use of FOBT between 2013 (11%) and 2016 (10%). Table 5 and Figure 16 display the results across all years. One of the hypotheses under Aim 1 was that FOBT screening rate would be higher in the rural population compared to the urban population. Findings suggest that rural members had higher percentages of FOBT use (e.g., 11.39% vs. 10.76% in 2012) compared to urban members ($P<.05$).

Rural members had a consistently higher FOBT use for age groups 50-54 and 55-59, but this pattern was reversed for the oldest age group of 60-64 years during the year 2016, where the rural members had a higher use of FOBT. In rural areas, females had a consistently higher use of FOBT compared to males. For instance, in 2012, 15% of females used FOBT while only 7% of males used FOBT in rural areas. In urban areas, the use of FOBT was similar between males and females. For both rural and urban areas, PCP visits were also related to the use of FOBT but with different size of association. In rural areas in 2012, 12% of those who had PCP visits used FOBT while only 6% of those without PCP visits used FOBT. A similar pattern was observed for urban areas.

Table 5. Annual Percentage of FOBT Use by Rural-urban Status, BCBSNE 2012–2016 (Aim 1)

	2012 (n=8,527)		2013 (n=8,827)		2014 (n=8,716)		2015 (n=7,870)		June, 2016 (n=7,229)	
Overall by location	Rural (n=4,706)	Urban (n=3,821)	Rural (n=4,827)	Urban (n=4,000)	Rural (n=4661)	Urban (n=4,055)	Rural (n=4,066)	Urban (n=3,804)	Rural (n=3,750)	Urban (n=3,479)
Characteristics	11.39 (11.09,11.7)	10.76 (10.44,11.0)	11.54 (11.24,11.8)	10.69 (10.37,11.0)	11.50 (11.19,11.8)	10.39 (10.09,10.6)	10.67 (10.36,10.98)	10.23 (9.92,10.53)	10.63 (10.31,10.95)	9.47 (9.17,9.77)
Age										
50-54	11.69 (11.16,12.2)	9.82 (9.31,10.35)	11.80 (11.29,12.3)	9.70 (9.21,10.20)	11.73 (11.21,12.2)	9.40 (8.92,9.88)	10.86 (10.34,11.38)	9.30 (8.82,9.79)	10.92 (10.39,11.46)	8.77 (8.30,9.25)
55-59	11.95 (11.42,12.4)	11.47 (10.90,12.0)	11.94 (11.41,12.4)	11.35 (10.79,11.9)	11.82 (11.29,12.3)	11.01 (10.48,11.5)	10.98 (10.45,11.51)	10.84 (10.30,11.38)	11.01 (10.47,11.56)	10.13 (9.61,10.67)
60-64	10.44 (9.91,10.97)	11.09 (10.50,11.6)	10.77 (10.22,11.3)	11.16 (10.58,11.7)	10.83 (10.27,11.4)	10.93 (10.36,11.5)	10.05 (9.49,10.62)	10.69 (10.10,11.27)	9.74 (9.16,10.33)	9.58 (9.02,10.14)
Gender										
Female	15.0 (14.53,15.4)	10.99 (10.55,11.4)	15.18 (14.71,15.6)	10.91 (10.48,11.3)	15.18 (14.70,15.6)	10.61 (10.20,11.0)	14.34 (13.86, 14.82)	10.53 (10.11,10.95)	14.27 (13.76,14.77)	9.56 (9.16,9.97)
Male	7.34 (6.97,7.70)	10.47 (10.0,10.95)	7.47 (7.11,7.85)	10.42 (9.95,10.88)	7.40 (7.03,7.78)	10.12 (9.67,10.57)	6.52 (6.16,6.88)	9.85 (9.40,10.30)	6.53 (6.15,6.90)	9.36 (8.91,9.81)
PCP visit										
Yes	12.27 (11.92,12.6)	11.90 (11.54,12.2)	12.32 (11.98,12.6)	11.69 (11.34,12.0)	12.29 (11.94,12.6)	11.47 (11.14,11.8)	11.45 (11.10,11.80)	11.35 (11.01,11.70)	11.52 (11.16,11.88)	10.90 (10.55,11.24)
No	6.40 (5.79,7.02)	2.58 (2.11,3.05)	6.75 (6.10,7.39)	2.62 (2.13,3.11)	6.49 (5.84,7.15)	2.18 (1.76,2.61)	6.02 (5.39,6.67)	1.97 (1.56,2.38)	5.63 (5.01,6.25)	1.40 (1.09,1.71)

Annual Colonoscopy Screening Use

Overall, colonoscopy use increased slightly from 14% in 2012 to 15% in 2015. Table 6 and Figure 16 display the results across all years. The third row of Table 6 shows the annual colonoscopy use by rural and urban status. One of the hypotheses under Aim 1 was that colonoscopy rate would be higher in the urban population compared to the rural population. We found that urban members had significantly higher percentages of colonoscopy use compared to rural members (P<.001). The proportion of individuals who used colonoscopy was highest in the youngest group (50-54 years) and lowest in the oldest group in both rural and urban areas. For example, in 2012 in rural areas, 17% of people aged 50-54 used colonoscopy compared to only 9% of people aged 60-64 years. Similarly, in 2012 in urban areas, 18% of people aged 50-54 used colonoscopy while only 11% of people aged 60-64 used colonoscopy.

In both rural and urban areas and across years, females had higher use of colonoscopy compared to males. Moreover, among females, there were significant differences between rural and urban areas where females who reside in urban areas had higher colonoscopy use; but the magnitude of differences was small. Likewise, among males, there was small magnitude of differences in the annual colonoscopy use. Further, we found differences between members who had PCP visits compared to those who did not, and the differences were large (e.g., 15% vs. 5% in 2012). Among members who visited PCPs, urban members had higher colonoscopy use compared to rural members. However, among members with no PCP visits, there were no differences between rural and urban areas in the use of colonoscopy.

Table 6: Annual Percentage of Colonoscopy Use by Rural-Urban Status, BDBSNE 2012-2016 (Aim 1)

	2012 (n=10,855)		2013 (n=11,421)		2014 (n=11,594)		2015 (n=11,164)		June, 2016 (n=10,502)	
Overall by location	Rural (n=5,595)	Urban (n=5,258)	Rural (n=5,757)	Urban (n=5,662)	Rural (n=5,721)	Urban (n=5,871)	Rural (n=5,473)	Urban (n=5,689)	Rural (n=5,116)	Urban (n=5,385)
Characteristics	13.55 (13.22,13.88)	14.81 (14.44,15.18)	13.77 (13.44,14.10)	15.13 (14.77,15.49)	14.12 (13.78,14.46)	15.05 (14.69,15.40)	14.37 (14.01,14.72)	15.29 (14.93,15.66)	14.50 (14.13,14.87)	14.66 (14.30,15.03)
Age										
50-54	16.77 (16.17,17.38)	17.59 (16.93,18.25)	16.89 (16.29,17.49)	17.94 (17.30,18.85)	17.23 (16.62,17.84)	17.80 (17.18,18.43)	17.63 (17.0,18.27)	18.03 (17.39,18.67)	17.75 (17.09,18.4)	17.44 (16.80,18.08)
55-59	14.31 (13.73,14.89)	15.47 (14.82,16.13)	14.33 (13.76,14.90)	15.54 (14.91,16.18)	14.56 (13.98,15.15)	15.26 (14.64,15.87)	14.67 (14.07,15.26)	15.38 (14.75,16.01)	14.87 (14.25,15.50)	14.63 (14.01,15.24)
60-64	8.98 (8.48,9.48)	10.83 (10.25,11.42)	9.37 (8.86,9.88)	11.21 (10.63,11.80)	9.70 (9.16,10.23)	11.35 (10.77,11.93)	9.85 (9.29,10.41)	11.69 11.08,12.30)	9.72 (9.14,10.31)	11.12 (10.52,11.72)
Gender										
Female	14.56 (14.10,15.04)	15.94 (15.42,16.45)	14.83 (14.36,15.30)	16.28 (15.78,16.78)	15.21 (14.73,15.69)	16.22 (15.73,16.72)	15.33 (14.83,15.82)	16.45 (15.95,16.96)	15.40 (14.89,15.92)	15.53 (15.03,16.02)
Male	12.40 (11.94,12.87)	13.42 (12.89,13.95)	12.58 (12.11,13.04)	13.71 (13.19,14.23)	12.90 (12.43,13.38)	13.59 (13.08,14.10)	13.28 (12.78,13.77)	13.87 (13.34,14.39)	13.48 (12.96,14.0)	13.58 (13.05,14.11)
PCP visit										
Yes	15.08 (14.71,15.46)	16.23 (15.82,16.64)	15.16 (14.79,15.53)	16.35 (15.95,16.75)	15.46 (15.08,15.84)	16.35 (15.96,16.75)	15.84 (15.45,16.24)	16.66 (16.26,17.06)	16.13 (15.72,16.55)	16.46 (16.05,16.87)
No	4.76 (4.23,5.29)	4.58 (3.96,5.20)	5.21 (4.64,5.78)	5.24 (4.56,5.97)	5.52 (4.92,6.13)	5.11 (4.47,5.75)	5.51 (4.90,6.12)	5.28 (4.63,5.94)	5.33 (4.73,5.94)	4.46 (3.91,5.0)

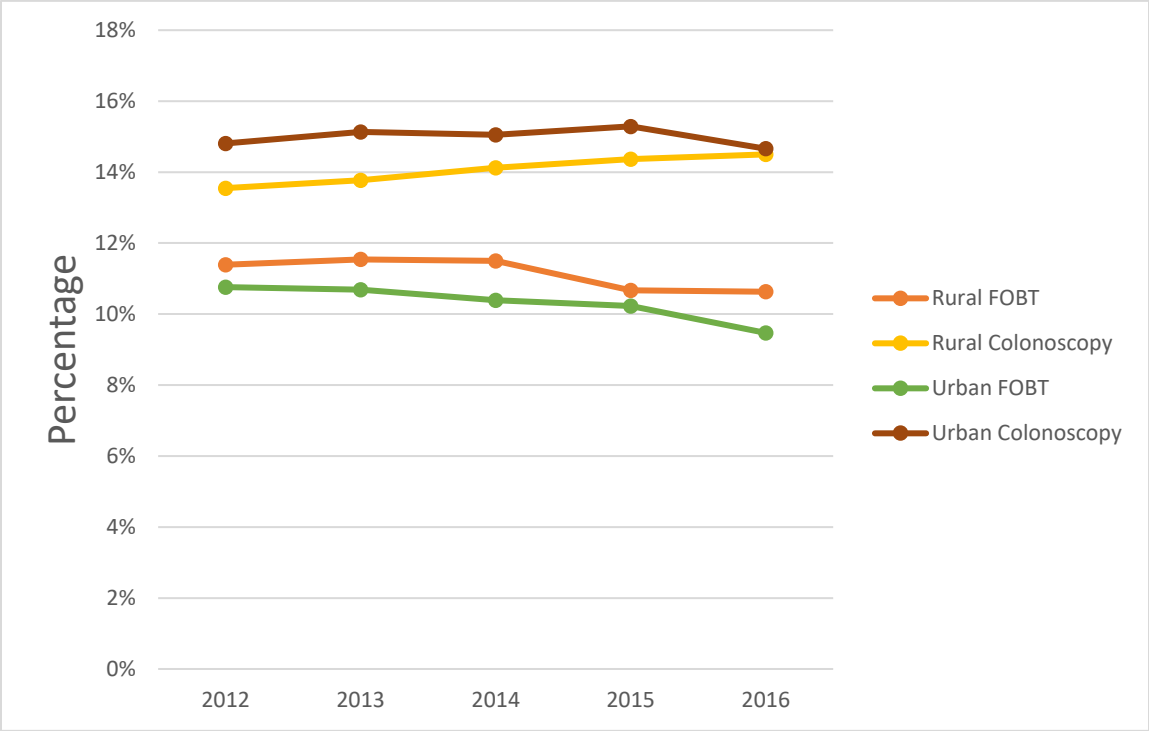

Figure 16. Annual Colonoscopy and Fecal Occult Blood Test in BlueCross BlueShield Nebraska Population, 2012-2016

Logistic Regression to Examine the Effect of Rural-Urban Status on FOBT Use

Logistic regression was used to assess the association between the prevalence of CRC screening and the individual place of residence (rural or urban), and to compute the odds ratios (ORs) and the 95% confidence intervals (CIs). Tables 7 and 9 show the ORs and the 95% CIs at the univariate and the multivariate levels. The models were adjusted for age[122,188-190], gender[122,189,191], PCPs visits[120,189,192] and CCI[56,193,194] based on prior literature demonstrating their association with CRC screening.

As shown in Table 7, at the univariate level, rural population was 51% more likely to use FOBT compared with the urban population. The female sex was associated with higher FOBT use and the PCP visits (up to 5 visits during 2013-2014) were associated with higher FOBT use. Multivariate analysis shows that rural members were 56% more likely to use FOBT compared with their urban counterparts: [OR=1.56 (95% CI: 1.45, 1.69)]. The PCP visits was also significantly associated with the FOBT use. Members who visited PCPs were more likely to use FOBT compared to those who did not, and the FOBT use is higher among members with more PCP visits [OR=1.37 (95% CI: 1.21, 1.56)].

Moreover, because we identified interaction between rural-urban status and age, gender and PCP visits, we stratified the analyses by these variables as displayed in Table 8. Among the urban population, those who are 55-59 or 60-64 were more likely to use FOBT compared with 50-54 years old [OR=1.20 (95% CI: 1.01, 1.41) and OR=1.30 (95% CI: 1.10, 1.54)]. Additionally, females who live in urban areas were 15% more likely to use FOBT compared with males [OR=1.20 (95% CI: 1.01, 1.41)], while those who live in rural areas were 68% less likely to use FOBT compared with males [OR=0.32 (95% CI: 0.28, 0.36)]. Finally, PCP visits of up to 5 times within 2 years was

associated with higher FOBT in the rural area while PCP visits was consistently (even > 5 visits) associated with higher FOBT use in the urban area compared with no visits.

Table 7. Univariate and Multivariate Analyses of Variables Associated with FOBT Screening Using Logistic Regression Models, BCBSNE 2013-2015 (Aim 1).

	FOBT use in 2015				
	FOBT use	**No FOBT use**	*P-value*	**Univariate OR (95% CI)**	**Multivariate OR (95% CI)**
Age					
50-54	729 (29.0)	17785 (32.0)	0.03	1.0	1.0
55-59	891 (36.0)	20056 (36.0)		1.08 (0.98,1.20)	1.05 (0.95,1.17)
60-64	863 (35.0)	18450 (33.0)		1.14 (1.03,1.26)	1.08 (0.97,1.19)
Gender					
Male	803 (32.0)	26441 (47.0)	<.0001	1.0	1.0
Female	1680 (68.0)	29850 (53.0)		1.85 (1.69,2.04)	1.85 (1.69,2.0)
Member Status					
Urban	952 (38.0)	27334 (49.0)	<.0001	1.0	1.0
Rural	1531 (62.0)	28955 (51.0)		1.51 (1.41,1.67)	1.56 (1.45,1.69)
PCP visits in 2013-2014					
0	396 (16.0)	12703 (23.0)	<.0001	1.0	1.0
1 to 2	646 (26.0)	15062 (27.0)		1.38 (1.21,1.56)	1.37 (1.21,1.56)
3 to 5	733 (30.0)	14796 (26.0)		1.59 (1.40,1.80)	1.59 (1.40,1.80)
6 to 9	457 (18.0)	8490 (15.0)		1.73 (1.50,1.98)	1.71 (1.49,1.96)
≥10	251 (10.0)	5240 (9.0)		1.54 (1.31,1.81)	1.49 (1.26,1.75)
CCI in 2013-2014					
0	1929 (78.0)	43847 (78.0)	0.92	1.0	1.0
1	373 (15.0)	7299 (15.0)		1.02 (0.91,1.14)	0.99 (0.87,1.11)
≥2	181 (7.0)	4145 (7.0)		0.99 (0.85,1.16)	0.95 (0.81,1.11)

Table 8. Adjusted association between rural-urban status and FOBT use by age, gender and PCP visits.

	Age		
Rural-urban status	**50-54**	**55-59**	**60-64**
Rural	1.0	0.97 (0.86,1.11)	0.96 (0.84,1.09)
Urban	1.0	1.20 (1.01,1.41)	1.30 (1.10,1.54)

	Gender	
	Male	**Female**
Rural	1.0	0.32 (0.28,0.36)
Urban	1.0	1.15 (1.01,1.31)

	PCP visits in 2013-2014				
	0	**1 to 2**	**3 to 5**	**6 to 9**	**≥10**
Rural	1.0	1.33 (1.15,1.55)	1.38 (1.18,1.60)	1.19 (0.99,1.42)	1.01 (0.81,1.25)
Urban	1.0	1.60 (1.25,2.05)	2.33 (1.84,2.94)	3.23 (2.53,4.12)	3.02 (2.29,3.98)

Adjusted for age, gender, PCP visits and CCI.

Logistic Regression to Examine the Effect of Rural-Urban Status on Colonoscopy Screening Use

As shown in Table 9, at the univariate level, the urban population was 9% more likely to use colonoscopy compared with the rural population. The male sex was associated with lower colonoscopy use while the PCPs visits 2013-2014 were associated with higher colonoscopy use. Multivariate analysis shows that female members were 16% more likely to use colonoscopy compared with male members: [OR=1.16 (95% CI: 1.09, 1.25)]. There was near significant increase in the odds of colonoscopy use among urban versus rural population [OR=1.06 (95% CI: 0.98, 1.14)]. The PCP visits was also significantly associated with the colonoscopy use. Members who visited PCPs were more likely to use colonoscopy compared to those who did not, and the colonoscopy use was higher among members with more PCP visits [OR=1.36 (95% CI: 1.21, 1.52)].

Furthermore, the results of the stratified analyses by age are displayed in Table 10. Among the rural population, those who are 55-59 or 60-64 were less likely to use colonoscopy compared with 50-54 years old [OR=0.63 (95% CI: 0.55, 0.71) and OR=0.64 (95% CI: 0.56, 0.72)].

Likewise, in the urban area, those who are 55-59 or 60-64 were less likely to use colonoscopy compared with 50-54 years old [OR=0.43 (95% CI: 0.38, 0.49) and OR=0.67 (95% CI: 0.59, 0.75)].

Table 9. Univariate and Multivariate Analyses of Variables Associated with the Use of Colonoscopy Using Logistic Regression Models, BCBSNE 2013-2015 (Aim 1).

	Colonoscopy use in 2015 (Limited to screening colonoscopy) *				
	Colonoscopy use	**No Colonoscopy use**	***P***	**Univariate OR (95% CI)**	**Multivariate OR (95% CI)**
Age					
50-54	1308 (43.0)	17206 (31.0)	<.0001	1.0	1.0
55-59	809 (27.0)	20138 (36.0)		0.53 (0.48,0.58)	0.56 (0.60,0.71)
60-64	926 (30.0)	18387 (33.0)		0.66 (0.61,0.72)	0.86 (0.80,0.93)
Gender					
Male	1297 (43.0)	25947 (47.0)		1.0	1.0
Female	1746 (57.0)	29784 (53.0)	<.0001	1.18 (1.09,1.26)	1.16 (1.09,1.25)
Member Status					
Rural	1515 (50.0)	28971 (52.0)	0.02	1.0	1.0
Urban	1528 (50.2)	26758 (48.0)		1.09 (1.01,1.17)	1.06 (0.98,1.14)
PCP visits in 2013-2014					
0	521 (17.0)	12578 (23.0)	<.0001	1.0	1.0
1 to 2	834 (27.0)	14874 (27.0)		1.35 (1.21,1.51)	1.36 (1.21,1.52)
3 to 5	895 (29.0)	14634 (26.0)		1.48 (1.32,1.65)	1.51 (1.35,1.68)
≥6	793 (26.0)	13645 (24.0)		1.40 (1.25,1.57)	1.47 (1.31,1.65)
CCI in 2013-2014					
0	2415 (79.0)	43361 (78.0)	0.03	1.0	1.0
1	439 (14.0)	8233 (15.0)		0.95 (0.86,1.06)	0.95 (0.85,1.05)
≥2	189 (6.0)	4137 (7.0)		0.82 (0.70,0.95)	0.84 (0.71,0.97)

*ICD DX codes for screening: 'V7651','Z1211','V7641','Z1212'

Table 10. Adjusted association between rural-urban status and colonoscopy use by age.

	Age		
Rural-urban status	**50-54**	**55-59**	**60-64**
Rural	1.0	0.63 (0.55,0.71)	0.64 (0.56,0.72)
Urban	1.0	0.43 (0.38,0.49)	0.67 (0.59,0.75)

Adjusted for age, gender, PCP visits and CCI.

Aim2: The Impact of Travel Time on the Metastatic Stage at Diagnosis of CRC

As shown in Figure 12 (Aim 2 Study Sample Selection Chart), a total of 307 individuals met the eligibility criteria for this aim: aged 50-64 years, active members of BCBSNE during the study period (2012-2016), had CRC diagnosis, and continuously enrolled for at least six months before CRC diagnosis.

Univariate and Multivariate Analysis of Travel Time Analysis for Metastatic Stage at Diagnosis of CRC

A total of 204 members were eligible for travel time analysis of whom 27 had metastatic CRC and 177 had metastatic CRC (Table 11). Note the sample included BCBS members diagnosed with CRC who had colonoscopy claim within four months before CRC diagnosis by metastatic status. The average travel time among the 204 members with colonoscopy was 34 minutes (SD=45). Approximately 25% of the members traveled within a time that is more than the mean travel time. The relationship between travel time or rurality and metastatic CRC diagnoses were not statistically significant. Therefore, the hypothesis “Shorter travel time to colonoscopy facility is associated with a non-metastatic diagnosis of CRC” was rejected. Also, for those who do not use preventive service, the odds of being diagnosed with metastatic CRC is 2.80 (95% CI: 1.00, 7.90) times larger than those who used preventive services.

Table 11. Univariate and Multivariate Analysis of Metastatic CRC Diagnosis (N=204) (Aim 2).

	Metastatic (n=27)		Non-Metastatic (n=177)		Univariate Model		Multivariate Model
	No	% or SD	No	% or SD	Odds Ratio (95% CI)	*P*	Odds Ratio (95% CI)
Age (year), mean	57.56	4.56	57.48	4.15	1.004 (0.91,1.01)	0.91	
Gender							
Male	17	63.0	95	54.0	1.0		1.0
Female	10	37.0	82	46.0	0.68 (0.29,1.57)	0.37	0.76 (0.32, 1.80)
Member location							
Rural	11	41.0	99	56.0	1.0		
Urban	16	59.0	78	44.0	1.84 (0.82,4.20)	0.14	2.14 (0.87,5.30)
Travel time (min), mean	34.85	51.53	33.38	38.12			1.0
Travel time median (IQR)	18.0	17.0	19.0	28.0	1.001 (0.99,1.01)	0.74	0.99 (0.98,1.01)
Preventive services							
Yes	5	19.0	69	39.0	1.0		1.0
No	22	81.0	108	61.0	2.81 (1.02,7.77)	0.04	**2.80 (1.00,7.90)**

Aim3: Rural-Urban Differences in Healthcare Utilization Among CRC Patients

Hospital Readmission Following CRC Surgery

The first hypothesis under Aim 1 was "Urban CRC patients who undergo surgery are more likely to have lower hospital readmission and emergency department visits." As shown in Figure 13, the sample for this hypothesis consists of 315 patients who met the following eligibility criteria: aged 50-64 years, active members of BCBSNE during the study period (2012-2016), had

CRC diagnosis, continuously enrolled for at least six months before CRC diagnosis, and had CRC surgery claims. The 30-day hospital readmission rate for this sample was 20%. The characteristics of patients readmitted and those non-readmitted within 30 days of index surgery are presented in Table 12. Readmitted patients were more likely to have higher Charlson Comorbidity Index 12 months prior to index surgery and with the slightly higher length of hospital stay after the procedure. For instance, 18% of patients who were readmitted have had >1 comorbidities 12 months prior to index surgery versus only 7% of non-readmitted patients. There were no statistically significant differences between the readmitted and non-readmitted patients regarding age, gender, geographic location and travel time to the surgical facility. The median length of stay was five days for readmitted patients versus four days for non-readmitted patients although the results did not meet the 0.05 level of significance.

Table 12. Patients Characteristics By 30-Days Readmission Status for Patients Who Survived Index Hospitalization For Colorectal Cancer, BCBSNE 2012-2016 (Aim 3-H1, N=315)

	Readmitted		Non-readmitted		P
	No	% or SD	No	% or SD	
Overall	62	20	253	80	
Age, mean	54	8.32	53.95	7.96	0.92
Gender					
Female	24	39	105	42	0.69
Male	38	61	148	58	
Member Location					
Rural	26	42	135	53	0.11
Urban	36	58	118	47	
Distance to provider					
Mean	21.91	26.25	22.78	40.31	0.29
Median	16.00	19.50	11.05	21.75	
Travel time					
Mean	27.69	27.19	27.92	40.46	0.22
Median	21.00	24.00	17.00	24.00	
Length of stay					
Mean	6.42	5.21	5.46	5.72	0.07
Median	5.00	5.00	4.00	3.00	
Charlson Comorbidity Index prior to surgery					
0	33	53	171	68	**0.02**
1	18	29	64	25	
>1	11	18	18	7	

A further analysis was conducted to compare characteristics of index surgery between patients with readmission and patients without readmission (Table 13). There were no significant differences between readmitted and non-readmitted patients in the site of the tumor, the site of surgery or whether the patients underwent stoma. However, readmitted patients were more likely to have undergone open surgery and were more likely to have presented with obstructed or perforated colon. Specifically, 77% of the readmitted patients underwent open CRC surgery

while only 50% of the non-readmitted patients underwent open CRC surgery. Furthermore, 58% of the readmitted patients had obstructed or perforated intestine during the index surgery versus 16% for non-readmitted patients.

Table 13. Index Surgery Characteristics By 30-Days Readmission Status for Patients Who Survived Index Hospitalization For Colorectal Cancer, BCBSNE 2012-2016 (Aim 3-H1, N=315)

	Readmitted		Non-Readmitted		
	No	%	No	%	**P**
Tumor location					
Colon	38	61	168	66	0.45
Rectum	24	39	85	34	
Surgery site					
Proximal	12	19	45	18	0.95
Distal	23	37	97	38	
Rectal /other	27	44	111	44	
Surgery approach					
Laparoscopic	14	23	127	50	**<0.0001**
Open	48	77	126	50	
Intestinal obstruction or perforation on admission					
Yes	36	58	41	16	**<0.0001**
No	26	42	212	84	
Stoma creation					
Yes	22	35	61	24	0.07
No	40	65	192	76	

After adjusting for Charlson Comorbidity Index, surgical approach and obstruction status there was no evidence of a difference in the odds of readmission for rural versus urban patients (Table 14). Therefore, the hypothesis about the rural and urban difference for readmission was rejected. Patients with Charlson Comorbidity Index >1, those with the open procedure and those who presented with obstruction or perforation at the time of surgery were more likely to be readmitted.

Table 14. Multivariable Analysis of Risk Factors for 30-Day Readmission, BCBSNE 2012-2016 (Aim 3-H1).

	OR	(95% CI)
Member Location		
Rural	1.0	
Urban	1.81	(0.96,3.42)
Charlson Comorbidity Index		
0	1.0	
1	1.11	(0.45,2.30)
>1	3.59	(1.41,9.11)
Surgery approach		
Laparoscopic	1.0	
Open	2.80	(1.39,5.63)
Intestinal obstruction or perforation on admission		
No	1.0	
Yes	7.17	(3.75,13.72)

The Utilization of CRC Surgery Among Patients with Metastatic CRC

The second hypothesis under Aim 3 was "Among patients with metastatic CRC, the proportion who undergo surgery is higher among the urban population compared with the rural population." As shown in Figure 14, the sample for this hypothesis consists of 69 patients who met the following eligibility criteria: aged 50-64 years, active members of BCBSNE during the study period (2012-2016), had metastatic CRC diagnosis and continuously enrolled for at least six months before CRC diagnosis.

Current NCCN guidelines recommend that patients with symptomatic mCRC undergo PTR. Asymptomatic patients can be treated with either systemic therapy or surgical intervention (see Chapter 2 for more details). The proportion of rural patients who underwent mCRC surgery is significantly lower than the proportion of urban patients with mCRC (Table 15). Therefore, the hypothesis was not rejected. For example, 39% of members who underwent metastatic CRC

surgery lives in rural areas versus 61% who lives in urban areas. Patients who underwent mCRC surgery tend to be older than 50 years old (87%), male (63%), urban residents (61%), had higher Charlson Comorbidity Index 12 months prior surgery (82% for CCI≥1) and were diagnosed with colon cancer (73%).

Table 15. Characteristics of Patients with Metastatic CRC (mCRC) By Surgery Uptake, BCBSNE 2012-2016 (N=69) (Aim 3-H2).

	With mCRC Surgery		No mCRC Surgery		
	No.	% / SD	No.	% / SD	P
Overall	33	47	36	52	
Age (mean)	54.49	8.28	54	8.83	0.81
<50	4	12	7	19	0.40
50-64	29	87	29	80	
Gender					
Female	12	36	18	50	0.25
Male	21	63	18	50	
Member location					
Rural	13	39	25	69	**0.01**
Urban	20	61	11	31	
CCI					
0	4	12	11	31	0.08
1	18	55	11	31	
>1	11	33	14	38	
Travel time					
Mean	30.76	27.23	34.39	36.09	0.93
Median(IQR)	22.00	21.00	24.00	38.00	
Primary tumor site					
Colon	24	73	28	78	0.62
Rectum	9	27	8	22	
Site of metastasis					
Liver	14	42	13	36	0.59
Others	19	58	23	64	
No. of metastatic sites					
1 site	16	48	20	56	0.55
>1 site	17	52	16	44	
Access to PCP services					
Mean (physician/10,000)	11.31	10.35	10.96	8.17	0.86
Median(IQR)	8.15	9.11	8.15	10.69	

Logistic Regression Results of the Receipt of Metastatic CRC Surgery

After adjusting for gender and Charlson Comorbidity Index (Table 16), urban CRC patients were more likely to undergo mCRC surgery compared with rural CRC patients 4.35 (95% CI: 1.40, 13.49).

Table 16. Multivariable Logistic Regression for Location Adjusted for Gender and Charlson Comorbidity Index, BCBSNE 2012-2016 (Aim 3-H2)

	OR 95% CI	P
Gender		
Female	1.0	0.07
Male	2.84 (0.90,8.95)	
Member Location		
Rural	1.0	**0.01**
Urban	4.35 (1.40,13.49)	
Intestinal obstruction or perforation on admission		
No	1.0	0.34
Yes	1.88 (0.52,6.80)	
CCI		
0	1.0	
1	4.36 (1.03,18.53)	0.05
>1	2.22 (0.50,9.84)	0.91

Sphincter Sparing Surgery Among Patients with Rectal Cancer

The last hypothesis for Aim 3 was "Among rectal cancer patients, the proportion who undergo sphincter-preserving surgery is higher among the urban population compared with the rural population." As shown in Figure 15, the sample for this hypothesis consists of 90 patients who met the following eligibility criteria: aged 50-64 years, active members of BCBSNE during the study period (2012-2016), had a rectal cancer diagnosis and continuously enrolled for at least six months before CRC diagnosis. Three-quarters of the patients diagnosed with rectal cancer and treated surgically underwent sphincter-sparing surgery. There were no significant differences in the characteristics of patients including rural residency (Table 17). Therefore, the hypothesis was rejected.

Table 17. Characteristics of Patients with Rectal Cancer by Type Of Surgery, BCBSNE 2012-2016 (N=90) (Aim 3-H3)

	Sphincter Sparing Surgery		Non-Sphincter Sparing Surgery		
	No.	% / SD	No.	% / SD	P
Overall	69	77.0	21	23.0	
Age, mean	52.10	8.56	53.38	10.37	0.24
Gender					
Female	33	48.0	7	33.0	0.24
Male	36	52.0	14	67.0	
Member Location					
Rural	33	48.0	10	48.0	0.99
Urban	36	52.0	11	52.0	
CCI					
≤1	32	47.0	9	43.0	0.78
>1	37	53.0	12	57.0	
Distance to provider (miles)					
Mean	16.51	16.70	24.61	61.80	0.38
Median	12.40	20.50	5.90	16.10	
Travel time (minutes)					
Mean	21.27	18.08	28.33	55.60	0.38
Median	19.0	22.0	16.0	25.0	
Surgery approach					
Laparoscopic	39	57.0	11	52.0	0.74
Open	30	43.0	10	48.0	

CHAPTER 5: DISCUSSION

Summary of Findings

To our knowledge, this is one of the few published studies that used privately-insured data to investigate the differences between the rural and the urban populations in CRC screening rates, stage at diagnosis and the receipt of surgery. In this privately insured population, there was an overall significant increase in the colonoscopy use between 2012 and 2016 (14% to 15%) and an overall decrease in FOBT use between 2013 and 2016 (11% to 10%). While the urban population was more likely to use colonoscopy, the rural population was more likely to use FOBT. Although the percentage changes in screening were significant, the changes were small. When adjusting for covariates, the rural population was 56% more likely to use FOBT compared with the urban population.

Although there was no association between travel time to a colonoscopy facility and metastatic stage at diagnosis, we found that patients who had no preventive services (vs. those who had preventive services) to be 2.80 times more likely to present with mCRC. Additionally, for the utilization of mCRC surgery, we found that the urban population was 4.35 times more likely to receive mCRC surgery compared to their rural counterpart, but there was no significant difference in the receipt of SSS or the 30 days hospital readmission between the two populations.

Colorectal Cancer Screening in BCBSNE Population by Rural and Urban Status

Prior research on CRC indicates that screening reduces both incidence and mortality rates by detecting polyps or tumors at a precancerous or early stage.[58,195] In spite of the demonstrated effectiveness of CRC screening tests, CRC screening rates remain less than optimal. In 2015, only 62.4% of Americans who were eligible for screening received one of the recommended screening tests, which is lower than the 80% target set by the Centers for Disease Control and Prevention's Colorectal Cancer Program.[196]

Our findings of the declining use of FOBT and the increasing use of colonoscopy are similar to other studies.[12,86] These studies have the same age group as our study (50-64 years old). While one of the studies used claims data the other used survey data and both used data from earlier period (1998-2005). Furthermore, we found that the annual FOBT use was between 10% and 11%, which is slightly higher than recent FOBT rates from national surveys. For example, the latest rates from BRFSS in 2014 and NHIS in 2015 were 8% and 6%.[3,13,16] The differences in FOBT rates could be due to the differences between claims and self-reported data such as the survey.[197,198] For instance, studies that are based on surveys are prone to recall bias.[197,198]Additionally, some of the population surveyed are uninsured or underinsured, which might result in lower screening rates.

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In this study, the annual colonoscopy rates were fluctuating between 14% in 2012 and 15% in 2016. Among the Medicare population who were 50-64 years old, Schenck et al. found that the annual colonoscopy rates were increasing from 5% in 1998 to 9% in 2005. Their findings is the latest comparable rates because recent (non-comparable) rates are based on ten years data and combine the endoscopy tests (colonoscopy and sigmoidoscopy), which is hard to compare

with the annual rates reported in this study.[12,199] For instance, the 2015 NHIS data showed that 55% of the surveyed individuals (50-64 years old) had used sigmoidoscopy within the past five years or used colonoscopy within the past ten years.[13] Likewise, the 2012 BRFSS data showed that 65% of the survey individuals (all age groups) reported that they ever had an endoscopy.[87]

We examined factors associated with FOBT and colonoscopy use. We found that the FOBT screening across age groups did not change between 2012 and 2016. However, age was an important factor in the use of colonoscopy because there was a large difference in the use of colonoscopy between the younger and older individuals across the years. For instance, in 2016 the use of colonoscopy was 17% among the 50-54 years old, 15% among the 55-59 years old and 11% among the 60-64 years old. This pattern observed across the entire study period. It is possible that the younger age group are more likely to initiate CRC screening once they turn 50 years old compared with older individuals. Furthermore, after adjustment for age, gender and PCP visits, there was no difference in the use of FOBT or colonoscopy between males and females. Although studies that used data from 1999 or 2000 reported that males were more likely to use screening, [87,200,201] recent studies from 2012 and 2013 showed no difference in the use of CRC screening between males and females.[87,88]

When placed in the context of primary care literature, our findings corroborate results from several studies.[84,179,202,203] In our study, both univariate and multivariate analyses showed that higher PCP visits are associated with significantly higher FOBT and colonoscopy screening. Ata and colleagues assessed the impact of time since last doctor visit on CRC screening and found that the odds of screening decrease according to the last time of doctor's visit.[202] Compared with those who had doctor visits more than 2 years, the odds ratio for those with a visit within six months, between six months and one year and between 1-2 years were 7.59, 5.86 and 2.76.[202]

Studies from 30 primary care practices found both FOBT and colonoscopy were increasing with the increase in the number of PCP visits.[203] Moreover, we found that FOBT use is more common in women compared to men [OR=1.85 (95% CI: 1.69, 2.0)]. This is similar to other studies that assessed the difference in CRC screening between males and females,[189,204] though other study found similar use.[122] We also found that females are more likely to use colonoscopy compared to males. This is different from previous studies that found male reported higher use.[122,189] Part of the inconsistent findings is due to the methodology used in previous studies. For example, some studies combined all endoscopy test, others did not distinguish between the purpose of colonoscopy test (i.e., screening versus others), while others measure colonoscopy use in previous ten years. Our results are not directly comparable with results from survey data because we only have access to shorter period (<10 years).

Travel Time and Metastatic Stage at Diagnosis of CRC

The reason to conduct this analysis was based on the idea that, unlike Medicare population, the younger working-age population are less motivated to travel to a colonoscopy facility to receive screening test and therefore are more likely to present with metastatic CRC.[190,205,206] In the current study, we also examined the roles of the use of preventive services as the rural population characteristics are different from the urban population and the access to services is a big concern in the rural areas.

There was no significant association between rural residence and the late stage diagnosis of CRC in the current study. This is similar to results from recent studies that used cancer registry data from Iowa, Nebraska, and Geogia[106,111,118] with the exceptions from a registry study conducted in Illinois.[207] In addition, our study did not find a significant association between travel time and metastatic CRC. The findings from this study confirm the results from studies that used

cancer registry data.[118,208] It was unexpected to find no association between rurality and distance, and late-stage diagnosis especially that BCBSNE rural residents are significantly less likely to undergo screening colonoscopy compared with the urban residents. Additionally, survey data indicate a lower adherence rate of CRC screening among rural residents compared to urban residents.[86,88] A potential explanation for the lack of association is because the magnitude of difference in screening between the rural and the urban is small (e.g., in 2012 the colonoscopy use among rural residents was 13.55% and among urban residents was 14.81%). Subsequently, this small difference is not translated into differences in CRC stage at diagnosis. Alternatively, the discrepancy could be explained by the differences between registry and claims data versus survey data. Surveys might results in potential biases (e.g., recall bias) while registry data, as well as claims-based data, are more valid because of the accuracy of reporting for registry and because claim's reimbursement is conditional on patient's health-encounter.

Results on the role of preventive services give some insight on the importance of CRC prevention. We found that patients who did not use preventive services within 12 months before CRC diagnosis were two times more likely to get diagnosed with metastatic CRC compared to those who had such services. The result may reflect the notion that cancer screening communication between the patient and the provider may occur during an annual checkup or other routine care settings.[64,209,210] It is also possible that patients who perceive screening as less beneficial are less likely to use other types of preventive services.[123,211] The health belief model,[212] which was developed to elucidates health behavior changes, has extensively been used in cancer screening literature.[211,213] Using the model, prior research found that the construct of 'perceived benefits' to be associated with more screening uptake.[188,214-216] This finding is similar to other diseases as well (e.g., breast cancer) such that the more health-conscious an individual, the more

likely such individual is to seek healthy behaviors including preventive services such as screening.[194]

Rural-Urban Status and Hospital Readmission After CRC Surgery

Our retrospective cohort study of the privately-insured adults who were diagnosed with CRC and treated surgically over the period from January 2012 to June 2016 resulted in 20% readmission rate and 6% emergency department visit. The readmission rates that have been reported in the literature are ranging between 9% and 25% and the emergency department visit around 7% and 9%.[180,181,217] The consequences of readmission can be serious since those readmitted within 30 days of the index surgery have 2.44 increased in the odds of mortality compared with those who were not readmitted.[161] In this study, the rural-urban status was not a predictor factor for 30-day hospital readmission. This finding is similar to a study conducted among Medicare population that found no differences between the rural and urban populations in the 30-day readmission rates.[161] However, it is dissimilar to another study which found that rural population is more likely to get readmitted.[160]

Part of the discrepant findings could be because of different definitions for readmission depending on the data source used. For example, National Surgical Quality Improvement Program (NSQIP) uses clinical reviewer to check medical records for postoperative complications that derive readmission and use phone calls to follow up with patients. However, the University Health System Consortium (UHC) database is a discharge billing data set that is limited to inpatient records.[218] Another difference is that NSQIP defines readmission starting from the date of surgery while UHC uses the day after discharge.[218] Moreover, surgery volumes were not measured in the current study and therefore we were unable to adjust for it in the analysis.

Among the risk factors of 30-day readmission identified in this study are the use of open surgery approach, Charlson Comorbidity Index (CCI) score of >1 and the presence of obstruction or perforation at the time of admission. Since the introduction of laparoscopic CRC surgery in 1991,[219,220] the association between the laparoscopic CRC surgery (versus open approach) and the decreased readmission rates has been debated. The impact of the surgical approach on the risk of hospital readmission after CRC surgery is somewhat anticipated. Although the laparoscopic procedure is associated with longer operation time, several studies have found that the minimally invasive laparoscopic approach is associated with favorable outcomes including lower readmission rates.[180,221] As a result, there has been an increase in the utilization of laparoscopy during the CRC surgery (37% in 2008 and 44% in 2011).[222] Additional favorable outcomes associated with the laparoscopy use are a lower postoperative pain, shorter duration of ileus, improved pulmonary function, better overall quality of life during the 30 days postoperatively and less postoperative LOS.[221] The latter have been found to be associated with lower 30 days hospital readmission; in the current study, we found near-significant higher LOS among readmitted patients (P=0.07).

In our study, we found that patients who underwent open surgery had 2.8 the odds of being readmitted to the hospital within 30 days of the index surgery compared to those who underwent laparoscopic surgery; 2.8 (95% CI: 1.39, 5.63). Congruent with our findings, Damle et al. assessed the association between surgery approach and 30 days readmission and found that patients who underwent open surgery to be 24% more likely to get readmitted compared to those with laparoscopic surgery; 1.24 (95% CI: 1.17, 1.31).[102] Likewise, Bartlett et al. found that patients who underwent laparoscopic surgery to be less likely to get readmitted; 0.90 (95% CI: 0.85,0.96).[163] However, other studies reported non-significant findings.[162,165,167] Therefore, given

that the higher the use of the laparoscope the lower the LOS, and that the lower the LOS the lower the hospital readmission, the evidence suggests an association between laparoscopic use and the lower readmission rate.

We also found that patients with >1 comorbidity score within 12 months before surgery to be 3.59 more likely to get readmitted to the hospital within 30 days after index surgery. Several studies from diverse populations found that the higher the comorbidity, the higher the likelihood of readmission.[159,160,163,223] Comorbidity is associated with higher mortality, lower quality of life and higher complications of treatment.[224] For instance, Greenblatt and colleagues found that patients who were readmitted within 30 days of discharge to be 2.44 more likely to die compared to those who were not readmitted after controlling many variables including comorbidities.[161]

Lastly, we found that 24% of readmitted patients had obstructed or perforated bowel at the time of index surgery. This is slightly higher than some studies,[139] but similar to others.[225,226] Part of the differences could be different age groups among these studies. Patients with obstructed or perforated bowel were 7.17 more likely to get readmitted to the hospital within 30 days after index surgery, which is similar to some studies that found worse outcomes associated with patients who are presented with obstructed or perforated tumors.[155,161]

Rural-Urban Status and Differences in Surgery Utilization Among Patients with Metastatic CRC

Due to the higher likelihood of cure, the current National Comprehensive Cancer Network (NCCN) guidelines recommend the surgical resection of the metastatic tumor in CRC patients with resectable metastases.[67] Several studies have shown a 5-year disease-free survival of 20%, and meta-analysis reported a median survival of 38%.[227-231] Additionally, numerous studies have

demonstrated a 5-year overall survival of up to 71% following resection for patients with liver-only metastasis.[232-234] Almost half of the metastases that occur among CRC patients take place in the liver, up to 25% in the lung and the rest occur in other organs. Since most of the CRC deaths occur in patients with mCRC and because chemotherapy is not a curative treatment for mCRC, surgical intervention is the only cure for mCRC patients.[235]

While 61% of our study population who were living in the urban area underwent mCRC surgery, only 39% of those who were living in the rural area underwent mCRC surgery. In the multivariate analysis, we found that urban population is 4.65 times more likely to receive mCRC surgery compared to their rural counterparts. Hu and colleagues assessed the secular trends of primary tumor resection among patients with metastatic CRC between 1988 and 2010 using elderly population. The authors found a decrease in the surgery use from 67.4% and 57.4%. Half of patients who live in the West underwent tumor resection and 15.9% of patients who live in the Midwest received the surgery. However, the study didn't distinguish patients' rural-urban status.

There are several possible explanations for the difference in mCRC surgery rates between the rural and the urban populations. First, given the complexity of the surgical resection of metastatic tumors and the required multidisciplinary expertise especially for rectal cancer,[74] rural hospitals are possibly less equipped with such resources. Although current treatment guidelines will minimize regional variations in surgery uptake, access to technology, surgeon's supply, and patients' own belief are potential determinants of utilization.[73,236] Second, it is possible that some patients at rural hospitals presented with asymptomatic unresectable tumors, NCCN guidelines recommend against operating on such patients, hence the lower rate of rural surgery reported in our study assuming that surgeons adhere to such guidelines.

Rural-Urban Status and Differences in Sphincter-Sparing Surgery (SSS) Utilization Among Patients with Rectal Cancer

In resemblance to sphincter-sacrificing surgery, sphincter-sparing surgery (SSS) for rectal cancer is associated with comparable oncological outcomes. Both procedures lead to similar rates of tumor recurrence and equivalent rates of survival.[237] However, SSS is associated with better patients' satisfactions and lower morbidity. For example, the social, psychological and physical well-being is better among patients treated with SSS.[81,83] Because of the better outcomes associated with SSS, the rate of SSS have steadily increased between 1988 and 2006: 27% in 1988 and 60% in 2006. In our study, the rate of SSS use is 77%.

We found that the rate of SSS uptake is similar in both the rural and the urban privately-insured populations. Paquette and colleagues assessed the association between rural residents and SSS utilization and found that urban patients are more likely to receive the surgery.[108] Although authors controlled for the effect of hospital procedure volumes, the discrepancy in procedure volume between hospitals did not explain the higher SSS uptake in urban residents. According to the authors, although the SSS rates increased in both the rural and the urban areas, the rates remained higher among the urban population. In our study, given that patients are privately-insured, it is possible that the null finding is due to higher access to treatment among the rural and urban populations. One also can speculate that the no difference findings in this study could be due to an increase in the SSS uptake due to the overall better outcome.

Strengths and Limitations

Claims-based data are type of data that issued by institutions and providers for reimbursement purposes.[238,239] Examples of such institutions are insurance firms, healthcare

systems or government agencies. The purpose of collecting the data is for organizing, tracking patient health and interaction with the healthcare system. As a result, claims data are not collected for research purposes. Instead, the ideal data source for cancer outcome and treatment would be the clinical trials. This type of data allows investigators to have detailed clinical information about patient's comorbidities and possible preventive or risk factors.[240,241] The lack of selection bias in such data ensures that the relationship between predictors and outcome is not confounded. Unfortunately, only 3%-5% of adult cancer patients are enrolled in clinical trials.[242]

Unlike clinical trials, claims-based data represent a large population since they contain thousands of insured individuals.[239,243] Given that, it is an ideal data source for investigating rare outcomes such as cancer. Claims-based data include extensive demographic information, procedure and treatment information, and providers or organizational characteristics. Unlike data generated from clinical trials, claims data are readily available, relatively less expensive and reflect the usual care for patients. Studies that assessed the accuracy of claims data in comparison with medical records found high validity.[243]

In addition to their uniqueness, claims data have several limitations.[238,244,245] They lack key clinical variables. For instance, claims data do not contain information about cancer staging because the reimbursement process is not conditioned on disease characteristics.[238] Further, not all diagnoses and procedures are captured in claims data. In general, the higher the reimbursement of a specific procedure, the more likely for such procedure to be captured in the data. For instance, major surgeries are more likely to be captured while comorbidities are less likely. Likewise, lab results that are not covered or reimbursed are usually not captured. Moreover, access to claims data can be prohibitive because of the data user agreement, requires

substantial learning-curve and programming skills, high patient turn-over, contain procedure information but without results, delay in data release (time lag) and the study design might impact data sensitivity and specificity.

Accordingly, there are specific limitations that should be considered when interpreting the findings of this study. First, about 2% of BCBSNE members ended their membership during December 2014, although the impact is minimal, it is possible that this might have contributed to the lower screening rates, compared to the year 2015, especially assuming that some of those who left BCBSNE were eligible for CRC screening. Second, because claims data are used mainly for billing purposes, they do not distinguish the type of colonoscopy use (screening versus none screening).[246] However, we were able to exclude high-risk populations (e.g., with previous CRC diagnosis, IBD, polyps, and UC) and thus were able to limit our population to average-risk individuals who are more likely to use screening colonoscopy. We also restricted our population to those with continuous enrollment to ensure that the exclusion criteria were met.

Third, we excluded 30% of the study sample from the travel time analysis because we were not able to identify colonoscopy claims within four months prior to CRC diagnosis for these individuals. A potential explanation is that some of these patients were diagnosed at the time of surgery due to an obstructed colon. Nonetheless, excluded cases were not significantly different from the ones that were not excluded in all measured characteristics in this study. Fourth, we were uncertain about the intent of colonoscopy test because classifications were based on claims that occurred within 4-months prior to diagnosis; thus, it is possible that misclassification might have occurred if symptoms happened before this time or they have never been captured in the data. Fifth, findings should be interpreted with cautions since the six months period for identifying preventive services use might not entirely capture the health behavior of an individual.

For instance, one might use more health services only during or after an acute illness and thus, will be less likely to be captured within the window of six months. Ideally, we should examine the preventive services use within one or two years of CRC diagnosis.[56,183]

Sixth, we were unable to adjust for hospital volume when assessing the association between rural-urban status and surgery uptake because the hospital data are not linked to patient's data. Seventh, BCBSNE provides no information about the intent of PTR; therefore, it is possible that patients could have undergone resection as palliative therapy or PTR with the resection of the metastatic tumor as curative intent. Eighth, although the BCBSNE population represents the population of Nebraska fairly well, this privately insured population does not include the underinsured or uninsured population of Nebraska. Thus, one should be cautious when comparing BCBSNE to findings from survey studies that included both insured and uninsured populations. Lastly, due to the low statistical powers for aim 2 and aim 3, our findings for these aims should be interpreted cautiously.

The implication of using claims data to answer research question include their effect on information bias, selection bias or confounding. For instance, information bias might arise if underreported diagnosis or procedure are used which will lead to biased effect estimate. In this study, we expect that such bias might lead to non-differential misclassification. Another example is the occurrence of confounding by indication. This type of selection bias can occur if patients selected for treatment are different from those who are not. The selection process is either motivated by clinical indication or via referral (e.g., complex cases are referred to certain hospitals).

Conclusion

In our privately-insured population in Nebraska, FOBT screening use is higher among rural population while colonoscopy screening is higher among the urban population. There are profound disparities by gender, the use of preventive services and by PCP visits. To increase CRC screening use, patients should be educated about the benefits of CRC screening including the fact that more convenient and less expensive tests are readily available. The discussion can be initiated during PCP visits when the use of preventive services is more likely to be discussed at the checkup visits. Given that the CRC is a preventable disease, it is also imperative to educate patients about the risk factors for CRC since around 40% of the disparities in CRC incidence is attributed to differences in the prevalence of risk factors such as smoking, unhealthy diet, and obesity. [247,248]

This study did not find an association between travel time to the colonoscopy service and the diagnosis of the metastatic CRC. The fact that 13% of this privately insured working-age population present with metastatic CRC suggests some non-compliance with screening guidelines. It is also possible that in this young cohort population some cases present with the aggressive and fast-growing form of the disease with the potential development of mCRC between screening colonoscopies. Nevertheless, it is possible that this working-age population faces logistic barriers that prevent them from getting off work to get screened.[190,205,206] Alternately, this young cohort population might have a lower perceived risk of getting CRC compared with the older population and thus forgo screening.

The 30-day readmission occurs in about 20% of our population. The identified predictable factors were patients who underwent an open procedure, those presented with obstructed or perforated colon and patients with higher comorbidities. Hospital readmission is a quality of care indicator for patients with CRC and identifying the most predictor factors is crucial to preventing

readmission. For patients diagnosed with mCRC, we found no major differences between patients with and those without surgery. Despite that, the urban population is more likely to undergo surgery. These findings indicate an underuse of mCRC surgery among the rural population. For patients diagnosed with rectal surgery, the majority (77%) underwent SSS, but we did not find an association between rural-urban status and the SSS use.

Implications and Recommendations

Colonoscopy is the gold standard screening test and all other screening tests with positive findings must be followed by colonoscopy. In this study, patients with screening colonoscopy were less likely to be diagnosed with metastatic CRC compared with those who used surveillance or diagnostic colonoscopy. Accordingly, we recommend alleviating barriers that prevent rural patients from getting screening-colonoscopy and therefore increase the likelihood of early detection of CRC. Until these obstacles have been lessened, screening with more convenient tests should be encouraged. One option would be to encourage the use of mailed FOBT/FIT screening test since screening with any test that is recommended by the guidelines is better than no screening. This type of CRC screening is more convenient because it is taken at home and does not require a visit to the healthcare provider.[249] In particular, FIT does not require dietary restriction and thus can be easily accepted by patients. Whereas specialists with training in colonoscopy are needed, PCPs can prescribe FOBT/FIT tests and thus facilitate more CRC screening.

There are many implications for the associations between rural-urban status and 30-day hospital readmission. We found that readmission occurs frequently, and some predictor factors are preventable. For instance, patients with ≥2 comorbidities were more likely to be readmitted.

Institutions should adopt the use of risk prediction calculator to be able to expect the most common readmission predictors.[250,251]

For patients diagnosed with mCRC, our findings indicate that there is unawareness or disagreement with current guidelines among surgeon in rural areas. The unawareness is concerning since the studied patients have similar characteristics. For patients diagnosed with rectal surgery, the study indicates a similar use of SSS between the rural and urban populations. More than half of the patients in this study underwent laparoscopic SSS, which found to be associated with better oncologic outcomes (e.g., surgical margins or lymph node harvest) compared with open surgery. Although not captured in BCBSNE, better outcomes can be achieved by the use of robotics.[80]

Suggestions for Future Research

Integrated healthcare or organized delivery system is a network of organizations that coordinate continuum of services to a defined population and is willing to be held clinically and fiscally accountable for the outcomes and the health status of the population it served.[252] In this integrated healthcare, we found that members with a higher number of PCP visits had higher rates of CRC screening. It is, however, unknown if other unmeasured factors have contributed to the increased CRC screening. For example, population outreach efforts (e.g., FIT/gFOB Kit distribution) or system that are used to invites for screening could have contributed to the increased CRC screening uptake. Future studies should illuminate the mechanism of CRC screening uptake other than PCP visits. In this population, it is yet to be determined if other mechanisms play a role in CRC screening uptake and the extent of their future potential in CRC prevention. Identifying the mechanism of CRC screening and their extent in eliciting CRC screening will be useful for interventions to increase public health awareness and uptake of CRC screening.

Additional avenues for future research should shed light on the "follow-up screening" during the CRC screening detection process. For instance, given the importance of following up patients with positive FOBT, it is imperative to see what proportion of such population will undergo colonoscopy screening. Because claims data does not report the findings of the tests (i.e., positive /negative FOBT), we encourage future researchers to ascertain the proportion of test completers through linking claims data with electronic health records. Determining the percentage of test completers is feasible in integrated health system such as BCBSNE because those with positive FOBT will be more likely, assuming they undergo colonoscopy screening, to remain within the same insurers since the majority of follow up colonoscopy occur during the three months of positive FOBT.[253]

Further, in this study, we found that women are more likely to undergo FOBT test compared to men. We also found that there was an interaction between rural-urban status and gender such that females in the rural areas are less likely to use FOBT while females in the urban areas are more likely to use FOBT. Although this finding has been reported previously, it is unclear why such disparity in access to FOBT use exist among women in a privately-insured population. Future studies should elucidate factors associated with gender differences in FOBT screening among the urban and the rural populations.

Future studies should also acknowledge the limitations of claims data and work to mitigates such limitations. For example, since claims data lack information about the stage at diagnosis information, the linkage of Nebraska Cancer Registry with the BCBSNE data in future studies is warranted. Unlike claims data, cases ascertainment in registry data is more optimal and with less likelihood of selection bias. Although previous research showed that claims data are

associated with improved validity using ICD codes,[175] registry data is the gold standard and would complement the available variables in BCBSNE data.

The current study was limited to annual screening rates because we had access to 4.5 years of BCBSNE data. Future studies should obtain 6-11 years of data to measure CRC screening rates according to the USPSTF guidelines. Given that sigmoidoscopy is recommended every five years, a period of at least six years would be ideal to operationalize sigmoidoscopy use. Likewise, the 11 years period would be enough to compute colonoscopy use in this privately-insured population. Moreover, future studies with enough data should design a matched retrospective cohort study to assess the association between rural-urban status and CRC surgery uptake. Specifically, propensity score matching is an ideal approach to compare patients who have received CRC surgery from those who have not. Doing so helps to minimize potential confounding by indication and make the observed characteristics of the two compared groups similar.

Lastly, we found that urban population is more likely to undergo mCRC surgery. The finding persisted after accounting for the intestinal obstruction or perforation, which we arguably assume it distinguishes patients who present with symptomatic and asymptomatic status. However, in this study, we were unable to account for the impact of surgery volume (both the hospital volume and the surgeon volume) on the receipt of mCRC surgery between the two populations.

Appendices

Appendix A. Rural-Urban Commuting Area Codes Definitions

Category	Definition
A	1-Urban focused 2-Large Rural City/Town (micropolitan) focused 3-Small Rural Town focused 4-Isolated Small Rural Town focused
B	1-Urban 2-Large Rural City/Town 3-Small and Isolated Small Rural Town
C	1-Urban 2-Rural City
D	1-Urban (≥30% of workers go to Census Bureau-defined urbanized area) 2-Rural City
E	1-Urban 2-Large Rural City/Town 3-Small Rural Town 4-Isolated Small Rural Town
F	Adding group that is non-urban and non-large rural

Appendix B. ICD and CPT Codes

B1. High-risk groups excluded from the study samples

High-Risk Group	ICD Diagnosis
CRC diagnosis	153.0,C183,153.1,C184,153.2,C186,153.3,C187,153.4,C180,153.6,C182, 153.7,C185,153.8,C188,153.9,C189,154.0,C19,154.1,C20,154.8,C218.
Polyps diagnosis	V1272,Z86010
Inflammatory Bowel Disease	5551,K5010,5552,K5080,5559,K5090, 5561,K5180, 5562,K5120,5563,K5130, 5565,K5150,5566,K5100, 5568,K5180,5569,K5190,5581,K520,5582,K521, 5589,K5289,K529

B2. CRC screening tests

Test type	CPT/ICD Codes
FOBT and FIT	82270, 82272, G0328, 82274
Colonoscopy	4521,4522,4523,4525,44388,44389,44392,44393,44394,44397,45355, 45378,45379,45380,45381,45382,4533,4538,45385,45386,45387.

B3. Diagnosis of CRC

ICD codes	Description
153.0/C183	Malignant neoplasm of hepatic flexure
153.1/C184	Malignant neoplasm of transverse colon
153.2/C186	Malignant neoplasm of descending colon
153.3/C187	Malignant neoplasm of sigmoid colon
153.4/C180	Malignant neoplasm of cecum
153.6/C182	Malignant neoplasm of ascending colon
153.7/C185	Malignant neoplasm of splenic flexure
153.8/C188	Malignant neoplasm of other specified sites of large intestine
153.9/C189	Malignant neoplasm of colon, unspecified site
154.0/C19	Malignant neoplasm of rectosigmoid junction
154.1/C20	Malignant neoplasm of rectum
154.8/C218	Malignant neoplasm of other sites of rectum, rectosigmoid junction, and anus

B4. Diagnosis of Metastatic CRC

ICD codes	Description
1960/C770	Secondary and unspecified malignant neoplasm of lymph nodes of head, face, and neck
1961/C771	Secondary and unspecified malignant neoplasm of intrathoracic lymph nodes
1963/C773	Secondary and unspecified malignant neoplasm of lymph nodes of axilla and upper limb
1965/C774	Secondary and unspecified malignant neoplasm of lymph nodes of inguinal region and lower limb
1970/C7800	Secondary malignant neoplasm of lung
1971/C781	Secondary malignant neoplasm of mediastinum
1972/C782	Secondary malignant neoplasm of pleura
1973/C7839	Secondary malignant neoplasm of other respiratory organs
1974/C784	Secondary malignant neoplasm of small intestine including duodenum
1976/C786	Secondary malignant neoplasm of retroperitoneum and peritoneum
1977/C787	Malignant neoplasm of liver, secondary
1978/C7889	Secondary malignant neoplasm of other digestive organs and spleen
1980/C7900	Secondary malignant neoplasm of kidney
1981/C7911, C7919	Secondary malignant neoplasm of other urinary organs
1982/C792	Secondary malignant neoplasm of skin
1983/C793	Secondary malignant neoplasm of brain and spinal cord
1984/C7932,C7949	Secondary malignant neoplasm of other parts of nervous system
1985/C7951,C7952	Secondary malignant neoplasm of bone and bone marrow
1986/C7960	Secondary malignant neoplasm of ovary
1987/C7970	Secondary malignant neoplasm of adrenal gland
19881/C7981	Secondary malignant neoplasm of breast
19882/C7982	Secondary malignant neoplasm of genital organs
19889/C7989	Secondary malignant neoplasm of other specified sites
1990/C800	Disseminated malignant neoplasm without specification of site

B5. Colonoscopy claims

ICD/CPT codes	Description
4521	Transabdominal large bowel endoscopy
4522	Endoscopy large bowel through stoma
4523	Colonoscopy
4525	Colonoscopy large bowel biopsy
44388	Colonoscopy stoma dx including collection of specimen
44389	Colonoscopy stoma w/biopsy single/multiple
44392	Colonoscopy stoma removal of lesion by hot biopsy forceps
44393	Colonoscopy stoma ablation lesion
44394	Colonoscopy stoma w/ removal of tumor, polyp or other lesions by snare technique.

44397	Colonoscopy through stoma; with transendoscopic stent placement (includes pre-dilation)
45355	Colonoscopy rigid or flexible transabdominal via colotomy single or multiple
45378	Colonoscopy flexible dx w/collection of specimens when performed
45379	Colonoscopy flexible w/removal of foreign body(s)
45380	Colonoscopy w/biopsy single/multiple
45381	Colonoscopy flexible with directed submucosal injection any substance
45382	Colonoscopy flexible w/control bleeding any method
45383	Colonoscopy flexible proximal splenic flexure with ablation of lesion
45384	Colonoscopy flexible w/removal lesion by hot biopsy forceps
45385	Colonoscopy flexible w/ removal of tumor polyp lesion snare technique
45386	Colonoscopy flexible w/transendoscopic balloon dilation
45387	Colonoscopy flexible proximal splenic flexure transendoscopic stent placement

B6. Use of preventive services

ICD/CPT codes	Description
V700	Routine general medical examination at a health care facility
V708	Other specified general medical examinations
V709	Unspecified general medical examination
V7231	Routine gynecological examination
V7232	Encounter for Papanicolaou cervical smear to confirm findings of recent normal smear following initial abnormal
Z0000	Encounter for general adult medical examination without abnormal findings
Z008	Encounter for other general examination
Z0141	Encounter for routine gynecological examination
Z01411	Encounter for gynecological examination (general) (routine) with abnormal findings
Z01419	Encounter for gynecological examination (general) (routine) without abnormal findings
Z0142	Encounter for cervical smear to confirm findings of recent normal smear following initial abnormal smear
99386	Initial preventive medicine new patient 40-64
99396	Periodic preventive medicine established patient 40-64 years

B7. Colon cancer surgery

ICD/CPT	Description
4571/0dbe0zz,0dbe3zz,0dbe7zz, 0dbe8zz	Open Multi-Segment Resection Of Large Intestine
4572/0dth0zz, 0dth7zz, Dth8zz	Open Cecectomy Nec
4573/0dtf0zz, 0dtf7zz, 0dtf8zz, 0dtk0zz	Open Right Hemicolectomy Nec
4574/0dtl0zz, 0dtl7zz, 0dtl8zz	Open Transverse Colon Res Nec
4575/0dtg0zz, 0dtg7zz, 0dtg8zz	Open Left Hemicolectmy Nec
4576/0dtn0zz, 0dtn7zz, 0dtn8zz	Open Sigmoidectomy Nec
4579	Partial Large Intestine Excision NEC/NOS
4581/0dte4zz	Laparoscopic Total Intra-Abdominal Colectomy
4582/0dte0zz	Open Total Intrabdominal Colectomy
4583/0dte7zz, 0dte8zz	Total Abdominal Colectomy Nec/Nos
1731/0dbe4zz	Laparoscopic Multi- Segment Resection Large Intestine
1732/0dth4zz	Laparoscopic Cecectomy
1733/0dtf4zz	Laparoscopic Right Hemicolectomy
1734/0dtl4zz	Laparoscopic Resection Transverse Colon
1735/0dtg4zz	Laparoscopic Left Hemicolectomy
1736/0dtn4zz	Laparoscopic Sigmoidectomy
1739/0dbe4zz	Laparoscopic Partial Excision Large Intestine Nec
44140	Colectomy Partial W/Anastomosis
44141	Colectomy Partial W/Skin Level Cecostomy/Colostomy
44143	Colectomy Partial W/End Colostomy & Closure Of Distal Segment.
44144	Colectomy Partial W/ Colostomy /Ileostomy & Mucofistula.
44145	Colectomy Partial W/Coloproctostomy
44146	Colectomy Partial W/Coloproctostomy & Colostomy
44147	Colectomy Partial Abdominal & Transanal Approach
44150	Colectomy Total Abdominal W/O Proctectomy W/ Ileostomy
44151	Colectomy Total Abdominal W/O Proctectomy W/Continent Ileostomy
44155	Colectomy Total Abdominal W/Proctectomy W/Ileostomy
44157	Colectomy Total Abdominal W/Proctectomy Ileoanal Anastomosis
44158	Colectomy Total Abdominal W/ Proctectomy Ileoanal Anastomosis & Reservoir
44160	Colectomy Partial W/Removal Terminal Ileum & Ileocolostomy
44204	Laparoscopic Colectomy Partial W/Anastomosis
44205	Laparoscopic Colectomy Partial W/ Removal Terminal Ileum

44206	Laparoscopic Colectomy Partial W/End Colostomy & Closure Of Distal Segment
44207	Laparoscopic Colectomy Partial W/Coloproctostomy Low Pelvic Anastomosis
44208	Laparoscopic Colectomy Partial W/ Coloproctostomy Low Pelvic Anastomosis W/Colostomy
44210	Laparoscopic Colectomy Total W/O Proctectomy W/Ileostomy/Ileoproctostomy
44211	Laparoscopic Colectomy Total Abdominal W/Proctectomy Ileoanal Anastomosis
44212	Laparoscopic Colectomy Abdominal W/Proctectomy W/Ileostomy

B8. Rectal cancer surgery

ICD/CPT	Description
44145	Colectomy Prtl W/Coloproctostomy.
44146	Colectomy Prtl W/Coloproctostomy & Colostomy.
44147	Colectomy Prtl Abdominal & Transanal Approach.
44155	TPC - Total Proctocolectomy, Ileostomy Includes Stoma.
44156	TPC - Total Proctocolectomy, Continent Ileostomy Includes Stoma.
44157	TPC, IAA - Ileo-Anal Anastomosis, Straight With Or Without Stoma, Code Stoma Separately When Done.
44158	TPC, IPAA - Ileal Pouch-Anal Anastomosis.
44207	Laps Colectomy Prtl W/Colopxtstmy Lw Anast.
44208	Laps Colectomy Prtl W/Colopxtstmy Lw Anast W/Clst
44211	Laps Colct Ttl Abd W/Prctect Ileoanal Anastomosis
44212	Laparoscopic TPC - Total Proctocolectomy, Includes Stoma
44238	*Unlisted Laparoscopy Procedure, Intestine.*
45499	Unlisted Laparoscopy Rectum.
45110	Proctectomy , APR, Colostomy Includes Stoma
45111	Prctect Prtl Rescj Rectum Tabdl Appr
45112	Prctect Cmbn Abdominoprnl Pull-Thru Px
45113	Prctect Prtl W/Mucosec Ileoanal Anast Rsvr
45114	Proctectomy, Combined Abdominal And Transsacral Approach With Or Without Stoma
45116	Proctectomy, Partial, Parasacral (Kraske Or York-Mason Approach) Anorectal Procedures Transanal Excision
45119	Prctect Cmbn Pull-Thru W/Rsvr W/Ntrstm
45120	Prctect Compl W/Pull-Thru Px & Anastomosis
45121	Proctocolectomy, For Congenital Megacolon, Including Total Colectomy With Pull-Through (Eg, Swenson, Duhamel, Or Soave) With Or Without Stoma, Code Stoma Separately When Done
45123	Prctect Prtl W/O Anast Prnl Appr
45126	Pelvic Exenteration For Colorectal Malignancy, With Proctectomy (With Or Without Colostomy), With Removal Of Bladder And Ureteral

	Transplantations, And Hysterectomy, Or Cervicectomy, With Or Without Removal Of Tube(S), With Or Without Removal Of Ovary(S),
45160	Exc Rct Tum Proctotomy Transsac/Transcoccyge
45170	Excision Of Rectal Tumor, Transanal Approach CPT Expanded
45171	Exc Rct Tum Not Incl Muscularis Propria
45172	Exc Rct Tum Incl Muscularis Propria
45190	Destruction Rectal Tumor Transanal Approach
45395	Proctectomy, APR, Colostomy, Laparoscopic Includes Stoma
45999	Unlisted Procedure, Rectum (Open)
45397	Laps Proctectomy Combined Pull-Thru W/Reservoir
483	Local Excision Or Destruction Of Lesion Or Tissue Of Rectum
4831	Radical Electrocoagulation Of Rectal Lesion Or Tissue
4832, 0d5p0zz, 0d5p3zz,0d5p4zz, 0d5p7zz, 0d5p8zz	Other Electrocoagulation Of Rectal Lesion Or Tissue
4833	Destruction Of Rectal Lesion Or Tissue By Laser
4834	Destruction Of Rectal Lesion Or Tissue By Cryosurgery
4835, 0dbp3zz, 0dbp7zz, 0dbp8zz	Local Excision Of Rectal Lesion Or Tissue
4836, 0dbp4zz, 0dbp8zz	[Endoscopic] Polypectomy Of Rectum
4840,0dtp0zz, 0dtp4zz	Pull-Through Resection Of Rectum, Not Otherwise Specified
4841	Soave Submucosal Resection Of Rectum
4842, 0dtp4zz	Laparoscopic Pull-Through Resection Of Rectum
4843, 0dtp0zz	Open Pull-Through Resection Of Rectum
4849, 0dtp0zz, 0dtp4zz	Other Pull-Through Resection Of Rectum
4850, 0dtp0zz , 0dtp4zz , 0dtp7zz , 0dtp8zz, 0d1n0z4	Abdominoperineal Resection Of The Rectum, Not Otherwise Specified
4851, 0dtp4zz, 0d1n0z4	Laparoscopic Abdominoperineal Resection Of The Rectum
4852, 0dtp0zz, 0d1n0z4	Open Abdominoperineal Resection Of The Rectum
4859, 0dtp7zz, 0dtp8zz, 0d1n0z4	Other Abdominoperineal Resection Of The Rectum
486	Other Resection Of Rectum
4861	Transsacral Rectosigmoidectomy
4862, 0dtp0zz, 0dtp4zz, 0d1n0z4, 0d1n4z4	Anterior Resection Of Rectum With Synchronous Colostomy
4863, 0dtp0zz, 0dtp4zz	Other Anterior Resection Of Rectum
4864	Posterior Resection Of Rectum

4865	Duhamel Resection Of Rectum

B9. Primary Care Physician Codes

ICD/CPT	Description
001	General practice
011	Internal medicine
008	Family practice

B10. Stoma Codes

ICD/CPT	Description
4610, 0D1H0Z4,0D1H4Z4,0D1H8Z4,0D1K0Z4, 0D1K4Z4,0D1K8Z4,0D1L0Z4,0D1L4Z4,0D1L8Z4, 0D1N0Z4,0D1N4Z4,0D1N8Z4,4620,0D1B0Z4, 0D1B4Z4,0D1B8Z4,4621,0D1B0Z4 ,0D1B4Z4,0D1B8Z4,	Colostomy NOS
4611	Temporary colostomy
4613	Permanent colostomy
4620, 0D1B0Z4,0D1B4Z4,0D1B8Z4	Ileostomy NOS
V44.2	Ileostomy
V44.3	colostomy
4621	Temporary ileostomy
4623	Permanent ileostomy NEC
44141	COLECTOMY PRTL W/SKIN LEVEL CECOST/COLOSTOMY
44143	COLECTOMY PRTL W/END COLOSTOMY & CLSR DSTL SGMT
44144	COLECTOMY PRTL W/COLOST/ILEOST & MUCOFISTULA
44146	COLECTOMY PRTL W/COLOPROCTOSTOMY & COLOSTOMY
44150	COLCT TOT ABDL W/O PRCTECT W/ILEOST/ILEOPXTS
44155	COLECTOMY TOT ABDL W/PROCTECTOMY W/ILEOSTOMY

Appendix C. Sensitivity Analyses

C1. Definitions to Identify CRC Diagnosis

C1.1. Definition#1[175]

First: Before applying any definition: We identify members 50-64 years old who were continuously enrolled for each single year. For example, there were 113,333 members who were continuously enrolled in the year of 2015 (see tables below). For those members, we identify any diagnosis of CRC according to the year of diagnosis. For instance, there were 390 members (out of the 113,333 members) with any CRC diagnosis in the year 2015, 362 in the year 2014 and so on.

Eligibility Criteria

BCBS members ages 50-64 - Continuously Enrolled January 1, 2015 - December 31, 2015

N = 113333

Any dx of CRC

	2012	2013	2014	2015
N	230	269	362	390

Eligibility Criteria

BCBS members ages 50-64 - Continuously Enrolled January 1, 2014 - December 31, 2014

N = 119732

Any dx of CRC

	2012	2013	2014
N	259	312	412

Eligibility Criteria

BCBS members ages 50-64 - Continuously Enrolled January 1, 2013 - December 31, 2013

N = 122531

Any dx of CRC

	2012	2013
N	307	363

Eligibility Criteria

BCBS members ages 50-64 - Continuously Enrolled January 1, 2012 - December 31, 2012

N = 115474

Any dx of CRC

	2012
N	336

Second: After applying definition#1 (Among cohort with ≥ 1 CRC DX + any surgery related during the same hospitalization and/or visit).

A total of 241 members 50-64 years old were continuously enrolled for the year 2015 had CRC diagnosis.

Eligibility Criteria

BCBS members ages 50-64 - Continuously Enrolled January 1, 2015 - December 31, 2015

N = 241

Any dx of CRC

	2012	2013	2014	2015
N	42	53	72	69

Eligibility Criteria

BCBS members ages 50-64 - Continuously Enrolled January 1, 2014 - December 31, 2014

N = 260

Any dx of CRC

	2012	2013	2014
N	49	62	80

Eligibility Criteria

BCBS members ages 50-64 - Continuously Enrolled January 1, 2013 - December 31, 2013

N = 266

Any dx of CRC

	2012	2013
N	57	73

Eligibility Criteria

BCBS members ages 50-64 - Continuously Enrolled January 1, 2012 - December 31, 2012

N = 255

Any dx of CRC

	2012
N	59

Third: Variations in timing of CRC DX according to different periods of continuous enrollment in BCBSNE.

	N	Any CRC dx in 2012	1st CRC dx in 2012	Any CRC dx in 2013	1st CRC dx in 2013	Any CRC dx in 2014	1st CRC dx in 2014	Any CRC dx in 2015	1st CRC dx in 2015
Enrolled > 4 months	317	67	67	78	73	89	84	76	69
Enrolled > 6 months	316	67	67	78	73	89	84	76	69
Enrolled > 9 months	312	67	67	78	73	87	82	76	69
Enrolled > 12 months	308	64	64	78	73	87	82	75	68

Fourth: Variations in period of continuous enrollment by different CRC-free periods (4-12 months)

FOR THOSE ENROLLED > 4 MONTHS

Number of cases with at least 1 CRC dx with no other CRC dx in prior 4 months

N	2012	2013	2014	2015
284	44	72	82	64

FOR THOSE ENROLLED > 6 MONTHS

Number of cases with at least 1 CRC dx with no other CRC dx in prior 6 months

N	2012	2013	2014	2015
267	34	70	78	64

FOR THOSE ENROLLED > 12 MONTHS

Number of cases with at least 1 CRC dx with no other CRC dx in prior 12 months

N	2012	2013	2014	2015
222	0	67	73	62

C1.2. Definition#2

First: Before applying any definition (see C1.1. above)

Second: After applying definition#2 (Among cohort with ≥2 CRC within 2 months).

Eligibility Criteria

BCBS members ages 50-64 - Continuously Enrolled January 1, 2015 - December 31, 2015

N = 414

Any dx of CRC

	2012	**2013**	**2014**	**2015**
N	124	72	107	71

Eligibility Criteria

BCBS members ages 50-64 - Continuously Enrolled January 1, 2014 - December 31, 2014

N = 455

Any dx of CRC

	2012	**2013**	**2014**
N	141	93	115

Eligibility Criteria

BCBS members ages 50-64 - Continuously Enrolled January 1, 2013 - December 31, 2013

N = 478

Any dx of CRC

	2012	**2013**
N	177	104

Eligibility Criteria

BCBS members ages 50-64 - Continuously Enrolled January 1, 2012 - December 31, 2012

N = 479

Any dx of CRC

	2012
N	206

Third: Variations in timing of CRC DX according to different periods of continuous enrollment in BCBSNE

	N	Any CRC dx in 2012	1st CRC dx in 2012	Any CRC dx in 2013	1st CRC dx in 2013	Any CRC dx in 2014	1st CRC dx in 2014	Any CRC dx in 2015	1st CRC dx in 2015
Enrolled >4 months	637	231	231	117	102	141	124	95	86
Enrolled >6 months	633	229	229	116	101	141	124	95	86
Enrolled >9 months	613	224	224	116	101	137	120	94	85
Enrolled >12 months	592	211	211	115	100	134	117	91	82

Fourth: Variations in period of continuous enrollment by different CRC-free periods (4-12 months)

FOR THOSE ENROLLED > 4 MONTHS

Number of cases with at least 1 CRC dx with no other CRC dx in prior 4 months

N	2012	2013	2014	2015
456	95	107	127	83

FOR THOSE ENROLLED > 6 MONTHS

Number of cases with at least 1 CRC dx with no other CRC dx in prior 6 months

N	2012	2013	2014	2015
405	64	103	115	81

FOR THOSE ENROLLED > 12 MONTHS

Number of cases with at least 1 CRC dx with no other CRC dx in prior 12 months

N	2012	2013	2014	2015
316	0	95	106	74

C1.3. Definition#3

First: Before applying any definition (see C1.1. above)

Second: After applying definition#4 (Among Cohort with At Least 1 Inpatient or at Least 2 Outpatient Visits with CRC Diagnoses During Study Period).

Eligibility Criteria

BCBS members ages 50-64 - Continuously Enrolled January 1, 2015 - December 31, 2015

N = 514

Any dx of CRC

	2012	**2013**	**2014**	**2015**
N	201	251	332	369

Eligibility Criteria

BCBS members ages 50-64 - Continuously Enrolled January 1, 2014 - December 31, 2014

N = 562

Any dx of CRC

	2012	**2013**	**2014**
N	226	292	376

Eligibility Criteria

BCBS members ages 50-64 - Continuously Enrolled January 1, 2013 - December 31, 2013

N = 587

Any dx of CRC

	2012	**2013**
N	270	337

Eligibility Criteria

BCBS members ages 50-64 - Continuously Enrolled January 1, 2012 - December 31, 2012

N = 580

Any dx of CRC

	2012
N	296

Third: Variations in timing of CRC DX according to different periods of continuous enrollment in BCBSNE.

	N	Any CRC dx in 2012	1st CRC dx in 2012	Any CRC dx in 2013	1st CRC dx in 2013	Any CRC dx in 2014	1st CRC dx in 2014	Any CRC dx in 2015	1st CRC dx in 2015
Enrolled >4 months	774	333	333	390	130	437	152	428	105
Enrolled >6 months	769	330	330	389	129	437	152	428	105
Enrolled >9 months	744	323	323	389	129	433	148	427	104
Enrolled >12 months	719	310	310	387	128	428	144	418	98
Enrolled >18 months	674	289	289	363	123	419	140	403	85
Enrolled >24 months	611	259	259	326	111	404	130	383	76

Fourth: Variations in period of continuous enrollment by different CRC-free periods (4-12 months)

FOR THOSE ENROLLED > **4** MONTHS: 774

Number of cases with at least 1 CRC dx with no other CRC dx in prior 4 months

N	**2012**	**2013**	**2014**	**2015**
500	129	113	128	88

FOR THOSE ENROLLED > **6** MONTHS: 769

Number of cases with at least 1 CRC dx with no other CRC dx in prior 6 months

N	**2012**	**2013**	**2014**	**2015**
437	83	109	120	85

FOR THOSE ENROLLED > **12** MONTHS: 719

Number of cases with at least 1 CRC dx with no other CRC dx in prior 12 months

N	**2012**	**2013**	**2014**	**2015**
327	0	99	110	79

FOR THOSE ENROLLED > **18** MONTHS: 674

Number of cases with at least 1 CRC dx with no other CRC dx in prior 18 months

N	**2012**	**2013**	**2014**	**2015**
262	0	47	105	74

FOR THOSE ENROLLED > **24** MONTHS: 611

Number of cases with at least 1 CRC dx with no other CRC dx in prior 24 months

N	**2012**	**2013**	**2014**	**2015**
205	0	0	104	66

C2. The impact of sensitivity and specificity of various definitions on the association between travel time and stage at diagnosis.

Scenario	travel time	induction period (cancer-free)	Se*	Sp**	Metastatic	Non-Metastatic	total	Corrected estimates due to Misclassifications			Bias direction
								ORcorr†	lnORm††	up/down	
	<17	0	1	1	13	88	101				
1	≥17	0	1	1	14	89	103	0.93912	Ref.	-	-
	<17	0	0.8118	0.9922	15.19	85.81	101				
2	≥17	0	0.8118	0.9922	16.41	86.59	103	0.934	0.006	Up	Toward
	<17	6	0.8398	0.9935	14.81	86.19	101				
3	≥17	6	0.8398	0.9935	16.00	87.00	103	0.93472	0.005	Up	Toward
	<17	6	0.8398	0.97	12.31	88.69	101				
4	≥17	6	0.8398	0.97	13.47	89.53	103	0.92249	0.018	Up	Toward
	<17	6	0.6725	0.9935	18.53	82.47	101				
5	≥17	6	0.6725	0.9935	20.02	82.98	103	0.93178	0.008	Up	Toward
	<17	12	0.8434	0.9938	14.78	86.22	101				
6	≥17	12	0.8434	0.9938	15.96	87.04	103	0.935	0.005	Up	Toward
	<17	18	0.8475	0.9938	14.71	86.29	101				
7	≥17	18	0.8475	0.9938	15.88	87.12	103	0.93495	0.004	Up	Toward
	<17	24	0.8555	0.9939	14.58	86.42	101				
8	≥17	24	0.8555	0.9939	15.74	87.26	103	0.935	0.004	Up	Toward
	<17	30	0.8579	0.994	14.55	86.45	101				
9	≥17	30	0.8579	0.994	15.71	87.29	103	0.93517	0.004	Up	Toward
	<17	36	0.8616	0.994	14.49	86.51	101				
10	≥17	36	0.8616	0.994	15.64	87.36	103	0.935	0.004	Up	Toward

*Sensitivity,** Specificity, † Corrected odds ratio.†† lnORm (Natural log of odds ratio due to misclassification)= Ln(ORobserved/ORcorrected).
The range of sensitivity and specify were derived from Setoguchi et. al.[175]

C3. The Magnitude of Change in Odds Ratio According to Different Travel Times

Time variations	OR
Original	0.996 (0.985,1.008)
1 minute	0.996 (0.985,1.008)
10 minutes	0.997 (0.985,1.009)
20 minutes	0.997 (0.985,1.009)
30 minutes	0.998 (0.986,1.010)

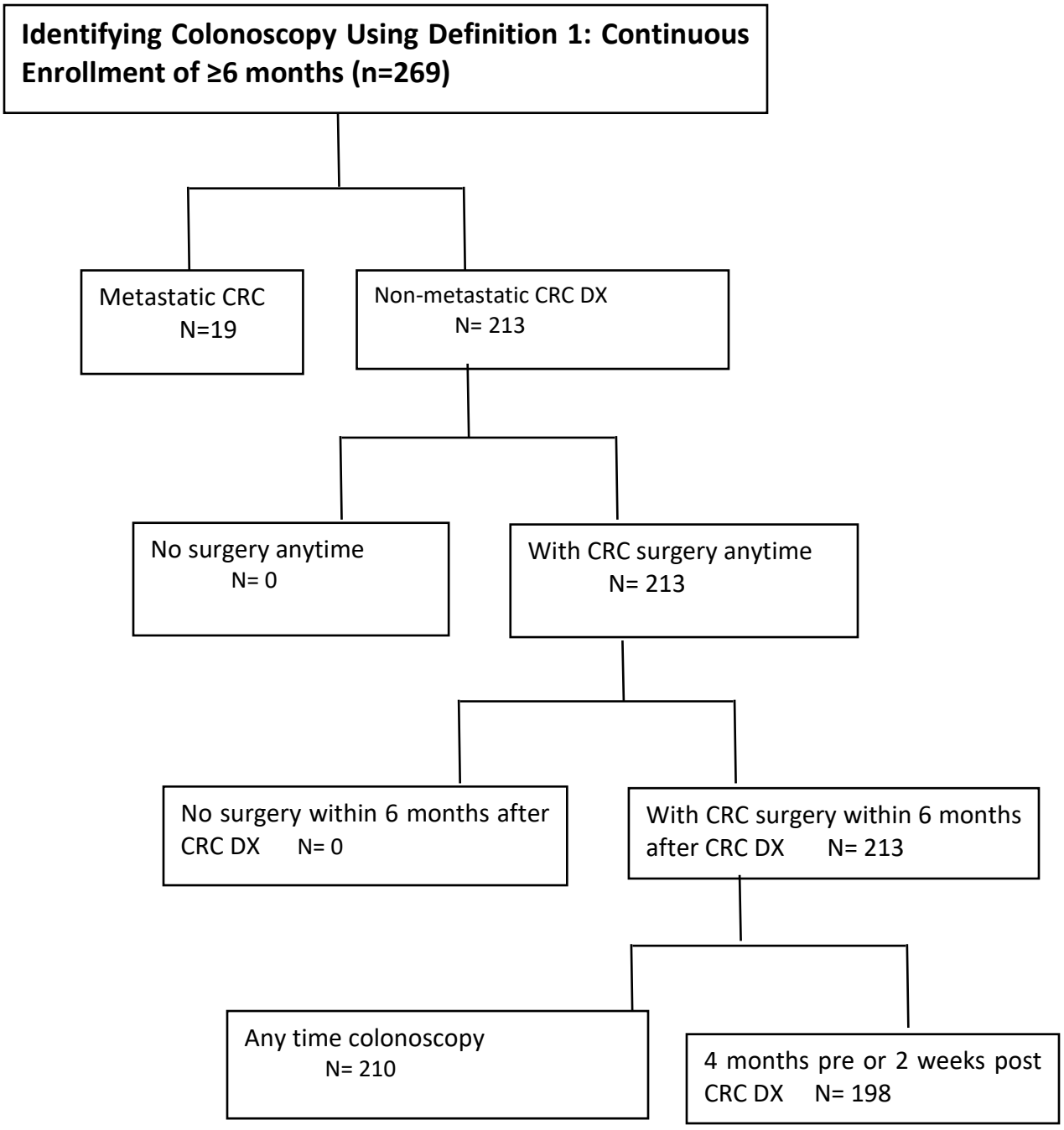
C4. Frequency of Colorectal Cancer Cases Identified According to Different Periods of Colonoscopy Use

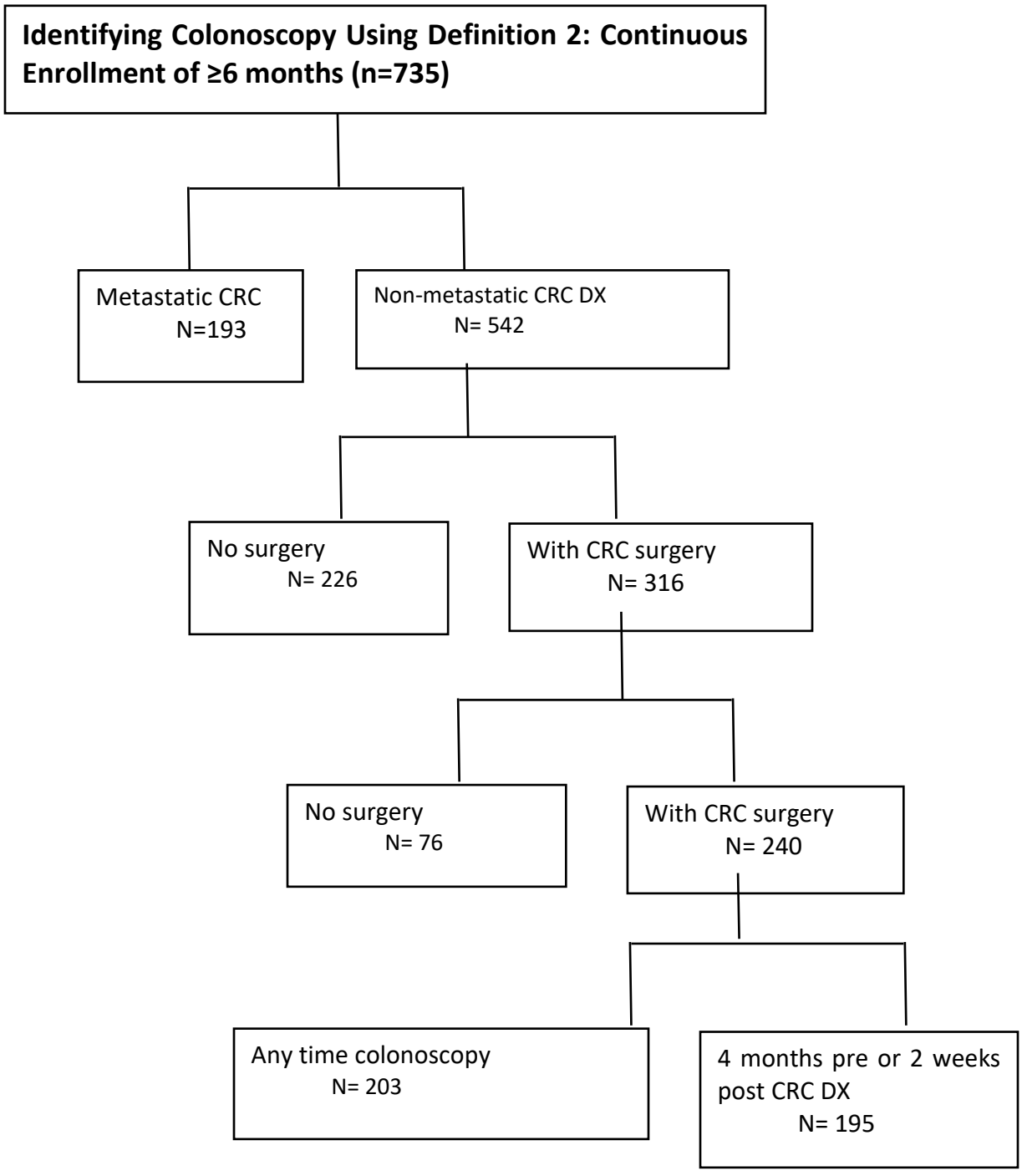
Continuous enrollment period	Total CRC cases
3 months before or 14 days after CRC diagnosis	200
4 months before or 14 days after CRC diagnosis	204
6 months or 14 days after CRC diagnosis	210
12 months or 14 days after CRC diagnosis	258

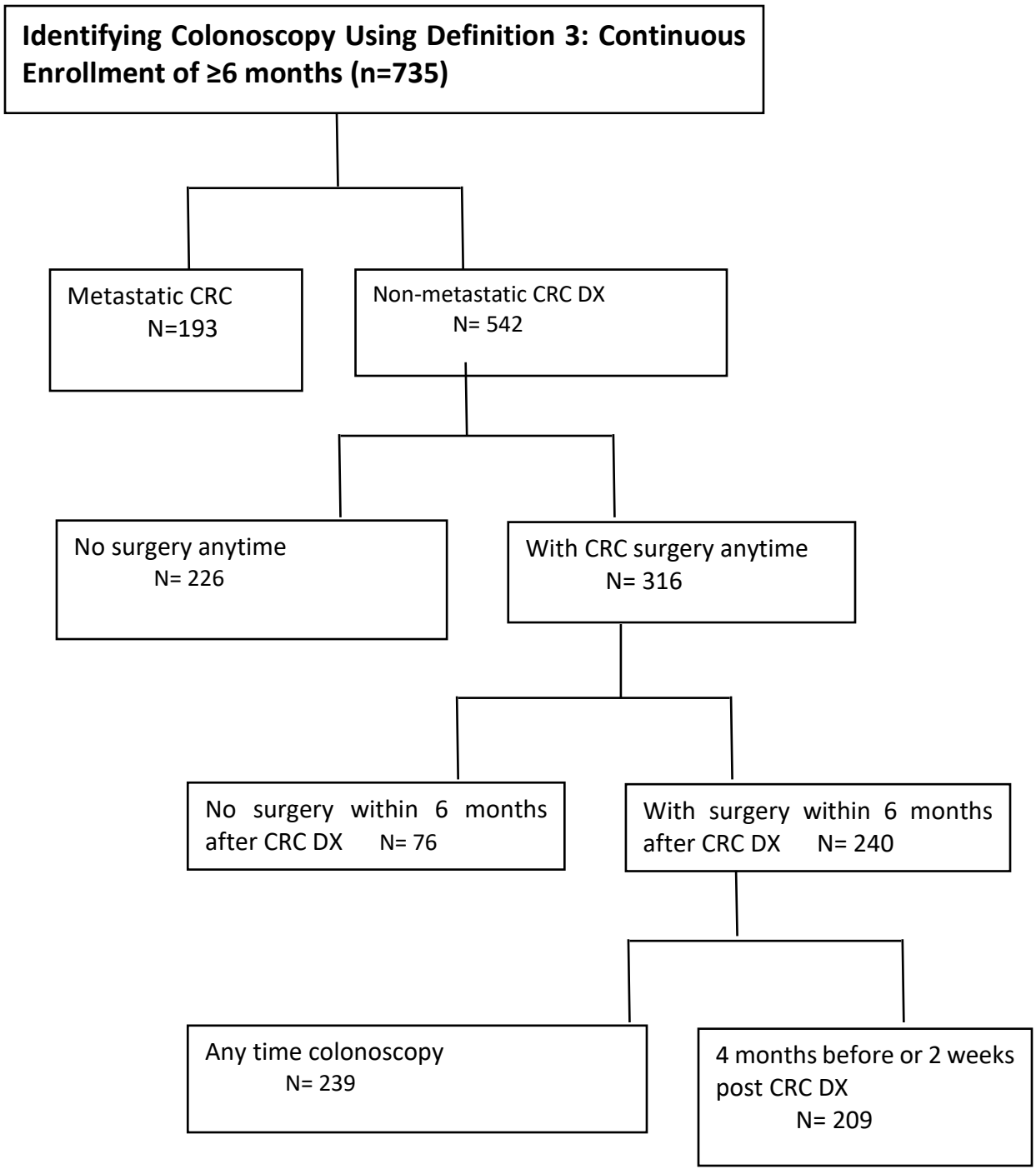
C5. Identification of Colorectal Cancer Cases According to Periods of Continuous Enrollment

Continuous enrollment period	Total CRC cases
3 months before CRC Diagnosis	453
4 months before CRC Diagnosis	429
6 months before CRC Diagnosis	366
12 months before CRC Diagnosis	279
18 months before CRC Diagnosis	228

C6. Definitions to Identify Colonoscopy Use




Identifying Colonoscopy Using Definition 2: Continuous Enrollment of ≥6 months (n=735)
Metastatic CRC N=193
Non-metastatic CRC DX N= 542
No surgery N= 226
With CRC surgery N= 316
No surgery N= 76
With CRC surgery N= 240
Any time colonoscopy N= 203
4 months pre or 2 weeks post CRC DX N= 195


Identifying Colonoscopy Using Definition 3: Continuous Enrollment of ≥6 months (n=735)
Metastatic CRC N=193
Non-metastatic CRC DX N= 542
No surgery anytime N= 226
With CRC surgery anytime N= 316
No surgery within 6 months after CRC DX N= 76
With surgery within 6 months after CRC DX N= 240
Any time colonoscopy N= 239
4 months before or 2 weeks post CRC DX N= 209

C7. Definition of CRC Diagnosis by Year of Diagnosis

BCBS members ages 50-64 - continuously enrolled between…	N	Definition 1	Definition 2	Definition 3
January 1, 2012 - December 31, 2012	115,474	255	479	580
January 1, 2013 - December 31, 2013	122,531	266	478	587
January 1, 2014 - December 31, 2014	119,732	260	455	562
January 1, 2015 - December 31, 2015	113,333	241	414	514

N: Members who were continuously enrolled during a single year

Definition 1: Among cohort with ≥ 1 CRC + any surgery related during the same hospitalization and/or visit.

Definition 2: Among cohort with ≥2 CRC diagnosis within 2 months

Definition 3: Among cohort with at least 1 inpatient or at least 2 outpatient visits with CRC diagnoses during the study period.

Appendix D. Comparison between the BCBSNE and the State of Nebraska Population

D. Frequencies and Percentages of BCBSNE and The State of Nebraska Population by Regional Health Department

Region	BCBSNE members		The State of Nebraska	
	N	%	N	%
Panhandle Public Health District	25731	3.74	88403	4.85
North Central District Health Department	19938	2.90	46394	2.54
Northeast Nebraska Public Health Department	10331	1.50	31387	1.72
Dakota County Health Department	2656	0.39	21006	1.15
West Central District Health Department	1584	0.23	39433	2.16
Loup Basin Public Health Department	14229	2.07	31140	1.71
East Central District Health Department	21093	3.06	51992	2.85
Elkhorn Logan Valley Public Health Department	23461	3.41	57002	3.13
Three Rivers Public Health Department	32598	4.74	77705	4.26
Lincoln/Lancaster County Health Department	122961	17.86	285407	15.65
Sarby/Cass Department of Health and Wellness	67846	9.86	184081	10.10
Douglas County Health Department	189848	27.58	517110	28.36
Southwest Nebraska Public Health Department	18061	2.62	36987	2.03
Two Rivers Public Health Department	38224	5.55	94797	5.20
South Heartland District Health Department	19033	2.77	46218	2.53
Central District Health Department	26997	3.92	75576	4.14
Public Health Solutions District Health Department	21768	3.16	55176	3.03
Four Corners Health Department	17086	2.48	44216	2.42
Southeast District Health Department	14844	2.16	39341	2.16
Total	673445	100.0	1823371	100.0

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