AVERAGE RISK COLORECTAL CANCER SCREENING: UNDERSTANDING THE CONSEQUENCES OF INTRODUCING COMPETING DEMANDS FOR LIMITED COLONOSCOPY RESOURCES

by

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DEDICATION PAGE

For Jack

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ABSTRACT

Population-level average risk screening is becoming an important strategy for the control of colorectal cancer. When implementing a population-level colorectal cancer screening program, it is essential to consider how to manage both the short- and long-term consequences of the screening yield and the shifting effects of disease prevalence and population demographics. Of particular concern is the competition for limited colonoscopy resources among average-risk screening program participants, symptomatic or high-risk patients, and the ongoing surveillance requirements for all groups. Failure to understand the effects of operational decisions such as screening test selection, positivity threshold, and follow-up test modality may cause unintended harm, hinder the program's effectiveness, and make inefficient use of limited health care resources. Two-step screening attempts to mitigate the burden on colonoscopy services by requiring a positive stool test before colonoscopy follow-up, however there are many tests available with different abilities to detect true positive and negative cases. A discrete event simulation model, the Simulation of Cancer Outcomes for Planning Exercises (SCOPE) Model, was constructed to compare the effects of various colorectal cancer screening decisions on demand for colonoscopy services, crude colorectal cancer incidence, and cumulative colorectal cancer mortality. Unlike previous screening evaluations, SCOPE considers the effects of competition for constrained colonoscopy services between patient groups on patient and health system outcomes. The study results indicated an increase of 33% to 54% of total colonoscopy services depending on the test selected and the uptake rate. Increased demand for screening follow-up and surveillance colonoscopy services was not offset by modest reductions in disease prevalence and subsequent diagnostic service demand. Failure to provide adequate colonoscopy services reduced the effectiveness of screening. Increasing the FIT positivity threshold reduced the demand for additional average risk screening follow-up colonoscopies by 65%. Screening programs that select a stool test that permits raising the threshold at which a result is considered positive may take advantage of potential benefits of screening without overwhelming colonoscopy services.

LIST OF ABBREVIATIONS USED

AA	Advanced adenoma
ACRN	Advanced colorectal neoplasm (advanced adenoma or colorectal cancer)
CAG	Canadian Association of Gastroenterology
CRC	Colorectal cancer
CT	Computed tomography
CTC	Computed tomographic colonography (CT colonography)
FIT	Fecal immunochemical test (interchangeable with i-FOBT)
FOBT	Fecal occult blood test
FS	Flexible sigmoidoscopy
g-FOBT	Guaiac fecal occult blood test
Hb	Hemoglobin
i-FOBT	Immunochemical fecal occult blood test (interchangeable with FIT)
NNH	Number needed to harm
NNS	Number needed to screen
NPV	Negative predictive value
PPV	Positive predictive value
RCT	Randomised controlled trial
ROC	Receiver operating characteristic
SCOPE	Simulation of Cancer Outcomes for Planning Exercises
SEER	Surveillance, Epidemiology, and End Results
Sens	Sensitivity
Spec	Specificity
#CN	Number of colonoscopies needed to detect CRC or ACRN in persons with a positive test
+LR	Positive likelihood ratio
-LR	Negative likelihood ratio

GLOSSARY

Adenoma	A benign neoplasm of epithelial tissue in which the tumour cells form glands or gland-like structures
Carcinoma	A malignant neoplasm of epithelial tissue (e.g., colorectal cancer)
Cecum	Junction of the large and small intestine
Colon	The large intestine
Colonoscopy	Visual examination of the interior of the entire colon, from the rectum to the cecum
Distal colon	Also called left colon; includes rectum, sigmoid, descending colon
Dysplasia	Abnormal tissue development
Endoscopy	A broad term used to describe examinations inside the body using a lighted, flexible instrument called an endoscope. Endoscopic procedures include upper and lower gastrointestinal examinations.
Metastatic	Cancer that has spread to distant parts of the body
Node	Lymph node
Polyp	A mass protruding from the colorectal mucosa into the interior of the bowel
Positivity threshold	The value at or above which a test result is considered positive
Proximal colon	Right colon; includes transverse and ascending colon and cecum
Rectum	Final straight portion of the colon; ends at anus
Sigmoid colon	Part of the colon closest to the rectum
Sigmoidoscopy	Visual examination of the interior of the distal colon (including the descending colon, sigmoid colon, and rectum) either by means of rigid or flexible endoscopy
Transverse colon	Longest section of colon, lying horizontally between the ascending and descending colon

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CHAPTER ONE INTRODUCTION

The objective of this study was to explore the population and health system effects of the implementation of population-level average risk colorectal cancer screening. Such programs are expected to increase demand for colonoscopy services for both provision of screening follow-up, particularly during initial or prevalence rounds of screening, and ongoing surveillance colonoscopies. These increases may be offset to a degree by decreases in demand for diagnostic colonoscopy services should screening programs prove effective. Changes in demand are further influenced by the aging population. The various contributions of these factors on demand, and in turn the effects of changes in demand on system and patient outcomes for both screening participants as well as higher risk or symptomatic patients requiring colonoscopy services is not well understood.

To understand the patient and system effects of the operational decisions made when implementing population-level colorectal cancer screening, a discrete event simulation model was constructed to examine the demand generated based on the natural history of colorectal cancer in an aging population in the absence of screening interventions and compared to various screening scenarios. The aggregate differences between the scenarios provided the study outcomes, namely: (1) demand and wait times for colonoscopy services by service type (diagnostic/higher risk screening, average risk screening follow-up or surveillance), (2) crude colorectal cancer incidence, and (3) cumulative colorectal cancer mortality over a 15 year time horizon. Inadequacy of colonoscopy services to meet changes in demand was examined for its effects on (1) crude colorectal cancer incidence, and (2) cumulative colorectal cancer mortality.

This dissertation is presented in the form of a series of related papers. As such, there is some repetition in the background sections. Each chapter builds upon the work presented in the previous paper. The first paper (Chapter Two) provides an overview of population-level average risk screening programs in Canada, including an overview of alternative screening modalities, relative risks and benefits of screening, and current challenges in implementing average risk screening. Chapter Three presents an introduction to the various modelling approaches that may be used for examining the effects of the

implementation of population screening programs on population and health service outcomes. Strengths and limitations of the various approaches are discussed within the context of average risk colorectal cancer screening.

Chapter Four presents a new discrete event simulation model (Simulation of Cancer Outcomes for Planning Exercises, or SCOPE) developed to explicitly consider the effects of the implementation of programmatic colorectal cancer screening on the demand for colonoscopy services by service type. Colonoscopy service types included average risk follow-up screening, higher risk screening and diagnostic evaluation of symptomatic patients, and ongoing surveillance for all patient types. The SCOPE model can be used to guide planning for population-level average risk colorectal cancer screening to ensure adequate resource allocation between patient groups. The model employed a natural history approach, simulating the progression of colorectal cancer in a study population to provide an epidemiological baseline of the status quo with which to compare screening interventions. Verification and validation results are presented.

Chapter Five reports the results of an application of the SCOPE model to evaluate the impact of colorectal cancer screening on colonoscopy services by comparing a baseline scenario without screening and two-step average risk screening scenarios using stool tests followed by colonoscopy for positive cases. The outcomes of interest included (1) demand and wait times for colonoscopy services by service type (average risk screening follow-up, higher risk screening and diagnostic, and surveillance), (2) crude annual colorectal cancer incidence at year 15 of follow-up, and (3) cumulative colorectal cancer mortality rates over a 15-year study horizon. Scenarios employing fecal immunochemical tests (FIT) and sensitive guaiac fecal occult blood tests (g-FOBT) were compared to the baseline scenario, as were varying participation rates in FIT screening (ranging from 30% to 50% uptake). The maximum potential benefits of screening were identified using scenarios that assumed unlimited colonoscopy services. The effect of constrained services was then examined for the potential reduction of screening benefits in terms of patient outcomes (crude colorectal cancer incidence and cumulative mortality).

Chapter Six presents the results of a potential strategy to alleviate the additional demand for colonoscopy services created by average risk colorectal cancer screening activities. To

exploit the potential benefits of screening while mitigating the demand for additional colonoscopy services, the screening scenario was run with lower FIT sensitivity values for adenomas and colorectal cancer and higher FIT specificity to simulate raising the threshold at which a FIT was considered positive. Increasing the FIT sensitivity decreases the number of false positive results being directed for colonoscopic follow-up. Outcomes of interest were colonoscopy demand and wait times, crude annual colorectal cancer incidence in year 15 of follow-up, and 15-year cumulative colorectal cancer mortality in the test scenario compared to the usual strategy of a lower FIT positivity threshold. Finally, Chapter Seven identifies opportunities to apply the study findings to policy and decision making settings, and next steps for further research.

Supplemental information is provided in the appendices. Appendix One is an overview of studies evaluating fecal occult blood tests (FIT and g-FOBT). Appendix Two lists the assumptions of the simulation model. Appendix Three provides the annual transition probabilities for the progression to any stage in the adenoma-carcinoma sequence, as used in the natural history module. The distribution of starting stages in the adenoma-carcinoma sequence is specified in Appendix Four for average and higher risk males and females. The life tables for the simulated population are provided in Appendix Five.

CHAPTER TWO AVERAGE RISK COLORECTAL CANCER SCREENING: INTRODUCING COMPETITION FOR LIMITED COLONOSCOPY SERVICES

Abstract

BACKGROUND: Colorectal cancer is the second leading cause of cancer death in Canada, accounting for 12% of all cancer deaths. Survival following a colorectal cancer diagnosis is dependent upon early identification and access to effective therapies, as the disease is highly treatable if detected and treated early in its course, usually prior to the onset of symptoms. Population-level average risk colorectal cancer screening has become an important strategy in the control of colorectal cancer. However, the implications of screening strategies for already constrained colonoscopy services are not well understood.

METHOD: A review of population-based colorectal cancer screening strategies and programs in Canada, including an overview of screening modalities and implications for colonoscopy services.

RESULTS: While an important component of colorectal cancer control strategies, the advent of provincial screening programs is expected to significantly increase the demand for already overburdened colonoscopy services. Further, colonoscopy services are shared by follow-up screening, diagnostic and surveillance patients, each with varying risks of disease. The effects of competing demands for these limited resources are not well understood, despite being critical for optimal resource planning.

DISCUSSION: Much of the evaluation of average risk colorectal cancer screening to date has focused on clinical and cost effectiveness. While support for screening has generally been provided by randomised trials and observational studies, there is relatively little information regarding the effects of operational decision making on system performance or the potential for an overwhelmed system to limit the effectiveness of screening and cause harm to higher risk patients.

INTRODUCTION

The lower gastrointestinal tract is a common site for carcinoma among men and women in Canada, with an estimated 23,900 new cases of colorectal cancer in 2013.(1) Several risk factors are associated with the incidence of colorectal cancer, most notably age and hereditary factors, as well as a number of lifestyle and environmental factors.(2) Incidence of colorectal cancer rises sharply after age 50, with more than 90% of cases occurring in this age group.(2) As a result, the aging population is expected to have a large impact on the incidence and costs associated with colorectal cancer.(3) An important strategy in the control of colorectal cancer is the screening of average risk individuals over the age of 50 years. However, such screening activities are anticipated to further burden many colonoscopy services already functioning at or near capacity and struggling to meet the needs of patients at higher risk of disease, who are symptomatic, or require surveillance for established colorectal cancer.

This paper presents an overview of population-level average risk colorectal cancer screening programs in Canada, with an outline of available screening modalities, the relative risks and benefits of screening, and current challenges faced in implementing, maintaining, and evaluating programmatic screening.

DEVELOPMENT OF COLORECTAL CANCER

Colorectal cancer develops in a stepwise sequence from normal epithelial tissue to dysplastic changes in cells to carcinoma in an approximately 10-15 year long process known as the adenoma-carcinoma (or polyp-cancer) sequence (Figure 2.1).(4–6) The majority of colorectal cancers develop from polyps; however, only a small proportion of polyps go on to become cancer.(6) Potential for malignancy varies by polyp size, histological type, and the grade of epithelial abnormality.(4) Accordingly, polyps may be categorized as low or high risk. Once cancer has developed, it is classified as either localized (early), regional, or advanced (metastasized) disease (Table 2.1). The disease is highly curable if detected and treated early in its course, usually prior to the onset of

symptoms. Five-year survival rates for early stage colorectal cancer are upwards of 90%, falling to less than 10% for advanced metastatic disease.(7)

Figure 2.1 The Adenoma-Carcinoma Sequence

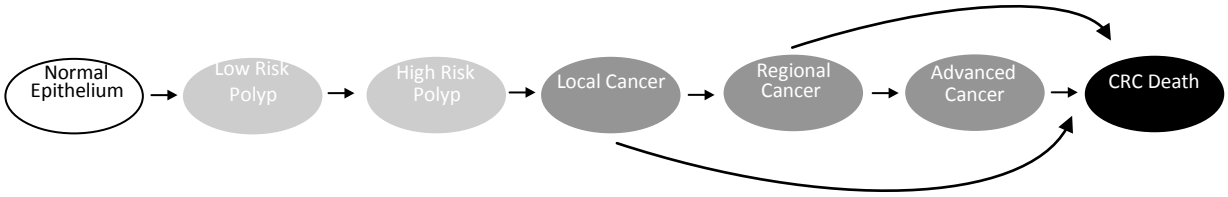


Table 2.1 Colorectal Cancer Staging

Modelled Stage	AJCC Stage	Dukes Stage	TNM Stage
Local cancer	0, I , IIA-C	Dukes A & B	Tis-T4b, N0, M0[1]
Regional cancer	IIIA-C	Dukes C	T1-4b, N1-2b, M0[2]
Advanced cancer	IVA-B	Dukes D	Any T, any N, M1[3]

TNM = Tumour, Node, Metastasis
AJCC = American Joint Committee on Cancer
[1]Includes carcinoma in situ, or tumours (T) confined to the connective tissue or muscular layer surrounding the colon; no nodal (N) or metastatic (M) involvement
[2]Includes tumours of any size/extent, involvement of regional lymph nodes, no metastatic involvement
[3]Includes tumours of any size/extent, any nodal involvement, metastatic involvement

POPULATION-LEVEL COLORECTAL CANCER SCREENING

The purpose of colorectal cancer screening is twofold - to detect those at risk of disease or those in its early stages, with the intention of preventing disease among the former and improving prognosis and outcomes among the latter.(4,8) Screening tests are conducted among asymptomatic individuals, unlike diagnostic tests, which are performed after the onset of clinical signs or symptoms. In population-level colorectal screening, average risk individuals are identified by age (usually 50 years and older and less than 75 years), lack of family or personal history of adenomas or colorectal cancer, known genetic syndromes (e.g., Lynch syndrome), or diseases associated with higher risk (e.g., Crohns disease), and

asymptomatic status. Individuals deemed higher risk are referred for screening tailored to their level of risk.

Intuitively, it appears sensible to undertake population-level screening. According to Wilson and Jungner's classic principles for programmatic screening, colorectal cancer is generally well suited to screening, as it is a highly prevalent and often fatal disease process with a long latent stage that is relatively well understood, is preventable or curable with early detection, and for which adequate, acceptable screening and diagnostic tests and treatment facilities exist.(9) However, in light of current constraints on colonoscopy services, their availability for screening activities must be carefully assessed prior to and for the duration of a screening program.

SCREENING TESTS

Several screening modalities exist for identifying polyps and/or colorectal cancer, including digital rectal exam, barium enema, fecal occult blood testing (FOBT) either in the form of guaiac (g-FOBT) or immunochemical testing (i-FOBT or FIT), computed tomography (CT) colonography, flexible sigmoidoscopy, and colonoscopy. Each differs widely in terms of sensitivity and specificity, level of supporting evidence, invasiveness, risks, costs, availability and acceptability to patients.

Digital rectal exam (DRE) is an examination of the rectum in which a clinician inserts a gloved, lubricated finger into the lower rectum to feel for lumps. DRE is not generally considered adequate for colorectal cancer screening as very little of the colorectal mucosa is examined.

Double contrast barium enema exams consist of a series of X-rays of the lower abdomen following infusion of barium contrast medium into the colon. Diagnostic yields are generally lower than other imaging methods, with greater radiation doses.(10–12) As such, barium enema is not as useful for colorectal cancer screening as other methods and is now used and taught infrequently.(10,13,14) The Canadian Association of Gastroenterology (CAG) does not support its use for population screening.(10)

Fecal occult blood testing (FOBT) refers collectively to a number of tests for occult blood in stool. FOBT technologies detect any of the three classes of haemoglobin product (haem, globin, or porphyrin) or cellular DNA material in feces. The tests are broadly categorized by the type of technology employed: 1) guaiac FOBT (g-FOBT), which detects the peroxidase activity of heme; 2) fecal immunochemical tests (FIT, or i-FOBT), which detect antibodies to globin; 3) haem-porphyrin assays, which detect intact haem and porphyrins not detectable by gFOBT; and 4) fecal DNA tests, which detect DNA alterations associated with cancer. At present, neither porphyrin nor fecal DNA testing is likely to be adopted for population-level screening due to prohibitive processing costs.

CT colonography (also known as virtual colonoscopy) employs a series of CT scans to produce a 3D image of the colon, which can be inspected for abnormalities by a radiologist. It has been shown to have similar sensitivity as colonoscopy for polyps >1cm in size, with poorer accuracy for smaller polyps.(14) Successful interpretation of images is reliant upon the experience of the reader.(15) While it is less invasive than colonoscopy, administers smaller radiation doses than those required for barium enemas, and is generally preferred by patients to either sigmoidoscopy or colonoscopy, the expense and limitations of CT colonography make it inappropriate as a first-line screening tool.(10,12,14,16,17) In Canada, it is used mainly in the case of failed colonoscopies rather than as a primary screening modality.

Sigmoidoscopy (rigid or flexible) involves visual examination of the interior of the distal colon (“left-sided” colon, including the descending colon, sigmoid colon, and rectum) either by means of rigid or flexible endoscopy. While it only allows visualisation of a limited section of the colon (approximately 60 cm), it requires less preparation (usually enema only), is less invasive than a colonoscopy, and does not require sedation. Further, approximately 2/3 colorectal cancers are located in the left side of the large intestine (rectum and distal colon).(18) Endoscopists may remove any polyps or colorectal cancer found during the exam, although a full colonoscopy may be recommended to examine the proximal (right) colon. The sensitivity of sigmoidoscopy for detecting high risk adenomas or colorectal cancer is similar to that of colonoscopy for distal tumours.(19,20) Risks of perforation of the colon and bleeding following polyp removal are similar to

colonoscopy, while anaesthesia-related adverse events may be fewer. CAG guidelines endorse flexible sigmoidoscopy for average risk screening, with intervals of 10 years between normal exams.(10)

Finally, colonoscopy is considered the reference standard of colorectal cancer investigation, as it provides visual examination of the interior of the entire colon, from the rectum to the cecum (junction with the small intestine). Preparation requires thorough clearing of all solids out of the colon, either by means of liquid diets, laxative, and/or enema prior to the procedure. The procedure is usually performed under conscious sedation. Any observed polyps are removed and biopsy samples of abnormal tissue taken for analysis. In Canada, colonoscopy is not used as a primary screening modality among average risk populations due to its increased risks and costs and lack of demonstrated benefit over flexible sigmoidoscopy in usual clinical practice.(10) Rather, it is used as a follow-up to positive stool tests.

TWO-STEP SCREENING

Screening tests may be used alone or in combination in a multi-step screening process, such as use of endoscopy (sigmoidoscopy or colonoscopy) as a follow-up to positive FOBT. Two-step screening programs consisting of FOBT followed by colonoscopy are generally considered to be practical from both patient and health system perspectives, in that they provide average risk individuals with a non-invasive, convenient option for screening while providing a means of rationing colonoscopy resources that may be insufficient for high volume screening of the entire population.(21) Similarly, repeat FOBT may be used in the event of a weak positive first test as a means of conserving colonoscopy resources and minimising the risk of harms of invasive colonoscopy.

Selection of Fecal Occult Blood Test

There is wide variation in estimates of sensitivity and specificity between FOBTs reported in the literature (Appendix 1). Observed variations are the result of a number of factors, including the type of population tested (e.g., low or high risk, asymptomatic or symptomatic), positivity threshold, single or repeated testing, number of fecal samples, adequacy of colonoscopic follow-up, age and dietary restrictions. FIT is generally considered to be the preferred option for population colorectal cancer screening as it shows somewhat superior performance characteristics, particularly for precursor lesions (adenomas), which are desirable for a population-based screening program. It performs with higher selectivity for colorectal vs. gastric bleeding, and facilitates better compliance through improved sampling methods and lack of dietary or medication restrictions. It is also generally more specific than g-FOBT, meaning fewer false positives are referred for colonoscopic follow-up. As with any stool test, repeated (annual or biannual) testing is necessary to maximize the potential for detection of lesions.(13,22–24) Current research focuses on comparison of performance of the various FITs.(25)

There are several other characteristics of stool tests that require consideration when implementing population-level screening, such as collection, uptake rates, processing, quality assurance and cost. A particular advantage over g-FOBT is the ability of some FITs to provide a numeric value for the amount of blood detected in the stool, rather than a positive/negative result. This allows for flexibility in the selection of a positivity threshold for referral for follow-up colonoscopy, which has direct implications for colonoscopy resources. Provided there are sufficient local resources, the threshold may be lowered to capture more cases while accommodating the increased false positive rate. The CAG recommends FIT or high-sensitivity g-FOBT for screening average risk individuals provided there are sufficient local colonoscopy resources for timely follow-up of positive tests.(10)

Selection of Endoscopic Technology

While colonoscopy has been demonstrated to be an effective method of colorectal cancer prevention under strict study conditions, its effectiveness for screening in the community setting may be substantially lower and limited primarily to distal cancers.(19,20) In a population-based study of patients with newly diagnosed colorectal cancer, up to 6% had undergone a colonoscopy in the previous 6 months to 3 years, suggesting a substantial miss rate in a community setting.(26) Further, these studies suggest that colonoscopy is actually no more effective for proximal tumours than flexible sigmoidoscopy, potentially as the result of incomplete exams or, more likely, due to differences between the proximal and distal colon in terms of histology or effectiveness of bowel preparation.

Due to its invasiveness and need for sedation, colonoscopy is associated with more frequent and serious adverse events than other screening modalities. Serious risks include perforation (approximately 1 per 1000 procedures) and bleeding (5-7/1000), particularly with biopsy or polypectomy, and cardiovascular events secondary to anesthesia (11-23/1000).(27–30) Risk of death is estimated to be 10% that of the serious complication rate.(31)

Colonoscopy services are human resource and cost intensive, and require greater skills of clinicians than those needed for flexible sigmoidoscopy. In light of its poorer performance in preventing right-sided colorectal cancer in community settings, the benefit of colonoscopy over flexible sigmoidoscopy for population-based colorectal cancer screening has been questioned.(32) Weighing the need for resources, sedation, intensive bowel preparation, and greater risk of complications against the lack of demonstrated benefit over flexible sigmoidoscopy, CAG concluded that the evidence does not support colonoscopy as a first-line population-based strategy at this time.(10) This is in contrast to American guidelines, which support colonoscopy at 10-year intervals as a first-line screening modality among average risk adults.(13,33)

AVAILABILITY OF COLONOSCOPY SERVICES TO SUPPORT SCREENING

A prerequisite for programmatic population-based screening according to Wilson and Jungner's principles is "facilities for diagnosis and treatment should be available" .(9) While pre-screening with FOBTs may mitigate the need for additional colonoscopy services, availability of colonoscopy services is a key consideration in implementing and maintaining a screening program. In a population-level, two-step screening program, asymptomatic individuals are sought based on broad inclusion criteria and invited to take a test which is unable to either confirm or rule out disease. In the event of inadequate colonoscopy resources, decision makers could be faced with the ethical problem of identifying potential cases without the ability to confirm or rule out a diagnosis of cancer in a timely fashion. Further, aside from causing additional distress and inconvenience, prolonged wait times for colonoscopic follow- up of positive screening stool tests could diminish the potential benefits of screening, weaken participation rates, as well as impede access and impair outcomes for higher risk or symptomatic patients. While much of the literature focuses on the risks versus benefits of the screening at the patient level, the additional risks that may arise from resource constraints have not been well examined at the system level.(34–36) It is imperative to weigh these risks against potential benefits as nonmaleficence, or doing no harm, is a cornerstone of medical ethics and a fundamental principle of health service delivery.

Efforts to ensure timely access to screening follow-up colonoscopies have the potential to hinder access for higher risk and symptomatic individuals. As colonoscopy resources are shared between average risk follow-up screening, high risk screening, diagnostic, and surveillance activities for individuals with colorectal cancer as well as other gastrointestinal diseases (such as inflammatory bowel diseases), measures to manage the competition for colonoscopic resources (such as triage or allocation policies) must be evaluated for their effects on access, demand for downstream services, and outcomes for all patient types. While it would be unethical to identify possible cases through screening activities without the resources in place to confirm a diagnosis in a timely fashion, protecting access for this patient group must not impede access for other, higher risk patient groups. Again, the system and patient outcomes of such policies have not been

well examined to date. Understanding the potential risks associated with population screening is essential for planning and implementing strategies for their mitigation.

Wait Times for Colonoscopy Services

While reasonable wait times are a necessary feature of an efficient health care system (it isn't difficult to imagine the exorbitantly high cost of having colonoscopy suites full of health care providers standing by at the ready should a patient in need of a procedure happen to come along), excessive wait times are distressing and inefficient with potential to lead to suboptimal patient care, increased costs, and poor outcomes. In a benchmarking exercise conducted to compare reported total wait times (from referral to procedure) with recommended wait times for health care for digestive diseases, the CAG reported that prior to the advent of average risk screening, total wait times exceeded consensus targets at sites across Canada, with the majority of patients (including urgent cases such as probable cancer) not seen within the target periods ranging from two weeks to two months.(37) Population-level screening is likely to add substantially to the demand for colonoscopy services, both initially in ruling out positive stool tests and for the ongoing surveillance of increasing numbers of patients with findings. Understanding the yield from screening activities is essential to planning for adequate colonoscopy services.

SCREENING YIELD

Numerous factors are likely to affect both the short and long term consequences of the yield from screening. The underlying prevalence of undiagnosed disease in the target population is the major factor in the higher screening yield observed in initial prevalence rounds of screening as a result of case finding. This is expected to lessen in subsequent incidence rounds of screening; however, the ongoing surveillance of positive cases will create a cumulative demand for colonoscopy resources. On the other hand, the number of symptomatic individuals requiring diagnostic colonoscopy services will likely decline over time, as successful screening should eventually result in fewer polyps and cancers

progressing to advanced stages. The extent of the effect of these influences on the health care system, particularly over time, is not known.

Aside from the effects of prevalence, several factors may be manipulated to influence the screening yield, including positivity threshold. While seemingly straightforward, this is not a trivial task given the significant trade-offs between the risks of false negatives and false positives that must be considered. In the case of stool testing, setting the positivity threshold low would increase sensitivity and lower specificity, resulting in fewer false negatives. Fewer cases of cancer or its precursor lesions would be missed; however, the accompanying high false positive rate could overwhelm colonoscopy services.

Conversely, selecting a high positivity threshold would lower sensitivity and increase specificity, resulting in fewer false positives, which would reduce the immediate burden on patients and colonoscopy resources. A high threshold would also increase the number of false negatives and result in the detection of fewer curable colorectal cancers.(38) For population-based screening programs in which reduction of colorectal cancer mortality is the goal, detection of early-stage cancers is more relevant than detecting those in later stages.(39) Nonetheless, this must be balanced against the practical constraints of limited colonoscopy resources and increasing the exposure of healthy individuals to the risks of colonoscopic procedures.

The results from a recent study by Park and colleagues demonstrate the effects of varying the positivity threshold of stool tests.(40) Seven hundred and seventy average risk patients who were undergoing screening colonoscopy provided stool samples for testing with FIT at various thresholds. At a low threshold of ≥50ng/ml Hb, 109 of the 770 tests were deemed positive and would require follow-up colonoscopy. While more cases of neoplasia would be captured (n = 38), the number of false positives would be high (n = 71). Raising the threshold to ≥150ng/ml Hb would reduce both the number of positive tests that would require colonoscopic follow-up to 72 as well as the number of false positives (n = 45), but would mean that an increased number of cases of advanced adenoma or colorectal cancer would be missed (n = 45) and fewer cases of neoplasia captured (n = 27). The extent of the effect of varying positivity thresholds observed in a

study of 771 participants would be multiplied considerably in a screening population consisting of hundreds of thousands of people.

Priority Setting in Colonoscopy Services

Colonoscopy services are required to support screening (both average and higher risk), surveillance and diagnostic activities for individuals with colorectal cancer and other gastrointestinal diseases. When implementing a new population-level screening program, the effect of the demand generated by screening activities must be considered for its effects on access to colonoscopy for other purposes. While it would be unethical to identify possible cases without the resources in place to confirm a diagnosis in a timely fashion, protecting access for this patient group must not hinder access for other, higher risk patient groups.

Therefore, in addition to the decisions regarding choice of screening test and positivity thresholds, management of patient groups with varying risk profiles and competing interests is in need of further study. In addition to using observational opportunities to monitor the effects of priority setting, modelling methods may also be used to examine its effects on the health system and population and patient health outcomes.

Average Risk Colorectal Cancer Screening Programs

In light of evidence from randomised controlled screening trials demonstrating reductions in the incidence and mortality associated with colorectal cancer among average risk individuals, the Canadian Task Force on Preventative Health Care, Canadian Digestive Health Foundation, and Canadian Association of Gastroenterology (CAG) have published guidelines for screening average risk individuals in Canada.(10,22–24,41,42) To that end, several provinces in Canada have recently established or are planning population-based screening programs similar to those in place in the United Kingdom and other regions of Europe.(43,44)

While all Canadian population-based colorectal cancer screening programs follow the general two-step process recommended in the CAG guidelines, the operationalization of programs varies between, and often within, provinces (Table 2.2).(10,42) Target populations in each province include individuals between the guideline recommended ages of 50 to 74 years. Most target "average risk" individuals (although the definition varies somewhat, "average risk" generally refers to asymptomatic individuals with no personal or family history of colorectal cancer or diseases of the colon). All provinces use a two-step screening process with a fecal occult blood test (FOBT) followed by colonoscopy of positive cases. However, some provinces employ guaiac FOBT (g-FOBT) and others fecal immunochemical (i-FOBT or FIT) testing. Methods of program delivery also differ between regions, with some requiring self or physician referral and others providing mailed invitations, kits, or both. Follow-up of positive stool tests also varies by program, with some programs dependent on family physicians for arranging follow-up (e.g., Ontario), and some providing follow-up directly (e.g., Nova Scotia).

Table 2.2 Canadian Population-Based Colorectal Cancer Screening Programs

Province/ Territory	Population	Tests	Referral	Follow-up
Alberta	All individuals 50-74 years, or high risk	g-FOBT/ colonoscopy	Physician referral required; mailed invitations in future	Physician
British Columbia	Asymptomatic (may have family hx), 50-74 years	FIT/ colonoscopy	Physician referral	Physician
Manitoba	Average risk[a], 50-74 years	g-FOBT (Hemoccult II Sensa) /colonoscopy	Self or physician referral; several invitation strategies	Program
New Brunswick	---	---	No information	---
Newfoundland	---	---	In development	---
Northwest Territories	Average risk[b], 50-74 years	FIT/ colonoscopy	Note: Guidelines only	---

Province/ Territory	Population	Tests	Referral	Follow-up
Nova Scotia	Healthy individuals with no family history, 50-74 years	FIT (Hemoccult ICT) /colonoscopy	Mailed FIT following introduction letter	Program
Nunavut	---	---	No information	---
Ontario	Average risk[c], 50-74 years	g-FOBT/ colonoscopy	Physician referral; mailed invitation in pilot stages	Family physician
Prince Edward Island	(Over 50 years)	g-FOBT/ colonoscopy	Self-referral	Program
Québec	Will target 50-74 year olds	---	In planning phase	---
Saskatchewan	No symptoms or diagnosis of CRC, 50-74 years	FIT/ colonoscopy	Mailed invitation letter, kit	Physician/ program
Yukon	---	---	Under consideration	---

[a] No symptoms or personal history of CRC, polyps, or diseases of the colon requiring monitoring by colonoscopy
[b] No signs or symptoms, personal history, first degree relatives with CRC or genetic syndromes or Inflammatory Bowel Disease
[c] No family history of CRC in one or more first degree relatives

OPERATIONALIZATION OF POPULATION SCREENING

While there are several elements common to the various provincial screening programs, the delivery of programs differs across the provinces. These variations in approach may be due to differences in context, or as the result of a lack of evidence regarding optimal implementation strategies.(45) Trends in prevalence as well as the choices of screening population, fecal test, positivity cut off, and colonoscopic follow-up may have substantial implications for health services systems, particularly over time. This diversity in operationalization may translate to important differences in health system and patient outcomes. During the 2007 Colorectal Cancer Screening and Access Roundtable sponsored by the Colorectal Cancer Association of Canada it was noted that by taking different approaches, provinces could learn from each other regarding the benefits or

downsides of different delivery models.(46) However, insight into these differences may be more efficiently provided, or at very least supplemented, by means of decision analysis such as simulation modelling methods.

THE EVALUATION OF COLORECTAL CANCER SCREENING

As it stands, many jurisdictions have relied mainly on the findings of effectiveness studies conducted in controlled settings or high risk populations and as such may be embarking upon programs without the opportunity to fully understand the system and health consequences. To a certain extent, this is an unavoidable risk when implementing new programs, as one has to start new programs before this kind of information can be obtained. However, it is critical to undertake investigation of system and population consequences so that we can refine programs and better inform the development of future programs.

To date, efforts to quantify the colonoscopy demand generated by screening programs have provided widely varying estimates due to differences in underlying assumptions, making uptake of the results by decision makers difficult.(47–49) Further, these studies have not addressed the competition for resources at the local level, nor the effects of constrained colonoscopy services on screening outcomes.

For example, in Ontario, the funding model for the average risk colorectal cancer screening program included an investment of $11 million in the spring of 2007 for additional hospital-based colonoscopies (a 15% increase) to meet the expected demand for services for those at increased risk due to a family history or positive screening stool test.(50) Colonoscopies of symptomatic patients were not included in the program, as they were meant to be captured under hospitals' general obligations. Access to service was to be assessed through mandatory reporting of total colonoscopy volumes by type (i.e., screening vs. diagnostic).(50) However, it is not clear how this was to be evaluated, as the total denominator of need for service would include patients in need of colonoscopy but who did not receive the service, which is presumably not included in

reported volumes. In light of a lack of information in this regard, individual institutions will likely implement different strategies for monitoring and reporting access for all patient types.

Informed health services planning and decision making requires a better grasp of the consequences of the operationalization of programmatic colorectal cancer screening. This can be supported by employing a decision analysis approach within an epidemiological framework to study the system and population effects of population-based screening activities, and to understand the consequences of inadequately resourced colonoscopy services. Analytical tools, such as simulation modelling, incorporate information from a variety of sources to provide an understanding of system behavior and facilitate the comparison of the effects of various decisions and strategies when observational or controlled trials are not feasible.

CONCLUSION

To date, much of the evaluation of average risk colorectal cancer screening has focused on clinical and cost effectiveness. Trade-offs between potential harms and benefits are often limited to the patient perspective. While support for screening has generally been provided by randomised trials (22–24), observational studies (3,51–55), systematic reviews and meta-analyses (56), and health technology assessments (57,58), there is relatively little information regarding the effects of operational decision making on system performance, or the potential for an overwhelmed system to limit the effectiveness of screening and cause harm to higher risk patients. Clearly, there is potential for unintended harms from population screening in the face of inadequate colonoscopy resources.

Currently, the system, population and patient health effects of common operational decisions regarding programmatic average risk colorectal cancer screening are not well understood. In particular, interventions to ensure access to colonoscopic follow-up for screening participants have not been evaluated for their effects on access to care and

outcomes for others competing for colonoscopy services, such as diagnostic and surveillance patients. The picture is complicated by the effects of case finding, increasing prevalence due to an aging population, and the cumulative demand generated by ongoing surveillance of identified colorectal cancer. To addresses this gap in knowledge, it is necessary to examine the trade-offs between system resource requirements and health outcomes when making common operational decisions such as the choice of screening stool test by type (g-FOBT vs. FIT) and positivity threshold, the choice of screening and surveillance endoscopic technologies by type (colonoscopy vs. sigmoidoscopy), and the implementation of priority setting by means of triage or resource allocation policies.

Such research represents a shift from an emphasis on cost effectiveness as justification for population-level colorectal cancer screening to the use of decision analysis that considers the trade-offs in risks and benefits to participants, patients and the health care system that accompany common operational decisions affecting competition for scarce resources. It also provides an interdisciplinary perspective, incorporating a combination of epidemiological and decision analysis methods, allowing synthesis of best available evidence to inform decision making. In the next chapter, an overview of various decision analysis modelling methods, their strengths, limitations, and applicability to the evaluation of colorectal cancer screening is presented.

CHAPTER THREE MODELLING METHODS IN COLORECTAL CANCER SCREENING: ADDRESSING COMPETITION FOR CONSTRAINED RESOURCES

Abstract

INTRODUCTION: In light of the recent implementation of population-level screening for colorectal cancer in several Canadian provinces, clinicians and decision makers are faced with accommodating an increased burden on already strained colonoscopy services. Understanding the implications of choice of test, disease and population factors is critical for establishing and maintaining a successful screening program. Using naturalistic studies or randomised controlled trials to inform decision making is not feasible due to the need for multiple complex scenarios and long follow-up periods for many outcomes of interest. Simulation modelling approaches are useful in this context, but are relatively unfamiliar to clinicians and decision makers.

METHODS: An overview of the various modelling approaches, their strengths, limitations, and applicability to studying the management of the competition for limited colonoscopy services with the advent of population-based colorectal cancer screening.

RESULTS: Decision tree analyses provide a basic graphical representation of an initial decision and subsequent pathways. State transition models can be used to describe a cohort's progression through health states over a given period of time. Discrete event simulation can simulate the complex behavior of patients, resources and queues within a system. System dynamic models represent system behaviours as influenced by interactions with its components. Agent-based modelling techniques allow representation of complex interactions between model elements.

DISCUSSION: Of the methods presented, discrete event simulation is best suited for addressing patient-level health research questions, particularly if the effects of competition for constrained resources are to be considered.

INTRODUCTION

Recent efforts to control colorectal cancer have focused on the screening of asymptomatic, average risk individuals to identify the disease in early, treatable stages, or to prevent the development of cancer through the removal of precancerous polyps. In light of evidence from randomised controlled guaiac fecal occult blood (g-FOBT) screening trials that demonstrated reductions in the incidence and mortality associated with colorectal cancer among average risk individuals,(22–24) the Canadian Task Force on Preventative Health Care, Canadian Digestive Health Foundation, and Canadian Association of Gastroenterology (CAG) published general guidelines for screening average risk individuals in Canada.(10,41,42) To that end, several provinces in Canada have recently established or are planning population-based screening programs. While necessary for the prevention or early identification of colorectal cancer, population-level screening activities may increase the demand on already burdened colonoscopy services considerably. In systems that are functioning at or near capacity, as many in Canada are, these individuals compete with existing patient populations comprising mainly higher risk diagnostic and surveillance patients for timely access to limited colonoscopy resources. As such, screening programs do not function independently of diagnostic or surveillance services.

While the effectiveness of colorectal cancer screening for improving patient or economic outcomes has been demonstrated in controlled or modelling studies,(22–24,59,60) the effects of operational decisions regarding the choice and prioritisation of screening, diagnostic and surveillance activities on system factors, population, or patient outcomes are not well understood, particularly in population-based programs. Screening modalities and strategies are numerous and many outcomes of interest require follow-up periods of 10 to 20 years. As such, operational and policy-related questions are not readily informed by controlled trials or observational studies.

Several screening tests exist for polyps and colorectal cancer, including digital rectal exam, fecal occult blood testing (FOBT), fecal immunochemical testing (FIT), barium enema, CT colonography, rigid or flexible sigmoidoscopy, and colonoscopy. In practice, however, stool tests and colonoscopy are the main screening modalities. Stool testing for

small amounts of blood, either in the form of guaiac or immunochemical testing (g-FOBT or FIT, respectively), is the least invasive and least expensive of the screening tests, making it a common first method of choice for population-level screening, and is recommended as such in Canadian guidelines.(10,42) Positive stool tests are typically followed up with colonoscopy, although the feasibility and effectiveness of follow-up by means of the less resource intensive, risk favourable flexible sigmoidoscopy are currently under study.(61) While colonoscopy has been demonstrated to be an effective method of colorectal cancer prevention under strict study conditions, its effectiveness for screening in the community setting may be substantially lower and limited primarily to distal cancers.(19,20) Canadian screening programs currently use stool tests (g-FOBT or FIT) as a first-line test in a two-step process, with positive tests followed up with colonoscopy.

Several factors are involved in the selection of screening test(s) and strategies, including sensitivity/specificity, cost, level of invasiveness, risk of serious complications, acceptability to participants, and uptake rates. While the choice of test and positivity threshold strongly affect positivity rates and ensuing burden on colonoscopy services, several disease and population factors should also influence decision making. The underlying prevalence of undiagnosed disease in the target population, effects on prevalence of an aging population, increases in case finding resulting from previously undetected disease, the expected decline in prevalence and shift toward earlier stage at presentation with successive rounds of a successful screening program, increased surveillance needs of identified cases, prioritization of competing needs of other patient groups requiring colonoscopy (e.g., high risk screening populations, diagnosis and surveillance of individuals with inflammatory bowel diseases) and colonoscopy service capacity all require careful consideration.

Operational and policy level decisions regarding the provision of population-based colorectal cancer screening programs are of particular relevance at present, given the growing pressures on colonoscopy services. Wait times for gastroenterology patients, including patients requiring urgent attention such as those with probable cancer, substantially exceed consensus targets. In a study by Leddin and colleagues (37) a minority (33%) of Canadian patients with probable cancer were seen within the target

time frame of two weeks. Nationally, patients with a diagnosis of probable cancer waited a median of 26 days for investigation.(37) Clearly, exacerbation of these wait times is undesirable. However, an important strategy in colorectal cancer control is the earlier identification of disease or precancerous polyps, which requires widespread screening of asymptomatic individuals. Consequently, in addition to the usual considerations of clinical and cost effectiveness, decision makers must anticipate the effects of their decisions on the demand for services and on the outcomes for competing patient groups.

This is not a trivial task, given the complexity of the questions and systems under study and the need for lengthy follow-up to observe many important outcomes of interest. A systems-minded evaluation requires tools capable of handling these factors, often operating in the presence of uncertainty and variability. Modelling methods provide such tools, as they can enhance understanding of the system under study, allow data from multiple sources to be combined, demonstrate the interaction of system factors, or answer "what if" questions.(48,62,63) They have a long history in operations research and management science, and are being increasingly adopted by health services researchers.

The purpose of this paper is to provide clinicians, decision- and policy-makers with a review of common modelling approaches and discuss their applicability to fundamental decisions regarding the implementation and maintenance of population-level colorectal cancer screening, particularly in light of competition for limited resources.

MODELLING APPROACHES

Models are tools that simulate real-world facilities or processes.(64) Process models come in many forms, varying in terms of how they handle the function of time (discrete or continuous), populations (individuals or cohorts), processes (deterministic or stochastic), and attributes such as risk over time (static or dynamic) and interactions between model components.(64) The most commonly used process modelling approaches in health services research include analytical (e.g., decision trees, state transition (Markov) models) and computational (e.g., discrete event simulation (DES) and system dynamics (SD)

models) techniques. Each has strengths and limitations that make them particularly suited for various types of policy or research questions (Table 3.1).

Table 3.1 Summary Comparison of Modelling Approaches

Method	**Decision Tree**	**State Transition (Including Markov)**	**Discrete Event Simulation**	**System Dynamics**	**Agent Based Simulation**
Flexibility	Low	Low	High	Moderate	Very high
Follow-up	Short	Long	Long	Long	Long
Time	Discrete	Discrete	Discrete	Continuous	Discrete
Risk over Time	Static	Static, simple dynamic	Dynamic	Dynamic	Dynamic
Level	Cohort	Cohort	Individual	Individual	Cohort
Memory	No	Simple only (with use of tunnel states)	Yes	Yes	Yes
Inputs	Cohort size, transition probabilities	Cohort size, transition probabilities	Entity types, attributes, resources, queuing parameters, resource scheduling, process flows	Stocks, rates, flows	Agents, attributes, interaction rules, environment characteristics
Outputs	Proportions of cohort per state	Proportions of cohort per state, time spent in state	Throughput, wait times, resource utilization	Dynamics, steady state values	Numerous

ANALYTICAL MODELS

Decision Tree Models

Decision trees are the most straightforward of the commonly used analytical techniques, and are often used in clinical decision making. They provide graphical representations of

an initial decision followed by all possible pathways, which are represented as branches and assigned their respective probabilities and consequences. The probabilities associated with each branch are determined at either chance or decision nodes as appropriate and establish the proportions of individuals following that branch. The total probability at each node must sum to 1 (100%), accounting for all individuals in the model. As such, all outcomes must be accounted for. The effect of a decision or intervention is measured by the proportion of the cohort completing the tree at each of the mutually exclusive endpoints, to which values (e.g., costs) may be assigned.(65)

For our example of population-level colorectal cancer screening, basic analyses such as the expected numbers of true and false positives and negatives for given values of test sensitivity and specificity, uptake rate, and prevalence of disease in the population of interest may be estimated using decision tree analyses. Altering any of the values at the decision or chance nodes would result in differing proportions of individuals at the ends of the branches, providing a form of comparison of scenarios or sensitivity analyses.

While straightforward and transparent, decision trees have several important limitations for addressing complex health service decisions. Analyses are restricted to specific time frames reflecting average times between events for each unique pathway in the model.(66,67) As such, decision trees would not be able to provide information on wait times. Resources are not modelled explicitly, therefore questions regarding competition for resources, triage or prioritization policies could not be addressed.(68) Finally, accommodation of recurrent events or a prolonged period of observation would require the potentially cumbersome computation of all possible pathways, usually multiple times.(69) Therefore, decision trees are most useful for analysing relatively uncomplicated scenarios involving short time horizons.

State Transition Models

Unlike decision trees, state transition (Markov) models can accommodate recurrent events and long time horizons.(67) These models represent health systems as a series of states and provide a description of the transitions of a cohort between health states over

time.(67,68) Individuals within a modelled cohort are considered independent of one another and in one of a finite number of mutually exclusive states at any given time. The time horizon of interest is divided into clinically relevant, equal time increments (e.g., monthly, yearly).(67) The cohort may begin in the same state, or be distributed among the possible states according to initial probabilities. In each cycle, individuals may remain in their current state or move to another state, making no more than one transition per cycle. The probability of movement between states during a single cycle is known as a state transition probability. Transitions between states may be either deterministic or made stochastic by means of Monte Carlo simulation.(68,70)

Markov models may be categorized according to whether the transition probabilities are constant or changing over time.(66,68) Models in which the transition probabilities are constant over time are called Markov chains, and are a subset of the more general, time-dependent Markov processes.(69) Markov chains that include absorbing states (states from which exit is not possible, such as death) can be solved for both time spent in transient states and probabilities of ending up in absorbing states using matrix algebra.(71)

While solving Markov chains using matrix algebra has been made relatively straightforward by spreadsheet programs, several inherent assumptions may limit their usefulness for modelling complex health service systems. For example, transitions are not dependent on the time individuals have spent in a given state or their previous history before entering that state. This "memoryless" property is known as the Markovian assumption, and is central to Markov processes.(69) Despite making the mathematical solution of the model relatively straightforward by means of matrix algebra, it does not allow for changing risk over time, such as in the case of increases in risk of colorectal cancer based on increasing age or history of polyps. For most disease processes constant transition probabilities are realistic only over short time horizons and for homogenous populations.(67,69) Additionally, continuous features of diseases or processes must be forced into discrete states.(72) Perhaps most limiting, however, is the constraint that each individual in the model can be in only one state at any given time, requiring the representation of all possible ways of transitioning from one state to another through the

creation of manifold distinct states.(69,72) In these circumstances, models may quickly become unmanageable.

The random generation of inputs from probability distributions through Monte Carlo simulation adds flexibility to state transition models by enabling the representation of processes at the individual level. However, it does not account for competition for resources, resource constraints, or queues.(70) Therefore, the accurate depiction of a complex system may require choosing between considerable simplification of the system and immense complexity of the model; gross oversimplifications hamper their suitability for informing real decision making.(72)

Markov modelling was used throughout the 1990s to analyse the effectiveness of various screening strategies on colorectal cancer incidence and mortality.(73–78) Analysts generally employed a natural history modelling approach, where screening effectiveness was estimated by comparing outcomes with those observed following a natural, uninterrupted progression of the disease. While models provide initial evidence of the effectiveness of colorectal cancer screening, in terms of both health and cost effects, they do not allow the representation of all of the factors that may influence decision making, such as resource constraints, interaction between various patient groups competing for resources, or wait times. In the mid to late 1990s, analysts began to employ the flexible discrete event simulation to evaluate the effectiveness of colorectal cancer screening.(79,80)

COMPUTATIONAL MODELS

Discrete Event Simulation

Discrete event simulation (DES) has an advantage over the previously described methods in that it is able to mimic the dynamics of a system by simulating the actions of its individual units.(64,81) Therefore, it is ideal for modelling complex and dynamic systems which involve interaction between individuals and operational factors such as resource

constraints and competition for resources. It is the most widely used simulation approach in health.(82)

Systems are represented as linked, chronological sequences of events (e.g., screening activities, polyp growth, onset of CRC, diagnosis, surgery or chemotherapy) and queues (e.g., wait times for diagnostic procedures or treatments). Typical building blocks include entities (e.g., patients) and their attributes (e.g., age, sex, family history of CRC, presence of polyps, screening activities), resources (e.g., physicians, colonoscopy suites) and queues. Unlike regular state transition models that require a constant cycle length, time may progress in varying discrete intervals or can be event-based. While events may be modelled by means of either deterministic or stochastic processes, most systems contain at least some random elements.(64) Entities' states change at discrete moments in time; at each event or interval, entities' attributes are re-evaluated and updated if appropriate. The simulated system is then repeated many times to obtain statistical observations of the system's performance over the time horizon of interest, providing aggregate-level outcomes.

DES has several advantages over decision tree and state transition models. It can more closely mimic real world systems, as flexibility is afforded by modelling at the individual level. Further, unlike 'memoryless' Markov models, the accommodation for time spent in previous states allows for a more realistic depiction of individuals' pathways as well as greater flexibility in data requirements. Drawing input parameters from probability distributions enables DES models to capture more detail about the uncertainty in the system being modelled.(67) Unlike the previously described methods, DES can readily accommodate changing risk over time. It is therefore possible for the timing or occurrence of future events to be dependent on entities' attributes (such as in the case of increasing risk of developing polyps or colorectal cancer with age). As such, it is well suited to modelling heterogenous populations.

DES is helpful for gaining insight into real world systems by facilitating experiments otherwise unfeasible due to prohibitive costs or time requirements.(81,83) However, while DES models provide more flexibility in their representation of a system, the benefits should outweigh the consequences of greater granularity. Over-specification may

add unnecessary complexity to the model, resulting in substantially increased data requirements.(67,72) Despite the apparent ease of programming, highly complex DES models require sophisticated understanding of the underlying processes, which may lead both to an increased demand for analyst time and problems in validation in the event of poor communication between analysts and decision makers. Successful uptake of the results of such models relies on the transparency of the process.(72)

Of the identified modelling approaches, DES has been used most frequently in the evaluation of CRC screening interventions. Applications include broad evaluations of the effectiveness of screening and treatment options, including the development of colorectal cancer modules for the MISCAN (Microsimulation Screening Analysis) model,(79,80) the National Cancer Institute's Cancer Intervention and Surveillance Modeling Network (CISNET) in the U.S.,(84) and the Statistics Canada/Canadian Partnership Against Cancer (CPAC) Cancer Risk Management Model.(62) DES models have also been used to optimize the scheduling of colonoscopy services at the local level.(85–87) As most simulation models have either examined the effectiveness of various CRC screening strategies or have been used to optimize colonoscopy services, there appears to be a gap in terms of modelling the operationalisation of population-level colorectal cancer screening programs, or understanding the relationship between quality, access, and resource requirements. In particular, models commonly assume an unlimited colonoscopy resource, which effectively overlooks competition for services. While perhaps a reasonable assumption in unconstrained systems, this is not true in the case of jurisdictions with limited resources in which patients compete for timely access to services.

System Dynamics Modelling

System dynamic (SD) models are based on the principle that the structure of a system and the interaction of its components determine the overall behaviour of the system over time.(88,89) Continuous deterministic processes, rather than discrete changes in state, are described by differential equations and the influence of one variable on others is

identified, measured, and assessed for relevance.(90) SD models comprise both qualitative and quantitative components. Causal loop diagrams provide a qualitative understanding of the identified system elements by identifying feedback loops, while stock and flow models quantify the included variables by means of differential equations that represent the rates of change of the levels of stocks (e.g., patients).(91)

SD models are particularly useful if feedback loops are a factor, such as in the presence of service constraints where service load affects system performance and vice versa.(92) Feedback loops may be positive (self-reinforcing), in which system outcomes are reinforced or amplified, or negative (self-correcting), in which change is counteracted, serving to balance the system.(88,93) The direction and effect of feedback mechanisms may not be immediately obvious, and in fact may be delayed or counterintuitive, reinforcing the need for a systems-minded approach to health services research.(88,94)

In health services research, SD models are used mainly for policy analysis at the strategic level.(90) In contrast to DES, SD models are numerical solutions, describing patterns of system behaviours rather than generating point estimates.(94) Where DES models are capable of providing highly detailed information at the individual level, SD models offer the insight of a higher level of understanding of overall system behaviour.(95)

There have been examples of SD in the areas of breast cancer (96), Chlamydia (97), prenatal screening (98), and diabetes (99). In terms of colorectal cancer, Cooke and colleagues are modelling the proposed CRC screening program in Alberta, integrating disease progression, treatment, and screening in a stock and flow structure.(100) Refinements to the model to include age-varying parameters and risk factors are under way.

Agent-Based Modelling

Agent-based modelling (ABM) is perhaps the most recently adopted modelling method in health services research. Similar to DES, agent-based models consist of autonomous entities, or agents, acting within an environment. Agents are assigned rules that govern

their interaction with other agents and/or with their environment. As such, both individual and system-level analyses are possible. A distinguishing feature of ABM is the added complexity of the focus on interactions between agents and their environments, whether spatial or relational or otherwise influential.(101) The activity of agents describes the behaviour of a system over time, allowing representation of attributes independent of a predefined system process, unlike DES modelling.(101) The drawback of this flexibility is that it is difficult to separate the effects of individual parameters in highly complex models.

Commonly used in the social sciences, the method may be useful in the study of behaviours associated with participation in screening programs, allowing for the interactions between individuals as well as with the health care system to determine outcomes. To date, however, the application of ABM in cancer research has been mainly in the area of tumour development, where tumours are modelled as complex dynamic biosystems.(102)

DISCUSSION

Average risk screening of asymptomatic individuals with the goal of early identification of colorectal cancer or precancerous polyps is an important strategy in colorectal cancer control. While it is intuitively sensible to identify the disease in its earliest, most treatable stages, or to prevent it through the identification and removal of polyps, population-level colorectal cancer screening of average risk individuals is not without its pitfalls. Alongside the anticipated benefits of a screening program are potential risks and unintended consequences, including impeding access to colonoscopy services for higher risk and symptomatic patients. As such, the potential harms of screening are not borne by screening participants alone. Failure to understand the consequences of competition for limited colonoscopy services may result in suboptimal screening outcomes as well as poorer outcomes for higher risk patients already in the system. Consequently, in addition to the usual considerations of clinical and cost effectiveness, decision makers must

anticipate the effects of their decisions on the demand for services and on the outcomes for competing patient groups.

As colonoscopy resources are shared between average risk follow-up screening, higher risk screening, diagnostic, and surveillance activities, measures to manage the competition for colonoscopy resources (such as triage or resource allocation policies) must be evaluated for their effects on access, demand for downstream services, and outcomes for all patient types. The system, population, and patient outcomes of such policies have not been well examined to date. Understanding the potential risks associated with population screening, including the effects of inadequately resourced colonoscopy services, is key to their mitigation. Efforts to provide observational evidence are prudent, but unlikely to elucidate complex system interactions or long term outcomes.

Modelling provides a useful tool for the study of colorectal cancer screening. It allows "what if" experimentation when research is not otherwise feasible by means of randomised controlled trials or observational studies.(63,70,93,103) However, not all models are well suited to every research, clinical, or policy question. Decision tree analyses provide basic information on discrete choices for groups of patients; they have proven most useful in clinical decision making rather than the evaluation of screening. State transition models have been useful for examining cost-effectiveness of colorectal cancer screening, but do not provide information at the level of the individual patient. (73–78) Similarly SD models are useful for broadly focused questions at the population level.

Simulation models such as the MISCAN and CISNET models in the U.S. (79,80,84) and the CPAC Cancer Risk Management Model in Canada (62) evaluate various interventions for colorectal cancer, including population-level screening. DES models are capable of providing valuable insight at the individual level into estimated test positivity, disease incidence, costs and mortality rates as the result of selection of screening modality and strategy. However, as the majority of extant models do not explicitly model colonoscopy resources, they do not recognize competition for resources among patient groups nor allow for the investigation of resource allocation or triage policies.

In a system functioning at capacity, entities (in this case, patients) compete for colonoscopy resources insofar as the number and types of patients waiting in queues for services directly influences the access and subsequent wait times for incoming patients. To disregard this interaction is to overlook an important aspect of population-level colorectal cancer screening in many Canadian jurisdiction - the introduction of lower risk individuals into direct competition with higher risk patients for limited colonoscopy services.

Colorectal cancer screening does not function in isolation from diagnostic and surveillance colonoscopy services. Initial FOBT screening allows for selection of positive tests for colonoscopic follow-up; varying the positivity threshold further refines positivity rates. Nevertheless, the burden on colonoscopy services can be expected to increase substantially, particularly in the initial prevalent rounds of programmatic screening. In a system functioning at or near capacity, this introduces competition for resources between patient groups of varying risks. Increasing colonoscopy resources may not often be possible, or be an effective use of limited health care resources. Efforts to increase throughput, such as relaxing accreditation standards for participating endoscopists, may jeopardize quality of services. It is therefore essential to understand the effects of the introduction of average-risk screening patients to the system. In the absence of clinical evidence, simulation modelling, particularly DES, provides a tool capable of studying the problem of competition for limited resources, allowing careful implementation of population-level colorectal cancer screening.

However, given the limitations of existing simulations models as described above, we present in the next chapter a new simulation model (SCOPE) which explicitly considers average risk colorectal cancer screening in a system with constrained colonoscopy resources. Using the SCOPE model, we are able to study the demand for colonoscopy services by type (average risk screening follow-up, higher risk screening and diagnostic, and surveillance) and the effects of limited colonoscopy services on the effectiveness of screening activities.

CHAPTER FOUR UNDERSTANDING THE COMPETITION FOR COLONOSCOPY SERVICES WITH THE INTRODUCTION OF POPULATION-LEVEL SCREENING: A DISCRETE EVENT SIMULATION MODEL

Abstract

INTRODUCTION: Median wait times for gastroenterology services in Canada exceed consensus conference recommended targets and have worsened substantially over the past decade. Meanwhile, efforts to control colorectal cancer have shifted their focus to screening asymptomatic, average risk individuals. Along with increasing prevalence of colorectal cancer due to an aging population, screening programs are expected to add substantially to the existing burden on colonoscopy services. Failure to understand the effects of operational screening decisions may cause unintended harm to both screening participants and higher risk patients, make inefficient use of limited health care resources and ultimately hinder the program's success.

METHODS: We present a new simulation model (Simulation of Cancer Outcomes for Planning Exercises, or SCOPE) for colorectal cancer screening which, unlike many other colorectal cancer screening models, explicitly considers the effects of competition for limited colonoscopy services between patient groups and can be used to guide planning to ensure adequate resource allocation. As well, we present verification and validation results for the SCOPE model.

RESULTS: A discrete event simulation model was developed based on an epidemiological representation of colorectal cancer in a study population. Colonoscopy service and screening modules were added to allow observation of screening scenarios and resource considerations.

DISCUSSION: The study model differs from existing screening models in that it explicitly considers the colonoscopy resource implications of screening activities and the impact of constrained resources on screening effectiveness.

INTRODUCTION

There were approximately 23,900 new cases of colorectal cancer in Canada in 2013.(1) Incidence of the disease rises sharply after age 50, with more than 90% of cases occurring in this age group.(2) As a result, an aging population is expected to have a large impact on the incidence and costs associated with the disease.(3) Recent efforts to control colorectal cancer have shifted from screening higher risk individuals, such as those with a family history of the disease among first degree relatives, or who themselves have inflammatory bowel diseases, inherited syndromes or who are symptomatic, to screening asymptomatic average risk individuals from the ages of approximately 50 to 75 years. The goal of average risk population-level screening is twofold: (1) to interrupt the disease in earlier, more treatable stages, or (2) to prevent cancer by identifying and removing precancerous polyps or adenomas. (104,105).

To that end, several provinces in Canada have recently established or are planning population-based colorectal cancer screening programs (Table 2.2). Published recommendations provide general guidance for average risk screening, such as the target age group and the use of two-step screening by means of stool testing as a primary screening modality with colonoscopic follow-up of positive tests.(10,22–24,41,42) While most colorectal cancer screening programs in Canada follow the guidelines in these respects, considerable variation exists in terms of choice of stool test, positivity threshold, frequency of testing, recruitment methods, and allocation of colonoscopy resources. As these programs are recent initiatives, the effects of these decisions over time are not known.(45,46,106) Understanding the patient and health system effects of screening programs is essential for their sustainability, for justification of the opportunity costs of their operation, and to avoid unintentional harms.

Two-step colorectal cancer screening generally consists of the use of initial stool testing using either guaiac fecal occult blood testing (g-FOBT) or fecal immunochemical testing (FIT or i-FOBT) to identify trace amounts of blood in the stool. Positive cases are referred to colonoscopy services for colonoscopy to either confirm or rule out disease as the cause of bleeding. In the event of the detection of polyps, the growths are removed when possible and sent to pathology for examination. Several factors contribute to the

determination of risk of cancer based on the findings, including the number of polyps, cellular features and presence/grade of dysplasia (pre-cancerous changes). Patients are then referred for surveillance colonoscopies at time intervals ranging from a few months to 10 years, as determined by their risk of cancer.(107) Upon the detection of cancer, patients are referred to treatment (surgery, radiotherapy, and/or chemotherapy as appropriate).

Colonoscopy resources are required to provide colonoscopy services for a variety of patient groups. These include follow-up confirmation of positive stool tests for average risk screening program participants, including the provision of screening examinations for higher risk patients, diagnostic services for symptomatic patients, and surveillance services for all patient groups requiring follow-up. The implementation of average risk colorectal cancer screening is expected to add substantially to the existing demand for colonoscopy services in the short term as the result of positive stool tests requiring follow-up, and in the long term due to cumulative numbers of cases requiring surveillance. While useful in average risk screening programs for reducing the number of individuals requiring colonoscopy, stool tests have high false positive rates. Depending upon the selected test's positivity threshold, and resulting sensitivity and specificity, as many as 40% of patients presenting for average risk screening follow-up colonoscopies may have false positive stool tests.(13,108)

Alongside the anticipated benefits of a population-level screening program are potential risks and unintended consequences, both for patients and for the health care system. While an important strategy for the successful control of colorectal cancer, without adequate colonoscopic capacity average risk screening programs have the potential to impede access for other patient groups. A challenge for decision makers is to balance the needs of these different groups, ensuring adequate resources to allow timely access for those likely to have serious underlying disease while enabling the early detection of treatable disease or prevention of disease through the identification of polyps.

Determination of the sufficiency of local colonoscopy resources for the support of screening efforts is not straightforward. While it is generally possible to estimate the number of initial colonoscopies required to follow-up positive tests for any given stool

test or positivity threshold in the first round of screening, the shifting influences of disease prevalence, demographic characteristics, and uptake rates as well as the effects of variability and uncertainty over time quickly complicate the picture. A screening program should decrease the prevalence of the disease in the population over time, but this depends on uptake rates and effectiveness of the program. If effective, the need for diagnostic colonoscopies should decrease over time. However, to be effective, the program would require adequate numbers of screening follow-up colonoscopies. In the case of colorectal cancer where age of 50 years or older is a leading risk factor, an aging population is likely to increase the need for both diagnostic and screening follow-up colonoscopies, which in turn leads to increases in the demand for surveillance colonoscopies. The relative contributions of each of these influences over time are not well understood.

Further, considerable thought must be given to the triage of those competing for limited colonoscopy resources. In the event of inadequate resources, decision-makers could be faced with the ethical problem of identifying potential cases without the ability to confirm or rule out a diagnosis of cancer in a timely fashion. Wait times for confirmation of diagnosis have been shown to cause similar distress in the form of reduced quality of life and increased anxiety and depression measures for individuals with and without colorectal cancer, a week after being informed of their diagnosis. (109) Aside from causing nontrivial additional distress and inconvenience, prolonged wait times for colonoscopic follow-up of positive screening tests could reduce the effectiveness of screening.

On the other hand, efforts to minimise wait times for screening follow-up colonoscopies are likely to hinder access for higher risk individuals and as a result negatively impact patient outcomes. As colonoscopy resources are shared between follow-up average risk screening, high risk screening, diagnostic and surveillance activities, measures to manage the competition for resources must be evaluated for their effects on access, demand for downstream services, and outcomes for all patient groups.

Current decision-making for average risk screening has been based largely upon results extrapolated from limited clinical trials and observational studies, and is to be further

informed by the opportunity for the naturalistic observation of the implementation of various screening programs across Canada.(46) While it is clearly sensible to compare experiences, the dangers in this approach include an inadequate period of observation for several long-term outcomes of interest as well as an inability to differentiate between the effects of and interrelationships between various patient and system factors, particularly with a limited number of screening programs creating insufficient naturalistic variation in many variables of interest. Further, programs differ in multiple ways making it impossible to separate out the impact of individual variables.

The evaluation of programmatic colorectal cancer screening is complex, requiring the comparison of multiple strategies and interventions over long periods of follow-up – in the nature of 15 years or more for long-term outcomes. Consequently, such questions do not easily lend themselves to randomised controlled trials (RCTs) or observational studies. Further, these studies are not well suited to providing information regarding the dynamic interrelationship between population, patient, and system factors.

A systems-minded evaluation of the effects of health services decision-making requires tools capable of handling these factors. Decision analyses such as state transition or discrete event simulation (DES) models provide such tools as they can enhance the understanding of the system understanding by requiring close scrutiny of the various components and their interactions, combine data from multiple sources, and allow for the examination of "what if" questions.(63,70,93,103)

Indeed, simulation modelling has been used to understand various population and system implications of average risk colorectal cancer screening efforts.(48,79,110) Most models have not explicitly modelled colonoscopy resources, or have assumed unlimited colonoscopy capacity. This is a reasonable assumption when health care resources are sufficient. In the event of constrained resources, however, patients in the system compete with one another in that one cannot access services if the services are occupied providing care to another patient. Without additional colonoscopy resources, the greater the number of patients in the system, the longer one would expect to wait for services to become available. This is of particular concern when proposing a program that would effectively introduce a new patient population into an already constrained system.

A DES model (Simulating Cancer Outcomes for Planning Exercises, or "SCOPE") was constructed to evaluate the effects of the implementation and maintenance of a population-level colorectal cancer screening program on patient and system outcomes in a simulated publically funded health district, with particular attention paid to the competition for limited colonoscopy resources between different patient groups. Patient groups included those for follow-up of positive stool tests in an average risk screening program, higher risk screening and diagnostic patients, and patients requiring colonoscopic surveillance following positive findings on colonoscopic examination. This paper presents the SCOPE model, delineates its assumptions and reports validation and calibration results.

THE SCOPE MODEL

While there have been several efforts to examine colorectal cancer screening using simulation, most models do not incorporate the effects of competition for colonoscopy resources. (48,79,110) As such, they do not account for the competition for colonoscopy resources between average risk and high risk screening, diagnostic, and surveillance patients, which is a key concern in a system with limited resources. Of the modelling methods, discrete event simulation (DES), in particular, readily enables the representation of competition for resources, operational factors such as resource constraints (e.g. limited colonoscopic facilities or endoscopists) and queuing, as well as handling stochasticity and uncertainty.(64,111,112)

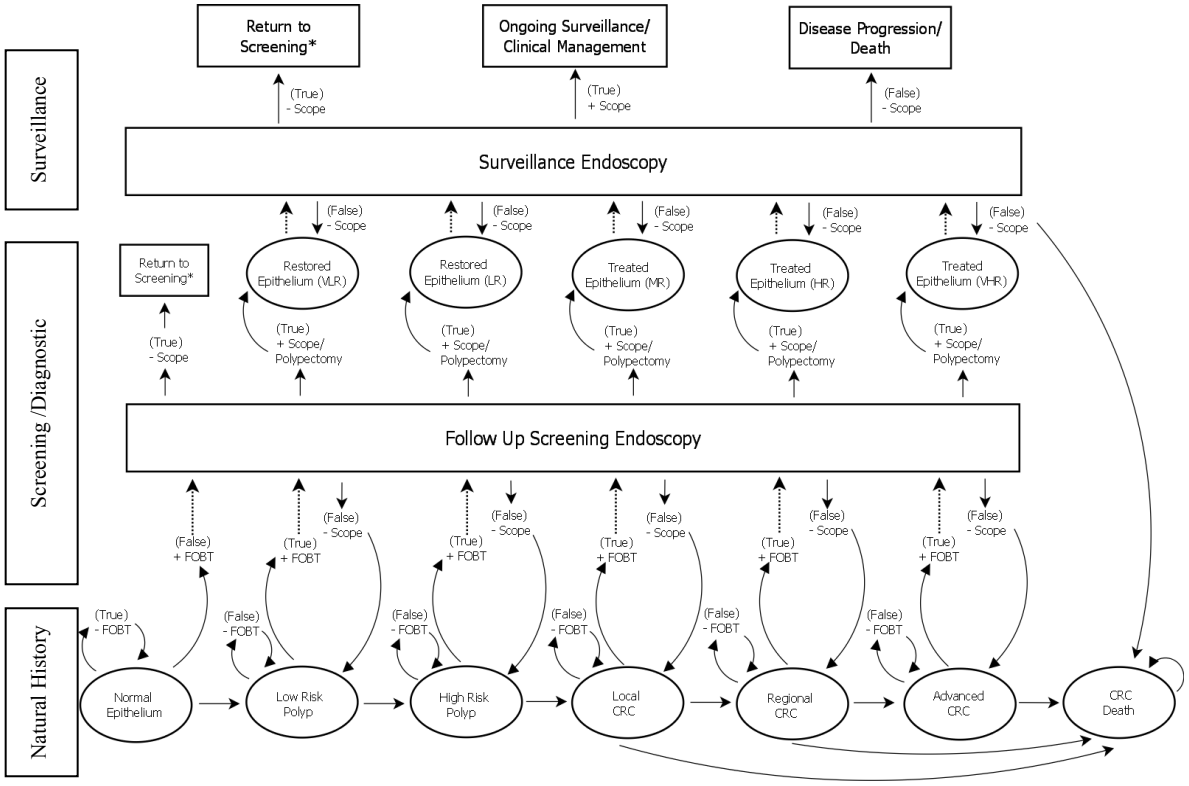
Accordingly, a DES model consisting of natural history, screening, and colonoscopy service modules was constructed using Arena® simulation modelling software.(113) A base model was constructed, with increasing complexity introduced as needed. The research questions, performance measures and availability of data guided the level of detail specified in the model.

The natural history module acted as the foundation of the model. It simulated the progression of colorectal cancer in the study population, providing an epidemiological

baseline of the status quo with which to compare screening and surveillance interventions. Individuals in the model aged, grew polyps and developed cancer according to observed rates. Treatment was not explicitly modelled; rather, treatment effects were reflected in the incorporation of five-year colorectal cancer survival rates into the transition probabilities between cancer stages and deaths, with increased survival in earlier stages. For example, five-year survival rates for early stage colorectal cancer are upwards of 90%, falling to less than 10% for advanced stages.(7) Model assumptions and input data are provided in Appendix 2.

The full SCOPE model integrated the natural history, screening/diagnostic, and surveillance modules as depicted in Figure 4.1. Screening, diagnostic and surveillance colonoscopy activities were layered upon the natural history module. Integration of all modules was necessary for observing the interaction between the various model components and screening program and service delivery strategies, such as the priority setting of specific patient types of interest.

Figure 4.1 Process Map of Full SCOPE Model



Definitions:
Normal epithelium: Absence of polyps or colorectal cancer
Low risk polyp: <1cm, tubular histology, ≤ 2 polyps
High risk polyp: >1cm, high-grade dysplasia, villous histology, between 3-10 polyps
Local colorectal cancer: Invasion into or through the bowel wall (no lymph node involvement) (Dukes A&B)
Regional colorectal cancer: Involvement of lymph nodes (Dukes C)
Advanced colorectal cancer: Widespread metastases (Dukes D)

Restored Epithelium:
VLR = Very low risk (e.g., small rectal hyperplastic polyps) are considered normal epithelium – repeat colonoscopy in 10 years
LR = Low risk (e.g., 1 or 2 small (<1cm) tubular adenomas with only low-grade dysplasia) – repeat colonoscopy in 5-10 years
MR = Moderate risk (e.g., 3-10 adenomas or adenoma ≥ 1cm or with villous features or high-grade dysplasia) – repeat colonoscopy in 3 years if removed completely

Treated Epithelium:
HR = High risk (e.g., >10 adenomas at 1 exam) – repeat colonoscopy in < 3 years
VHR = Very high risk (e.g., sessile adenomas removed piecemeal) – repeat colonoscopy every 2-6 months until cleared, then as per endoscopist judgment

Natural History Module

The natural history module simulated the development of colorectal cancer based on the adenoma-carcinoma sequence.(4–6) Briefly, the adenoma-carcinoma (or polyp-cancer) sequence is an approximately 10-year stepwise process in which the normal epithelial tissue lining the large intestine transitions through dysplastic (precancerous) changes in cells to carcinoma (cancer).(4–6) The majority of colorectal cancers develop from polyps; however, only a small proportion of polyps go on to become cancer.(6) Due to a lack of direct evidence of the rate of development of de novo cancers, all colorectal cancers in the model were assumed to develop from pre-existing adenomas.

Potential for malignancy varies by polyp size, histological type, and the grade of epithelial abnormality.(4) Polyps were categorized in the sequence as low or high risk. Cancer was broadly classified as either early (localized), regional, or advanced (metastasized) disease.

The population was stratified into two adenoma-carcinoma risk groups: average and high risk. For the average risk group, the onset of and progression to any stage in the adenoma-carcinoma sequence was assigned based upon transition probabilities derived from age-specific incidence rates in average risk Western populations (Appendix 3).(114–

118) Higher risk individuals were those with a history of colorectal cancer among first degree relatives or with predisposing conditions such as inflammatory bowel disease or inherited disorders.(119–121) Higher risk individuals were considered twice as likely to develop polyps as those at average risk.(41) Annual transition probabilities and initial stages for higher risk individuals were adjusted based on this assumption.

The natural history model also incorporated background mortality. For each individual in the model, age- and sex-specific background mortality rates (deaths from all causes) were applied annually based on Statistics Canada Life Tables (2007-2009).(122) Individuals were subject to competing risks of both background and colorectal cancer mortality, assuming conditional independence of the risks. Using standard approaches to handling competing risks widely used in multi-decrement life tables, individuals were exposed to the risk of both causes of death each year, and the attribution of cause was stochastic and proportional to the force of mortality for each cause.(123)

Adenoma-carcinoma stages were updated yearly for individuals who survived the year; individuals remained in a given stage or progressed to the next stage. Colorectal cancer mortality rates depended on stage. Colorectal cancer death occurred as a result of local, regional, or distant cancer states. (Input data are provided in Appendix 2.)

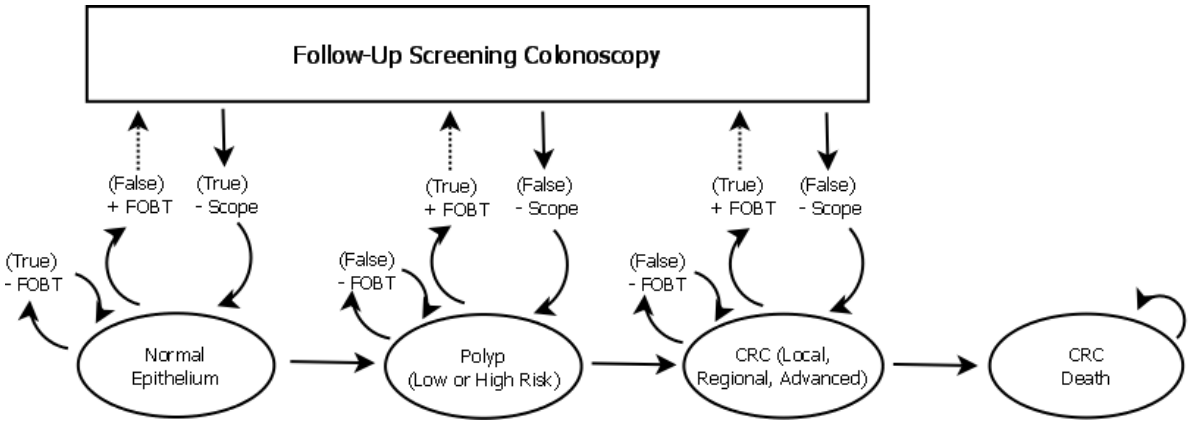
Screening Module

The purpose of the screening module was to simulate the uptake and outcomes of fecal occult blood test screening. Screening activities were layered on to the natural history module. They allowed the simulation of screening programs directed to asymptomatic, average risk, 50 to 74 year olds and examined changes in case capture due to variations in participation rates, test sensitivity and specificity, demographic factors and disease prevalence. Higher risk individuals were screened using primary colonoscopy.

In a two-step average risk screening program such as recommended in Canadian guidelines, fecal occult blood testing (FOBT) could be simulated using either guaiac (g-FOBT) or immunochemical (FIT) test parameters, and follow-up of positive tests

modelled using repeat FOBT (g-FOBT or FIT), colonoscopy or flexible sigmoidoscopy as the modality of choice. A simplified version of the relationship between screening activity and colonoscopy services is provided in Figure 4.2.

Figure 4.2 SCOPE Simulation of Screening Activities



As individuals progressed through the model, random draws from probability scores determined the uptake of and outcome of stool testing and colonoscopy (positive or negative, and in the case of positive colonoscopy, stage of findings) based on the uptake, sensitivity and specificity of the exams as reported in the literature for each stage in the adenoma-carcinoma sequence. There is substantial uncertainty around the estimates of sensitivity and specificity of stool tests reported in the literature. This uncertainty was captured using sensitivity testing of the range of values reported in studies of average risk individuals. Individuals' screening outcomes (whether true or false positive/negative) depended upon their true status as assigned by the natural history module and the sensitivity and specificity of the test.

Identification of adenomas or cancer as a result of screening led to follow-up investigation and treatment sequelae (e.g. removal of adenomas or effective treatments) that altered the underlying adenoma-carcinoma sequence provided by the natural history module. Thus, the model measured screening effectiveness as aggregate differences in

outcomes between screening and no screening scenarios. As such, various screening strategies could be compared both with the status quo, and against each other.

In the event of nonparticipation in screening, or in the case of participation in screening with false negative results, individuals progressed to advanced disease stages, as per the natural history module, with increasing likelihood of detection through symptomatic presentation and diagnosis.

Colonoscopy Services Module

Individual patients presented to colonoscopy services by one of three main pathways: (1) due to a positive screening test, (2) by becoming symptomatic, or requiring a higher risk screening by colonoscopy, and (3) by requiring ongoing surveillance colonoscopy due to a positive colonoscopy in any patient group. Individuals were classified into patient types: average risk screening follow-up, diagnostic or higher risk colonoscopy screening, and surveillance patients. Colonoscopy services were apportioned by patient type. In this way, it was possible to represent triage strategies by each of the three pathways. This approach allowed for the representation of competition for colonoscopy services by the various patient types, and enabled the examination of the effect of various triage strategies on patient and system outcomes.

Colonoscopy resources were modelled as available colonoscopy "slots". Factors influencing their availability, such as human resource requirements, equipment availability or funding decisions were considered exogenous to the model; although the model could be extended to explicitly model these factors. Colonoscopy slots were specified to be either for average risk screening follow-up, diagnostic or high risk screening, or surveillance activities, and were reserved for the appropriate patient group. This allowed for manipulation of the distribution of colonoscopy resources to approximate triage strategies to estimate patient population and system outcomes.

Following colonoscopy, colorectal epithelium was assumed to be either: 1) restored following removal of either very low risk (VLR) or low risk (LR) small (< 1 cm) tubular

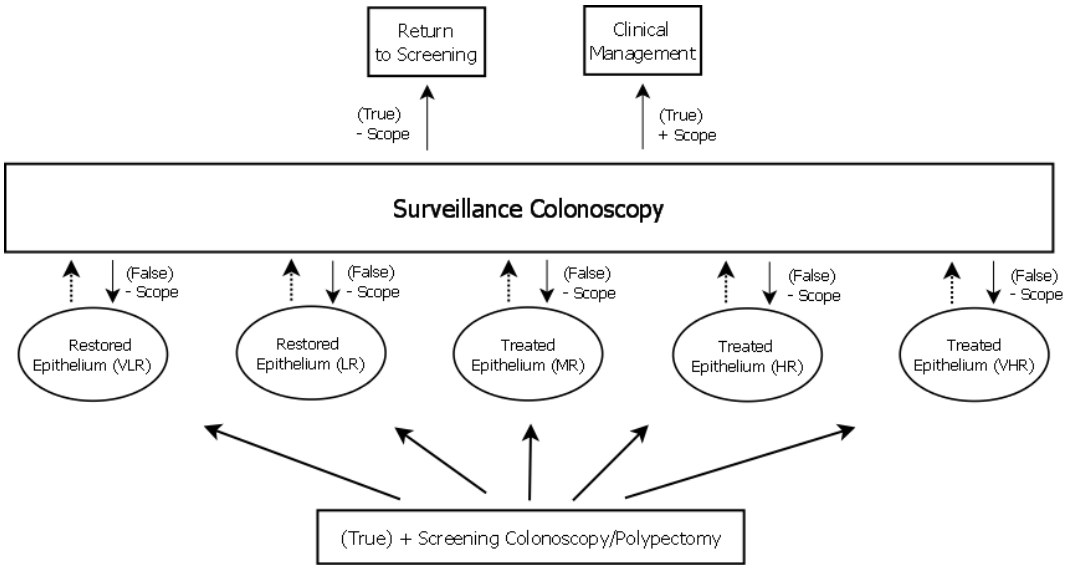
adenomas with only low-grade dysplasia, or 2) treated following removal of either moderate risk (MR) adenomas (3-10 in number or adenomas ≥ 1 cm or with villous features or high-grade dysplasia), high risk (HR) adenomas greater than 10 in number, or very high risk (VHR) sessile adenomas removed piecemeal. Colonoscopy findings were based on increasing likelihood of detection with increasing stage in the adenoma-carcinoma sequence.

In most jurisdictions in Canada, primary screening with colonoscopy is limited to higher risk individuals. Due to resource constraints, it is generally not offered as a primary screening modality for average risk individuals. However, the SCOPE model can be set up to model the use of colonoscopy as a primary screening modality among average risk individuals by directing screening participants directly to colonoscopy services rather than requiring a positive stool test.

Surveillance Activities

Surveillance activities (Figure 4.3), whereby patients with adenomas or carcinomas detected through colonoscopy undergo subsequent surveillance with colonoscopy, were also modelled within the colonoscopy services module. This enabled modelling of the demand for colonoscopy services resulting from surveillance. Individuals from either of the average risk follow-up screening or the diagnostic colonoscopy arms could be directed to surveillance colonoscopy services based on the findings of their index or subsequent surveillance colonoscopies. The frequency of surveillance varied according to the findings, and was based upon North American guidelines for follow-up.(10,42,124)

Figure 4.3 SCOPE Surveillance Module



Screen shots of the population creation, natural history, and colonoscopy process modules are provided in Figures 4.4 – 4.8.

Figure 4.4 SCOPE Model – Population Module Screen Shot

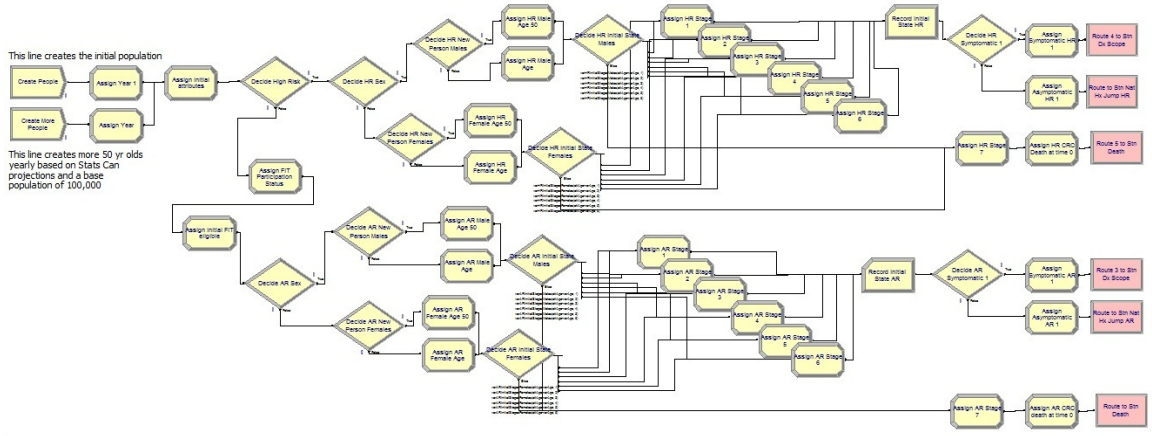


Figure 4.5 SCOPE Model – Natural History Module Screen Shot

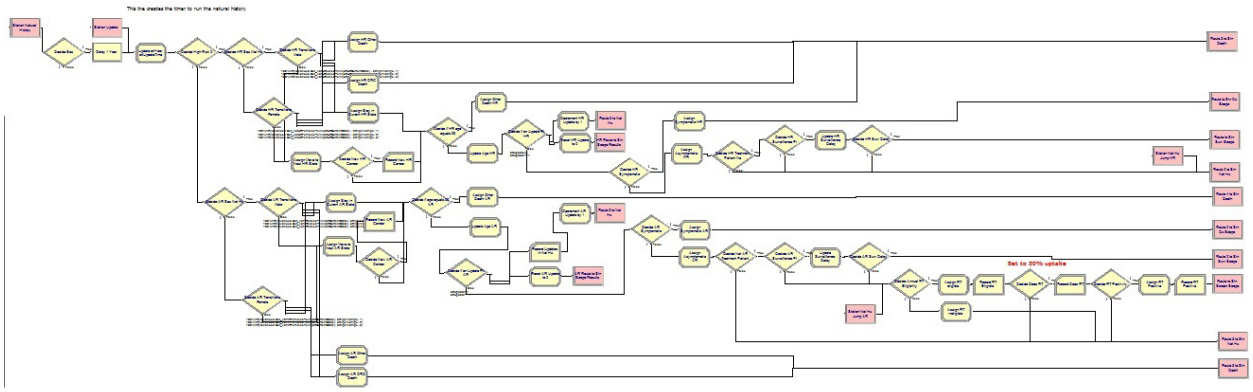


Figure 4.6 SCOPE Model – Colonoscopy Process Module Screen Shot (1)

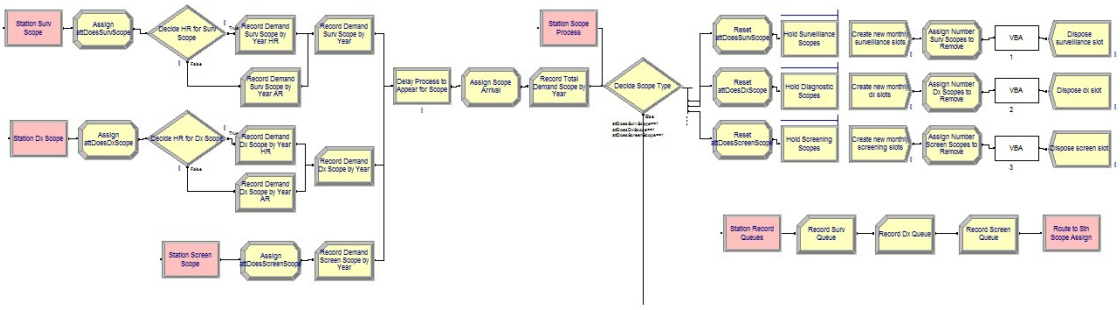
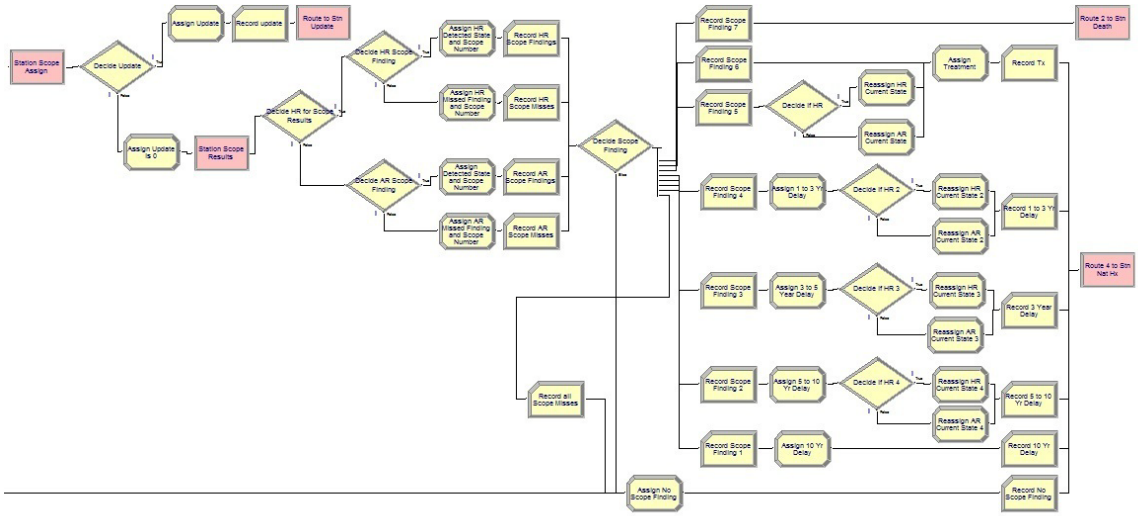


Figure 4.7 SCOPE Model – Colonoscopy Process Module Screen Shot (2)



INPUT DATA

Data for the SCOPE model parameters and transition probabilities were collected from a variety of sources, including publically available administrative and survey data sources, published RCTs and observational studies, and expert opinion. Input-output relationships were examined to determine whether they were reasonable. A detailed list of assumptions, data elements and their sources can be found in Appendix 2. Annual transition probabilities are provided in Appendix 3, and the distribution of starting stages in the adenoma-carcinoma sequence is specified in Appendix 4.

Where possible, parameter values represented those observed in community settings rather than RCTs, in order to more accurately reflect observations outside of strict study protocols. The model consisted of a combination of deterministic and stochastic variables. For example, variables such as the number of colonoscopy slots are not random and were specified to reflect the availability of services. On the other hand, patient arrival rates to colonoscopy services or transition probabilities between states were represented as stochastic variables to more accurately reflect uncertainty in the system.

Alternative estimates were available for many model parameters, and verification and validation processes were used to select final model parameters among plausible estimates. Estimates were selected initially based upon available rates for the adenoma-carcinoma as conceptualized in the model. Observations derived from average risk populations were selected over higher risk clinical subpopulations, and were refined by age- and sex-specific rates where available. Parameter estimates were tested by running the model and evaluating their effect on the main outcomes of interest.

Sensitivity analysis was used to determine the effects of input data parameters to determine which components had a significant impact on performance measures. By running the model with a range of values, it was possible to determine whether measures of system performance changed significantly.(125) If system performance measures were highly sensitive to changes for an input parameter, close attention was paid to the quality and reliability of the input data for confidence in the model results. For example, the outcomes of interest were not sensitive to changes in background mortality or age, but

were very sensitive to transition probabilities for changes between stages in the adenoma-carcinoma sequence. Therefore, much of the calibration of the model concentrated on refinement of these transition probabilities.

VALIDATION AND VERIFICATION

Validation and verification of simulation models aims to determine whether models and their outputs are "correct". Validation confirms accurate representation of the system under study (i.e., "Did I build the right thing?"), while verification ensures that the programming and implementation are correct (i.e., "Did I build the thing right?").(126) Every opportunity was taken to validate and verify the SCOPE model during the development process. Construction of the model using Arena® software afforded visual representations of the model to aid with communication to interested parties.(113) Validation and verification is an iterative process, and is outlined in detail below.(64) Briefly, the conceptual model was validated initially for the accuracy of its representation of the system. Once built, the simulation model was verified to determine whether the assumptions in the conceptual model had been accurately programmed through debugging, testing of extreme input values, tracing the paths of individuals through the program, and review by team members. Finally, output data were validated by comparison with existing performance measures and other models, where available.

Conceptual Model Validation

Standard practices were followed for the initial validation of DES models.(64) The conceptual and simulation models were validated as being representative of the system under study through consultation with those familiar with colorectal cancer development and progression, screening activities, and colonoscopy service provision. Assumptions were acknowledged in a written document (Appendix 2) and were validated for accuracy through interviews with gastroenterologists, colorectal cancer screening nurses, and colonoscopy booking clerks prior to programming the simulation model. A time study

was conducted in an active colonoscopy suite to confirm assumptions regarding process and capacity.

Simulation Verification

The model was run initially for debugging, which involved methodologically reviewing the computer programming to detect and correct errors. The model was constructed in stages, beginning with moderate levels of detail and adding increasing detail and subprograms as necessary, which were debugged successively before they were built upon. The model was debugged again in its entirety once completely constructed. Coding and processes were reviewed by team members.

Extreme values were tested and probabilistic input data replaced with deterministic values to test whether the output was reasonable. Deterministic Markov models were used for comparison when appropriate, such as when verifying the outcomes of the natural history process to ensure the accuracy of the Monte Carlo processes employed in the probabilistic aspects of the DES model. The point estimates generated in the Markov models of the natural history were included in the confidence intervals generated by the DES model. The model's behaviour was observed graphically as the simulation clock ran and patient flow pathways monitored. Individuals were traced as they progressed through the model to ensure flow was as expected. Counters were placed at several intervals and checked using hand calculations to ensure the program operated as envisioned.(64)

Output Validation

Key to validation of a DES model is validation of the model's output.(64) The natural history module was validated by assessing its ability to reflect Canadian colorectal cancer incidence and mortality data. Once successfully running, the model was calibrated by comparing model and patient outcomes and system performance measures with real world observations where possible. The SCOPE model can be initialized for either a population or a cohort, and both were used for validation purposes.

Initialization of the SCOPE model with a cohort of 50-year old individuals permitted the calculation of life tables from the model from which could be compared with Canadian life tables generated from vital statistics data.(122) The model was run over a 50-year horizon with cohorts of 100,000 50-year old individuals (males and females of average and higher risk) and replicated 100 times to generate 95% confidence intervals of sufficient width for reasonable precision. Capturing the numbers of deaths at yearly intervals allowed for the construction of life tables and the calculation of life expectancies for comparison with those provided by the Statistics Canada Life Tables (2007-2009). The life tables generated from the model are presented in Appendix 5.

Life expectancies for the synthetic cohorts entered into the natural history module were slightly lower than those reported in Canadian life tables. This is not unexpected, as the cohorts were exposed to the mortality of colorectal cancer in addition to the background mortality rates (which includes colorectal cancer and related causes of death). The life expectancies for males and females of average risk were not significantly different than those for the Canadian population ($p=0.8317$ and $p=0.8073$, respectively). Similarly, the life expectancies for males and females of higher risk were lower than those for average risk individuals but again, were not significantly different from than those for the Canadian population ($p = 0.8030$ and $p = 0.7585$, respectively). Sensitivity analyses to setting background mortality rates ±5% of observed rates made no difference to the results. These results provided confidence in the comparability of the synthetic life expectancies generated by the model with those observed in the Canadian population.

The model was run again with populations of individuals of ages 50 to 99 years, distributed by age and sex based on the 2006 Canadian Census.(127) This permitted comparison of the proportion of colorectal cancer deaths in the synthetic populations with those reported in the Canadian population in 2006.(128) While the purpose of the SCOPE model was not to simulate death rates for the population, the CANSIM rates provided a useful comparison for the observed patterns of colorectal cancer mortality by age, sex and risk levels. Proportions were compared for average and higher risk individuals, and for males, females and both sexes (Figures 4.8-4.10).

Figure 4.8 Proportion of Colorectal Cancer Deaths/All Deaths – Males

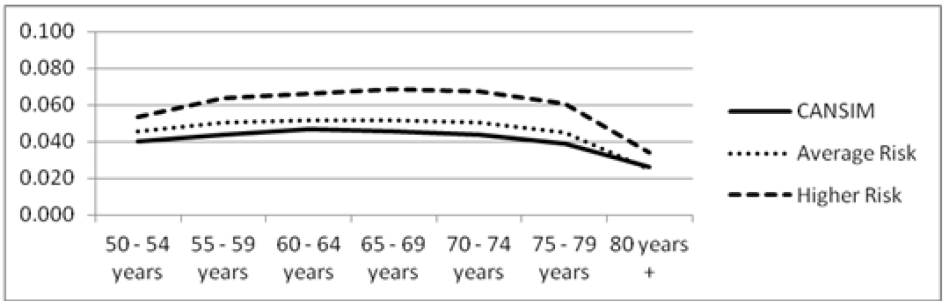


Figure 4.9 Proportion of Colorectal Cancer Deaths/All Deaths – Females

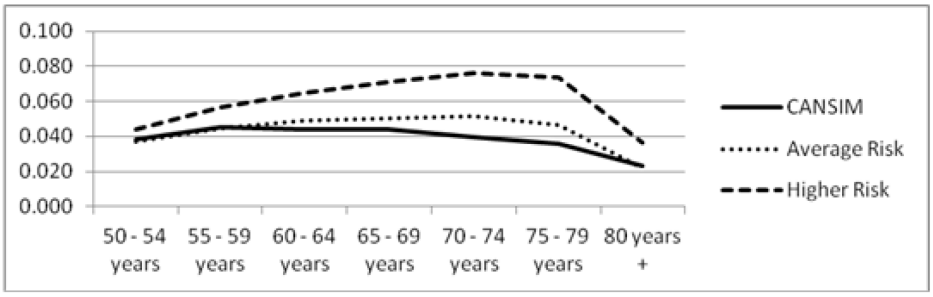
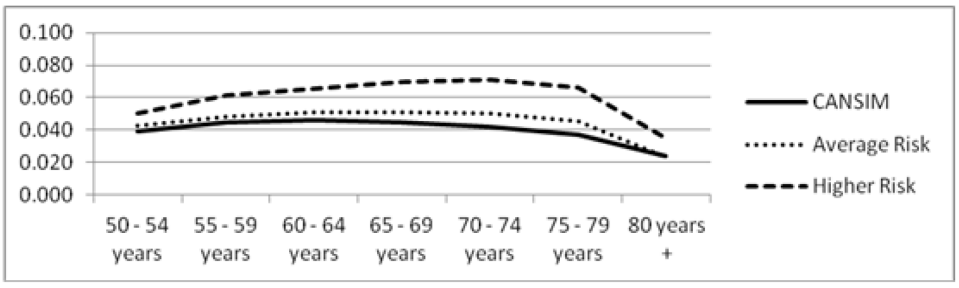


Figure 4.10 Proportion of Colorectal Cancer Deaths/All Deaths - Both Sexes



The proportions of colorectal cancer deaths in the simulated populations mirrored those observed in the Canadian population. The proportion of colorectal cancer deaths among the synthetic average risk population is slightly higher than that observed in the Canadian population. This is likely due to the assumption of independence between colorectal cancer death and all-cause mortality in the SCOPE model. In fact, due to shared risk factors, those at risk of colorectal cancer mortality are also at higher risk of other related causes of mortality, such as other cancers, cardiovascular disease and diabetes.(129) This phenomenon is reflected in the CANSIM figures. However, this relationship is highly complex, with little supporting data to elucidate a clear picture of the nature of the relationship, and as such we chose not to adjust mortality by introducing dependence into death probabilities. The consequence is that the model may slightly overestimate the proportion of deaths due to CRC.

As expected, colorectal cancer deaths accounted for consistently greater proportions of deaths among the higher risk populations. Adjusting the transition probabilities from normal epithelium to low risk polyps to twice that of the average risk population allowed for calibration of the model to reflect the higher observed rates of disease and disease-related mortality among the population at higher risk of colorectal cancer. Higher risk individuals, such as those with IBD or first degree relatives with colorectal cancer, are approximately twice as likely to develop the disease than average risk individuals.(120)

To validate the colonoscopy module, total demand for colonoscopies were comparable to the observed numbers of colonoscopies performed among Ontario residents 50 to 74 years of age in the absence of organized population screening (Table 4.1). Schultz and colleagues reported colonoscopy rates ranging from 286.8 per 10,000 people in the eastern region to 463.1 colonoscopies per 10,000 people in the northern region.(130) The figures estimated by the model are conservative in the initial years, given that the demand for surveillance colonoscopy reflects only the demand generated onward from time 0. The model also does not account for opportunistic screening, which would have contributed to the rates observed by Schultz and colleagues. Opportunistic screening rates vary significantly by province, with some provinces having very little or no capacity to offer it.

Table 4.1 Demand for Colonoscopies per 10,000 Population

Year	Colonoscopies/10,000 without Average Risk Screening (95% CI)	Colonoscopies/10,000 with Average Risk FIT Screening† (95% CI)	Colonoscopies/10,000 with Average Risk g-FOBT Screening† (95% CI)
1	155.7 (154.9-156.5)	237.2 (236.3-238.1)	283.5 (282.6-284.5)
2	156.4 (155.6-157.2)	235.7 (234.7-236.7)	280.8 (279.7-281.9)
3	156.0 (155.2-156.7)	231.5 (230.7-232.3)	279.2 (278.1-280.3)
4	163.7 (162.8-164.6)	240.1 (239.2-241.0)	287.0 (285.9-288.2)
5	165.4 (164.6-166.3)	240.0 (238.9-241.0)	287.0 (285.8-288.2)
6	175.6 (174.8-176.5)	252.5 (251.4-253.5)	299.1 (297.9-300.2)
7	180.9 (180.0-181.9)	257.7 (256.7-258.7)	304.0 (302.8-305.1)
8	182.3 (181.4-183.3)	258.6 (257.5-259.6)	304.6 (303.5-305.6)
9	183.1 (182.2-183.9)	258.8 (257.8-259.7)	304.4 (303.3-305.4)
10	184.4 (183.4-185.4)	260.5 (259.4-261.5)	304.6 (303.6-305.7)
11	188.6 (187.8-189.4)	264.9 (263.8-266.0)	308.3 (307.2-309.4)
12	191.0 (190.1-191.9)	263.8 (262.9-264.8)	307.4 (306.3-308.4)
13	193.4 (192.5-194.3)	264.4 (263.4-265.4)	307.1 (305.9-308.4)
14	195.8 (194.9-196.6)	265.4 (264.3-266.5)	307.5 (306.4-308.6)
15	197.9 (197.2-198.7)	263.9 (262.8-264.9)	305.8 (304.6-307.0)

†Assumes average risk population ages 50-74 years, biannual administration, 30% uptake rate. Sensitivity and specificity are listed in Appendix 2.

Between-Model Validation

Independent development of simulation models provides an opportunity to test corroboration.(131) The SCOPE model's outputs were compared to published results of other simulation models employing a natural history perspective, particularly the Canadian Cancer Risk Management Model (CRMM), as it incorporates Canadian demographic data and assumes a publicly funded health care system. While the SCOPE model differed from the CRMM in terms of assumptions and the consideration of competing patients, both models similarly reproduced observed Canadian colorectal cancer incidence and all-cause mortality rates.(132) System outcomes, such as wait times for colonoscopy, could not be compared as these are not modelled by the CRMM.

DISCUSSION

Simulation modelling is becoming an increasingly popular tool in health services research. It provides a powerful means for evaluating policy decisions in a complex, dynamic environment. However, most efforts assume unlimited colonoscopy resources, which does not adequately reflect the reality of the competition between patients for often scarce resources in a constrained health care system. The SCOPE model was constructed to facilitate the study of the effects of various population-level screening decisions on competing patient groups within a constrained colonoscopy service system. Attention to the system requirements of alternative screening scenarios by service type (e.g., screening, diagnostic, or surveillance colonoscopy) is necessary for appropriate triage strategies and useful for informing decisions regarding the allocation of resources.

The introduction of new patient populations into a constrained health care system, such as occurs with the advent of population-based screening, requires the careful consideration of both the short- and long-term consequences of the screening yield and cumulative surveillance requirements amid the fluctuating effects of disease prevalence and demographic factors. Of particular concern with colorectal cancer screening is the competition for limited colonoscopy resources between patient groups of varying risk. In a population-level, two-step screening program, asymptomatic average risk individuals are invited to take a test which is unable to either confirm or rule out disease. In addition to the ensuing anxiety and relatively high likelihood of false negative results, they may then need to be referred for follow-up colonoscopic examinations with nontrivial risk profiles. In the event of inadequate colonoscopy resources, this could create a situation in which individuals are unable to have a potentially serious diagnosis confirmed or ruled out in a timely fashion. Further, prolonged wait times could serve as a general disincentive to participation in screening activities which would in turn hinder the programs' effectiveness.

Conversely, efforts to minimise wait times for screening follow-up colonoscopies have the potential to hinder access for higher risk and symptomatic individuals. Failure to understand the effects of priority setting decisions may hinder the program's success, cause unintended harm, and make inefficient use of limited health care resources. Unlike

many previous colorectal cancer screening models, the study model specifically considers the effects of competition for resources among patient groups of varying risk. This can be observed under varying conditions such as at the start-up of the screening program, when the prevalence of late stage cancer would be expected to be higher than after several rounds of screening.

As in all models, there are many sources of uncertainty. It is usual to compare different modelling approaches to the same problem; however, the choice of approach was limited by the need to represent interaction between patient types within the system. Comparison with deterministic Markov models was limited to the verification of the outcomes of the natural history process due to the complexity of the conceptual model. However, this was useful for ensuring the accuracy of the stochastic processes employed in the SCOPE model. Desired accuracy of the point estimates was achieved by running large populations and cohorts (100,000 individuals) over 100 repetitions.

There are also limitations to consider. The SCOPE model assumes the independence of colorectal cancer mortality and all-cause mortality, which is not the case. In actual fact, individuals at higher risk of colorectal cancer mortality are also at higher risk of other causes of mortality, through shared risk factors. For example, physical inactivity and obesity increase the risk of developing colorectal cancer, cardiovascular disease and diabetes.(129) As well as being beyond the scope of this model, this relationship is unlikely to affect the comparison of outcomes between the synthetic average and higher risk populations. Colorectal cancer mortality was not subtracted from of all-cause mortality, as modelling patient mortality was not a primary purpose of the SCOPE model. This was unlikely to affect demand or competition for colonoscopies, which were the main outcomes of interest. Opportunistic screening was not considered as it varies considerably between provinces and relies upon availability of colonoscopy resources. It is unlikely to alter the study findings, as it would be provided only if resources were available beyond the demand of programmatic or higher risk screening, diagnostic and surveillance activities.

The main strengths of the SCOPE model reside in its recognition and representation of the competition for limited colonoscopy services between different patient groups,

integration of the most currently available information, and the inclusion of observations from population screening programs where available. This approach is essential for an accurate understanding of the effect of the introduction of a lower risk patient population into a health care system already struggling to meet the needs of a higher risk patient population, and has applications to other population-level screening endeavours. The model is flexible in that it permits study of various screening scenarios, including two-step screening with a stool test followed by colonoscopy as well as primary screening with colonoscopy as in use in other jurisdictions such as the United States.

CHAPTER FIVE THE EFFECTS OF AVERAGE RISK COLORECTAL CANCER SCREENING ACTIVITIES ON THE DEMAND FOR COLONOSCOPY SERVICES

Abstract

INTRODUCTION: Average risk colorectal cancer screening activities are expected to initially increase demand for colonoscopies as a result of case finding, but if successful could lead to decreases in disease prevalence and diagnostic colonoscopies over time, resulting in fewer individuals requiring services. Expected demand for colonoscopy services is not well understood.

METHODS: A discrete event simulation model ("SCOPE") was constructed to examine the influence of population-level screening on the demand for colonoscopy services for average risk screening follow-up, diagnostic/higher risk screening, and surveillance purposes over a 15-year time horizon. Average risk screening scenarios utilizing tests of varying sensitivity and specificity were compared to a baseline scenario without screening to observe the effects on relative additional demand for colonoscopy services and associated wait times. Secondary outcomes included crude colorectal cancer incidence and cumulative colorectal cancer mortality.

RESULTS: The additional demand for follow-up of positive stool tests in average risk screening programs and subsequent surveillance colonoscopies ranged from 33% to 54% higher than the no screening baseline scenario and was not offset by decreases in demand for diagnostic colonoscopies, regardless of screening strategy. With unconstrained colonoscopy resources, average risk screening reduced crude annual colorectal cancer incidence by 13.2% to 17.3%, and cumulative colorectal cancer mortality by 8.6% to 10.4%, depending on the stool test selected. When colonoscopy services were constrained, incidence rates were approximately 8% higher in each screening scenario and mortality rates were 1% higher compared to the unconstrained resource scenarios.

DISCUSSION: Without the provision of additional colonoscopy resources, wait times for follow-up screening and surveillance colonoscopies were well beyond consensus recommendations, and the full potential benefits of screening were not realised.

INTRODUCTION

Many jurisdictions in Canada and Europe recommend two-step average risk colorectal cancer screening consisting of a stool test followed by colonoscopy for positive cases as a means of offering the benefits of screening while mitigating the additional demand on colonoscopy services.(10,42–44) Stool tests suitable for programmatic screening include sensitive guaiac fecal occult blood tests (g-FOBT) and fecal immunochemical tests (FIT, or i-FOBT). There are several versions of each available on the market, with widely differing estimated levels of sensitivity and specificity reported in the literature (Appendix 1).(40,52,53,133–138) Generally, the FITs appear to have higher specificity than g-FOBTs for advanced neoplasia, resulting in fewer false positive tests.(138,139) FITs may also be more sensitive to smaller lesions.(40,52) The sensitivity and specificity of selected tests influences the number of positive tests requiring colonoscopic follow-up.

When implementing a population-based colorectal cancer screening program, it is essential to consider how to manage both the short and long term consequences of the yield from screening. The underlying prevalence of undiagnosed disease in the target population is a major factor in determining the number of previously unrecognised cases detected by screening (case finding). At the onset of population screening, it is anticipated that the relatively high prevalence of previously undetected cases will initially lead to a substantial increase in the burden on the health care system. While this should lessen after several rounds of screening, the cumulative nature of the ongoing surveillance of positive cases with follow-up colonoscopies will likely create a growing demand for colonoscopy services.

On the other hand, the number of symptomatic individuals requiring diagnostic colonoscopy services will likely decline somewhat over time, as the screening program should eventually result in fewer cancers progressing to advanced stages.(104,105,140) The relative magnitude of these offsetting influences on the demand for colonoscopy services, particularly over time, are not known. This may be further influenced by the aging population, as age greater than 50 years is the single greatest risk factor for the disease, and screening programs typically target ages 50 to 75.(2,10,42)

While population screening aims to control colorectal cancer through early detection or (ideally) prevention of the disease, anticipated benefits of a screening program are accompanied by potential risks and unintended consequences. It is important to weigh risk of harm against potential benefits since nonmaleficence is a cornerstone of medical ethics and a fundamental principle of health service delivery. In a population-level, two-step screening program (e.g., stool testing with colonoscopic follow-up of positive tests), average risk, asymptomatic individuals are sought based on broad inclusion criteria and invited to take a screening test which is unable to either confirm or rule out disease. Aside from the anxiety caused by this experience, as well as the relatively high likelihood of false negative results particularly in the case of polyps, those with positive results are then referred for a follow-up examination with a nontrivial risk profile. Serious risks of colonoscopy include perforation of the bowel (approximately 1/1000), bleeding (5-7/1000) and cardiovascular events with anesthesia (11-23/1000).(27–30) In the event of false positive stool tests or low risk polyps unlikely to become malignant, the risks of harm from colonoscopy outweigh the benefits of screening. Further, in the event of inadequate colonoscopy resources, decision makers could be faced with the ethical problem of identifying potential cases without the ability to confirm or rule out a diagnosis of cancer in a timely fashion. In addition to causing additional distress and inconvenience, prolonged wait times for colonoscopic follow-up of positive screening tests could serve as a disincentive for participation in screening activities.(141)

Efforts to ensure timely access for screening follow-up colonoscopies in the absence of sufficient colonoscopy resources have the potential to hinder access for other patients requiring examinations (e.g., symptomatic, higher risk screening, or surveillance patients) and negatively impact their outcomes. As colonoscopy resources are shared between average risk follow-up screening, higher risk screening, diagnostic, and surveillance activities, measures to manage the demand and competition for resources must be evaluated for their effects on access, need for downstream services, and outcomes for all patient types. However, the system, population, and patient outcomes of such decisions have not been well examined to date. Understanding the potential risks associated with population screening is key to their mitigation.

The evaluation of the effects of decisions regarding screening and surveillance technologies, and priority setting between competing patient groups is clearly complex, requiring an understanding of the effects of interaction, variability and uncertainty. Such research questions do not readily lend themselves to randomised trials or observational studies due to the wide range of possible scenarios under study and long follow-up periods required to observe the outcomes of interest. Simulation modelling methods thus play a timely and important role in predicting the impact of screening programs on both resource requirements and population and patient health outcomes.

The primary objective of this paper is to understand the implications of population factors, disease prevalence and average risk screening activities on the additional demand for colonoscopy services amongst competing patient groups, to inform the system planning and implementation of population-based colorectal cancer screening programs. Specifically, this analysis seeks to answer the following questions. (1) What is the additional demand for colonoscopy services generated by the introduction of average risk colorectal cancer screening? (2) How does choice of stool test influence colonoscopy demand and potential improvement in patient outcomes? (3) How does screening participation rate affect colonoscopy demand and potential improvement in patient outcomes? (4) How great are the losses in potential benefits of average risk colorectal cancer screening in the event of constrained colonoscopy resources?

METHODS

The Simulation of Cancer Outcomes for Planning Exercises (SCOPE) model has been described in detail elsewhere (Chapter Four). Briefly, a discrete event simulation (DES) model was constructed to evaluate the patient and health system effects of population-level average risk colorectal cancer screening activities, with particular attention paid to the competition for limited colonoscopy resources between different patient groups. Patient groups were identified as those presenting for follow-up of positive stool tests in an average risk screening program, higher risk screening and diagnostic patients, and those requiring surveillance following positive findings on colonoscopic examination.

Using Arena® simulation modelling software, a discrete event simulation (DES) model consisting of natural history, screening, and colonoscopy service modules was constructed.(113) The SCOPE model simulated a population of individuals who age and develop colorectal adenomas and carcinomas, and who generate demand for colonoscopies according to different pathways (average risk screening follow-up, diagnostic, higher risk screening with colonoscopies, and follow-up surveillance of positive colonoscopies). In this way, the model examines competition for colonoscopy services between the pathways.

The natural history of colorectal cancer was simulated based on the adenoma-carcinoma sequence, and served as the foundation of the model.(4–6) It simulated the progression of normal epithelium to polyps to colorectal cancer in the population, providing an epidemiological baseline of the status quo with which to compare screening activities. The model also incorporated age projections for the population, stage-specific mortality from colorectal cancer, and mortality from background causes.

Screening activities were added to the natural history module to simulate the uptake and outcomes of screening using a stool test followed by colonoscopic examination of positive cases, similar to many population based programs in Canada, the United Kingdom and France.(10,42–44) Asymptomatic, average risk individuals aged 50 to 74 years were presented with an opportunity to "take" a stool test once every 2 years. Based on estimates in the literature, stool test sensitivity rates improved with increasing stage of the adenoma-carcinoma sequence, while the specificity was assumed to be 95% for the FIT, and 88% for g-FOBT.(51,137,142,143) Individuals with positive results (whether true or false) were directed to the colonoscopy services module for follow-up by means of colonoscopy.

In the colonoscopy module, resources were represented by the availability of colonoscopy "slots" for each of average risk screening follow-up, diagnostic or high risk screening, or surveillance activities. Factors influencing their availability, such as human resource requirements, equipment availability or funding decisions were considered exogenous to the model. Patients waiting in queues were advanced to the colonoscopy service modules in order of first-come, first-served.

INPUT DATA

The model was run in yearly time steps. Age, mortality due to background causes or colorectal cancer, adenoma-carcinoma progression and staging, screening participation, symptomatic presentation, and demand for colonoscopy services were updated based on observed probabilities (Appendix 2).(114,115,122,127,144,145) The model was initialized with a starting population of 100,000 50- to 99-year old individuals with an age distribution corresponding to the Canadian population in 2006. Simulations were run over 15-year horizons and replicated 100 times in a large population of 100,000 individuals to obtain reasonable precision reflected by stable point estimates and narrow confidence intervals. Given the number of comparisons in each analysis, narrow confidence intervals were desirable to reduce the chance of Type I errors.(146)

New cohorts of fifty-year old individuals were introduced to the model yearly based on Statistics Canada medium population projections. Demographic assumptions were tested in a sensitivity analysis of low, medium, and high population projections.(147) It was assumed that 8% of the population was at higher than average risk of colorectal cancer due to either a history of the disease in first-degree relatives, or a personal history of colorectal cancer, familial polyposis or inflammatory bowel disease (IBD), such as Crohn's Disease or ulcerative colitis.(121,148) Lower and higher proportions (6% and 10%) of the population were assigned higher risk status in sensitivity analyses.

The FIT sensitivity and specificity rates were based on those reported by Morikawa and colleagues in their 2005 randomised controlled trial (RCT).(143) These rates were selected for use in the base scenario as the study is one of the few RCTs to report sensitivity and specificity by performing follow-up colonoscopies on all participants rather than only those with positive stool tests, and had a robust sample size (N=21,805). The model was run again using estimates of the sensitivity and specificity of a g-FOBT, which is generally less specific than FITs, and less sensitive for small adenomas than the FIT, but more sensitive for advanced cancer (Appendix 2).(79,80) Sensitivity analyses of the sensitivity and specificity estimates were conducted for both the FIT and g-FOBT (Appendix 2).

Participation was randomly assigned to individuals, meaning that prior participation had no influence on future participation. The assumption of random participation was tested in a sensitivity analysis in which 30% of the population was assigned to "participator" status and participated in screening whenever eligible (i.e. those assigned to participator status were assumed to participate in all future years as per recommended intervals).

MEASURES

Demand for colonoscopy services was generated from the natural history module. Average risk individuals participating in screening activities and with positive stool tests were sent to the colonoscopy services module for screening follow-up colonoscopies. Average and higher risk individuals were sent to the service module for diagnostic colonoscopies if they became symptomatic. Higher risk individuals presented to services for targeted screening. All patients with significant findings on initial colonoscopy returned to the service module for surveillance colonoscopies at intervals recommended by Canadian guidelines.(42,107)

Additional demand was calculated from the difference between screening and non-screening scenarios for diagnostic, surveillance and total colonoscopic demand. By definition, all average risk screening follow-up colonoscopies were considered additional demand, as no average risk screening follow-up colonoscopies were required in the non-screening scenario.

Wait times were reported for average risk screening follow-up, higher risk screening and diagnostic, and surveillance colonoscopy services. Sufficiency of colonoscopy services by type was determined by calibrating service levels to target wait times. Colonoscopy services were deemed insufficient if the numbers of colonoscopy slots provided were inadequate for maintaining wait times within target periods.

Crude colorectal cancer incidence was captured as all new local cancers in the adenoma-carcinoma sequence staging of the natural history module, and was not limited to disease

detected clinically or by means of screening. Colorectal cancer mortality was reported separately from other causes of mortality.

ANALYSIS

A scenario without average risk programmatic colorectal cancer screening was used as a baseline against which the screening scenarios were compared. Average risk screening scenarios using stool tests with follow-up colonoscopies for positive tests were then run and aggregate outcomes compared to the baseline scenario. Scenarios were selected to test the effects of the following on colonoscopy demand, colorectal cancer incidence and mortality: (1) the introduction of two-step average risk colorectal screening; (2) choice of stool test (g-FOBT or the more specific FIT); and (3) screening participation rates (30% and 50% FIT participation). Insufficiency of colonoscopy services to meet the expected additional demand was examined for its effect on colorectal cancer incidence and mortality and wait times for colonoscopy services.

The analyses compared differences between baseline and alternative screening scenarios for each of the following outcomes: 1) additional demand and wait times for colonoscopy by type (diagnostic and high risk screening, average risk screening follow-up, and surveillance), 2) crude colorectal cancer incidence and 3) 15-year cumulative colorectal cancer mortality.

Colonoscopy demand by service type (average risk screening follow-up, diagnostic or higher risk screening, and surveillance) was calculated by running scenarios with unlimited colonoscopy slots to avoid any effects of queuing. Additional demand was calculated by comparing the difference in demand between screening and non-screening scenarios. To assess the effect of insufficient colonoscopy resources to meet demand, mortality and incidence reductions from screening were first calculated assuming unlimited colonoscopy resources over the 15-year horizon and compared with outcomes from scenarios in which resources were not increased beyond initial levels to meet the expected additional demand. This provided the upper and lower bounds of the potential

benefits of screening. Finally, the scenarios were run again to calculate the colonoscopy resources required to maintain target wait times for each year of study.

RESULTS

As per the Statistics Canada medium population projection models, average age increased over the study period, from 63.97 years (95% CI 63.89-64.07) in year 1 to 70.14 years of age in year 15 (95% CI 70.09-70.20).(147) The numbers of individuals eligible to participate in average risk screening (asymptomatic individuals ages 50-74 years) decreased over the study period by 14% (3,674 to 3,156/10,000), even with annual in-migration of 50 year olds, due to the aging population.

Table 5.1 Population Characteristics – Base Model

Year	Mean Age (Years)	Eligible for Average Risk Screening* (N/10,000)
1	64.0	3,674
2	64.3	3,626
3	64.6	3,624
4	64.9	3,594
5	65.2	3,584
6	65.5	3,561
7	66.0	3,532
8	66.5	3,502
9	67.0	3,469
10	67.4	3,439
11	67.9	3,395
12	68.5	3,347
13	69.0	3,286
14	69.6	3,225
15	70.1	3,156

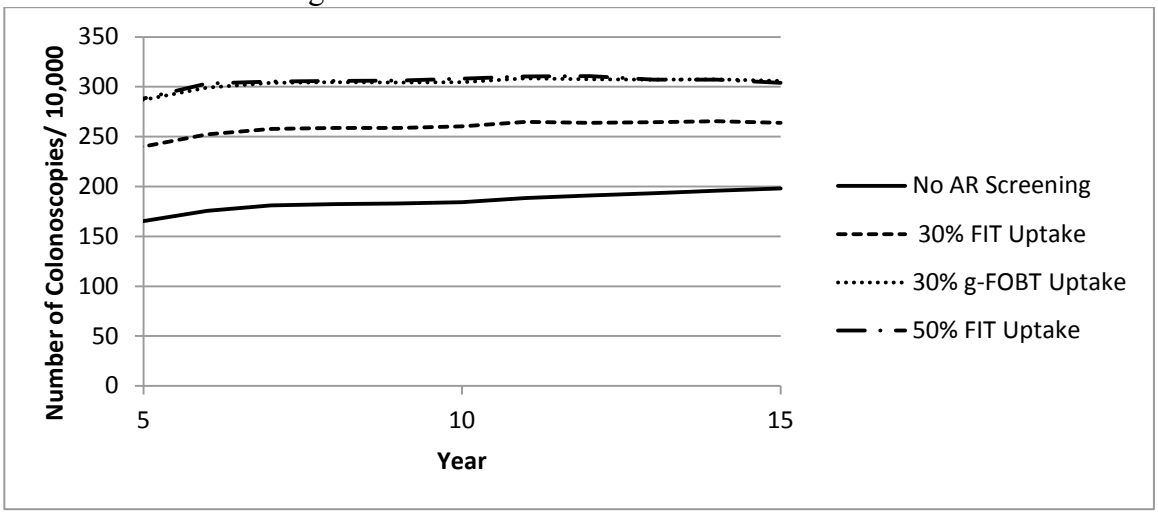
* Asymptomatic individuals aged 50-74 years

Colonoscopy Demand by Choice of Stool Test

In neither screening scenario was the relative additional demand for follow-up screening, nor surveillance, colonoscopies offset by decreases in demand for diagnostic colonoscopies (Figure 5.1). Both the FIT and g-FOBT screening scenarios generated significant additional demand for all colonoscopy services compared to the no screening baseline scenario. With 30% participation, FIT screening generated additional demand 33% higher per year after 15 years of follow-up, while the less specific g-FOBT screening required 54% more than the no screening scenario.

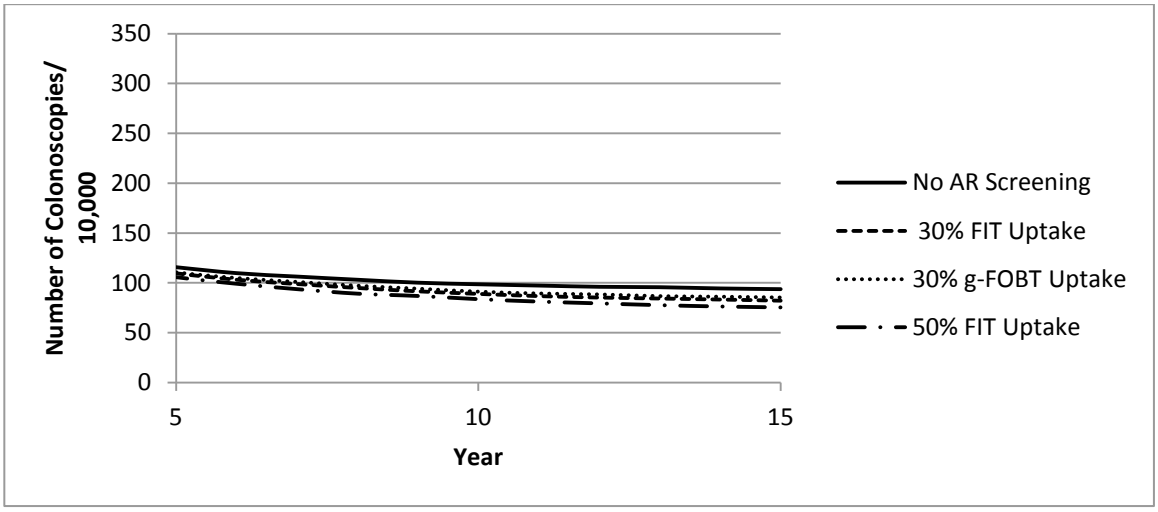
The FIT screening scenario resulted in significantly fewer total colonoscopies than the g-FOBT scenario. After 15 years of follow-up, the FIT scenario generated 263.9 colonoscopies per 10,000 individuals aged 50+ years (95% CI 262.8-264.9), while the g-FOBT scenario required 305.8 per 10,000 (95% CI 304.6-307.0). By comparison, the baseline scenario of no average risk screening required a total of 197.9 colonoscopies per 10,000 (95% CI 197.2-198.7) by year 15.

Figure 5.1 Relative Annual Demand for All Colonoscopy Services by Choice of Stool Screening Test



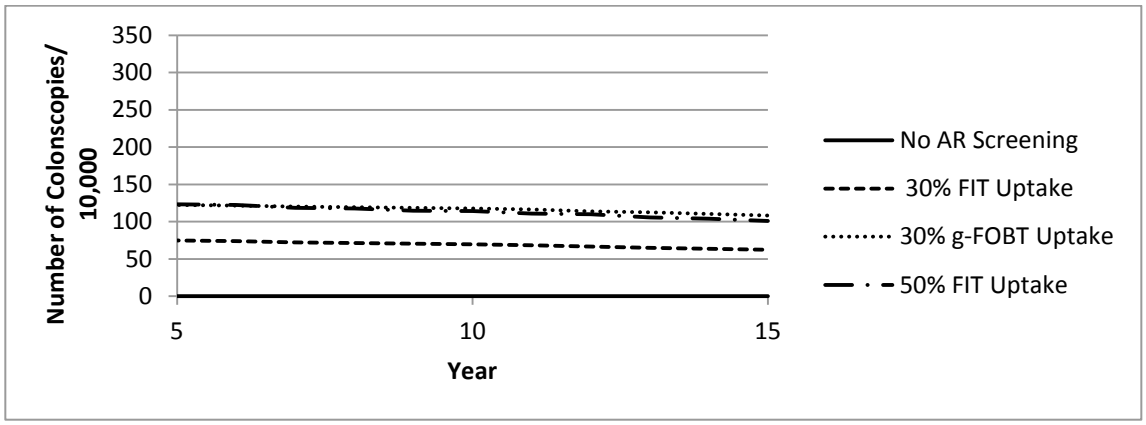
The FIT slightly outperformed the g-FOBT in terms of reducing additional demand for diagnostic colonoscopies by the end of the study period (Figure 5.2) relative to the no screening baseline scenario. In year 15, the numbers of diagnostic/higher risk screening colonoscopies required per 10,000 for the no screening, FIT and g-FOBT screening scenarios were 93.7 (95% 93.1-94.3), 82.2 (95% CI 81.6-82.8) and 85.4 (95% CI 84.8-86.1) respectively.

Figure 5.2 Relative Annual Demand for Diagnostic Colonoscopies by Choice of Stool Screening Test



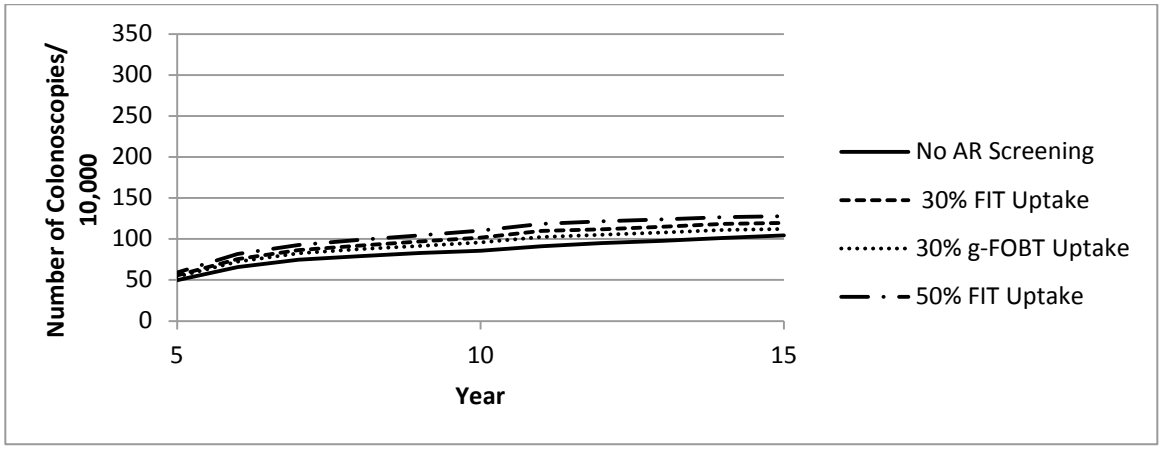
The FIT screening scenario required significantly fewer screening follow-up colonoscopies than the g-FOBT scenario (Figure 5.3), likely due to its greater specificity. In year 1, the FIT scenario generated additional demand for 81.8 follow-up screening colonoscopies per 10,000 (95% CI 81.2-82.3), while the g-FOBT scenario required 128.2 screening colonoscopies per 10,000 (95% CI 127.6-128.9). By year 15, the relative additional demand had reduced for both strategies likely due to the aging population, but the FIT strategy continued to require significantly fewer screening follow-up colonoscopies than the g-FOBT scenario (62.2 (95% CI 61.6-62.7) vs. 108.1 (95% CI 107.4-108.9) per 10,000 respectively).

Figure 5.3 Relative Annual Demand for Screening Follow-up Colonoscopies by Choice of Stool Screening Test



Both the FIT and g-FOBT screening strategies significantly increased the number of annual surveillance colonoscopies per 10,000 compared to the no screening baseline scenario (Figure 5.4). The FIT scenario generated more surveillance colonoscopies by year 15 than g-FOBT screening (119.5 per 10,000 (95% CI 118.7-120.3) vs. 112.2 per 10,000 (95% CI 111.5-113.0), likely due to its higher sensitivity for precancerous adenomas. By comparison, the baseline no screening scenario surveillance colonoscopy demand was significantly lower than either screening strategy, at 104.2 per 10,000 (95% CI 103.5-105.0).

Figure 5.4 Relative Annual Demand for Surveillance Colonoscopies by Choice of Stool Screening Test



Wait Times for Colonoscopy Services

Without the provision of additional colonoscopy resources necessary to keep up with increasing demand, wait times quickly escalated beyond benchmarked standards, particularly for the g-FOBT screening scenario as a result of the higher false positive rate than the FIT. When screening follow-up colonoscopy slots were adjusted annually to meet fluctuating demand and maintain target wait times (within eight weeks) over 15 years of screening, 30% more screening follow-up slots were required on average for the g-FOBT scenario than the FIT scenario due to the test's lower specificity. However, 15% fewer surveillance slots were required, likely due to the g-FOBT's poorer sensitivity for adenomas. There were no substantial differences in numbers of diagnostic slots required between the screening strategies.

Colorectal Cancer Incidence

In year 15 of follow-up, with unlimited colonoscopy resources the FIT screening scenario reduced the crude annual colorectal cancer incidence by 17.3% compared to the no screening scenario (13.3 cases/10,000 50+ year olds vs. 16.1 cases/10,000 50+ year olds). By comparison, the g-FOBT reduced annual incidence by 13.2% (14.8 cases/10,000 50+ year olds). However, achieving such outcomes was dependent upon the provision of adequate colonoscopy services. Constraints on colonoscopy resources diminished the potential benefit for screening to reduce incidence rates. In year 15 of follow-up in an inadequately resourced system, crude incidence rates were approximately 7.7% higher for the FIT (14.3 cases/10,000 50+ year olds) and 10.2% higher (15.4 cases/10,000 50+ year olds) for the g-FOBT screening scenarios compared to the adequately resourced screening scenarios.

Colorectal Cancer Deaths

With unlimited colonoscopy resources, the FIT screening scenario reduced 15-year cumulative colorectal cancer deaths by 10.4% over the no screening baseline scenario

(209 and 233 deaths, respectively). The g-FOBT scenario performed less well than the FIT, reducing colorectal cancer deaths by 8.6% (213 deaths) compared to the no screening scenario over the 15-year study period. In year 15 of follow-up, failure to adequately increase colonoscopy resources to meet growing demand resulted in no change in colorectal mortality in the FIT screening scenario (209 deaths), and a small increase in colorectal cancer deaths for the g-FOBT scenario (215 deaths).

The Effects of Increased FIT Screening Participation

Increasing FIT screening participation from 30% to 50% resulted in 54% higher additional demand for total colonoscopy services compared to the no screening baseline scenario. As with the lower participation rate scenario, the additional demand for follow-up screening and surveillance colonoscopies was not offset by reductions in demand for diagnostic colonoscopies.

Increasing participation in screening to 50% while providing unlimited colonoscopy resources further reduced colorectal cancer deaths after 15-year follow-up, with 16.1% reduction in cumulative deaths compared to the no screening baseline scenario. Similarly, the crude incidence rate 15 years after follow-up was 26.7% lower than the baseline scenario. However, failure to adequately meet growing demand for colonoscopy services meant that some of the potential benefits of screening were not realized, as crude incidence was 8.4% higher in year 15 and cumulative mortality over 15 years was 1.3% higher than in the optimally resourced scenario.

Sensitivity Analyses

Sensitivity analyses of low, medium and high population projections made no significant difference to the overall demand for colonoscopies. Similarly, use of lower and higher prevalence rates (6% and 10%) for the assignment of higher risk status did not significantly affect the results, nor did altering participation status in screening activities

from annual random assignment of 30% of the study population to fixed assignment of a 30% subgroup of the population to participate in screening biannually.

Sensitivity analyses of the sensitivity and specificity estimates of the FIT and g-FOBT did not alter the conclusions of the study (Appendix 2). Use of a less sensitive g-FOBT would likely result in more false positive results and fewer detected cancers, although this was not tested in a sensitivity analysis. Increasing specificity decreased the demand for colonoscopies overall, largely due to reductions in demand for screening follow-up colonoscopies. This subsequently increased crude annual incidence by approximately 3% in year 15 and increased cumulative mortality by 1.0 – 2.0%, depending on the test. Conversely, decreasing specificity increased demand for screening follow-up colonoscopies, with attendant small decreases in crude incidence and cumulative mortality.

DISCUSSION

Average risk colorectal cancer screening using a two-step process of a stool test followed by colonoscopy of positive tests significantly increased the demand for colonoscopy services compared to a no screening scenario. In both the FIT and g-FOBT screening scenarios examined using the SCOPE model, the additional demand for screening follow-up and surveillance colonoscopies was not offset by reductions in demand for diagnostic colonoscopies, even after 15 years of follow-up. Thus, health care systems must plan for substantial increases in the demand for colonoscopies if two-step screening is introduced.

Study screening scenarios employing a two-step process saw total additional demand for colonoscopy services of 33% (FIT) to 54% (g-FOBT) by year 15. The FIT screening scenario generated higher demand for surveillance colonoscopies than the g-FOBT over the study period due to its greater ability to detect small adenomas, but this was offset by its lower demand for screening follow-up exams as a result of fewer false positives than the g-FOBT.

The FIT screening scenario performed better than the g-FOBT scenario in terms of reducing both crude incidence and cumulative deaths due to colorectal cancer when compared to a no screening scenario when colonoscopy services were unlimited. FIT reduced annual incidence by 17% and g-FOBT by 13% compared to no screening after 15 years of follow-up. These estimates can be considered the upper bound of the benefits of screening achievable with sufficient colonoscopy resources.

The potential benefits of screening in terms of reduced colorectal cancer incidence and mortality were not fully realized when colonoscopy services were constrained, and inadequate for meeting increasing demand. Crude colorectal cancer incidence in year 15 of follow-up was 7.7% higher in the FIT screening scenario and 10.2% higher in the g-FOBT scenario when resources were not increased to meet growing demand compared to scenarios in which resources were unlimited. Similarly, colorectal mortality was 3.4% higher and 9.4% higher in the FIT and g-FOBT constrained scenarios respectively, compared to scenarios with unlimited colonoscopy resources.

The FIT parameters used in the SCOPE model reflected the test's better ability to detect small adenomas, somewhat poorer ability to detect advanced colorectal cancer and lower false positive rate than the g-FOBT as observed in many studies to date.(40,52,134,137,143) However, there is much variation in the estimated true and false positivity rates of the various FIT and g-FOBT tests reported in the literature, likely due to the small sample sizes, varying study design and differences in study populations. The values for sensitivity and specificity used in the present study were selected based on studies in average risk populations with large sample sizes and colonoscopic follow-up of all stool tests regardless of results. Sensitivity analyses of these parameters did not affect the conclusions of the study. While it is difficult (if not impossible) to predict the sensitivity or specificity for a given stool test in a given population, the values used in the present study are useful for demonstrating the effects of trade-offs between sensitivity and specificity generally.

Sensitivity and specificity of either test are affected by the threshold at which results are considered positive (the positivity threshold). Generally, lowering the positivity threshold will improve sensitivity (detect more true positives) and reduce specificity (capture more

false positives). While population screening efforts will often accept poor specificity to cast the net wide and capture as many cases as possible, our results show that the consequent higher rate of false positives plays a large role in driving increased demand for colonoscopy services. This has substantial resource consequences, which will impact the cost-effectiveness of screening programs. Moreover, if resources are not, or cannot, be expanded to meet additional demand, patient and system outcomes alike will also be affected.

In the case of constrained colonoscopy services, false positivity rates are a concern. In addition to the burden on limited health care resources, there are significant consequences for patients exposed unnecessarily to an invasive procedure with risks of serious adverse outcomes. Further, substantial distress is associated with the investigation of suspected cancers, regardless of outcome.(109) As observed with a 7% absolute difference in specificity between tests in the current study, the subsequent increase in false positives led to substantially higher requirements for screening follow-up colonoscopies in the g-FOBT scenario compared to the FIT scenario.

The study demonstrated the potential for average risk colorectal cancer screening to improve incidence and mortality rates in a community setting. However, adequate colonoscopy resources are necessary to support such efforts and to maximize the potential benefits of screening. Inadequate colonoscopy resources resulted in rapidly increasing wait times for services, and poorer health outcomes in the form of increased crude incidence and colorectal cancer mortality. In the event adequate colonoscopy resources are not provided to support programmatic colorectal cancer screening, the potential benefits observed in randomised controlled trials and pilot studies may not be realised.

Colonoscopy services are required to support screening (both average and high risk), surveillance and diagnostic activities for individuals with colorectal cancer and other gastrointestinal diseases. The introduction of average risk colorectal cancer screening using FIT adds significantly to the total demand for colonoscopy services, and without adequate planning is likely to jeopardize access to services for all patient groups. In implementing population screening, the effect of the demand generated by screening activities must be considered for its effects on other aspects of the service. Although it

would be unethical to identify possible cases through screening activities without the resources in place to confirm a diagnosis in a timely fashion, protecting access for this patient group must not hinder access for other, higher risk, patient groups.

While the reduction of costly idle periods through resource constraint is a necessary feature of an efficient health care system, excessive constraints are distressing and inefficient in that they can lead to suboptimal patient care, increased costs, and poor outcomes. In a benchmarking exercise conducted to compare reported total wait times (from referral to procedure) with recommended wait times for digestive health care, the Canadian Association of Gastroenterology (CAG) reported that prior to the advent of average risk screening, total wait times exceeded consensus targets, with the majority of patients (including urgent cases and probable cancer) not seen within the target period.(37) Without understanding that the implementation of a two-step screening program leads to substantial and continued increases in demands for colonoscopy services, these wait times are likely to worsen.

The present study is the first to our knowledge to explicitly consider the competition for limited resources among various patient groups and to assess the relative contribution of inadequate resources on both patient and system outcomes. This is a major consideration when introducing a new patient population to a service with constrained resources. Care must be taken to evaluate potential unintended harms in relation to anticipated benefits. The results of the present study demonstrate the potential for inadequate provision of colonoscopy services to erode the benefits of screening. It is likely that this also translates into reduced cost-effectiveness of programmatic screening. This was not examined in the present study, but can be accommodated using the study model and is an important area for future research.

The study took demographic factors into account, as these are potentially important contributors to the demand for colonoscopy services.(2,3) The aging population is likely to contribute to increased prevalence of colorectal cancer and its precursor lesions. At the same time, as the model demonstrated, the shifting demographic means that fewer people will be eligible for average risk screening programs targeting individuals aged 50 to 74 years.

Limitations of the study include the assumption of independence between background and colorectal cancer mortality. In reality, individuals at higher risk of colorectal cancer mortality are also at higher risk of other causes of mortality due to common risk factors.(129) This is unlikely to significantly affect the results of the model. Additionally, the model did not account for opportunistic screening. This may result in higher demand for services, or be offset by participation in programmatic screening. Future studies using the model could incorporate jurisdiction-specific rates of opportunistic screening.

A secondary objective of the present study was to examine the effects of screening decisions on population outcomes, including crude colorectal cancer incidence and cumulative mortality. While more sensitive to change than colorectal cancer death, incidence must be interpreted with caution. It cannot be assumed that all detected cancers will result in improved outcomes such as reduction in death. Rather, cancer incidence may be subject to lead-time or overdiagnosis bias.(149)

The study did not explicitly consider the relationship between measures of quality of colonoscopy services and the outcomes of interest. The detection rate of adenomas and cancers has been shown to vary by endoscopist due to differences in training, volume of colonoscopies performed, and measure of completeness and thoroughness of the colonoscopic exam including cecal intubation rate and withdrawal time.(150,151) The model incorporated colonoscopic detection rates of adenomas and carcinomas, which reflect quality of the exams. Future studies using the SCOPE model can incorporate various quality measures and examine their influence on detection rates, and patient and system outcomes.

Finally, prioritization of urgency of triage among symptomatic patients was not considered in the current study. Future iterations of the model could incorporate a more granular representation of triage policies and explicitly examine their effect on patient and system outcomes. The SCOPE model provides a useful foundation for several future areas of research which may be used to anticipate the increased demand for colonoscopy services with the adoption of population based colorectal cancer screening.

CHAPTER SIX MANAGING THE ADDITIONAL DEMAND FOR COLONOSCOPY SERVICES FOLLOWING THE INTRODUCTION OF AVERAGE RISK COLORECTAL CANCER SCREENING

Abstract

INTRODUCTION: The introduction of a two-step average risk colorectal cancer screening program increases the overall demand for colonoscopy services both to provide screening follow-up colonoscopies for positive stool tests as well as for ongoing surveillance, which are not offset by reductions in demand for diagnostic colonoscopies as the result of reductions in disease incidence with screening activities. The objective of this study was to examine the patient and system effects of increasing the specificity of a first-line screening stool test on additional demand for colonoscopy services.

METHODS: A discrete event simulation model ("SCOPE") was constructed to evaluate strategies to accommodate average risk screening while mitigating unmanageable increased demand for colonoscopy services. The test scenario simulated a higher positivity threshold for the FIT.

RESULTS: The demand for screening follow-up colonoscopies was reduced by 65% with the increased positivity threshold compared to a lower FIT positivity threshold. Many of the benefits of screening were maintained. Crude colorectal cancer incidence was reduced by 7.6% in year 15 of follow-up, and cumulative colorectal cancer mortality reduced by 7.2% compared to no screening after 15 years of follow-up.

DISCUSSION: Raising the positivity threshold of the FIT reduces the demand for follow-up colonoscopy services while maintaining many of the benefits of screening.

INTRODUCTION

The introduction of average risk colorectal cancer screening increases the overall demand for colonoscopy services by 33% to 54% depending upon the sensitivity and specificity of the stool test selected and screening uptake rates (Chapter Five). In a two-step average risk screening program consisting of an initial stool test (either guaiac fecal occult blood test (g-FOBT) or fecal immunochemical test (FIT)) followed by colonoscopic examination of positive cases, increased demand results both from the need to provide screening follow-up colonoscopies for positive tests as well as for the ongoing surveillance of individuals with positive colonoscopic findings.

This is of particular concern at present, as colonoscopy services in many jurisdictions in Canada are already under strain and unable to meet recommended wait time targets. (152,153) With average risk colorectal cancer screening programs recently implemented or under consideration in most provinces, capacity planning for adequate colonoscopy service provision is essential both to support screening programs as well as to continue to meet the needs of higher risk individuals requiring primary screening and diagnostic services. Wilson and Jungner's classic principles for programmatic screening recognise the availability of adequate diagnostic follow-up resources as an essential element of a screening program, and acknowledge the potential for pitfalls with inadequate planning.(9)

In an earlier paper (Chapter Five), a discrete event simulation model (the Simulation of Cancer Outcomes for Planning Exercises, or "SCOPE" model) was used to examine the effects of average risk colorectal cancer screening activities on colonoscopy demand. A two-step colorectal cancer screening program employing a fecal immunochemical test (FIT) offered every 2 years to asymptomatic, average risk individuals aged 50 to 74 years increased the total demand for colonoscopy services by 33% to 54% over a 15-year study period, depending on uptake rates (30% vs. 50%) and stool test selected. In addition to the demand for screening follow-up colonoscopies, demand for surveillance colonoscopies was also significantly higher compared to the no screening scenario. These increases were not offset by reductions in diagnostic exams resulting from lower population prevalence

rates of the disease with successful screening. Without the provision of additional colonoscopy resources, wait times quickly escalated beyond targets and the full potential benefit of screening was not realized. These harms were shared between average risk screening participants and higher risk screening/diagnostic patients alike. This subjects non-participants to a possible "double jeopardy" in that by not participating they miss the opportunity for prevention or early detection of colorectal cancer screening, and if they become symptomatic, face longer wait times for diagnostic colonoscopy services.

To support a population-level colorectal cancer screening program without overwhelming colonoscopy services, it may be possible to mitigate the demand for screening follow-up and subsequent surveillance colonoscopy services while still providing much of the benefit of screening. A reasonably simple strategy for alleviating the demand for follow-up screening colonoscopies and lowering the risk of unnecessary colonoscopies is to increase the threshold at which a FIT is considered positive. This can be achieved using a quantitative FIT, which provides a numeric value for the result rather than a positive/negative outcome based on a predetermined threshold. Increasing the positivity threshold has the effect of increasing the test's specificity and reducing sensitivity. Fewer true cases will be detected, but fewer false positive results will be referred for colonoscopic follow-up. While population screening programs generally aim to capture as many true cases as possible, in the case of colorectal cancer screening the accompanying high false positive rate has the potential to create unmanageable demand for colonoscopy services.

This paper reports the results of a discrete event simulation model, the Simulation of Cancer Outcomes for Planning Exercises (SCOPE) Model, designed to examine the effects of strategies intended to manage the additional demand on colonoscopy services generated by average risk colorectal cancer screening activities. The test strategy evaluated the effects of increasing the specificity of the FIT, with accompanying reductions in sensitivity, as would be observed by increasing the positivity threshold. Study outcomes of interest include the demand for diagnostic, screening follow-up, and surveillance colonoscopies, wait times for colonoscopy services, incident colorectal cancer cases and colorectal cancer deaths over a 15-year study period. The numbers of

additional colonoscopy "slots" necessary to maintain target wait times was compared between screening scenarios employing baseline and higher positivity thresholds.

METHODS

The development of the SCOPE model has been described in detail elsewhere (Chapter Four). Briefly, a discrete event simulation (DES) model was constructed using Arena® software to investigate the effect of the introduction of average risk colorectal cancer screening on the demand for colonoscopy services. Unlike other colorectal cancer screening models, it explicitly considers the effects of constrained colonoscopy resources on patient and system outcomes. Individuals presenting to colonoscopy services were identified as those requiring follow-up of positive stool tests in an average risk screening program, diagnostic and higher risk screening patients, and all those requiring surveillance following positive findings on a previous colonoscopic examination.

The SCOPE model was constructed using layered modules. The natural history of colorectal cancer provided the foundation for the model and was conceptually based on the adenoma-carcinoma sequence.(4–6) It simulated the progression of the lining of the colon from normal epithelium to polyps to colorectal cancer in the population, providing an epidemiological baseline of the status quo with which to compare outcomes of screening activities.

Screening scenarios were layered on to the natural history module to allow the simulation of the uptake and outcomes of a two-step screening program using a stool test followed by colonoscopic examination of positive cases, as introduced recently in many regions in Canada and Europe.(10,42–44) Asymptomatic, average risk individuals aged 50 to 74 years were eligible for participation in stool testing once every 2 years. The test sensitivity rates improved with increasing stage of the adenoma-carcinoma sequence.(51,137,142,143) Those with positive results were sent to the colonoscopy services module for follow-up colonoscopy.

Colonoscopy "slots" were generated monthly, and were specific to average risk screening follow-up, diagnostic/ high risk screening, or surveillance activities. As such, they were reserved for the corresponding patient group. Factors influencing their availability, such as funding decisions, human resource requirements, suite or equipment availability were considered exogenous to the model.

The model was initialized with a population of 100,000 50- to 99-year old individuals and run over a 15-year horizon in yearly time steps. Fifty-year old individuals were introduced to the model yearly based on Statistics Canada medium population projections.(147) Age, mortality due to background causes or colorectal cancer, adenoma-carcinoma stage, and symptomatic presentation were updated annually based on Statistics Canada Life tables and Canadian medium population projections (Appendix 2).(114,115,122,127,144,145)

Runs were replicated 100 times to obtain the desired precision. Eight percent of the population was randomly assigned higher than average risk of colorectal cancer due to either a history of the disease in first-degree relatives, or a personal history of colorectal cancer, familial polyposis or inflammatory bowel disease (IBD), such as Crohn's Disease or ulcerative colitis based on observed prevalence rates.(121,148)

The test scenario consisted of a two-step average risk colorectal cancer screening program using a higher threshold FIT followed by colonoscopy of positive tests. Comparison scenarios consisted of a two-step screening program using a lower threshold FIT (100 ng/ml) and a baseline no-screening scenario.

MEASURES

The higher FIT positivity threshold was approximated by comparing trade-offs in sensitivity and specificity reported in Imperiale and colleagues' 2014 paper.(154) A higher value for specificity was selected and the corresponding lower value for sensitivities for polyps and cancers were estimated based on the receiver operating

characteristic (ROC) curve (Appendix 2). This had the effect of simulating a higher positivity threshold.

Demand for colonoscopy services was generated by the natural history module for each colonoscopy service type (average risk screening follow-up, higher risk screening or diagnostic, and surveillance colonoscopies). Aggregate relative differences in demand were compared annually between the higher and lower threshold screening and non-screening baseline scenarios for each service type as well as for the demand for all colonoscopy service types.

Colonoscopy resources were represented by numbers of monthly colonoscopy "slots" for each type of service. Wait times were reported for colonoscopy services by service type. Sufficiency of colonoscopy resources by type was determined by calibrating service levels to consensus target wait times.(37,152,153) Colonoscopy resources were considered to be insufficient if the numbers of colonoscopy slots provided were unable to keep wait times within targets.

All new local cancers in the adenoma-carcinoma sequence staging of the natural history module were captured for crude annual incidence rates, and were not limited to those detected clinically or by means of screening. Colorectal cancer mortality was reported separately from other causes of mortality.

ANALYSIS

The analysis assessed the effects of trade-offs between increasing the specificity and estimated subsequent decreases in the sensitivity of a FIT, effectively increasing the threshold at which a FIT would be considered positive. The higher FIT positivity threshold test scenario was compared with both a baseline no screening scenario and a screening scenario with a lower FIT positivity threshold (100 ng/ml).

The baseline and test scenarios were run over a 15-year study horizon and aggregate outcomes compared to determine the effects on the outcomes of interest. The analyses

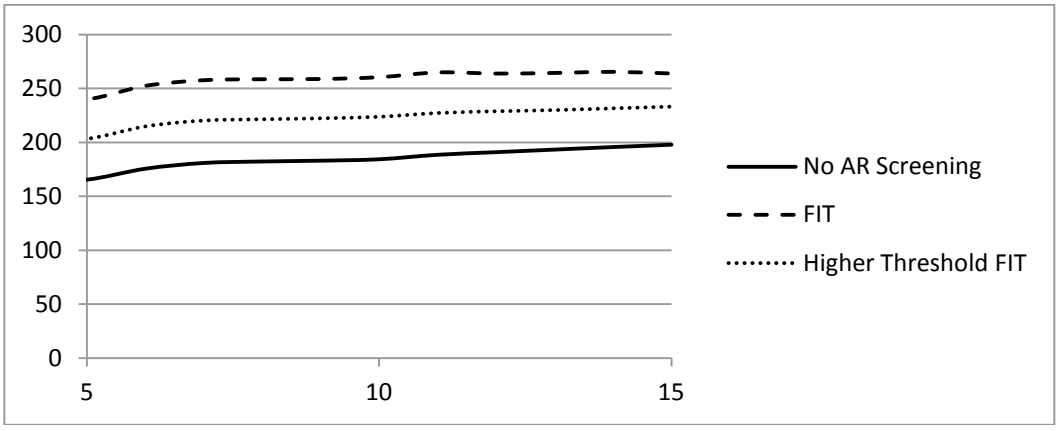
compared differences in outcomes of: 1) relative additional demand and wait times for colonoscopy by type (diagnostic and high risk screening, average risk screening follow-up, and surveillance), 2) crude annual colorectal cancer incidence and 3) 15-year cumulative colorectal cancer mortality between the no screening, lower threshold FIT screening and alternative higher threshold FIT screening scenarios. Colonoscopy demand was calculated initially by running scenarios with unlimited colonoscopy slots to avoid any effects of queuing. The scenarios were run again with colonoscopy slots calibrated to the number needed to maintain target wait times, which were determined based on consensus targets.(37,152,153)

RESULTS

Colonoscopy Demand

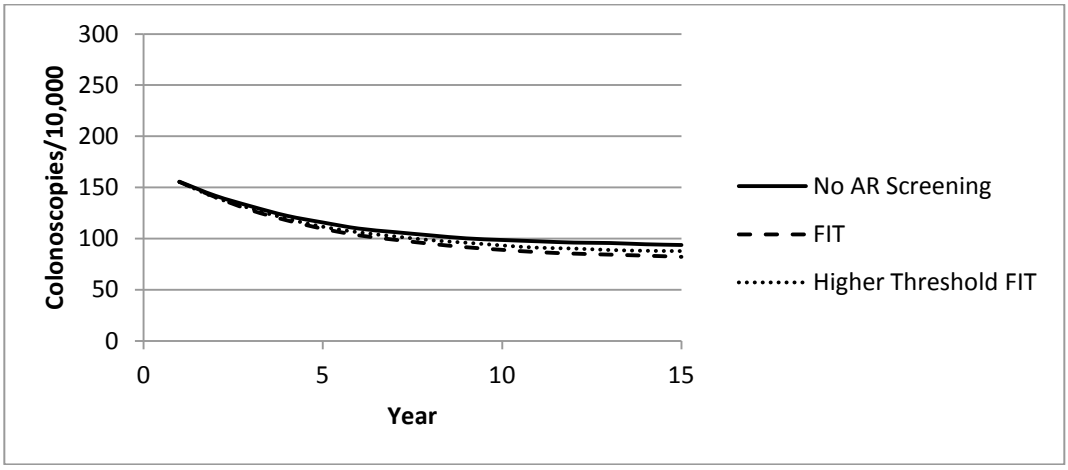
Nearly 12% fewer colonoscopies were required annually for the higher FIT positivity threshold scenario compared to the lower threshold scenario. The annual demand for all colonoscopy services was17.7% greater in year 15 for the higher FIT threshold screening scenario, compared to the no screening scenario (Figure 6.1). In contrast, the standard lower threshold screening scenario required 33.3% more colonoscopies in year 15 than the status quo without screening.

Figure 6.1 Relative Annual Demand for All Colonoscopy Services by FIT Positivity Threshold



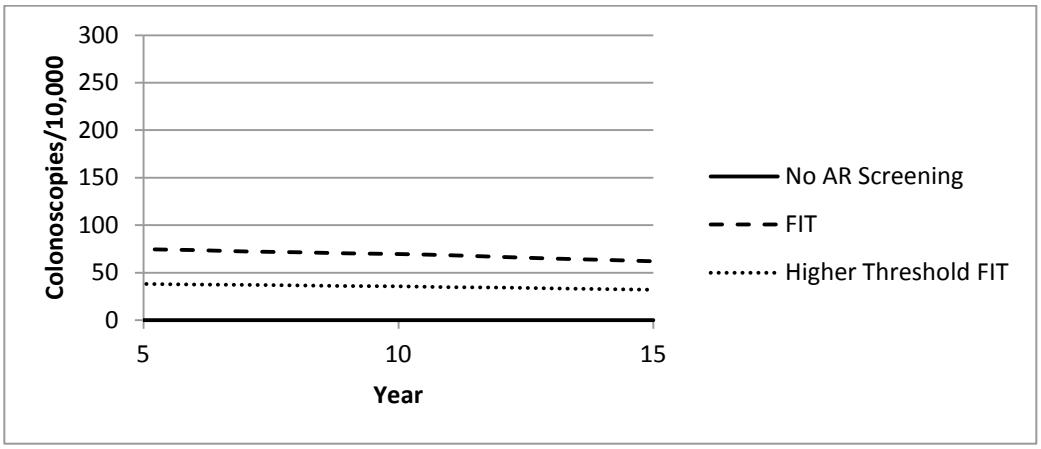
Annual demand for diagnostic colonoscopies was 6.4% lower in the lower FIT positivity threshold screening scenario than for the higher positivity threshold scenario. Compared to the no screening baseline scenario, the higher FIT positivity threshold scenario reduced annual demand for diagnostic colonoscopies by 6.3%, while the lower FIT threshold reduced demand by 12.3% in year 15 (Figure 6.2).

Figure 6.2 Relative Annual Demand for Diagnostic Colonoscopies by FIT Positivity Threshold



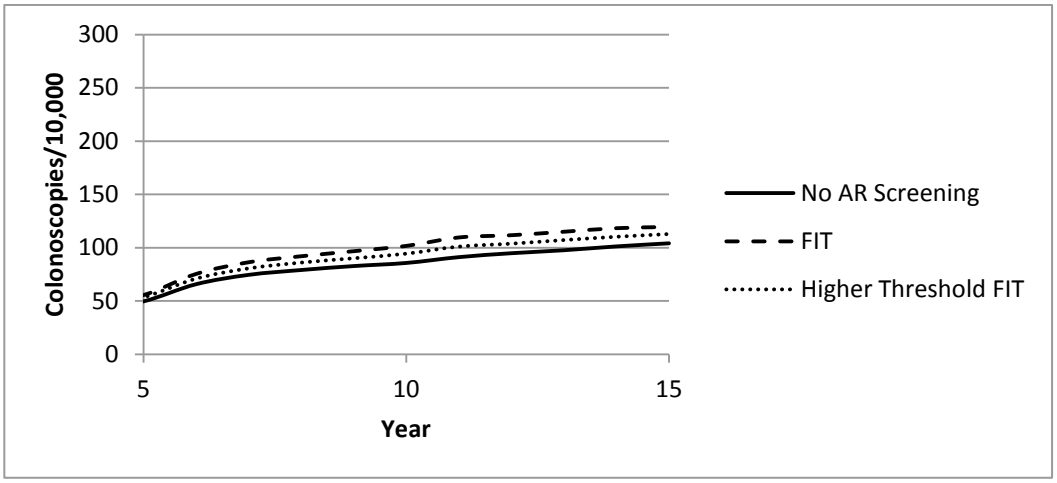
The higher threshold FIT scenario required 48.2% fewer screening follow-up colonoscopies annually in year 15 of observation than the lower threshold scenario, generating 32.2 screening follow-up colonoscopies per 10,000 50+ year olds annually in year 15, compared to 62.1/10,000 for the lower threshold screening scenario (Figure 6.3). The status quo no screening baseline scenario generates no average risk screening follow-up colonoscopies, by definition.

Figure 6.3 Relative Annual Demand for Screening Follow-Up Colonoscopies by FIT Positivity Threshold



In year 15 of follow-up, the annual demand for surveillance colonoscopies was 5.5% lower for the higher FIT positivity threshold screening scenario than the lower threshold scenario (113.0/10,000 individuals vs. 119.5/10,000 annually). The higher FIT positivity threshold screening strategy increased annual demand for surveillance colonoscopies by 8.4% compared to the no screening scenario (Figure 6.4) in year 15 of follow-up. In comparison, the lower threshold strategy increased annual demand for surveillance colonoscopies by 14.7% over the no-screening scenario in year 15.

Figure 6.4 Relative Annual Demand for Surveillance Colonoscopies by FIT Positivity Threshold



Wait Times for Colonoscopy Services

When screening follow-up colonoscopy slots were calibrated to meet the demand generated and maintain target wait times (less than eight weeks) over 15 years of screening, 65% fewer screening follow-up slots were required on average for the higher FIT positivity threshold scenario, compared to the lower threshold scenario. In year 15 of observation, 97 slots per month were required to maintain target wait times per month with the lower threshold FIT screening scenario. In the higher threshold screening scenario, 34 colonoscopy slots per month were required to maintain target wait times.

Colorectal Cancer Incidence

With unlimited colonoscopy resources, the crude annual colorectal cancer incidence rate was 11.7% higher in the higher FIT positivity threshold scenario than the lower threshold scenario in year 15 of observation. The higher threshold FIT scenario reduced crude annual incidence of colorectal cancer by 7.6% (14.84 cases/10,000 50+ year olds) after 15 years of follow-up, compared to the no screening scenario (16.06 cases /10,000). By comparison, the lower threshold screening strategy reduced crude annual incidence by 17.3% (13.29 cases/10,000) after 15 years of follow-up with unlimited colonoscopy resources.

Colorectal Cancer Deaths

In the presence of unlimited colonoscopy resources, the cumulative colorectal cancer mortality was 3.9% higher in the higher FIT positivity threshold scenario than the lower threshold scenario. The higher threshold FIT strategy reduced cumulative colorectal cancer mortality by 7.2% (N = 216.78) compared to no screening (N = 233.49). By comparison, the lower threshold screening strategy reduced colorectal cancer deaths by 10.6% (N = 208.68) over the study period when unlimited colonoscopy services were available.

DISCUSSION

Colorectal cancer screening attempts to identify the disease early in its development to improve patient outcomes, or to prevent disease through the identification and removal of pre-cancerous polyps. Most jurisdictions in Canada do not have the excess colonoscopy resources available to support primary screening with colonoscopy. As a result, current Canadian guidelines recommend primary screening with stool tests (preferably FITs), with positive tests followed-up by colonoscopy.(10,42)

Unfortunately, due to the relatively poor sensitivity of stool tests for precancerous adenomas, the goal of prevention may be difficult to attain. Further, imperfect specificity results in a high number of false positive results requiring unnecessary colonoscopy. This exposes healthy individuals to the risks associated with an invasive exam as well as places a high burden on the health care system. In the event of insufficient colonoscopy resources, diagnostic and higher risk individuals face longer wait times as average risk screening follow-up patients are added to the queues and placed in relative priority.

A strategy to attempt to mitigate the increase in colonoscopy demand generated by average risk screening has been presented. Increasing the threshold at which a FIT is considered positive decreases the number of false positive results directed to colonoscopy services, but at the price of lower sensitivity (a higher false-negative rate). This aims to reduce both the number of individuals undergoing an unnecessary procedure as well as prevent overwhelming the system to the detriment of all patients, both of average and higher risk. The results of the analyses indicate that this strategy is indeed effective at reducing the number of false positive stool tests requiring follow-up with colonoscopy. Increasing the FIT positivity threshold decreased the demand for screening follow-up colonoscopies by 65% compared to the lower threshold screening scenario, largely by reducing the numbers of individuals with false positive results presenting to colonoscopy services.

Even with reductions in the number of screening follow-up colonoscopies conducted, many of the potential benefits of screening were realised with the higher threshold strategy. With adequate colonoscopy resources, the crude annual colorectal cancer

incidence rate was 14.8/10,000 50+ year olds in year 15 for the higher threshold scenario compared to 13.3/10,000 50+ year olds for the lower threshold scenario. Cumulative colorectal cancer mortality estimates over the 15 year study period were higher for the higher than lower FIT positivity threshold scenarios (217 vs. 209 deaths, respectively), but lower than the no screening scenario (233 deaths). While less effective in reducing incidence and mortality than the lower FIT threshold screening strategy with optimal colonoscopy resources, substantially fewer colonoscopy resources were required to support the program.

As demonstrated in a previous study (Chapter Five), failure to adequately resource a colorectal cancer screening program results in harms both to average risk screening participants and the higher risk patients awaiting colonoscopy services. When resources were constrained, many of the potential benefits of screening were not realised. In year 15 of follow-up in a constrained system, crude annual incidence rates were approximately 7.7% higher for the FIT (14.3 cases/10,000 50+ year olds) compared to the adequately resourced screening scenarios (13.3 cases/10,000 50+ year olds).

While there are challenges in accurately anticipating colonoscopy demand when initiating a screening program, the operationalization of population-level screening programs is difficult to alter once initiated. Programs often involve province-wide coordination, and as such, adjusting screening strategies to meet changing demand and manage burden on colonoscopy services is often not feasible. Relatively straightforward strategies that can be implemented and amended based on the availability of colonoscopy resources are critical for meeting shifting demand and avoiding excessive wait times and accompanying poor outcomes. One such strategy has been presented here. Use of a quantitative FIT that provides a numeric value rather than a positive/negative result allows adjustment of the threshold at which tests would be considered positive. If colonoscopy resources were limited, the threshold could be raised to minimize false positive results and ease demand. The results of the current study illustrate that raising the threshold can substantially reduce demand for follow-up colonoscopy services while maintaining many of the benefits of screening.

Ideally, strong positive results on a first test would be referred to colonoscopy as these are more likely indicative of true pathology. Identifying weak first positive tests would be more likely to weed out false negative results. Programmatic use of a quantitative FIT test that provides a measure of the quantity of blood found in the stool would allow for determination of a weak positive test. Colonoscopy may be reserved, and perhaps better suited, for the screening follow-up of individuals with strong positive results.

Other strategies for the management of the additional demand on colonoscopy services may include the consideration of clinical factors when deciding to follow-up positive FITs with a colonoscopy. For example, a risk model that considers other factors in conjunction with FIT test results may help reduce the numbers of false positive tests being referred for follow-up colonoscopy. Until more accurate tests are developed for the detection of adenomas and early cancers, it may be possible to employ such strategies within screening programs to mitigate the additional demand for colonoscopy services while facilitating the early detection of colorectal cancer.

CHAPTER SEVEN CONCLUSION

The potential benefits of average risk colorectal cancer screening in the form of reductions in incidence and mortality are accompanied by considerable demand on colonoscopy services. Two-step programs employing initial stool testing followed by colonoscopy of positive tests are intended as a means of identifying cancer in its early stages, and in some cases detecting pre-cancerous polyps, without the resource requirements of primary colonoscopy screening.(10,42) However, we have found that even two-step screening programs with moderate (30%) participation rates may create 33% - 54% additional demand for colonoscopy services, compared to no screening. The additional burden of average risk screening follow-up and ongoing surveillance colonoscopies required to support programmatic screening was not offset by attendant reductions in need for diagnostic colonoscopies resulting from reductions in disease prevalence. Decision makers must be prepared to provide substantial increases in colonoscopy resources and/or consider alternative strategies to mitigate the additional burden of average risk colorectal cancer screening.

While much of the literature focuses on the trade-offs between the risks and benefits of colorectal cancer screening at the patient level, the additional risks that may arise from resource constraints have not been well examined at the system level.(34–36) The results presented in Chapter Five demonstrated that the harms incurred by initiating screening programs in the absence of adequate colonoscopy resources were not borne by screening participants alone but were shared by average risk screening participants and, notably, higher risk patients requiring higher risk screening and diagnostic services. Further, when resources were not provided to keep up with increasing demand, many of the intended benefits of screening were not realised. Crude colorectal incidence and 15-year cumulative mortality rates were approximately 8% and 1% higher respectively than adequately resourced scenarios when colonoscopy services were fixed to meet demand levels generated within the first two years of screening and were not increased to meet growing demand.

When implementing two-step average risk colorectal cancer screening, as has been recommended in Canada and many parts of Europe (10,22–24,41,42, 43,44), a key question for decision and policy makers is, "what is the plan to meet the initial additional colonoscopy demand and to accommodate its fluctuations over time?". Initial demand can be estimated, but may exceed expectations, as has occurred recently in some Canadian jurisdictions.(155,156) As the effects of screening uptake, positivity rates and an aging population interact and shift over time, some flexibility is necessary for meeting initial and ongoing colonoscopy requirements. However, most population-level screening programs by virtue of their size and nature are not able to quickly respond to fluctuating needs. Demand for colonoscopy services cannot be met in real time, as it takes time to train and recruit endoscopists and to acquire space for colonoscopy suites, equipment, and support processes. As capacity is added, any surplus would likely be absorbed by increased surveillance and opportunistic screening.

A more feasible approach to resource planning may be to address the need for flexibility within the delivery of screening itself. The selection of screening technology will be critical, as will its implementation. For example, when deliberating among available stool tests, in addition to anticipated positivity and uptake rates it is important to consider whether the test provides qualitative or quantitative results. Qualitative, or yes/no results, rely on fixed positivity thresholds. Quantitative tests that provide a numeric value for the amount of blood in the stool sample allow for variable positivity thresholds or determination of weak positive results that can then be repeated or combined with clinical factors before recommending a follow-up colonoscopy. As demonstrated in Chapter Six, selection of a quantitative fecal immunochemical test (FIT) that allows for changes in the threshold at which tests are considered positive allowed for the realization of many of the benefits of screening without overwhelming the system with false positive tests. Raising the positivity threshold also reduced the numbers of individuals with false positive results from presenting to colonoscopy services for an unnecessary and invasive follow-up procedure. While it also reduced the numbers of true positive cases being identified, many of the benefits of screening were maintained at the population level.

Much of the value of FIT testing in an average risk population relies on repeat testing annually or biannually, as weak positives or false negatives missed in initial rounds of screening are detected in subsequent rounds. An important goal for screening programs will be ensuring ongoing participation of individuals with initial negative FIT results. High FIT false positive rates may reduce uptake of following rounds of screening, either due to negative experiences of unnecessary colonoscopies or unacceptable wait times for follow-up colonoscopies.

Estimation of the additional demand for colonoscopy services to support screening efforts is clearly complex as it is dependent on a number of variables and will change over time. Experience with two-step colorectal cancer screening in Canada is relatively recent and evidence to date is largely observational. Large-scale interventional studies are few and far between, and limited largely to guaiac fecal occult blood tests (g-FOBTs) from which expected results for FIT screening have been extrapolated. As such, it is difficult to apply this information to new jurisdictions contemplating screening, or for those jurisdictions struggling to meet increasing demands on colonoscopy services. Decision modelling may provide decision makers with the ability to better anticipate the intended as well as unintended effects of their choices.

The Simulation of Cancer Outcomes for Planning Exercises (SCOPE) model simulates the development of colorectal cancer in both average and higher risk populations. The model is based on this natural history platform; screening and surveillance scenarios are layered upon the platform to observe differences between various scenarios. The screening scenario can accommodate both two-step screening using a stool test followed by colonoscopy of positive tests as well as screening using primary colonoscopy. The model parameters can be adapted to reflect the properties of different stool tests, triage strategies, system constraints, and quality measures. As SCOPE explicitly models colonoscopy resources, the model can be used to estimate both the demand for colonoscopy services and effects of resource constraints as well as traditionally studied patient outcomes for a variety of screening and service delivery scenarios.

Given the model's flexibility, it can be adapted for several future research directions. Prospective iterations of the SCOPE model could incorporate quality measures of interest to screening programs. The adenoma detection rate, which is the proportion of screening colonoscopies performed by an endoscopist that identify at least one histologically confirmed adenoma or adenocarcinoma, has been recommended as a quality benchmark.(157) In a recently published study, Corley and colleagues reported an inverse linear relationship between adenoma detection rates and risk of interval cancer and suggest further studies to determine whether improving the adenoma detection rates leads to improved outcomes are warranted.(158) The SCOPE model can be used to explore the effects of improved adenoma detection rates on both patient outcomes, such as improved colorectal cancer incidence and mortality, and system outcomes, including changes in demand for diagnostic and surveillance colonoscopies. This would aid in the evaluation of quality control strategies including education interventions for screening endoscopists, or limiting participation in screening programs to endoscopists with high adenoma detection rates.

Similarly, SCOPE can evaluate the effects of interventions to increase screening program participation rates. Using the model, screening programs could estimate the effects of changes to participation rates on immediate demand for average risk screening follow-up colonoscopies, as well as ongoing demand for surveillance colonoscopies. In this way, programs can estimate their capacity to accommodate expected increases in participation through advertising or educational interventions targeting potential screening participants.

The model can also be used to examine various surveillance scenarios to reflect the trade-offs between potential benefits and harms of changes to the frequency of surveillance following an initial colonoscopy. In Chapters Five and Six, the model was run with the assumption that normal findings on average risk screening follow-up colonoscopy were redirected to average risk screening participation in 10 years' time. This results in relatively conservative estimates of demand on both average risk screening follow-up and surveillance colonoscopies. Decreasing the interval to return to screening could be modelled and evaluated for potential benefits to participants in the form of improved

colorectal cancer incidence and mortality rates, as well as on the demand for colonoscopy services.

Increasing the granularity at which the model has been developed would allow for further investigation of patient and system factors. For example, future iterations of the model could incorporate the adverse events associated with colonoscopy to more closely examine the risk/benefit ratio of colorectal cancer screening at the patient level, or refine the higher risk patient category to allow for examination of triage or prioritization strategies.

The model can also be reconfigured to accommodate emerging technologies. Imperiale and colleagues compared a non-invasive multitarget stool DNA test with a FIT among persons at average risk for colorectal cancer.(154) While more sensitive than the FIT, the DNA test was less specific, resulting in a higher false positive rates. While sensitive tests are generally preferable in population screening, a test with low specificity will result in higher numbers of individuals requiring follow-up colonoscopies and will not improve the burden of screening on colonoscopy services. However, there may be opportunities to use sensitive tests such as DNA tests in conjunction with FIT tests to more appropriately identify individuals for follow-up colonoscopy examinations. The SCOPE model can be used to aid in the evaluation of such strategies.

The SCOPE model addresses a gap in the evaluation of average risk population-level colorectal cancer screening in that it explicitly evaluates the interaction between colonoscopy resources and patient and system outcomes. It differs from other colorectal cancer screening simulation models such as the Canadian Partnership against Cancer's Cancer Risk Management Model (CRMM), as it incorporates colonoscopy resources of varying risk levels and assumes constraints on resources. In this way, it enables an examination of the competition for limited colonoscopy resources among competing patient groups.

Models can be used to help decision-makers work through the implications of many of the necessary decisions involved in the implementation of a screening program. Using information available at the jurisdiction level, it is possible to represent pre-screening levels of demand for services. Together with our understanding of the natural history of colorectal cancer, it is possible to replicate various screening scenarios and observe both patient and system outcomes. In addition to consideration of patient and system outcomes such as colorectal cancer incidence, mortality, wait times, costs, adverse events and demand, it is possible to examine the effects of inadequate service capacity on those outcomes. As such, modelling exercises may allow decision makers to compare alternative screening technologies both in terms of the maximum potential benefits of screening as well as the likely benefits given constraints on the availability of resources.

An important area for future research includes assessment of the cost effectiveness of colorectal cancer screening in the event of constrained colonoscopy resources. Much of the literature supporting the cost effectiveness of average risk colorectal cancer screening assumes adequate colonoscopy resources.(34,49,76,159–163) However, as has been demonstrated in the present study, the effectiveness of screening as measured by colorectal cancer incidence and mortality wanes with inadequate colonoscopy resources. The SCOPE model can be adapted to capture costs of alternative screening strategies and assessed in light of varying levels of colonoscopy resource provision.

Similarly, the model can be used to question whether cost savings from strategies aimed at reducing the numbers of colonoscopies required to support programmatic screening, such as setting higher FIT positivity thresholds, offset the higher cost of FIT compared to g-FOBT. This would add a more complete understanding of the implications of screening program decisions.

These exercises are not limited to the planning or initiation of screening, but can and should be used for optimal ongoing program planning. Collection of data for the duration of a screening program is imperative, both for monitoring resource utilization, patient and system outcomes, and for ensuring that resources are not appropriated from higher risk screening or symptomatic individuals in order to meet target wait times in screening programs. With jurisdiction level data, models such as SCOPE (Simulation of Cancer

Outcomes for Planning Exercises) can be further refined and used to anticipate ongoing service needs.

As a tool, simulation models can be combined with clinical evidence and availability of resources to assist with the development of scenarios for screening or surveillance and used to present the outcomes to decision makers. A collaborative process using modelling may involve the provision of potential screening scenarios, constraints (including availability of endoscopists, colonoscopy suites, and budgets), timeframes, and delivery dates by decision and policy makers. The models may then be developed from the conceptual framework and used to simulate the various scenarios to observe outcomes which can be presented to and interpreted by the decision and policy makers to assist with their decision making. Gaps between anticipated demand and supply may be identified and further examination of strategies to increase resources within given limitations would be possible.

The use of simulation models as aids with real potential to assist with decision making will require a number of next steps. First, the value of such tools must be demonstrated to decision and policy makers. This may be accomplished by working together to identify gaps in knowledge and demonstrating the ability of modelling to address them. Application to real world implementation questions will lift models from perception as an academic exercise, to one with utility for problem solving.

Along with the strengths of modelling, it is also necessary to understand their limits. While it is tempting to use such models for long term forecasting, their real value lies in their usefulness for elucidating important elements and interrelationships within a system under study. For example, the relative contributions of various patient, population, and system factors such as risk level, age, size of target population, and screening modality can be assessed for contributions to expected positivity rates and accompanying demand for screening follow-up colonoscopy. While much attention is paid to anticipated increased demands for colonoscopy services due to an aging population, results from the present study indicate a relatively small decrease in specificity of a stool screening test outweighs any contributions from an aging population. Similarly, decision makers often aim to increase screening participation in anticipation of increased benefits, while it has

been demonstrated in the present study that there are diminishing returns and more worryingly, potentially unanticipated harms to participants and patients if screening is initiated in the absence of adequate colonoscopy resources.

The study presents a reasonably generic model that may be refined to better represent specific settings, such as health authorities or individual colonoscopy services. Local stakeholders would provide invaluable insights into the service pathways and input parameters. For example, the higher risk screening and diagnostic patient population could be modeled in greater detail, allowing for subgroups of patients to be further stratified by risk. System level considerations such as triage strategies could then be examined in greater detail. Jurisdiction-specific models can then be used with decision maker input to evaluate key decisions or screening goals.

Decision and policy makers along with clinicians are key partners in evaluation screening interventions. Understanding the system under study requires detailed understanding of all of the elements of the system, their interrelationships, and plausible input values. This is critical to their usefulness and ultimately to their application to complex health services decision making, such as the implementation and management of colorectal cancer screening.

Average risk colorectal cancer screening shows great promise, given adequate colonoscopy resources. However, to allow the realisation of the potential benefits of screening, careful evaluation of operational decisions is necessary. Given the limitations of observational studies and randomised controlled trials in understanding the real world behaviour of a complex system, simulation models such as the SCOPE model are an essential component of informed decision making.

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APPENDIX 1: EVALUATION OF FECAL OCCULT BLOOD TESTS (FIT AND G-FOBT)

Table 1

Study	Design	Population	Test	Results	Comments
Imperiale et al (2014) (154)	Cross-sectional study at 90 sites in US and Canada	Asymptomatic average risk persons aged 50 – 84 years. 9989 participants included in primary analysis.	Multitarget stool DNA test Fecal immunochemical stool test (FIT)	Sensitivity: CRC: DNA 92.3% FIT 73.8% Advanced precancerous lesions: DNA 42.4% FIT 23.8% Specificity: DNA 89.8% FIT 96.4%	DNA testing more sensitive, but less specific meaning detected more cancers but returned more false positives.
Chubak et al (2013) (164)	Parallel 3-arm RCT of 3 mailed high-sensitivity FOBTs	2263 50-74 year olds in Washington State	FITs: 1-sample OC-Auto 2-sample InSure g-FOBT: 3-sample Hemoccult SENSA	Uptake: OC-Auto 64.0% InSure 60.1% SENSA 53.4% PPV (any adenoma or cancer): OC-Auto 58% InSure 38% SENSA 50%	Test with fewest samples may have best uptake. Colonoscopies performed only on positive stool tests.

Study	Design	Population	Test	Results	Comments
Huang et al (2013) (165)	Prospective, cluster randomised mass screening trial to evaluate qualitative vs quantitative FITs.	9,000 participants aged 40-74 years in a small town in China	Qualitative FIT: HemoSure Quantitative FIT: OC-Sensor	Qualitative FIT PPV (n=238): Polyps ≤5mm 41 Polyps 6-9mm 19 Polyps ≥10mm 22 >3 polyps 16 Cancer suspect 5 Quantitative FIT PPV (n=161): Polyps ≤5mm 30 Polyps 6-9mm 15 Polyps ≥10mm 27 >3 polyps 19 Cancer suspect 9	Scope of positive tests only on qualitative FIT or >50 ng/ml on quantitative FIT
Raginel et al (2013) (166)	Comparison of yield of g-FOBT and FIT tests.	19,797 participants in average-risk screening program in 2 counties in France	Quantitative FITs: Magstream OC-Sensor (1 sample x2 BMs each) g-FOBT: Hemoccult II (2 samples x 3 BMs)	1-sample OC Sensor detected more advanced neoplasia than 3-sample g-FOBT. Positivity rate: 1.6% – 4.05%	Scope of positive FOBTs (all 3 tests) only.

Study	Design	Population	Test	Results	Comments
Guittet et al (2011a)(25)	Literature based indirect comparison of quantitative i-FOBTs in general average risk populations	Published studies of average risk pop'ns Castiglione et al 2002 Grazzini et al 2009 Guittet et al 2009 Hol et al 2009, 2010 Launoy et al 2005 Van Rossum et al 2008, 2009	Magstream OC-Sensor	Slightly better performance of OC Sensor vs Magstream, especially for ACRNs.	1-sample could provide similar performances to 2-sample test in avg risk population if different cut-off is used.
Van Roon et al (2011)(167)	Comparison of attendance and dx yield of 1-sample vs 2-sample FIT screening at range of different cut off values	Random samples from screening-naïve residents 50-74 years in Netherlands	i-FOBT: OC-Sensor (50ng/ml threshold)	**1-sample,2-sample (≥1+)** Positivity rate: 8.1, 12.8 PPV (ACRN): 41, 34 PPV (CRC): 7, 5 PPV (AA): 34, 29 NNScope (AA): 2.4, 2.9 NNScope (CRC) 14.1, 18.5 Det Rate (ACRN): 3.1, 4.1 Det Rate (CRC): 0.5, 0.6 NNScreen (ACRN): 32, 25 NNScreen (CRC): 186, 156	Scope of positive FOBTs only. Decisions regarding 1 vs. 2 tests, cutoffs have implications for scopes needed. Requiring 2 positive samples = ↑ACRNs and ↓ scopes, so good for areas with limited resources. If unlimited resources, requiring only 1 of 2 tests to be positive better than 1 test only. *Efficient frontier* plotted.

Study	Design	Population	Test	Results	Comments
Chiang et al (2011)(133)	Prospective cohort study of bidirectional endoscopies to assess performance of i-FOBT in predicting lesions of lower GIT	Asymptomatic volunteers undergoing bidirectional endoscopy in Taiwan. N=2871 volunteered, 2796 included	i-FOBT: OC-Light (one-step, positivity cutoff of 50ng/ml)	**CRC:** Sens: 96.4, Spec: 86.6 PPV: 6.8, NPV: 99.9 +LR: 7.21, -LR: 0.04 Accuracy: 86.7 **Adenoma :** Sens: 21.4, Spec: 88.9 PPV: 34.9, NPV: 80.3 +LR: 1.93, -LR: 0.88 Accuracy: 74.2 **CRC or adenoma :** Sens: 24.8, Spec: 88.9 PPV: 39.2, NPV: 80.2 +LR: 2.23, -LR: 0.85 Accuracy: 74.4 **Any important lesion:** Sens: 24.3, Spec: 89.0 PPV: 41.3, NPV: 78.7 +LR: 2.22, -LR: 0.85 Accuracy: 73.4	14.2% positivity rate

Study	Design	Population	Test	Results	Comments
Guittet et al (2011b)(168)	Observational comparison of 3 i-FOBTs 1. Reproducibility of test 2. Sensitivity to temp and delay	Healthy volunteers <50 years N=10	i-FOBTs: Magstream OC-Sensor FOB Gold	1. Intertube variability observed. OC-Sensor best (Magstream better at <75µg Hb/g), FOB gold worst. 2. Good stability over time. OC-Sensor best.	Small sample size.
Levi et al (2011)(134)	Cluster RCT (9 clinics of various SES) with scopes for positive FOBTs, cancer registry follow-up at 2 years	Average risk persons 50-75 years in Tel Aviv N=12,537 (invited), 3490 tested	g-FOBT: Hemoccult SENSA i-FOBT: OC-Micro	**CRC (i-FOBT, g-FOBT):** Sens: 100, 61.5 Spec : 85.9, 96.4 PPV: 3.9, 9.1 NPV: 100, 99.8 **PPV (CRC and AAP):** g-FOBT: 25.0 i-FOBT: 22.9	Registry only f/u of negative FOBTs.

Study	Design	Population	Test	Results	Comments
Rozen et al (2010)(136) (Includes Levi et al 2007(169) and Rozen et al 2009(135))	Prospective cross sectional double-blind study of 3 consecutive i-FOBTs for various Hb thresholds	Asymptomatic colonoscopy patients, high-risk family clinic pts, and mildly symptomatic volunteers in Tel Aviv. 6.3% refused, 22.2% lost to f/u or incorrectly prepared test, leaving N=1682 (analysed)	i-FOBT: OC-Micro	**Results vary widely by # of tests, cutoff level and for CRC vs. AAP.** Sens range: 21.7-100 Spec range: 84.5-97.8 +LR range: 4.51-14.73 -LR range: 0.00-0.80	ROC curves to determine best cut-off value.

Study	Design	Population	Test	Results	Comments
Park et al (2010)(40)	Prospective comparison of various g-FOBT and i-FOBT thresholds (50-150ng/ml) with colonoscopy	Average risk, asymptomatic persons aged 50-75 years in South Korea. N= 1020 invited; 891 completed	g-FOBT: Hemoccult II i-FOBT: OC-Sensa	**AA (i-FOBT, g-FOBT):** Sens: 27.1-44.1, 13.6 Spec: 88.3-92.1, 92.4 +LR: 3.4-3.8, 1.8 -LR: 0.6-0.8, 0.9 #CN: 4.2-4.5, 7.6 **Cancer (i-FOBT, g-FOBT):** Sens: 84.6-92.3, 30.8 Spec: 87.2-91.9, 92.4 +LR: 7.2-10.5, 4.0 -LR: 0.1-0.2, 0.8 #CN: 6.5-9.1, 15.2 **ACRN (i-FOBT, g-FOBT) :** Sens: 37.5-52.8, 16.7 Spec: 89.8-93.6, 92.9 +LR: 5.2-5.8, 2.3 -LR: 0.5-0.7, 0.9 #CN: 2.7-2.9, 5.1	Best cutoff value : 118ng/ml Scopes on all study subjects. 3 consecutive standard GTs and FITs.

Study	Design	Population	Test	Results	Comments
Parra-Blanco et al (2010)(52)	Observational comparison of g-FOBT and i-FOBT, colonoscopy	General (Naïve, asymptomatic) pop'n 50-79 years in Tenerife, Spain. N=2,288 (included)	g-FOBT: Hemofec i-FOBT: OC-light	**CRC (i-FOBT, g-FOBT):** Sens: 100, 54.2 Spec: 92.7, 96.9 PPV: 10.8, 13.6 NPV: 100, 99.6 **AA (i-FOBT, g-FOBT):** Sens: 56.8, 19.8 Spec : 94.5, 97.4 PPV: 36.5, 29.4 NPV: 97.5, 95.6	Qualitative FIT. Only 15.8% negative FOBTs underwent scope (93.7% positive FOBTs scoped).
Haug et al (2010)(139)	Prospective screening study	Average risk participants undergoing screening scopes in Germany N=1319 analysed	Comparison of two quantitative ELISA i-FOBTs for identifying adenomas. 1. RIDASCREEN Haemoglobin and 2. RIDASCREEN Haemo/haptoglobin complex	**Sensitivity** ↑ with number and size of adenomas for both tests (12-50%) across range of cutoff values. Specificities ranged from 90-99%. **PPV (Hb):** 64% **NPV (Hb):** 73% **+ LR (Hb):** 4.1 **- LR (Hb):** 0.85	All participants scoped.

Study	Design	Population	Test	Results	Comments
Hundt et al (2009)(137)	Prospective screening study	Average risk participants undergoing screening scopes in Germany N=1319 analysed	Comparison of six qualitative i-FOBTs and 1 guaiac FOBT for identifying adenomas. i-FOBTs: 1. FOB Advanced 2. Bionexia FOBplus 3. Bionexia Hb/Hp Complex 4. immoCARE-C 5. Prevent-ID CC 6. QuickVue iFOB g-FOBT: 1. HemOccult	**i-FOBT (ranges), g-FOBT:** **Positivity rates:** 5.8-46.4%, 4.5% **Sensitivity:** Any A: 11.4-58.0, 5.4 Adv A: 25.4-71.5, 9.4 Other A: 4.7-51.6, 3.5 **Specificity:** None or hyperplastic polyp: 58.8-96.7, 95.9 **PPV (Any A):** 38.4-60.5, 32.1 **NPV (Any A):** 71.1-76.0, 69.9 **+LR (Any A):** 1.41-3.46, 1.09 **-LR (Any A):** 0.71-0.92, 1.00	immoCARE-C was least sensitive/most specific, Bionexia Hb/HP Complex was most sensitive/least specific. For all iFOBTs, sensitivity increased with greater number and size of adenomas. Most tests more sensitive for distal than proximal adenomas (except QuickVue iFOB and HemOccult).

Study	Design	Population	Test	Results	Comments
Hol et al (2009a)(170)	Randomised pop'n based screening trial comparing g-FOBT, i-FOBT and flex sigmoidoscopy (followed by scope)	Representative sample of asymptomatic Dutch pop'n aged 50-74 years. N = 15,011 (invited), 6876 (participated)	g-FOBT: Hemoccult II i-FOBT: OC-Sensor micro (automated) cut-off at 100ng/ml	**(g-FOBT/i-FOBT)** **PPV (ACRN):** 45.2/53.3 **PPV (CRC):** 9.7/10.2	Only positive tests scoped. 12% higher FIT participation.

Study	Design	Population	Test	Results	Comments
Hol et al (2009b)(171)	Randomised pop'n based trial comparing test characteristics of g-FOBT and i-FOBT at various thresholds	Representative sample of asymptomatic Dutch pop'n aged 50-74 years. N = 10,011 (invited), 5326 returned samples	g-FOBT: Hemoccult II i-FOBT: OC-Sensor micro (automated) cut-off at 100ng/ml	**PPV (ACRN):** g-FOBT: 45 i-FOBT: 42-62 **PPV (CRC):** g-FOBT: 10 i-FOBT: 7-12 **Specificity* (ACRN):** g-FOBT: 98.5 i-FOBT: 95.5-98.8 **Specificity* (CRC):** g-FOBT: 97.6 i-FOBT: 92.9-97.1 **NNScope (ACRN):** g-FOBT: 2.2 i-FOBT: 1.6-2.4 **NNScope (CRC):** g-FOBT: 10.3 i-FOBT: 8.2-14.1 **NNScreen (ACRN):** g-FOBT: 84 i-FOBT: 31-49 **NNScreen (CRC):** g-FOBT: 392 i-FOBT: 186-248	75ng/ml determined to be optimal cutoff. Scopes for positive FOBTs only. 3 consecutive samples for g-FOBT, 1 sample for FIT. 8.1% positivity rate for i-FOBTs at 50ng/ml (3.5% at 200 ng/ml), 2.8% for g-FOBT. *Specificity calculated under rare disease assumption.

Study	Design	Population	Test	Results	Comments
Guittet et al (2009a)(54)	Observational comparison of performance of i-FOBT, across various thresholds and numbers of samples, with g-FOBT.	Average risk pop'n 50-74 years, participating in screening program in Calvados (France). N = 20,322 (FOBTs), 1,363 (scopes)	g-FOBT: Hemoccult II i-FOBT: Magstream (quantitative)	**PPV:** 24.5 Increasing positivity threshold decreased sensitivity, increased specificity. At a fixed threshold, increasing number of samples increased sensitivity/decreased specificity.	Scope for positive FOBTs only. 5.1% positivity rate.
Guittet et al (2009b)(172)	Observational comparison of performance of i-FOBT, according to type and location of lesion, with g-FOBT.	Average risk pop'n 50-74 years, participating in screening program in Calvados (France). N = 20,322 (FOBTs), 1,363 (scopes)	g-FOBT: Hemoccult II i-FOBT: Magstream (quantitative)	Amounts of bleeding highest for invasive cancers, then high-risk adenomas, small adenomas, then normal colon. Gains in sensitivity for i-FOBT higher for high-risk adenomas than cancers.	Scope for positive FOBTs only. 5.1% positivity rate.
van Rossum et al (2009)(3)	Comparison of stage distribution of CRC pts detected with FOBT screening vs. symptoms	Asymptomatic subjects 50-75 years old, no family hx, with positive FOBTs invited for scope. Symptomatic CRC patients with no family hx.	g-FOBT: Hemoccult II i-FOBT: OCSensor	Stage distribution for CRC pts detected with g-FOBT not different than symptomatic pts. CRC detected significantly earlier in those with i-FOBT than symptomatic pts.	All participants scoped. Included symptomatic individuals.

Study	Design	Population	Test	Results	Comments
Dancourt et al (2008)(55)	Observational comparison of g-FOBT and i-FOBT, colonoscopy	Average risk population 50-74 years on 2nd round of screening in Burgundy N=17,215 (completed)	g-FOBT: Hemoccult II i-FOBT: Instant-view	**PPV (cancers):** g-FOBT: 5.2% i-FOBT: 5.9% **PPV (AAs):** g-FOBT: 17.5% i-FOBT: 26.9%	Significant proportion of FITs did not undergo scope. Only scoped positive FITs.
van Rossum et al (2008)(173)	Population RCT with scopes for positive FOBTs	General (asymptomatic) population 50-75 years in Amsterdam N=20,623 (invited), 10993 tested	g-FOBT: Hemoccult II i-FOBT: OC-Sensor (quantitative)	**PPV (all polyps/ CRC):** g-FOBT: 77.7 i-FOBT: 77.9 **Specificity (All AAs/CRC):** g-FOBT: 99.0 i-FOBT: 97.8 **PPV (all AAs/ CRC):** g-FOBT: 55.3 i-FOBT: 51.8	Only scoped positive FITs so can only calculate PPV. Estimation of specificity using rare disease assumption. Used quantitative FIT.
Guittet et al (2007)(174)	Observational comparison of g-FOBT and i-FOBT at 3 cutoff points (20, 50, and 75 ng/ml)	Average risk pop'n 50-74 years participating in average risk screening program in Calvados (France) N = 10804 (participated)	g-FOBT: Hemoccult II i-FOBT: Immudia/RPHA (quantitative)	**PPV (CRC):** g-FOBT: 7.3 i-FOBT: 4.0, 7.7, 8.7 **PPV (CRC/AA):** g-FOBT: 27.7 i-FOBT: 30.2, 44.7, 49.2	Scope for positive FITs only. Positivity rate 6.9% (vs. 2.4% for g-FOBT) i-FOBT more sensitive for both CRC and AA irrespective of cutoff.

Study	Design	Population	Test	Results	Comments
Allison et al (2007)(51)	Observational comparison of sensitive g-FOBT and i-FOBT	Average risk pop'n 50-80 years in Northern California. N=11,564 (invited), 5,932 screened by FOBT	g-FOBT: Hemoccult Sensa i-FOBT: Hemoccult ICT (aka FlexSure OBT) (qualitative)	**Distal CRC (i-FOBT, g-FOBT):** Sens: 81.8, 64.3 Spec: 96.9, 90.1 PPV: 5.2, 1.5 +LR: 26.7, 6.5 **Distal adenomas (≥1cm) (i-FOBT, g-FOBT):** Sens: 29.5, 41.3 Spec: 97.3, 90.6 PPV: 19.1, 8.9 +LR: 11.0, 4.4 **Distal ACRN (i-FOBT, g-FOBT):** Sens: 33.1, 43.1 Spec: 97.5, 90.7 PPV: 23.1, 10.1 +LR: 13.0, 4.6	Each test done on 3 samples. Scope only for positive FOBTs. Sigmoidoscopy for –ve FOBTs. Ability of tests to detect neoplasias of right colon not tested b/c not all pts scoped. 3.2% positivity rate for FlexSure (FIT), 10.1% for g-FOBT.
Fraser et al (2006)(142)	Observational comparison of g-FOBT and i-FOBT	Screening pop'n 50-69 years with positive g-FOBT while awaiting scope in Scotland N=1486 (invited)	g-FOBT: Hemascreen i-FOBT: Instant-view	**CRC:** Sens: 95.0 Spec: 39.5 + LR: 1.57 - LR : 0.13 **CRC and HR polyps :** Sens: 90.1 Spec: 47.8 + LR: 1.73 - LR : 0.21	High (47%) non-participtionrate. Only scoped positive g-FOBTs.

Study	Design	Population	Test	Results	Comments
Morikawa et al (2005)(143)	Retrospective analysis of dataset of simultaneous single sample i-FOBT and colonoscopy for sens, spec of i-FOBT and for prevalence and location of neoplasia	Asymptomatic pop'n (family hx, prior screening info not available). N=22,666 (enrolled), 22,259 (scoped)	i-FOBT: Magstream 1000/ Hem SP (20mg Hb/L)	**PPV** (neoplasia): 36.5 **PPV** (ACRN): 16.0 **PPV** (inv CRC): 4.2 **Sens** (ACRN): 27.1 **Sens** (inv CRC): 65.8 **Spec** (ACRN): 95.1 **Spec** (inv CRC): 94.6	5.6% positivity rate Sens for ACRN and adenomas ≥10mm better for distal tumours than proximal Less sensitive for local than invasive CRC. Possible selection bias. Young pop'n.
Launoy et al (2005)(175)	Observational comparison of performance of automated FIT at various Hb cut off points with scope.	Average risk pop'n 50-74 years in Normandy, France. N=7,421	i-FOBT: Magstream 1000 (automated) (20ng/ml Hb)	**Results 20/50/75 ng/ml** **PPV** (CRC): .06/.09/.13 **PPV** (large A): .28/.40/.41 **Sens** (at 2 years): .85/.68-.83/.61-.81 **Spec**: .94/.97/.98	2 samples on 2 different days. All participants scoped. Positivity rate: 5.8% (20ng/ml), 3.1% (50ng/ml), 2.0% (75ng/ml). 84.3% compliance with scope. F/u with cancer registry.
Federici et al (2005)(176)	Cluster RCT, 4 armed factorial (GP vs hospital and g-FOBT vs i-FOBT) for acceptability of tests	Random sample of screening pop'n 50-74 years in Lazio, Italy. N=7320 (tested)	g-FOBT: Hemo-Fec i-FOBT: OC-Hemodia	**PPV (CRC/High grade adenoma):** g-FOBT: 19.7 i-FOBT: 29.3	Higher participation rate among i-FOBT group (35.8% vs 30.4%). Different results than Ko.

Study	Design	Population	Test	Results	Comments
Hughes et al (2005)(177)	Cluster quasi-RCT, g-FOBT vs i-FOBT, scope offered for positive FOBTs	All pts 50-74 years in 4 general practices in rural Queensland, Australia N=1,219 (completed)	g-FOBT: Hemoccult-II i-FOBT: !nform	**PPV (CRC or AA):** i-FOBT: 37.8 g-FOBT: 40.4	Better participation with i-FOBT. 29% had prior scope. Lacked statistical power to detect differences in CRC.
Kronborg et al (2004) (178)	RCT of biannual g-FOBT vs no screening	Participants recruited from Funen, Denmark. Aged 45-75 years, known CRC, polyps or metastatic Ca excluded. N=137,485 invited, 61,933 randomised. (30,967 to screening, 20,672 of whom were screened, 9,367 screened in latest round)	g-FOBT: Hemoccult II Dietary restrictions x 3 days. No rehydration.	CRC mortality less in screened group after 17 years, but not sig after post-op complications included. Screening more effective at preventing death due to proximal CRC.	Colonoscopy for positive tests only. Inclusion only of those who accepted first screening rounds.
Ko et al (2003)(179)	Cluster quasi-RCT g-FOBT vs i-FOBT, scope/BE for positive FOBTs	Usual care pop'n at VA general medical clinic in Seattle N=5929 (invited)	g-FOBT: Hemoccult SENSA i-FOBT: FlexSure OBT	**PPV (any adenoma):** i-FOBT: 58% g-FOBT: 59% **PPV (AA/CRC):** i-FOBT: 17% g-FOBT: 30%	Not all pts with negative tests were scoped. Lack of research protocol.

Study	Design	Population	Test	Results	Comments
Scholefield et al (2002) (180) 11 year f/u of Hardcastle et al (1996)	RCT of biannual g-FOBT vs no screening	Participants recruited from family practices in Nottingham, UK. Aged 50-74, serious illness (including prior CRC) excluded. N=152,850 randomised, 76,466 to screening. 44,838 accepted screening.	g-FOBT: Hemoccult (non-rehydrated) 2 samples from each of 3 consecutive stools	13% reduction in mortality in screened group (RR 0.87, 0.78-0.97, p=0.010)	Median f/u of 11 years.
Mandel et al (2000) (181)	RCT of effectiveness of g-FOBT in reducing CRC *incidence*. 3 arms: yearly, biannual, or control groups.	Volunteers aged 50-80 years recruited from various groups in Minnesota, US, 1975-77. Reasonably average risk (not specifically screened). N=46,551.	g-FOBT: Hemoccult (rehydrated) 6 slides from 3 consecutive samples	Significant reduction in incidence of CRC, perhaps due to removal of polyps during the several colonoscopies rather than the sensitivity of g-FOBT.	18 years of f/u. Various forms of f/u for positive tests. Enrolled volunteers – limited external validity.
Mandel et al (1999) (182)	RCT of effectiveness of g-FOBT in reducing CRC *mortality*. 3 arms: yearly, biannual, or control groups.	Volunteers aged 50-80 years recruited from various groups in Minnesota, US, 1975-77. Reasonably average risk (not specifically screened). N=46,551.	g-FOBT: Hemoccult (rehydrated) 6 slides from 3 consecutive samples	33% reduction in mortality in annual group. 21% reduction in mortality in biannual group. Fewer stage D CRCs in screened groups.	18 years of f/u. Various forms of f/u for positive tests. Enrolled volunteers – limited external validity.

Study	Design	Population	Test	Results	Comments
St. John et al (1993)(183)	Observational comparison of g-FOBT, sensitive g-FOBT, Hb i-FOBT and heme-porphyrin i-FOBT	Pts with newly dx CRC, colonic or rectal adenoma, and healthy subjects.	g-FOBT: Hemoccult II g-FOBT: Hemoccult SENSA (more sensitive g-FOBT) i-FOBT: HemeSelect (qualitative) i-FOBT: HemoQuant (heme-porphyrin)	**PPV(CRC):** 88.8, 93.5, 97.2, 71.0 **PPV(Adenoma):** 30.9, 44.4, 58.0, 37.0	HemeSelect had greatest potential for screening due to high sensitivity and specificity.
Kronborg et al (1996) (24)	RCT of biannual g-FOBT vs no screening	Participants recruited from Funen, Denmark. Aged 45-75 years, known CRC, polyps or metastatic Ca excluded. N=137,485 invited, 61,933 randomised. (30,967 to screening, 20,672 of whom were screened)	g-FOBT: Hemoccult II Dietary restrictions x 3 days. No rehydration.	**PPV(CRC):** 8-17 **PPV (Adenoma ≥10m):** 21-38 18% reduction in CRC mortality. Stage A CRC sig lower in screening group, Stage C sig higher in control gp.	Colonoscopy for positive tests only.

Study	Design	Population	Test	Results	Comments
Hardcastle et al (1996) (22)	RCT of biannual g-FOBT vs no screening	Participants recruited from family practices in Nottingham, UK. Aged 50-74, serious illness (including prior CRC) excluded. N=152,850 randomised, 76,466 to screening. 44,838 accepted screening.	g-FOBT: Hemoccult (non-rehydrated) No dietary restrictions on first test 2 samples from each of 3 consecutive stools	15% reduction in mortality in screened group (OR 0.85, 0.74-0.98, p=0.026) Higher proportion of Stage A CRC in screened group, lower Stages C&D.	Median f/u of 7.8 years. <5 + squares were given repeat FOBT with dietary restrictions. F/u with double-contrast barium enema, sigmoidoscopy.
Mandel et al (1993)(23)	RCT of effectiveness of g-FOBT in reducing CRC mortality. 3 arms: yearly, biannual, or control groups.	Volunteers aged 50-80 years recruited from various groups in Minnesota, US, 1975-77. Reasonably average risk (not specifically screened). N=46,551.	g-FOBT: Hemoccult (rehydrated) 6 slides from 3 consecutive samples	33% reduction in CRC mortality, improved survival, shift to earlier stage at detection with annual g-FOBT screening. **Non-rehydrated*:** Sens: 80.8 Spec: 97.7 PPV: 5.6 **Rehydrated *:** Sens : 92.2 Spec : 90.4 PPV : 2.2	13 years of f/u. Various forms of f/u for positive tests. *negative FOBTs not scoped, but followed x 1 year. If cancer occurred, assumed false negative test. Enrolled volunteers – limited external validity.

Potential sources of variation in findings: Different definitions of advanced adenoma, different populations.

By only conducting colonoscopies on positive FOBTs, estimates of disease prevalence will differ from average-risk population, causing inaccurate sensitivity and specificity estimates.
g-FOBT = guaiac fecal occult blood test
i-FOBT/FIT = immunochemical fecal occult blood test/ fecal immunochemical test
AA = advanced adenoma
CRC = colorectal cancer
ACRN = advanced colorectal neoplasia *NB – definition may vary by study
Sens = sensitivity PPV = positive predictive value +LR = positive likelihood ratio
Spec = specificity NPV = negative predictive value -LR = negative likelihood ratio
#CN = number colonoscopies needed to detect cancer or ACRN in persons with a positive test

APPENDIX 2: SCOPE MODEL ASSUMPTIONS

Demographic Assumptions

- Entities represent individuals.
- Background mortality is age- and sex-specific, based on Statistics Canada's Life Tables for Canada (2007-2009), and is representative of the Canadian population.(122)
- Background mortality rates include colorectal cancer deaths. Cancer deaths were not backed out of background mortality rates due to insufficient data by year of age.(127,128)
- Individuals are subject to competing risks of both background and colorectal cancer mortality, assuming conditional independence of the risks (both for model simplicity and due to lack of relevant data).
- Competition between risks of background mortality and colorectal cancer mortality was accounted for by proportionally attributing cause of death (background or colorectal cancer) in a given year.
- "Higher risk" individuals represent those with at least 1 family member with advanced adenoma or colorectal cancer, or individuals with a personal history of inflammatory bowel disease (IBD) (e.g., Crohn's disease or ulcerative colitis), or familial polyposis.
- Age is truncated at 100 due to instability of estimates of mortality at older ages.

Natural History Assumptions

- The natural history model represents 7 states based on the adenoma-carcinoma sequence:
    1. Normal epithelium
    2. Low risk polyps
    3. High risk polyps
    4. Local CRC (Dukes stage A and B)

5. Regional CRC (Dukes stage C)
6. Advanced CRC (Dukes stage D)
7. CRC death

- Individuals entering the model are assigned an initial stage in the CRC sequence (including healthy epithelium) based on the observed prevalence among 50 year olds in the general population.
- Transition probabilities between normal epithelium and low risk polyps are age-specific and risk-specific (i.e., average vs. higher risk).
- "Higher risk" individuals are more likely to be in stages 2-7 at model initialization than their "average risk" counterparts of the same age, and of transitioning between stages 1 and 2 (see Appendix 3 for transition probabilities).
- Natural history states are updated annually (i.e., individuals remain in a given stage for the year).
- Individuals may present symptomatically, according to stage-specific probabilities. Individuals are increasingly likely to present with symptoms at higher stages of disease. If symptomatic, individuals are not eligible for average risk screening. Rather, they proceed directly to the diagnostic colonoscopy process.
- Stage-specific survival encompasses treatment effects, which are not modelled explicitly.
- Stage-specific survival remains constant over the time horizon modelled.

Screening Program Assumptions

- Asymptomatic, average risk individuals aged 50 – 74 years are offered programmatic screening biannually.
- Higher risk individuals are not eligible for participation in programmatic average risk screening. Rather, they go directly to diagnostic colonoscopy processes if symptomatic or for targeted screening, or to surveillance colonoscopy processes for follow-up as appropriate.

- Sensitivity, specificity and uptake rates are based on the screening test of choice (i.e., sensitive guaiac fecal occult blood test (g-FOBT) or fecal immunochemical test (FIT)).
- Sensitivity of stool tests is stage-specific, with increasing sensitivity at higher stages.
- Individuals with positive stool test results (whether true or false positive) are directed to follow-up screening colonoscopy processes.

Treatment Assumptions

- Treatment is not explicitly modelled. The effectiveness of treatment at the population-level is captured in the survival probabilities for colorectal cancer.
- Individuals with early (local) or regional stages of colorectal cancer identified by colonoscopy are decremented by 1 stage in the adenoma-carcinoma sequence to account for increased survival probability post detection.

Colonoscopy Services Assumptions

- Average risk follow-up screening, diagnostic (symptomatic or higher risk targeted screening) and surveillance individuals compete for colonoscopy resources.
- Colonoscopy resources may be shifted between average risk follow-up screening, diagnostic, or surveillance activities.
- Colonoscopy services are modelled in terms of availability of colonoscopy "slots". Slots are classified by purpose: screening, diagnostic (for symptomatic or higher risk screening individuals), or surveillance.
- Factors that influence the availability of colonoscopy slots (such as gastroenterologist and nursing staff, colonoscopy suites, equipment, funding or policy decisions, etc.) are considered exogenous to the model.
- Arrivals for colonoscopy services occur randomly with a uniform distribution over the course of a year.

- Sensitivity of colonoscopy varies by stage of the adenoma-carcinoma sequence, with increasing sensitivity at higher stages.
- Colonoscopy findings are stage-specific.

Colorectal Cancer (CRC) Model Details: Attributes and Variables

Table 2a SCOPE Model Attributes

Attribute	Definition	Value	Assumptions	Data, Source
attAge	Synthetic individual's age	50 at entry to model (for calibration cohort) Age distributed as per Stats Can values for population (for population cohort)	Age increments by 1 year every yearly cycle (if not dead).	Deterministically assigned.
attSex	Synthetic individual's sex	1 = Male 2 = Female	50-50 assignment	Assigned probabilistically.
attInitialState	Natural history state at initialization for average risk population	1 = Normal epithelium 2 = Low risk polyp 3 = High risk polyp 4 = Local CRC 5 = Regional CRC 6 = Advanced CRC 7 = CRC death NB: 0 = Higher Risk	Distribution of initial state according to prevalence in unscreened average risk population. Age and sex dependent.	Assigned probabilistically.(114–118) Probabilities stored in initial state variables.
attCurrentState	Updated natural history stage. Stage updates yearly. Individuals may remain in current stage or progress depending upon transition probabilities.	1 = Normal epithelium 2 = Low risk polyp 3 = High risk polyp 4 = Local CRC 5 = Regional CRC 6 = Advanced CRC 7 = CRC death	Transition from stage 1 to stage 2 is age and risk dependent. Individuals advance along adenoma-carcinoma pathway with no spontaneous regression. Females lag 10 years behind males in the development of low risk adenomas.	Assigned probabilistically. (114–118) Annual transition probabilities contained in transition matrix variables based on sex, age and current stage (see Variables "varARFemalesT1TxAA", etc.).

Attribute	Definition	Value	Assumptions	Data, Source
attHighRisk	Higher risk for colorectal cancer	0 = No 1 = Yes	8% prevalence of higher risk based on estimated combined population prevalence of IBD (0.78%) and those with family histories of advanced adenomas or colorectal cancer among first degree relatives (5-10%). Assumed colonoscopies required for ~30% annually	Randomly assigned to 8% of population for scenario models. Sensitivity test 6%, 10%. IBD prevalence 0.78% (148) Fam hx prevalence 5.0-10.0% (121,184)
attHRInitialState	Natural history state at initialization for higher risk population	1 = Normal epithelium 2 = Low risk polyp 3 = High risk polyp 4 = Local CRC 5 = Regional CRC 6 = Advanced CRC 7 = CRC death	Risk of colorectal cancer assumed to be twice that (overall) of average risk population. (Summary measure includes those with at least 1 family member with colorectal cancer.) Age and sex dependent.	Assigned probabilistically. Probabilities stored in higher risk initial state variables. (185)
attHRCurrentState	Updated natural history state. State updates yearly. Individuals may remain in current state or progress depending upon transition probabilities.	1 = Normal epithelium 2 = Low risk polyp 3 = High risk polyp 4 = Local CRC 5 = Regional CRC 6 = Advanced CRC 7 = CRC death	Higher risk individuals have twice the risk of colorectal cancer as average risk individuals. No adjustment is made to transition to CRC death per se, as increases in likelihood of adenomas/CRC will result in increased likelihood of CRC death.	Assigned probabilistically. (114–118,185)
attOtherDeath	Non-colorectal cancer death (background mortality)	0 = No 1 = Yes	Other death flagged if individual dies of background (all-cause) mortality.	Randomly assigned based on partitioned probability of background mortality.
attCRCdeath	Colorectal cancer death	0 = No 1 = Yes	Colorectal cancer death if either initial state or current state = 7.	Randomly assigned based on partitioned probability of background mortality.

Attribute	Definition	Value	Assumptions	Data, Source
attDead	Dead	0 = No 1 = Yes	Individuals may die of either colorectal cancer or background (all-cause) mortality.	Randomly assigned based on probability of colorectal cancer death(22–24,128) or background (all-cause) mortality.(122)
attSymptomatic	Presents with symptoms	0 = No 1 = Yes	Increasing likelihood of presenting symptomatically with increasing state along adenoma-carcinoma sequence.	Assigned probabilistically.(145) Values contained in varSymptomatic.
attAgeGroup	Age by categories	50-54 55-59 60-64 65-69 70-74 75-79 80+		Assigned deterministically based on age.
attDoesSurvScope	Does surveillance colonoscopy in given year	0 = No 1 = Yes		Assigned based on Canadian recommendations for surveillance intervals.
attDoesDxScope	Does diagnostic colonoscopy in given year	0 = No 1 = Yes	95% symptomatic presentations have diagnostic colonoscopy. 25% higher risk patients have diagnostic colonoscopy.	Assigned probabilistically.
attDoesScreenScope	Does follow-up screening colonoscopy in given year	0 = No 1 = Yes	85% participation rate following positive FIT.	Assigned probabilistically. Rnd <= 0.85(186)
attScopeArrive	Time of arrival for scope	TNOW (current simulation time)	Unit: days	Simulation clock.
attNumSurvScopes	Number of surveillance colonoscopies	Count (per individual)	Increments by 1 with each colonoscopy	Assigned incrementally.
attNumDxScopes	Number of diagnostic colonoscopies	Count (per individual)	Increments by 1 with each colonoscopy	Assigned incrementally.
attNumScreenScopes	Number of screening colonoscopies	Count (per individual)	Increments by 1 with each colonoscopy	Assigned incrementally.

Attribute	Definition	Value	Assumptions	Data, Source
attScopeFinding	Findings on colonoscopy	1 = Normal epithelium 2 = Low risk polyp 3 = High risk polyp 4 = Local CRC 5 = Regional CRC 6 = Advanced CRC 7 = CRC death	1 - No false positives. Return to screening eligibility in 10 years. 2 - Return to surveillance scope in 3 years. 25% miss rate. 3 - Return to surveillance scope in 1 year. 10% miss rate. 4 - Sent to treatment (. 5 - 0.10578% miss rate 6 – 0% miss rate. 4-6 - sent to treatment process.	Assigned probabilistically. Adenomas (187) Cancers (188) Values stored in varScopeFindings
attNumScopes	Total number of colonoscopies	Count (per individual)	Increments by 1 with each colonoscopy	Assigned incrementally.
attFITeligible	Eligible to take a stool test (every 2 years)	0 = No 1 = Yes	50% of population randomly assigned to be eligible in year 1. If eligible in year 1, then ineligible in year 2 and vice versa. Eligible if asymptomatic, 50-74 years old, and not in surveillance.	Eligibility criteria based on colorectal cancer screening program criteria.
attTreatment	Treatment patient	0 = No 1 = Yes		
attDelay	Delay return to screening for surveillance based on colonoscopy finding.	1 - 10 years	1-3 year delay for high risk polyps 3-5 year delay for intermediate risk polyps 5-10 year delay for low risk polyps 10 year delay for normal epithelium	Based on Canadian guidelines for surveillance.(10,42)
attScopeMiss	Pathology present as per natural history, but not detected on colonoscopy.			Assigned probabilistically.
attHRScopeMiss	Pathology present as per natural history, but not detected on colonoscopy.			Assigned probabilistically.
attYear	Simulation year.			Simulation clock.

Attribute	Definition	Value	Assumptions	Data, Source
attFITpositive	Result of screening stool test	0 = Negative 1 = Positive	Stage-specific FIT (sensitivity analyses)*: 1 = 0.05 (0.02, 0.08) 2 = 0.104 (0.07, 0.135) 3 = 0.271 (0.23, 0.31) 4 = 0.565 (0.51, 0.62) 5 = 0.75 (0. 7, 0.8) 6 = 0.80 (0.75, 0.85) 7 = 0 (CRC death) Stage-specific sensitive g-FOBT (sensitivity analyses)*: 1 = 0.12 (0.09, 0.15) 2 = 0.075 (0.05, 0.1) 3 = 0.185 (0.15, 0.22) 4 = 0.5 (0.45, 0.55) 5 = 0.7 (0.65, 0.75) 6 = 0.87 (0.8, 0.92) 7 = 0 (CRC death) Higher Threshold FIT* 1 = 0.025 2 = 0.052 3 = 0.1355 4 = 0.42375 5 = 0.5625 6 = 0.6 7 = 0.0 (CRC death) *At stage 1 (normal epithelium), specificity is expressed as false positives. At stages 2-6 (presence of pathology), sensitivity is expressed as true positives.	Assigned probabilistically.(79,80,143,189) (see varFITpositivity)
attNormEpi	Normal epithelium discovered at colonoscopy.	0 = No 1 = Yes		Derived based on attScopeFinding

Table 2b SCOPE Model Variables

Attribute	Definition	Value	Assumptions	Data, Source
varSymptomatic	Probability of presenting symptomatically with increasing stage	1 = 0.0 2 = 0.02 3 = 0.08 4 = 0.32 5 = 0.59 6 = 0.854 7 = 0.0	Increases with stage.	(145)
varAge	Variable set to allow subtraction from age 50 for reading index value in matrices.	49	N/A	50-49 = 1 51-49 = 2 52-49 = 3 and so on.
varHRMalesT1TxAA	Transition probability matrix – Higher risk males in stage 1	See Appendix 3	Annual transition probabilities for higher risk males. Vary by age, current stage (for adenoma-carcinoma sequence transitions) and sex (for background mortality).	Transition probability matrix – Higher risk males in stage 1
varHRMalesT2TxAA	Transition probability matrix – Higher risk males in stage 2	See Appendix 3	As above.	Transition probability matrix – Higher risk males in stage 2
varHRMalesT3TxAA	Transition probability matrix – Higher risk males in stage 3	See Appendix 3	As above.	Transition probability matrix – Higher risk males in stage 3
varHRMalesT4TxAA	Transition probability matrix – Higher risk males in stage 4	See Appendix 3	As above.	Transition probability matrix – Higher risk males in stage 4
varHRMalesT5TxAA	Transition probability matrix – Higher risk males in stage 5	See Appendix 3	As above.	Transition probability matrix – Higher risk males in stage 5
varHRMalesT6TxAA	Transition probability matrix – Higher risk males in stage 6	See Appendix 3	As above.	Transition probability matrix – Higher risk males in stage 6

Attribute	Definition	Value	Assumptions	Data, Source
varHRFemalesT1TxAA	Transition probability matrix – Higher risk females in stage 1	See Appendix 3	Annual transition probabilities for higher risk females. Vary by age, current stage (for adenoma-carcinoma sequence transitions) and sex (for background mortality).	Transition probability matrix – Higher risk females in stage 1
varHRFemalesT2TxAA	Transition probability matrix – Higher risk females in stage 2	See Appendix 3	As above.	Transition probability matrix – Higher risk females in stage 2
varHRFemalesT3TxAA	Transition probability matrix – Higher risk females in stage 3	See Appendix 3	As above.	Transition probability matrix – Higher risk females in stage 3
varHRFemalesT4TxAA	Transition probability matrix – Higher risk females in stage 4	See Appendix 3	As above.	Transition probability matrix – Higher risk females in stage 4
varHRFemalesT5TxAA	Transition probability matrix – Higher risk females in stage 5	See Appendix 3	As above.	Transition probability matrix – Higher risk females in stage 5
varHRFemalesT6TxAA	Transition probability matrix – Higher risk females in stage 6	See Appendix 3	As above.	Transition probability matrix – Higher risk females in stage 6
varARMalesT1TxAA	Transition probability matrix – Average risk males in stage 1	See Appendix 3	Annual transition probabilities for average risk males. Vary by age, current stage (for adenoma-carcinoma sequence transitions) and sex (for background mortality).	Transition probability matrix – Average risk males in stage 1
varARMalesT2TxAA	Transition probability matrix – Average risk males in stage 2	See Appendix 3	As above.	Transition probability matrix – Average risk males in stage 2
varARMalesT3TxAA	Transition probability matrix – Average risk males in stage 3	See Appendix 3	As above.	Transition probability matrix – Average risk males in stage 3
varARMalesT4TxAA	Transition probability matrix – Average risk males in stage 4	See Appendix 3	As above.	Transition probability matrix – Average risk males in stage 4

Attribute	Definition	Value	Assumptions	Data, Source
varARMalesT5TxAA	Transition probability matrix – Average risk males in stage 5	See Appendix 3	As above.	Transition probability matrix – Average risk males in stage 5
varARMalesT6TxAA	Transition probability matrix – Average risk males in stage 6	See Appendix 3	As above.	Transition probability matrix – Average risk males in stage 6
varARFemalesT1TxAA	Transition probability matrix – Average risk females in stage 1	See Appendix 3	Annual transition probabilities for average risk females. Vary by age, current stage (for adenoma-carcinoma sequence transitions) and sex (for background mortality).	Transition probability matrix – Average risk females in stage 1
varARFemalesT2TxAA	Transition probability matrix – Average risk females in stage 2	See Appendix 3	As above.	Transition probability matrix – Average risk females in stage 2
varARFemalesT3TxAA	Transition probability matrix – Average risk females in stage 3	See Appendix 3	As above.	Transition probability matrix – Average risk females in stage 3
varARFemalesT4TxAA	Transition probability matrix – Average risk females in stage 4	See Appendix 3	As above.	Transition probability matrix – Average risk females in stage 4
varARFemalesT5TxAA	Transition probability matrix – Average risk females in stage 5	See Appendix 3	As above.	Transition probability matrix – Average risk females in stage 5
varARFemalesT6TxAA	Transition probability matrix – Average risk females in stage 6	See Appendix 3	As above.	Transition probability matrix – Average risk females in stage 6
varMalePopulation	Initial age distribution for males in population models.		Based on Canadian Census information.	Based on 2006 Canadian Census information.
varFemalePopulation	Initial age distribution for females in population models.			Based on 2006 Canadian Census information.

Attribute	Definition	Value	Assumptions	Data, Source
varFITpositivity	Probability of positive stool test	1 = positive 2 = negative	Stage-specific FIT* (sensitivity analyses): 1 = 0.05 (0.02, 0.08) 2 = 0.104 (0.07, 0.135) 3 = 0.271 (0.23, 0.31) 4 = 0.565 (0.51, 0.62) 5 = 0.75 (0. 7, 0.8) 6 = 0.80 (0.75, 0.85) 7 = 0 (CRC death) Stage-specific FOBT* (sensitivity analyses): 1 = 0.12 (0.09, 0.15) 2 = 0.075 (0.05, 0.1) 3 = 0.185 (0.15, 0.22) 4 = 0.5 (0.45, 0.55) 5 = 0.7 (0.65, 0.75) 6 = 0.87 (0.8, 0.92) 7 = 0 (CRC death) Higher Threshold FIT*: 1 = 0.025 2 = 0.052 3 = 0.1355 4 = 0.42375 5 = 0.5625 6 = 0.6 7 = 0.0 (CRC death) *At stage 1 (normal epithelium), specificity is expressed as false positives. At stages 2-6 (presence of pathology), sensitivity is expressed as true positives.	Assigned probabilistically. (79,80,143,189)

Attribute	Definition	Value	Assumptions	Data, Source
varScopeFinding	Probability of finding on colonoscopy	1 = Normal epithelium 2 = Low risk polyp 3 = High risk polyp 4 = Local CRC 5 = Regional CRC 6 = Advanced CRC		Assigned probabilistically
varNewArrivals	Number of new arrivals annually		Based on Statistics Canada population projections	(147)

APPENDIX 3 ANNUAL TRANSITION PROBABILITIES BY SEX, RISK AND STAGE

Table 3a Annual Transition Probabilities for Average Risk Females with Normal Epithelium

Age	Other Death	Normal Epithelium	Low Risk Polyp
50	0.00208	0.99443	0.00349
51	0.00226	0.99425	0.00349
52	0.00247	0.99404	0.00349
53	0.00270	0.99381	0.00349
54	0.00295	0.99356	0.00349
55	0.00322	0.99329	0.00349
56	0.00353	0.99298	0.00349
57	0.00386	0.99265	0.00349
58	0.00423	0.99228	0.00349
59	0.00464	0.99188	0.00348
60	0.00510	0.98993	0.00497
61	0.00560	0.98943	0.00497
62	0.00615	0.98888	0.00497
63	0.00677	0.98826	0.00497
64	0.00745	0.98759	0.00496
65	0.00821	0.98534	0.00645
66	0.00905	0.98451	0.00644
67	0.00999	0.98357	0.00644
68	0.01102	0.98255	0.00643
69	0.01218	0.98140	0.00642
70	0.01347	0.97864	0.00789
71	0.01490	0.97722	0.00788
72	0.01650	0.97563	0.00787
73	0.01828	0.97387	0.00785
74	0.02028	0.97188	0.00784
75	0.02250	0.96968	0.00782
76	0.02499	0.96721	0.00780
77	0.02777	0.96445	0.00778
78	0.03088	0.96137	0.00775
79	0.03437	0.95790	0.00773
80	0.03828	0.94672	0.01500
81	0.04267	0.94240	0.01493
82	0.04760	0.93754	0.01486
83	0.05313	0.93210	0.01477
84	0.05935	0.92598	0.01467
85	0.06634	0.91909	0.01457
86	0.07421	0.91135	0.01444
87	0.08308	0.90262	0.01430
88	0.09308	0.89277	0.01415

Age	Other Death	Normal Epithelium	Low Risk Polyp
89	0.10435	0.88168	0.01397
90	0.11708	0.88124	0.00168
91	0.13112	0.86723	0.00165
92	0.14622	0.85216	0.00162
93	0.16236	0.83605	0.00159
94	0.17950	0.81894	0.00156
95	0.19754	0.80094	0.00152
96	0.21631	0.78220	0.00149
97	0.23596	0.76259	0.00145
98	0.25639	0.74220	0.00141
99	0.27744	0.72119	0.00137

Table 3b Annual Transition Probabilities for Average Risk Females with Low Risk Polyp

Age	Other Death	Low Risk Polyp	High Risk Polyp
50	0.00208	0.97796	0.01996
51	0.00226	0.97779	0.01995
52	0.00247	0.97758	0.01995
53	0.00270	0.97735	0.01995
54	0.00295	0.97711	0.01994
55	0.00322	0.97684	0.01994
56	0.00353	0.97654	0.01993
57	0.00386	0.97622	0.01992
58	0.00423	0.97585	0.01992
59	0.00464	0.97545	0.01991
60	0.00510	0.97500	0.01990
61	0.00560	0.97451	0.01989
62	0.00615	0.97397	0.01988
63	0.00677	0.97337	0.01986
64	0.00745	0.97270	0.01985
65	0.00821	0.97195	0.01984
66	0.00905	0.97113	0.01982
67	0.00999	0.97021	0.01980
68	0.01102	0.96920	0.01978
69	0.01218	0.96806	0.01976
70	0.01347	0.96680	0.01973
71	0.01490	0.96540	0.01970
72	0.01650	0.96383	0.01967
73	0.01828	0.96209	0.01963
74	0.02028	0.96013	0.01959
75	0.02250	0.95795	0.01955
76	0.02499	0.95551	0.01950
77	0.02777	0.95279	0.01944
78	0.03088	0.94974	0.01938
79	0.03437	0.94632	0.01931
80	0.03828	0.94249	0.01923
81	0.04267	0.93818	0.01915
82	0.04760	0.93335	0.01905
83	0.05313	0.92793	0.01894
84	0.05935	0.92184	0.01881
85	0.06634	0.91499	0.01867
86	0.07421	0.90727	0.01852
87	0.08308	0.89858	0.01834
88	0.09308	0.88878	0.01814
89	0.10435	0.87774	0.01791
90	0.11708	0.86526	0.01766
91	0.13112	0.85150	0.01738

Age	Other Death	Low Risk Polyp	High Risk Polyp
92	0.14622	0.83670	0.01708
93	0.16236	0.82089	0.01675
94	0.17950	0.80409	0.01641
95	0.19754	0.78641	0.01605
96	0.21631	0.76802	0.01567
97	0.23596	0.74876	0.01528
98	0.25639	0.72874	0.01487
99	0.27744	0.70811	0.01445

Table 3c Annual Transition Probabilities for Average Risk Females with High Risk Polyp

Age	Other Death	High Risk Polyp	Local Cancer
50	0.00208	0.97297	0.02495
51	0.00226	0.97280	0.02494
52	0.00247	0.97259	0.02494
53	0.00270	0.97237	0.02493
54	0.00295	0.97212	0.02493
55	0.00322	0.97186	0.02492
56	0.00353	0.97156	0.02491
57	0.00386	0.97124	0.02490
58	0.00423	0.97088	0.02489
59	0.00464	0.97048	0.02488
60	0.00510	0.96804	0.02686
61	0.00560	0.96755	0.02685
62	0.00615	0.96702	0.02683
63	0.00677	0.96641	0.02682
64	0.00745	0.96575	0.02680
65	0.00821	0.95410	0.03769
66	0.00905	0.95329	0.03766
67	0.00999	0.95239	0.03762
68	0.01102	0.95140	0.03758
69	0.01218	0.95028	0.03754
70	0.01347	0.93720	0.04933
71	0.01490	0.93585	0.04926
72	0.01650	0.93433	0.04918
73	0.01828	0.93263	0.04909
74	0.02028	0.93073	0.04899
75	0.02250	0.92863	0.04888
76	0.02499	0.92626	0.04875
77	0.02777	0.92362	0.04861
78	0.03088	0.92066	0.04846
79	0.03437	0.91735	0.04828
80	0.03828	0.91363	0.04809
81	0.04267	0.90946	0.04787
82	0.04760	0.90478	0.04762
83	0.05313	0.89953	0.04734
84	0.05935	0.89362	0.04703
85	0.06634	0.88698	0.04668
86	0.07421	0.87950	0.04629
87	0.08308	0.87107	0.04585
88	0.09308	0.86157	0.04535
89	0.10435	0.85087	0.04478
90	0.11708	0.83877	0.04415
91	0.13112	0.82544	0.04344

Age	Other Death	High Risk Polyp	Local Cancer
92	0.14622	0.81109	0.04269
93	0.16236	0.79576	0.04188
94	0.17950	0.77948	0.04103
95	0.19754	0.76234	0.04012
96	0.21631	0.74451	0.03918
97	0.23596	0.72584	0.03820
98	0.25639	0.70643	0.03718
99	0.27744	0.68643	0.03613

Table 3d Annual Transition Probabilities for Average Risk Females with Local Cancer

Age	Other Death	CRC Death	Local Cancer	Regional Cancer
50	0.00206	0.02083	0.94808	0.02903
51	0.00224	0.02083	0.94791	0.02903
52	0.00244	0.02083	0.94771	0.02902
53	0.00267	0.02082	0.94749	0.02902
54	0.00292	0.02082	0.94725	0.02901
55	0.00319	0.02082	0.94699	0.02900
56	0.00349	0.02081	0.94670	0.02899
57	0.00382	0.02081	0.94639	0.02898
58	0.00419	0.02081	0.94604	0.02897
59	0.00459	0.02080	0.94565	0.02896
60	0.00505	0.02080	0.94521	0.02895
61	0.00554	0.02079	0.94473	0.02893
62	0.00609	0.02079	0.94421	0.02892
63	0.00670	0.02078	0.94362	0.02890
64	0.00737	0.02077	0.94298	0.02888
65	0.00812	0.02077	0.94225	0.02886
66	0.00896	0.02076	0.94146	0.02883
67	0.00989	0.02075	0.94056	0.02880
68	0.01090	0.02074	0.93958	0.02877
69	0.01205	0.02072	0.93848	0.02874
70	0.01333	0.02071	0.93726	0.02870
71	0.01474	0.02070	0.93590	0.02866
72	0.01633	0.02068	0.93438	0.02861
73	0.01809	0.02066	0.93269	0.02856
74	0.02007	0.02064	0.93079	0.02850
75	0.02227	0.02062	0.92868	0.02844
76	0.02473	0.02059	0.92631	0.02837
77	0.02748	0.02056	0.92367	0.02829
78	0.03056	0.02053	0.92072	0.02820
79	0.03401	0.02049	0.91740	0.02809
80	0.03788	0.02045	0.91369	0.02798
81	0.04223	0.02041	0.90951	0.02785
82	0.04711	0.02035	0.90483	0.02771
83	0.05258	0.02029	0.89958	0.02755
84	0.05874	0.02023	0.89367	0.02737
85	0.06565	0.02015	0.88703	0.02716
86	0.07344	0.02007	0.87955	0.02694
87	0.08222	0.01998	0.87112	0.02668
88	0.09212	0.01987	0.86162	0.02639
89	0.10328	0.01975	0.85092	0.02606
90	0.11588	0.01961	0.83882	0.02569
91	0.12978	0.01946	0.82548	0.02528

Age	Other Death	CRC Death	Local Cancer	Regional Cancer
92	0.14473	0.01929	0.81114	0.02484
93	0.16071	0.01911	0.79580	0.02437
94	0.17768	0.01893	0.77952	0.02387
95	0.19555	0.01872	0.76238	0.02335
96	0.21414	0.01851	0.74455	0.02280
97	0.23360	0.01829	0.72588	0.02223
98	0.25384	0.01806	0.70647	0.02164
99	0.27469	0.01781	0.68647	0.02102

Table 3e Annual Transition Probabilities for Average Risk Females with Regional Cancer

Age	Other Death	CRC Death	Regional Cancer	Distant Cancer
50	0.00201	0.06878	0.87431	0.05490
51	0.00218	0.06877	0.87416	0.05489
52	0.00238	0.06877	0.87397	0.05488
53	0.00261	0.06876	0.87377	0.05486
54	0.00285	0.06875	0.87355	0.05485
55	0.00311	0.06874	0.87332	0.05484
56	0.00341	0.06873	0.87304	0.05482
57	0.00373	0.06872	0.87276	0.05480
58	0.00408	0.06871	0.87243	0.05478
59	0.00448	0.06869	0.87207	0.05476
60	0.00492	0.06868	0.87167	0.05473
61	0.00541	0.06866	0.87123	0.05470
62	0.00594	0.06864	0.87075	0.05467
63	0.00653	0.06862	0.87021	0.05464
64	0.00719	0.06860	0.86961	0.05460
65	0.00792	0.06857	0.86894	0.05456
66	0.00874	0.06854	0.86821	0.05452
67	0.00964	0.06851	0.86738	0.05446
68	0.01064	0.06847	0.86648	0.05441
69	0.01176	0.06843	0.86547	0.05434
70	0.01300	0.06839	0.86434	0.05427
71	0.01438	0.06834	0.86308	0.05419
72	0.01593	0.06829	0.86168	0.05411
73	0.01765	0.06823	0.86012	0.05401
74	0.01958	0.06816	0.85837	0.05390
75	0.02172	0.06808	0.85642	0.05378
76	0.02412	0.06800	0.85424	0.05364
77	0.02681	0.06790	0.85181	0.05349
78	0.02981	0.06779	0.84908	0.05331
79	0.03318	0.06767	0.84602	0.05312
80	0.03696	0.06754	0.84260	0.05291
81	0.04119	0.06739	0.83875	0.05267
82	0.04596	0.06722	0.83443	0.05239
83	0.05130	0.06703	0.82959	0.05209
84	0.05730	0.06681	0.82414	0.05175
85	0.06406	0.06657	0.81801	0.05136
86	0.07166	0.06629	0.81112	0.05093
87	0.08023	0.06598	0.80335	0.05044
88	0.08989	0.06563	0.79459	0.04989
89	0.10078	0.06523	0.78471	0.04927
90	0.11309	0.06478	0.77356	0.04857
91	0.12666	0.06428	0.76126	0.04780

Age	Other Death	CRC Death	Regional Cancer	Distant Cancer
92	0.14126	0.06374	0.74803	0.04697
93	0.15687	0.06316	0.73389	0.04608
94	0.17345	0.06254	0.71887	0.04514
95	0.19091	0.06188	0.70306	0.04415
96	0.20908	0.06119	0.68662	0.04311
97	0.22810	0.06046	0.66940	0.04203
98	0.24789	0.05969	0.65150	0.04091
99	0.26829	0.05890	0.63306	0.03975

Table 3f Annual Transition Probabilities for Average Risk Females with Distant Cancer

Age	Other Death	CRC Death	Distant Cancer
50	0.00167	0.36869	0.62964
51	0.00181	0.36866	0.62953
52	0.00198	0.36862	0.62940
53	0.00216	0.36858	0.62925
54	0.00236	0.36854	0.62910
55	0.00258	0.36849	0.62893
56	0.00283	0.36844	0.62873
57	0.00309	0.36838	0.62852
58	0.00339	0.36832	0.62829
59	0.00372	0.36825	0.62803
60	0.00409	0.36817	0.62774
61	0.00449	0.36809	0.62742
62	0.00493	0.36799	0.62708
63	0.00543	0.36789	0.62669
64	0.00597	0.36777	0.62626
65	0.00658	0.36764	0.62578
66	0.00725	0.36750	0.62525
67	0.00801	0.36734	0.62465
68	0.00883	0.36716	0.62400
69	0.00977	0.36696	0.62327
70	0.01080	0.36674	0.62246
71	0.01195	0.36650	0.62156
72	0.01323	0.36622	0.62055
73	0.01466	0.36592	0.61942
74	0.01626	0.36557	0.61816
75	0.01805	0.36519	0.61676
76	0.02005	0.36476	0.61519
77	0.02228	0.36429	0.61344
78	0.02478	0.36375	0.61147
79	0.02758	0.36315	0.60927
80	0.03072	0.36247	0.60680
81	0.03425	0.36171	0.60403
82	0.03822	0.36086	0.60092
83	0.04267	0.35990	0.59743
84	0.04767	0.35882	0.59351
85	0.05330	0.35760	0.58910
86	0.05964	0.35622	0.58413
87	0.06680	0.35466	0.57854
88	0.07487	0.35290	0.57223
89	0.08398	0.35091	0.56512
90	0.09427	0.34864	0.55708
91	0.10564	0.34613	0.54823

Age	Other Death	CRC Death	Distant Cancer
92	0.11788	0.34342	0.53870
93	0.13099	0.34049	0.52852
94	0.14493	0.33737	0.51770
95	0.15964	0.33405	0.50632
96	0.17496	0.33056	0.49447
97	0.19104	0.32689	0.48208
98	0.20779	0.32302	0.46919
99	0.22510	0.31900	0.45590

Table 3g Annual Transition Probabilities for Average Risk Males with Normal Epithelium

Age	Other Death	Normal Epithelium	Low Risk Polyp
50	0.00322	0.99180	0.00498
51	0.00354	0.99148	0.00498
52	0.00389	0.99113	0.00498
53	0.00427	0.99075	0.00498
54	0.00470	0.99032	0.00498
55	0.00516	0.98837	0.00647
56	0.00568	0.98786	0.00646
57	0.00624	0.98730	0.00646
58	0.00686	0.98668	0.00646
59	0.00755	0.98600	0.00645
60	0.00830	0.98377	0.00793
61	0.00914	0.98293	0.00793
62	0.01005	0.98203	0.00792
63	0.01106	0.98103	0.00791
64	0.01217	0.97993	0.00790
65	0.01340	0.97723	0.00937
66	0.01475	0.97589	0.00936
67	0.01624	0.97441	0.00935
68	0.01788	0.97279	0.00933
69	0.01969	0.97100	0.00931
70	0.02168	0.96306	0.01526
71	0.02388	0.96089	0.01523
72	0.02630	0.95851	0.01519
73	0.02898	0.95587	0.01515
74	0.03193	0.95297	0.01510
75	0.03518	0.94977	0.01505
76	0.03877	0.94623	0.01500
77	0.04273	0.94234	0.01493
78	0.04711	0.93802	0.01487
79	0.05193	0.93328	0.01479
80	0.05726	0.94095	0.00179
81	0.06314	0.93508	0.00178
82	0.06963	0.92860	0.00177
83	0.07680	0.92145	0.00175
84	0.08471	0.91355	0.00174
85	0.09345	0.90483	0.00172
86	0.10311	0.89519	0.00170
87	0.11378	0.88454	0.00168
88	0.12556	0.87278	0.00166
89	0.13858	0.85978	0.00164
90	0.15297	0.84313	0.00390
91	0.16852	0.82766	0.00382

Age	Other Death	Normal Epithelium	Low Risk Polyp
92	0.18490	0.81135	0.00375
93	0.20204	0.79429	0.00367
94	0.21988	0.77653	0.00359
95	0.23440	0.76208	0.00352
96	0.25251	0.74405	0.00344
97	0.27115	0.72550	0.00335
98	0.29020	0.70653	0.00327
99	0.30953	0.68729	0.00318

Table 3h Annual Transition Probabilities for Average Risk Males with Low Risk Polyp

Age	Other Death	Low Risk Polyp	High Risk Polyp
50	0.00322	0.97684	0.01994
51	0.00354	0.97653	0.01993
52	0.00389	0.97619	0.01992
53	0.00427	0.97582	0.01991
54	0.00470	0.97539	0.01991
55	0.00516	0.97494	0.01990
56	0.00568	0.97443	0.01989
57	0.00624	0.97388	0.01988
58	0.00686	0.97328	0.01986
59	0.00755	0.97260	0.01985
60	0.00830	0.97187	0.01983
61	0.00914	0.97104	0.0198233
62	0.01005	0.97015	0.01980
63	0.01106	0.96916	0.01978
64	0.01217	0.96807	0.01976
65	0.01340	0.96687	0.01973
66	0.01475	0.96555	0.01971
67	0.01624	0.96408	0.01968
68	0.01788	0.96248	0.01964
69	0.01969	0.96070	0.01961
70	0.02168	0.95875	0.01957
71	0.02388	0.95660	0.01952
72	0.02630	0.95423	0.01947
73	0.02898	0.95160	0.01942
74	0.03193	0.94871	0.01936
75	0.03518	0.94552	0.01930
76	0.03877	0.94201	0.01922
77	0.04273	0.93812	0.01915
78	0.04711	0.93383	0.01906
79	0.05193	0.92911	0.01896
80	0.05726	0.92389	0.01885
81	0.06314	0.91812	0.01874
82	0.06963	0.91176	0.01861
83	0.07680	0.90474	0.01846
84	0.08471	0.89698	0.01831
85	0.09345	0.88842	0.01813
86	0.10311	0.87895	0.01794
87	0.11378	0.86850	0.01772
88	0.12556	0.85695	0.01749
89	0.13858	0.84419	0.01723
90	0.15297	0.83009	0.01694
91	0.16852	0.81485	0.01663

Age	Other Death	Low Risk Polyp	High Risk Polyp
92	0.18490	0.79880	0.01630
93	0.20204	0.78200	0.01596
94	0.21988	0.76452	0.01560
95	0.23440	0.75029	0.01531
96	0.25251	0.73254	0.01495
97	0.27115	0.71427	0.01458
98	0.29020	0.69560	0.01420
99	0.30953	0.67666	0.01381

Table 3i Annual Transition Probabilities for Average Risk Males with High Risk Polyp

Age	Other Death	High Risk Polyp	Early Cancer
50	0.00322	0.97086	0.02592
51	0.00354	0.97055	0.02591
52	0.00389	0.97021	0.02590
53	0.00427	0.96984	0.02589
54	0.00470	0.96942	0.02588
55	0.00516	0.96897	0.02587
56	0.00568	0.96847	0.02585
57	0.00624	0.96792	0.02584
58	0.00686	0.96732	0.02582
59	0.00755	0.96665	0.02580
60	0.00830	0.96096	0.03074
61	0.00914	0.96014	0.03072
62	0.01005	0.95926	0.03069
63	0.01106	0.95828	0.03066
64	0.01217	0.95721	0.03062
65	0.01340	0.94911	0.03749
66	0.01475	0.94781	0.03744
67	0.01624	0.94638	0.03738
68	0.01788	0.94480	0.03732
69	0.01969	0.94306	0.03725
70	0.02168	0.92843	0.04989
71	0.02388	0.92634	0.04978
72	0.02630	0.92404	0.04966
73	0.02898	0.92150	0.04952
74	0.03193	0.91870	0.04937
75	0.03518	0.91561	0.04921
76	0.03877	0.91221	0.04902
77	0.04273	0.90845	0.04882
78	0.04711	0.90429	0.04860
79	0.05193	0.89972	0.04835
80	0.05726	0.89560	0.04714
81	0.06314	0.89002	0.04684
82	0.06963	0.88385	0.04652
83	0.07680	0.87704	0.04616
84	0.08471	0.86953	0.04576
85	0.09345	0.86122	0.04533
86	0.10311	0.85205	0.04484
87	0.11378	0.84191	0.04431
88	0.12556	0.83072	0.04372
89	0.13858	0.81835	0.04307
90	0.15297	0.80468	0.04235
91	0.16852	0.78991	0.04157

Age	Other Death	High Risk Polyp	Early Cancer
92	0.18490	0.77435	0.04076
93	0.20204	0.75806	0.03990
94	0.21988	0.74111	0.03901
95	0.23440	0.72732	0.03828
96	0.25251	0.71012	0.03737
97	0.27115	0.69241	0.03644
98	0.29020	0.67431	0.03549
99	0.30953	0.65595	0.03452

Table 3j Annual Transition Probabilities for Average Risk Males with Local Cancer

Age	Other Death	CRC Death	Local Cancer	Distant Cancer
50	0.00319	0.02082	0.94699	0.02900
51	0.00350	0.02081	0.94669	0.02899
52	0.00385	0.02081	0.94636	0.02898
53	0.00423	0.02081	0.94600	0.02897
54	0.00465	0.02080	0.94559	0.02896
55	0.00511	0.02080	0.94515	0.02894
56	0.00562	0.02079	0.94466	0.02893
57	0.00617	0.02079	0.94413	0.02891
58	0.00679	0.02078	0.94354	0.02889
59	0.00747	0.02077	0.94288	0.02887
60	0.00821	0.02077	0.94217	0.02885
61	0.00904	0.02076	0.94137	0.02883
62	0.00995	0.02075	0.94051	0.02880
63	0.01094	0.02074	0.93955	0.02877
64	0.01204	0.02072	0.93849	0.02874
65	0.01326	0.02071	0.93732	0.02870
66	0.01460	0.02070	0.93604	0.02867
67	0.01607	0.02068	0.93462	0.02862
68	0.01769	0.02067	0.93307	0.02857
69	0.01948	0.02065	0.93135	0.02852
70	0.02145	0.02063	0.92946	0.02846
71	0.02363	0.02060	0.92737	0.02840
72	0.02603	0.02058	0.92507	0.02833
73	0.02868	0.02055	0.92252	0.02825
74	0.03160	0.02052	0.91972	0.02817
75	0.03481	0.02048	0.91663	0.02807
76	0.03837	0.02045	0.91322	0.02797
77	0.04229	0.02040	0.90946	0.02785
78	0.04662	0.02036	0.90530	0.02772
79	0.05139	0.02031	0.90072	0.02758
80	0.05667	0.02025	0.89565	0.02743
81	0.06249	0.02019	0.89007	0.02726
82	0.06891	0.02012	0.88390	0.02707
83	0.07601	0.02004	0.87709	0.02686
84	0.08384	0.01996	0.86957	0.02663
85	0.09249	0.01986	0.86127	0.02638
86	0.10205	0.01976	0.85209	0.02609
87	0.11261	0.01965	0.84196	0.02578
88	0.12428	0.01952	0.83077	0.02544
89	0.13717	0.01938	0.81840	0.02506
90	0.15141	0.01922	0.80472	0.02464
91	0.16681	0.01905	0.78995	0.02419

Age	Other Death	CRC Death	Local Cancer	Distant Cancer
92	0.18303	0.01887	0.77439	0.02371
93	0.20001	0.01867	0.75810	0.02322
94	0.21767	0.01847	0.74116	0.02270
95	0.23206	0.01831	0.72736	0.02227
96	0.25000	0.01810	0.71016	0.02175
97	0.26846	0.01789	0.69245	0.02121
98	0.28734	0.01766	0.67435	0.02065
99	0.30649	0.01744	0.65598	0.02009

Table 3k Annual Transition Probabilities for Average Risk Males with Distant Cancer

Age	Other Death	CRC Death	Distant Cancer	Regional Cancer
50	0.00311	0.06874	0.87332	0.05484
51	0.00342	0.06873	0.87304	0.05482
52	0.00375	0.06872	0.87273	0.05480
53	0.00412	0.06870	0.87240	0.05478
54	0.00454	0.06869	0.87202	0.05475
55	0.00498	0.06867	0.87162	0.05473
56	0.00548	0.06866	0.87116	0.05470
57	0.00602	0.06864	0.87067	0.05467
58	0.00662	0.06862	0.87013	0.05464
59	0.00729	0.06859	0.86952	0.05460
60	0.00801	0.06857	0.86887	0.05456
61	0.00882	0.06854	0.86813	0.05451
62	0.00970	0.06851	0.86733	0.05446
63	0.01068	0.06847	0.86645	0.05440
64	0.01175	0.06844	0.86547	0.05434
65	0.01293	0.06839	0.86440	0.05428
66	0.01424	0.06835	0.86321	0.05420
67	0.01568	0.06830	0.86191	0.05412
68	0.01726	0.06824	0.86047	0.05403
69	0.01901	0.06818	0.85889	0.05393
70	0.02093	0.06811	0.85714	0.05382
71	0.02305	0.06803	0.85521	0.05370
72	0.02539	0.06795	0.85309	0.05357
73	0.02798	0.06786	0.85075	0.05342
74	0.03082	0.06776	0.84816	0.05326
75	0.03396	0.06765	0.84531	0.05308
76	0.03743	0.06752	0.84217	0.05288
77	0.04125	0.06739	0.83870	0.05266
78	0.04548	0.06723	0.83486	0.05242
79	0.05014	0.06707	0.83064	0.05216
80	0.05528	0.06688	0.82597	0.05186
81	0.06096	0.06668	0.82082	0.05154
82	0.06723	0.06645	0.81513	0.05118
83	0.07416	0.06620	0.80885	0.05079
84	0.08180	0.06593	0.80192	0.05035
85	0.09025	0.06562	0.79426	0.04987
86	0.09958	0.06528	0.78580	0.04934
87	0.10990	0.06490	0.77645	0.04875
88	0.12128	0.06448	0.76613	0.04811
89	0.13387	0.06402	0.75472	0.04739
90	0.14779	0.06350	0.74211	0.04660
91	0.16283	0.06294	0.72849	0.04574

Age	Other Death	CRC Death	Distant Cancer	Regional Cancer
92	0.17868	0.06234	0.71414	0.04484
93	0.19526	0.06172	0.69912	0.04390
94	0.21253	0.06106	0.68349	0.04292
95	0.22659	0.06052	0.67077	0.04212
96	0.24414	0.05984	0.65490	0.04112
97	0.26220	0.05914	0.63857	0.04010
98	0.28066	0.05841	0.62188	0.03905
99	0.29940	0.05766	0.60495	0.03798

Table 3l Annual Transition Probabilities for Average Risk Males with Distant Cancer

Age	Other Death	CRC Death	Distant Cancer
50	0.00258	0.36849	0.62893
51	0.00284	0.36844	0.62872
52	0.00312	0.36838	0.62850
53	0.00342	0.36831	0.62826
54	0.00377	0.36824	0.62799
55	0.00414	0.36816	0.62770
56	0.00455	0.36807	0.62737
57	0.00500	0.36798	0.62702
58	0.00550	0.36787	0.62663
59	0.00605	0.36775	0.62619
60	0.00665	0.36763	0.62572
61	0.00733	0.36748	0.62519
62	0.00806	0.36733	0.62462
63	0.00887	0.36715	0.62398
64	0.00976	0.36696	0.62328
65	0.01074	0.36675	0.62250
66	0.01183	0.36652	0.62165
67	0.01302	0.36627	0.62071
68	0.01434	0.36599	0.61968
69	0.01579	0.36568	0.61853
70	0.01739	0.36533	0.61728
71	0.01915	0.36496	0.61589
72	0.02110	0.36454	0.61436
73	0.02325	0.36408	0.61267
74	0.02562	0.36357	0.61081
75	0.02823	0.36301	0.60876
76	0.03112	0.36239	0.60650
77	0.03430	0.36170	0.60400
78	0.03782	0.36095	0.60123
79	0.04170	0.36011	0.59819
80	0.04599	0.35918	0.59483
81	0.05072	0.35816	0.59112
82	0.05595	0.35702	0.58702
83	0.06173	0.35577	0.58250
84	0.06811	0.35438	0.57751
85	0.07517	0.35284	0.57199
86	0.08297	0.35113	0.56590
87	0.09160	0.34923	0.55917
88	0.10114	0.34713	0.55173
89	0.11169	0.34479	0.54352
90	0.12336	0.34220	0.53444
91	0.13600	0.33937	0.52463

Age	Other Death	CRC Death	Distant Cancer
92	0.14933	0.33637	0.51429
93	0.16331	0.33321	0.50348
94	0.17788	0.32990	0.49222
95	0.18976	0.32718	0.48306
96	0.20461	0.32376	0.47163
97	0.21992	0.32021	0.45987
98	0.23561	0.31654	0.44785
99	0.25156	0.31278	0.43566

Table 3m Annual Transition Probabilities for Higher Risk Females with Normal Epithelium

Age	Other Death	Normal Epithelium	Low Risk Polyp
50	0.00208	0.99268	0.00524
51	0.00226	0.99250	0.00524
52	0.00247	0.99229	0.00524
53	0.00270	0.99206	0.00524
54	0.00295	0.99182	0.00523
55	0.00322	0.99155	0.00523
56	0.00353	0.99124	0.00523
57	0.00386	0.99091	0.00523
58	0.00423	0.99054	0.00523
59	0.00464	0.99013	0.00523
60	0.00510	0.92028	0.07462
61	0.00560	0.91982	0.07458
62	0.00615	0.91931	0.07454
63	0.00677	0.91874	0.07449
64	0.00745	0.91811	0.07444
65	0.00821	0.89509	0.09670
66	0.00905	0.89433	0.09662
67	0.00999	0.89348	0.09653
68	0.01102	0.89255	0.09643
69	0.01218	0.89151	0.09631
70	0.01347	0.97469	0.01184
71	0.01490	0.97328	0.01182
72	0.01650	0.97170	0.01180
73	0.01828	0.96994	0.01178
74	0.02028	0.96796	0.01176
75	0.02250	0.96577	0.01173
76	0.02499	0.96331	0.01170
77	0.02777	0.96056	0.01167
78	0.03088	0.95749	0.01163
79	0.03437	0.95404	0.01159
80	0.03828	0.93922	0.02250
81	0.04267	0.93493	0.02240
82	0.04760	0.93011	0.02229
83	0.05313	0.92471	0.02216
84	0.05935	0.91864	0.02201
85	0.06634	0.91181	0.02185
86	0.07421	0.90413	0.02166
87	0.08308	0.89546	0.02146
88	0.09308	0.88570	0.02122
89	0.10435	0.87469	0.02096
90	0.11708	0.85776	0.02516
91	0.13112	0.84412	0.02476

Age	Other Death	Normal Epithelium	Low Risk Polyp
92	0.14622	0.82945	0.02433
93	0.16236	0.81377	0.02387
94	0.17950	0.79712	0.02338
95	0.19754	0.77959	0.02287
96	0.21631	0.76135	0.02234
97	0.23596	0.74226	0.02178
98	0.25639	0.72242	0.02119
99	0.27744	0.70197	0.02059

Table 3n Annual Transition Probabilities for Higher Risk Females with Low Risk Polyp

Age	Other Death	Low Risk Polyp	High Risk Polyp
50	0.00208	0.97796	0.01996
51	0.00226	0.97779	0.01995
52	0.00247	0.97758	0.01995
53	0.00270	0.97735	0.01995
54	0.00295	0.97711	0.01994
55	0.00322	0.97684	0.01994
56	0.00353	0.97654	0.01993
57	0.00386	0.97622	0.01992
58	0.00423	0.97585	0.01992
59	0.00464	0.97545	0.01991
60	0.00510	0.97500	0.01990
61	0.00560	0.97451	0.01989
62	0.00615	0.97397	0.01988
63	0.00677	0.97337	0.01986
64	0.00745	0.97270	0.01985
65	0.00821	0.97195	0.01984
66	0.00905	0.97113	0.01982
67	0.00999	0.97021	0.01980
68	0.01102	0.96920	0.01978
69	0.01218	0.96806	0.01976
70	0.01347	0.96680	0.01973
71	0.01490	0.96540	0.01970
72	0.01650	0.96383	0.01967
73	0.01828	0.96209	0.01963
74	0.02028	0.96013	0.01959
75	0.02250	0.95795	0.01955
76	0.02499	0.95551	0.01950
77	0.02777	0.95279	0.01944
78	0.03088	0.94974	0.01938
79	0.03437	0.94632	0.01931
80	0.03828	0.94249	0.01923
81	0.04267	0.93818	0.01915
82	0.04760	0.93335	0.01905
83	0.05313	0.92793	0.01894
84	0.05935	0.92184	0.01881
85	0.06634	0.91499	0.01867
86	0.07421	0.90727	0.01852
87	0.08308	0.89858	0.01834
88	0.09308	0.88878	0.01814
89	0.10435	0.87774	0.01791
90	0.11708	0.86526	0.01766
91	0.13112	0.85150	0.01738

Age	Other Death	Low Risk Polyp	High Risk Polyp
92	0.14622	0.83670	0.01708
93	0.16236	0.82089	0.01675
94	0.17950	0.80409	0.01641
95	0.19754	0.78641	0.01605
96	0.21631	0.76802	0.01567
97	0.23596	0.74876	0.01528
98	0.25639	0.72874	0.01487
99	0.27744	0.70811	0.01445

Table 3o Annual Transition Probabilities for Higher Risk Females with High Risk Polyp

Age	Other Death	High Risk Polyp	Local Cancer
50	0.00208	0.97297	0.02495
51	0.00226	0.97280	0.02494
52	0.00247	0.97259	0.02494
53	0.0027	0.97237	0.02493
54	0.00295	0.97212	0.02493
55	0.00322	0.97186	0.02492
56	0.00353	0.97156	0.02491
57	0.00386	0.97124	0.02490
58	0.00423	0.97088	0.02489
59	0.00464	0.97048	0.02488
60	0.0051	0.96804	0.02686
61	0.0056	0.96755	0.02685
62	0.00615	0.96702	0.02683
63	0.00677	0.96641	0.02682
64	0.00745	0.96575	0.02680
65	0.00821	0.95410	0.03769
66	0.00905	0.95329	0.03766
67	0.00999	0.95239	0.03762
68	0.01102	0.95140	0.03758
69	0.01218	0.95028	0.03754
70	0.01347	0.93720	0.04933
71	0.0149	0.93585	0.04926
72	0.0165	0.93433	0.04918
73	0.01828	0.93263	0.04909
74	0.02028	0.93073	0.04899
75	0.0225	0.92863	0.04888
76	0.02499	0.92626	0.04875
77	0.02777	0.92362	0.04861
78	0.03088	0.92066	0.04846
79	0.03437	0.91735	0.04828
80	0.03828	0.91363	0.04809
81	0.04267	0.90946	0.04787
82	0.0476	0.90478	0.04762
83	0.05313	0.89953	0.04734
84	0.05935	0.89362	0.04703
85	0.06634	0.88698	0.04668
86	0.07421	0.87950	0.04629
87	0.08308	0.87107	0.04585
88	0.09308	0.86157	0.04535
89	0.10435	0.85087	0.04478
90	0.11708	0.83877	0.04415
91	0.13112	0.82544	0.04344

Age	Other Death	High Risk Polyp	Local Cancer
92	0.14622	0.81109	0.04269
93	0.16236	0.79576	0.04188
94	0.1795	0.77948	0.04103
95	0.19754	0.76234	0.04012
96	0.21631	0.74451	0.03918
97	0.23596	0.72584	0.03820
98	0.25639	0.70643	0.03718
99	0.27744	0.68643	0.03613

Table 3p Annual Transition Probabilities for Higher Risk Females with Local Cancer

Age	Other Death	CRC Death	Local Cancer	Regional Cancer
50	0.00206	0.02083	0.94808	0.02903
51	0.00224	0.02083	0.94791	0.02903
52	0.00244	0.02083	0.94771	0.02902
53	0.00267	0.02082	0.94749	0.02902
54	0.00292	0.02082	0.94725	0.02901
55	0.00319	0.02082	0.94699	0.02900
56	0.00349	0.02081	0.94670	0.02899
57	0.00382	0.02081	0.94639	0.02898
58	0.00419	0.02081	0.94604	0.02897
59	0.00459	0.02080	0.94565	0.02896
60	0.00505	0.02080	0.94521	0.02895
61	0.00554	0.02079	0.94473	0.02893
62	0.00609	0.02079	0.94421	0.02892
63	0.00670	0.02078	0.94362	0.02890
64	0.00737	0.02077	0.94298	0.02888
65	0.00812	0.02077	0.94225	0.02886
66	0.00896	0.02076	0.94146	0.02883
67	0.00989	0.02075	0.94056	0.02880
68	0.01090	0.02074	0.93958	0.02877
69	0.01205	0.02072	0.93848	0.02874
70	0.01333	0.02071	0.93726	0.02870
71	0.01474	0.02070	0.93590	0.02866
72	0.01633	0.02068	0.93438	0.02861
73	0.01809	0.02066	0.93269	0.02856
74	0.02007	0.02064	0.93079	0.02850
75	0.02227	0.02062	0.92868	0.02844
76	0.02473	0.02059	0.92631	0.02837
77	0.02748	0.02056	0.92367	0.02829
78	0.03056	0.02053	0.92072	0.02820
79	0.03401	0.02049	0.91740	0.02809
80	0.03788	0.02045	0.91369	0.02798
81	0.04223	0.02041	0.90951	0.02785
82	0.04711	0.02035	0.90483	0.02771
83	0.05258	0.02029	0.89958	0.02755
84	0.05874	0.02023	0.89367	0.02737
85	0.06565	0.02015	0.88703	0.02716
86	0.07344	0.02007	0.87955	0.02694
87	0.08222	0.01998	0.87112	0.02668
88	0.09212	0.01987	0.86162	0.02639
89	0.10328	0.01975	0.85092	0.02606
90	0.11588	0.01961	0.83882	0.02569
91	0.12978	0.01946	0.82548	0.02528

Age	Other Death	CRC Death	Local Cancer	Regional Cancer
92	0.14473	0.01929	0.81114	0.02484
93	0.16071	0.01911	0.79580	0.02437
94	0.17768	0.01893	0.77952	0.02387
95	0.19555	0.01872	0.76238	0.02335
96	0.21414	0.01851	0.74455	0.02280
97	0.23360	0.01829	0.72588	0.02223
98	0.25384	0.01806	0.70647	0.02164
99	0.27469	0.01781	0.68647	0.02102

Table 3q Annual Transition Probabilities for Higher Risk Females with Regional Cancer

Age	Other Death	CRC Death	Regional Cancer	Distant Cancer
50	0.00201	0.06878	0.87431	0.05490
51	0.00218	0.06877	0.87416	0.05489
52	0.00238	0.06877	0.87397	0.05488
53	0.00261	0.06876	0.87377	0.05486
54	0.00285	0.06875	0.87355	0.05485
55	0.00311	0.06874	0.87332	0.05484
56	0.00341	0.06873	0.87304	0.05482
57	0.00373	0.06872	0.87276	0.05480
58	0.00408	0.06871	0.87243	0.05478
59	0.00448	0.06869	0.87207	0.05476
60	0.00492	0.06868	0.87167	0.05473
61	0.00541	0.06866	0.87123	0.05470
62	0.00594	0.06864	0.87075	0.05467
63	0.00653	0.06862	0.87021	0.05464
64	0.00719	0.06860	0.86961	0.05460
65	0.00792	0.06857	0.86894	0.05456
66	0.00874	0.06854	0.86821	0.05452
67	0.00964	0.06851	0.86738	0.05446
68	0.01064	0.06847	0.86648	0.05441
69	0.01176	0.06843	0.86547	0.05434
70	0.01300	0.06839	0.86434	0.05427
71	0.01438	0.06834	0.86308	0.05419
72	0.01593	0.06829	0.86168	0.05411
73	0.01765	0.06823	0.86012	0.05401
74	0.01958	0.06816	0.85837	0.05390
75	0.02172	0.06808	0.85642	0.05378
76	0.02412	0.06800	0.85424	0.05364
77	0.02681	0.06790	0.85181	0.05349
78	0.02981	0.06779	0.84908	0.05331
79	0.03318	0.06767	0.84602	0.05312
80	0.03696	0.06754	0.84260	0.05291
81	0.04119	0.06739	0.83875	0.05267
82	0.04596	0.06722	0.83443	0.05239
83	0.05130	0.06703	0.82959	0.05209
84	0.05730	0.06681	0.82414	0.05175
85	0.06406	0.06657	0.81801	0.05136
86	0.07166	0.06629	0.81112	0.05093
87	0.08023	0.06598	0.80335	0.05044
88	0.08989	0.06563	0.79459	0.04989
89	0.10078	0.06523	0.78471	0.04927
90	0.11309	0.06478	0.77356	0.04857
91	0.12666	0.06428	0.76126	0.04780

Age	Other Death	CRC Death	Regional Cancer	Distant Cancer
92	0.14126	0.06374	0.74803	0.04697
93	0.15687	0.06316	0.73389	0.04608
94	0.17345	0.06254	0.71887	0.04514
95	0.19091	0.06188	0.70306	0.04415
96	0.20908	0.06119	0.68662	0.04311
97	0.22810	0.06046	0.66940	0.04203
98	0.24789	0.05969	0.65150	0.04091
99	0.26829	0.05890	0.63306	0.03975

Table 3r Annual Transition Probabilities for Higher Risk Females with Distant Cancer

Age	Other Death	CRC Death	Distant Cancer
50	0.00167	0.36869	0.62964
51	0.00181	0.36866	0.62953
52	0.00198	0.36862	0.62940
53	0.00216	0.36858	0.62925
54	0.00236	0.36854	0.62910
55	0.00258	0.36849	0.62893
56	0.00283	0.36844	0.62873
57	0.00309	0.36838	0.62852
58	0.00339	0.36832	0.62829
59	0.00372	0.36825	0.62803
60	0.00409	0.36817	0.62774
61	0.00449	0.36809	0.62742
62	0.00493	0.36799	0.62708
63	0.00543	0.36789	0.62669
64	0.00597	0.36777	0.62626
65	0.00658	0.36764	0.62578
66	0.00725	0.36750	0.62525
67	0.00801	0.36734	0.62465
68	0.00883	0.36716	0.62400
69	0.00977	0.36696	0.62327
70	0.01080	0.36674	0.62246
71	0.01195	0.36650	0.62156
72	0.01323	0.36622	0.62055
73	0.01466	0.36592	0.61942
74	0.01626	0.36557	0.61816
75	0.01805	0.36519	0.61676
76	0.02005	0.36476	0.61519
77	0.02228	0.36429	0.61344
78	0.02478	0.36375	0.61147
79	0.02758	0.36315	0.60927
80	0.03072	0.36247	0.60680
81	0.03425	0.36171	0.60403
82	0.03822	0.36086	0.60092
83	0.04267	0.35990	0.59743
84	0.04767	0.35882	0.59351
85	0.05330	0.35760	0.58910
86	0.05964	0.35622	0.58413
87	0.06680	0.35466	0.57854
88	0.07487	0.35290	0.57223
89	0.08398	0.35091	0.56512
90	0.09427	0.34864	0.55708
91	0.10564	0.34613	0.54823

Age	Other Death	CRC Death	Distant Cancer
92	0.11788	0.34342	0.53870
93	0.13099	0.34049	0.52852
94	0.14493	0.33737	0.51770
95	0.15964	0.33405	0.50632
96	0.17496	0.33056	0.49447
97	0.19104	0.32689	0.48208
98	0.20779	0.32302	0.46919
99	0.22510	0.31900	0.45590

Table 3s Annual Transition Probabilities for Higher Risk Males with Normal Epithelium

Age	Other Death	Normal Epithelium	Low Risk Polyp
50	0.00322	0.98930	0.00748
51	0.00354	0.98899	0.00747
52	0.00389	0.98864	0.00747
53	0.00427	0.98826	0.00747
54	0.00470	0.98784	0.00746
55	0.00516	0.98514	0.00970
56	0.00568	0.98463	0.00969
57	0.00624	0.98407	0.00969
58	0.00686	0.98346	0.00968
59	0.00755	0.98277	0.00968
60	0.00830	0.97980	0.01190
61	0.00914	0.97897	0.01189
62	0.01005	0.97807	0.01188
63	0.01106	0.97707	0.01187
64	0.01217	0.97598	0.01185
65	0.01340	0.97254	0.01406
66	0.01475	0.97121	0.01404
67	0.01624	0.96974	0.01402
68	0.01788	0.96812	0.01400
69	0.01969	0.96634	0.01397
70	0.02168	0.95543	0.02289
71	0.02388	0.95328	0.02284
72	0.02630	0.95092	0.02278
73	0.02898	0.94830	0.02272
74	0.03193	0.94542	0.02265
75	0.03518	0.94224	0.02258
76	0.03877	0.93874	0.02249
77	0.04273	0.93487	0.02240
78	0.04711	0.93059	0.02230
79	0.05193	0.92589	0.02218
80	0.05726	0.94005	0.00269
81	0.06314	0.93419	0.00267
82	0.06963	0.92772	0.00265
83	0.07680	0.92057	0.00263
84	0.08471	0.91268	0.00261
85	0.09345	0.90397	0.00258
86	0.10311	0.89433	0.00256
87	0.11378	0.88369	0.00253
88	0.12556	0.87195	0.00249
89	0.13858	0.85896	0.00246
90	0.15297	0.84119	0.00584
91	0.16852	0.82574	0.00574

Age	Other Death	Normal Epithelium	Low Risk Polyp
92	0.18490	0.80948	0.00562
93	0.20204	0.79245	0.00551
94	0.21988	0.77474	0.00538
95	0.23440	0.76032	0.00528
96	0.25251	0.74233	0.00516
97	0.27115	0.72382	0.00503
98	0.29020	0.70490	0.00490
99	0.30953	0.68571	0.00476

Table 3t Annual Transition Probabilities for Higher Risk Males with Low Risk Polyp

Age	Other Death	Low Risk Polyp	High Risk Polyp
50	0.00322	0.97684	0.01994
51	0.00354	0.97653	0.01993
52	0.00389	0.97619	0.01992
53	0.00427	0.97582	0.01991
54	0.00470	0.97539	0.01991
55	0.00516	0.97494	0.01990
56	0.00568	0.97443	0.01989
57	0.00624	0.97388	0.01988
58	0.00686	0.97328	0.01986
59	0.00755	0.97260	0.01985
60	0.00830	0.97187	0.01983
61	0.00914	0.97104	0.01982
62	0.01005	0.97015	0.01980
63	0.01106	0.96916	0.01978
64	0.01217	0.96807	0.01976
65	0.01340	0.96687	0.01973
66	0.01475	0.96555	0.01971
67	0.01624	0.96408	0.01968
68	0.01788	0.96248	0.01964
69	0.01969	0.96070	0.01961
70	0.02168	0.95875	0.01957
71	0.02388	0.95660	0.01952
72	0.02630	0.95423	0.01947
73	0.02898	0.95160	0.01942
74	0.03193	0.94871	0.01936
75	0.03518	0.94552	0.01930
76	0.03877	0.94201	0.01922
77	0.04273	0.93812	0.01915
78	0.04711	0.93383	0.01906
79	0.05193	0.92911	0.01896
80	0.05726	0.92389	0.01885
81	0.06314	0.91812	0.01874
82	0.06963	0.91176	0.01861
83	0.07680	0.90474	0.01846
84	0.08471	0.89698	0.01831
85	0.09345	0.88842	0.01813
86	0.10311	0.87895	0.01794
87	0.11378	0.86850	0.01772
88	0.12556	0.85695	0.01749
89	0.13858	0.84419	0.01723
90	0.15297	0.83009	0.01694
91	0.16852	0.81485	0.01663

Age	Other Death	Low Risk Polyp	High Risk Polyp
92	0.18490	0.79880	0.01630
93	0.20204	0.78200	0.01596
94	0.21988	0.76452	0.01560
95	0.23440	0.75029	0.01531
96	0.25251	0.73254	0.01495
97	0.27115	0.71427	0.01458
98	0.29020	0.69560	0.01420
99	0.30953	0.67666	0.01381

Table 3u Annual Transition Probabilities for Higher Risk Males with High Risk Polyp

Age	Other Death	High Risk Polyp	Local Cancer
50	0.00322	0.97086	0.02592
51	0.00354	0.97055	0.02591
52	0.00389	0.97021	0.02590
53	0.00427	0.96984	0.02589
54	0.00470	0.96942	0.02588
55	0.00516	0.96897	0.02587
56	0.00568	0.96847	0.02585
57	0.00624	0.96792	0.02584
58	0.00686	0.96732	0.02582
59	0.00755	0.96665	0.02580
60	0.00830	0.96096	0.03074
61	0.00914	0.96014	0.03072
62	0.01005	0.95926	0.03069
63	0.01106	0.95828	0.03066
64	0.01217	0.95721	0.03062
65	0.01340	0.94911	0.03749
66	0.01475	0.94781	0.03744
67	0.01624	0.94638	0.03738
68	0.01788	0.94480	0.03732
69	0.01969	0.94306	0.03725
70	0.02168	0.92843	0.04989
71	0.02388	0.92634	0.04978
72	0.02630	0.92404	0.04966
73	0.02898	0.92150	0.04952
74	0.03193	0.91870	0.04937
75	0.03518	0.91561	0.04921
76	0.03877	0.91221	0.04902
77	0.04273	0.90845	0.04882
78	0.04711	0.90429	0.04860
79	0.05193	0.89972	0.04835
80	0.05726	0.89560	0.04714
81	0.06314	0.89002	0.04684
82	0.06963	0.88385	0.04652
83	0.07680	0.87704	0.04616
84	0.08471	0.86953	0.04576
85	0.09345	0.86122	0.04533
86	0.10311	0.85205	0.04484
87	0.11378	0.84191	0.04431
88	0.12556	0.83072	0.04372
89	0.13858	0.81835	0.04307
90	0.15297	0.80468	0.04235
91	0.16852	0.78991	0.04157

Age	Other Death	High Risk Polyp	Local Cancer
92	0.18490	0.77435	0.04076
93	0.20204	0.75806	0.03990
94	0.21988	0.74111	0.03901
95	0.23440	0.72732	0.03828
96	0.25251	0.71012	0.03737
97	0.27115	0.69241	0.03644
98	0.29020	0.67431	0.03549
99	0.30953	0.65595	0.03452

Table 3v Annual Transition Probabilities for Higher Risk Males with Local Cancer

Age	Other Death	CRC Death	Local Cancer	Regional Cancer
50	0.00319	0.02082	0.94699	0.02900
51	0.00350	0.02081	0.94669	0.02899
52	0.00385	0.02081	0.94636	0.02898
53	0.00423	0.02081	0.94600	0.02897
54	0.00465	0.02080	0.94559	0.02896
55	0.00511	0.02080	0.94515	0.02894
56	0.00562	0.02079	0.94466	0.02893
57	0.00617	0.02079	0.94413	0.02891
58	0.00679	0.02078	0.94354	0.02889
59	0.00747	0.02077	0.94288	0.02887
60	0.00821	0.02077	0.94217	0.02885
61	0.00904	0.02076	0.94137	0.02883
62	0.00995	0.02075	0.94051	0.02880
63	0.01094	0.02074	0.93955	0.02877
64	0.01204	0.02072	0.93849	0.02874
65	0.01326	0.02071	0.93732	0.02870
66	0.01460	0.02070	0.93604	0.02867
67	0.01607	0.02068	0.93462	0.02862
68	0.01769	0.02067	0.93307	0.02857
69	0.01948	0.02065	0.93135	0.02852
70	0.02145	0.02063	0.92946	0.02846
71	0.02363	0.02060	0.92737	0.02840
72	0.02603	0.02058	0.92507	0.02833
73	0.02868	0.02055	0.92252	0.02825
74	0.03160	0.02052	0.91972	0.02817
75	0.03481	0.02048	0.91663	0.02807
76	0.03837	0.02045	0.91322	0.02797
77	0.04229	0.02040	0.90946	0.02785
78	0.04662	0.02036	0.90530	0.02772
79	0.05139	0.02031	0.90072	0.02758
80	0.05667	0.02025	0.89565	0.02743
81	0.06249	0.02019	0.89007	0.02726
82	0.06891	0.02012	0.88390	0.02707
83	0.07601	0.02004	0.87709	0.02686
84	0.08384	0.01996	0.86957	0.02663
85	0.09249	0.01986	0.86127	0.02638
86	0.10205	0.01976	0.85209	0.02609
87	0.11261	0.01965	0.84196	0.02578
88	0.12428	0.01952	0.83077	0.02544
89	0.13717	0.01938	0.81840	0.02506
90	0.15141	0.01922	0.80472	0.02464
91	0.16681	0.01905	0.78995	0.02419

Age	Other Death	CRC Death	Local Cancer	Regional Cancer
92	0.18303	0.01887	0.77439	0.02371
93	0.20001	0.01867	0.75810	0.02322
94	0.21767	0.01847	0.74116	0.02270
95	0.23206	0.01831	0.72736	0.02227
96	0.25000	0.01810	0.71016	0.02175
97	0.26846	0.01789	0.69245	0.02121
98	0.28734	0.01766	0.67435	0.02065
99	0.30649	0.01744	0.65598	0.02009

Table 3w Annual Transition Probabilities for Higher Risk Males with Regional Cancer

Age	Other Death	CRC Death	Regional Cancer	Distant Cancer
50	0.00311	0.06874	0.87332	0.05484
51	0.00342	0.06873	0.87304	0.05482
52	0.00375	0.06872	0.87273	0.05480
53	0.00412	0.06870	0.87240	0.05478
54	0.00454	0.06869	0.87202	0.05475
55	0.00498	0.06867	0.87162	0.05473
56	0.00548	0.06866	0.87116	0.05470
57	0.00602	0.06864	0.87067	0.05467
58	0.00662	0.06862	0.87013	0.05464
59	0.00729	0.06859	0.86952	0.05460
60	0.00801	0.06857	0.86887	0.05456
61	0.00882	0.06854	0.86813	0.05451
62	0.00970	0.06851	0.86733	0.05446
63	0.01068	0.06847	0.86645	0.05440
64	0.01175	0.06844	0.86547	0.05434
65	0.01293	0.06839	0.86440	0.05428
66	0.01424	0.06835	0.86321	0.05420
67	0.01568	0.06830	0.86191	0.05412
68	0.01726	0.06824	0.86047	0.05403
69	0.01901	0.06818	0.85889	0.05393
70	0.02093	0.06811	0.85714	0.05382
71	0.02305	0.06803	0.85521	0.05370
72	0.02539	0.06795	0.85309	0.05357
73	0.02798	0.06786	0.85075	0.05342
74	0.03082	0.06776	0.84816	0.05326
75	0.03396	0.06765	0.84531	0.05308
76	0.03743	0.06752	0.84217	0.05288
77	0.04125	0.06739	0.83870	0.05266
78	0.04548	0.06723	0.83486	0.05242
79	0.05014	0.06707	0.83064	0.05216
80	0.05528	0.06688	0.82597	0.05186
81	0.06096	0.06668	0.82082	0.05154
82	0.06723	0.06645	0.81513	0.05118
83	0.07416	0.06620	0.80885	0.05079
84	0.08180	0.06593	0.80192	0.05035
85	0.09025	0.06562	0.79426	0.04987
86	0.09958	0.06528	0.78580	0.04934
87	0.10990	0.06490	0.77645	0.04875
88	0.12128	0.06448	0.76613	0.04811
89	0.13387	0.06402	0.75472	0.04739
90	0.14779	0.06350	0.74211	0.04660
91	0.16283	0.06294	0.72849	0.04574

Age	Other Death	CRC Death	Regional Cancer	Distant Cancer
92	0.17868	0.06234	0.71414	0.04484
93	0.19526	0.06172	0.69912	0.04390
94	0.21253	0.06106	0.68349	0.04292
95	0.22659	0.06052	0.67077	0.04212
96	0.24414	0.05984	0.65490	0.04112
97	0.26220	0.05914	0.63857	0.04010
98	0.28066	0.05841	0.62188	0.03905
99	0.29940	0.05766	0.60495	0.03798

Table 3x Annual Transition Probabilities for Higher Risk Males with Distant Cancer

Age	Other Death	CRC Death	Distant Cancer
50	0.00258	0.36849	0.62893
51	0.00284	0.36844	0.62872
52	0.00312	0.36838	0.62850
53	0.00342	0.36831	0.62826
54	0.00377	0.36824	0.62799
55	0.00414	0.36816	0.62770
56	0.00455	0.36807	0.62737
57	0.00500	0.36798	0.62702
58	0.00550	0.36787	0.62663
59	0.00605	0.36775	0.62619
60	0.00665	0.36763	0.62572
61	0.00733	0.36748	0.62519
62	0.00806	0.36733	0.62462
63	0.00887	0.36715	0.62398
64	0.00976	0.36696	0.62328
65	0.01074	0.36675	0.62250
66	0.01183	0.36652	0.62165
67	0.01302	0.36627	0.62071
68	0.01434	0.36599	0.61968
69	0.01579	0.36568	0.61853
70	0.01739	0.36533	0.61728
71	0.01915	0.36496	0.61589
72	0.02110	0.36454	0.61436
73	0.02325	0.36408	0.61267
74	0.02562	0.36357	0.61081
75	0.02823	0.36301	0.60876
76	0.03112	0.36239	0.60650
77	0.03430	0.36170	0.60400
78	0.03782	0.36095	0.60123
79	0.04170	0.36011	0.59819
80	0.04599	0.35918	0.59483
81	0.05072	0.35816	0.59112
82	0.05595	0.35702	0.58702
83	0.06173	0.35577	0.58250
84	0.06811	0.35438	0.57751
85	0.07517	0.35284	0.57199
86	0.08297	0.35113	0.56590
87	0.09160	0.34923	0.55917
88	0.10114	0.34713	0.55173
89	0.11169	0.34479	0.54352
90	0.12336	0.34220	0.53444
91	0.13600	0.33937	0.52463

Age	Other Death	CRC Death	Distant Cancer
92	0.14933	0.33637	0.51429
93	0.16331	0.33321	0.50348
94	0.17788	0.32990	0.49222
95	0.18976	0.32718	0.48306
96	0.20461	0.32376	0.47163
97	0.21992	0.32021	0.45987
98	0.23561	0.31654	0.44785
99	0.25156	0.31278	0.43566

APPENDIX 4 INITIAL STATES – DISTRIBUTION OF POPULATION AT MODEL INITIALIZATION

Table 4a Initial States for Average Risk Females

Age	Normal Epithelium	Low Risk Polyp	High Risk Polyp	Local Cancer	Regional Cancer	Distant Cancer	CRC Death
50	80.875	18.000	1.000	0.100	0.020	0.005	0.000
51	80.592	17.923	1.335	0.120	0.020	0.004	0.005
52	80.310	17.847	1.660	0.147	0.021	0.004	0.011
53	80.029	17.771	1.976	0.181	0.023	0.004	0.017
54	79.749	17.696	2.282	0.222	0.025	0.004	0.024
55	79.470	17.621	2.578	0.267	0.029	0.004	0.031
56	79.191	17.546	2.866	0.318	0.033	0.004	0.040
57	78.914	17.473	3.146	0.374	0.038	0.005	0.051
58	78.638	17.399	3.416	0.434	0.044	0.005	0.063
59	78.363	17.327	3.679	0.497	0.052	0.006	0.077
60	77.971	17.372	3.926	0.571	0.060	0.007	0.093
61	77.581	17.414	4.168	0.648	0.069	0.008	0.111
62	77.193	17.454	4.403	0.728	0.080	0.009	0.133
63	76.807	17.491	4.634	0.810	0.091	0.010	0.157
64	76.423	17.525	4.858	0.894	0.103	0.012	0.184
65	75.926	17.671	5.024	1.034	0.117	0.014	0.214
66	75.433	17.811	5.187	1.172	0.133	0.016	0.248
67	74.943	17.946	5.346	1.310	0.150	0.018	0.288
68	74.456	18.074	5.502	1.447	0.170	0.020	0.332
69	73.972	18.196	5.654	1.583	0.191	0.023	0.381
70	73.380	18.424	5.735	1.786	0.214	0.026	0.436
71	72.793	18.643	5.817	1.982	0.240	0.029	0.497
72	72.210	18.852	5.899	2.173	0.268	0.032	0.566
73	71.633	19.053	5.981	2.358	0.298	0.036	0.641
74	71.060	19.245	6.063	2.538	0.330	0.040	0.724
75	70.491	19.428	6.145	2.712	0.363	0.045	0.815
76	69.927	19.604	6.226	2.883	0.397	0.050	0.913
77	69.368	19.771	6.307	3.048	0.432	0.055	1.019
78	68.813	19.931	6.387	3.209	0.467	0.060	1.133
79	68.262	20.082	6.466	3.366	0.503	0.066	1.254
80	67.197	20.746	6.545	3.519	0.539	0.071	1.383
81	66.149	21.379	6.632	3.669	0.574	0.077	1.520
82	65.117	21.983	6.728	3.815	0.610	0.082	1.664
83	64.101	22.560	6.831	3.958	0.645	0.088	1.816
84	63.101	23.108	6.941	4.100	0.680	0.094	1.975
85	62.117	23.631	7.056	4.240	0.715	0.099	2.142
86	61.148	24.127	7.176	4.378	0.750	0.105	2.316
87	60.194	24.598	7.300	4.515	0.784	0.110	2.498

Age	Normal Epithelium	Low Risk Polyp	High Risk Polyp	Local Cancer	Regional Cancer	Distant Cancer	CRC Death
88	59.255	25.045	7.427	4.652	0.818	0.116	2.687
89	58.331	25.469	7.556	4.788	0.851	0.122	2.883
90	58.220	25.070	7.688	4.924	0.885	0.127	3.086
91	58.109	24.680	7.805	5.059	0.918	0.132	3.297
92	57.999	24.296	7.908	5.194	0.951	0.138	3.514
93	57.889	23.921	7.999	5.326	0.983	0.143	3.739
94	57.779	23.552	8.077	5.457	1.016	0.148	3.970
95	57.669	23.191	8.144	5.585	1.048	0.154	4.209
96	57.559	22.837	8.201	5.710	1.080	0.159	4.454
97	57.450	22.489	8.248	5.831	1.111	0.164	4.706
98	57.341	22.149	8.285	5.949	1.143	0.169	4.965
99	57.232	21.815	8.314	6.062	1.173	0.174	5.230

Table 4b Initial States for Average Risk Males

Age	Normal Epithelium	Low Risk Polyp	High Risk Polyp	Local Cancer	Regional Cancer	Distant Cancer	CRC Death
50	73.750	24.000	2.000	0.200	0.040	0.010	0.000
51	73.381	23.889	2.428	0.242	0.041	0.009	0.011
52	73.014	23.778	2.843	0.293	0.043	0.008	0.022
53	72.649	23.667	3.244	0.352	0.046	0.008	0.034
54	72.286	23.557	3.633	0.418	0.051	0.007	0.047
55	71.816	23.556	4.010	0.492	0.057	0.008	0.062
56	71.349	23.552	4.377	0.571	0.064	0.008	0.079
57	70.886	23.544	4.734	0.656	0.073	0.009	0.098
58	70.425	23.534	5.082	0.746	0.083	0.010	0.120
59	69.967	23.521	5.420	0.840	0.094	0.011	0.145
60	69.407	23.611	5.723	0.966	0.107	0.013	0.173
61	68.852	23.694	6.018	1.094	0.122	0.014	0.205
62	68.301	23.771	6.305	1.226	0.139	0.016	0.242
63	67.755	23.842	6.585	1.359	0.158	0.018	0.283
64	67.213	23.907	6.858	1.495	0.178	0.021	0.329
65	66.574	24.067	7.075	1.680	0.200	0.024	0.380
66	65.942	24.218	7.288	1.864	0.224	0.027	0.438
67	65.315	24.360	7.495	2.046	0.251	0.030	0.502
68	64.695	24.494	7.697	2.228	0.279	0.034	0.573
69	64.080	24.618	7.895	2.407	0.310	0.038	0.651
70	63.081	25.126	7.985	2.688	0.342	0.042	0.737
71	62.097	25.607	8.080	2.960	0.378	0.047	0.832
72	61.128	26.064	8.180	3.222	0.418	0.052	0.937
73	60.174	26.496	8.284	3.476	0.460	0.057	1.052
74	59.236	26.905	8.391	3.723	0.504	0.063	1.177
75	58.311	27.291	8.502	3.963	0.550	0.070	1.313
76	57.402	27.655	8.614	4.196	0.598	0.077	1.459
77	56.506	27.997	8.728	4.423	0.646	0.084	1.616
78	55.625	28.319	8.842	4.644	0.695	0.091	1.784
79	54.757	28.620	8.958	4.861	0.744	0.098	1.962
80	54.653	28.152	9.082	5.063	0.793	0.106	2.151
81	54.549	27.693	9.191	5.261	0.842	0.114	2.350
82	54.446	27.242	9.286	5.454	0.891	0.122	2.560
83	54.342	26.801	9.366	5.643	0.939	0.129	2.780
84	54.239	26.368	9.434	5.826	0.986	0.137	3.010
85	54.136	25.944	9.490	6.003	1.033	0.145	3.250
86	54.033	25.528	9.534	6.174	1.079	0.152	3.500
87	53.930	25.120	9.568	6.338	1.125	0.160	3.759
88	53.828	24.720	9.592	6.496	1.169	0.167	4.027
89	53.726	24.328	9.607	6.647	1.213	0.175	4.305
90	53.478	24.088	9.613	6.792	1.255	0.182	4.592
91	53.232	23.853	9.614	6.929	1.296	0.189	4.887

Age	Normal Epithelium	Low Risk Polyp	High Risk Polyp	Local Cancer	Regional Cancer	Distant Cancer	CRC Death
92	52.988	23.620	9.610	7.059	1.336	0.196	5.190
93	52.744	23.392	9.602	7.183	1.375	0.202	5.502
94	52.501	23.167	9.590	7.300	1.413	0.209	5.821
95	52.260	22.945	9.574	7.410	1.449	0.215	6.148
96	52.019	22.726	9.554	7.514	1.484	0.221	6.481
97	51.780	22.511	9.531	7.612	1.517	0.227	6.822
98	51.542	22.299	9.504	7.703	1.549	0.233	7.169
99	51.305	22.090	9.475	7.789	1.580	0.239	7.522

Table 4c Initial States for High Risk Females

Age	Normal Epithelium	Low Risk Polyp	High Risk Polyp	Local Cancer	Regional Cancer	Distant Cancer	CRC Death
50	71.653	27.000	1.200	0.120	0.022	0.006	0.000
51	71.276	26.836	1.710	0.144	0.023	0.005	0.006
52	70.902	26.674	2.204	0.179	0.024	0.004	0.012
53	70.530	26.512	2.682	0.225	0.026	0.004	0.019
54	70.160	26.352	3.146	0.281	0.030	0.004	0.027
55	69.791	26.194	3.594	0.346	0.034	0.004	0.037
56	69.425	26.036	4.028	0.418	0.040	0.005	0.048
57	69.060	25.880	4.448	0.497	0.047	0.005	0.061
58	68.698	25.725	4.854	0.584	0.056	0.006	0.077
59	68.337	25.571	5.248	0.675	0.066	0.007	0.095
60	67.978	25.419	5.617	0.783	0.078	0.008	0.117
61	67.621	25.267	5.974	0.895	0.091	0.010	0.141
62	67.266	25.117	6.318	1.011	0.106	0.012	0.170
63	66.913	24.968	6.650	1.130	0.123	0.014	0.203
64	66.562	24.819	6.970	1.253	0.140	0.016	0.240
65	66.213	24.673	7.201	1.454	0.160	0.018	0.281
66	65.865	24.527	7.421	1.654	0.183	0.021	0.329
67	65.519	24.382	7.629	1.853	0.208	0.024	0.384
68	65.175	24.238	7.827	2.049	0.237	0.027	0.446
69	64.833	24.096	8.015	2.243	0.267	0.031	0.515
70	64.493	23.954	8.096	2.530	0.300	0.036	0.592
71	64.154	23.814	8.170	2.807	0.337	0.040	0.679
72	63.817	23.674	8.238	3.074	0.377	0.045	0.775
73	63.482	23.536	8.299	3.330	0.420	0.051	0.882
74	63.149	23.398	8.355	3.577	0.465	0.057	0.999
75	62.817	23.262	8.405	3.814	0.512	0.063	1.126
76	62.488	23.126	8.450	4.041	0.560	0.070	1.265
77	62.160	22.992	8.490	4.259	0.608	0.077	1.413
78	61.833	22.858	8.526	4.468	0.657	0.085	1.573
79	61.509	22.726	8.557	4.669	0.706	0.092	1.742
80	61.186	22.594	8.583	4.860	0.754	0.100	1.922
81	60.864	22.464	8.606	5.044	0.802	0.108	2.112
82	60.545	22.334	8.625	5.219	0.849	0.115	2.313
83	60.227	22.205	8.640	5.386	0.896	0.123	2.522
84	59.911	22.077	8.652	5.546	0.941	0.130	2.742
85	59.596	21.950	8.661	5.698	0.986	0.138	2.970
86	59.283	21.824	8.667	5.843	1.029	0.145	3.208
87	58.972	21.699	8.670	5.981	1.071	0.152	3.454
88	58.663	21.574	8.671	6.112	1.112	0.159	3.709
89	58.355	21.451	8.669	6.237	1.151	0.166	3.972
90	58.048	21.328	8.664	6.355	1.189	0.173	4.242
91	57.744	21.206	8.658	6.467	1.226	0.179	4.521

Age	Normal Epithelium	Low Risk Polyp	High Risk Polyp	Local Cancer	Regional Cancer	Distant Cancer	CRC Death
92	57.440	21.085	8.649	6.572	1.261	0.186	4.806
93	57.139	20.965	8.638	6.673	1.295	0.192	5.098
94	56.839	20.846	8.626	6.767	1.328	0.197	5.397
95	56.540	20.727	8.611	6.856	1.359	0.203	5.703
96	56.244	20.610	8.595	6.940	1.389	0.208	6.014
97	55.948	20.493	8.578	7.019	1.417	0.214	6.331
98	55.655	20.377	8.559	7.093	1.445	0.218	6.654
99	55.362	20.261	8.538	7.162	1.471	0.223	6.982

Table 4d Initial States for High Risk Males

Age	Normal Epithelium	Low Risk Polyp	High Risk Polyp	Local Cancer	Regional Cancer	Distant Cancer	CRC Death
50	61.305	36.000	2.400	0.240	0.044	0.011	0.000
51	60.845	35.740	3.058	0.290	0.046	0.010	0.012
52	60.389	35.481	3.693	0.355	0.048	0.009	0.025
53	59.936	35.225	4.307	0.433	0.053	0.008	0.039
54	59.486	34.970	4.899	0.523	0.059	0.008	0.054
55	59.040	34.716	5.471	0.624	0.067	0.009	0.073
56	58.597	34.465	6.023	0.735	0.077	0.009	0.093
57	58.158	34.215	6.556	0.854	0.089	0.011	0.117
58	57.722	33.967	7.070	0.982	0.103	0.012	0.145
59	57.289	33.721	7.565	1.116	0.119	0.014	0.177
60	56.859	33.476	8.005	1.294	0.137	0.016	0.214
61	56.433	33.233	8.426	1.477	0.158	0.018	0.256
62	56.010	32.991	8.830	1.663	0.181	0.021	0.304
63	55.589	32.752	9.216	1.853	0.208	0.024	0.359
64	55.173	32.513	9.585	2.045	0.236	0.027	0.421
65	54.759	32.277	9.871	2.306	0.267	0.031	0.490
66	54.348	32.042	10.142	2.564	0.301	0.035	0.567
67	53.940	31.809	10.397	2.820	0.339	0.040	0.655
68	53.536	31.577	10.638	3.072	0.379	0.045	0.752
69	53.134	31.347	10.866	3.321	0.422	0.051	0.859
70	52.736	31.119	10.938	3.707	0.467	0.057	0.976
71	52.340	30.892	11.003	4.078	0.517	0.064	1.106
72	51.948	30.667	11.060	4.433	0.572	0.071	1.250
73	51.558	30.443	11.109	4.773	0.631	0.078	1.408
74	51.172	30.221	11.151	5.098	0.692	0.087	1.580
75	50.788	30.000	11.187	5.409	0.755	0.096	1.766
76	50.407	29.781	11.216	5.706	0.819	0.105	1.966
77	50.029	29.563	11.240	5.989	0.884	0.115	2.180
78	49.654	29.347	11.258	6.260	0.949	0.125	2.408
79	49.281	29.133	11.271	6.517	1.013	0.135	2.650
80	48.912	28.920	11.290	6.751	1.077	0.145	2.905
81	48.545	28.708	11.304	6.974	1.140	0.155	3.174
82	48.181	28.498	11.313	7.187	1.201	0.165	3.455
83	47.819	28.290	11.317	7.389	1.261	0.175	3.748
84	47.461	28.082	11.317	7.581	1.320	0.185	4.054
85	47.105	27.877	11.313	7.764	1.376	0.195	4.371
86	46.751	27.672	11.305	7.937	1.431	0.204	4.700
87	46.401	27.470	11.293	8.101	1.483	0.213	5.039
88	46.053	27.268	11.278	8.256	1.534	0.222	5.389
89	45.707	27.068	11.259	8.402	1.583	0.231	5.749
90	45.365	26.870	11.238	8.540	1.631	0.239	6.118
91	45.024	26.673	11.213	8.670	1.676	0.247	6.497

Age	Normal Epithelium	Low Risk Polyp	High Risk Polyp	Local Cancer	Regional Cancer	Distant Cancer	CRC Death
92	44.687	26.477	11.186	8.793	1.719	0.255	6.884
93	44.351	26.282	11.156	8.907	1.760	0.262	7.280
94	44.019	26.089	11.124	9.015	1.800	0.270	7.684
95	43.689	25.898	11.090	9.115	1.837	0.276	8.095
96	43.361	25.707	11.053	9.209	1.873	0.283	8.514
97	43.036	25.519	11.015	9.296	1.907	0.289	8.939
98	42.713	25.331	10.974	9.376	1.939	0.295	9.371
99	42.393	25.145	10.932	9.451	1.970	0.301	9.809

APPENDIX 5 LIFE TABLES

Table 5a Synthetic Life Tables for Average Risk Females

Age (x)	l_x	d_x	q_x	m_x	L_x	T_x	e_x
50	100000	214	0.0021	0.0021	99893	3427155	34.27
51	99786	232	0.0023	0.0023	99670	3327262	33.34
52	99554	252	0.0025	0.0025	99428	3227592	32.42
53	99302	274	0.0028	0.0028	99165	3128164	31.50
54	99028	300	0.0030	0.0030	98878	3028999	30.59
55	98728	326	0.0033	0.0033	98565	2930122	29.68
56	98402	359	0.0036	0.0037	98222	2831557	28.78
57	98043	390	0.0040	0.0040	97848	2733335	27.88
58	97654	426	0.0044	0.0044	97440	2635486	26.99
59	97228	468	0.0048	0.0048	96993	2538046	26.10
60	96760	512	0.0053	0.0053	96504	2441053	25.23
61	96248	557	0.0058	0.0058	95969	2344549	24.36
62	95691	611	0.0064	0.0064	95386	2248580	23.50
63	95081	673	0.0071	0.0071	94744	2153194	22.65
64	94408	733	0.0078	0.0078	94040	2058450	21.80
65	93674	803	0.0086	0.0086	93272	1964410	20.97
66	92871	873	0.0094	0.0094	92434	1871138	20.15
67	91998	961	0.0104	0.0105	91517	1778704	19.33
68	91037	1049	0.0115	0.0116	90512	1687188	18.53
69	89988	1143	0.0127	0.0128	89415	1596676	17.74
70	88845	1247	0.0140	0.0141	88220	1507260	16.97
71	87598	1360	0.0155	0.0156	86916	1419041	16.20
72	86237	1483	0.0172	0.0173	85494	1332125	15.45
73	84755	1617	0.0191	0.0193	83944	1246631	14.71
74	83138	1750	0.0211	0.0213	82260	1162687	13.98
75	81388	1902	0.0234	0.0236	80433	1080427	13.28
76	79486	2070	0.0260	0.0264	78446	999994	12.58
77	77416	2238	0.0289	0.0293	76291	921548	11.90
78	75178	2409	0.0320	0.0326	73967	845257	11.24
79	72769	2588	0.0356	0.0362	71467	771290	10.60
80	70180	2775	0.0395	0.0404	68783	699823	9.97
81	67405	2966	0.0440	0.0450	65911	631040	9.36
82	64438	3156	0.0490	0.0502	62847	565129	8.77
83	61282	3349	0.0546	0.0562	59592	502282	8.20
84	57934	3531	0.0609	0.0629	56150	442690	7.64
85	54403	3701	0.0680	0.0704	52531	386540	7.11
86	50702	3854	0.0760	0.0791	48750	334009	6.59
87	46848	3981	0.0850	0.0888	44828	285260	6.09
88	42867	4063	0.0948	0.0996	40802	240431	5.61
89	38804	4121	0.1062	0.1123	36705	199629	5.14

Age (x)	l_x	d_x	q_x	m_x	L_x	T_x	e_x
90	34683	4127	0.1190	0.1267	32576	162924	4.70
91	30556	4062	0.1329	0.1426	28477	130348	4.27
92	26494	3926	0.1482	0.1604	24479	101871	3.84
93	22569	3710	0.1644	0.1796	20658	77392	3.43
94	18858	3424	0.1815	0.2003	17089	56734	3.01
95	15435	3072	0.1990	0.2219	13842	39645	2.57
96	12363	2690	0.2176	0.2454	10963	25803	2.09
97	9673	2304	0.2382	0.2720	8469	14840	1.53
98	7369	1903	0.2582	0.2987	6371	6371	0.86
99	5466	5466	1.0000	1.0000	0	0	0

l_x = Number of survivors at age x
d_x = Number of deaths between ages x and x+1
q_x = Probability of death between ages x and x+1
m_x = Age-specific mortality rate
L_x = Total number of person-years lived by the cohort from ages x to x+1
T_x = Cumulative number of life years lived beyond age x
e_x = Life expectancy at age x

Table 5b Synthetic Life Tables for Average Risk Males

Age (x)	l_x	d_x	q_x	m_x	L_x	T_x	e_x
50	100000	336	0.0034	0.0034	99832	3059657	30.60
51	99664	365	0.0037	0.0037	99482	2959825	29.70
52	99299	399	0.0040	0.0040	99100	2860343	28.81
53	98900	435	0.0044	0.0044	98682	2761244	27.92
54	98465	478	0.0049	0.0049	98226	2662561	27.04
55	97987	522	0.0053	0.0053	97726	2564336	26.17
56	97465	575	0.0059	0.0059	97177	2466610	25.31
57	96890	626	0.0065	0.0065	96577	2369432	24.45
58	96265	682	0.0071	0.0071	95924	2272855	23.61
59	95583	750	0.0078	0.0079	95208	2176931	22.78
60	94834	820	0.0086	0.0087	94423	2081723	21.95
61	94014	889	0.0095	0.0095	93569	1987300	21.14
62	93125	972	0.0104	0.0105	92638	1893731	20.34
63	92153	1063	0.0115	0.0116	91620	1801093	19.54
64	91090	1154	0.0127	0.0128	90511	1709472	18.77
65	89936	1255	0.0140	0.0141	89306	1618961	18.00
66	88680	1361	0.0153	0.0155	87998	1529655	17.25
67	87319	1476	0.0169	0.0170	86579	1441657	16.51
68	85843	1601	0.0186	0.0188	85041	1355077	15.79
69	84243	1728	0.0205	0.0207	83376	1270037	15.08
70	82514	1858	0.0225	0.0228	81582	1186661	14.38
71	80657	2011	0.0249	0.0253	79647	1105079	13.70
72	78645	2154	0.0274	0.0278	77563	1025432	13.04
73	76491	2305	0.0301	0.0306	75333	947869	12.39
74	74186	2461	0.0332	0.0337	72948	872536	11.76
75	71725	2622	0.0366	0.0372	70406	799588	11.15
76	69103	2772	0.0401	0.0409	67707	729182	10.55
77	66330	2941	0.0443	0.0454	64848	661475	9.97
78	63389	3099	0.0489	0.0501	61826	596627	9.41
79	60290	3243	0.0538	0.0553	58653	534800	8.87
80	57047	3374	0.0591	0.0610	55343	476147	8.35
81	53673	3497	0.0651	0.0674	51905	420804	7.84
82	50176	3595	0.0717	0.0744	48356	368899	7.35
83	46581	3676	0.0789	0.0822	44718	320543	6.88
84	42905	3719	0.0867	0.0907	41018	275825	6.43
85	39186	3750	0.0957	0.1006	37280	234807	5.99
86	35436	3735	0.1054	0.1114	33534	197527	5.57
87	31701	3677	0.1160	0.1233	29825	163993	5.17
88	28024	3584	0.1279	0.1368	26191	134168	4.79
89	24440	3443	0.1409	0.1519	22675	107976	4.42
90	20997	3266	0.1555	0.1690	19318	85301	4.06
91	17731	3030	0.1709	0.1874	16169	65983	3.72
92	14702	2762	0.1879	0.2081	13273	49814	3.39

Age (x)	l_x	d_x	q_x	m_x	L_x	T_x	e_x
93	11940	2444	0.2047	0.2291	10671	36541	3.06
94	9495	2120	0.2233	0.2527	8390	25871	2.72
95	7375	1750	0.2372	0.2708	6461	17480	2.37
96	5625	1439	0.2558	0.2955	4870	11019	1.96
97	4186	1148	0.2742	0.3205	3582	6149	1.47
98	3038	891	0.2932	0.3471	2567	2567	0.84
99	2147	2147	1.0000	1.0000	0	0	0

l_x = Number of survivors at age x
d_x = Number of deaths between ages x and x+1
q_x = Probability of death between ages x and x+1
m_x = Age-specific mortality rate
L_x = Total number of person-years lived by the cohort from ages x to x+1
T_x = Cumulative number of life years lived beyond age x
e_x = Life expectancy at age x

Table 5c Synthetic Life Tables for Higher Risk Females

Age (x)	l_x	d_x	q_x	m_x	L_x	T_x	e_x
50	100000	215	0.0021	0.0022	99893	3408729	34.09
51	99785	233	0.0023	0.0023	99669	3308837	33.16
52	99552	252	0.0025	0.0025	99426	3209168	32.24
53	99300	276	0.0028	0.0028	99162	3109742	31.32
54	99024	302	0.0031	0.0031	98873	3010580	30.40
55	98722	327	0.0033	0.0033	98558	2911706	29.49
56	98395	362	0.0037	0.0037	98214	2813148	28.59
57	98033	393	0.0040	0.0040	97836	2714934	27.69
58	97640	430	0.0044	0.0044	97425	2617098	26.80
59	97210	473	0.0049	0.0049	96973	2519673	25.92
60	96737	517	0.0053	0.0054	96478	2422700	25.04
61	96220	563	0.0058	0.0059	95938	2326222	24.18
62	95657	618	0.0065	0.0065	95348	2230284	23.32
63	95039	682	0.0072	0.0072	94697	2134936	22.46
64	94357	744	0.0079	0.0079	93984	2040239	21.62
65	93613	816	0.0087	0.0088	93204	1946255	20.79
66	92797	886	0.0095	0.0096	92353	1853051	19.97
67	91911	976	0.0106	0.0107	91422	1760697	19.16
68	90935	1068	0.0117	0.0118	90400	1669275	18.36
69	89868	1166	0.0130	0.0131	89283	1578875	17.57
70	88701	1272	0.0143	0.0144	88064	1489591	16.79
71	87429	1391	0.0159	0.0160	86732	1401528	16.03
72	86038	1518	0.0176	0.0178	85277	1314796	15.28
73	84520	1657	0.0196	0.0198	83689	1229519	14.55
74	82863	1799	0.0217	0.0219	81960	1145831	13.83
75	81064	1953	0.0241	0.0244	80083	1063871	13.12
76	79111	2126	0.0269	0.0272	78043	983788	12.44
77	76985	2292	0.0298	0.0302	75834	905744	11.77
78	74694	2471	0.0331	0.0336	73451	829910	11.11
79	72222	2651	0.0367	0.0374	70888	756459	10.47
80	69571	2837	0.0408	0.0416	68143	685571	9.85
81	66734	3024	0.0453	0.0464	65211	617428	9.25
82	63710	3214	0.0504	0.0518	62090	552217	8.67
83	60497	3400	0.0562	0.0578	58780	490128	8.10
84	57097	3574	0.0626	0.0646	55290	431348	7.55
85	53523	3743	0.0699	0.0725	51629	376057	7.03
86	49780	3868	0.0777	0.0809	47820	324428	6.52
87	45912	3997	0.0871	0.0911	43883	276608	6.02
88	41915	4060	0.0969	0.1019	39850	232725	5.55
89	37855	4095	0.1082	0.1145	35769	192874	5.10
90	33760	4090	0.1211	0.1291	31671	157106	4.65
91	29671	4022	0.1355	0.1456	27611	125434	4.23
92	25649	3862	0.1506	0.1632	23666	97823	3.81

Age (x)	l_x	d_x	q_x	m_x	L_x	T_x	e_x
93	21787	3634	0.1668	0.1825	19915	74158	3.40
94	18153	3341	0.1841	0.2034	16426	54243	2.99
95	14812	2994	0.2022	0.2259	13258	37817	2.55
96	11817	2608	0.2207	0.2493	10459	24559	2.08
97	9209	2207	0.2396	0.2740	8056	14100	1.53
98	7003	1824	0.2605	0.3018	6045	6045	0.86
99	5178	5178	1.0000	1.0000	0	0	0

l_x = Number of survivors at age x
d_x = Number of deaths between ages x and x+1
q_x = Probability of death between ages x and x+1
m_x = Age-specific mortality rate
L_x = Total number of person-years lived by the cohort from ages x to x+1
T_x = Cumulative number of life years lived beyond age x
e_x = Life expectancy at age x

Table 5d Synthetic Life Tables for Higher Risk Males

Age (x)	l_x	d_x	q_x	m_x	L_x	T_x	e_x
50	100000	337	0.0034	0.0034	99831	3048535	30.49
51	99663	366	0.0037	0.0037	99479	2948704	29.59
52	99297	402	0.0040	0.0041	99095	2849224	28.69
53	98895	437	0.0044	0.0044	98676	2750129	27.81
54	98458	481	0.0049	0.0049	98217	2651453	26.93
55	97977	526	0.0054	0.0054	97713	2553236	26.06
56	97450	579	0.0059	0.0060	97160	2455523	25.20
57	96871	630	0.0065	0.0065	96555	2358362	24.35
58	96240	688	0.0072	0.0072	95896	2261807	23.50
59	95552	757	0.0079	0.0080	95173	2165911	22.67
60	94795	828	0.0087	0.0088	94380	2070738	21.84
61	93967	900	0.0096	0.0096	93517	1976358	21.03
62	93067	985	0.0106	0.0106	92574	1882842	20.23
63	92083	1077	0.0117	0.0118	91543	1790267	19.44
64	91006	1169	0.0128	0.0129	90420	1698724	18.67
65	89837	1274	0.0142	0.0143	89199	1608304	17.90
66	88563	1376	0.0155	0.0157	87874	1519105	17.15
67	87187	1496	0.0172	0.0173	86437	1431231	16.42
68	85692	1622	0.0189	0.0191	84878	1344794	15.69
69	84070	1753	0.0209	0.0211	83190	1259916	14.99
70	82316	1882	0.0229	0.0231	81372	1176726	14.30
71	80434	2035	0.0253	0.0256	79412	1095355	13.62
72	78399	2185	0.0279	0.0283	77301	1015943	12.96
73	76214	2334	0.0306	0.0311	75041	938641	12.32
74	73881	2495	0.0338	0.0344	72626	863600	11.69
75	71386	2649	0.0371	0.0378	70053	790974	11.08
76	68737	2800	0.0407	0.0416	67328	720920	10.49
77	65937	2964	0.0450	0.0460	64444	653593	9.91
78	62973	3120	0.0495	0.0508	61400	589149	9.36
79	59853	3264	0.0545	0.0561	58205	527750	8.82
80	56589	3391	0.0599	0.0618	54876	469544	8.30
81	53197	3512	0.0660	0.0683	51421	414669	7.79
82	49685	3604	0.0725	0.0753	47861	363247	7.31
83	46082	3677	0.0798	0.0832	44218	315386	6.84
84	42405	3718	0.0877	0.0918	40517	271169	6.39
85	38686	3738	0.0966	0.1016	36786	230652	5.96
86	34948	3716	0.1063	0.1124	33055	193866	5.55
87	31232	3657	0.1171	0.1245	29366	160811	5.15
88	27576	3552	0.1288	0.1379	25759	131445	4.77
89	24023	3413	0.1421	0.1532	22273	105686	4.40
90	20611	3229	0.1567	0.1704	18950	83413	4.05
91	17382	2989	0.1719	0.1887	15840	64462	3.71
92	14393	2711	0.1884	0.2087	12990	48622	3.38

Age (x)	l_x	d_x	q_x	m_x	L_x	T_x	e_x
93	11682	2408	0.2062	0.2309	10431	35632	3.05
94	9274	2077	0.2239	0.2535	8191	25200	2.72
95	7197	1722	0.2392	0.2734	6297	17009	2.36
96	5475	1404	0.2565	0.2964	4738	10712	1.96
97	4071	1120	0.2751	0.3217	3481	5974	1.47
98	2951	866	0.2936	0.3475	2493	2493	0.84
99	2085	2085	1.0000	1.0000	0	0	0

l_x = Number of survivors at age x
d_x = Number of deaths between ages x and x+1
q_x = Probability of death between ages x and x+1
m_x = Age-specific mortality rate
L_x = Total number of person-years lived by the cohort from ages x to x+1
T_x = Cumulative number of life years lived beyond age x
e_x = Life expectancy at age x