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Assessment of the Effectiveness of an Innovative Screening Colonoscopy Protocol in Producing High Quality Performance and Outcomes by Trained Primary Care Physicians

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ASSESSMENT OF THE EFFECTIVENESS OF AN INNOVATIVE SCREENING COLONOSCOPY PROTOCOL IN PRODUCING HIGH QUALITY PERFORMANCE AND OUTCOMES BY TRAINED PRIMARY CARE PHYSICIANS

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Abstract

This study assessed the effectiveness of specific elements of an innovative colonoscopy clinical protocol, namely use of a hands-on 2-person technique (vs. solo performance) and use of propofol sedation in enhancing the performance quality of screening colonoscopies by trained primary care physicians (PCP) and specialists. The study used data from a state-licensed ambulatory surgery center for endoscopy in South Carolina from September 4, 2001 to February 4, 2011. This center has trained 54 PCPs in colonoscopy performance since 2001. Post training, PCPs are credentialed to perform colonoscopy only with the 2-person technique with a specialist available onsite to provide rescue assistance. A total of 59 physicians performed colonoscopies, and 57 physicians (54 PCPs and 3 specialists) consistently complied with the 2-person technique, while 2 non PCPs (one colorectal surgeon and one general surgeon) used the conventional solo performance technique. Propofol sedation in lieu of the conventionally used midazolam-meperidine (MM) sedation was implemented since April 1, 2006.

The dependent variables of interest representing procedure quality were as follows: procedure time, the likelihood of finding a/an polyp/adenoma/advanced neoplasm, finding an additional polyp/adenoma, finding at least one right-sided polyp, and finding increasingly smaller polyps. These quality indicators were found to be positively associated with the 2-person technique protocol. There was a marginal gain on some of the measures with the use of propofol sedation. The findings suggest that the 2-person technique as implemented by this center improves the global quality of

colonoscopy performance on measures that are documented to predict colorectal cancer prevention effectiveness.

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Chapter 1 RESEARCH BACKGROUND AND SIGNIFICANCE

This chapter describes the background and the significance of the study topic.

1.1 Study Background

Colorectal cancer (CRC) is the third most prevalent cancer and second leading cause of cancer death in the U.S. (U.S. Cancer Statistics Working Group), with almost140, 000 new cases and 55,000 deaths annually. This large number affected can be mostly prevented by screening tests both by removing pre-cancerous lesions and by early detection. In the past decade, age-adjusted CRC incidence decreased from 51.8 per 100,000 in 1999 to 44.7 per 100,000 in 2009; as well as age-adjusted CRC mortality, which decreased from 20.5 per 100,000 to 16.9 per 100,000 (SEER 1990-2010).

Despite some degree of annual reductions in CRC incidence and mortality, CRC remains a major threat to public health when compared to the motor vehicle accident fatality rate of about 11 per 100,000 annually (NHTSA 2012). Evidence indicates that screening tests, such as fecal occult blood test (FOBT) and fecal immunochemical test (FIT), sigmoidoscopy, and colonoscopy etc, availed at appropriate intervals, can reduce the risk of CRC to some extent by enabling the early detection and removal of advanced polyps. The American Cancer Society in 1992 and the U.S. Preventive Services Task Force (USPSTF) in 1996 initiated the earliest guidelines recommending CRC screening of average risk individuals, who are aged 50 years and older to undergo routine

screenings until the age of 75. Currently, the USPSTF recommended screening tests and intervals are:

- Annual screening with high-sensitivity fecal occult blood testing
- Sigmoidoscopy every 5 years, with high-sensitivity fecal occult blood testing every 3 years
- Colonoscopy every 10 years

Colonoscopies have been recommended as the preferred screening method, including the American College of Obstetricians and Gynecologists, the American College of Gastroenterology (Rex 2000, Rex 2009) and the American Society for Gastrointestinal Endoscopy (ASGE) (David 2006). Although colonoscopy every 10 years is considered to be the preferred screening method, it is imperfect because of variable quality of screening colonoscopy under community-based practice conditions.

As the use of colonoscopy screening increases, the need for measurement of colonoscopy quality is inevitable to ensure quality in the performance of colonoscopies. Generally, the cecal intubation rate is most commonly studied. However, this is a very limited measure of quality, and widespread poor quality of colonoscopy performance continues to limit the CRC prevention potential.

Adenoma detection and removal is the mechanism of conferring CRC prevention and is the main goal of colonoscopy, and should be a key indicator for assessing colonoscopy quality. Among endoscopists a wide range of the adenoma detection rate (ADR) has been documented (Millan 2008, Barclay 2006, Wilkins 2009, Rex 2001). This implies that the quality of colonoscopies varies widely, which could reduce its efficacy in CRC protection. A meta-analysis of 12 studies focusing on colonoscopies performed by

primary care physicians (PCPs) with a total of 18,292 patients found an adenoma detection rate of 28.9%. The authors concluded that colonoscopy performance by PCPs can meet the professional, societies' recommended standards (Wilkins 2009). The association between colonoscope withdrawal times and adenoma detection rates was also studied. Barclay (2006) reported that physicians who had a mean withdrawal time less than 6 minutes (when no polyp was found) have an adenoma detection rate of 11.8%, while it was 28.3% for those with a mean withdrawal time of more than 6 minutes. This statistically significant difference persists in the next level of quality, the mean number of adenomas per subject, which were 0.17 vs. 0.61, respectively. Rex et al (2001) videotaped 10 procedures performed by 2 colonoscopists and got them reviewed/scored by 4 experts based on four quality criteria related to colonoscopic withdrawal technique. They reported that technique does matter to the adenoma miss rate, which could be further associated with the potential cancer protection efficacy of colonoscopy screening. There is concern about colonoscopy quality because of the variable results and outcomes in terms of CRC prevention in the literature. Also, colonoscopy is a physician-dependent procedure. To make sure that physicians are doing a good job is more important than how many they have carried out.

In this study, our setting is a community-based facility, which has followed a uniform protocol for almost all but not all physicians for 12 years. To evaluate the protocol elements, we explore the association between the quality of colonoscopy outcomes and two protocol elements, the 2-person technique pioneered by this center, and sedation type.

1.2 Objectives

The aim of this study was to evaluate the quality of colonoscopies. Of the risk factors which impact colonoscopy performance, our variables of interest were the clinical procedure protocol type and the sedation type. We tested the impact of the protocol type and the sedation type on the polyp/adenoma detection rate, the mean number of polyps/adenomas detected, polyp size, polyp location, and the procedure time.

We hypothesized that colonoscopy quality may be enhanced by applying the 2-person technique protocol relative to solo performance, and with deep sedation by propofol relative to the conventional Midazolam-meperidine combination.

The hypotheses tested are:

1. The screening colonoscopy quality of physicians using the 2-person technique yields more adenomas than with solo performers.
2. The screening colonoscopy quality of procedures with deep sedation by propofol yields more adenomas than with the conventional Midazolam-meperidine combination.

1.3 Significance of the research and methodology

Although colonoscopy is considered to be the reference gold standard against which the sensitivity of other colorectal cancer screening tests is compared, it is not perfect. Most of the evidence about the sensitivity of a colonoscopy comes from experienced examiners conducting study colonoscopies in research settings without detailed documentation on the protocol followed.

The innovative protocol at the community-based endoscopy center (hereafter referred to as “Study Center” or “Center”) has the following unique features: a) a hands-

on 2-person technique, in which the endoscopy technician advances the colonoscope while the physician manipulates the scope tip for polyp search and removal, b) propofol sedation to substitute the conventional midazolam-meperidine (MM) combination sedation starting in April 2006, and c) gradual insertion and withdrawal with polyp search and removal during both phases to maximize coverage of the colonic mucosal surface. The hands-on 2-person technique method avoids missing polyps due to physician's motor fatigue, confers the dexterity of two “right” hands for polyp search and removal, and ensures more persons (at least 3 persons, the third being the note taker) watching the video screen for polyps (avoiding visual error). Of these elements, item (a) was not followed by experts and some specialists, which enables study of the contribution of the hands on 2-person technique. Item (b), propofol sedation was implemented from April 2006 onwards, enabling pre- and post-comparison to assess the role of propofol sedation. This research aims to contribute to the literature by:

1. Using clinical data for the analysis
2. Studying a state-of-the-art colonoscopy protocol, which has been applied for over 10 years
3. Identifying the effect of protocol elements on screening colonoscopy quality
4. Analyzing differences in adenoma detection rates by sedation type and number of persons engaged in procedure performance.

1.4 Limitations

1. This clinical dataset is from a single endoscopy center in South Carolina, as such the observed findings may not generalize to the other settings.

2. Due to the strict implementation of a uniform protocol at this center, the vast majority of the procedures were under state-of-the-art protocol. Only 2% of the procedures were performed using the conventional industry practice of a one-person technique, compared to 98% of procedures performed with the 2-person technique distributed across 57 physicians. Therefore the observed results may not generalize to all physicians using the 1-person technique.

1.5 Conclusions

This study finds that an innovation of a hands-on 2-person technique is highly associated with superior colonoscopy performance and lesion detection outcomes. By every sensitive measure, the results with the 2-person technique are superior and consistent across measures. Regarding sedation type, we find that while there is a suggestion of a positive association of propofol sedation with improved lesion detection and clearance as measured by sensitive indicators, the results did not attain statistical significance except in respect of one indicator, the advanced adenoma detection rate. Another important indicator for logistic reasons is the procedure time. Because propofol induces rapid and deep sedation, as anticipated the study showed a mean reduction in procedure time adjusted for all other variables that may impact procedure time. Our findings suggest that propofol sedation may contribute marginally to improved colonoscopy quality. Our study also finds that quality improvement efforts may be more productive if focused on measures to improve patients' bowel preparation status through efforts directed at patients, for example, through patient navigation. Regarding propofol sedation itself, our findings indicate that endoscopist's decisions to adopt propofol sedation should be guided by considerations of patient comfort and satisfaction, and of

the efficiency of endoscopist time utilization rather than an expectation of improved lesion detection rates. Our study does not provide support for adoption of propofol sedation for the purpose of improving the colorectal cancer prevention effectiveness of colonoscopy screening.

Chapter 2 LITERATURE REVIEW

This chapter reviews the related colorectal cancer screening literature and makes the case for the significance of this study based on past research.

2.1 Overview of colorectal cancer in the United States

2.1.1 Incidence and mortality

Approximately 7.6 million people die of cancer each year. These deaths account for 13% of all deaths, and 64% occur in the developing countries. The burden of cancer is increasing both in the developed and developing countries due to the growth of population, aging, and changes in lifestyle, especially for the cancer-associated behaviors, such as obesity, smoking, and adoption of Western-style diets. (Globocan (IARC) 2008, WHO 2008, Jemal 2011). Colorectal cancer (CRC) is one of the most common cancers and the leading cause of death in the U.S. since the late 1990s. The incidence of colorectal cancer was 51.8 per 100,000 of the U.S. population in 1999 and the age-adjusted 2009 rate decreased to 44.7 per 100,000 in 2009. The death rate was 20.5 per 100,000 in 1999 and age-adjsuited rate in 2009 was 16.9 per 100,000 (SEER 1990-2010). About 140,000 new cases and 55,000 deaths occur each year in the US (Wingo et al 1995). Although the incidence rate and death rate are decreasing, CRC has remained a leading cancer on both incidence and deaths in the past two decades (USCS, CDC). The incidence rate of CRC rose between 1975 and 1985, since then the incidence rate had

steadily reduced except for a non-significant plateau during 1995-1998. In 2008, the incidence rate of CRC for men was 50.98 per 100,000 people and 39.64 per 100,000 people for women. The goal of Healthy People 2020 is to reduce CRC incidence to 38.6 per 100,000 people by 2020 (NCI 2012).

The significance of CRC is reflected both in the population affected and the rankings. Globally, in 2008, about 1.2 million new cases and 608,700 deaths occurred due to colorectal cancer (Globocan (IARC) 2008). It was found to be most prevalent in Oceania, Europe, and North America (Globocan (IARC) 2008). In 2010, an estimated 142,570 new CRC cases, 9.32% of all cancer new cases occurred in the United States. An estimated 51,370 people (9% of all cancer deaths) died from colorectal cancer (Jemal 2010, ACS 2010). The incidence and mortality rates of CRC rank as the 3rd most frequent for both sexes (Jemal 2010, ACS 2010). The overall cost of cancer as estimated by the National Institutes of Health was $263.8 billion, 9% for CRC amounts to about $23.74 billion. Among these costs, $9.25 billion is for health expenditure, $1.88 billion is for lost productivity due to illness, $12.61 billion is for lost productivity due to premature death (ACS 2010).

The lifetime risk of an individual being diagnosed with CRC has been estimated to be 5.42% for invasive CRC, and 5.73% if in situ CRC is included (SEER 1975-2004). The lifetime risk of dying from CRC is 2.20% in the U.S. The overall 5-year survival rate is 64%. It is 89-90% in persons with localized disease, 68-69% in persons with regional spread, and only 10-11% in those with distant metastases (Ries et al 2007; SEER Cancer Statistics Review 1975-2004). Even though the risk of CRC diagnosis or death exists, the survival rate of CRC is relatively high when diagnosed early. Almost 90% of those with

early CRC diagnosis survive for 5 years. But it is predicated upon early detection. Furthermore CRC can be prevented. Reducing the colorectal cancer death rate is one of the objectives of Healthy People 2020, the target rate being 14.5 deaths per 100,000. In 2008, the worldwide age-standardized mortality was 8.2%, accounted for approximately 0.6 million individuals, and the age-standardized incidence was17.2%, accounted for 1.24 million persons (Globocan (IARC) 2008).

2.2 Colorectal cancer prevention and the role of polyps

While the role of hyperplastic polyps in colon cancer is debated, benign adenomatous polyps have been documented to be the precursor for most cases of colon cancer, and polyps increase with age (Correa et al 1977, Rickert et al 1979). Detecting and removing adenomatous polyps is effective in reducing the incidence and mortality of CRC. Within polyps the proportion of villous architecture (showing rapid growth) is positively associated with the size of adenomatous polyps and, furthermore, the potential of having malignant characteristics (Rickert et al 1979). Evidence shows that adenomatous polyps smaller than 10mm in diameter are rarely found to be cancer. The villous architecture component is more likely to be found in adenomatous polyps larger than 10mm (Enterline et al 1962, Morson 1974, Muto et al 1975, Spjut et al 1977).

According to Surveillance Epidemiology and End Results 17 (SEER-17), which captures cancer data in 17 metropolitan/rural regions (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana and New Jersey) 2002-2004, the lifetime risk of being diagnosed with CRC is lowest in American Indians/Alaskan Natives (4.27% for invasive CRC and 4.45% for

invasive and in-situ CRC), followed by Hispanics (4.82% for invasive CRC and 5.08% for invasive and in-situ CRC), and highest in Asians/Pacific Islanders (5.58% for invasive CRC and 5.83% for invasive and in-situ CRC). The lifetime risk of dying from CRC is lowest in American Indians/Alaskan Natives at 1.86%, followed by Hispanics at 1.92%, and is highest in Blacks at 2.42% (Ries et al 2007). The pattern of lifetime risks between ethnics of being diagnosed with CRC mirrors the pattern of lifetime risk of dying from CRC.

Polyps in the colon are associated with different histology types. Some types of polyps are more likely to be found in the left colon while others were not. Hyperplastic polyps are most commonly found in the rectum – 86.1% of total polyps. Neoplastic adenomas are the second most common, and both increase with age and are more prevalent in men (Williams et al 1982). Although there is no consistent relationship between the size of adenomas and age, as age increases, adenomas larger than 1 cm in diameter are more prevalent. Sessile adenomas are more prevalent in the cecum, while pedunculated adenomas had an increasing prevalence in the distal colon and were most prevalent in the sigmoid colon (Williams et al 1982) While the role of hyperplastic polyps in colon cancer is debated, benign adenomatous polyps have been documented to be the precursor for most cases of colon cancer, and polyps increase with age (Correa et al 1977, Rickert et al 1979). Detecting and removing adenomatous polyps is effective in reducing the incidence and mortality of CRC. Within polyps the proportion of villous architecture (showing rapid growth) is positively associated with the size of adenomatous polyps and, furthermore, the potential of having malignant characteristics (Rickert et al 1979). Evidence shows that adenomatous polyps smaller than 10mm in diameter are

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2.3 Identifying at-risk population

2.3.1 Average-risk persons

Incidence and death rates of CRC increase with age. In the US population, the incidence rate exceeds 100 per 100,000 from the 60-64 age group, and the death rate accelerates from the 75-79 age group (SEER Cancer Statistics Review, 1975-2008). In South Carolina, the incidence rate of more than 10/100,000 is observed starting in the 55-59 age group, and death rate exceeds 10/100,000 in the 75-79 age group for the mortality rate (SC SCAN). Figure 2.1 – Figure 2.4 show the incidence rate and the mortality rate of CRC for South Carolina population and the trend-line from 1996 to 2009 (SC SCAN):

DHEC PROMOTE PROTECT PROSPER	Cancer Incidence: Full (Research) File For South Carolina Residents	PHSIS PROMOTE PROTECT PROSPER

County: All Counties in South Carolina

Primary Cancer Sites: Colorectal (colon, rectum, and rectosigmoid)

	Age										
	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Year	Rates	Rates	Rates	Rates	Rates	Rates	Rates	Rates	Rates	Rates	Rates
1996	10.5	19.1	36.1	69.6	100.7	156.2	190.8	275.5	316.5	366.7	429.6
1997	10.7	17.6	39.2	62.4	109.3	161.5	187.3	280.2	334.4	320.3	437.9
1998	13.8	18.2	38.7	64.4	110.6	161.9	214.0	302.2	344.0	418.1	402.5
1999	9.2	18.5	35.8	72.9	108.2	154.2	233.0	279.1	342.2	336.2	407.0
2000	8.6	21.8	45.6	65.2	108.1	161.2	210.6	274.9	321.3	414.1	402.8
2001	10.4	24.1	44.5	63.4	101.7	157.6	199.4	285.2	318.8	387.5	383.2
2002	11.3	23.5	45.1	70.9	105.4	161.2	233.1	283.1	326.6	362.5	364.0
2003	13.2	23.5	38.8	73.6	117.8	156.8	245.2	291.8	302.0	335.6	359.6
2004	16.2	27.3	34.5	79.2	110.1	138.0	216.7	259.4	323.1	346.1	370.4
2005	10.0	15.4	32.5	75.1	107.7	143.6	200.8	243.3	281.1	346.6	328.3
2006	14.3	21.2	41.9	66.0	91.0	131.1	195.3	221.9	259.8	280.2	256.0
2007	10.7	17.6	39.4	77.4	92.4	124.0	179.6	201.2	256.4	244.7	291.2
2008	8.9	20.1	39.4	68.5	84.4	115.1	159.0	186.4	228.8	260.2	277.4
2009	8.4	16.9	40.7	59.1	77.1	108.1	139.3	166.9	206.0	216.8	244.0

*Rate: Crude Rate calculated per 100,000 population

Figure 2-1 Colorectal cancer incidences in the past decade

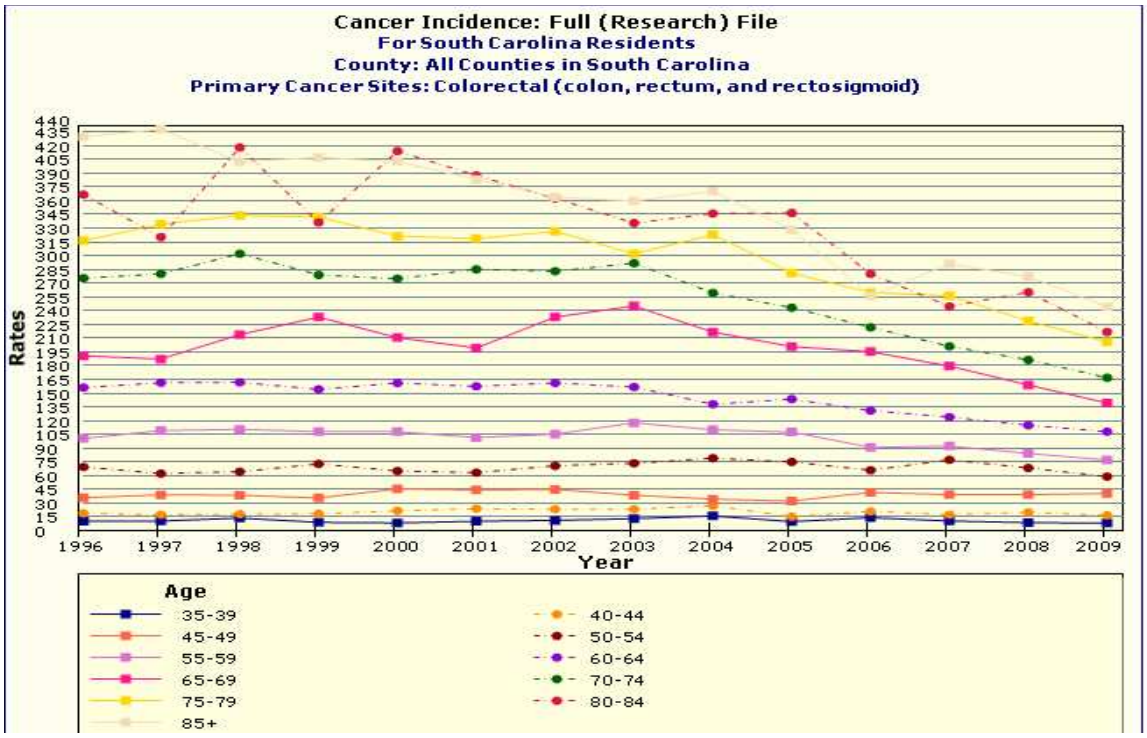

Figure 2-2 The trend line of colorectal cancer incidence in the past decade

	Cancer Mortality	
	For South Carolina Residents	

County: All Counties in South Carolina

Primary Cancer Sites: Colorectal (colon, rectum, and rectosigmoid)

	Age										
	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Year	Rates	Rates	Rates	Rates	Rates	Rates	Rates	Rates	Rates	Rates	Rates
1996	#	6.6	10.9	14.5	34.2	42.9	66.4	106.8	108.8	182.4	270.9
1997	#	5.1	12.0	18.9	33.2	40.7	63.8	91.2	123.0	157.6	246.7
1998	#	5.3	8.0	19.2	30.6	37.8	58.1	87.0	124.9	178.0	230.3
1999	#	6.8	10.3	21.4	30.1	49.6	67.6	80.4	123.1	166.5	252.8
2000	#	#	10.4	15.8	37.0	41.9	61.7	101.8	121.5	185.2	268.6
2001	#	8.6	11.5	16.9	23.8	39.5	75.7	79.3	129.9	153.5	229.2
2002	#	7.9	12.9	18.5	22.8	54.7	57.6	79.5	112.7	149.3	228.9
2003	#	7.3	13.4	14.7	26.7	46.8	57.5	84.4	102.6	161.6	222.7
2004	#	6.3	6.8	18.2	27.8	32.6	51.8	67.0	106.1	136.4	194.9
2005	#	5.7	12.7	15.1	26.1	37.5	59.2	60.6	106.5	145.3	231.0
2006	#	4.7	10.0	17.1	30.8	45.1	65.9	74.0	102.1	134.0	158.9
2007	#	#	8.7	13.7	25.3	44.3	50.7	67.8	113.4	84.4	172.4
2008	#	5.5	11.7	18.2	24.6	27.9	49.6	78.1	82.4	110.2	195.0
2009	#	#	10.9	17.9	26.2	35.4	40.4	58.8	81.0	118.3	167.0

*Rate: Crude Rate calculated per 100,000 population

Figure 2-3 Colorectal cancer mortalities in the past decade

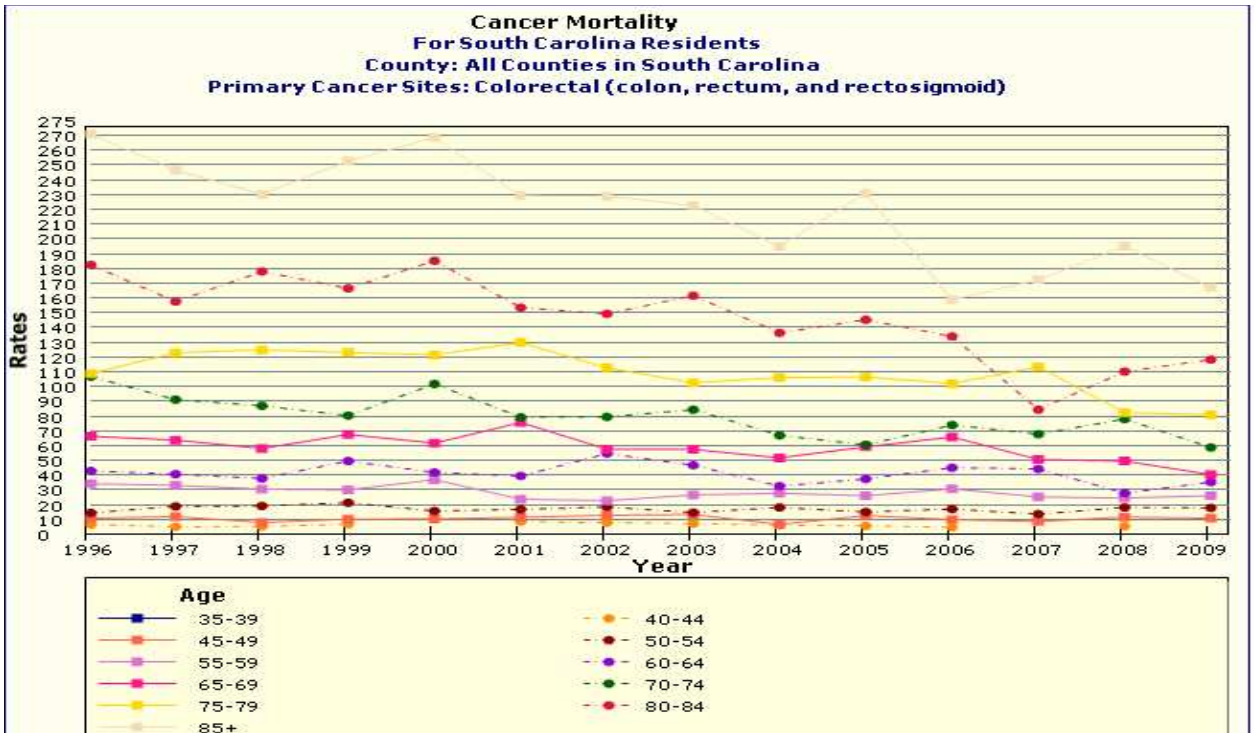

Figure 2-4 The trend line of colorectal cancer mortality in the past decade

The U.S. Preventive Services Task Force (USPSTF), the American Cancer Society (ACS), the National Comprehensive Cancer Network (NCCN), and the U.S. Multi-Society Task Force (MSTF) recommend periodic screenings of the average-risk population to prevent CRC, which includes men and women aged over 50 years with no history of adenomas, colorectal cancer, inflammatory bowel disease, and family history (USPSTF 2008, Levin 2008, NCCN 2012). The USPSTF recommends routine CRC screenings with fecal occult blood test (FOBT), sigmoidoscopy, or colonoscopy for adults aged 50-75 years. Between 76 and 85 years old, routine screening is not recommended, but it can be provided as required based on specific clinical considerations. For patients older than 85 years, CRC screening is not recommended (USPSTF, 2008).

2.3.2 High-risk persons

Asymptomatic individuals with a family history are categorized as high-risk for colorectal cancers. This group of persons is recommended to have screening at an earlier age than the average-risk group. The American College of Gastroenterology (ACG), the ACS and the NCCN have updated standards of the high-risk population and the recommended screening guidelines (Levin 2008, Rex 2009, NCCN 2012):

> *Persons with single first-degree relative with CRC or advanced adenoma diagnosed at age < 60 years or two first-degree relatives with colorectal cancer or advanced adenomas will be considered as high risk population, and are recommended to have colonoscopy screening every 5 years beginning at the age of 40 years, or 10 years younger than the age at diagnosis of the youngest affected relative. Or, with personal history of adenoma/sessile serrated polyps, colon cancer, or inflammatory bowel disease (i.e., ulcerative colitis, Crohn's disease) additional screenings are recommended.*

Other persons defined as high-risk have one of two hereditary syndromes (Byers 1997):

- Familial Adenomatous Polyposis syndromes (FAP)

  People with this condition develop hundreds of colorectal polyps and will almost certainly develop colorectal cancer unless the colon is removed.

- Hereditary Non-Polyposis Colorectal Cancer syndromes (HNPCC)

  HNPCC has been classically defined as colorectal cancer in three or more family members, two of whom are first-degree relatives of the third, involving people in at least two generations, and with at least one person diagnosed with colorectal cancer before age 50 years.

HNPCC, also known as the Lynch syndrome, accounts for approximately 5% of new cases of CRC each year (Winawar 1997).

Persons with a family history of hereditary syndromes, with relatives who received diagnoses of colorectal cancers at an early age, with two or more affected relatives, or with persistent ulcerative colitis have a high risk of colon cancers. The risk is especially high among younger persons (40-59 years old), but not associated with individuals after 60 (Fuchs et al 1994). Other principal risk factors include a history of colorectal cancers or adenomas in a first-degree relative, a personal history of large adenomatous polyps or colorectal cancers, and a prior diagnosis of endometrial, ovarian, or breast cancers (Rustogi 1994, USPSTF (Baltimore), 1996). Based on an ACS report in 1981, the high-risk population was described as (Eddy, 1981):

> *"Persons with familial polyposis, Gardner's syndrome, ulcerative colitis, a history of polyps or prior colon cancer, and a family history of cancer of the colon or rectum"*.

2.4 Early CRC detection and management

CRC is highly curable if detected in an early stage through routine screenings of the colon/rectum. When polyps/adenomas are detected and removed in the early developmental course, the 5-year relative survival rate is 90% (CDC 2011).

Among the screening methods, the effectiveness of the screening tool for detecting neoplasia lesions is critical. Theoretically, sensitivity is defined as the ability of the tool to identify true positives among all positives. In case of CRC, sensitivity is the percentage of people who have neoplastic lesions who are correctly identified by the screening tool as having the condition. Sensitivity is highest for colonoscopy, followed

by flexible sigmoidoscopy, followed by fecal tests, Hemoccult SENSA being the best followed by fecal immunochemical test, and lowest for Hemoccult II (USPSTF 2008). Specificity of the screening tool is defined as the ability to identify true negatives among all negatives. In case of CRC, specificity is the percentage of people with no neoplastic lesions who are correctly identified as clear. Specificity is highest for colonoscopy as well, followed by flexible sigmoidoscopy, then Hemoccult II, which is also approximately equal to fecal immunochemical test, and lowest for Hemoccult SENSA (USPSTF 2008).

One randomized clinical trial study in 1993 exploring the effect of FOBT screenings on CRC mortality for up to 13 years of follow-up reported that the annual FOBT group had the highest 13-year survival rate, with a 33% reduced mortality from colon cancers compared to the control group, and almost double the reduction observed in the biennial FOBT group (Mandel et al 1993). Although observational studies have reported incidence/mortality reductions associated with screening colonoscopy and polypectomy (Winawar et al 1993, Zauber et al 2012), less than half of the US screening-eligible population is covered by screening (Meissner et al 2006, Seeff et al 2004). Research has shown the effect of early detection and the removal of precancerous lesions through screening on CRC incidence and mortality reduction in the United States (Edwards et al 2010, Center et al 2009, Chu et al 1994).

Less than 40% of colorectal cancers are detected at an early stage (CDC 2011). According to the National Health Interview Survey (NHIS) in 2005, only 50% of U.S. people aged 50 to 75 years had received a colorectal cancer screening. Colorectal cancer

screening take up rate remains low and there is still a big gap to fill given that the target rate in the Healthy People 2020 is 70.5%.

Except for patients with bowel symptoms, the physician recommendation/referral is a required precondition for CRC screenings. Although Medicare coverage of colonoscopies since 2001 reduced the racial disparity in colonoscopy screenings between older Whites and Blacks (Shih et al 2006), studies suggest that physician recommendations are less frequent for Blacks than for Whites both in the general population, and among Medicare beneficiaries (Klabunde et al 2006), which translates to a lower screening rate among Blacks. The low take up rate and the disparity in the access of screening could be a potential reason for Blacks having a relatively high CRC incidence (Rex 2004, Daguise et al 2006).

2.5 History of CRC screening in the US

Before 1980, the American Cancer Society (ACS) recommended that people aged over 40 years should be screened with the annual sigmoidoscopy. The digital proctoscope and occult blood examinations were urged to be included in the regular health checkups for adults over age 40 by the ACS (Eddy 1980). Based on an ACS report in 1981, those at high risk were recommended to have more "*frequent*" and "*intensive*" examinations starting at an earlier age (Eddy, 1981). In a June 1992 meeting, revisions were made by the National Board of Directors of the American Cancer Society to the guidelines for asymptomatic individuals (Levin et al 1992):

1. Sigmoidoscopy, preferably flexible, for persons aged 50 and older, males and females, every three to five years.

2. "Fecal Occult Blood Test (FOBT)" substituted for "stool guaiac slide test" every year for individuals age 50 and over.

The ACS also made a revision to recommendations for the high-risk population at this meeting in June 1992 (Table 2-1) (Levin & Murphy 1992):

1. If first-degree relatives have a CRC diagnosis at an age less than 55 years, a colonoscopy or a double-contrast barium enema (DCBE) was recommended every 5 years starting at age 35 – 40 years.
2. If family members have a history of familial adenomatous polyposis, early flexible sigmoidoscopy is required.
3. If family members have a history of hereditary nonpolyposis CRC, early initiation and more intense colonoscopy screening is required.

Table 2-1 American Cancer Society Recommendations for the Early Detection of Colon Cancer in Asymptomatic Persons (1992)

Test or Procedure	Population		
	Sex	Age	Frequency
Sigmoidoscopy, Perferably Flexible	Male & Female	50 and over	Every 3 to 5 years
Fecal Occult Blood Test	Male & Female	50 and over	Every year
Digital Rectal Examination	Male & Female	40 and over	Every year

Source: Levin B, Murphy GP. Revision in American Cancer Society Recommendations for the Early Detection of Colorectal Cancer. CA Cancer J Clin. 1992; 42(5): 296-9.

Although FOBT alone is shown to have a significant effect on CRC mortality reduction (Mandel 1993), the 1997 ACS Clinical guidelines (Table 2-2) had an additional recommendation of "sigmoidoscopy screening every 5 years to complement the annual FOBT" (Byers 1997), due to later findings from RCT studies that about one third to one half of mortality reduction observed from FOBT may be attributed to colonoscopies (Lang 1994), and to substantial risk reduction conferred by sigmoidoscopies (Selby 1992, Newcomb 1992). The ACS recommends sigmoidoscopy screenings every 5 years in addition to the annual FOBT to intensively monitor the descending colon.

Table 2-2 The 1997 ACS colorectal screening guidelines (Byers 1997)

Average risk people (Single first-degree relative diagnosed with CRC, or adenomas after age 50, or no first-degree relative, or those without any personal or family history of CRC or adenomas)	Screening by either one of methods: 1. Annual FOBT with sigmoidoscopy every 5 years. 2. Annual FOBT with colonoscopy every 10 years. 3. Annual FOBT with DCBE every 5 to 10 years.
Moderate risk people (People who are diagnosed as having adenomatous polyps)	1. Remove adenomatous polyp at the procedure, followed by surveillance in 3 years. 2. If the original polyp was smaller than 1cm/non-villous pathology and the 3-year surveillance is negative, then back to average risk pool. 3. If the original polyp was larger than 1cm or villous pathology, the surveillance should be repeated every 5 years.
High risk people	1. If FAP confirmed, consider colectomy. 2. If HNPCC confirmed, colonoscopy every 2 years until age 40, every year thereafter.

In 1996, the USPSTF first published the guidelines for colorectal cancer screenings with these screenings were fecal occult-blood tests or sigmoidoscopies (USPSTF (AHRQ), 1996). Two years later, these screenings were covered by Medicare (http://healthservices.cancer.gov/seermedicare/considerations/testing.html); in 2000, most health plans covered at least one of four recommended colorectal cancer screening tests (Klabunde et al 2004). Medicare covered colonoscopies starting from 2001 (Shih 2006). In 2002, the USPSTF found strong evidence on the effectiveness of several screening methods in reducing mortality, such as 5-year sigmoidoscopy alone or in combination with the FOBT. However, the evidence that colonoscopies reduce mortality was still insufficient. The USPSTF also concluded that evidence was insufficient to assess the benefits and harms of computed tomographic colonography and fecal DNA testing as screening modalities for colorectal cancer (USPSTF 2002). In 2008, the USPSTF updated the recommendations for CRC screenings, recommending annual FOBT, 5-year

sigmoidoscopy, or colonoscopy, beginning at age 50 years and continuing until age 75 years (USPSTF 2008). In contrast to the 2002 USPSTF recommendation statements, the USPSTF updated the recommended screening eligibility from "individuals age 50 years and older" to "50 years and continuing to 75 years." Also, high-sensitivity FOBTs, sigmoidoscopies with interval FOBTs, or colonoscopies were recommended replacing the un-prioritized recommendations in 2002. For CT colongraphy and fecal DNA, the USPSTF concluded to maintain that there is insufficient evidence for recommendation (USPSTF 2008).

2.6 CRC screening methods

Screening tests for CRC prevention basically are categorized into 2 types, the fecal tests (such as the Fecal Occult Blood Test (FOBT)), and the full or partial structure tests, such as Digital Rectal Examination (DRE), sigmoidoscopy, barium enema, Computed Tomographic (CT) colonography, and colonoscopy.

There is insufficient evidence to determine which of these screening methods is preferable, or whether the combination of FOBT and sigmoidoscopy produces greater benefits than either test alone. Furthermore, there is insufficient evidence to recommend for or against routine screenings with digital rectal examinations, barium enemas, or colonoscopies, although recommendations against these screenings in average-risk persons may be made on other grounds (USPSTF (Baltimore) 1996). The USPSTF recommended 3 screening methods: 1) annual high-sensitivity fecal occult blood testing, 2) sigmoidoscopy every 5 years combined with a high-sensitivity fecal occult blood test every 3 years, and 3) screening colonoscopy at intervals of 10 years. Adherence to any of

the 3 methods is considered effective in detecting advanced adenomatous polyps and cancers at an early stage (USPSTF 2008).

The three CRC screening methods commonly used are – fecal occult blood test (FOBT), flexible sigmoidoscopy, and colonoscopy. All tests lead to colonoscopies if they are positive, which permits the visual detection of early stage cancers and removal of adenomatous polyps simultaneously during the procedure (Denis et al 2011).

2.6.1 Fecal occult blood test (FOBT) / Stool blood test

Stool blood tests are broadly known as guaiac fecal occult blood test (gFOBT) because the tests are designed to detect the occult blood in stool through guaiac method. CRC can be detected by finding occult blood in the stool, which is not readily visible. Also, the bleeding caused by cancers or advanced adenomatous polyps depends on the lesion size, friability, and location, and blood may might not be detected by the naked eye. But the problem with the stool blood test is its accuracy, because blood is unevenly distributed in the stool and the bleeding is intermittent. Further there are substances other than hemoglobin that can produce false positive results, such as iron in the diet (Eddy 1981). CRC screening cannot rely solely on FOBT results, but can use FOBT results as a preliminary test.

Besides false negatives caused by intermittent bleeding, faulty FOBT tests caused by diet should be avoided. Therefore, individuals are advised certain dietary limitations for two days before the stool blood test to avoid false positive results (most commonly caused by iron supplements and red meat) and false negative results (Vitamin C and citrus fruits) (Eddy 1981, Jaffe et al 1975, Garrick et al 1977).

Positive reactions on guaiac-impregnated cards, the most common form of testing, signal the presence of bleeding from premalignant adenomas and early-stage colorectal cancers (USPSTF (Baltimore) 1996).The stool blood test is far less likely to help prevent cancers compared to invasive tests such as flexible sigmoidoscopy or colonoscopy. To be effective, FOBT must be repeated at a regular interval, otherwise the protection is nil. When the test is positive, an invasive test, such as a colonoscopy, is needed (Levin et al 2008). If patients are not willing to repeat the FOBT or take the invasive test when the FOBT is abnormal, FOBT is ineffective and should not be recommended (Levin et al 2008). FOBT has very low test sensitivity (especially a single test) for detecting adenomas, and has a reasonable sensitivity for detecting colorectal cancers. However, regarding the program sensitivity (serial tests over time in a program), it is relatively high. Therefore, repeating testing each year is a very important key for ensuring the quality of FOBT (Levin et al 2008). In a randomized clinical trial of FOBT screening with a 13-year follow-up period, the results showed 33% reduction in colorectal cancer mortality, and better 5-year survival for those with annual FOBT screening (Mandel et al 1993).

Hemoccult, is the trademark for a guaiac reagent strip test for occult blood. Before the development of the Hemoccult, several chemical tests were used for blood stool test. These procedures require patients to have several samples of stool in cups or jars, which stand in the refrigerator for a couple days, which then have to be physically transported to the physician's office or the hospital. It is unpleasant for patients and for medical professionals who open the sample by the time of examination. Another problem for the guaiac fecal occult blood test is that guaiac is very sensitive to heat and light.

Due to the issue of intermittent bleeding of polyps and cancers, Hemoccult II Slides are designed so that patients can collect serial specimens at home from bowel movements over three days. This increases the probability of detecting hidden blood from polyps and cancer. After the patient prepares the Hemoccult II SENSA elite test, it may be returned in person or by mail to the laboratory, hospital or medical office for testing and interpretation. The test consists of two main components: 1) the test cards containing guaiac paper, 2) The Developer, a developing solution containing a stabilized mixture of less than 4.2% hydrogen peroxide and 80% denatured ethyl alcohol and enhancer in an aqueous solution. Research has shown that the rehydrated Hemocuult II slides show a high sensitivity in detecting CRC (92.2%) but disappointingly low specificity (90.4%), which causes too many colonoscopy referrals and produces high corresponding costs (Byers 1997, Mandel 1993).

A relatively new method for the fecal test is the fecal immunochemical test (FIT). FITs are highly specific in detecting human blood and in eliminating the dietary restrictions. Research on the sensitivity and specificity of detecting the advanced adenomas, however, is disappointing. Allison's (2007) study of three Northern Kaiser Permanente Medical Centers between April 1997 and October 1999 revealed that the sensitivity and specificity for advanced neoplasms in the left colon were only followed by colonoscopies within 2 years after the FOBT screening (29.5% for sensitivity and 97.3% for specificity).

2.6.2 Digital rectal examination (DRE)

The digital rectal examination is of limited value as a screening test for colorectal cancer. The examining finger, which is only 7-8 cm long, has limited access even to the

rectal mucosa, which is 11cm in length, where about one-sixth of the colon cancers occur (Eddy 1981, USPSTF (Baltimore) 1996).

A digital (finger) rectal examination is used to check for problems with organs or other structures in the pelvis and the lower belly. During the examination, the doctor gently puts a lubricated, gloved finger of one hand into the rectum. The doctor may use the other hand to press on the lower belly or pelvic area (Healthwise 2010). The results for DRE can be normal, where there are no problems such as organ enlargements or growths are felt, and vice versa. Growths such as hemorrhoids, polyps, tumors, or abscesses may be found in the lower rectum. Breaks in the skin around the anus (anal fissures) may be found; problems of the bladder may also be felt (Healthwise 2010). The DRE alone is not effective to check for colorectal cancers. If problems are found during a DRE, more advanced tests are needed, such as a sigmoidoscopy or a colonoscopy (Healthwise 2010).

There are no formal studies/reports for the effectiveness of DRE since the costs are small and its high safety feature, any benefits can be considered as worthwhile, the only potential harm is it might produce a false-positive results leading to other structure tests, such as sigmoidoscopies (Eddy 1980). Also, the DRE is not as effective as sigmoidoscopy because neoplasms can be hidden by mucus or any residual substances even within the area reached by exploring fingers (Eddy 1981).

2.6.3 Sigmoidoscopy

The sensitivity and the diagnostic yield of sigmoidoscopy screening varies with the type of instrument: the rigid (25cm) sigmoidoscope, the short (35cm) flexible sigmoidoscope, and the long (60cm) flexible fiberoptic sigmoidoscope (USPSTF

(Baltimore) 1996). The effectiveness of risk reduction for sigmoidoscopy has been widely documented (Lang 1994, Selby 1992, Mewcomb 1992).

i. Rigid sigmoidoscopy

The 25-cm rigid sigmoidoscopy was introduced in the 19th century but no longer used since 1982 (Eddy 1980, Mandel et al 1993). Theoretically, it can cover up to 25 cm of the colon, where about one-half to two-thirds of cancers and adenomatous polyps grow (Eddy 1981). There are pros and cons of rigid sigmoidoscopes. It allows direct visualization of the colon, biopsy, and removal of the suspicious lesions. Patient discomfort and the risk of perforation of the colon are problems to be considered, however (Eddy 1981). Due to patient discomfort and the development of new technology, the rigid sigmoidoscopy is no longer used. A retrospective study in 1992 on the effectiveness of rigid sigmoidoscopy showed that participants who had undergone one or more rigid sigmoidoscopy examinations within the past 10 years had only 30% of the risk of dying from distal colon or rectum cancers relative to those who did not (Selby 1992).

ii. Flexible sigmoidoscopy

The 35-cm flexible sigmoidoscope can visualize about 50-75% of the sigmoid colon and can detect about 50-55% of polyps (USPSTF (Baltimore) 1996). The 65-cm flexible fiberoptic sigmoidoscope enables a longer range visualization of the colon, however, the high cost and limited screening-only usage impedes its coverage in the United States (Eddy 1981). Men had a higher uptake rate of sigmoidoscopy than women (Meissner et al 2006). The detection rate of advanced neoplasia with sigmoidoscopy was three times higher than FOBT in an Italian randomized controlled trial (RCT) study (Segnan et al 2005). A randomized trial in the United Kingdom shows that a one-time

flexible sigmoidoscopy of adults aged 55-64 years reduced the incidence of colorectal cancer by 33%, and mortality by 43% (Atkin et al 2010).

Sigmoidoscopies can also produce false-positive results, primarily from polyps detected that are unlikely to become malignant during the patients' lifetime (USPSTF (Baltimore) 1996). It turns out that the majority of asymptomatic persons with colonic polyps discovered by routine sigmoidoscopic examinations will not develop into clinically significant malignancies during their lifetime. For these patients, interventions typically followed (i.e., biopsies, polypectomies, and frequent colonoscopies). Costly procedures, anxiety provoking, and potential harms are unlikely to make up for the clinical benefits of sigmoidoscopies (USPSTF(Baltimore), 1996). Flexible sigmoidoscopy was considered too expensive and specialized only for early detection usage (Eddy 1980).

Another disadvantage of sigmoidoscopy is the distribution of cancers in the colon. Studies indicated that the proximal colon cancer accounts for a significant portion of the colorectal cancers. The contribution of incident colon cancer in the proximal colon beyond the examination zone of sigmoidscopy is about 27% to 45% (Dinning 1994, Castiglione 1995, Lemmel 1996). The ratio of proximal cancer to total CRC is 0.338 among men and 0.421 among women (SEER CanQues 1973-2009).

A study explored the sites of primary CRC diagnosis from nine cancer registries between 1978 and 1988. It concluded that older population (70 years and older) has the greatest risk of CRC, and most commonly in the right colon (Rabeneck 2003). Although the incidence of CRC has steadily declined since 1975 (NCI 2012) due to increasing

aging population (65 years and older), the proportion of the population at risk of CRC is expanding with aging of the US population (Rabeneck 2003).

2.6.4 Barium enema

Barium enema is one variant of X-ray examination, and is of two types, single contrast barium enema (SCBE) and double contrast barium enema (DCBE).

Barium enema examinations have been shown to better identify most of the advanced, most likely incurable, carcinomas of the colon instead of the early, potentially curable carcinomas of the colon. Therefore, the routine use of barium enema examinations is not reliable and is recommended for discontinuation in the diagnostic evaluation of carcinomas of the colon (Gilbertsen et al 1979).

i. Double Contrast Barium Enema (DCBE)

During this procedure, the physician inserts a tube into the rectum, fills in barium sulfate, and drains its out, leaving a thin layer of barium on the wall of colon, and then air is filled in to define the outline of the colon. Then X-ray images from various angles are taken to better view the whole colon and detect abnormal growths (Byers 1997). A positive result in DCBE should be followed by a colonoscopy or a sigmoidoscopy (Byers 1997).

ii. Single Contrast Barium Enema (SCBE)

The difference between SCBE and DCBE is that the former fills the barium in the colon to outline the colon for detecting abnormal growths. The procedure time for SCBE is shorter than DCBE. SCBE is mostly performed for specific medical reasons or for older people who may not be able to tolerate the more time-consuming and uncomfortable DCBE procedure (Byers 1997).

The performance of barium enema varies by section of colon, and highest in the straight portions – descending colon (93%), transverse colon (89%), and ascending colon (88%); followed by the askew portions – the splenic flexure (86%), the hepatic flexure and the sigmoid flexure (83%). It is lowest in the globular portions – the rectum (77%) and the cecum (75%). The average sensitivity for cancer is 83%. In addition, the DCBE has better sensitivity than SCBE, with 0.78 being odds ratio of missed cancers (Rex, Rahmani, Haseman 1997).

Overall, barium enemas are less expensive than colonoscopies. But colonoscopies enable direct visualization of the colon and removal of the suspicious lesions directly for biopsy with a one-time procedure if the bowel prepared properly. Colonoscopies have a higher sensitivity and are least likely to miss cancers, with an odds ratio of 0.25 relative to barium enema (Byers 1997, Rex, Rahmani, Haseman, 1997).

2.6.5 CT colonography

CT colonography also known as “virtual colonoscopy” or “X-ray colonoscopy”, which is noninvasive and based on radio-imaging. Carbon dioxide gas is introduced into the rectum to inflate the colon, and computer tomography pictures of the colon are taken by a moving scanner. The pictures taken are integrated using computer programs to create a two- or three-dimensional virtual viewing of the colon (Wilkins 2008; NDDIC 2008). Nationally, according to a report using the National Health Interview Survey (NHIS) 2010, the use of CR colonography is extremely low (1.3%) (Shapiro 2010). CT colonography shows high sensitivity and specificity for detecting large polyps (>10 mm) but low sensitivity for smaller polyps. Pickhard and colleagues (2003) studied 1,233 asymptomatic individuals undergoing same-day CT colonography and colonoscopy using

the segment unblinded method, which declares the findings of each section of the colon after it is examined by colonoscopy. They reported a sensitivity of 93.8% and 96% specificity on polyps of 10 or more millimeters; however, when polyps more than 6 millimeters were included the sensitivity reduced to 88.7%, and specificity to 79.6%. Macari and colleagues (2005) using 2-dimensional views also reported the sensitivity of CT colongraphy reduced significantly with polyp size (>10 mm: 100%, 6-9 mm: 52.9%, 1-5 mm: 11.5%).

Besides the effectiveness of CT colonography in identifying a polyp, a study in 2008 of 2,531 asymptomatic individuals from 15 facilities using per-patient analysis showed that the sensitivity for polyps of 10 millimeters was 90% and 86% for specificity, which is consistent with the previous literature. However, the positive predictive value of CT colonography is 23% (with a high negative predictive value of 99%), which means the accuracy of diagnosis is extremely low, and the ability of radiologists identifying even the large polyps (>10mm) is an issue (Johnson 2008).

Interpreting CT colongraphy in non-academic environments has little evidence and poor outcomes. Burlings et al. (2006) investigated the interpretation accuracy of 13 radiologists from seven non-academic facilities in comparison with that of trained radiographic technicians and experienced academic radiologists. They showed that the individual accuracy highly varies among 13 non-academic radiologists (range from 53% to 93%). In addition, there are significant differences between these groups: the mean accuracy is highest in experienced academic radiologists (88%), followed by non-academic radiologists (75%), and lowest in trained radiographic technicians (56%). Because of the low sensitivity in small and/or diminutive polyps, it is not a valuable

method for the prevention of CRC. Also, the use of CT colonography has not been recommended by USPSTF due to the insufficient evidence on its benefits and harms (USPSTF 2008).

2.6.6 Colonoscopy

Evidence has shown that the rate of colonoscopy screening is increasing concurrent with a decline in the uptake of other screening tests. In the 2005 National Health Interview Survey (NHIS) study, the colonoscopy take up rate exceeded FOBT and sigmoidoscopy (Meissner et al 2006). This study also concluded that a large proportion of the take-up rate increment since 2000 was due to the increase in colonoscopy. The American College of Gastroenterology (2000) recommendation that colonoscopy was the preferred colorectal cancer screening test for average-risk individuals could have been the reason for the large increase in colonoscopy rate (Rex 2000).

Colonoscopy, which requires sedation and often involves the use of a hospital or surgery center suite, is more expensive than other screening tests and has a higher risk of sedation and procedural complications (USPSTF (Baltimore 1996)). Retrospective studies have reported the effectiveness of colonoscopy is superior to sigmoidoscopy because approximately 60% to 70% of proximal cancers are not accompanied by neoplasms in the distal colon, which is the examination zone of sigmiodoscopy (Dinning 1994, Castiglione 1995, Lemmel 1996). Therefore a large proportion of test-negatives with sigmoidoscopy are not CRC-free. Proximal cancers account for 40% of the colon cancers. These cancers remain undetected despite preventive screening using sigmoidoscopy.

Research has shown that individuals with any distal adenomatous polyps were more likely to have advanced proximal neoplasia, the risk of advanced proximal neoplasia is significantly enhanced by increasing severity of distal adenomatous polyps (compared to patients without distal polyps). The relative risk of harboring distal hyperplastic polyps, distal tubular adenomas, and advanced distal polyps were 2.6, 4.0, and 6.7, respectively. Colonoscopy is irreplaceable among individuals without any distal adenomas, because 2.7% had advanced proximal neoplasias (Lieberman 2000; Imperial 2000).

The effectiveness of colonoscopy in reducing CRC incidence and mortality depends on how thoroughly visualization of the entire colon is achieved, the diligence in examining the mucosa, and patient acceptance of the procedure (Denis et al 2011). Colonoscopy has an advantage over barium enemas because it can be both diagnostic and therapeutic. Its advantage over flexible sigmoidoscopy is that it can access the entire colon while flexible sigmoidoscopy can only access the distal colon (Robertson et al 2006). The use of colonoscopy in colorectal cancer screening has increased concurrent with the decline in barium enema and flexible sigmoidoscopy (Robertson 2006; Klbunde 2005).

In conclusion, FOBT serves as the most cost-effective in screening methods. Barium enema, although cheaper than colonoscopy, is not useful for therapeutic purpose. Sigmoidoscopy has similar features and is cheaper than colonoscopy. However, there is ample documentation of missed suspicious lesions beyond the examination range of sigmoidoscopy. Colonoscopy represents the most effective choice of screening method

because it enables both detection and removal of suspicious lesions in on step. Even with the price issue, screening with every 10 years makes it an attractive screening tool.

2.7 Quality of colonoscopy / effectiveness

Colonoscopy is currently regarded as the gold standard of colorectal cancer screening by removing polyps/adenomas (colonoscopic polypectomy) because there is strong evidence that polyps/adenomas are the precursor of colorectal cancer (Enterline et al 1967, Grinnell et al 1958, Kalus et al 1972, Muto et al, 1975). The effectiveness of colonoscopy screening in preventing the development of colorectal cancer depends on the quality of examination. A successful colonoscopy can be identified by the rate of polyps/adenomas detected and the cecum intubated by the performer's series of procedures. Achieving 95% cecal intubation rate is a recommended benchmark (USPSTF). Missed polyp/adenoma rates are documented at 6% to 27% depending on the size of polyps/adenomas (Hixson et al 1990, Rex et al 1997, Leaper et al 2004). Evidence regarding the effectiveness of colonoscopy has caused other screening methods to decline, and resulted in it being considered as the preferred method of CRC screening (Rex 2000, Rex 2009, Davila 2006, NCCN Clinical practice guidelines in oncology 2011).

With increasing use of colonoscopy, measuring colonoscopy quality is becoming inevitable to ensure its competent performance. Generally, the cecal intubation rate is the most commonly studied quality indicator, but is a very inadequate indicator. Poor quality colonoscopies limit its CRC protection potential.

Adenoma detection, which has a documented association with CRC prevention and is the main goal of colonoscopy, should be a key indicator for studying colonoscopy

quality. A wide range of ADR among endoscopists has been documented (Millan 2008, Barclay 2006, Wilkins 2009, Rex 2001). This implies that the quality of colonoscopies varies widely, which could severely undermine its efficacy in CRC protection. Another major issue is the specialist capacity to meet the demand for colonoscopy screening if it becomes the primary screening method. Some studies have explored the effectiveness of colonoscopies performed by trained PCPs.

A meta-analysis of 12 eligible studies of colonoscopies performed by PCPs with a total of 18,292 patients reported an adenoma detection rate of 28.9%. The authors concluded that the performance of PCPs can meet the professional Societies' recommended standards (Wilkins 2009). The association between colonoscope withdrawal time and adenoma detection rate was also studied, Barclay (2006) indicated that physicians who had a mean withdrawal time of less than 6 minutes (among patients with no polyp removed) had an overall adenoma detection rate of 11.8%, while it was 28.3% for physicians whose mean withdrawal time was more than 6 minutes (without a polyp found). This statistically significant difference persists in the mean number of adenomas detected per subject, which were 0.17 vs. 0.61, respectively.

Rex et al (2001) videotaped 10 procedures performed by 2 colonoscopists and got them reviewed/scored by 4 experts based on four quality criteria related to colonoscopic withdrawal technique. They reported that technique does matter to the adenoma miss rate, which could be further associated with the potential cancer protection efficacy of colonoscopy screening. Winawer et al (1993) conducted a prospective clinical trial of colonoscopy effectiveness (the National Polyp Study) over a mean follow-up of 5.92 years, documented a CRC prevention rate of 76% following colonoscopic adenectomy. A

retrospective cohort study under an academic medical center setting reported a 100% of CRC protection over a mean follow-up of 5.34 years (Imperiale et al 2008). Zauber et al (2012) reported a 53% reduction in CRC mortality over a mean follow-up of 15.8 years per subject.

Owing to its potential of a high level of CRC prevention, high-quality colonoscopy is recommended to be performed every 10 years for average risk population beginning at the age of 50 years, and 45 years for Blacks (Rex 2009). Colonoscopy every 5 years at the age of 40 years, or 10 years before the earliest age of CRC diagnosis in a first-degree relative (high risk population) is recommended.

2.7.1 Procedure quality indicators

The National Comprehensive Cancer Network (NCCN) guidelines for CRC screening indicate that to evaluate the quality of colonoscopy, the following indicators should be considered (NCCN 2011):

- Cecal intubation rate
- Withdrawal time
- Adenoma detection rate
- Appropriate intervals between endoscopic examinations based on family and personal history, and the number and histological type of polyps at last colonoscopy
- Minor and major complication rates
- Pre-procedure medical evaluations
- Appropriate bowel preparation instructions

The cecal intubation rate and withdrawal time can be signal indicators for the quality of colonoscopy screening. Cecum intubation is set as the standard for a completed colonoscopy since the cecum is considered as the beginning of the large bowel. Reaching the cecum implies that the colonoscope was inserted all the way through the colon and rectum starting from the anus. In addition, withdrawal time (an average of 6 minutes or more when no polyps are removed) can be the surrogate for the percentage of colonic mucosa inspected (Barclay et al 2006, Rex 2006).

i. Cecal intubation rate

Three types of cecal intubation rates are defined, the unadjusted rate, the MSTF-adjusted rate, and the circumstance-adjusted rate. The unadjusted rate measures the cecal intubation status for all study-eligible screenings. The MSTF-adjusted rate, according to the MSTF recommendations is calculated by excluding incomplete colonoscopies due to severe colitis or poor preparation (Rex 2002). The circumstance-adjusted rate further excludes procedures in which the endoscopist made a clinical decision not to attempt to reach the cecum because of severe diverticulosis, vital sign instability during the procedure, obstruction or stricture, or because it was a therapeutic procedure without the goal of cecal intubation, such as colon decompression, treatment of active lower gastrointestinal bleeding, removal of a previously discovered lesion, stent placement, etcetera (Aslinia 2006). The cecal intubation rate is the most commonly measured indicator and relatively easy to report as a preliminary quality indicator of colonoscopy (Aslinia 2006, Rex 2006, Rex 2002, Lieberman 2007).

ii. Procedure time

Colonoscope insertion time and withdrawal time are considered as appropriate quality indicators (Lieberman 2007, Rex 2009), especially when the ADR is low (Rex 2006). Longer withdrawal time is shown to be associated with a better polyp detection rate (Rex 2000, Sanchez et al 2004). In contrast, shorter withdrawal time periods were associated with higher polyp miss rates (Rex 2000, Sanchez et al 2004). Also, the insertion time, which is the examination time period from insertion to the anus to the visualization of cecum, is documented to be associated with the adenoma detection rate (Benson et al 2005). In a series of 550 average-risk consecutive colonoscopy screenings performed by academic gastroenterologists, the ratio of insertion time to withdrawal time was found to be positively related to the adenoma detection rate (Benson et al 2005).

2.7.2 Outcome indicators

i. Polyps

A polyp is an overgrow tissue with part of its body attached to the site of origin. Studies suggest that about 1 in 4 colon cancers develop from polyps (Morson 1974, Muto et al 1975,Jass 1989), it takes averagely 10-15 years from a polyp to become a cancer by progression through the Stages of an adenoma (Morson 1974). Identifying and removing polyps during the screening exam has been considered the key to reduce the risk of developing colon cancers (Pabby 2005, Rex 2002, Rex 2006). When there are multiple polyps detected, they are most likely to be found in the ascending and transverse colon (Correa et al 1977).

ii. Adenomas

The adenoma detection rate has lately attracted attention as a key quality indicator because the main goal of colonoscopy is to search for and remove all adenomas to

prevent the CRC (Rex 2006, Lieberman 2007, Rex 2009). A positive correlation is documented between withdrawal time and adenoma detection rate (Barclay 2006, Barclay 2008, Millan 2008). Barclay et al (2006) study reported wide variation in the mean number of adenomas per subject, in the adenoma detection rate, and in the mean withdrawal time. With a mean withdrawal time more than 6 minutes, the physician's detection rates of adenoma in their patient panels are higher than physicians with less than 6 minutes by around two and half folds (11.8% vs. 28.3%). The mean number of adenomas detected per subject for physicians with a mean withdrawal time more than 6 minutes are nearly 4-fold larger than physicians with less than 6 minutes (0.17 vs. 0.61). In another study Barclay et al (2008) studied the association of a minimum of 8 minutes withdrawal time (mean for the endoscopist), and found that compared with endoscopists with a mean withdrawal time less than 8 minutes, those with at least 8 minutes have significantly higher rates of any neoplasia (37.8% vs 23.3%) and advanced neoplasms (6.6% vs 4.5%). More importantly, among the advanced neoplasms found by those with at least 8 minutes withdrawal time, 25% were 9 mm or less while for those with less than 8 minutes, only 10% were 9 mm or less. This indicates that the more gradual inspection is, a higher number of smaller, potentially deadly neoplasms are found, some of which are missed otherwise.

The adenoma detection rate shows a negative association with the risk of interval cancer. With a higher adenoma detection rate at colonoscopy, the hazard ratio of interval cancer for those physicians' patients was reduced (Kaminski 2010). Compared with physicians having an ADR of more than 20%, the hazard ratio of interval cancer for

physicians with ADR less than 11% is 12.50, and about 11 for ADRs 11%-14.9% and 15.0–19.9% (Kaminski 2010).

2.8 Factors associated with CRC screening rates and adenoma rates

2.8.1 Patient factors

The factors associated with the uptake of CRC screening tests are widely documented, and are similar to other prevention screenings, including race/ethnicity, age, education, income, having health insurance coverage, and having a usual source of care. One study evaluated the 1987, 1992, 1998, 2000, and 2003 National Health Interview Survey (NHIS) findings (Meissner 2006). Use of CRC screenings was higher among individuals with private health insurance, a usual source of care, and who were older, White, married, having higher annual household income, and higher education (Meissner 2006). The prevalence of adenomatous polyps was positively associated with age, but increasing age was not associated with an increase in polyp size (Rickert et al 1979, Hughes 1968). The incidence of colorectal cancer is higher in males than in females (Globocan (IARC) 2008, Jemal 2011, Meissner et al 2006). Nationally, the CRC incidence for Blacks is 12.3% higher than Whites (Rex et al 2004). In South Carolina, the disparity is worse; Blacks have approximately 30% higher incidence rates than Whites (Daguise et al 2006). Overall, men have a higher screening take up rate than women (Green et al 1999, Brawarsky et al 2003, Etzioni et al 2004). In 2000, women had a greater use of FOBT than men, but men had a higher endoscopy rate than women (Seeff et al 2004). Men had a higher uptake rate of sigmoidoscopy than women (Meissner et al 2006).

The CRC death rate remains highest among Blacks (Gargiullo et al 2002). This may due to lower screening rates in this group (Thornton et al 2007; Zimmerman et all 2006; James et al 2006; Vlahor et al 2005; Shokar et al 2007; Shokar et al 2008; Zhao et al 2006). At a population-level, reduction in CRC incidence rates are about 50% less among Blacks than among Whites (Gargiullo et al 2002). CRC incidence rates among Whites have been decreasing since 1985, and Blacks rates have remained relatively unchanged (Gargiulo et al 2002; Jemal et al 2005; Ries et al 2000). Further, Blacks are at higher risk of being diagnosed at an advanced or metastatic stage, where Whites are more likely to be diagnosed at a non-advanced or localized stage (Weir et al 2003; Daguise et al 2006).

Studies have demonstrated that Blacks suffered a higher proportion of adenomas in the proximal colon than Whites, which in other words, more proximal adenomas in Blacks that are missed by sigmoidoscopies (Thornton 2007, Johnson 1986, Ozick 1995, Mayberry 1995, Nelson 1997, Thomas 1992, Rex 2000). What makes worse is Blacks are documented to be less frequently screened by colonoscopy but sigmoidoscopy (Peterson 2008).

2.8.2 Physician factors in screening coverage

Although the effectiveness of colonoscopy screening in preventing CRC is documented, screening colonoscopy coverage in the US population remains low. This is partly due to the low endoscopy capacity due to a shortage of providers. Currently, gastroenterologists are the main type of physician who performs screening colonoscopies. The capacity for screening colonoscopies by gastroenterologists shows a big gap between the supply of colonoscopies and the eligible population that needs to be screened.

According to the American Board of Internal Medicine, there are only 13,968 certified gastroenterologists in the US, annually increasing by460 gastroenterologists (ABIM 2013). The colonoscopy capacity is only 63% (14.2 millions) of the estimated annual 22.4 million colonoscopies (Seeff 2004), and the increase of the aging population, including baby boomers, widens the gap. To cover 100% of all age-eligible colonoscopies, an estimated additional 7,340 gastroenterologists are needed (Vijan 2004). In South Carolina, an estimated 484,000 colonoscopies are needed annually to screen the average-risk population older than 50 years; however, the current colonoscopy capacity that could be provided if needed is 157,000, which shows an unmet need of two-thirds of screening colonoscopies, which stands in the way of realizing the CRC prevention benefits of colonoscopies (Seeff 2006). Similarly in Tennessee, the current estimated colonoscopy capacity based on gastroenterologists' numbers alone is for 84,000 non-Medicare insured patients per year to be provided screenings, whereas an estimated 950,000 to 1.1 million additional screening colonoscopies are needed (Cattau 2010). An important point to consider is that when the supply of gastroenterologists is limited, especially in rural areas, colonoscopies provided by trained PCPs could be a solution to fill the gap. However, the widespread belief is that because gastroenterologists are specialists, they will have superior performance than non-gastroenterologists. One study showed that non-gastroenterologists detected colorectal cancer in 87% of patients with a true cancer compared to 97.3% of true cancer detected by gastroenterologists (Rex 1997). However, the distribution of incomplete colonoscopies among these groups was not reported, which may influence the interpretation of outcomes. Another factor noted by the author affecting the difference in cancer detection sensitivity of gastroenterologists

compared with non-gastroenterologists was the lack of information in the latters' training in colonoscopy. Some of them were self-trained and others had variable (not documented) levels of colonoscopy training.

Two Canadian studies reported that persons with colonoscopies performed by non-gastroenterologists had a higher risk of subsequent CRC compared to those performed by gastroenterologists. One retrospective cohort study of colonoscopies conducted in Canada during 1992-1997 with up to a 15-year follow-up of 110,000 patients reported higher risks of interval cancer after a negative colonoscopy when patients were provided the service in a hospital setting by non-gastroenterologists compared to gastroenterologists (40% higher for general surgeons and 30% higher for internists and family physicians), but no difference was found in physician office settings (Rabeneck 2010). Another study matched colonoscopies done in 1997-2002 with the Ontario Cancer Registry and also showed higher odds of CRC for non-gastroenterologists compared with gastroenterologists among both men (OR=1.77) and women (OR=1.85) (Bressler 2007).

In contrast, other research has shown that trained PCPs' performance is comparable or better than the current benchmarks of quality set by the US MultiSociety Task Force (USMSTF) for gastroenterologists, from both the patient safety and adenoma detection perspectives (Wilkins 2009, Xirasagar 2009). Pierzchajlo (1997) reported a 91.5% cecal intubation rate and 17.8% ADR among 751 colonoscopies performed by family physicians, which meets the USMSTF recommendation that ≥90% of colonoscopies should achieve cecal intubation consistently. This study's ADR

approaches the ADR standards of ≥15% for women and ≥25% for men (Rex, Bond, Winawer 2002).

Another series of 200 colonoscopies performed by family physicians documented highly competent performance by trained family physicians with 96.5% cecal intubation rate and 22.5% neoplastic polyp detection rate (Edwards 2004). A retrospective case review of 731 colonoscopies performed by two family physicians credentialed for sigmoidoscopy and initially supervised by their referral gastroenterologist reported that they had a ADR of 27.2% in men and 21.4% in women, though the cecal intubation rate was close but lower than the USMSTF standard (89.5%) in their starting phase (1996-1998) and improved to meet the USMSTF standard (94.6%) at a later phase (1999-2001) (Newman 2005).

Another potential reason to consider PCPs for screening colonoscopies is that racially concordant PCPs may be more acceptable to black patients due to historic race relations and trust issues. Black patients have a higher incidence of CRC (about 16%) and 47% higher CRC mortality than white patients. The age of CRC onset is earlier among black patients, and CRC is more aggressive among younger age groups. Therefore it is important to increase screening colonoscopy rates among black patients. A previous study on the black PCPs trained in colonoscopy screening showed that they have a significantly positive impact on their black patients' colonoscopy screening rates, 66% higher than those untrained in colonoscopy screening (9.4% before starting training vs. 48.3% after the PCP started doing procedures). For black patients of trained PCPs, they are 5 times more likely to get a colonoscopy than white patients in the post training period; during the same period, their white patients' colonoscopy screening rates remain

unchanged. In comparison, black patients of black untrained PCPs showed a change over the same period from 10.4% to 38.7%, and the white patients from13.3% to 13.2% (Xirasagar 2011).

Comparing estimates of the number of gastroenterologists needed with the newly qualifying gastroenterologists each year, it will take approximately fifteen years to fill the colonoscopy capacity gap (Vijan 2004, ABIM 2013). Having primary care physicians perform screening colonoscopies may be a solution to cover the unscreened population, which is 60% of currently eligible population (Seeff 2004). However, the training of primary care physicians in colonoscopy remains very low. Only 4% of graduating family medicine residents applied for colonoscopy credentialing in 2002 even though about half of the residency programs offered colonoscopy training to family medicine residents, and only 18% of these programs had anyone registering and getting trained (Wilkins 2004). While research has documented that "trained" primary care physicians can provide competent and safe colonoscopy (Edwards 2004, Newman 2005, Wilkins 2009), there is no documentation of the training process or of the protocols used by high-performing PCPs. This study presents the protocol that was consistently used to train primary care physicians, which requires a 2-person technique, and includes other elements to maximize colon surface inspection and to minimize the likelihood of missing polyps.

2.8.3 Procedure protocol features in colonoscopy quality – 2-person technique

Physician fatigue is reported to be a likely factor in adenoma detection rates, particularly as the day progresses. Physicians' ADRs for afternoon procedures were significantly lower than those of their own morning procedures (25.3% vs. 29.3%,

p=.008), with a 20% higher chance of detecting an adenoma in morning procedures relative to afternoon procedures (Sanaka 2009).

The phenomenon of potentially lower quality output due to fatigue is not limited to physicians. A study of the judicial system on the association between the likelihood of favorable parole ruling in the morning compared with the afternoon showed that judges were more likely to issue a favorable parole ruling in the morning than in the afternoon and immediately after the lunch break than in the later afternoons. The authors suggested that mental fatigue level may be less at the beginning of the work day and after a short break to eat a meal or rest (Danziger 2011). In the case of colonoscopies, studies on the presence of second observers in colonoscopy procedures are shown to increase the colonoscopy quality in terms of adenomatous polyp detection. A retrospective study of the involvement of an attending gastroenterologist and a gastroenterology (GI) fellow reported that those procedures have significantly better ADR (37% vs. 23%, p<.01). Similarly the mean number of adenomas detected per subject (MNA) was higher (0.56 vs. 0.3, p<.05), and the total number of adenomas detected among patients with adenomas was higher (procedures with 2 adenomas found was 13.1% vs. 5.6%, P<.05; 3 and more adenomas found: 6% vs. 1.6%, p<.05) (Rogart 2008). These procedures had the trained GI fellow performing the procedure while the attending gastroenterologist was present in the room throughout watching the video screen and physically took over the scope for the difficult or complicated situations encountered, letting the fellow complete the remaining procedure after assistance was no longer needed. The procedure itself was performed by one person (either the fellow or the attending gastroenterologist) at any given point. Another retrospective study that was not limited to screening colonoscopies

reported that the rate of small (<5mm) adenoma detection was significantly higher when a fellow performed the procedure and the attending gastroenterologist observed the screen, compared to the attending gastroenterologist performing the procedure without a GI fellow present (25%vs. 17%, p=.001) (Buchner 2011). The authors specified that more experienced fellows (e.g., the second-year and third-year fellows) can perform the entire procedure with attending physicians' oversight.

A reduced likelihood of missing lesions due to visual fatigue is one advantage of having a 2-person technique where an additional person watches the video screen. In a recent prospective study, having a dedicated endoscopy nurse observe the screen while the attending physician performed the colonoscopy significantly increased the number of polyps detected per patient (adjusted OR=1.26) compared to the attending physician performing without a nurse observer. This effect was sustained for non-pedunculated polyps, showing that the nurse observer contributed to the detection of flat/sessile polyps (Aslanian 2013).

Improvement in adenoma detection with a second participant in the procedure is further influenced by the experience level of the performer. Peters et al (2010) studied a similar protocol where fellows performed screening colonoscopies under the supervision of the attending physician. They compared these procedures with the GI attending physician performing alone. Similar to other studies, they reported that with a second practitioner involved in the procedure, tadenoma detection improved (odds ratio (OR) =1.32). Further, this improvement was correlated with the fellowship year of the GI fellow, the rate of adenoma detection for third-year fellows being almost double that of first year fellows (OR =1.7). In a prospective study in Korea, six hospitals followed a

protocol of having an endoscopy nurse administering the sedation under the endoscopist's supervision and also serving as a second observer of the video screen for the colon inspection. As an observer, the endoscopy nurse assisted in identifying suspicious lesions through the screen, with no hands-on assistance involved. With an endoscopy nurse as a second observer, the likelihood of finding a polyp/adenoma increased (OR =1.58 for polyp, and 1.47 for adenoma), an effect that was confined to fellows performing their 150th-500th procedures (OR =2.07) and this effect was not observed for senior attending gastroenterologists (Lee 2011).

However, another non-randomized prospective study conducted at a single-center reported no significant difference in polyp detection rates with additional observers (single-person: 32%, dual-observers: 33%) and in adenoma detection (19.3% vs 14.9%) (Eckardt 2009). This study shared similar design elements as other studies: the trainee performs the procedure while the attending physician supervises and provides rescue assistance. The dual-person procedures showed a similar PDR as the single person procedures, but showed a lower ADR because a higher proportion of diminutive (<5 mm) hyperplastic polyps were removed in the dual-person groups.

To our knowledge, research on the "2-pearson technique" thus far has studied similar protocols, namely, having a second person as "observer". In our study setting, the protocol uses a hands-on 2-person technique to compensate for the lack of specialist training of the PCPs. In this protocol, a trained endoscopy technician advances the colonoscope, and the PCP works the tip of the scope for polyp search and removal. This method has the additional advantage of avoiding missing polyps due to physician's motor fatigue particularly of the left or non-dominant hand. It confers the dexterity of two

"right" hands (of the two participants) for polyp search and removal, and further, ensures more persons watching the video screen for polyps. Additionally prior research on the 2-person technique protocols involved a second observer with the polyp search limited to the phase of withdrawing the scope. Our study center requires gradual insertion and withdrawal of the colonoscope with polyp search and removal both during insertion and withdrawal to maximize coverage of all mucosal surfaces and to minimize chances of "losing" a polyp that may be encountered during insertion but not traced during the withdrawal phase, which is the phase when gastroenterologists typically perform polypectomy. Because of these differences, the 2-person technique protocol in our study setting is unique and when applied to PCPs, the question arises, does this technique enable the quality of PCP-performed colonoscopies to be comparable to specialist-performed colonoscopies. This study addresses this research question.

2.8.4 Sedation during colonoscopy

Colonoscopy can be painful and stressful to patients. The fear of discomfort may prevent some persons from accepting CRC screening. Concerns regarding unsedated colonoscopy may provide a negative perception of colonoscopy to the public, and hence, diminish the acceptability of colonoscopy, impeding the early detection of adenomatous lesions and thereby, limiting CRC protection (Rex & Khalfan 2005, Sipe, Rex , Latinovich 2002). Pain control is a priority for patients. Deep sedation puts patients into an unconscious state during the procedure and relieves patients of the anxiety of the impending discomfort. Deep sedation is therefore recommended, based on evidence that patients experienced little/no pain and that the endoscope is more readily advanced

through the colon when the patient is deeply sedated (Rex & Khalfan 2005, Sipe, Rex, Latinovich 2002, Heuss 2004).

Sedation for routine colonoscopy is either moderate or deep. Moderate sedation induces a state of drowsiness or sleep during most of the procedure, and is commonly performed with a benzodiazepine alone or with narcotics/opioids. Patients with moderate sedation can be readily awakened when spoken to or touched (American Society of Anesthesiologists (ASA). Deep sedation is a state where patients are asleep throughout the procedure with little or no memory, commonly induced with propofol. Patients with deep sedation breathe slowly, requiring oxygen at times, and sleep deeply until the medication wears off (ASA).

Physical status is evaluated before sedating patients to assess fitness for the procedures as per the ASA Physical Status Classification System (Source: The Cleveland Clinic Foundation). This was developed in 1963 and is conventionally used:

- ASA PS1: the normal healthy patient (no organic, physiologic, or psychiatric disturbance; excludes the very young and very old; healthy with good exercise tolerance)
- ASA PS2: patients with mild systemic disease (no functional limitations; has well-controlled disease of one body system; controlled hypertension or diabetes without systemic effects, cigarette smoking without chronic obstructive pulmonary disease (COPD); mild obesity, pregnancy)
- ASA PS3: patients with severe systemic disease (some functional limitations; has a controlled disease of more than one body system or one major system; no immediate danger of death; controlled congestive heart failure (CHF), stable

angina, old heart attack, poorly controlled hypertension, morbid obesity, chronic renal failure; bronchospastic disease with intermittent symptoms)

- ASA PS4: patients with severe systemic disease that is a constant threat to life (has at least one severe disease that is poorly controlled or at the end-stage; possible risk of death; unstable angina, symptomatic COPD, symptomatic CHF, hepatorenal failure)
- ASA PS5: moribund patients who are not expected to survive without the operation (not expected to survive > 24 hours without surgery; imminent risk of death; multiorgan failure, sepsis syndrome with hemodynamic instability, hypothermia, poorly controlled coagulopathy)
- ASA PS6: a declared brain-dead patient whose organs can be removed for donation purposes

The efficacy of sedation is often assessed by the observer's assessment of the patient on the alertness/sedation scale (Table 2-3) (Chernick 1990):

Table 2-3 the observer's assessment of the patient on the alertness/sedation scale

Composite score	Responsiveness	Speech	Facial Expression	Eyes
5	Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis
4	Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (<1/2 eye)
3	Responds only after name is called loudly or repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and marked ptosis (>1/2 eye)
2	Responds only after mild prodding/shaking	Few recognized words	/	/
1	Does not respond to mild prodding/shaking	/	/	/

Source: Chernick DA, Gillings D, Laine H et al. Validity and reliability of the observer's assessment of alertness/sedation scale: study with intravenous midazolam. J Clin Psychopharmacol 1990; 10: 244-51.

2.8.5 Sedation type and colonoscopy quality

There is little documentation of associations between sedation type and colonoscopy procedure quality and outcomes. The available evidence is mixed. Two major quality indicators, the procedure completion rate (cecal intubation), and adenoma detection rate show positive associations with deeper sedation in some studies (Chelazzi 2009, Radaelli 2008, Wang 2010), and show no significant associations in other studies (Paspatis 2011, Rex 2012, Metwally 2011, Bannert 2012).

Chelazzi et al (2009) reported that procedures carried out under propofol sedation have a 100% completion rate, while non-sedated procedures had only 91.1% completion rate ($p<.05$). The median insertion time was 9 minutes for the propofol group and 10.5 minutes for the non-sedated group ($p=.0086$). In the same study, the total procedure time mirrored the insertion time pattern (15 min. vs. 19.5 min., $p=.09$). Because bowel preparation status significantly influences cecum intubation, Radaelli et al (2008) studied

the association between contribution of bowel preparation status, and sedation type. When compared to excellent bowel preparation, good bowel preparation is around 40% less likely to intubate the cecal (OR =0.586; poor: 0.246, inadequate: 0.013). Regarding sedation type, propofol-sedated procedures had the highest odds of cecal intubation (OR =2.355), followed by the benzodiazepines and opiate regimen (OR =2.128), followed by the benzodiazepines alone (OR =1.46), compared to the no sedation group (OR =1). This study also explored the associations with polyp detection, and reported similar direction of associations to cecal intubation. The likelihood of detecting any polyp was highest in the propofol group (OR =1.317) compared to the non-sedated group, followed by benzodiazepines alone (OR =1.121), and there was no significant difference between no sedation and the benzodiazepines and opiate group (OR=1.105, p>.05).

A study from Greece using midazolam and pethidine sedation for all procedures, distinguished between moderate sedation (MS) and deep sedation (DS) based on dosage. They reported no significant difference in polyp detection rates (MS: 61.5%, DS: 63.6%), adenoma detection rates (MS: 59.5%, DS: 60.4%), and right colon polyp detection rates (MS: 34.4%, DS: 36.8%) (Paspatis 2011). Another study showed no difference between procedures sedated by propofol and by midazolam/fentanyl in adenoma detection rates (OR=1.07 (95%CI: 0.91, 1.26 for propofol)) (Metwally 2011). A retrospective cohort study across 72 facilities reported that with moderate sedation, the polyp detection rate was higher than deep sedation (37.7% vs. 34.1%, p<.0001). However, the advanced adenoma rate was higher for deep sedation (7.2% vs. 6%, p=.01), the effect being greater in facilities where deep sedation procedures exceeded 10% of its total procedures (7.5% vs. 5.7%, p=.003) (Wang 2010).

While evidence for procedure completion and detection of adenomatous polyps is mixed, sedation use has shown higher patient satisfaction on pain control. Propofol sedated patients were the most consistent in reporting no pain (102 out of 102 patients), while the midazolam group (17 out of 23 patients) and no sedation group (11 out of 22 patients) had very low percentages indicating no pain (Gasparovic 2003).

The duration over which the patient achieves adequate sedation (onset time) and the duration in which the patient remains drowsy after the procedures (recovery time) remain important. When compared with moderate sedation, the deeply sedated group showed a shorter sedation onset time (time to sedate). Ulmer et al (2003) reported a mean sedation time of 2.1 minutes for propofol and 6.1 minutes for midazolam/fentanyl ($p<.0001$). For recovery time, studies have reported 7 to 16.5 minutes for propofol, 27.5 minutes for midazolam/ fentanyl, 20 minutes for midazolam alone, and 33 minutes for midazolam/meperidine (Sipe 2002, Gasparovic 2003, Ulmer 2003). Deep sedation by propofol is significantly time saving as both procedure time and recovery time are shortened, compared to moderate sedation by any other sedative or combination of sedatives. However, the mixed results for the other quality indicators suggest the need for studies in settings where other protocol-related and procedure-related elements that influence these quality indicators are fixed, enabling unambiguous determinations of the sedative effect on these indications. A major limitation in comparing the various studies in sedation type vs. adenoma rate is the wide (undocumented) variation in all the other elements of the colonoscopy protocol and procedure times that would impact the ADR. Our study setting compared patients sedated with propofol (all procedures starting from April 2006) with midazolam-meperidine procedures pre-April 2006.

2.9 Significance of the research

This research is based in a setting where all the remaining colonoscopy protocol elements other than the two study items were fixed throughout the study period. This allows the specific protocol elements (2-person technique or sedation type) to be accurately evaluated for their impact on ADR and other metrics of colonoscopy quality.

An earlier study of 10,958 colonoscopies performed by 51 PCPs between October 2002 and November 2007 in this setting documented the high quality of screening colonoscopies performed by PCPs, all of whom were required to use the 2-person technique along with polyp-maximizing protocol. The quality indicators in that study cohort exceeded the ASGE-recommended standards of quality. The cecal intubation rate was 98.1%, which is higher than the ASGE standard of 95%. The adenoma detection rate was 30%, 34.6% in men and 25.4% in women, which are both above the ASGE standard (men ≥25%, women≥15%). The minimum withdrawal time recommended by the ASGE when no polyps are found is 6 minutes compared to the mean withdrawal time of 8 minutes for no polyp procedures in a subset of the current study cohort (Xirasagar 2010). Other research has also documented that trained PCPs' performance quality can meet the current benchmarks of quality established by the US MultiSociety Task Force on colonoscopies for gastroenterologists on both patient safety indicators and adenoma detection rates (Pierzchajlo 1997, Edwards 2004, Wilkins 2009, Newman 2005).

It is possible that racially concordant PCPs may be more acceptable to black patients due to historic race relations and mistrust of black providers. A study of the patient panels of these PCPs showed high colonoscopy completion rates of 48.3% among

black patients of black PCPs trained in colonoscopy screening, showing a five-fold increase compared to before training rates (Xirasagar 2011).

Literature regarding the relationship between propofol sedation and colonoscopy quality has focused largely on shorter onsets of sedation and shorter recovery times (Sipe 2002, Gaspsarovic 2003, Ulmer 2003) and on better pain control (Gasparovic 2003) and procedure completion (Chelazzi 2009, Radaelli 2008). The evidence regarding propofol contribution to the detection of adenomatous polyps remains mixed, with no resolution in sight due to a lack of standardized procedure protocols across procedures with potential confounding.

In short, the associations of the study center's innovative hands-on 2-person technique with adenoma detection rates, and the associations of propofol sedation with clinical quality indicators need rigorous study. Additional indicators such as likelihood of finding smaller adenomas, and anatomic locations have not been studied so far. This study will test hypotheses regarding the associations of 2 protocol elements, 1) 2-person technique, and 2) propofol sedation, with adenoma detection rates, numbers of adenomas detected, procedure times, polyp sizes and polyp locations. The purpose is to further clarify whether these two protocol elements improve effectiveness in adenoma detection and therefore, effectiveness in preventing further colorectal cancer.

Chapter 3 METHODS

This chapter discusses the methodology used in this study. Sample selection and statistical analysis methods used to achieve the study objectives will be displayed in this chapter.

3.1 Research questions and Hypothesis

An earlier study documented the high quality of screening colonoscopies performed by PCPs in this study setting without assessing the role of the 2-person technique in the results (Xirasagar et al 2010). In that study a subset of the current series showed a cecal intubation rate of 98.1% , an adenoma detection rate of 30% (34.6% in men and 25.4% in women), and a mean colonoscope withdrawal time (when no polyps were found) of 8 minutes. The quality indicators in this study cohort exceed the ASGE-recommended standard (Xirasagar 2010). Studies regarding the 2-person technique have been limited to having a second observer in the procedure room (Rogart 2008, Buchner 2011, Lee 2011). The 2-person technique element of the protocol in this study refers to having an endoscopy technician provide “hands-on” assistance to the endoscopist throughout the procedure in advancing and withdrawing the endoscope. In this study setting, all 54 PCPs who performed colonoscopies were required to use the 2-person technique. Among specialists/experts, 2 of them chose not to use the two-person technique. We studied the quality indicators in these three groups of procedures.

The documented literature regarding propofol sedation has focused on sedation onset and recovery time (Sipe 2002, Gasparovic 2003, Ulmer 2003), or better pain control (Gasparovic 2003) and procedure completion (Chelazzi 2009, Radaelli 2008), while the effect on detection of adenomatous polyps remains controversial.

This study will address the following research questions:

1) Is the quality of colonoscopy performance by PCPs using a hands-on 2-person technique similar to that of specialists using a routine protocol (one person technique)?
2) Within specialists, does the 2-person technique improve the adenoma yield and other indicators of better adenoma clearance?
3) Does propofol sedation improve the quality of colonoscopy performance outcomes?

For all questions, we will study the indicators of adenoma detection rates, numbers of adenomas detected, procedure times, polyp sizes particularly small adenoma detections, and polyp anatomic locations.

3.1.1 Research questions

The literature and explanation documented in the previous chapters map out the research questions:

1) Does the protocol element, 2-person technique, improve screening colonoscopy quality in terms of the adenoma detection rate, the number of adenomas, the size of polyp, and the location of polyp?
2) Is sedation type associated with performance quality in terms of the adenoma detection rate, the number of adenomas, the size of polyp, and the location of polyp?
3) Is there an association between procedure time and 2-person technique?

4) Is there an association between procedure time and sedation type?

3.1.2 Study hypotheses

1) Hypotheses related to the hands-on 2-person technique:
    a) The likelihood of detecting a/an polyp/adenoma by PCPs using 2-person technique and specialists using 2-person technique is higher than specialists using 1-person technique. (In this center, no PCP was permitted to perform with the solo technique)
    b) More polyps/adenomas are detected by 2-person technique PCPs and specialists than solo-performing specialists.
    c) More number of small polyps will be detected by 2-person technique PCPs and specialists than that of solo performing specialists.
    d) The likelihood of detecting a right colon polyp will be higher for 2-person technique PCPs and specialists than solo-performing specialists.
2) Hypotheses related to sedation type:
    a) Propofol sedation procedures are more likely to be associated with a/an polyp/adenoma detected than Midazolam-meperidine sedation procedures, and the increased likelihood will be observed for large and small polyps.
    b) Propofol sedation procedures are more likely to be associated with detection of right colon polyps than Midazolam-meperidine sedation procedures.
3) Hypotheses related to procedure duration:
    a) Procedure time is longer with the 2-person technique than with 1-person technique after controlling for number of polyps found.

b) Procedure time is longer with the 2-person technique specialists than with 1-person technique specialists after controlling for number of polyps found.

4) Hypothesis related to the fourth research question:

a) Propofol is associated with longer procedure time than Midazolam-meperidine as patient will be well sedated and the endoscopist can take time to complete the procedure carefully.

3.2 Methodology

3.2.1 Data source

The setting of this study is a state-licensed ambulatory surgery center for endoscopy, South Carolina Medical Endoscopy Center (SCMEC), in Columbia, South Carolina. To begin with, the Center trains PCPs with didactic instruction followed by a colonoscopy simulation model, and then initiates clinical procedure training with patients. The Center requires hands-on supervision and participation by the specialist for the first 140 procedures (the ASGE-prescribed level for gastroenterology residents to be credentialed for independent colonoscopy performance, Faigel 2007). The specialist/expert (gastroenterologist/colorectal surgeon) initially provides the PCP with hands-on assistance to push the scope and assist with tip manipulation and polypectomy up to 140 procedures. The frequency of manual assistance by the expert/specialist is gradually reduced, and transitioned to the verbal assistance to navigate difficult colonic segments and/or diverticula. Finally, post-training the PCP performs without specialist oversight, and the specialist intervention is limited to therapeutic assistance when called upon to remove advanced adenomas, polyps at difficult locations, control bleeding,

and/or manage spasms. The Study Center's training of PCPs was started in 2001, and 54 PCPs were trained as of February 4, 2011.

The SCMEC protocol requires a 2-person technique for all PCPs regardless of training status, i.e., even after training. All PCPs have to bring their patients to the SCMEC and cannot perform the procedure at their own offices. The SCMEC innovative protocol has the following unique features: a) (After training procedures are completed) An endoscopy technician advances the colonoscope while the physician manipulates the scope tip for polyp search and removal. This method minimizes the missing of polyps due to physician's motor fatigue, confers the dexterity of two "right" hands for polyp search and removal, and ensures more persons watching the video screen for polyps. b) Since April 2006, propofol sedation occurs instead of the conventional midazolam-meperidine combination sedation, c) Gradual insertion and withdrawal for polyp search and removal maximizes the coverage of the colonic mucosal surface, d) A minimum of 3 persons watch the video-screen to identify abnormal mucosa and polyps to assist the performing physician.

This is a retrospective study of all screening colonoscopies performed between September 4, 2001, through February 4, 2011, at the SCMEC. Over the study period, 59 physicians performed the procedures included. The Center's innovative protocol of 2-person technique was consistently complied by 57 physicians (54 PCPs and 3 specialists), PCPs are defined as those with family medicine, internal medicine, pediatrics or obstetrics/gynecology specializations. Two specialists (one colorectal surgeon and one general surgeon during one year) did not follow the 2-person technique.

3.2.2 Approaches to test the study hypotheses

We first tested the effect of sedation type on 59 physicians performance in terms of procedure time, cecum intubation, polyp and adenoma detection before (Midazolam-meperidine sedation) and after the execution of propofol sedation at a procedure cut point of April, 2006. Our hypothesis regarding the effect of the two-person technique features of the new protocol is that specialists should perform better than PCPs within the two-person technique procedures in terms of our quality indicators. To validate the hypothesis, quality indicators were compared of two specialists who did not follow the innovative protocol with three specialists who did, and PCPs (all 2-person technique). The effect of the 2-person technique within specialists was also evaluated. Two specialists not following the new protocol were compared with the remaining specialist endoscopists who followed the protocol.

The hypothesis regarding sedation type is that patients sedated by propofol should have better outcomes than those sedated by Midazolam-meperidine in terms of our selected quality indicators. To validate the hypothesis, the quality indicators of patients sedated by Midazolam-meperidine were compared with patients sedated by propofol.

The quality indicators of interest were procedure time, cecum intubation rate, likelihood of polyp detection and adenoma detection, the number of polyps/adenomas detected per screened person (MNP/MNA), polyp size, and detection of right-sided polyps. MNP and MNA were to show the total polyps/adenomas each physician found among their procedures calculated into a mean per screened person. The size of the polyp is the diameter, categorized as ≦5mm, 6 – 9 mm, or 10+ mm. Polyp location refers to anatomic location in the colon, left colon or right colon.

3.2.3 Regression Models

In selecting the multivariate analysis method, we had to ensure that the statistical analyses address non-independence of data due to clustering of patients within physician. Random-effect regression models address such clustering by incorporating a random effect for physicians and fixed effects for other covariates in the model. Alternatively, fixed-effects regression models incorporate a fixed effect for each physician, though this approach is more difficult to translate to data from other physicians. Finally, generalized estimating equations (GEE) modeling, assumes a specific correlation structure for the repeated measures data per physician. We modeled our data using GEE Models for which we assumed an exchangeable correlation structure. This structure assumes that any two observations from different physicians are uncorrelated, and any two observations from the same physician are the same value (no matter which physician). Our inference was based on statistics constructed from the modified sandwich variance estimator so that inference is robust to any within-physician correlation structure no matter how different from exchangeable. GEE was used because it accommodates within-physician correlation without focusing attention on that aspect of the data analysis. The within physician correlation is treated as an ancillary problem to be accounted for but not of profound interest. When using the exchangeable correlation structure for a linear model, the regression parameters of the GEE are algebraically equivalent to the correlation among patients within a physician panel. The same is not quite true for inference of regression parameters from the logistic GEE and logistic random effect models. GEE was determined to be the optimum modeling tool for these analyses.

a. Testing the association of a protocol feature with procedure time

GEE is used to model covariates in a generalized linear model with either unknown or expected correlation between outcomes. It is described as follows:

> *"It is a method of analyzing correlated data that otherwise could be modeled as a generalized linear model. GEEs have become an important strategy in the analysis of correlated data. These data sets can arise from longitudinal studies, in which subjects are measured at different points in time, or from clustering, in which measurements are taken on subjects who share a common characteristic such as belonging to the same litter."* (SAS online support)

Linear GEE regression was used to study the association between the procedure time and our variables of interest. The hypotheses tested using this regression method were as follows:

1) Patients subjected to the 2-person technique will have longer procedure times than under the 1-person technique after controlling for the number of polyps found. (This is because having an extra person hands-on serves to reinforce the Center's requirement of gradual insertion and withdrawal of the colonoscope to carefully work with the folds and search for polyps covering all possible mucosal surfaces.)

2) Within the 2-person technique group, PCPs will have longer procedure times than specialists after controlling for the number of polyps found. (This is expected because PCPs may have less skill than specialists in navigating the colonoscope)

3) Propofol-sedated patients will have longer procedure times than midazolam-meperidine-sedated patients after controlling for the number of polyps found. (This is likely because of better pain control under propofol. Thus the need to rapidly wind down

the procedure due to patient discomfort should be less common with propofol than with Midazolam-meperidine.)

b. Testing the likelihood of finding any polyps/adenomas/advanced neoplasms

Logistic GEE regression, a regression model for dichotomous dependent variables, was used to test the hypotheses regarding PDRs, ADRs, and advanced neoplasms detection rates. Hypotheses tested by GEE were:

1) 2-person technique procedures will be more likely to have at least one polyp/adenoma/advanced neoplasm detected than 1-person technique procedures,
2) Within the 2-person technique group, PCPs will be as likely as specialists to detect at least one polyp/adenoma/advanced neoplasm,
3) Propofol sedated patients will be more likely to have at least one polyp/adenoma/advanced neoplasm detected than the Midazolam-meperidine sedated group.

c. Testing the likelihood of finding additional polyps and adenomas, and the likelihood of finding progressively smaller polyps as well as the likelihood of right colon polyps

Ordered logistic GEE regression, a regression modeling method for ordinal dependent variables was used to test whether the likelihood of finding each additional polyp/adenoma in a patient, the likelihood of finding progressively smaller polyps, and the likelihood of finding a right colon polyp, increased with the use of the 2-person technique.

Our study hypothesized that compared with the 1-person technique, 2-person technique procedures are more likely to be associated with at least one polyp found

relative to zero polyps. This relationship remains the same when moving to the next comparison level, i.e. finding 2 polys vs. only one polyp. Likewise, for the size of the polyp, we hypothesize that compared to the 1-person technique, 2-person technique procedures are more likely to be associated with a small (≦5 mm) polyp found relative to a medium (6-9 mm) polyp. The relationship is hypothesized to be similar for the next level of polyp size, that compared to the 1-person technique,2-person technique procedures are more likely to be associated with a medium (6-9 mm) polyp found relative to a large (10+mm) polyp. Finally, for polyp anatomic location, we hypothesize that relative to the 1-person technique procedures, 2-person technique procedures are more likely to be associated with at least one right colon polyp found relative to only left colon polyps found.

Regarding sedation type, the assumptions is that compared to midazolam-meperidine sedation, propofol-sedated procedures are more likely to be associated with at least one polyp found relative to zero polyps. The same association carries to the next level as explained above. As for polyp size, we hypothesize that compared to the midazolam-meperidine sedation, propofol-sedated procedures are more likely to be associated with detecting small (≦5 mm) polyp(s) relative to medium (6-9 mm) polyps. The relationship remains the same on the next level, which means compared to the midazolam-meperidine sedated group of procedures, the propofol sedated procedures are more likely to be associated with finding a medium (6-9 mm) polyp found relative to finding only a large (10+ mm) polyp. Lastly, compared to midazolam-meperidine

sedation, propofol-sedated procedures are more likely to be associated with finding at least one right colon polyp relative to only left colon polyps found.

3.3 Preparing and cleaning the data

3.3.1 Data extraction and sample data

A total of four datasets without personal identifying information on all colonoscopies conducted during September 4, 2001 and February 4, 2011were extracted into Microsoft EXCEL from the SCMEC computers into University of South Carolina (USC) computers. The four datasets were physician dataset, procedure dataset, polyp dataset, patient dataset (appointment and race gender information stored in Mysys and FoxPro at SCMEC).

The physician dataset includes the information related to the physician, such as the physician name, the gender, the race, age as of 2007, the year of graduation, the area of specialty, and board certification. The procedure dataset includes the clinical procedure notes: time of scope insert and time out of anus, the time of staring the withdrawal (when cecal was viewed), was the sequential number of this procedure under the training process, and the section of the colon up to which the colonoscope was advanced to for the patient in this procedure, the procedure date, and was this procedure performed by a specialist or a PCP etc.

The polyp dataset contains the histology of the polyp, was this polyp an adenoma, the size of the polyp, the hyperplasia percentage/severity of the polyp, dysplasia level, was the polyp removed, how was the polyp removed, and location of the polyp. The patient dataset contains data on patient age as of the procedure date, gender, race, and date of birth.

3.3.2 Linking, clearing and acquiring missing data

All datasets were linked by the procedure identifier (ID). In addition to the procedure ID, there is a patient ID linking multiple procedures for the same patient. In this study, we used data on only the first screening colonoscopies of each patient (initial colonoscopy).Over 10,000 patient charts were reviewed to fill in missing data and to resolve typographical errors/discrepant information between the datasets. Updates were carried out in the summer and fall 2011, and the summer and fall of 2012. Variables corss-checked were patient date of birth, procedure date, bowel preparation status, procedure time points (time of insertion, viewing cecum, and withdrawal), and all variables of the polyp data to verify a polyp characteristics.

After merging the above datasets and missing data/discrepant data entered, duplicates were removed, cancelled patient appointments were removed, procedures that were performed by the SCMEC director at a neighboring hospital were removed, and variables were renamed and labeled. Some variables were recoded/extracted from text fields, some of the data categories were recoded, such as dysplasia level recode, which accommodated information from two variable fields, pathologytext and path_results. In October 2012, two rounds of manual review of text fields and recoding of polyp_results were done to retrieve missing data for 4,746 polyps due to the mis-categorized information by SCMEC staff in a different variable field in the polyp dataset. After cleaning the procedure and polyp datasets, we summarized the polyp data by procedure and linked the summarized polyp information to procedure dataset by procedure ID for studying indicators of procedure performance.

3.4 Inclusion and exclusion criteria

We selected only screening colonoscopies of average risk population consistent with the objective of this study. Therefore, we first excluded the second and later procedures for each patient. After extracting initial procedures, patients aged less than 30 years or older than 90 years were excluded because these age groups are not the target of routine screening as per USPSTF screening guidelines. In addition to age exclusion, we excluded patients with prior history of colon/rectum resection because they are no longer in the average risk pool once they were diagnosed as colon/rectum related diseases.

3.5 Sample selection

Retrospective data on all 26,523 colonoscopy procedures performed from September 4, 2001 to February 4, 2011 were evaluated for selection of screening colonoscopies (the first colonoscopy of the patient). A total of 5,611 second and later procedures were excluded. Of the 20,912 patients with an initial colonoscopy, we excluded patients less than 30 years of age or older than 90 years (342 patients) and those with prior history of colon/rectum resection (30 patients). Figure 3-1 shows the sample selection flow chart with exclusions by the above criteria leading up to the study sample of 20,540 consecutive colonoscopies conducted by 54 PCPs and 5 specialists during the study period of September 4, 2001 through February 4, 2011.

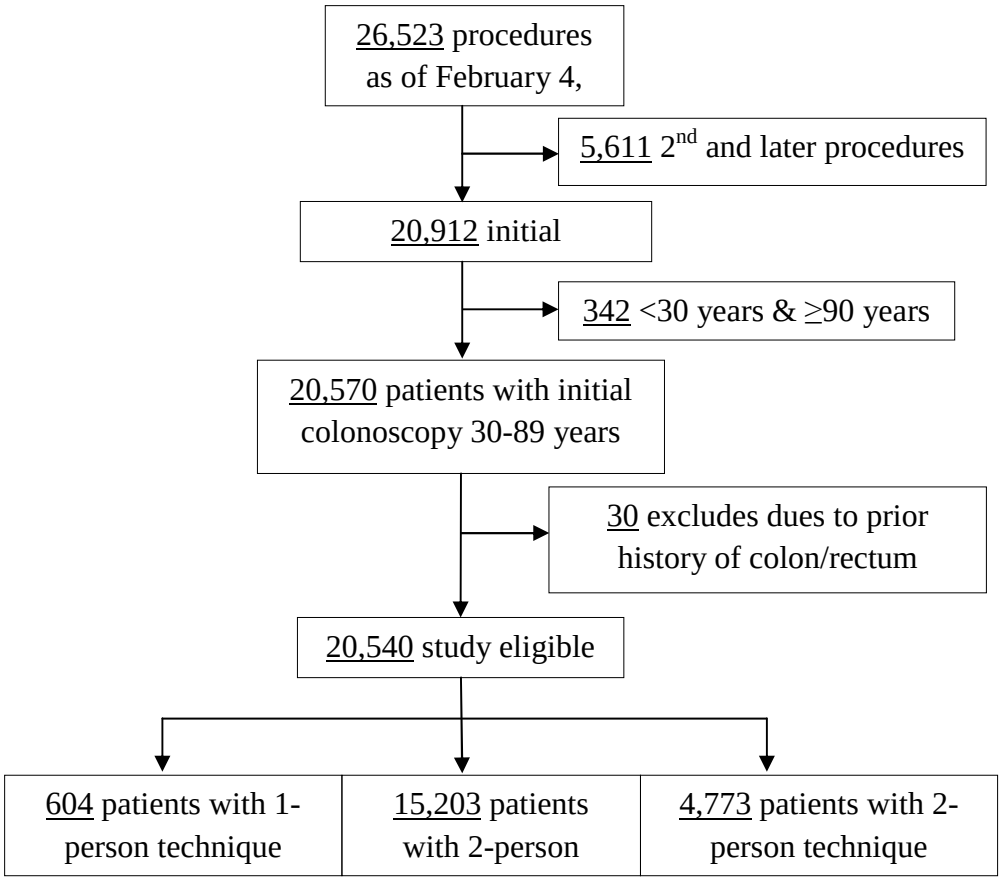

Figure 3-1 Sample Selection Flowchart

3.6 Defining the key variables of interest

To identify patients with and without polyps, we summarized polyps by *patientid* in polyp dataset. Below are list of our study variables:

- Patient age
- Patient race
- Patient gender
- Sedation type
- Protocol type
- Polyp
- Adenoma

- Number of polyp found per subject
- Number of adenoma found per subject
- Procedure time
- Bowel preparation

Quality indicators

The procedure time, named *Timeproc* is calculated from the original downloaded fields from SCMEC – *starttime* and *endtime*. Time during the day was extracted as *starttime* and *endtime* usng the raw variables *ScopeIn* and *Scopeout*. The interval in seconds between *ScopeIn* and *ScopeOut* was taken and divided by 60 to calculate *TimeProc* in minutes.

For polypsize, variable *polypsizemm* is used to categorize polyps into three groups, "≤5mm", "6-9mm", and "10+mm". For polyp location, *PolypLocation* was the original variable used to create the intermediate variables. Polyp location was defined as proximal if located in the cecum, ascending colon, hepatic flexure, and transverse colon, and as distal if located in the splenic flexure, descending colon, sigmoid colon, or rectum. For those located in the proximal, we coded as "right colon", for the remaining, "left colon" .

Adenoma and polyp detection rate

Adenoma detection is our key dependent variable to define the quality. To detect adenomas (which are identified by pathologic examination of polyps), endoscopists must first find the polyps during the colonoscopy, classify the polyp by gross appearance, and take part of the lesion to lab for biopsy to confirm the histology of the polyp. Therefore,

we first study the polyp detection and then proceed to adenoma detection as our key variables of interest.

Polyp detection rate is defined as the percentage of patients with at least one polyp found. Each polyp has a *polypid* and a *procedureid* to link to the patient it belongs to. To identify the likelihood of a patient having a polyp, we summarized the polyps in each patient into a polyp dataset. If a patient ID exists in the polyp summary dataset, the patient was coded as "Yes" for the *polyps* variable in the procedure dataset, and if not, it was coded"No". To calculate the polyp detection rate, patients with *polyps* equal to "Yes" are divided by total patients. Adenoma detection rate is calculated by the same process.

For the number of polyps found per subject, polyps were summarized within each patient using patient ID in the polyp dataset and the variable with count of polyps was merged into procedure dataset as *SumPolyps* using the *patientid*. A similar process was used for the number of adenomas found per subject, named *SumAdenomas*.

Protocol type

The protocol type was classified at the level of provider using the *providerID* from SCMEC. Per SCMEC, *providerID* equal to 56 and 64 were classified as 1-person technique specialists, whereas *providerID* equal to 1, 22 and 59 were classified as 2-person technique specialists, and the remaining physicians were PCPs all using 2-person technique. Procedures by these respective physicians were thus assigned to the protocol category stated above.

Sedation type

The sedation type is categorized by procedure date. Every procedure conducted before April 1, 2006 was categorized as Midazolam-meperidine sedated procedure, while April 1, 2006 and after were propofol-sedated procedure.

Control variables classified

Patient age was calculated from patient date of birth downloaded from the SCMEC's administrative billing system. The continuous variable of age was recoded into four age groups: <50 years, 50-59 years, 60-69 years, and 70-89 years. Patient gender was downloaded from the SCMEC's administrative system coded as male and female. Patient race is coded as Whites, Blacks, Other and unknown (missing information).

The bowel preparation status, *bowelprep*, is based on a field directly downloaded from SCMEC data system called *ColPrep*. If *ColPrep* was equal to missing, it remains missing in *bowelprep*. If *ColPrep* equal to "excellent", it remains the same in *bowelprep*. If *ColPrep* indicated "fair" or "good", it was re-coded "fair" in *bowelprep*. If *ColPrep* equal to "poor", it remains the same in *bowelprep*.

The variable to classify training procedure or not, named *training* is based on a field directly downloaded from SCMEC administrative system called *ColPCPSeq*. All primary care physicians had their cumulative procedures assigned for each procedure because their very first training procedures started at the study center. Specialists do not qualify for procedure volume variable and have a missing value in this field because all of the specialists completed their first 140 training procedures before getting credentialed in colonoscopy during their training. Therefore, if *ColPCPSeq* equals to "missing" or more than 140, *training* of this physician will be coded as "No (0)". If *ColPCPSeq* less than or equal to 140, *training* value is "Yes (1)".

Interaction terms to be tested

We further studied the interaction between bowel preparation status (excellent, fair and poor) and sedation type. To test the effect of interaction six categories were created based on *bowelprep* and *sedation* variables, which are Midazolam-meperidine/Poor, Midazolam-meperidine/Fair, Midazolam-meperidine /Excellent, Propofol/Poor, Propofol/Fair, Propofol/Excellent.

The cecal intubation rate, named *cecalintub*, is coded based on original fields downloaded from SCMEC – *termileumintubated* and *advnacedupto*. If *termileumintubated* equal to "Yes" or *advancedupto* equal to "the cecum", then *cecalintub* equal to "Yes." To calculate the cecal intubation rate, patients with *cecalintub* equal to "Yes" are divided by total patients.

3.7 Data analysis

3.7.1 Unit of analysis

To address the research questions, the unit of analysis is the patient. Because there is only one procedure per patient in our sample, the number of colonoscopies" implies the same number of patients.

3.7.2 Study period

Retrospective data on 20,540 screening colonoscopies from a licensed ambulatory surgery center for endoscopy in South Carolina, performed during September 4, 2001 and February 4, 2011 were analyzed.

3.7.3 Table of variables

The variables used are listed in Table 3-1. A total of twelve variables were used from the procedure dataset and two variables were extracted from the polyp dataset. The

variables are three categorical variables (patient age, patient race, and protocol type), six dichotomous variables (patient gender, polyp found (or not), adenoma found, sedation type, good bowel preparation (yes/no), and training procedure (yes/no), and three continuous variables (number of polyps found in a patient, number of adenomas found in a patient, and procedure time).

Two variables were extracted from polyp dataset, which were polyp size in millimeter and polyp location. Each was summarized into procedure data set based on procedureID, and hierarchically categorized into “no polyp”, “at least one small polyp (≤5mm)”, “only medium polyps (6-9mm)”, and “only large polyps (10+mm) found” in a patient; and “no polyp”, “at least one right-sided polyp found” or “only left-sided polyps found” in a patient.

Table 3-1 variables of interest

Variable name	Variable description	Level of variable	Variable categories	Type of variable
Procedure dataset				
PatAgeGrp	Patient age	4	<50 years, 50-59 years, 60-69 years, 70-89 years	Categorical
PatGender	Patient gender	2	Male, Female	Dichotomous
PatRace	Patient race	3	White, Black, Other	Categorical
protocol	Protocol type	3	1-person technique specialist, 2-person technique specialist, 2-person technique PCP	Categorical
polyps	Does this patient have any polyps?	2	Yes, No	Dichotomous
adenoma	Does this patient have any adenomas?	2	Yes, No	Dichotomous
SumPolyps	The number of polyps detected for this patient	NA	NA	Continuous
SumAdenoma	The number of adenomas detected for this patient	NA	NA	Continuous
TimeProc	Total procedure time	NA	NA	Continuous
Sedation	Sedation type	2	Midazolam-meperdine, Propofol	Dichotomous
bowelprepgood	Bowel preparation status	2	Yes: If it was Excellent, Good, Fair bowel preparation status No: If it was Poor bowel preparation status	Dichotomous
Training procedure status	Is procedure a PCP training procedure? (<140th procedure for the PCP)	2	Yes: If it was 1-139th procedure for the PCP No: >140th procedure for PCP or any specialist procedure.	Dichotomous
Polyp dataset				
Polypsizemm	Polyp size in mm	4	No polyp, ≦5 mm, 6-9 mm, 10+ mm	Ordinal
Polyploc	Whether the polyp	3	No polyp, left colon,	Ordinal

	site is in the left colon or the right colon?		right colon	

3.8 Statistical analysis

To answer the research questions, statistical models were run to examine associations between the independent variables of interest and screening colonoscopy quality indicators (dependent variables). Indicators studied are defined earlier. For the protocol type, we compared the 1-person technique specialists group and the 2-person technique specialists group with 2-person technique PCPs group. As for the sedation type, we compared the propofol sedation procedures with midazolam-meperidine sedation procedures. In each model, we controlled for bowel preparation status because bowel preparation is a patient-dependent variable that greatly influences the quality indicators. GEE modeling was used to account for patients clustered within physician. SAS version 9.3 is used.

3.8.1 Model 1: Procedure time (continuous variable)

A linear GEE regression model was used to investigate protocol type/sedation type using "proc genmod" syntax in SAS.

$$Y_{\text{procedure time}} = \beta_0 + \beta_1^{*}\text{2-person technique/physician specialty} + \beta_2^{*}\text{patient age} + \beta_3^{*}\text{patient gender} + \beta_4^{*}\text{patient race} + \beta_5^{*}\text{number of polyps found} + \beta_6^{*}\text{sedation type} + \beta_7^{*}\text{bowel preparation} + \beta_8\text{*sedation type*bowel preparation} + \beta_9^{*}\text{training procedure status} + \varepsilon_{\text{error}}$$

This linear GEE regression model tested the association between protocol type (1-person technique vs. 2-person technique) and the sedation type and the procedure durations controlling for the remaining variables.

For all models we tested the interaction term of sedation type with bowel preparation and because it was statistically significant, we compared procedure times for Midazolam-meperidine/Fair (bowel prep), Midazolam-meperidine/Excellent, Propofol/Poor, Propofol/Fair, and Propofol/Excellent to Midazolam-meperidine/Poor. However on comparing the models with the above categories with the two variables modeled separately, the results were not substantially different, but readily interpretable. Hence the latter results were used for interpretation.

3.8.2 Model 2: Polyp detection likelihood (dichotomous variable)

A logistic GEE regression model was used to investigate protocol type/sedation type using "proc genmod" syntax in SAS.

$$\mathbf{Y_{polyp\ detected} = \beta_0 + \beta_1{}^{*}2\text{-person technique/physician specialty} + \beta_2{}^{*}\text{patient age} + \beta_3{}^{*}\text{patient gender} + \beta_4{}^{*}\text{patient race} + \beta_5{}^{*}\text{ sedation type} + \beta_6{}^{*}\text{ bowel preparation} + \beta_7{}^{*}\text{sedation type*bowel preparation} + \beta_8{}^{*}\text{training procedure status} + \varepsilon_{error}}$$

This logistic GEE regression model tested the association between protocol type (1-person technique vs. 2-person technique) and the sedation type and the polyp detection controlling for the remaining variables.

3.8.3 Model 3: adenoma detection likelihood (dichotomous variable)

A logistic GEE regression model was used to investigate protocol type/sedation type using "proc genmod" syntax in SAS.

$$\mathbf{Y_{adenoma\ detected} = \beta_0 + \beta_1{}^{*}2\text{-person technique/physician specialty} + \beta_2{}^{*}\text{patient age} + \beta_3{}^{*}\text{patient gender} + \beta_4{}^{*}\text{patient race} + \beta_5{}^{*}\text{sedation type} + \beta_6{}^{*}\text{ bowel preparation} + \beta_7{}^{*}\text{sedation type*bowel preparation} + \beta_8{}^{*}\text{training procedure status} + \varepsilon_{error}}$$

This logistic GEE regression model tested the association between protocol type (1-person technique vs. 2-person technique) and the sedation type and the adenoma detection controlling for the remaining variables.

3.8.4 Model 4: Advanced neoplasms detection likelihood (dichotomous variable)

A logistic GEE regression model was used to investigate protocol type/sedation type using "proc genmod" syntax in SAS.

$$Y_{\text{advanced neoplasms detected}} = \beta_0 + \beta_1{}^{*}\text{2-person technique/physician specialty} + \beta_2{}^{*}\text{patient age} + \beta_3{}^{*}\text{patient gender} + \beta_4{}^{*}\text{patient race} + \beta_5{}^{*}\text{sedation type} + \beta_6{}^{*}\text{ bowel preparation} + \beta_7{}^{*}\text{sedation type*bowel preparation} + \beta_8{}^{*}\text{training procedure status} + \varepsilon_{\text{error}}$$

This logistic GEE regression model tested the association between protocol type (1-person technique vs. 2-person technique)/sedation type and advanced neoplasm detection likelihood controlling for the remaining variables.

3.8.5 Model 5: likelihood of finding additional polyps (ordinal variable)

An ordered logistic GEE regression model to investigate protocol type/sedation type using "proc genmod" syntax with "dist=multinomial" option in SAS.

$$Y_{\text{number of polyps found}} = \beta_0 + \beta_1{}^{*}\text{2-person technique/physician specialty} + \beta_2{}^{*}\text{patient age} + \beta_3{}^{*}\text{patient gender} + \beta_4{}^{*}\text{patient race} + \beta_5{}^{*}\text{ sedation type} + \beta_6{}^{*}\text{ bowel preparation} + \beta_7{}^{*}\text{sedation type*bowel preparation} + \beta_8{}^{*}\text{training procedure status} + \varepsilon_{\text{error}}$$

This ordered logistic GEE regression model tested the association between protocol type (1-person technique vs. 2-person technique) and the sedation type and likelihood of finding an additional polyp in a patient controlling for the remaining variables.

3.8.6 Model 6: likelihood of finding additional adenomas (ordinal variable)

An ordered logistic GEE regression model to investigate protocol type/sedation type using "proc genmod" syntax with "dist=multinomial" option in SAS.

$$Y_{\text{number of adenomas found}} = \beta_0 + \beta_1{}^{*}\text{2-person technique/physician specialty} + \beta_2{}^{*}\text{patient age} + \beta_3{}^{*}\text{patient gender} + \beta_4{}^{*}\text{patient race} + \beta_5{}^{*}\text{ sedation type} + \beta_6{}^{*}\text{ bowel preparation} + \beta_7{}^{*}\text{ sedation type*bowel preparation} + \beta_8{}^{*}\text{training procedure status} + \varepsilon_{\text{error}}$$

This ordered logistic GEE regression model will test the association between protocol type (1-person technique vs. 2-person technique) and the sedation type and the ability of finding an additional adenoma in a patient, which controls for the remaining variables.

3.8.7 Model 7: right colon polyps (ordinal variable) likelihood

An ordered logistic GEE regression model was used to investigate protocol type/sedation type using "proc genmod" syntax with "dist=multinomial" option in SAS.

$$Y_{\text{at least one right colon polyp detected}} = \beta_0 + \beta_1{}^{*}\text{2-person technique/physician specialty} + \beta_2{}^{*}\text{patient age} + \beta_3{}^{*}\text{patient gender} + \beta_4{}^{*}\text{patient race} + \beta_5{}^{*}\text{ sedation type} + \beta_6{}^{*}\text{ bowel preparation} + \beta_7{}^{*}\text{ sedation type*bowel preparation} + \beta_8{}^{*}\text{training procedure status} + \varepsilon_{\text{error}}$$

This ordered logistic GEE regression model tested the association between protocol type (1-person technique vs. 2-person technique PCPs and 2-person technique specialists) and sedation type vs. the likelihood of a right colon polyp detection, which controls for the remaining variables.

3.8.8 Model 8: likelihood of finding increasingly smaller polyps (ordinal variable)

An ordinal logistic GEE regression model to investigate protocol type/sedation type using "proc genmod" syntax with "dist=multinomial" option in SAS.

$$\mathbf{Y_{polyp\ size} = \beta_0 + \beta_1{}^{*}2\text{-person technique/physician specialty} + \beta_2{}^{*}\text{patient age} + \beta_3{}^{*}\text{patient gender} + \beta_4{}^{*}\text{patient race} + \beta_5{}^{*}\text{ sedation type} + \beta_6{}^{*}\text{ bowel preparation} + \beta_7{}^{*}\text{ sedation type*bowel preparation} + \beta_8{}^{*}\text{training procedure status} + \varepsilon_{error}}$$

This ordered logistic GEE regression model tested the association between protocol type (1-person technique vs. 2-person technique) and the sedation type and the likelihood of finding a small adenoma vs. medium adenoma and large adenoma in a patient controlling for the remaining variables.

3.9 Preliminary review of sample distribution by key dependent variables

Sample distributions for the number of polyps and adenomas found in each subject were cross tabulated by protocol type and sedation type in order to assess the suitability of the variable categories for the planned analyses considering statistical power and model convergence potential. The distributions and the subsequent changes in variable categorization for the final analyses are presented below.

Table 3-2 shows that the number of polyps was missing for 117 patients (similarly for the number of adenomas found in Table 3-5). Majority of the patients had no polyps (38.5%), one polyp (31.5%), two polyps (16.5%), and three polyps (8%). Beyond three polyps, the sample percentage (6%) is low. Therefore, we categorized patients into four levels: 0, 1, 2, and 3+. Table 3-3 shows the breakdown of these four categories by protocol type (1-person technique vs. 2-person technique with physician specialty). Based on the distribution, the percentages in each cell appear reasonable except for 39 patients with three or more polyps under the 1-person technique specialist group which could

breakdown into zero cells in multiple regression analysis. Table 3-4 shows the distribution of sedation type (Midazolam-meperidine vs. propofol) by number of polyps found in four categories. The range was 29% to 39% of patients in each sedation type with zero polyps or one polyp. The percentages of patients with zero or one polyp in Midazolam-meperidine sedation were higher than propofol sedation, however, the pattern was reversed for patients with two polyps and three and more polyps which are higher in those with propofol sedation.

Table 3-5 shows the distribution of the number of adenomas found in a patient, 117 patients with missing polyp information. Table 3-6 and 3-7 showed the breakdown by protocol type (1-person technique vs. 2-person technique with physician specialty) and sedation type (Midazolam-meperidine vs. propofol). The patterns mostly mirrored the number of polyps found.

Table 3-8 shows the distribution of the study sample by protocol type and sedation type: 604 patients (3%) were served by 1-person technique specialist (two specialists), 4,733 patients (23%) were served by 2-person technique specialist (three specialists), and the majority of patients (15,203, 74%) were served by 2-person technique PCP (54 PCPs). About 55% of the patients were provided Midazolam-meperidine sedation and 45% of the patients provided propofol sedation. Most patients were aged 50 to 59 years (45%), followed by 60 to 69 years (25%), <50 years (18%) and 70 to 89 years (12%). Slightly more females (54%) and Blacks (52%) were represented in our study sample.

Table 3-9 and 3-10 shows the distribution of dependent variables by the major independent variables of interest. These tables show the distribution of the sample in each

cell relevant for multiple regression analysis. For example patients under 1-person technique specialist with three or more polyps broken down by sedation type yielded only five patients under Midazolam-meperidine sedation group. The sample distribution by number of adenomas found is more extreme with only three patient in this category and 11 patients under the propofol sedation group.

The preliminary reviews of the sample distributions guided our scheme of variable recoding and the models used to address our research questions.

Table 3-2 Distribution of the number of polyps found per subject

Polyps found per subject	Frequency	Percentage(%)
Missing	117	0.57
0	7,772	37.84
1	6,383	31.08
2	3,346	16.29
3	1,634	7.96
4	716	3.49
5	323	1.57
6	134	0.65
7	64	0.31
8	25	0.12
9	15	0.07
10	3	0.01
11	6	0.03
13	1	0.00
14	1	0.00

Table 3-3 Distribution of the number of polyps found per subject by protocol type

Polyps found per subject	1-person technique specialist	2-person technique specialist	2-person technique PCP
Missing	2 (0.33%)	42 (0.89%)	73 (0.48%)
0	322 (53.31%)	1713 (36.19%)	5737 (37.74%)
1	174 (28.81%)	1480 (31.27%)	4729 (31.11%)
2	67 (11.09%)	765 (16.16%)	2514 (16.54%)
3+	39 (6.46%)	733 (15.49%)	2150 (14.14%)

Table 3-4 Distribution of the number of polyps found per subject by sedation type

Polyps found per subject	Midazolam-meperidine	Propofol
Missing	83 (0.74%)	34 (0.37%)
0	4,386 (38.93%)	3,386 (36.51%)
1	3,726 (33.07%)	2,657 (28.65%)
2	1,791 (15.90%)	1,555 (16.77%)
3+	1,280 (11.36%)	1,642 (17.71%)

Table 3-5 Distribution of the number of adenomas found per subject

Adenomas found per subject	Frequency	Percentage(%)
Missing	117	0.57
0	14,003	68.17
1	4,054	19.74
2	1,456	7.09
3	557	2.71
4	225	1.10
5	73	0.36

6	29	0.14
7	13	0.06
8	7	0.03
9	5	0.02
11	1	0.00

Table 3-6 distribution of the number of adenomas found per subject by protocol type

Adenomas found per subject	1-person technique specialist	2-person technique specialist	2-person technique PCP
Missing	2 (0.33%)	42 (0.89%)	73 (0.48%)
0	459 (75.99%)	3,245 (68.56%)	10,299 (67.74%)
1	101 (16.72%)	911 (19.25%)	3,042 (20.01%)
2	28 (4.64%)	353 (7.46%)	1,075 (7.07%)
3+	14 (2.32%)	182 (3.85%)	714 (4.70%)

Table 3-7 Distribution of the number of adenomas found per subject by sedation type

Adenomas found per subject	Midazolam-meperidine	Propofol
Missing	83 (0.74%)	34 (0.37%)
0	7,706 (68.40%)	6,297 (67.90%)
1	2,224 (19.74%)	1,830 (19.73%)
2	814 (7.23%)	642 (6.92%)
3+	439 (3.90%)	471 (5.08%)

Table 3-8 Distribution of study sample by key independent variables

	No. patients n (%)	
Protocol type		No. performing physicians
1-person technique specialist	604(2.94)	2
2-person technique specialist	4,733(23.04)	3
2-person technique PCP	15,203(74.02)	54
Sedation type		
Midazolam-meperidine	11,266(54.85)	
Propofol	9,274(45.15)	
Patient age		
<50 years	3,792(18.46)	
50-59 years	9,138(44.49)	
60-69 years	5,066(24.66)	
70-89 years	2,544(12.39)	
Patient gender*		
Male	9,390(45.72)	
Female	11,054(53.82)	

Patient Race*	
Whites	9,139(44.49)
Blacks	10,623(51.72)
Other	682(3.32)
Number of polyps found**	
0	7,772(37.84)
1	6,383(31.08)
2	3,346(16.29)
3+	2,922(14.23)

Table 3-9 Breakdown of study sample by key independent variables with the number of polyps found

Protocol type	No. patients n (%)	sedation type	No. patients n (%)	polyp number	No. patients n
1-person technique specialist	604(2.94)	Midazolam-meperidine	262 (43.38)	missing	0
				0	164
				1	78
				2	15
				3+	5
		Propofol	342 (56.62)	missing	2
				0	158
				1	96
				2	52
				3+	34
2-person technique specialist	4,733(23.04)	Midazolam-meperidine	2692 (56.88)	missing	32
				0	1073
				1	910
				2	389
				3+	288
		Propofol	2041 (43.12)	missing	10
				0	640
				1	570
				2	376
				3+	445
2-person technique PCP	15,203(74.02)	Midazolam-meperidine	8312 (54.67)	missing	51
				0	3149
				1	2738

				2	1387
				3+	987
				missing	22
				0	2588
				1	1991
			6891(45.33	2	1127
		Propofol	)	3+	1163

Table 3-10 Breakdown of study sample by key independent variables with the number of adenomas found

Protocol type	No. patients	sedation type	No. patients	adenoma number	No. patients
	n (%)		n (%)		n
1-person technique specialist	604(2.94)	Midazolam-meperidine	262 (43.38)	missing	0
				0	255
				1	30
				2	4
				3+	3
		Propofol	342 (56.62)	missing	2
				0	234
				1	71
				2	24
				3+	11
2-person technique specialist	4,733(23.04)	Midazolam-meperidine	2692 (56.88)	missing	32
				0	1889
				1	498
				2	197
				3+	76
		Propofol	2041 (43.12)	missing	10
				0	1356
				1	413
				2	156
				3+	106
2-person technique PCP	15,203(74.02)	Midazolam-meperidine	8312 (54.67)	missing	51
				0	5592
				1	1696
				2	613
				3+	360
		Propofol	6891(45.33	missing	22

			)	0	4707
				1	1346
				2	462
				3+	354

Chapter 4 CONCLUSIONS AND DISCUSSION

In lieu of chapter 4 and 5, the following manuscripts are included:

Manuscript #1: **Does a hands-on 2-person colonoscopy technique affect screening colonoscopy quality and outcomes of primary care physicians and specialists?**

Abstract

Background: Colorectal cancer (CRC) is the third most prevalent cancer and 2nd leading cause of cancer death in the U.S. Colonoscopy has been recommended as the preferred screening method to prevent cancer by removing polyps before they transform into cancer. Although the effectiveness of colonoscopy in preventing CRC is documented, screening colonoscopy coverage in the US population remains low. This is partly due to low colonoscopy capacity due to a shortage of gastroenterologists (GI). When the supply of GIs is limited, training primary care physicians (PCP) effectively in screening colonoscopy with quality assurance safeguards could be a solution to address the gap. Objectives: To assess if the "hands-on" 2-person technique innovative clinical protocol enables the quality of PCP-performed colnoscopies to be comparable to specialist-performed colonoscopies.

Methods: The study center, a state-licensed ambulatory surgery center, the South Carolina Medical Endoscopy Center (SCMEC) requires an innovative 2-person technique protocol for all PCPs all the time regardless of trained status. 59 physicians performed

colonoscopies, the 2-person technique was consistently complied with by 57 physicians (54 PCPs and 3 specialists), and 1-person technique was used by 2 non PCPs (one colorectal surgeon and one general surgeon). 2-person technique will be examined for its effect on the quality of screening colonoscopies. The study hypotheses is that screening colonoscopy quality among the 2-person protocol group is better than among solo technique protocol group. Only the screening colonoscopy procedures of all patients served during this period. Subsequent (surveillance) procedures are not included as lesion rates may be different at these procedures.

Results: About 3% of the patients were served by 1-person technique specialists, 23% by 2-person technique specialists, and the remaining 74% by 2-person technique PCPs. The likelihood of polyp detection was highest for the 2-person technique specialists (adjusted OR=1.39) compared to 2-person technique PCPs, and 1-person technique specialists were 79% less likely to detect a polyp(s) relative to 2-person technique PCPs (adjusted OR=0.56). The effect is sustained for adenoma detection and for the likelihood of finding each additional polyp/adenoma. Similarly, 2-person technique specialists were significantly more likely to detect a right colon polyp than solo specialists (estimated OR: 2.42). The likelihood of finding small polyp(s) mirrors the pattern of quality indicators described above.

The adjusted procedure time is longest for 2-person technique PCPs. Compared to 2-person technique PCPs, 2-person technique specialists take an average of 1.01 minutes ($p=.184$) shorter, while 1-person technique specialists use 3.77 minutes ($p<.0001$) shorter time to finish the procedure controlling for other factors.

Conclusions: This study finds that an innovation of a hands-on 2-person technique is associated with superior colonoscopy performance and lesion detection outcomes, and that by every discriminating measure, the results with the 2-person technique are superior, and consistent across measures. A study limitation is the small numbers of 2 person technique specialists and 1-person technique specialists.

Introduction

Colorectal cancer (CRC) is the 3rd most prevalent cancer and 2nd leading cause of cancer death in the U.S. (SEER 2013). Colonoscopy has been recommended as the preferred screening method to prevent cancer by removing polyps before they transform into cancer (Rex 2000, Rex 2009, David 2006). Investigations have focused on adenoma clearance for reducing the risk of developing CRC (Kaminski 2010, Rex 2006, Lieberman 2007, Rex 2009). Although the effectiveness of colonoscopy in preventing CRC is documented, screening colonoscopy coverage in the US population remains low. This is partly due to low colonoscopy capacity due to a shortage of gastroenterologists (GIs), the major physician type performing screening colonoscopies. There is a big gap between GI supply and screening-eligible population (Seeff 2004). The annual new addition of the aging baby boomer population keeps the gap growing. Currently, there are about 13,968 board-certified GIs in the US, increasing annually by a count of 460 (less retirements) (ABIM 2013). To cover 100% of all screening-eligible US population, an estimated additional 7,340 GIs are needed (Vijan 2004).

When the supply of GIs is limited, trained primary care physicians (PCPs) could be a solution to address the gap, especially for underserved populations and regions (including rural areas). However, there is a widespread conviction that GIs being specialized perform better in their specialty functions than non-GIs. Some studies support this view. Non-GIs detected colorectal cancer in 87% of patients with a true cancer compared to 97.3% for GIs, although this study did not report the results adjusted for incomplete colonoscopy (Rex 1997). The authors also noted the lack of specific information on a major factor, namely non-GI providers' training in colonoscopy, noting

that some of the study providers were self-trained and others had variable (no documented) training. Examining colonoscopy quality by the ultimate outcome, CRC incidence following colonoscopy, two Canadian studies reported that following colonoscopies by non-GIs, the incidence of CRC was significantly higher compared to colonoscopies by GIs (Rabeneck 2010, Bressler 2007).

In contrast, other research has shown that trained PCPs' colonoscopy performance is comparable with GIs (Wilkins 2009, Xirasagar 2009). Cecum intubation rates for PCPs are documented at 96.5% (Edwards 2004), 89.2% (Wilkins 2009), and 98.1% (Xirasagar 2010), and adenoma detection rates (ADR) at 22.5% (Edwards 2004), 28.9% (Wilkins 2009), and 29.9% (Xirasagar 2010) provided by trained PCPs. Another series reported that PCPs had an ADR of 27.2% in men and 21.4% in women (Newman 2005).

Training PCPs effectively in screening colonoscopy with quality assurance safeguards may be a solution to cover the unscreened population. However, the uptake of colonoscopy by PCPs remains very low. Only 4% of graduating family medicine residents applied for colonoscopy credentialing in 2002 although half of the residency programs offered it, and only 18% of these programs had any candidate registered for the training (Wilkins 2004). While research has documented that "trained" PCPs can provide competent and safe colonoscopy (Edwards 2004, Newman 2005, Wilkins 2009, Xirasagar 2010), there is no documentation of the training process or the clinical protocols used by high-performing PCPs. This study presents the effectiveness of two protocol elements that were consistently used and documented at the endoscopy center to train PCPs. This protocol requires a hands-on 2-person technique, and includes other

elements to maximize colon surface inspection and to minimize the likelihood of missing polyps.

The 2-person technique used by the study center may be important because fatigue is a likely factor in adenoma detection rates, particularly as day progresses. Physicians' ADR for afternoon procedures were significantly lower than for their own morning procedures (25.3% vs. 29.3%, p=.008) (Sanaka 2009). The phenomenon of potentially lower quality performance due to fatigue is not limited to physicians. A study of the judicial system on the association between a favorable parole ruling and timing of the review (morning vs. afternoon) showed that judges were more likely to issue a favorable parole ruling in the mornings than in the afternoon, and immediately after the lunch break than in the later afternoons. The authors suggested that mental fatigue may be less at the beginning of the work day and after a short break for a meal or rest (Danziger 2011). In the case of colonoscopies, studies show that having a second observer in the procedure room is associated with higher ADR/polyp detection rates (PDR), while one person performs the procedure (either the fellow or the attending GI), having the other as observer significantly increased the ADR, 37% vs. 23% (p<.01) among screening colonoscopies (Rogart 2008). Another retrospective study that was not limited to screening colonoscopies reported that the detection rate for small adenoma (<5mm) was significantly higher when there is a second observer (25%vs. 17%, p=.001) noting that the rate and independent performance was higher for non-experienced fellows (second and third-year fellows) (Buchner 2011).

One advantage of having a second observer watching the video screen is reduced likelihood of missed lesions due to visual fatigue. Supporting this explanation is one

study of a dedicated endoscopy nurse observing the video screen while the attending physician performed the screening colonoscopy. This study showed significantly more polyps detected per patient (adjusted OR=1.26) than when the attending physician performed solo with no observer (Aslanian 2013).

Experience level of the performer is an additional factor in performance quality. Peters et al (2010) reported that senior (third year) fellows supervised by the attending physician had almost double the ADRs of junior fellows (OR =1.7). A study from Korea noted that an endoscopy nurse observer of the video screen increased the likelihood of finding a lesion (OR =1.58 for polyp, and 1.47 for adenoma), when a fellow performed the procedure even though it was their 150th-500th procedures (OR =2.07), but no increase was observed for senior attending GIs (Lee 2011).

In contrast to the above studies, a non-randomized prospective study conducted at a single-center reported no significant difference in polyp detection rates with an additional observer (single, attending GI alone 32%, second observer with fellow performing and attending GI supervising, 33%) and in adenoma detection rates (19.3% vs 14.9%) (Eckardt 2009). When the GI performed solo they removed fewer diminutive (<5 mm) hyperplastic polyps but relatively more adenomas than fellows.

To our knowledge, the documented “2-person technique” studies have had similar protocols, namely, having a second observer. In our study setting, the protocol requires a “hands-on” 2-person technique to compensate for the lack of specialist training of the PCPs which may confer additional advantages that solo performing GIs do not have. Additionally prior studies on the 2-person technique protocols were also associated with the conventional polyp search limited to the phase of withdrawing the colonoscope. Our

study setting, in addition of the hands-on 2-person technique requires for PCPs, also requires gradual insertion and withdrawal of the colonoscope with polyp search and removal during both insertion and withdrawal to maximize coverage of all mucosal surface. This latter requirement also minimizes chances of "losing" a polyp that may be encountered during insertion but not traceable during the withdrawal phase, which is the phase when gastroenterologists typically perform polypectomy. However, large polyps are removed only during withdrawal as hemorrhage may lead to aborting the procedure if removal is attempted during insertion. Because of the major differences, the 2-person technique protocol in our study setting is unique and being applied to PCPs, the question arises, does this technique enable the quality of PCP-performed colonoscopies to be comparable to specialist-performed colonoscopies? Secondly, within specialists/experts, does the hands-on 2-person technique improve ADRs?

Methods

The study center, a state-licensed ambulatory surgery center, the South Carolina Medical Endoscopy Center (SCMEC) has trained 54 PCPs since 2001 in colonoscopy with 140 training procedures supervised by specialists/experts credentialed in screening colonoscopy, subsequent colonoscopies by PCPs at the center require adherence to the prescribed protocol, with the specialist always available on site for rescue assistance (therapeutic assistance to remove advanced adenomas, polyps at difficult locations, control bleeding, and/or manage spasms). The Center protocol requires a 2-person technique for all PCPs all the time regardless of trained status. Over the study period, September 4, 2001 through February 4, 2011, 59 physicians performed colonoscopies, the 2-person technique was consistently complied with by 57 physicians (54 PCPs and 3

specialists), and 1-person technique was used by 2 non PCPs (one colorectal surgeon and one general surgeon), PCPs are defined as those with family medicine, internal medicine, pediatrics or obstetrics/gynecology specialization (Figure 4-1).

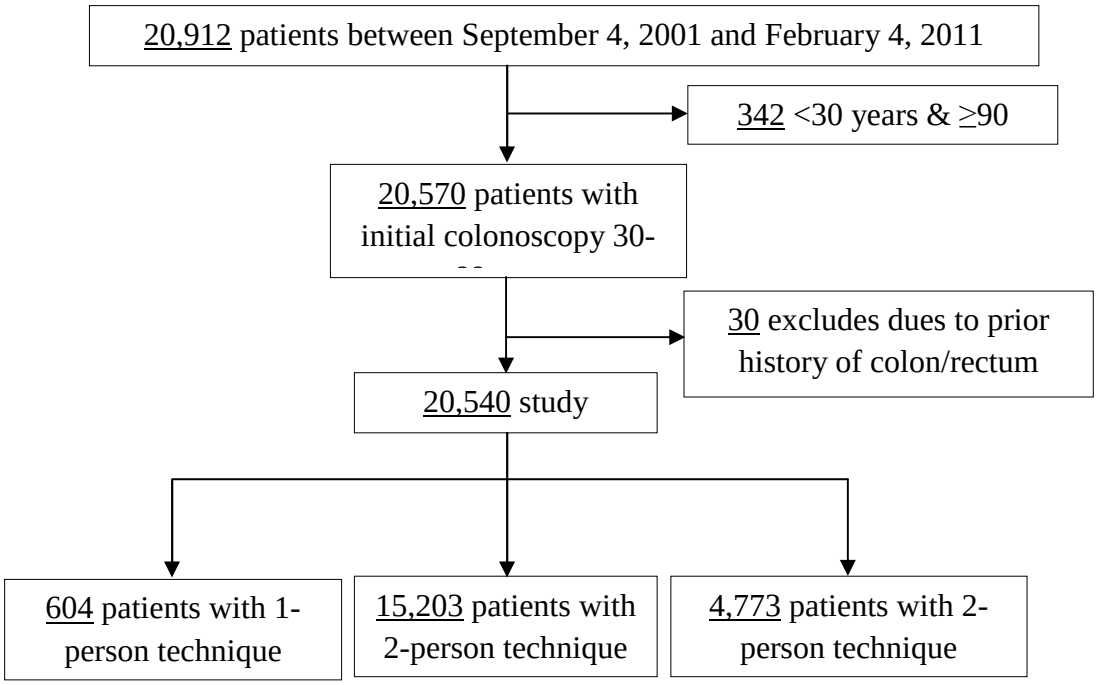

Figure 4-1: Study sample selection flowchart

The innovative 2-person technique protocol requires an endoscopy technician to advance the colonoscope while the performing physician manipulates the scope tip for polyp search and removal. This method has the additional advantage of avoiding missing polyps due to physician's motor fatigue particularly of the left or non-dominant hand. It confers the dexterity of two “right” hands (of the two participants) for polyp search and removal, and further, ensures more persons watching the video screen for polyps. The study center has used propofol sedation since April 1, 2006 instead of the conventional midazolam-meperidine (MM) combination sedation. 2-person technique will be examined for its effect on the quality of screening colonoscopies. Additional protocol features followed in all 2-person technique procedures are: a) gradual insertion and withdrawal for polyp search and removal to maximize coverage of the colonic mucosal surface, b) at least 3 persons watching the video screen.

The study hypotheses is that screening colonoscopy quality among the 2-person protocol group is better than among solo technique protocol group. Our dependent variables of interest representing procedure quality are following: likelihood of polyp detection (Yes vs. No), likelihood of adenoma detection (Yes vs. No), the likelihood of advanced neoplasms detection (Yes vs. No), likelihood of additional polyps detected in subjects (0, 1, 2+), likelihood of additional adenomas detected in subjects (0, 1, 2+), likelihood of detecting small polyps (No polyp, Small (≤5mm), Medium (6-9mm), Large (10+mm)), likelihood of detecting right-sided polyp (polyp location in the cecum, ascending colon, hepatic flexure, or transverse colon proximal to the splenic flexure; No polyp, Left only, At least one right polyp) , and the procedure time.

Our statistical analyses must address non-independence of data due to clustering of patients within physician. We expect physician effects to be similar within their patient group (for example, each physician's dexterity of hand movements) but no systematic distribution of physician effects across physicians. Therefore, we use generalized estimating equations (GEE) modeling. This method assumes a specific correlation structure of the repeated measures data within physician, in this case, an exchangeable correlation structure. This structure assumes that any two observations from different physicians are uncorrelated, and any two observations from the same physician are correlated at the same value (no matter within which physician the observations arise). GEE was used because it accommodates within-physician correlation without focusing attention on that aspect of the data analysis. The within physician correlation is treated as an ancillary problem for which to be accounted but is not of profound interest. When using the exchangeable correlation structure for a linear model, the regression parameters

of the GEE are algebraically equivalent to the association among patients within a physician panel. The same is not quite true for inference of regression parameters from the logistic GEE and logistic random effect models. GEE was determined to be the preferred modeling tool for these analyses.

Only the screening colonoscopy procedures of all patients served during this period. Subsequent (surveillance) procedures are not included as lesion rates may be different at these procedures. Linear GEE regression was used to study the association between the procedure time and our variables of interest. Logistic GEE regression was applied to test the hypotheses regarding likelihood of any lesion detected. The ordered logistic GEE regression was used to test whether the likelihood of finding additional polyp(s)/adenoma(s) in a subject, right colon polyp(s), and smaller polyp(s) in a patient increased with the use of the 2-person technique. The score test was used to verify the assumption of ordered logistic regression.

Results

The demographic distribution of the study sample 20,540 patients and by provider type is shown in Table 4-1. About 3% of the patients were under 1-person technique specialist, 23% of the patients were under 2-person technique specialist, and the remaining 74% of the patients were using 2-person technique PCP. Female (53%) and Blacks (51%) were slightly preponderant in the study cohort, and 7,772 (37.84%) patients had no polyps.

Table 4-1: Demographic and procedure characteristics of the study sample

	No. patients n (%)
Cecum intubation rate (% of cases)	96.48%
Protocol type	
1-person technique specialist	604 (2.94)
2-person technique specialist	4,733 (23.04)
2-person technique PCP	15,203 (74.02)
Patient age	
<50 years	3,792(18.46)
50-59 years	9,138(44.49)
60-69 years	5,066(24.66)
70-89 years	2,544(12.39)
Patient gender*	
Male	9,390(45.72)
Female	11,054(53.82)
Patient Race*	
Whites	9,139(44.49)
Blacks	10,623(51.72)
Other	682(3.32)
Number of polyp found**	
0	7,772 (37.84)
1	6,383 (31.08)
2+	6,268 (30.52)
Polyp size†	
No polyps	7,772 (37.84)
Small (≦5mm)	11,727 (57.09)
Medium (6-9mm)	591 (2.88)
Large (10+mm)	377 (1.84)
Polyp anatomic location†	
No polyps	7,772 (37.84)
Left colon	6,387 (31.10)
Right colon	6,273 (30.54)

* Total of 96 patients missing information on gender and race.
**Total of 117 patients with missing information on number of polyps.
† 73 patients had missing polyp size information, 108 patients were missing information on polyp anatomic location.

Table 4-2 shows the sample distribution by quality indicators. The PDR and the mean number of polyps detected per subject (MNP) for solo performing specialists is lower with PDR: 46.7% and MNP: 0.74 compared to 2-person technique specialists 63.8% and 1.23, and 2-person technique PCPs 62.3% and 1.18, respectively. Adenoma detection for the 3 groups mostly mirrors the polyp detection pattern, being 23.7%, 30.6%, and 31.8% rates for the respective groups, and MNA 0.34, 0.49, and 0.52 respectively. Mean procedure time is shortest in the 1-person technique group (19.68 minutes) higher for 2-person technique specialists (24.78 minutes), and highest for 2-person technique PCP (26.21 minutes). Breaking down to procedures with polyps and without polyps found, the pattern of procedure time differences are sustained. Compared to solo performers (38.74%), the 2-person technique groups found small, ≤5mm polyps in larger proportions of patients (PCP: 57.23%, specialist: 58.99%). Similarly, solo performance specialists have lower proportion right colon polyp detected (19.04%) compared to the 2-person technique groups (PCP: 30.74%, specialist: 31.35%).

Table 4-2: Indicators of colonoscopy quality by procedure protocol

	1-person technique specialists	2-person technique specialists	2-person technique PCPs	p-value
	mean / n(%)	mean / n(%)	mean / n(%)	
No. of performing physicians	2	3	54	
Cecum intubation rate (% of cases)	87.91%	93.24%	97.83%	P<.0001
Lesion detection rates				
Polyp detection rate (% of cases)*	46.69	63.81	62.26	P<.0001
Number of polyps detected per subject (mean, SD)*	0.74±1.02	1.23±1.39	1.18±1.36	P<.0001
Adenoma detection rate (% of cases)*	23.68	30.55	31.78	P<.0001
Number of adenomas detected per subject (mean, SD)*	0.34±0.74	0.49±0.90	0.52±0.95	P<.0001
Advanced neoplasms (% of cases)*	6.79	6.44	6.85	P=.017
Procedure duration				
All colonoscopies				
Total procedure time (min)*	19.68±8.74	24.78±22.56	26.21±12.13	P<.0001
Colonoscopies with no polyp found				
Total procedure time (min)*	17.58±6.57	21.66±12.74	22.02±10.24	P<.0001
Colonoscopies with polyp(s) found				
Total procedure time (min)*	21.97±10.14	26.23±25.75	28.67±12.47	P<.0001
Polyp size*†				P<.0001
No polyps	53.31	36.19	37.74	
Small (≦ 5 mm)	38.74	58.99	57.23	
Medium (6 – 9 mm)	3.64	2.45	2.98	
Large (10+ mm)	2.98	2.09	1.71	
Polyp anatomic location*†				P<.0001
No polyps	53.31	36.19	37.74	
Left colon	27.65	32.45	30.81	
Right colon	19.04	31.35	30.74	

† 73 patients had missing polyp size information, 108 patients were missing information on polyp anatomic location.

Table 4-3 and Table 4-4 present multiple regression analyses of the associations between technique and the variables of interest. The adjusted procedure time is longest for 2-person technique PCPs. Compared to 2-person technique PCPs, 2-person technique specialists take an average of 1.01 minutes (p=.184) less, while 1-person technique specialists took 3.77 minutes (p<.0001) less time for the procedure, controlling for other factors. The adjusted procedure time was longer for older patients (60 – 69 years: 2.06 mins, p<.0001; 70 – 89 years: 2.93 minus, p<.0001) compared to <50 years. Females had longer procedure time (1.11 mins, p<.0001), and if the procedure was a PCP training procedure (≤140procedures), it was longer (3.93 mins, p<.0001), as also for each additional polyp found (3.16 mins, p<.0001).

The likelihood of polyp detection was highest for 2-person technique specialist procedures (adjusted OR=1.39) compared to 2-person technique PCPs. The 1-person technique specialists had 79% less likelihood of detecting a polyp(s) than 2-person technique PCPs (adjusted OR=0.56). The effect is sustained for the adenoma yield. Compared to 2-person technique PCPs, solo technique specialists were 37% less likely to chance in detecting adenoma(s) (adjusted OR: 0.73, p=.005). Specialists using the 2-person technique have a significantly higher likelihood of detecting adenoma(s) (adjusted OR: 1.23, p<.0001). For advanced neoplasm(s), there was no difference between solo performing specialists and 2-person technique PCPs (adjusted OR: 1.05, p=.811). But 2-person technique specialists were slightly more likely to find an advanced neoplasm(s) (adjusted OR: 1.14, p=.008).

The likelihood of finding a polyp or an additional polyp (given the first polyp) for 2-person technique PCP is 85% higher relative to 1-person technique specialist (adjusted

OR 0.54, 95%CI: 0.36, 0.80). Within specialists, 2-person technique specialists were much more likely to find an additional polyp than 1-person technique specialists (adjusted OR: 2.48). The adjusted OR for 2-person technique specialists vs. 2-person technique PCPs was 1.34 (95%CI: 1.16, 1.54). This pattern was sustained for the likelihood of finding each additional adenoma, and within specialists, 2-person technique was significantly more likely to be associated with finding each additional adenoma than relative to solo specialist performance (adjusted OR: 1.73).

Because right-sided colon polyps are more likely to be missed (Bressler 2004, Hewett 2011), polyp anatomic location was modeled. The likelihood of finding right colon polyp(s) by solo performing specialists was 82% lower than 2-person technique PCPs (OR: 0.55 for 1-person technique specialists). Similar to the findings on other indicators, 2-person technique specialists were significantly more likely to detect a right colon polyp than solo performing specialists (estimated OR: 2.42).

The likelihood of finding small polyp(s) mirrors the pattern of quality indicators described above. Solo technique specialists were significantly less likely to find a small (≤5mm) polyps than 2-person PCPs (adjusted OR: 0.52, 95%CI: 0.36, 0.77) and 2-person technique specialists were the most likely to find increasingly smaller polyp(s) (adjusted OR: 1.36, 95%CI: 1.18, 1.56). We did not model cecum intubation rate as a quality indicator because the rate was 96.48% for the sample, and 93.24%, 97.83% and 87.91% for the 2-person technique specialists, 2-person technique PCPs, and solo performing specialists.

Table 4-3: Adjusted estimates of colonoscopy performance and outcome quality indicators by protocol type***

Dependent variables (colonoscopy quality indicators)								
	Procedure time (mins)		Likelihood of finding polyp(s) (logistic GEE) †		Likelihood of finding an adenoma(s) (logistic GEE) †		Likelihood of finding an advanced neoplasm(s) (logistic GEE) †	
	β	p-value	OR	95%CI	OR	95%CI	OR	95%CI
Protocol type								
1-person technique specialist	-3.77	P<.0001	0.56	0.37,0.83	0.73	0.38,1.38	1.05	0.69,1.59
2-person technique specialist	-1.01	P=.184	1.39	1.19,1.62	1.23	1.12,1.34	1.14	1.04,1.26
2-person technique PCP	0	0	1.00	1.00	1.00	1.00	1.00	1.00
Patient age								
<50 years	0	0	1.00	1.00	1.00	1.00	1.00	1.00
50-59 years	0.52	P=.166	1.33	1.21,1.47	1.51	1.35,1.68	1.31	1.08,1.60
60-69 years	2.06	P<.0001	1.61	1.48,1.75	2.17	1.97,2.38	1.81	1.54,2.13
70-89 years	2.93	P<.0001	1.83	1.60,2.09	3.02	2.69,3.38	2.17	1.75,2.70
Patient gender**								
Male	0	0	1.00	1.00	1.00	1.00	1.00	1.00
Female	1.11	P<.0001	0.75	0.70,0.80	0.64	0.60,0.68	0.65	0.57,0.74
Patient race**								
Whites	0	0	1.00	1.00	1.00	1.00	1.00	1.00
Blacks	-0.86	P=.082	0.90	0.80,1.01	0.88	0.81,0.97	1.03	0.90,1.17
Other	0.65	P=.202	0.89	0.73,1.10	0.84	0.69,1.01	0.79	0.55,1.15
Was this a PCP training procedure? (≤140th procedure for the PCP)								
Yes	0	0	1.00	1.00	1.00	1.00	1.00	1.00
No	-3.93	P<.0001	0.92	0.80,1.05	0.90	0.81,0.99	0.88	0.75,1.02
Number of polyps found	3.16	P<.0001	-	-	-	-	-	-

**** Total of 96 patients was missing information on gender and race and excluded from analysis.
*** Models controlled for sedation type and bowel preparation status.
† Categories modeled are “No” and “Yes”.

Table 4-4: Adjusted estimates of colonoscopy performance and outcome quality indicators by protocol type*

Dependent variables (colonoscopy quality indicators)								
	Likelihood of finding an additional polyp†		Likelihood of finding an additional adenoma†		Likelihood of finding at least one right colon polyp(s) (ordered logistic GEE) ††		Likelihood of finding increasingly smaller polyp(s) (ordered logistic GEE) †††	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Protocol type								
1-person technique specialist	0.54	0.36,0.80	0.71	0.37,1.38	0.55	0.34,0.90	0.52	0.36,0.77
2-person technique specialist	1.34	1.16,1.54	1.23	1.12.1.35	1.33	1.12,1.58	1.36	1.18,1.56
2-person technique PCP	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Patient age								
<50 years	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
50-59 years	1.33	1.22,1.45	1.52	1.37,1.69	1.38	1.26,1.51	1.31	1.20,1.44
60-69 years	1.68	1.55,1.81	2.26	2.06,2.48	1.79	1.67,1.92	1.55	1.43,1.68
70-89 years	1.87	1.66,2.10	3.15	2.82,3.51	2.20	1.97,2.46	1.72	1.51,1.95
Patient gender**								
Male	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Female	0.73	0.68,0.78	0.62	0.59,0.66	0.72	0.68,0.77	0.78	0.72,0.83
Patient race**								
Whites	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Blacks	0.87	0.78,0.97	0.89	0.81,0.97	0.92	0.83,1.02	0.89	0.79,1.00
Other	0.85	0.70,1.02	0.84	0.69,1.02	0.85	0.71,1.02	0.93	0.76,1.13
Was this a PCP training procedure? (≤140th procedure for the PCP)								
Yes	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
No	0.92	0.80,1.06	0.89	0.81,0.99	0.93	0.81,1.05	0.93	0.81,1.07

* The model controlling for sedation type and bowel preparation.

** Total of 96 patients missing information on gender and race.

† Categories modeled are 0, 1, 2+.

†† Categories modeled are “No polyp”, “Left only”, “at least one Right polyp”.

††† Categories modeled are “No polyp”, “Small”, “Medium”, “Large”.

Discussion

This study finds that an innovation of a hands-on 2-person technique is highly associated with superior colonoscopy performance and lesion detection outcomes, and that by every discriminating measure, the results with the 2-person technique are superior, and consistent across measures. The polyp yield is much higher with 2-person technique PCPs than with 1-person technique specialists, which is by far the most widespread protocol in routine screening colonoscopies. Consistent with the literature of high competent performance by trained family physicians (Edwards 2004). The effect remains significant even when considering adenoma yields and advanced neoplasms yields, which indicates that PCPs are able to distinguish adenomas from normal tissue polyps on a similar scale as specialists.

With the help of another element of this study center's innovative protocol, which requires the polyp search and removal in both ways in and out and the gradual spiral withdrawal, chance of missing the polyps is proposed to be lower. Because the routine protocol performs polypectomy when withdrawing the colonoscope even if polyps were detected in insertion period, this might highly missed the polyps because most of the time, physicians cannot find the polyps after coming back due to the distortion of the colon or mistakenly locate the polyps in memory. Polyp and adenoma detections are consistently higher in 2-person technique groups, with regard to the number of polyps/adenomas detected in a patient, the 2-person technique groups still have higher chance of detecting more polyps/adenomas. This tells us that 2-person technique protocol is not only superior in detecting a/an polyp/adenoma, but also trying to catch any polyps/adenomas to make screening colonoscopy more beneficial in colorectal cancer

prevention to the patients. Regarding to the polyp anatomic location, a constant relation was observed, 2-person technique groups (PCPs: 1.82, specialists: 2.42, respectively) are about 2 times more likely to detect right colon polyps than 1-person technique specialist. Therefore, we are confident to state that 2-person technique protocol offers physicians to perform a thorough colon inspection and this is evenly improved both in the left and right colon. No specific segment of colon was favored.

When comparing among specialists, those under 2-person technique protocol are consistently showing about 2-fold yields than those under 1-person technique protocol with regard to the quality indicators we studied. The 2-person technique protocol plays an important role in improving the colon clearance even among specialists by providing an additional person with hands-on assistance in manipulating the colonoscope to convey two dominant hands for errors caused by motor fatigue (Rogart 2008, Sanaka 2009, Buchner 2011) and more persons watching on the video screens for polyp search to reduce vision errors (Aslanian 2013). These elements of 2-person technique protocol render the warranty of a thorough colon inspection, so that the missed chance reduces with potential colorectal cancer protection increases.

This study suggests that the 2-person technique by PCPs with onsite specialist support may be a solution to the insufficient colonoscopy capacity which stands in the way of realizing the CRC prevention benefits of colonoscopy (Seeff 2006). PCPs performing colonoscopy has been debated due to the lack of specialty training. The study center provides PCPs a training program since 2001 and the unique element of 2-person technique protocol improves the colonoscopy quality in general, the 2-person technique

for PCPs rebuts the controversy of the inferiority of PCP colonoscopy quality in the literature (Rex 1997Rabneck 2010, Bressler 2007).

Manuscript #2: Does sedation type (midazolam-meperidine vs. Propofol) affect screening colonoscopy performance quality and polyp detection outcomes?

Abstract

Background: Over the past decade the age-adjusted colorectal cancer (CRC) incidence has significantly decreased. Most CRC cases and deaths can potentially be prevented by colonoscopy screening which enables both primary prevention through removal of pre-cancerous polyps and secondary prevention through early detection of cancer cases. However the at-risk population's uptake of screening colonoscopy has been less than optimal. One reason could be public perceptions of colonoscopy as an invasive and potentially painful procedure, particularly concerns about partially or unsedated colonoscopy. Offering deep sedation which is documented to provide a well anesthetized procedure experience and to alleviate patient fear of comfort may increase the acceptability of colonoscopy. There is little systematic documentation of how sedation type affects colonoscopy performance quality and lesion detection outcomes. It is important to systematically study whether deep sedation independently improves colonoscopy performance quality in ways that significantly impacts its CRC prevention potential.

Objectives: This study examines the effect of propofol sedation relative to midazolam-meperidine (MM) sedation in a setting where a high-performance, polyp detection-maximizing colonoscopy protocol has been in place for 10 years.

Methods: Retrospective cohort study of all screening colonoscopies done at a state-licensed ambulatory surgery endoscopy center in South Carolina from September 4, 2001 and February 4, 2011. Propofol sedation in lieu of MM sedation was implemented since

April 1, 2006. Because all other clinical protocol and patient navigation elements were consistently implemented, these series enable the study of the independent associations of propofol sedation with procedure quality and lesion detection outcomes. Patient is the unit of analysis. The dependent variables representing procedure quality and outcomes are procedure time and lesion detection captured at several levels of difficulty. The key independent variable of interest is sedation type (propofol or MM).

Our study hypothesizes that propofol sedation is more likely to be associated with finding a polyp/adenoma relative to no polyp/adenoma, and the same odds applies to finding each additional polyp/adenoma Bowel preparation status significantly affects procedure completion and therefore lesion detection rates. Therefore in assessing the effectiveness of sedation type it is essential to adjust for bowel preparation status.

Results: Of total 20,540 study-eligible patients provided a screening colonoscopy from September 4, 2001 through February 4, 2011, 11,266 patients were sedated with MM (54.85%, all pre-April 1, 2006), and 9,274 patients with propofol (45.15%, from April 1, 2006). The polyp detection rate was higher in propofol-sedated patients (63.49%) compared to MM (61.07%, $p<.05$), as was the mean number of polyps found per patient (1.33 vs. 1.06, $p<.0001$), with similar differences in most lesion detection indicators. Mean procedure time was shorter with propofol sedation (25.08 vs. 26.25 min for MM). Propofol sedation was associated with slightly higher odds of finding an advanced neoplasm (adjusted OR: 1.14, 95%CI: 1.01, 1.29) and with finding an additional polyp (adjusted OR: 1.25, 95%CI: 1.07, 1.46) compared to MM sedation.

Conclusions: Propofol sedation may contribute marginally to improved colonoscopy quality, although quality improvement efforts may be better rewarded if focused on measures to improve patient bowel preparation including patient navigation.

Introduction

Over the past decade the age-adjusted colorectal cancer (CRC) incidence decreased from 51.8/100,000 in 1999 to 44.7/100,000 in 2009, and the age-adjusted decreased from 20.5/100,000 to 16.9/100,000 (SEER 2013). Despite these reductions, CRC remains a significant public health problem, affecting over 5% of Americans over their lifetime (U.S. Cancer Statistics Working Group 2013) and killing 50% more Americans than motor vehicle accidents (NHTSA 2012). Colonoscopy is recommended as the preferred screening method because it enables primary prevention through removal of pre-cancerous polyps (Rex 2000, Davila 2006, Rex 2009). However the uptake of colonoscopy by at-risk population (aged 50 years or older, 40 years for those with a family history of CRC) has been less than optimal, being 13.4% in 2005 and 36.4% in 2010 (calculated from the National Health Interview Survey 2005 and 2010 data).

One reason for low uptake of colonoscopy could be perceptions of colonoscopy as an invasive and potentially painful procedure, particularly concerns about partially sedated or unsedated colonoscopy, limiting CRC prevention efforts (Rex & Khalfan 2005, Sipe, Rex, Latinovich 2002). Offering deep sedation which is documented to provide a well anesthetized procedure experience and to alleviate patient fear of discomfort (Sipe, Rex, Latinovich 2002, Heuss 2004) may increase the acceptability of colonoscopy. However deep sedation entails additional costs, notably personnel cost (nurse anesthetists). Payers are more likely to cover costs that facilitate better quality and

colonic clearance of polyps enhancing the CRC prevention impact of colonoscopies, which in turn would reduce future treatment costs from the CRC cases prevented.

There is little systematic documentation of how sedation type affects colonoscopy performance quality and polyp detection outcomes. The available evidence is mixed, based on retrospective studies of procedure series that were not standardized for other protocol elements that greatly impact the reported outcomes. Three studies of important quality indicators, procedure completion rate (cecal intubation), and adenoma detection rate showed positive associations with deeper sedation relative to mild sedation (Chelazzi 2009, Radaelli 2008, Wang 2010), while three others showed no significant associations (Paspatis 2011, Rex 2012, Metwally 2011, Bannert 2012). Chelazzi et al (2009) reported 100% procedure completion rate under propofol sedation compared to 91.1% for non-sedated procedures ($p<.05$), with 1.5 minutes shorter insertion time the propofol group (9 minutes) than the non-sedated group ($p=.0086$). Radaelli et al reported the highest odds of cecal intubation with propofol sedation (OR =2.36 relative to the non-sedated group), followed by benzodiazepine-opiate (OR =2.13), and benzodiazepine alone (OR =1.46). They also reported a similar pattern of increasing polyp detection with increasing sedation (highest likelihood of detection with propofol sedation (OR=1.32) followed by benzodiazepines (OR =1.12). A study of midazolam and pethidine used in specified doses to produce moderate (MS) and deep sedation (DS) found no significant difference in the polyp detection rate (MS: 61.5%, DS: 63.6%), adenoma detection rate (MS: 59.5%, DS: 60.4%), and right colon polyp detection rate (MS: 34.4%, DS: 36.8%) (Paspatis 2011). Another study found no difference in adenoma detection rates of procedures sedated by propofol vs. midazolam/fentanyl (Metwally 2011). A retrospective cohort study across 72

facilities reported a somewhat higher polyp detection rate with moderate sedation than with deep sedation (37.7% vs. 34.1%, p<.0001) but lower advanced adenoma detection (6% vs. 7.2%, p=.01), the latter effect being greater in facilities where deep sedation procedures exceeded 10% of their respective total procedures (7.5% vs. 5.7%, p=.003) (Wang 2010). None of the studies reported on propofol sedation compared to the most commonly used sedation type, midazolam-meperidine.

The evidence on procedure completion and adenoma detection rates by sedation type/level remains mixed. However, the evidence is clear regarding patient satisfaction with pain control. All propofol-sedated patients reported no pain (102 out of 102 patients), compared to 17 out of 23 persons in the midazolam group, and 11 out of 22 in the no sedation group (Gasparovic 2003).

The above evidence suggests that deep sedation by propofol may be time saving and it achieves full pain control compared to other sedatives. The mixed results for other colonoscopy quality indicators are reasonably attributable to the documented widely variable colonoscopy protocols and performance preferences of endoscopists (Barclay 2006, Rex 2001). It is important to systematically study whether deep sedation independently improves colonoscopy performance quality in ways that significantly impacts its CRC prevention potential. This is a key issue of interest to medical professionals and payers. This study addresses this need by examining the effect of propofol sedation relative to midazolam-meperidine (MM) sedation in a setting where a high-performance, polyp detection-maximizing colonoscopy protocol has been in place for 10 years. (The details of these clinical protocol elements are described in a previous paper.) All providers either adhered to the colonoscopy protocol (57 of 59) or were

identified as non-adherent, and uniform patient navigation to reinforce bowel preparation instructions was provided to all patients. The center has maintained rigorous documentation of procedures and outcomes since 2001 enabling a systematic study of the independent associations of propofol sedation (instituted for all center procedures since April 1 2006) with procedure quality and lesion detection outcomes, by comparing propofol sedated procedures with MM procedures (pre-April 1, 2006).

Methods

This is a retrospective cohort study of all screening colonoscopies done at a state-licensed ambulatory surgery endoscopy center in South Carolina from September 4, 2001 and February 4, 2011. Propofol sedation in lieu of MM sedation was implemented since April 1, 2006. Because all other clinical protocol and patient navigation elements were consistently implemented, these series enable the study of the independent associations of propofol sedation with procedure quality and lesion detection outcomes. Patient is the unit of analysis of. Of total 20,912 patients, 20,540 patients were study-eligible after excluding 342 patients aged less than 30 years and over 89 years, and 30 patients with a prior history of colon/rectum resection. The sample selection flow chart is shown in Figure 4-2.

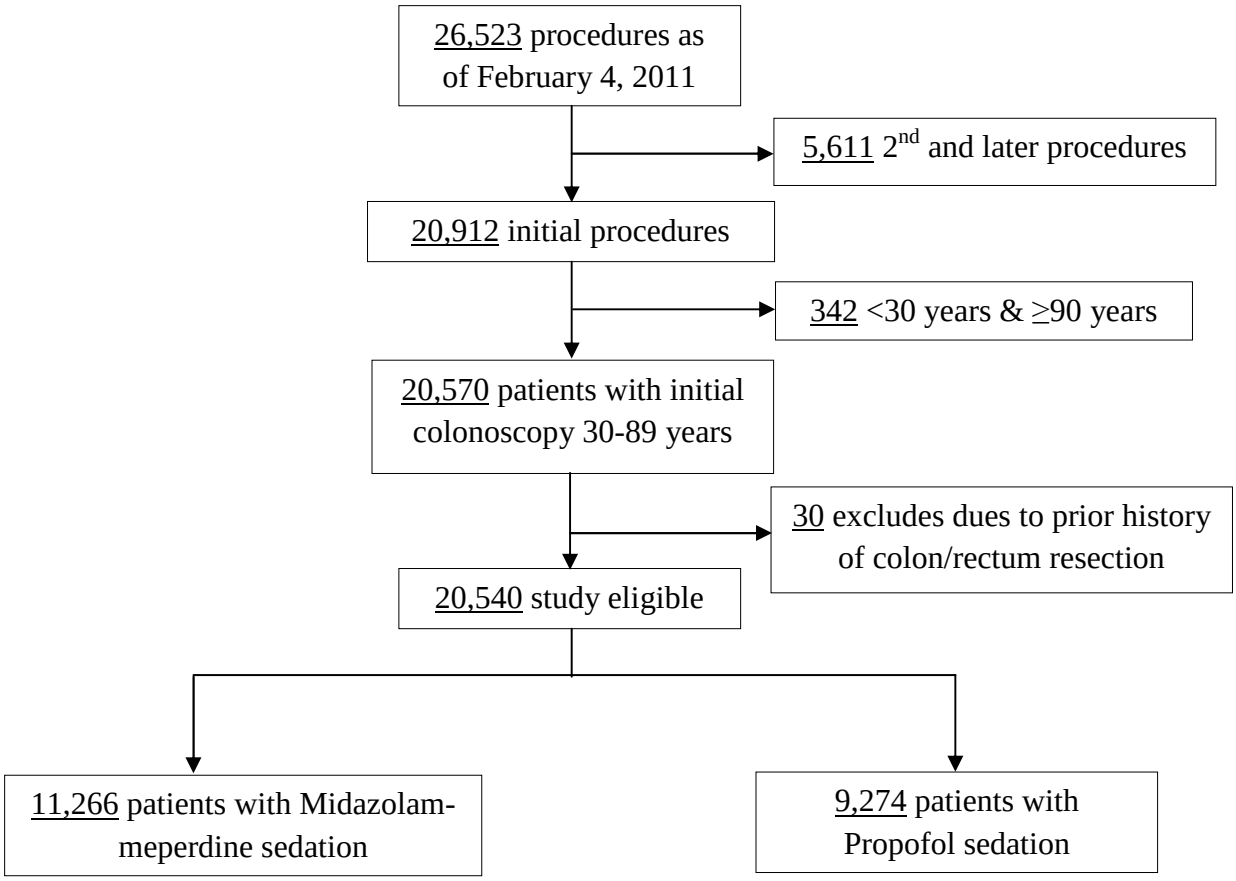

Figure 4-2: Sample selection flowchart

The dependent variables representing procedure quality and outcomes are as follows: likelihood of finding a polyp (Yes vs. No), likelihood of finding an adenoma (Yes vs. No), likelihood of finding an advanced neoplasm (Yes vs. No), likelihood of finding each additional polyp (0, 1, 2+), likelihood of finding each additional adenoma (0, 1, 2+), likelihood of finding a right-sided polyp (no polyp, left only, at least one right-sided polyp found), and likelihood of finding a smaller polyp (no polyp, at least one small(≦5mm) polyp found, at least one medium (6-9mm) found, at least one large(10+mm) polyp found). The key independent variable of interest is sedation type (propofol or MM) and the control variables are bowel preparation status, patient age, race, gender, was this a PCP training procedure, and the number of polyps found.

Because patients are nested within physician and are likely to experience a unique physician level effect, we conducted multilevel modeling. Patients within a physician panel are considered to have an exchangeable correlation, and any two patients served by different physicians are considered uncorrelated. Generalized estimating equation (GEE) is used to test the associations of interest. To model dichotomous dependent variables, such as the likelihood of detecting a polyp/adenoma/advanced adenoma in subjects, logistic GEE regression model was used. For ordinal variables, such as the likelihood of finding each additional polyp/adenoma, the likelihood of finding at least one right colon polyp, likelihood of finding increasingly smaller polyps, and the likelihood of having a shorter procedure duration an ordered logistic GEE regression model was used. The score test in SAS applied to verify the validity of this assumption. Our study hypothesizes that propofol sedation is more likely to be associated with finding a polyp/adenoma relative to no polyp/adenoma, and the same odds applies to finding an additional polyp/adenoma Bowel preparation status significantly affects procedure completion and therefore lesion detection rates. Radaelli showed 40% lower odds of procedure completion with good bowel preparation vs. excellent (Radaelli 2008). Therefore in assessing the effectiveness of sedation type it is essential to adjust for bowel preparation status.

Results

Of total 20,540 study eligible patients (provided screening colonoscopies from September 4, 2001 through February 4, 2011), all pre-April 1 2006 patients were sedated with MM, 11,266 (54.85%), and from April 1, 2006 with propofol, 9,274 patients (45.15%). Table 4-5 shows the sample distribution by demographic and procedure characteristics. The majority were aged 50 – 59 years (44.5%), female (53.82%), and

Black (51.72%). Polyps were detected in 61.6% of patients, and majority of patients had only small polyps (91.8% ≤5mm). Among those with polyps, half of the patients had at least one right colon polyp (49%).

Table 4-5: Demographic and procedure characteristics of the study sample

	No. of patients n (%)
Sedation type	
M-M	11,266 (54.85)
Propofol	9,274 (45.15)
Good bowel preparation†	
Yes	18,613 (90.62)
No	1,561 (7.60)
Patient age	
<50 years	3,792(18.46)
50-59 years	9,138(44.49)
60-69 years	5,066(24.66)
70-89 years	2,544(12.39)
Patient gender*	
Male	9,390(45.72)
Female	11,054(53.82)
Patient Race*	
Whites	9,139(44.49)
Blacks	10,623(51.72)
Other	682(3.32)
Number of polyp found**	
0	7,772 (37.84)
1	6,383 (31.08)
2+	6,268 (30.52)
Polyp size†	
No polyps	7,772 (37.84)
Small (≦5mm)	11,727 (57.09)
Medium (6-9mm)	591 (2.88)
Large (10+mm)	377 (1.84)
Polyp anatomic location††	
No polyps	7,772 (37.84)
Left colon	6,387 (31.10)
Right colon	6,273 (30.54)

* Total of 96 patients missing information on gender and race.
**Total of 117 patients with missing information on number of polyps.
† 366 patients missed sedation type in combination with bowel preparation information.
†† 73 patients had missing polyp size information, 108 patients were missing information on polyp anatomic location.

Table 4-6 presents the colonoscopy performance quality and lesion outcomes distributed by sedation type. The polyp detection rate was higher in propofol-sedated patients (63.49%) compared to MM (61.07%) ($p<.05$), as was the mean number of polyps found per patient (1.33 vs. 1.06) ($p<.0001$). The patterns of differences in adenoma detection and advanced neoplasm detection also follow the above pattern (propofol: 31.73%, MM: 30.86% for adenomas and 7.12% vs. 6.46% for advanced neoplasms, all $p<.05$), as also the mean number of adenomas found per patient screened (0.53 vs. 0.48), the detection rate for small polyps (58.01% vs. 56.34%), and for any right colon polyp (31.3% vs.29.9%). The mean procedure time is shorter with propofol sedation (25.08 vs. 26.25 min for MM), both when polyps were detected (27.51 vs. 28.33 min.) and no polyps detected (20.69 vs. 22.66 min.).

Table 4-6: Indicators of colonoscopy quality by sedation type

	Midazolam-meperdine	Propofol	p-value
	mean / n(%)	mean / n(%)	
No. of patients	11,266(54.85)	9,274(45.15)	
Cecum intubation rate (% of cases)	10,719 (95.14)	9,098 (98.10)	P<.0001
Good bowel preparation			P<.0001
Yes	10,112 (89.76)	8,501 (91.66)	
No	847 (7.52)	714 (7.70)	
Lesion detection rates			
Polyp detection rate (% of cases)*	61.07	63.49	P=.0004
Number of polyps detected per subject(mean, SD)**	1.06±1.19	1.33±1.52	P<.0001
Adenoma detection rate (% of cases)**	30.86	31.73	P=.001
Number of adenomas detected per subject(mean, SD)**	0.48±0.88	0.53±1.00	P<.0001
Advanced neoplasms (% of cases)**	6.46	7.12	P=.0004
Procedure duration			
All colonoscopies			
Total procedure time (min)**	26.25±17.52	25.08±11.48	P<.0001
Colonoscopies with no polyp found			
Total procedure time (min)**	22.66±11.62	20.69±9.33	P<.0001
Colonoscopies with polyp(s) found			
Total procedure time (min)**	28.33±19.86	27.51±11.84	P<.0001
Polyp size**†			P=.003
No polyps	4,386 (38.93)	3,386 (36.51)	
Small polyp with or without medium or large polyp(≦5mm)	6,347 (56.34)	5,380 (58.01)	
Medium with/without large polyp (6-9mm), no small polyp	306 (2.72)	285 (3.07)	
Large polyp only (≥ 10mm)	189 (1.68)	188 (2.03)	
Polyp anatomic location**†			P<.0001
No polyps	4,386 (38.93)	3,386 (36.51)	
Left colon only	3,402 (30.20)	2,985 (32.19)	
Right colon (with or without left colon polyp)	3,370 (29.91)	2,903 (31.30)	

† 73 patients had missing polyp size information, 108 patients were missing information on polyp anatomic location.

Table 4-7 and 4-8 show the associations between sedation type and colonoscopy quality indicators adjusting for patient demographics and other procedure-related factors. The adjusted procedure time is showed somewhat longer duration with MM sedation than

propofol sedation although it did not attain statistical significance (0.97 min longer, p=.093). Propofol sedation was associated with slightly higher odds of finding advanced neoplasm(s) (adjusted OR: 1.14, 95%CI: 1.01, 1.29) and slightly higher odds of finding an additional polyp (adjusted OR: 1.25, 95%CI: 1.07, 1.46) compared to MM sedation. The associations were not statistically significant for the likelihood of finding at least one polyp and finding an adenoma (adjusted ORs: 1.11 and 1.08, respectively). Similarly the likelihood of finding at least one right-sided polyp(s) was not significant (adjusted OR: 1.10), as was the likelihood of finding increasingly smaller polyp(s) (adjusted OR: 1.08) because all confidence intervals spanned 1.0.

Unlike the sedation type, bowel preparation status is showing consistently high and statistically significant associations. Good bowel preparation is significantly associated with a shorter procedure durations (3.46 min, p<.0001). Better bowel preparation was also associated with higher likelihood of finding polyp(s) (1.43, p<.0001), finding adenoma(s) (1.18, p=.005), finding an additional polyp (1.38, p<.0001), finding at least one right-sided polyp (1.31, p<.0001) and finding increasingly smaller polyp(s) (1.42, p<.0001). The likelihood of finding advanced neoplasm(s) was not associated with bowel preparation status with the exception of finding an additional adenoma when the bowel preparation status was good vs. poor (adjusted OR: 1.16, 95%CI: 1.03, 1.30).

Table 4-7: Adjusted estimates of colonoscopy performance and outcome quality indicators by sedation type*

Dependent variables (colonoscopy quality indicators)								
	Procedure time (min)		Likelihood of finding polyp(s) (logistic GEE)†		Likelihood of finding adenoma(s) (logistic GEE)†		Likelihood of finding advanced neoplasm(s) (logistic GEE)†	
	β	p-value	OR	95%CI	OR	95%CI	OR	95%CI
Sedation type								
M-M	0	0	1.00	1.00	1.00	1.00	1.00	1.00
Propofol	-0.97	P=.093	1.11	0.97,1.26	1.08	0.98,1.19	1.14	1.01,1.29
Good bowel preparation								
Yes	-3.46	P<.0001	1.43	1.29,1.60	1.18	1.05,1.33	1.10	0.89,1.35
No	0	0	1.00	1.00	1.00	1.00	1.00	1.00
Patient age								
<50 years	0	0	1.00	1.00	1.00	1.00	1.00	1.00
50-59 years	0.52	P=.166	1.33	1.21,1.47	1.51	1.35,1.68	1.31	1.08,1.60
60-69 years	2.06	P<.0001	1.61	1.48,1.75	2.17	1.97,2.38	1.81	1.54,2.13
70-89 years	2.93	P<.0001	1.83	1.60,2.09	3.02	2.69,3.38	2.17	1.75,2.70
Patient gender**								
Male	0	0	1.00	1.00	1.00	1.00	1.00	1.00
Female	1.11	P<.0001	0.75	0.70,0.80	0.64	0.60,0.68	0.65	0.57,0.74
Patient race**								
Whites	0	0	1.00	1.00	1.00	1.00	1.00	1.00
Blacks	-0.86	P=.082	0.90	0.80,1.01	0.88	0.81,0.97	1.03	0.90,1.17
Other	0.65	P=.2017	0.89	0.73,1.10	0.84	0.69,1.01	0.79	0.55,1.15
Was this a PCP training procedure? (≤140th procedure for the PCP)								
Yes	0	0	1.00	1.00	1.00	1.00	1.00	1.00
No	-3.93	P<.0001	0.92	0.80,1.05	0.90	0.81,0.99	0.88	0.75,1.02
Number of polyp found	3.16	P<.0001	-	-	-	-	-	-

* Model controlled for protocol type and whether bowel preparation is "Good" or "No Good".
** Total of 96 patients was missing information on gender and race and excluded from analysis.
† Categories modeled are "No" and "Yes".

Table 4-8: Adjusted estimates of colonoscopy performance and outcome quality indicators by sedation type*

Dependent variables (colonoscopy quality indicators)								
	Likelihood of finding an additional polyp†		Likelihood of finding an additional adenoma†		Likelihood of finding at least right colon polyp(s) (ordered logistic GEE)††		Likelihood of finding increasingly smaller polyp(s) (ordered logistic GEE)†††	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Sedation type								
M-M	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Propofol	1.25	1.07,1.46	1.09	0.99,1.20	1.10	0.96,1.26	1.08	0.95,1.23
Good bowel preparation								
Yes	1.38	1.24,1.52	1.16	1.03,1.30	1.31	1.19,1.45	1.42	1.29,1.57
No	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Patient age								
<50 years	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
50-59 years	1.33	1.22,1.45	1.52	1.37,1.69	1.38	1.26,1.51	1.31	1.20,1.44
60-69 years	1.68	1.55,1.81	2.26	2.06,2.48	1.79	1.67,1.92	1.55	1.43,1.68
70-89 years	1.87	1.66,2.10	3.15	2.82,3.51	2.20	1.97,2.46	1.72	1.51,1.95
Patient gender**								
Male	0	0	0	0	1.00	1.00	1.00	1.00
Female	0.73	0.68,0.78	0.62	0.59,0.66	0.72	0.68,0.77	0.78	0.72,0.83
Patient race**								
Whites	0	0	0	0	1.00	1.00	1.00	1.00
Blacks	0.87	0.78,0.97	0.89	0.81,0.97	0.92	0.83,1.02	0.89	0.79,1.00
Other	0.85	0.70,1.02	0.84	0.69,1.02	0.85	0.71,1.02	0.93	0.76,1.13
Was this a PCP training procedure? (≤140th procedure for the PCP)								
Yes	0	0	0	0	1.00	1.00	1.00	1.00
No	0.92	0.80,1.06	0.89	0.81,0.99	0.93	0.81,1.05	0.93	0.81,1.07

* Model controlled for protocol type and whether bowel preparation is “Good” or “No Good”.
** Total of 96 patients was missing information on gender and race and excluded from analysis.
† Categories modeled are 0, 1, 2+.
†† Categories modeled are “No polyp”, “Left only”, “at least one Right polyp”.
††† Categories modeled are “No polyp”, “Small”, “Medium”, “Large”.

Discussion

Propofol sedation has been of interest to gastroenterologists because it enables very rapid induction of deep sedation and rapid recovery. This enables more efficient utilization of the endoscopist's time as well as the additional costs of the associated staff and infrastructure while supporting patients' gradual recovery with MM and other sedation types. Additional advantages of propofol that are well-documented are far better and reliable pain control and higher patient satisfaction.

A key question however is whether it improves the quality of the procedure in terms of achieving pan-colonic polyp clearance, because the additional costs incurred for propofol administration may be justifiable to payers if the ultimate clinical outcomes and downstream cost reductions to be achieved can be demonstrated. This is the first study to evaluate this question using a very large series in an unusual setting where rigorous quality assurance mechanisms and documentation are in place, elements of the clinical protocol other than sedation type were kept constant across providers (or documented for providers not adhering to certain colonoscopy protocol elements), and a large number of providers' procedures are included in the sample (59 providers).

We find that while there is a suggestion of a positive association of propofol sedation with improved lesion detection and clearance as measured by sensitive indicators, the results did not attain statistical significance except in respect of one indicator, the advanced adenoma detection rate, and in a reduction in procedure time. We used several uncommon indicators of colonoscopy quality in addition to the standard measures reported routinely such as adenoma detection rates, mean number of adenomas per screened patient. These include the likelihood of detecting a small adenoma detection,

and of detecting the relatively elusive right colon polyp. Although we found a consistent pattern of slightly better detection of lesions with propofol sedation compared to MM sedation, the results did not attain statistical significance despite our large sample size. Our findings are similar to those of other studies that examined the depth of sedation rather than sedation agents used (Paspatis 2011). Our findings may be due to the possibility that the study center ensures deep sedation for all patients regardless of sedation type.

An important study finding is the role of bowel preparation status in the detection rates of all types of lesions, particularly the more elusive lesions such as smaller adenomas and right colon polyps which could be perilous to the patient if left behind. Our study validates the findings of Radaelli et al and adds to the literature by extending the documented associations to the finer indicators of quality, small adenoma detection, likelihood of detecting each additional adenoma, and likelihood of detecting a right colon polyp. Missing of right colon polyps at colonoscopy is documented to be widespread and thought to be a major driver of a large proportion of colorectal cancers arising despite colonoscopy screening.

In summary, our findings suggest that propofol sedation may contribute marginally to improved colonoscopy quality, although quality improvement efforts may be better rewarded if focused on measures to improve patient bowel preparation through efforts directed at patients for example, through patient navigation. Regarding propofol sedation itself, our findings suggest that endoscopists' decisions to adopt propofol sedation should be guided more by considerations of patient comfort and satisfaction, as well as efficiency of endoscopist time utilization rather than an expectation of improved

lesion detection rates. Our study does not provide support for adoption of propofol sedation for the purpose of improving the colorectal cancer prevention effectiveness of colonoscopy screening.

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Appendix A DATA MANAGEMENT PROCESS

- Preparing and cleaning the data:

De-identified data on all colonoscopies conducted during September 4, 2001 and February 4, 2011 were downloaded from the SCMEC's administrative and clinical datasets for this study. To prepare and clean the data ready for analysis, the data collection and management processes are as below:

V:\ColScope\SCMEC\Data\SASfilz\old stuff\ImportData\ImportData.sas

Several datasets imported from SCMEC on October 10, 2007 including physician dataset, appointment dataset, billing dataset, and polyp dataset imported to USC system. (Import Data. sas)

V:\ColScope\SCMEC\Data\SASfilz\old stuff\CombineData\2011\CombineData\PCP Data.sas

Physician demographics data was imported from the SCMEC in 2007 including ID, name, gender, race, age as of 2007, year of graduation, area of specialty, years of experience since graduation as of 2007, is this physician board certified and the reason for exclusion if this physician is not qualified to our study. Total of 64 physicians were read in (Rawdat.pcp) and extra 3 physicians (extrapcp) were updated later adding up to 67 physicians in our original physician dataset (Rawdat.pcp2).

V:\ColScope\SCMEC\Data\SASfilz\DA2012\Polyp Data 10-17-12.sas

oldraw.polypupdate2 (n=180)

This is an update patch done in 2008. This file has polypid and the polyp_results coded as 1-9 (this was obviously from patient charts). This file contained polyp data 2001-2002, was originally found no pathology text, but discovered path_results in colonoscopy sheet of "Coldata.xls". "Compress" function was used to return a character string with specified characters removed from the original string for operationid and polypid.

Old polyp data was read in from polyps sheet of Coldata.xls covering polyp information from 9/1/1999 to 11/1/2007. Remove duplicates due to data download (n=16,426) and data entry (n=1). Old polyp data (N=16,427) was merged with the 2008 update (N=180) after it was cleaned, named as "OldPolyps1 (N=16,607).

New polyp dataset of 32,726 observations was then read in, this polyp dataset covered from 2001 to 2011 (V:\ColScope\SCMEC\Data\Rawdata\2011\polyps 2011.xlsx). "ignoredestroyed" and "dysplasia" were reformatted from characters to numeric variables. After cleaning up some default setting of the dataset, old polyp data that were missing data with info was updated from the new polyp data.

AllPolyps: Update old polyps (n=16,607) with new polyps (n=32,726). Because oldraw.polypupdate2 (n=180) is not contained in newpolyps, the combined AllPolyps has 32,908.

Several correction and updating codings were applied afterwards as bellows:

1. “Substr” function for taking substrings of matrix elements for “OperationId” to “OperId”,
2. Data value recode – erroneous value due to limitation when importing and missing value format recode,
3. Variable rename,
4. Dysplasia update coding from pathologytext and path_results matching both by OperId/polypno and polypId.

Apply correction code for missing data and recodes to all polyps (%include 'V:\ColScope\SCMEC\Data\SASfilz\DA2012\CorrectionUpdateCoding\MissingDataUpdates10-10-12.sas';)

The updates of Summer 2011 for missing value were read in from Access worksheet, the datasets were: (Access datasets are at "V:\ColScope\SCMEC\Data\Rawdata\2011\NewMissingData\SCMEC Missing Data updated 09292011\SCMEC Missing Data 1.accdb" and DATABASE="V:\ColScope\SCMEC\Data\Rawdata\2011\NewMissingData\SCMEC Missing Data updated 09292011\SCMEC Missing Data 2.accdb";)

1. PolRes for polyp_result update,
2. PolSize for Polypsize update, after reading in we manually recoded various formats couldn’t be specified due to data entry,
3. PolQuant for PolypQuantity update,
4. PolLoc for Polyplocation update,
5. PolCol for Color update, the “color” variable was renamed to “morphology” variable, and a “macro” function for morphology was used to create

"PeduncSessile", "Erythematous", Flat", " Multilobular", "Violaceous", and " Serrated" variables. For " Serrated" variable, text search was additional used on pathologytext to fully capture the endoscopist procedure notes,

6. PolHow for polypectomy update.

"V:\ColScope\SCMEC\Data\SASfilz\DA2012\CorrectionUpdateCoding\PolypResultsUpdate10-16-12.sas", this program used pathologytext (hierarchical text search) and pathresults (linked by combination of OperID and polypno) and manual review as total of 4,746 to update to polyp_result.

Now, we have pathresults, pathologytext and polyp_result variables all for coding the results of the polyp, therefore, we incorporated and updated them into "polyp_result" variable using the Correction and Update Coding.

Remove polyps from Minhas Hospital procedures

After the updating program was applied, we removed Minhas-procedure polyps by getting the operationid of the procedures from Rawdat.MinhasHospital dataset. (polyps from 34 procedures were removed) (See line 449-461)

How we produced final product of "Rawdat.finalpolyps2012" of this program

It was created after categorizing Adenoma, AdvAdenoma SerratedAdenoma, HyperPolyp, NormoPolyp, Carcinoid, Carcinoma, and AdvNeoplasm variables using polyp_result and dysplasia level.

V:\ColScope\SCMEC\Data\SASfilz\old stuff\CombineData\2011\CombineData\Colonoscopy Data.sas

Rawdat.colonoscopy was imported from “coldata.xls” as colonoscopy procedure data from the SCMEC (Rawdat.colonoscopy has 17,790 procedures, 30 duplicated entries by SCMEC staff were deleted. Total now is 17,760.)

The revised colonoscopy dataset is now updated with n=17,773 from rawdat.colonupdate (this should be chart review, missing data capture on procedure times etc.) The output as “colonoscopy01” has 17,761 observations.

This was now updated with missing operation time, intubation and prep status data for 227 observations (rawdat.colonupdate2(n=227)) from

V:\ColScope\SCMEC\Data\Rawdata\Update7-21-08\ ColonoscopyUpdateN227.xls. This update output as “colnoscopytemp” has 17,761 observations.

Update new procedures May 2008 to Dec 2011 are now updated using V:\ColScope\SCMEC\Data\Rawdata\2011\Colonoscopy2011.xlsx (n=9848). [colonoscopytemp(17,761) + colonoscopyNew3 (n=9,848) should be = 27,609, obviously some duplicates in new dataset, therefore colonoscopy has 27,472.]

All of the updates were updated to Rawdat.colonoscopy, "V:\ColScope\SCMEC\Data\SASfilz\old stuff\Correction coding\CorrectTimes.sas" and "V:\ColScope\SCMEC\Data\SASfilz\old stuff\Correction coding\CorrectAge.sas" were both brought in for procedure times and age corrections. Procedures prior September 2001 were output to pre9_2001 (n=808), procedures with missing patientID were output to noptid(n=10), and the remaining eligible were output as colnoscopy1temp(n=26,654), which is post September 2001 procedure dataset.

In Summer of 2011 over 10,000 patient charts review for data collection on missed/discrepant patient/procedure information including check on patient date of birth, date of procedure, bowel preparation, incomplete reason, procedure time point (time of insertion, viewing cecum and withdrawal),and pathology report to verify polyp information including polyp size, location, how taken, and polyp result. Updates were stored as Access format as "newmissing1"(n=2,024) and "newmissing2"(n=2,023) from "V:\ColScope\SCMEC\Data\Rawdata\2011\NewMissingData\SCMEC Missing Data updated 09292011\SCMEC Missing Data 1.accdb" and "V:\ColScope\SCMEC\Data\Rawdata\2011\NewMissingData\SCMEC Missing Data updated 09292011\SCMEC Missing Data 2.accdb" when two teams were working on-site collecting data. After combining and the management of the dataset (e.g., we could not find the patientid for the patient chart, and it turns out there were two patientids for one patient and we got the old one, the SCMEC helped us to figure out the corresponding new patientid for the patient so that we can locate the patient chart for review, therefore patientid update was done here and calculated the procedure time as minute per the documented timing of start and end of the colonoscopy and timing of viewing cecum, patient age calculated using interval function (int) between procedure date and patient date of birth), two missing update datasets were output as "allrecentnewupdate"(n=4,047) and update into colonoscopy1temp (post September 2001 procedure dataset).

In colonoscopy2, "V:\ColScope\SCMEC\Data\SASfilz\old stuff\Correction coding\CorrectTimes.sas", "V:\ColScope\SCMEC\Data\SASfilz\old stuff\Correction coding\CorrectAge.sas", "V:\ColScope\SCMEC\Data\SASfilz\old stuff\Correction coding\IncompleteReasons.sas", and "V:\ColScope\SCMEC\Data\SASfilz\old

stuff\Correction coding\PolypMissing.sas" were brought in for procedure times, age, incomplete reasons, and polypmiss (polyp data not found in records-exclude from denominator) corrections.

Text search on "ProcComments" was used here for excluding cancelled procedures (n=39) and on "comments" PLUS providerID in (**19**,**36**,**37**,**57**) for excluding Minhas trained procedures (n=34).

After excluding, procedures in Colonoscopy2(n=26,523), cancandnull(cancelled procedures and null, appointment taken not show up, n=55), ColPrepNull(n=2), howmany(patientid available chart not traceable, n=1), rawdat.MinhasHospital(n=34) and 39 cancelled appointments.

Physician specialty was recoded based on "V:\ColScope\SCMEC\Data\Rawdata\PCP\PhysicianList go through with Dr Lloyd 5-03-2012.xlsx", this file was new update since 2008 that we went through with Dr Lloyd of each physician to determine the specialty and the training process and does the physician should be included or excluded from our study.

Based on the "PhysicianList go through with Dr Lloyd 5-03-2012.xlsx", physician specialty was categorized here of providerID in (**1**,**64**,**22**,**56**,**59**) as specialist, PCPCs for the remaining physicians.

The physician specialty now is correctly classified under "specialist" variable. The "ColPCPSeq" variable was created using macro function and patched in "colonoscopy2" procedures data and output as "colonoscopy3". The provider

demographics were read in from “rawdat.pcp2” and patched in “colonoscopy3”, output as “Colonoscopy4”.

V:\ColScope\SCMEC\Data\Rawdata\2011\MissingRaceAndGender 8-19-2011.xlsx

During August of 2011, a round of data collection on filling in 2645 missing patient gender and race after exporting data from the SCMEC (MISYS) was carried (refer to MissRaceSex sheet). After this round of collecting on patient gender and race, the data was checked on duplicity and 2390 patients were found to have conflicts on duplicated entries from MISYS (DuplicateRace&Sex MYSIS sheet).

The RaceandGender updates in 10-18-2012 was fold in the updates in Spring 2012 “rawdat.racegenderregdata4_30_2012” by include function of 'V:\ColScope\SCMEC\Data\SASfilz\DA2012\CorrectionCodeForTheRegistry\PatAgeGenderRaceCorrectionCode SCMEC 10-17-2012.sas'(n=2722) and 'V:\ColScope\SCMEC\Data\SASfilz\DA2012\CorrectionCodeForTheRegistry\PatGenderRaceCorrectionCode.sas'(n=2714), output as “RaceAndGender”. “RaceAndGender” was later merged in “Colonoscopy4” and output as final permanent product of “Colonoscopy Data.sas” as “rawdat.FinalColonoscopy2012”.

V:\ColScope\SCMEC\Data\SASfilz\DA2012\ Combine polyp and procedure datasets 10-17-2012.sas

Final product of Polyp Data 10-17-12.sas of “rawdat.finalpolyps2012” and Colonoscopy Data.sas of “rawdat.FinalColonoscopy2012” were read in.

1. Summarize polyps as “SumPolyps” and polyp type as “SumPolypTypes” by procedure.

2. ReferalReason and HistColSurgDis updates were fold in "rawdat.FinalColonoscopy2012" by include function of 'V:\ColScope\SCMEC\Data\SASfilz\DA2012\CorrectionCodeForTheRegistry\ReferalReason_HistColSurgDisCorrectionCode07252012.sas'.
3. Identify subjects with multiple procedures using frequency function in "rawdat.finalcolonoscopy2012" to count the number of procedure for each patientid and output as "MultiCol". Merged "MultiCol" back into "rawdat.finalcolonoscopy2012" by patientid to identify the "FirstProcedure" and "RepeatCol" variables using first.id function and count product, output as "Procedures2".
4. "SumPolyps" and "SumPolypTypes" were merged with "Procedures2" by operationid.
5. The "referralreasongrp" variable was in a separate dataset called "RawDat.Ref (n=456)" and was not read in to "analytic.UpdatedRevProcFinalOct192012", so bring them in here, then manually applied 10 corrections made from "Surgical referrals 10262011+ History Colon.xlsx".
6. Output as "analytic.UpdatedRevPolypFinalOct192012" and "analytic.UpdatedRevProcFinalOct192012" as final products of polyp and procedure datasets for analysis in this study.

E. Defining the key variables of interest

The question to be answered in this research is the screening colonoscopy quality. Adenoma detection is our key dependent variable to define the quality. To define the

adenoma, endoscopists first find the polyps during the colonoscopy, classify the polyp by its appearance, and take part of the lesion to lab for biopsy to confirm the histology of the polyp. Therefore, we first look at polyp detection and go to adenoma detection as our main interest variable.

Polyp detection rate is defined as the percentage of patients with at least one polyp was found. Each polyp has a *polypid* and a *procedureid* to link to the patient it belongs to. To identify the patient with polyp or not, we summarize the polyp by *patientid* in polyp dataset. If the patientid exist in the polyp summary dataset, the patient was coded as "Yes" in *polyps* column in procedure dataset, and vice versa. To calculate polyp detection rate, patients with *polyps* equal to "Yes" are divided by total patients. Adenoma detection rate follows the same logic when creating.

```
data SCMECProcPolyp1 (drop=polres rename=(pcp=ProviderID)) polyponly;
merge Procedures2 ( in=inprocs )
    SumPolypTypes (in=inPolpyps)
    SumPolyps (rename=(count=SumPolyps) drop=percent);
by operationid;
ProcedureId=operationid;
 **  create polyps yn  **;
if inprocs and inPolpyps then polyps=1; else polyps=0; format polyps yn.;
 **  add missing to polyp level histology  **;
if polyps eq 0 then
 Do;
```

```
    SumPolyps=0; SumAdenoma=0; SumAdvAdenoma=0; SumSerratedAd=0;
SumHyperPolyp=0; SumNormoPolyp=0; SumCarcinoid=0; SumCarcinoma=0;
SumAdvNeoplasm=0;
  End;
else if polres eq . then
  Do;
   SumPolyps=.m; SumAdenoma=.m; SumAdvAdenoma=.m; SumSerratedAd=.m;
SumHyperPolyp=.m; SumNormoPolyp=.m; SumCarcinoid=.m; SumCarcinoma=.m;
SumAdvNeoplasm=.m;
  End;
```

For the number of polyps found per subject, the polyp was summarized by *patientid* in polyp dataset and the exact number of count was merged into procedure dataset as *SumPolyps* by *patientid*, as well as the number of adenomas found per subject, named *SumAdenomas*.

```
proc freq data=SCMECpolyps noprint;
tables operationid/out=SumPolyps;
run;
proc sort data=SCMECpolyps; by operationid;
proc summary data=SCMECpolyps noprint;
var  CountPolyp Adenoma AdvAdenoma SerratedAdenoma HyperPolyp NormoPolyp
Carcinoid Carcinoma AdvNeoplasm PolypQuantity Polyp_result;
output out=SumPolypTypes (drop=_type_ _freq_)
```

```
sum = SumPolyps SumAdenoma SumAdvAdenoma SumSerratedAd SumHyperPolyp
SumNormoPolyp SumCarcinoid SumCarcinoma SumAdvNeoplasm SumPolypQuantity
PolRes;
by operationid;
run;
```

The protocol type is classified based on *providerID* from SCMEC, *providerID* equal to 56 and 64 were classified as 1-person technique specialists, whereas *providerID* equal to 1, 22 and 59 were classified as 2-person technique specialists, and remaining procedures are all 2-person technique PCPs.

```
    if ProviderID in (56,64) then protocol=1;*56=Kudchadkar, 64=Sweeney (n=604);
else if ProviderID  in (1,22,59)   then protocol=2;*1=Lloyd, 22=Minhas, 59=Yunis
(n=4742);
else protocol=3;* PCP (n=15224);
format protocol protocol.;
proc format library=library;
value protocol  1 = '1-person Specialist'
                2 = '2-person Specialist'
                3 = '2-person PCP';
run;
```

The sedation type is categorized by procedure date, every procedure conducted prior April 1, 2006 was categorized as Midazolam-meperdine sedated procedure, while the counter part of the procedure dataset was coded as propofol sedated procedure.

```
if . lt procdate LT mdy(4,1,2006) then Anesthesia=0;
```

```
else Anesthesia=1;
format Anesthesia Anesthesia.;
proc format library=library;
value Anesthesia 0='Dermol'
                 1='Propofol';
run;
```