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Cost-Effectiveness Analysis of Colorectal Cancer Screening Strategies Using Active Learning and Montecarlo Simulation

Amirhosein Fouladi

COST-EFFECTIVENESS ANALYSIS OF COLORECTAL CANCER SCREENING STRATEGIES USING ACTIVE LEARNING AND MONTECARLO SIMULATION

by

Amirhosein Fouladi, B.S.

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Dr. Mahboubeh Madadi, Supervisor of Thesis Research

Dr. David Hall,
Head of Industrial Engineering

Members of the Thesis Committee:
Dr. Eric Sherer
Dr. Jung-Ing Ker

Approved:

Hisham Hegab
Dean of Engineering & Science

Approved:

Ramu Ramachandran
Dean of the Graduate School

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ABSTRACT

Colorectal cancer (CRC) is one of the deadliest types of cancer in the US due to its high incidence and mortality rates. Detection of CRC in the early stages through available screening tests increases the patient's survival chances. In this study, we investigate the cost-effectiveness of a wide variety of multi-modal CRC screening policies. More specifically, we develop a Monte Carlo simulation framework to model the CRC natural history and preventive interventions. Age-specific and size-specific progression rates of adenomatous polyps are estimated using an innovative active learning method. Specifically, we develop a decision tree model to estimate size-specific and age-specific adenoma progression and regression rates. Compared to traditional methods, the proposed calibration process expedites the searching of the model parameter space significantly. CRC age-specific incidence rates and CRC stage distribution are the two output measures used in the calibration process. Seventy-eight CRC screening policies are applied to a cohort of U.S. male population using the simulation model and compared in terms of expected Quality Adjusted Life Years (QALY) and costs. Eleven policies are identified as efficient frontier policies. Among these 9 are identified as cost-effective at the willingness to pay (WTP) threshold of $50,000. Fecal Occult Blood Test (FOBT) biennially in conjunction with one time Colonoscopy at 60, FOBT biennially along with one time Colonoscopy at 50, Fecal Immunochemical Test (FIT) biennially in conjunction with two times Flexible Sigmoidoscopy (FS) at 60 and 65. FIT biennially

with one time Colonoscopy at 65, Colonoscopy at 50, 60 and 70, FOBT biennially along with two times Colonoscopy at 55 and 65, FOBT annually with 2 times FS at 70 and 75, FOBT annually in conjunction with FS at 50 and 55, and FIT biennially along with FS every 5 years are the nine identified cost-effective policies.

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CHAPTER 1

INTRODUCTION

Colon and rectal cancer are often grouped together and called colorectal cancer (CRC) since they have many features in common (American Cancer Society 2018). It is estimated that in 2018, more than 140,000 people are diagnosed with CRC and more than 50,000 patients are dead from CRC (National Cancer Institute 2018a). More than 8% of cancer incidences and deaths are estimated to be CRC related (National Cancer Institute 2018a). According to the Surveillance, Epidemiology, and End Result (SEER) program 1975-2015 review, between 2011 and 2015, approximately 9% of all new cancer cases are CRC and about 9% of all cancer-related deaths are due to CRC, making it the second deadliest cancer and the fourth most common cancer among all different types of cancer. CRC starts with a polyp in the innermost layer of the colon or rectum and may grow through other layers of the colon if not detected and treated (American Cancer Society 2018). There are two main types of polyp in the colon and rectum. Adenomatous polyps, also called adenomas, are the type which can develop to cancer. The second type of polyps is hyperplastic and inflammatory polyps which generally do not develop into cancer (American Cancer Society 2018). While in the wall of the colon or rectum, cancer cells may spread to adjacent lymph nodes or distant body parts through the blood or lymph vessels. Stages of CRC are based on how deep they have grown into the colon or

rectum wall or how far they have traveled outside of their organ of origin (American Cancer Society 2018).

CRC mortality risk can be reduced through detection of cancer in early stages when there is a higher survival chance. The overall five-year surveillance rate for CRC is 64.6%. This ratio for cases who are diagnosed in the localized and distant stage is 90% and 13.9%, respectively. These ratios show the importance of detecting CRC in an early stage. Currently, there are several early CRC detection screening tests available, such as Fecal Immunochemical Test (FIT), Fecal Occult Blood Test (FOBT), Flexible Sigmoidoscopy (FS), and colonoscopy (Lansdorp-Vogelaar et al. 2011). These tests vary in different features. Sigmoidoscopy and colonoscopy use a camera on a flexible tube introduced through the anus to examine the colon and rectum for abnormal growths. These tests are categorized into visual (structural) exams since they look at the structure inside the colon and rectum for any abnormal areas that might be cancer or adenomas. Sigmoidoscopy is performed on an alert patient and reaches at most the first third of the large colon. Any polyps detected are recorded (and maybe removed and biopsied) and the patient is generally referred for colonoscopy. Colonoscopy is the most aggressive and expensive procedure performed on a sedated patient, and permits an examination of the entire colon. During a colonoscopy, any suspicious polyps can be removed, which may prevent cancer occurrence in the future (National Cancer Institute 2018b). FIT and FOBT are stool-based tests and look for evidence of occult (hidden) blood in the stool. FIT reacts to the part of the human hemoglobin protein, found in red blood cells. FOBT detects occult blood in the stool through a chemical reaction, in a different way than FIT. Neither FIT nor FOBT can specify if the blood is from the colon or other parts of the

digestive tract since the blood can be from cancers or polyps or some other non-CRC-related causes (American Cancer Society 2018). Therefore, a positive FIT or FOBT requires a follow-up colonoscopy. One of the weaknesses associated with FIT and FOBT is low specificity which results in higher false positives in test results. The associated high false positive results increase the number of unnecessary colonoscopy tests (Lejeune et al. 2014). To avoid false positive results, patients are required to follow some dietary restrictions before FOBT tests. However, no dietary restriction is required before FIT (American Cancer Society 2018). Stool-based tests are usually associated with low costs which come with lower sensitivity as well (Knudsen et al. 2016; Prakash et al. 2017).

Currently, there is no evidence on which CRC screening policy is most effective in early detection of CRC cases at the population level (Prakash et al. 2017; Stracci et al. 2014). A review of the current literature on CRC screening shows that clinicians need more guidance to choose the best screening policy for their patients based on the patient's different risk factors such as age, sex, and health condition. This is also manifested as a result of the differences in CRC screening tests and thereby different utility levels of these tests for patients with different risk factors. Multi-modal screening policies can benefit patients by providing more diverse screening options with different sensitivity and specificity based on the patient's risk. For example, a screening strategy which recommends stool-based tests at younger ages and colonoscopy at older ages can be a potential improvement for a low-risk patient compared to only colonoscopy screening policy since the stool-based tests are less aggressive (Dinh et al. 2013). Table 1-1 presents the in-practice CRC screening guidelines recommended by different health agencies in the US. It includes the most recent in-practice screening policies provided by

the United States Preventive Service Task Force (USPSTF), the US Multi-Society Task Force (USMSTF), and the American Cancer Society (ACS). All three agencies recommend patients start screening at age 50. None of the three health agencies recommend individuals older than 75 to undergo any screening unless under special circumstances. Among the nine policies listed in Table 1-1, only one policy recommended by the USPSTF is a multi-modal policy recommending a mixture of screening tests.

Table 1-1: In-practice screening policies recommended by different health agencies.

Agency	Age	Recommended Test	Frequency
USPSTF	50-75	FOBT Colonoscopy FS-FOBT	Annually Every 10 years FS every 5 years along with FOBT every 3 years
	76-85	The USPSTF recommends against routine screening for colorectal cancer in adults 76 to 85 years of age. There may be considerations that support colorectal cancer screening in an individual patient.	NA
	85+	The USPSTF recommends against screening for colorectal cancer in adults older than age 85 years.	NA
ACS	50-75	FIT FOBT Multi-target stool DNA test Colonoscopy CT Colonography FS	Annually Annually Every 3 years Every 10 years Every 5 years Every 5 years
	76-85	The ACS recommends that clinicians individualize CRC screening decisions for individuals based on patient preferences, life expectancy, health status, and prior screening history	NA
	85+	The ACS recommends that clinicians discourage individuals over age 85 from continuing CRC screening	NA
USMSTF	50-75	Colonoscopy FIT CT Colonography FIT-fecal DNA test FS Capsule colonoscopy	Every 10 years Annually Every 5 years Every 3 years Every 5 years Every 5 years

1.1 Active Learning as a Simulation Calibration Tool

Simulation models must be adequately calibrated to ensure a valid representation of the actual system. A review of the literature shows that more than 85% of the cancer simulation models used a calibration method to adjust their output (Stout et al. 2009). Trial and error, random sampling, and grid search are some of the popular approaches used (Stout et al. 2009). Although these methods work for simple simulation models, they are not efficient enough or even practical for more complex models with a large parameter set. Grid search and random search, specifically, conduct an extensive search in the parameters solution space. This makes these methods very intriguing for smaller simulation models, but very time-consuming and sometimes impractical for more complex simulation models. The extensive search of the parameter combinations can be avoided by identifying smaller neighborhoods which are more likely to contain the "optimum" combinations. Hence, machine learning methods such as decision tree algorithms or regression models can be used to search the parameter set more efficiently (Cevik et al. 2016). Active learning (also known as query learning) is considered as a sub-field of machine learning and, more generally, artificial intelligence. As it is shown in Figure 1-1, the key concept of active learning is that the learning algorithm is able to interactively query the user (or some other information source) to obtain the desired outputs at new data points. This results in an improved performance with less training (Russell and Norvig 2016). Supervised learning is the machine learning task of learning a function that maps an input to an output based on sample input-output pairs (Russell and Norvig 2016). Each example is a pair consisting of an input object (typically a vector) and the desired output value. A supervised learning algorithm analyzes the training data

and produces a function, which can be used for mapping new examples. An optimal scenario will allow for the algorithm to correctly determine the class labels for unseen instances. This requires the learning algorithm to generalize from the training data to unseen situations in a reasonable way (Mohri et al. 2012). For any supervised learning system to perform well, it must often be trained on a large set of labeled instances. Sometimes these labels come at little or no cost, but for many other sophisticated supervised learning tasks, labeled instances are very difficult, time-consuming, or expensive to obtain. Therefore, the ability to learn with less data is considered a desirable property for learning algorithms (Settles 2012). Active learning algorithms enable the calibration models to efficiently choose a better combination of parameters to guide the model outputs to the output measure targets in clinical reports. The idea of the use of active learning in simulation calibration process was first introduced by Cevik et al. (2016). In that study authors used active learning to calibrate a breast cancer simulation model developed at the University of Wisconsin. A small set of evaluated parameters are labeled with a scoring approach to train an artificial neural network as a prediction model. The prediction model is used to constrain parameter combinations to a smaller neighborhood where parameters are more likely to produce the desired output.

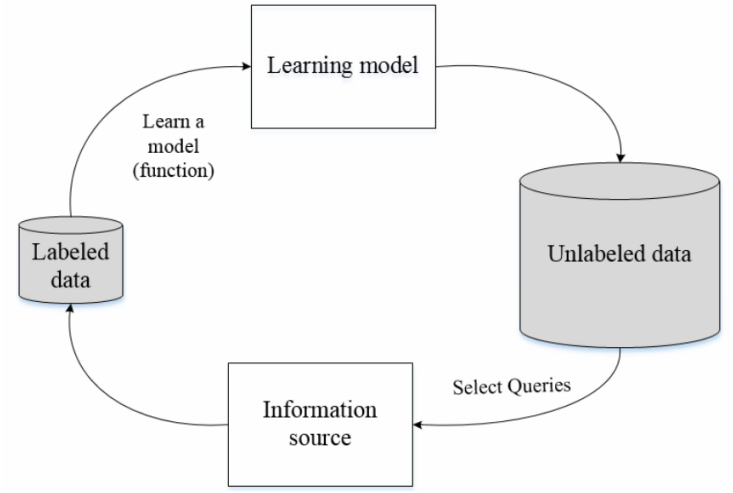

Figure 1-1: Learning cycle of a schematic supervised active learning model (City University of Hong Kong 2018).

In this study, we investigate the cost-effectiveness of a wide range of multi-modal CRC screening policies. Moreover, we conduct a comprehensive evaluation of in-practice policies listed in Table 1-1. The alternative policies are compared with the in-practice policies. To the best of our knowledge, current studies on CRC screening policy cost-effectiveness analysis are limited in the extent of the details in capturing the disease dynamics in pre-cancerous stages. In this study, age-specific and stage-specific pre-cancerous progression and regression rates are estimated using an innovative active learning approach. More specifically, the main contributions of this study are as follows. 1) We developed a detailed CRC natural history model which captures the dynamics of pre-cancerous states as well as the cancer states. The proposed model incorporates three different adenomatous polyps' sizes and the possibility of adenomas' regression. The proposed detailed model enables us to study the disease dynamics and the impact of possible intervention more precisely. 2) We estimated the parameters of the detailed proposed natural history model using innovative active learning methods. Currently, there

is no detailed data available to estimate age and stage specific transition rates in the pre-cancerous states. As a result, the existing models use simplified models in characterizing the CRC natural history which may introduce some bias in the corresponding analysis. In this study, using active learning, specifically decision trees, we devise a more efficient and faster calibration process to estimate the detailed natural history model parameters. 3) We investigated the cost-effectiveness of a variety of CRC screening policies. Screening policies are generated based on different screening tests' features and the disease dynamics in the average-risk population. Policies are designed as a combination of stool-based and visual screening tests to take advantage of both types of tests.

This thesis is structured as follows. In CHAPTER 2 we present a review of the literature on the effectiveness and cost-effectiveness analysis of CRC screening strategies. In CHAPTER 3, the proposed CRC natural history and intervention simulation models are presented. The proposed method for simulation calibration is also presented in this section. Parameters estimation details are discussed in CHAPTER 4. Numerical results are presented in CHAPTER 5 followed by the conclusion presented in CHAPTER 6.

CHAPTER 2

LITERATURE REVIEW

A review of the studies on the effectiveness/cost-effectiveness of CRC screening policies is given by Lansdorp-Vogelaar et al. (2011), Patel and Kilgore (2015), and Pignone et al. (2002). Table 2-1 lists studies that are most relevant to ours and their models' specifications. Currently, most of the recommended screening guidelines, suggested by recent studies and in-practice screening policies, are uni-modal (Dinh et al. 2013; Sharaf and Ladabaum 2013). A partially observed Markov chain (POMC) model is developed by Li et al. (2014) to evaluate the cost-effectiveness of colonoscopy and determine the effect of the length of the intervals between colonoscopy tests. They developed a natural history model which includes three pre-cancerous states (small, medium, and large adenomas). Cancer states are categorized into localized, regional, and distant cancers. All three cancerous states are divided into clinical and preclinical states. However, adenoma regression is not included in the proposed model. Data are taken from literature and the model is calibrated against clinical data of a specific group of patients. Their results show that colonoscopy intervals have a significant impact on the cost-effectiveness of the screening policies. Vijan et al. (2007) has also developed a Markov model to evaluate the performance of three uni-modal screening policies: CT colonography every 5 years, CT colonography every 10 years and colonoscopy every 10 years. Cancer states are similar to the model presented by Li et al. (2014); however, this

model divides the pre-cancerous states based on the risk of becoming cancer into low-risk polyps and high-risk polyps. Transition rates from high-risk adenoma to cancer are assumed to be 100%. No calibration method is used and the possibility of adenomatous polyps' regression and symptomatic cancers are not considered in the proposed model. Screening policies are compared based on diagnostic accuracy in detecting polyps and cancer tissues. They found that CT colonography every 5 or 10 years is cost-effective compared to no-screening policy. However, colonoscopy every 10 years between the age of 50 and 80 is still the most cost-effective policy. Pil et al. (2016) developed a Markov model to analyze the cost-effectiveness of biennial FOBT for both men and women aged 56 to 74. Incremental cost-effectiveness ratio (ICER), when compared with no-screening policy, is used to evaluate the policy. They adopted the tumor, node, and metastasis (TNM) tumor classification system for CRC modeling. TNM is a CRC stage classification system presented by the American Joint Committee on Cancer (AJCC). Adenomatous polyps in the proposed model are assumed to be low-risk or high-risk. Results show that for the tested policies, the probability of being cost-effective is 100% for men and 97% for women. This study does not incorporate the possibility of adenoma regression and symptomatic cancer in the CRC modeling. Van Rossum et al. (2011) developed a Markov model to evaluate the cost-effectiveness of one round of FOBT compared to one round of FIT for patients aged between 50 and 75. Similar to Pil et al. (2016), they adopted the TNM classification system for cancer states modeling and assumed that there is only one pre-cancerous state as advanced adenoma. No calibration method is discussed in Pil et al. (2016) and Van Rossum et al. (2011). However, they performed sensitivity analysis to assess the outputs' sensitivity to changes in the value of

the parameters with a high level of uncertainty. The result shows that among the tested policies, FIT outperforms FOBT while both policies are shown to be cost-effective versus no-screening. Lee and Park (2016) developed a Markov model to evaluate the cost-effectiveness of annual FOBT and its effect on health disparity compared to no-screening policy. They used a very simplified natural history model including only three states: polyp, early cancer, and advanced cancer. The proposed model used in this study does not incorporate the effect of symptomatic cancer in the natural history, and there is no calibration process to reduce the error of the Markov model against epidemiological reports. The Atkinson ICERs (ICER adjusted by the Atkinson Inequality Index (Atkinson 1970)) are calculated based on the gained QALYs, total screening, and treatment costs to evaluate the screening policies. Hypothetical participants are tested via different policies between age 50 and 80. Results show that the annual FOBT between 50 and 80 is cost-effective and has a higher health disparity compared to no-screening. Prakash et al. (2017) developed a micro-simulation model based on Colon Modeling Open Source Tool (CMOST) to calculate the optimal timing of colonoscopy tests. The proposed micro-simulation model calculates the impact of different screening policies and their incorporated costs. CMOST models the natural history of CRC providing automated calibration of model parameters to meet the epidemiological benchmarks. Their proposed natural history model is limited as it includes only early adenomas, advanced adenomas, cancer, and direct cancer. A greedy search algorithm is used to calibrate this model. They have shown that CRC incidence and mortality rates are reduced most efficiently by colonoscopy between ages 56 and 59 while colonoscopy at 59 is the most cost-effective screening policy.

There are a few studies evaluating CRC screening policies with a combination of CRC screening tests (Byers et al. 1997; Eisen et al. 2000; Lieberman et al. 2001; Rex et al. 2000; Winawer et al. 1997). Telford et al. (2010) developed a probabilistic Markov model to estimate the cost-effectiveness of CRC screening policies and to derive the optimal screening policy among all available policies. Low-risk polyp and advanced adenoma are the two pre-cancer states in their proposed model. The proposed model includes localized cancer, regional cancer, and distant cancer which are also divided into clinical and preclinical cancers. The model does not include possible adenomatous polyps' regression. No calibration process is described as being used in this study. Ten different screening policies are examined using the data from the literature. They concluded that all of the ten screening policies are cost-effective. Colonoscopy every 10 years between 50 and 75 is introduced as the most effective policy as a result of significant reduction in CRC incidence and mortality rates. However, annual FIT between 50 and 75 is determined as the most cost-effective policy. Frazier (2000) developed a model similar to Telford et al.'s (2010) model to assess the cost-effectiveness of CRC screening policies in average-risk patients. Pre-cancerous adenomas are divided into two levels based on their risk of becoming cancer, low-risk adenoma, and high-risk adenoma, and the model is calibrated based on logistic regression methods. Distal and proximal parts of the colon are considered separately in this model in order to evaluate the performance of the FS more accurately. Follow-up colonoscopy is modeled as well for the patient diagnosed with high-risk polyps and positive FS. The comparison is done based on ICER, discounted lifetime costs and life expectancy. Annual FOBT from age 50 to 85 in conjunction with FS every 5 years is shown to be the most cost-effective policy

in this study. Sharaf and Ladabaum (2013) used a similar Markov model to explore the comparative effectiveness and cost-effectiveness of colonoscopy against FS and other CRC screening tests. The natural history model categorizes adenomas into small and large adenomas. The model is calibrated and related outputs are validated against several trials and studies such as the Minnesota Colon Cancer Control Study and UK Flexible Sigmoidoscopy Trial. Calibration methods are not discussed in the published article. Symptomatic cancer is included in this model; however, the study lacks modeling adenoma regression possibility. Results show higher adherence on FIT tests and colonoscopy is shown to be cost-effective versus FS. They concluded that the cost-effectiveness of colonoscopy versus FS and FIT is dependent on the adherence rate associated with colonoscopy. Dinh et al. (2013) developed a simulation model to evaluate the cost-effectiveness of multi-modal CRC screening scenarios. The developed model, called Archimedes, is a large-scale simulation of human physiology, diseases, interventions, and health care systems. The model has separated the natural history into three major steps: adenoma development, tumor growth, and cancer symptoms. The CRC sub-model of the Archimedes was developed in collaboration with the ACS using published epidemiological studies and clinical trials data. The sub model is calibrated against several reports including the SEER report although authors have not discussed their calibration method in the published article. Annual or biennial FIT between 50 and 65 with one time colonoscopy at 66 shown to be cost-effective and comparable with cost-effective uni-modal policies with favorable impact on resources demands.

The studies listed above fall short in the level of the details they incorporate in modeling adenomatous polyps (pre-cancerous states) due to lack of available data.

Moreover, some of the available models (Lee and Park 2016; Van Rossum et al. 2011) have not simulated multiple adenomatous polyps growths. Natural history model validation is another restriction for different studies (Pil et al. 2016; Telford et al. 2010; Van Rossum et al. 2011; Vijan et al. 2001).

Table 2-1: Specifications of the similar studies published in the literature.

Study	Model	Hybrid scenarios	Age range for screening	Calibration method.	Adenoma stages	Cancer stages	Adenoma regression	Symptomatic cancer	Source CRC natural history relate data	Best result/final conclusion
Telford et al. 2010	Markov	Yes	50-75	N/A	Low risk polyp Advanced adenoma	Localized, regional, distant (Preclinical and clinical)	No	No	Literature SEER	50-75 Colonoscopy every 10 years
Frazier 2000	Markov	Yes	50+	Logistic regression analysis.	Low risk polyp High risk polyp	Localized, regional, distant	No	Yes	Literature SEER	50-85 Annual FOBT, FS every 5 years
Sharaf and Ladabaum 2013	Markov	Yes	50-80	Methods is not discussed	Small Polyp Large Polyp	Localized, regional, distant	No	Yes	Literature SEER MEDLINE	Cost-effectiveness is depended on the adherence rate
Dinh et al. 2013	Archimedes	Yes	50-75	Methods is not discussed	Benign polyp Adenomatous polyp	Cancer lesion	No	Yes	MEDLINE, Cochrane Database of Systematic Reviews, Web of Science, PubMed	50-65 Annual or biennial FIT, colonoscopy at 66
Li et al. 2014	Markov	No	50-80	Methods is not discussed	Small, medium, large	Localized, regional, distant (Preclinical and clinical)	No	Yes	Clinical data Literature	Colonoscopy interval affects cost-effectiveness
Vijan et al. 2007	Markov	No	50-80	N/A	Low risk polyp High risk polyp	Localized, regional, distant (Preclinical and clinical)	No	No	Literature SEER	50-80 colonoscopy every 10 years
Pil et al. 2016	Markov	No	50+	N/A	Low-risk polyp High-risk polyp	TNM CRC stage classification	No	No	Clinical data Literature	Policies are 100 % cost-effective for males and 97% for women
Van Rossum et al. 2011	Markov	No	50-75	N/A	Advanced adenoma	TNM CRC stage classification	No	Yes	Clinical data	One time FIT between 50 and 75
Lee and Park 2016	Markov	No	50-80	Not mentioned N/A	Polyp	Early cancer Cancer Advanced cancer	No	Yes	Literature	50-80 Annual FOBT
Prakash et al. 2017	CMOST	No	NA	Greedy search algorithm	Early adenoma Advanced adenoma	Cancer, direct cancer	Yes	Yes	Literature SEER MEDLINE	One time colonoscopy between 56 and 59

CHAPTER 3

METHODOLOGY

In this section, the proposed natural history and simulation model modules are presented. A detailed Markov framework is developed to model CRC dynamics. The details of the proposed Markov model are presented in Section 3.1. Simulation models characterizing CRC dynamics and possible preventive interventions through CRC screening tests are presented in Sections 3.2 and 3.3, respectively. The detail of the calibration process for estimating the age-specific and size-specific transition probabilities of the Markov model is provided in Section 3.4.

3.1 CRC Natural History Model

A Markov chain framework is used to model the CRC natural history. The proposed Markov framework is shown in Figure 3-1. The state space of the proposed Markov model is $\Gamma = \{0, 1, 2, \dots, 6\}$, where state 0 represents no adenoma. Similar to MISCAN-Colon model (Loeve 2000), states 1 through 3 represent a diminutive adenoma ($\leq 5\ mm$), a medium adenoma ($6 - 9\ mm$) and a large adenoma ($\geq 10\ mm$), respectively. States 4 through 6 represents localized, regional, and distant stage cancers, respectively. The localized stage represents the stage where the cancer tissue is still confined to the primary site. The regional stage represents the stage at which cancer has spread to regional lymph nodes. The last stage is the distant stage where the cancer tissue has metastasized to the other parts. Based on the TNM classification of malignant tumors

system, we assume that localized, regional and distant stages refer to stage I, both stage II and III, and stage IV, respectively (National Cancer Institute). The transition probability from state i to state j for age group t is denoted by p_{ij}^{t}. The transition periods are assumed to be one year. Based on a previous study (Rex et al. 1997), and as reflected in the Markov model, an adenomatous polyp can grow or regress spontaneously. However, once an adenomatous polyp grows to become cancer, the probability of cancer regression without a treatment involvement is negligible. For simplification, we assume these rates are zero. The probability of more than one transition from a given state in one year (e.g., the growth of a localized cancer from no adenoma state) is considered to be zero due to the negligibility of these rates (Sharaf and Ladabaum 2013).

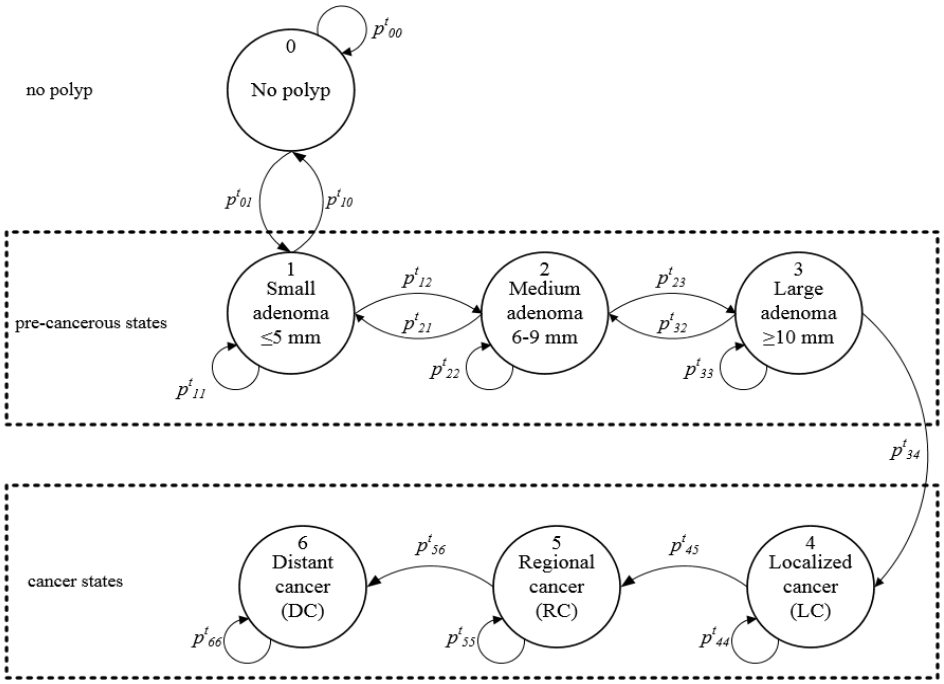

Figure 3-1: Proposed Markov model representing dynamics of adenomatous polyps.

We refer to a patient status by a vector of length six, that is ($N_s,\ N_m,\ N_l,\ N_{LC},\ N_{RC},\ N_{DC}$), where N_s, N_m, and N_l represent the number of small, medium, and large

adenomatous polyps, respectively, and N_{LC}, N_{RC}, and N_{DC} represent the number of localized cancer (LC), regional cancer (RC), and distant cancer (DC) tissues, respectively. For instance, a patient with two small and a large adenomatous polyps and a regional cancer tissue is represented by (2, 0, 1, 0, 1, 0). Previous studies have shown that the probability of having more than six adenomas/cancer tissues in an individual is negligible (Sherer et al. 2013). Therefore, we assume that the maximum number of adenomatous polyps/cancer tissues in our model is limited to six (i.e., $(N_s + N_m + N_l + N_{LC} + N_{RC} + N_{DC}) \leq 6$).

3.2 CRC Natural History Simulation Model

Figure 3-2 presents a one-year dynamics of the proposed CRC natural history simulation model. Simulation of each patient starts at birth (age zero) and the patient is followed until he is terminated from the model either due to CRC related death or a competing cause of death. Age 100 is considered the simulation terminating age, consistent with the maximum life expectancy in the U.S. life table (Arias et al. 2017). Note that the maximum number of adenomatous polyps is assumed to be six. Each individual adenomatous polyp and cancer tissue dynamics (incidence, progression, and regression) are simulated according to the natural history model presented in Figure 3-1. At the beginning of each year, the possibility of adding adenomatous polyp(s) is evaluated based on adenomatous polyps' incidence rates and the number of existing adenomatous polyps. Existing adenomas may progress or regress during the year as captured by the natural history model. We assume that the patient status (number and type of adenomas/ cancerous tissues) is updated at the beginning of each year and remains the same during the year.

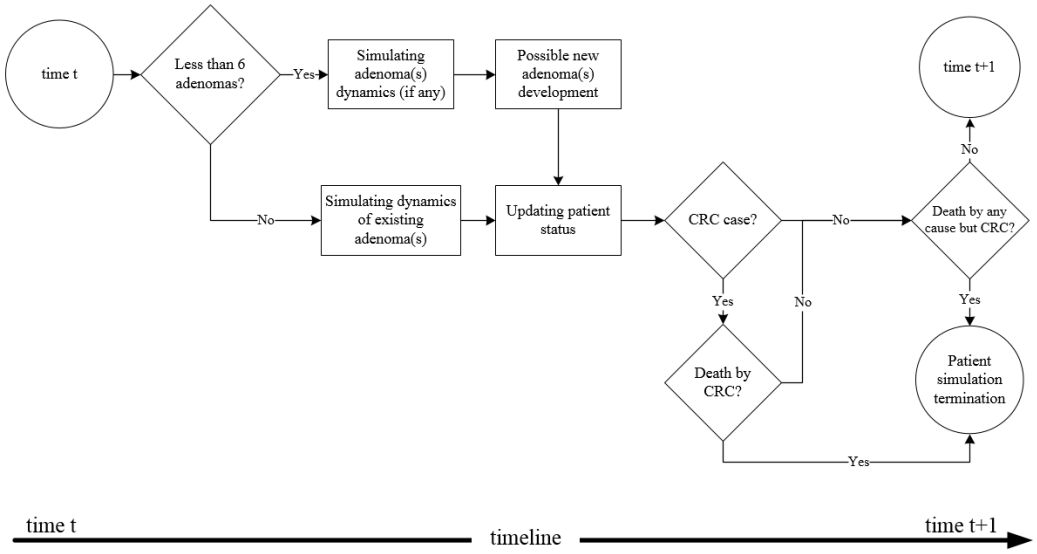

Figure 3-2: CRC natural history simulation framework

3.3 Screening Module Simulation

Figure 3-3 and Figure 3-4 show the screening and cancer detection simulation modules for stool-based and visual CRC screening tests, respectively. As discussed in Section 3.1, at the beginning of each year the patient status is updated using the natural history model. If a screening test is prescribed in a year, the patient undergoes the screening test (perfect adherence to the prescribed test). During each year, if CRC is present in the patient's body, it may either become symptomatic or be detected through screening tests. We assume that any positive result from a stool-based test is followed up by a colonoscopy (Figure 3-4) and a biopsy test is performed after receiving a positive result on an endoscopic-based test (Figure 3-3). A biopsy may be performed during a colonoscopy or any other endoscopic procedures where a gastroenterologist is able to retrieve a sample from colon or rectum (Cancer Treatment Centers of America 2015). Due to the high sensitivity of biopsy test for cancer in this study, we assume that biopsy is a perfect test and reveals the true health status of the patient (Petrelli et al. 1999). It is

assumed that there is a disutility associated with each test depending on the aggressiveness of the test. Patients may receive false positive or false negative results depending on the sensitivity and specificity of the prescribed screening test. We assume that there is a disutility associated with receiving a false positive result. If not detected through screening, the cancer may develop symptoms. Symptomatic cancers are modeled using CRC mean sojourn time concept. Cancer sojourn time is defined as the time between the onset of preclinical cancer and the point at which cancer becomes symptomatic (Zheng and Rutter 2012). Cancer sojourn times are randomly generated according to the available distributions at the time of cancer onset. If a CRC case remains undetected, either due to false negative results or as a result of no scheduled screening test in the period between the cancer onset and the time that the cancer becomes symptomatic, cancer will show symptoms at the simulated scheduled time. The proposed simulation model does not incorporate the post-diagnosis procedures (cancer treatment and surveillance). Instead, we assume that upon cancer detection, the remaining stage-specific life expectancy and expected treatment and surveillance costs are accumulated and the patient's simulation is terminated.

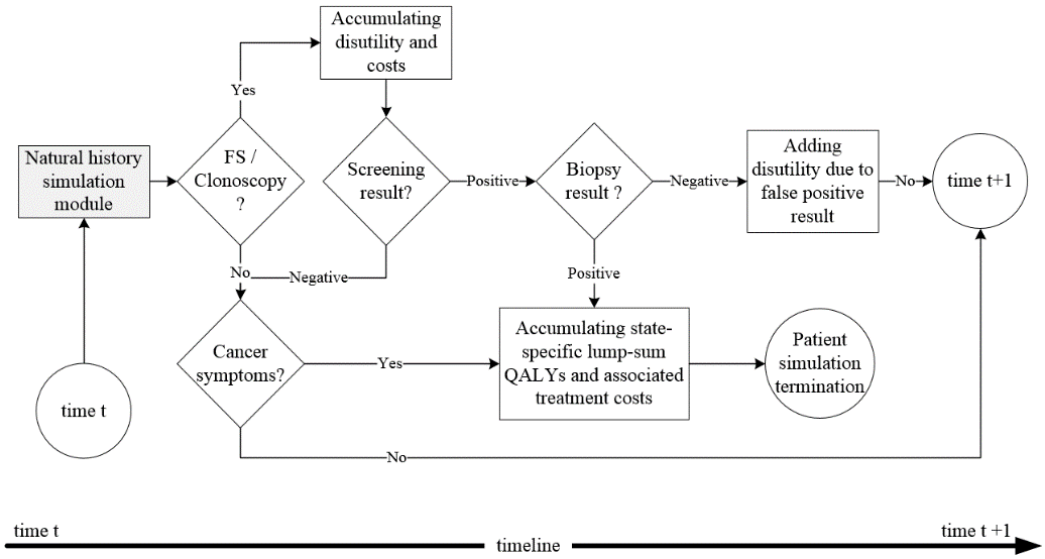

Figure 3-3: Endoscopic-based CRC screening module of the simulation model.

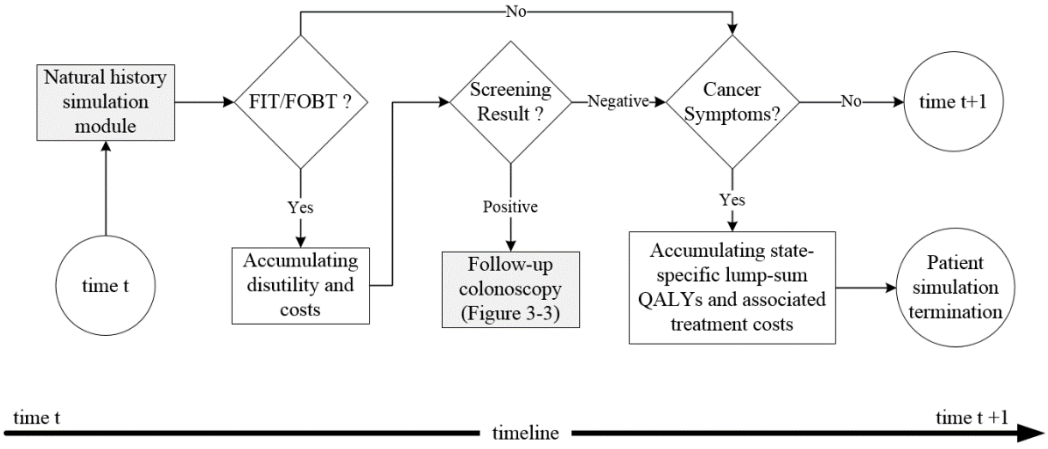

Figure 3-4: Stool-based CRC screening module of the simulation model.

3.4 Model Calibration Process

The dynamics of adenomatous polyps (colonic polyps in general) is not well-studied. In this study, we calibrate the parameters of the proposed simulation model (representing a detailed dynamics of pre-cancerous (adenomatous polyps) and post cancerous states) using age-specific CRC incidence rates and CRC stage distribution reported by the SEER as output measures. The proposed model transition rates are age-

specific to account for the impact of age as a significant CRC risk factor. SEER report (Howlader et al. 2016) includes the number CRC incidences per 100,000 individuals for 18 different age-groups, including 17 age-groups in 5-year increments for patients younger than 85 and an age-group of patients older than 85.

In this study, a combination of random search and machine learning approaches are used for the simulation model calibration. Figure 3-5 shows the proposed calibration process. Note that the proposed model parameters are age-specific and are estimated in five year increments. The calibration process consists of two main phases. In the first phase, a random search method is used to find neighborhoods yielding acceptable errors below predefined thresholds. In the second phase, machine learning classification methods are applied to search the parameter set space to expedite the calibration process.

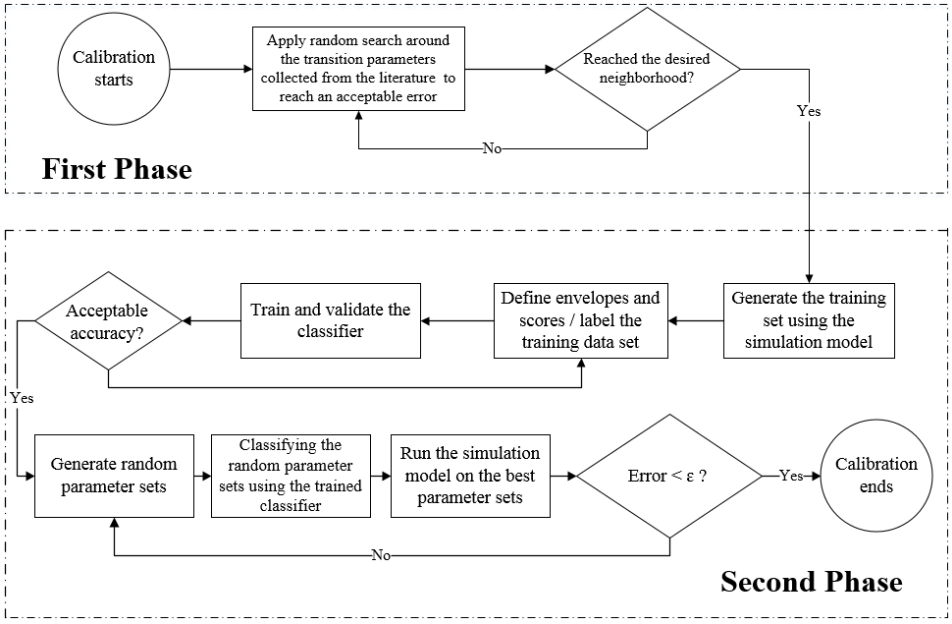

Figure 3-5: An overview of the calibration process.

For the first output measure, CRC age-specific incidence rates, the weighted sum of relative errors of the estimated measures is used to evaluate the goodness of fit of an

estimation. Let i_t and $\widehat{i_t}$ represent the observed and estimated CRC incidence rates of age-group t ($t = 1, \dots, T$), respectively. The goodness of fit value for the first output measure is

$$E_1 = \sum_{t=1}^{T} w_t \cdot \left| \frac{i_t - \widehat{i_t}}{i_t} \right| \qquad \textbf{Eq. 3-1}$$

where w_t is the weight associated with the t^{th} age group. The necessity of using weights is discussed in Section 3.4.1.

For the second output measure, CRC stage distribution, the minimum of the sum of absolute errors (SAE) as presented in **Eq. 3-2** is used to select best parameter sets.

$$E_2 = \sum_{\omega \in \Omega} \left| d_\omega - \widehat{d_\omega} \right| \qquad \textbf{Eq. 3-2}$$

where $\omega \in \Omega = \{LC, RC, DC\}$ denotes different CRC stages, and d_ω and $\widehat{d_\omega}$ represent the observed and estimated ratio of CRC cases in stage ω, respectively.

3.4.1 Characterization of the Training Data

In the calibration process, the training data includes sets of Markov model transition probabilities (to be estimated) as inputs and a set of classes each representing a level of deviation from the SEER reported measures as the output. As the two output measures (incidence rates and CRC stage distribution) are continuous variables, we discretized (labeled) the outputs into different classes in order to apply classification machine learning methods. The discretization process occurs through defining envelopes and scores for the continued outputs based on the deviation from the observed measures reported by the SEER. An envelope is an interval or a set of two intervals defined around an observed output measure and represents a level of deviation from the observed measure. Let $E_{k,t}^{l}, k = 1, \dots, N$ denote the k^{th} envelope defined around the observed

incidence rate for age-group t, and $\sigma_{1,k} \in (0,1)$ denote a predefined threshold controlling the tolerance of deviation from the observed incidence rate in the k^{th} envelope. The last (N^{th}) envelope models an infinite error theoretically. Let s_k be the score assigned to the k^{th} envelope representing how close the estimated rates are from the observed rates. Table 3-1 represents a SEER incidence rate, hypothetical envelopes surrounding the rate, and the associated scores.

Table 3-1: Schematic envelopes formed around an incidence rate and their associated scores.

Tolerance	**Envelope**	**Score**
$\boldsymbol{\sigma_{1,1}}$	$(i_t - (\sigma_{1,1}.i_t)\ ,\ i_t + (\sigma_{1,1}.i_t))$	s_1
$\boldsymbol{\sigma_{1,2}}$	$(i_t - (\sigma_{1,2}.i_t)\ ,\ i_t - (\sigma_{1,1}.i_t)]$ & $[i_t + (\sigma_{1,1}.i_t)\ ,\ i_t + (\sigma_{1,2}.i_t)$	s_2
…	…	…
$\boldsymbol{\sigma_{1,k}}$	$(i_t - (\sigma_{1,j}.i_t)\ ,\ i_t - (\sigma_{1,j}.i_t)]$ & $[i_t + (\sigma_{1,j}.i_t)\ ,\ i_t + (\sigma_{1,j}.i_t)$	s_k
…	…	…
-	$(-\infty,\ i_t - (\sigma_{1,N-1}.i_t)]$ & $[i_t + (\sigma_{1,N-1}.i_t)\ , +\infty)$	s_N

Let S_1 denote the final score associated with the estimated incidence rates ($\widehat{i_t}, \dots, \widehat{i_T}$) obtained from the simulation model. The final score of a parameter set is calculated as the weighted sum (over all the age-groups) of scores of the envelopes which include the estimated incidence rates. Eq. 3-3 calculates the final score of a parameter set based on the estimated incidence rates. Note that a larger score implies a larger error and the goal is to minimize the overall score. Therefore, lower scores must be assigned to the envelopes with smaller tolerance.

$$S_1 = \sum_{t=1}^{T} \sum_{k=1}^{N} \delta_{kt}.s_k.w_t, \qquad \textbf{Eq. 3-3}$$

where δ_{kt} is the Kronecker delta function and is defined in Eq. 3-4, s_k the score associated with the k^{th} envelope, and $w_t = \frac{i_t}{\sum_{t=1}^{T} i_t}$ is the weight associated with age-group t.

$$\delta_{kt} = \begin{cases} 1, & \text{if } \widehat{i_t} \in E_{kt}^{I} \\ 0, & otherwise. \end{cases} \quad \textbf{Eq. 3-4}$$

The length of an envelope is calculated based on the magnitude of the associated incidence rates of the corresponding age-group. At younger ages, when the incidence rates are lower, the envelopes are smaller. As the patients become older, the envelope sizes increase. Therefore, the k^{th} envelopes at a younger age-group represents a smaller error compared to the counterpart envelope k at older age-group. To account for the different error representation of envelopes at different age-groups, envelope scores are weighted to enforce more weights on the age-groups with wider envelopes.

Similarly, envelopes are developed around the observed CRC stage ratios d_ω with a predefined tolerance $\sigma_{2,k} \in (0,1)$, specifying the envelope's size. Let $E_{k,\omega}^{D}, k = 1, \dots, N$ denote the k^{th} envelope defined around the actual rate d_ω.

The final score associated with the estimated ratios, ($\widehat{d_\omega}$) obtained from the simulation model, is calculated as the summation of the scores of the envelopes which include the estimated cancer stage ratio, as presented in Eq. 3-5.

$$S_2 = \sum_{\omega \in \Omega} \sum_{k=1}^{N} \delta_{k,\omega} . s_k \,, \quad \textbf{Eq. 3-5}$$

where $\delta_{k,\omega}$ is the Kronecker delta function and is defined similar to Eq. 3-4 and it takes value 1 if $\widehat{d_\omega} \in E_{k,\omega}^{D}$, and 0, otherwise.

The final class that a set of parameters belongs to is determined based on the maximum value of S_1 and S_2, i.e., $S_{max} = \max\{S_1, S_2\}$. Note that S_{max} is always between s_1 and s_N. Let $C_k, k = 1, \dots, N-1$, denote the k^{th} class. Class C_k is defined as parameter sets for which $S_{max} \in [s_k, s_{k+1})$, where s_k is the score assigned to the k^{th} envelopes. Using the above process, the simulation data is transformed into labeled data.

A balanced training data set is desirable in machine learning in order to increase the accuracy and precision of machine learning methods (Batista et al. 2004). Balance of a training data set is a function of tolerances and envelope scores since the final score of a parameter set is calculated based on the envelope scores of the age-groups. For example, given that we have four envelopes, desired tolerances and scores divide the training data into three different classes with each class containing approximately 33% of the data.

3.4.2 Decision Tree Model

A Decision Tree (DT) is an inductive learning algorithm consisting of several recursive decision rules, arranged hierarchically similar to the structure of a tree (Pradhan 2013). The algorithm is based on the "divide and conquer" strategy and generates a classification tree using the training data/samples. The tree includes internal nodes (D_2 and D_2 in Figure 3-6) and external ($C_1, \dots, C_6$ in Figure 3-6) nodes. At each internal node, a test is applied to one or more attribute values to decide which node to visit next. An external node, also known as a terminal node, characterizes the output class. DT are recommended to extract unknown patterns from large data-sets with distinction purposes.

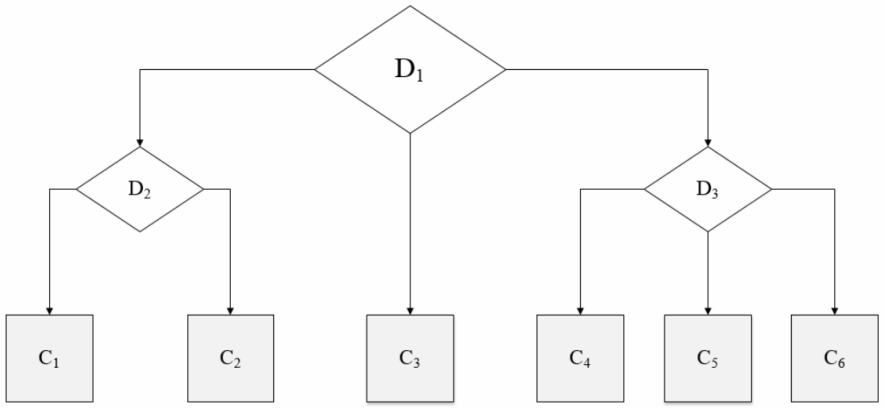

Figure 3-6: A schematic decision tree.

In order to train the DT, a training data set is first generated using the simulation model. Generated data are labeled using the approach described in Section 3.4.1. The DT is then trained and validated using the labeled data set. If the trained DT does not meet the acceptable level of accuracy, a new set of envelopes and scores will be generated. This process is iterated until an acceptable level of accuracy is reached. After the DT is trained, random parameter sets are generated to be classified by the trained DT. Note that a random parameter set is a set of transition probabilities (without the output measures). The DT classifies (labels) the randomly generated parameter sets into different classes. Parameter sets that are classified into the best class (with $S_{max} \in [s_1, s_2)$) are then fed into the simulation model to be evaluated. Among the parameter sets examined by the simulation model, the one which gives the smallest errors, calculated using Eq. 3-1 and Eq. 3-2, is selected. If the errors associated with the best data set are less than the acceptable thresholds (ϵ_1 and ϵ_2 respectively), the calibration process is completed. Otherwise, new parameter sets are randomly generated and the process is repeated until an acceptable error level is reached.

In summary, the proposed calibration method expedites the calibration process by exploiting machine learning tools. Specifically, instead of searching the transition probability space through time-consuming simulation model, the DT identifies the neighborhoods that are more likely to have the "optimal" parameter sets at a significantly faster pace. The simulation is then run only on the parameter sets identified as good solutions by the DT. For example, for 1000 parameter sets, the simulation model (simulating 100,000 patients per parameter set) takes over 140 hours. The DT, however, classifies the same number of parameter sets in less than a minute.

CHAPTER 4

MODEL PARAMETER ESTIMATION

The main challenge in the parameter estimation of the proposed model is to estimate the Markov model age-specific transition probability matrices. Particularly, the proposed model is very complex since it incorporates low level details of adenomas dynamics, including regression probabilities. An active learning approach, as discussed in Section 3.4, is used to estimate these parameters. Section 4.1 provides the details of the calibration process results for estimation of age-specific transition probabilities. Please note that the model is calibrated to represent the U.S. male population. Section 4.2 presents the data sources used for estimation of the remaining parameters.

4.1 Calibration Results

Using the normalization constraint in the proposed Markov model, the number of the transition probabilities to be estimated for a given age-group is decreased from 15 to 9. Therefore, given that there are 18 age-groups, the total number of transition probabilities to be estimated is 162.

Using the random search method, at the end of the first phase of the calibration process the minimum error achieved for each output measure is 8%. In the second phase, three thousand random parameter sets in the neighborhoods of the estimated parameters (obtained in the first phase of the calibration process) are generated. The generated

parameter sets are then fed into the simulation model to calculate the output measures of interest. The result of the simulation model is then used to specify the characteristics of the discretization process which includes specifying envelopes and scores and to train the classification tool. Note that too many envelopes, and therefore classes, make the model more complicated and thereby slower. Moreover, note that we are only interested in the class with the smallest error. Therefore, there is no need to make the model more complicated by defining too many envelopes. There is no specific rule on what the numbers of envelopes, tolerance values and score must be. Therefore, using a trial and error approach, different combinations are examined for the model tuning. The results implied that setting the number of envelopes to three does not reach the desired accuracy and the model does not clearly differentiate the classes. Table 4-1 presents the best parameter values found in the calibration process. The score associated with the fourth envelope is considerably larger than that of the other envelopes to ensure that parameters sets with high deviation from the actual output measures in one or more age groups are not classified in the first class (with the lowest overall score).

The classifiers are then trained using 80% of the training data set and validated using the remaining 20% of the data. Three different machine learning methods, namely Multilayer Perceptron (MLP), Naive Bayes (NB) and Decision Tree (DT) are tested. DT model outperformed the other two models in terms of accuracy and precision. We use the Gini Index to evaluate splits in the data set when training the DT. The DT reached an accuracy of 91%.

Table 4-1: List of the tolerances and scores obtained in the model tunning process.

Incidence rate tolerance	Stage distribution tolerance	Score
0.1	0.05	0
0.2	0.1	3
0.4	0.2	6
>0.4	>0.2	200

After the DT is trained and validated, new parameter sets are randomly generated and classified using the trained model. The parameter sets that are classified in the first class with the lowest score then are fed into the simulation model for exact error evaluation. Acceptable error threshold for CRC incidence rates (ϵ_1) and CRC stage distribution (ϵ_2) are set to 5% and 1%, respectively. The error threshold for the CRC incidence rate is selected to be higher since this error measures the deviation from the observed incidence under 18 different age-groups and therefore even a reasonable error in each age-group may add up to a big error. The minimum error for the first output measure (incidence rate) and second output measure (CRC stage distribution) achieved are 3.1% and 0.46%, respectively. Figure 4-1 and Figure 4-2 show the estimated incidence rates and CRC stage distribution, respectively, plotted against the same measures reported by the SEER. The estimated age-specific transition probabilities are presented in Table A-1 and Table A-2 in APPENDIX A.

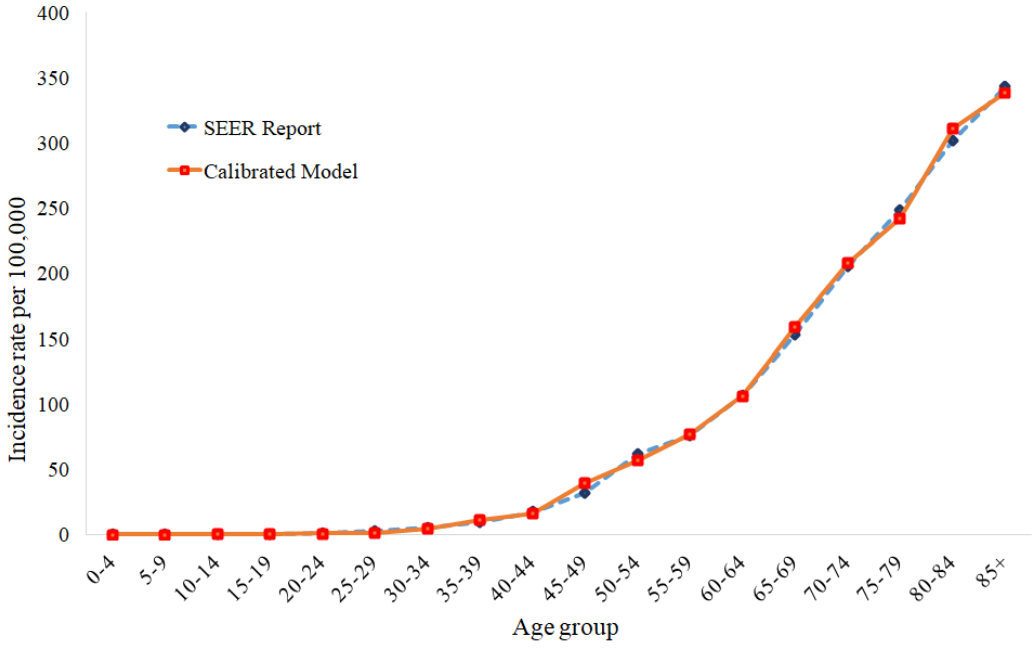

Figure 4-1: Age specific estimated incidence rates using DT (red) and incidence rates reported by SEER (blue).

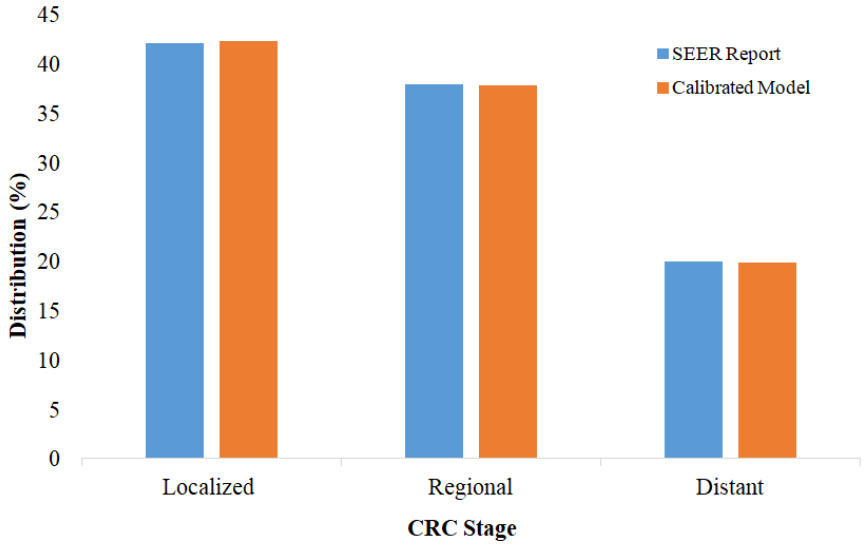

Figure 4-2: CRC stage distribution obtained by the calibration model compared with those reported by SEER.

4.2 Other Parameters

Table A-6 presents the data sources used for parameter estimations. Natural cause and CRC related mortality rates are calculated using SEER cancer statistics review (Howlader et al. 2016) and the US life table (Arias et al. 2017). Age and stage specific life expectancy of CRC patients are estimated using the MD Anderson CRC survival calculator (MD Anderson Cancer Center CRC Survival Calculator 2009). Screening specifications are adopted from recently published literature (Erenay et al. 2014; Knudsen et al. 2016). Screening costs are the source of most of the disparities in cost-effectiveness studies. In order to retrieve the most accurate cost estimates, we adopted the screening and treatment costs from most recent published studies to make sure there are no significant technology changes. In addition, all costs are adjusted to the calendar year 2018 dollars by using the Bureau of Labor Statistics Consumer Price Index (Bureau of Labor Statistics 2018). The CRC sojourn time is assumed to follow an exponential distribution (Loeve 2000) and the mean parameters are adopted from Brenner et al.'s (2011) study.

Table 4-2: Data source and estimated parameters used in the simulation model.

Parameter	Value	Reference
Age-specific precancerous transition probabilities	Table A-1	Sherer et al. 2013
Age-specific post-cancerous transition probabilities	Table A-2	Macafee et al. 2008
Age-specific mortality rates	US. Life Table	Arias et al. 2017
CRC localized stage mortality rates CRC regional stage mortality rates CRC distant stage mortality rates	0.0542 0.1677 0.6469	Macafee et al. 2008
Age-specific quality adjusted life year <= 44 45-54 55-64 65-74 75+	 0.91 year 0.78 year 0.77 year 0.75 year 0.73 year	Fryback and Lawrence 1997
Colonoscopy disutility FS disutility FIT disutility FOBT disutility	11 days 2 days 1 days 1 days	Erenay et al. 2014 Mayo clinic 2018 American Cancer Society 2018 American Cancer Society 2018
Stage-specific CRC life expectancy	Table A-3	MD Anderson Cancer Center CRC Survival Calculator 2009
CRC mean sojourn time	Table A-4	Brenner et al. 2011
Screening tests sensitivities	Table A-5	Knudsen et al. 2016
Colonoscopy specificity FS specificity FIT specificity FOBT specificity	86% 87% 89.8% 92.5%	Knudsen et al. 2016
Colonoscopy cost FS cost FIT cost FOBT cost	$1192.6 $548.47 $24.88 $24.88	Prakash et al. 2017 Sharaf and Ladabaum 2013 Bureau of Labor Statistics 2018
Treatment costs	Table A-6	Joseph 2018

CHAPTER 5

NUMERICAL RESULTS

Different screening policies are implemented to a cohort of one hundred thousand males. Screenings are applied to the cohort of individuals aged from 50 to 75. The screening policies differ in the type of screening tests and screening intervals. A cost-effectiveness analysis on a broad set of uni-modal and multi-modal CRC screening policies is performed. Specifically, we assess 78 different policies including no-screening, five CRC screening policies recommended by different US health agencies, and 72 alternative multi-modal screening policies. The five in-practice screening policies analyzed are Colonoscopy at 50, 60 and 70, annual FIT, annual FOBT, FS every 5 years and FOBT every 3 years in conjunction with FS every 5 years. FIT, FOBT, colonoscopy, and FS are the screening modalities considered in the alternative screening policies. Policies are generated by combining policies recommended by the health agencies and some recent studies. In the evaluated multi-modal policies, patients undergo two different types of tests: a stool-based test and a visual test. Stool-based tests are associated with lower cost and are less aggressive compared to visual tests. Visual tests, on the other hand, are more sensitive and costly. We assume each year at most one screening test is performed on a patient unless the patient receives a positive result and is referred for a biopsy. In a year with a confluence of two different screening tests, only the visual test (FS or colonoscopy) is used. The frequencies of the tests are selected based on the

recommended frequencies by the health agencies and the literature. Stool-based tests are prescribed annually or biennially, and FS and colonoscopy are prescribed at 5-year and 10-year frequencies, respectively. The policies investigated in this study are listed in Table 5-1.

All 78 policies considered in this study are represented in Figure 5-1. The blue points are the “inefficient” or "dominated" policies, or the policies that are each dominated by other screening policy(ies) with a higher QALYs and lower cost. The identified “efficient" or "dominant" and in-practice policies are presented in green and red, respectively. FOBT biennially in conjunction with one time Colonoscopy at 60, FOBT biennially along with one time Colonoscopy at 50, FIT biennially in conjunction with two times FS at 60 and 65, FIT biennially with one time Colonoscopy at 65, Colonoscopy at 50, 60 and 70, FOBT biennially along with two times Colonoscopy at 55 and 65, FOBT annually with 2 times FS at 70 and 75, FOBT annually in conjunction with FS at 50,55 and FIT biennially along with FS every 5 years are the nine identified dominant policies. The structure of the identified dominant policies show that undergoing endoscopic-based tests between age 55 and 65 benefits the patients. In addition, prescribing stool-based tests for the patients biennially is shown to be more cost-effective as suggested by 6 of the identified dominant policies. Prescribing stool-based tests annually seems to unnecessarily increase the expected cost while it does not significantly affect the expected QALYs. As the results show, for each in-practice policy, there is an alternative policy that results in higher QALYs with the same or a lower cost of the in-practice policy. For instance, consider the in-practice policy of FS every 5 years. This policy yields the highest expected QALYs (67.05 years), with an associated expected cost

of $3,762, among the in-practice polices. However, the alternative policy of FOBT annually, in conjunction with FS at 70 and 75 yields both higher expected QALYs (67.06 years) and lower expected cost ($3,684). The results show all the 77 policies evaluated in this study benefit the patients through increased QALYs and decreased CRC mortality compared to no screening policy. In most cases, combining stool-based tests with visual tests will benefit patients with higher life expectancy and lower expected cost. Multi-modal policies are associated with higher reduction rates in CRC incidence and mortality compared with uni-modal scenarios.

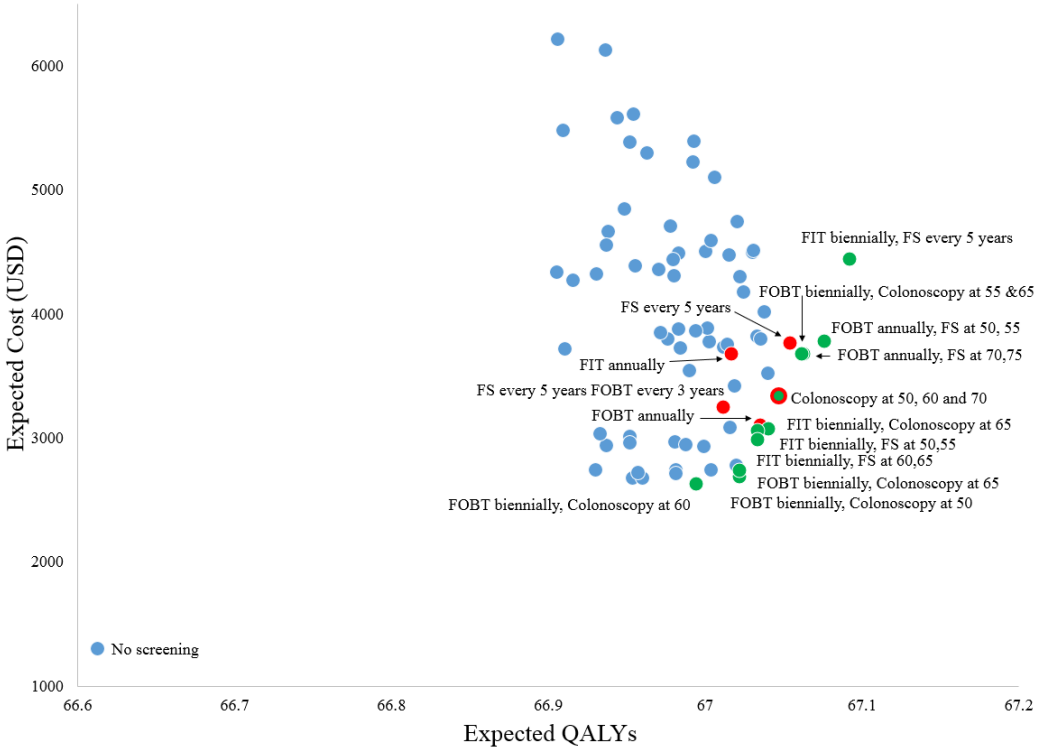

Figure 5-1: Efficient frontier versus the in-practice policies.

In order to evaluate the performance of different CRC screening policies, incremental cost-effectiveness ratio (ICER) is calculated. ICER is calculated as the expected cost difference per expected QALYs difference for every 2 consecutive policies

while all screening policies are sorted in expected QALYs in an increasing order. Let p_i and p_j denote two consecutive policies with associated $QALYs_i$ and $QALYs_j$, respectively and $QALYs_i > QALYs_j$. Eq. 5-1 calculates the ICER value when comparing policies p_i and p_j and represents the ratio of the additional cost that must be paid under policy p_i for one additional unit of QALYs when compared with policy p_j. A negative value for $ICER_{ij}$ represents that policy p_j is dominated by policy p_i since policy p_j is associated with higher expected cost and lower expected QALYs. ICER for dominant screening policies is calculated as the cost difference per QALY gained relative to the nearest efficient frontier policy (Dinh et al. 2013).

$$ICER_{ij} = \frac{Expected\ Cost_i - Expected\ Cost_j}{Expected\ QALY_i - Expected\ QALY_j} \qquad \textbf{Eq. 5-1}$$

Table 5-1: Cost, QALYs, and ICER associated with the investigated policies.

Policy	QALYs	Cost	ICER	Policy	QALYs	Cost	ICER
No screening	66.61	$1,306	NA	FOBT annually, Colonoscopy at 60	66.99	$3,870	Dominated
FIT annually, Colonoscopy at 50, 60, 70	66.91	$6,221	Dominated	FOBT biennially, Colonoscopy at 60	66.99	$2,634	$3,486
FIT annually, FS at 55,60	66.91	$4,342	Dominated	FOBT biennially, Colonoscopy at 65, 75	66.99	$3,546	Dominated
FIT biennially, Colonoscopy at 60, 70	66.91	$3,718	Dominated	FIT annually, Colonoscopy at 60	67.00	$4,505	Dominated
FOBT annually, Colonoscopy at 55, 65, 75	66.91	$5,480	Dominated	FIT biennially, Colonoscopy at 70	67.00	$2,934	Dominated
FIT annually, FS at 70, 75	66.92	$4,273	Dominated	FIT biennially, Colonoscopy at 50, 60, 70	67.00	$4,591	Dominated
FIT annually, FS at 60, 65	66.93	$4,328	Dominated	FOBT annually, FS at 55, 60	67.00	$3,776	Dominated
FIT biennially, Colonoscopy at 75	66.93	$3,034	Dominated	FOBT annually, Colonoscopy at 50	67.00	$3,886	Dominated
FOBT biennially, FS at 55, 60	66.93	$2,748	Dominated	FOBT biennially, Colonoscopy at 55	67.00	$2,744	Dominated
FIT annually, Colonoscopy at 55, 65, 75	66.94	$6,129	Dominated	FOBT every 3 years , FS every 5 years	67.01	$3,245	Dominated
FIT biennially, Colonoscopy at 60	66.94	$2,941	Dominated	FOBT annually, FS at 60, 65	67.01	$3,735	Dominated
FOBT annually, Colonoscopy at 60, 70	66.94	$4,666	Dominated	FOBT annually, FS every 5 years	67.01	$5,101	Dominated
FOBT annually, Colonoscopy at 65, 75	66.94	$4,559	Dominated	FOBT annually, Colonoscopy at 75	67.01	$3,755	Dominated
FOBT annually, Colonoscopy at 50, 60, 70	66.94	$5,582	Dominated	FIT annually	67.02	$3,680	Dominated
FIT annually, Colonoscopy at 55, 65	66.95	$5,391	Dominated	FIT annually, Colonoscopy at 65	67.02	$4,479	Dominated
FIT annually, FS every 5 years	66.95	$5,610	Dominated	FIT biennially, Colonoscopy at 55	67.02	$3,085	Dominated
FIT biennially, Colonoscopy at 55, 65, 75	66.95	$4,852	Dominated	FOBT annually, Colonoscopy at 50, 60	67.02	$4,750	Dominated
FIT biennially, FS at 55, 60	66.95	$3,016	Dominated	FOBT biennially, FS at 50,55	67.02	$2,781	Dominated
FIT biennially, FS at 65, 70	66.95	$2,963	Dominated	FOBT biennially, FS every 5 years	67.02	$4,183	Dominated
FOBT biennially, FS at 70, 75	66.95	$2,682	Dominated	FOBT biennially, Colonoscopy at 50	67.02	$2,692	$2,031

Policy	QALYs	Cost	ICER	Policy	QALYs	Cost	ICER
FIT annually, Colonoscopy at 75	66.96	$4,388	Dominated	FOBT biennially, Colonoscopy at 65	67.02	$2,737	$177,503
FIT annually, Colonoscopy at 60, 70	66.96	$5,304	Dominated	FOBT biennially, Colonoscopy at 60, 70	67.02	$3,424	Dominated
FOBT biennially, Colonoscopy at 70	66.96	$2,682	Dominated	FOBT biennially, Colonoscopy at 50, 60, 70	67.02	$4,306	Dominated
FOBT biennially, Colonoscopy at 75	66.96	$2,724	Dominated	FIT annually, Colonoscopy at 50	67.03	$4,502	Dominated
FIT annually, FS at 50, 55	66.97	$4,364	Dominated	FIT biennially, FS at 50, 55	67.03	$3,064	$332,458
FOBT annually, Colonoscopy at 55	66.97	$3,855	Dominated	FIT biennially, FS at 60, 65	67.03	$2,985	$22,856
FIT annually, Colonoscopy at 55	66.98	$4,492	Dominated	FOBT annually, Colonoscopy at 65	67.03	$3,820	Dominated
FIT annually, Colonoscopy at 70	66.98	$4,441	Dominated	FOBT biennially, Colonoscopy at 55, 65, 75	67.03	$4,517	Dominated
FIT annually, FS at 65, 70	66.98	$4,312	Dominated	FOBT annually	67.04	$3,100	Dominated
FIT biennially, Colonoscopy at 50	66.98	$2,974	Dominated	FIT biennially, Colonoscopy at 65	67.04	$3,070	$834
FIT biennially, Colonoscopy at 50, 60	66.98	$3,803	Dominated	FIT biennially, Colonoscopy at 55, 65	67.04	$4,023	Dominated
FIT biennially, Colonoscopy at 65, 75	66.98	$3,883	Dominated	FOBT annually, Colonoscopy at 70	67.04	$3,804	Dominated
FOBT annually, FS at 65, 70	66.98	$3,726	Dominated	FOBT biennially, Colonoscopy at 50, 60	67.04	$3,528	Dominated
FOBT annually, Colonoscopy at 55, 65	66.98	$4,714	Dominated	Colonoscopy at 50, 60, 70	67.05	$3,341	$44,760
FOBT biennially, FS at 60, 65	66.98	$2,747	Dominated	FS every 5 years	67.05	$3,762	Dominated
FOBT biennially, FS at 65, 70	66.98	$2,718	Dominated	FOBT annually, FS at 70, 75	67.06	$3,684	$4,387
FIT annually, Colonoscopy at 50, 60	66.99	$5,397	Dominated	FOBT biennially, Colonoscopy at 55, 65	67.06	$3,682	$22,824
FIT annually, Colonoscopy at 65, 75	66.99	$5,226	Dominated	FOBT annually, FS at 50, 55	67.08	$3,781	$6,859
FIT biennially, FS at 70, 75	66.99	$2,947	Dominated	FIT biennially, FS every 5 years	67.09	$4,442	$43,183

Table 5-1 presents all the policies investigated in this study with their associated QALYs, cost and ICER. Willingness to pay (WTP) is defined as the maximum price at or below which the patient (consumer) will buy a service (product) (Miller et al. 2011). At $50,000 WTP threshold (Sharaf and Ladabaum 2013), among the 11 dominant policies, 9 policies are cost-effective out of which 8 policies are multi-modal. Multi-modal policies are also associated with lower ICER compared with the identified cost-effective uni-modal policy (Colonoscopy at 50, 60 and 70).

The performance of the in-practice policies and best alternative policies in terms of expected QALYs, incidence reduction, and mortality reduction, when compared with no screening policy are compared in Table 5-2. Among the in-practice policies colonoscopy at 50, 60 and 70 outperforms other policies in terms of expected QALYs (67.05), incidence and mortality reduction (86.5% and 89.4% respectively). Comparing this policy with the alternative policies, FIT biennially in conjunction with FS every 5 years benefits the patients with higher expected QALYs (67.09). FOBT biennially along with three times colonoscopy at 50, 60 and 70 serves the patients with higher incidence reduction (88.6%) and FIT annually, colonoscopy at 55, 65 and 75 benefits patients with higher mortality reduction (93%) compared to the best identified in-practice policy.

Table 5-2: In-practice policies and best identified alternative policies in terms of the expected QALYs, incidence reduction, and mortality reduction - number in parentheses represent confidence intervals (CI).

	Policy	Expected QALYs	Incidence Reduction	Mortality Reduction
In-practice	No screening	66.61 (66.59,66.63)	-	-
	FIT annually	67.02 (67.00,67.04)	69.8%	85.4%
	FOBT annually	67.04 (67.01,67.07)	60.4%	80.1%
	FS every 5 years	67.05 (67.03,67.07)	71.1%	81.1%
	FOBT every 3 years, FS every 5 years	67.01 (66.99,67.03)	62.7%	79.0%
	Colonoscopy at 50, 60 and 70	67.05 (67.02,67.07)	86.5%	89.4%
Alternative	FIT biennially, FS every 5 years	67.09 (67.07,67.11)	75.8%	87.1%
	FOBT biennially, Colonoscopy at 50, 60, 70	67.02 (67.00,67.04)	88.6%	91.9%
	FIT annually, Colonoscopy at 55, 65, 75	66.94 (66.91,66.97)	87.1%	93.0%

CHAPTER 6

CONCLUSION

As implied by multiple health agencies, currently there is no consensus on which CRC screening policy is the most effective. In this study, we adopted a Markov chain framework to model CRC natural history. We used Monte Carlo simulation approach to model the CRC dynamics and quantify the effectiveness of CRC preventive interventions. Using active learning, specifically a decision tree, we devised an innovative calibration process to estimate the parameters of the detailed proposed natural history model, i.e., age-specific and size-specific adenoma progression and regression rates as well as age-specific CRC progression rates. This method calibrates the proposed simulation model through a more efficient and faster process compared to other methods used in the literature such as trial and error, random sampling, and grid search.

A cohort of 100,000 males is simulated under 78 different CRC screening policies using the calibrated model. A cost-effectiveness analysis is performed on different screening policies. Screening policies are compared in terms of the associated expected screening and treatment cost, expected QALYs, and reduction in the CRC incidence and mortality rates. The numerical analysis results show that in most cases, combining stool-based tests with visual tests will benefit patients with higher life expectancy and lower expected cost. Multi-modal policies are associated with higher reduction rates in CRC incidence and mortality compared with uni-modal scenarios. Among the nine identified

dominant policies under $50,000 WTP threshold, eight policies are multi-modal. Multi-modal policies are also associated with lower ICER compared with the identified cost-effective uni-modal policy.

This study has several limitations. First, using multiple data sources for parameter estimation introduces some potential sources of errors. Screening and treatment costs are usually difficult to estimate due to the wide estimation variation in the literature. Second, a discretization approach is taken in this study when calibrating the model through the DT training as DT is a classification approach. The discretization introduces some errors due to classifying different errors in one class. Employing prediction models that can work with continuous variables, and thereby avoiding discretization, would result in eliminating this error in the calibration process. This study is limited to male population and incorporates age as the only CRC risk factor. However, other risk factors such as gender and family history, etc., need to be taken into account for more precise disease modeling. A risk stratification model which takes into account patient-specific risk factors and recommend policies accordingly would be a possible future direction.

APPENDIX A

MODEL PARAMETERS USED IN THE SIMULATION MODEL

Table A-1: Age-specific pre-cancer transition probabilities

Age group	P_{00}	P_{01}	P_{10}	P_{11}	P_{12}	P_{21}	P_{22}	P_{23}	P_{32}	P_{33}	P_{34}
1-4	0.992	0.008	0.008	0.966	0.026	0.013	0.960	0.026	0.005	0.975	0.020
5-9	0.999	0.001	0.004	0.991	0.004	0.008	0.988	0.005	0.003	0.994	0.003
10-14	0.996	0.004	0.005	0.983	0.012	0.008	0.979	0.013	0.003	0.988	0.010
15-19	0.996	0.004	0.003	0.985	0.012	0.006	0.982	0.012	0.002	0.989	0.009
20-24	0.996	0.004	0.004	0.982	0.014	0.007	0.979	0.015	0.002	0.987	0.011
25-29	0.996	0.004	0.004	0.982	0.014	0.007	0.978	0.015	0.003	0.986	0.011
30-34	0.993	0.007	0.005	0.972	0.023	0.008	0.968	0.024	0.003	0.979	0.018
35-39	0.990	0.010	0.006	0.960	0.034	0.010	0.955	0.035	0.004	0.970	0.026
40-44	0.994	0.006	0.006	0.975	0.019	0.011	0.970	0.019	0.004	0.982	0.014
45-49	0.989	0.011	0.009	0.953	0.038	0.016	0.946	0.038	0.006	0.965	0.029
50-54	0.990	0.010	0.011	0.957	0.032	0.018	0.949	0.033	0.007	0.969	0.025
55-59	0.990	0.010	0.009	0.958	0.032	0.016	0.951	0.033	0.006	0.969	0.025
60-64	0.989	0.011	0.009	0.955	0.035	0.016	0.948	0.036	0.006	0.967	0.027
65-69	0.987	0.013	0.012	0.944	0.044	0.020	0.934	0.045	0.008	0.958	0.034
70-74	0.988	0.012	0.010	0.951	0.039	0.018	0.943	0.040	0.007	0.964	0.030
75-79	0.988	0.012	0.011	0.948	0.041	0.018	0.940	0.042	0.007	0.961	0.032
80-84	0.988	0.012	0.011	0.948	0.041	0.019	0.939	0.042	0.007	0.962	0.031
85+	0.990	0.010	0.010	0.957	0.033	0.017	0.950	0.034	0.006	0.968	0.025

Table A-2: Age-specific cancer states transiotion probabilities.

Age group	P_{44}	P_{45}	P_{55}	P_{56}
1-4	0.710	0.290	0.581	0.419
5-9	0.709	0.291	0.580	0.420
10-14	0.701	0.299	0.580	0.420
15-19	0.695	0.305	0.576	0.424
20-24	0.694	0.306	0.576	0.424
25-29	0.694	0.306	0.576	0.424
30-34	0.692	0.308	0.571	0.429
35-39	0.687	0.313	0.568	0.432
40-44	0.686	0.314	0.568	0.432
45-49	0.686	0.314	0.563	0.437
50-54	0.686	0.314	0.545	0.455
55-59	0.686	0.314	0.553	0.447
60-64	0.684	0.316	0.549	0.451
65-69	0.685	0.315	0.548	0.452
70-74	0.685	0.315	0.547	0.453
75-79	0.674	0.326	0.541	0.459
80-84	0.674	0.326	0.539	0.461
85+	0.670	0.330	0.539	0.461

Table A-3: Stage-specific life expectancy of CRC patients.

Age	Localized	Regional	Distant	Age	Localized	Regional	Distant
1	64.76	50.41	5.32	**51**	23.06	17.00	1.97
2	63.95	49.81	5.25	**52**	22.35	16.49	1.66
3	63.10	49.19	5.23	**53**	21.63	15.96	1.52
4	62.31	48.62	5.23	**54**	20.89	15.41	1.40
5	61.49	48.00	5.21	**55**	20.18	14.87	1.36
6	60.66	47.34	5.21	**56**	19.44	14.38	1.10
7	59.85	46.70	5.19	**57**	18.67	13.79	0.73
8	58.99	46.02	5.17	**58**	17.86	13.16	0.71
9	58.08	45.23	5.12	**59**	17.01	12.43	0.65
10	57.12	44.30	4.52	**60**	16.06	11.52	0.63
11	56.32	43.62	4.51	**61**	15.42	11.03	0.60
12	55.51	43.02	4.46	**62**	14.80	10.62	0.58
13	54.66	42.41	4.44	**63**	14.17	10.17	0.56
14	53.87	41.83	4.43	**64**	13.54	9.76	0.55
15	53.06	41.21	4.42	**65**	12.88	9.30	0.54
16	52.23	40.55	4.42	**66**	12.23	8.87	0.54
17	51.42	39.91	4.40	**67**	11.54	8.38	0.52
18	50.56	39.24	4.38	**68**	10.78	7.80	0.51
19	49.66	38.45	4.33	**69**	9.96	7.11	0.50
20	48.69	37.52	3.73	**70**	9.02	6.21	0.50
21	47.91	36.85	3.72	**71**	8.56	5.95	0.47
22	47.12	36.26	3.66	**72**	8.12	5.67	0.36
23	46.28	35.66	3.64	**73**	7.65	5.36	0.34
24	45.49	35.09	3.64	**74**	7.19	5.08	0.28
25	44.69	34.48	3.62	**75**	6.71	4.75	0.26
26	43.87	33.82	3.62	**76**	6.20	4.44	0.25
27	43.06	33.19	3.60	**77**	5.63	4.07	0.25
28	42.21	32.52	3.58	**78**	5.01	3.62	0.24
29	41.31	31.73	3.54	**79**	4.26	3.02	0.23
30	40.34	30.80	2.94	**80**	3.36	2.18	0.22
31	39.57	30.14	2.93	**81**	3.25	2.12	0.21
32	38.78	29.55	2.88	**82**	3.11	2.02	0.19
33	37.94	28.95	2.86	**83**	2.80	1.98	0.13
34	37.16	28.38	2.85	**84**	2.62	1.91	0.13
35	36.36	27.77	2.83	**85**	2.42	1.84	0.08
36	35.54	27.12	2.83	**86**	2.17	1.75	0.06
37	34.74	26.49	2.81	**87**	1.81	1.63	0.06
38	33.89	25.82	2.79	**88**	1.61	1.44	0.05
39	32.99	25.03	2.75	**89**	1.29	1.06	0.04
40	32.02	24.10	2.28	**90**	0.83	0.69	0.04
41	31.26	23.45	2.15	**91**	0.82	0.65	0.04
42	30.48	22.88	2.14	**92**	0.78	0.58	0.04
43	29.66	22.29	2.10	**93**	0.72	0.58	0.03
44	28.90	21.73	2.07	**94**	0.66	0.51	0.02
45	28.11	21.13	2.06	**95**	0.63	0.47	0.02
46	27.30	20.49	2.05	**96**	0.56	0.45	0.01
47	26.51	19.87	2.05	**97**	0.56	0.40	0.01
48	25.66	19.20	2.03	**98**	0.52	0.36	0.01
49	24.77	18.42	2.01	**99**	0.48	0.34	0.01
50	23.81	17.49	2.00	**100**	0.27	0.31	0.01

Table A-4: Age-specific mean sojourn time.

Age	Mean Sojourn Time (years)
1-59	5.5
60-64	5.2
65-69	4.7
70-74	4.9
75-79	5.0
80-100	5.5

Table A-5: Screening sensitivities.

	Colonoscopy	FS	FOBT	FIT
Small adenoma	0.75	0.75	N/A	N/A
Medium adenoma	0.85	0.85	N/A	N/A
Large adenoma	0.95	0.95	N/A	N/A
CRC	0.95	0.95	0.70	0.74

Table A-6: CRC stage-specific treatment costs.

Stage	Initial cost (Year 1)	Surveillance Costs (Years 2-5)
Localized	$20,247	$1,305
Regional	$26,008	$2,345
Distant	$30,085	$15,057

APPENDIX B

PROGRAMMING CODE OF THE MODEL

```
#library(xlsx)
#list of policies
Policies<-matrix(0,100,81)
Policies[c(50:75),2]<-3
Policies[c(50,60,70),3]<-1
Policies[seq(50,75,5),4]<-4 ; Policies[seq(50,75,3),4]<-3
Policies[c(45:75),5]<-2
Policies[c(45:75),6]<-3
Policies[c(45,55,65,75),7]<-1
Policies[seq(45,75,5),8]<-4
Policies[c(50:75),9]<-2

Policies[seq(50,75,1),10]<-2 ; Policies[50,10]<-1
Policies[seq(50,75,1),11]<-2 ; Policies[55,11]<-1
Policies[seq(50,75,1),12]<-2 ; Policies[60,12]<-1
Policies[seq(50,75,1),13]<-2 ; Policies[65,13]<-1
Policies[seq(50,75,1),14]<-2 ; Policies[70,14]<-1
Policies[seq(50,75,1),15]<-2 ; Policies[75,15]<-1
Policies[seq(50,75,1),16]<-2 ; Policies[c(50,60),16]<-1
Policies[seq(50,75,1),17]<-2 ; Policies[c(55,65),17]<-1
Policies[seq(50,75,1),18]<-2 ; Policies[c(60,70),18]<-1
Policies[seq(50,75,1),19]<-2 ; Policies[c(65,75),19]<-1
Policies[seq(50,75,1),20]<-2 ; Policies[seq(50,75,10),20]<-1
Policies[seq(50,75,1),21]<-2 ; Policies[seq(55,75,10),21]<-1

Policies[seq(50,75,1),22]<-2 ; Policies[c(50,55),22]<-4
Policies[seq(50,75,1),23]<-2 ; Policies[c(55,60),23]<-4
Policies[seq(50,75,1),24]<-2 ; Policies[c(60,65),24]<-4
Policies[seq(50,75,1),25]<-2 ; Policies[c(65,70),25]<-4
Policies[seq(50,75,1),26]<-2 ; Policies[c(70,75),26]<-4
Policies[seq(50,75,1),27]<-2 ; Policies[seq(50,75,5),27]<-4

Policies[seq(50,75,2),28]<-2 ; Policies[50,28]<-1
Policies[seq(50,75,2),29]<-2 ; Policies[55,29]<-1
Policies[seq(50,75,2),30]<-2 ; Policies[60,30]<-1
```

```
Policies[seq(50,75,2),31]<-2 ; Policies[65,31]<-1
Policies[seq(50,75,2),32]<-2 ; Policies[70,32]<-1
Policies[seq(50,75,2),33]<-2 ; Policies[75,33]<-1
Policies[seq(50,75,2),34]<-2 ; Policies[c(50,60),34]<-1
Policies[seq(50,75,2),35]<-2 ; Policies[c(55,65),35]<-1
Policies[seq(50,75,2),36]<-2 ; Policies[c(60,70),36]<-1
Policies[seq(50,75,2),37]<-2 ; Policies[c(65,75),37]<-1
Policies[seq(50,75,2),38]<-2 ; Policies[seq(50,75,10),38]<-1
Policies[seq(50,75,2),39]<-2 ; Policies[seq(55,75,10),39]<-1

Policies[seq(50,75,2),40]<-2 ; Policies[c(50,55),40]<-4
Policies[seq(50,75,2),41]<-2 ; Policies[c(55,60),41]<-4
Policies[seq(50,75,2),42]<-2 ; Policies[c(60,65),42]<-4
Policies[seq(50,75,2),43]<-2 ; Policies[c(65,70),43]<-4
Policies[seq(50,75,2),44]<-2 ; Policies[c(70,75),44]<-4
Policies[seq(50,75,2),45]<-2 ; Policies[seq(50,75,5),45]<-4

Policies[seq(50,75,1),46]<-3 ; Policies[c(50,55),46]<-4
Policies[seq(50,75,1),47]<-3 ; Policies[c(55,60),47]<-4
Policies[seq(50,75,1),48]<-3 ; Policies[c(60,65),48]<-4
Policies[seq(50,75,1),49]<-3 ; Policies[c(65,70),49]<-4
Policies[seq(50,75,1),50]<-3 ; Policies[c(70,75),50]<-4
Policies[seq(50,75,1),51]<-3 ; Policies[seq(50,75,5),51]<-4

Policies[seq(50,75,1),52]<-3 ; Policies[50,52]<-1
Policies[seq(50,75,1),53]<-3 ; Policies[55,53]<-1
Policies[seq(50,75,1),54]<-3 ; Policies[60,54]<-1
Policies[seq(50,75,1),55]<-3 ; Policies[65,55]<-1
Policies[seq(50,75,1),56]<-3 ; Policies[70,56]<-1
Policies[seq(50,75,1),57]<-3 ; Policies[75,57]<-1
Policies[seq(50,75,1),58]<-3 ; Policies[c(50,60),58]<-1
Policies[seq(50,75,1),59]<-3 ; Policies[c(55,65),59]<-1
Policies[seq(50,75,1),60]<-3 ; Policies[c(60,70),60]<-1
Policies[seq(50,75,1),61]<-3 ; Policies[c(65,75),61]<-1
Policies[seq(50,75,1),62]<-3 ; Policies[seq(50,75,10),62]<-1
Policies[seq(50,75,1),63]<-3 ; Policies[seq(55,75,10),63]<-1

Policies[seq(50,75,2),64]<-3 ; Policies[c(50,55),64]<-4
Policies[seq(50,75,2),65]<-3 ; Policies[c(55,60),65]<-4
Policies[seq(50,75,2),66]<-3 ; Policies[c(60,65),66]<-4
Policies[seq(50,75,2),67]<-3 ; Policies[c(65,70),67]<-4
Policies[seq(50,75,2),68]<-3 ; Policies[c(70,75),68]<-4
Policies[seq(50,75,2),69]<-3 ; Policies[seq(50,75,5),69]<-4

Policies[seq(50,75,2),70]<-3 ; Policies[50,70]<-1
Policies[seq(50,75,2),71]<-3 ; Policies[55,71]<-1
```

```
Policies[seq(50,75,2),72]<-3 ; Policies[60,72]<-1
Policies[seq(50,75,2),73]<-3 ; Policies[65,73]<-1
Policies[seq(50,75,2),74]<-3 ; Policies[70,74]<-1
Policies[seq(50,75,2),75]<-3 ; Policies[75,75]<-1
Policies[seq(50,75,2),76]<-3 ; Policies[c(50,60),76]<-1
Policies[seq(50,75,2),77]<-3 ; Policies[c(55,65),77]<-1
Policies[seq(50,75,2),78]<-3 ; Policies[c(60,70),78]<-1
Policies[seq(50,75,2),79]<-3 ; Policies[c(65,75),79]<-1
Policies[seq(50,75,2),80]<-3 ; Policies[seq(50,75,10),80]<-1
Policies[seq(50,75,2),81]<-3 ; Policies[seq(55,75,10),81]<-1


SCRES<-matrix(0,81,22) #scenario matrix that has each scenario

#for (h in c(1:1)) { #for one scenario
for (h in c(41:81)) { #policy index
  Scenario<-Policies[,h] # selecting the scenario


t<-1 #number of

load(file ="C:\\Users\\amirhosein.fouladi\\Dropbox\\LA
Tech\\Research\\Dessertation\\ACL\\Scenarios\\BRates20205000-4.RData") #importing
the set of parameters
dim(BRates2020)

##################Variables for calibration process
BERROR<-matrix(0,t,1) # sum of errors between seer and estimated incidence rates
BMSERROR<-matrix(0,t,1) #sum squared error recorder between seer and estimated
incidence rates
BIGRES<-matrix(0,t,18) # estimated incidence rates
BDIF<-matrix(0,t,18) # difference between each estimated and actual incidence rates
#####################################################

SEER_Males<-
matrix(c(0,0,0,0.4,1.3,2.5,5.3,9.2,17.4,32.1,61.9,76.1,106.7,153.1,205.4,248.3,301.7,342.
7),18,1,dimnames = list(
                    c("0-4","5-9","10-14","15-19","20-24","25-29","30-34","35-39","40-
44","45-49","50-54","55-59","60-64","65-69","70-74","75-79","80-84","85+"),"Males"))
#SEER reported incidence rates


GDR<-
(matrix(c(5498,419,283,210,183,151,131,114,98,83,75,84,120,189,284,384,486,600,726,
856,990,
```

```
1112,1203,1254,1277,1291,1309,1326,1348,1372,1399,1426,1454,1485,1521,1573,1642,
1723,

1813,1914,2027,2164,2332,2542,2795,3068,3366,3716,4116,4548,4989,5435,5901,6401,
6942,

7527,8140,8771,9406,10051,10736,11478,12273,13128,14057,15076,16204,17483,1892
3,20533,

22439,24653,27135,29737,32404,35321,38796,42852,47377,52749,58353,64396,71496,
79699,88491,

97689,109336,122073,135933,150930,167061,184300,202596,221873,242028,262931,2
84431,306354,
          328515,350719),100,1))/1000000 #general death rates

CDR<-
(matrix(c(rep(0,4),rep(c(0,0,0,0.2,0.5,1.2,2.5,4.7,8.8,15.4,23.5,35.2,48.8,70.6,99.5,137.3,
213.4,213.4,213.4),each = 5),213.4),100,1))/10000 #CRC death rates

DR<-GDR-CDR #death rates based om any causes but CRC

ASDR<-matrix(c(rep(.0542,100),rep(0.1677,100),rep(0.6469,100)),100,3) #stage specific
CRC death rates

Utilities<-matrix(c(rep(.91,44),rep(c(.78,.77,.75),each=10),rep(0.73,26)),100,1,dimnames
= list(
  c(1:100),c("Healthy State Life Expectancy")))  #Healthy State Life Expectancy

Disutilities<-matrix(c(0.0301,0.0027,0.0027,0.0055),4,1,dimnames =
list(c("Colonoscopy","FIT","FOBT","FS"),"Disutilities")) #test disutilities

DQ<-read.csv("C:\\Users\\amirhosein.fouladi\\Dropbox\\LA Tech\\Research\\CRC-
Simulation files\\Excel Files\\MD Anderson.csv",header = TRUE) # stage specific age
specific CRC life expectancy

TSen<-
matrix(c(c(.75,.85,.95,.95),.076,.076,.238,.74,.075,.124,.239,.7,.75,.85,.95,.95),4,4,dimna
mes =
list(c("Dimunitive","Medium","Large","CRC"),c("Colonoscopy","FIT","FOBT","FS")))
# Test sensitivities

TSpec<-matrix(c(.86,.898,.925,.87),4,1,dimnames =
list(c("Colonoscopy","FIT","FOBT","FS"),"Specifity")) # test specificity
FSF<-matrix(c(1,1,1,1),1,4) #a matrix to disable a test in ascenario (for testing the code)
```

```
SojT<-matrix(c(rep(5.5,54),rep(c(5.5,5.2,4.7,4.9,5),each=5),rep(5.5,21)),100,1,dimnames
= list(
  c(1:100),c("Sojourn Time")))  #mean Sojourn time

##Cost information

Price<-matrix(c(1192.6,24.88,24.88,548.47),4,1,dimnames =
list(c("Colonoscopy","FIT","FOBT","FS"),"Price")) # test prices

TRC<-
matrix(c(20247.20,1305.04,26007.5,2346.72,30085.20,15057,24544.13,1576.24),2,4,dim
names = list(c("Initial","Surveillance"),c("Local","Regional","Distant","Weighted
Average"))) #Treatment cost

##########################################################################
###################

        for(x in c(1:t)){#parameter set index

        CC<-matrix(0,100,1) #new cancer cases

        DC<-matrix(0,100,1) #death cases

        AC<-matrix(0,100,1) #alive cancer cases

        Rates<-BRates2020[,,4250] # importing different rates from an array
        ##############################
        K<-100000 # of patients
        n<-7 #maximum number of adenomas (one fewer than n)
        ######################################
        BQALYs<-matrix(0,K,1) #QALYs recorde
        BCosts<-matrix(0,K,1) # costs recorde
        CQALYs<-matrix(0,K,1) # a test measure
        CCosts<-matrix(0,K,1) # a test measure
        FSR<-matrix(0,K,9) # a test measure
        CSR<-matrix(0,100,3) # a test measure
        PREC<-array(0,dim=c(100,9,K)) # a test measure
        WQUALY<-matrix(0,100,K) # a test measure
        WCOST<-matrix(0,100,K) # a test measure
 for(k in c(1:K)){ #starting simulation of K patients

    S<-matrix(c(0),100,9,byrow=TRUE,dimnames = list(c(1:100),c("Adenoma-
D","Adenoma-M","Adenoma-L","CRC-L","CRC-R","CRC-D","Alive?","Death
Cause","# OF Years With CRC"))) # patient life matrix
    i<-1 #aging index
    A<-0 #alive or dead index (0 is alive)
```

```
W<-0 # a test measure
QALYs<-0 #patinet QALYs recorder
Costs<-0  #patient Cost recorder
STF<-0 # Sojourn time flag
RST<-101 # sojourn time
CF<-0 #cancer flag to distinguish cancer cases from non cancer cases
while(i<=100 & A==0){ #start aging from 1 to 100 for a person
 AQ<-0 #Adding QALYs permission
 CR<-S[i,5] #number of CRC-R adenomas in this state

 if(CR>=1){ #in case the patient have at least one CRC-R adenoma
  for(u in c(1:CR)){ #counting adenoma
   r5<-runif(1,0,1)

   if(r5>Rates[(ceiling(i/5)),19]){ #56

    S[i,5]<-S[i,5]-1
    S[i,6]<-S[i,6]+1
    CSR[c(i:100),3]<-CSR[c(i:100),3]+1
    CSR[c(i:100),2]<-CSR[c(i:100),2]-1
   }
   u<-u+1 #next adenoma
  }
 }
 CL<-S[i,4] #number of CRC-L adenomas in this state
     if(CL>=1){ #in case the patient have at least one CRC-L adenoma
  for(r in c(1:CL)){ #counting adenoma
   r4<-runif(1,0,1)

   if(r4>Rates[(ceiling(i/5)),17]){ #45

    S[i,4]<-S[i,4]-1
    S[i,5]<-S[i,5]+1
    CSR[c(i:100),2]<-CSR[c(i:100),2]+1
    CSR[c(i:100),1]<-CSR[c(i:100),1]-1
   }

   r<-r+1 #next adenoma
  }
 }
 L<-S[i,3] #number of large adenomas in this state

 if(L>=1){ #in case the patient have at least one large adenoma
  for(o in c(1:L)){ #counting adenoma
   r3<-runif(1,0,1)
   if(r3<=Rates[(ceiling(i/5)),14]){ #stage 3 to 2
```

```
    S[i,3]<-S[i,3]-1
    S[i,2]<-S[i,2]+1
   }
          if(r3>=(1-Rates[(ceiling(i/5)),16])){ #stage 3 to 4

    if(S[i,4]==0){ #a test measure
     CC[i]<-CC[i]+1
     CSR[c(i:100),1]<-CSR[c(i:100),1]+1
     SCRES[h,5]<-SCRES[h,5]+1 #a test measure
     CF<-1 #a test measure
               RST<-rexp(1,(1/SojT[i])) #generate mean sojourn time
     if(STF==0){
      S[i,9]<-1
      STF<-1
     }
    }

    S[i,3]<-S[i,3]-1
    S[i,4]<-S[i,4]+1
   }
   o<-o+1 #next adenoma
  }
}


M<-S[i,2] #number of medium adenomas in this state

if(M>=1){ #in case the patient have at least one medium adenoma
  for(m in c(1:M)){ #counting adenoma
   r2<-runif(1,0,1)
   if(r2<=Rates[(ceiling(i/5)),9]){ #stage 2 to 1
    S[i,2]<-S[i,2]-1
    S[i,1]<-S[i,1]+1
   }
         if(r2>=(1-Rates[(ceiling(i/5)),11])){ #stage 2 to 3
    S[i,2]<-S[i,2]-1
    S[i,3]<-S[i,3]+1
   }
   m<-m+1 #next adenoma
  }
}
D<-S[i,1] #number of dimunitive adenomas

if(D>=1){ #in case the patient have at least one dimunitive adenoma
  for(l in c(1:D)){ #counting adenoma
```

```
      r1<-runif(1,0,1)
      if(r1<=Rates[(ceiling(i/5)),4]){ #stage 1 to 0
        S[i,1]<-S[i,1]-1
      }

      if(r1>=(1-Rates[(ceiling(i/5)),6])){ #stage 1 to 2
        S[i,1]<-S[i,1]-1
        S[i,2]<-S[i,2]+1
      }

      l<-l+1 #next adenoma
    }
  }



  if(sum(S[i,])<n){ #checking the maximum allowed number of adenoma condition to see if we can have adenoma incidence or not
    r0<-runif(1,0,1)
    f<-0
    for(j in c((n-sum(S[i,])):1)){#number of adenoma that can be generated
      if(r0<=(Rates[(ceiling(i/5)),2])^(j) & f==0){ #number of adenoma that the body generates
        S[i,1]<-S[i,1]+(j) #adding generated adenomas life matrix
        f<-1
      }
      j<-j-1
    }
  }
  if(i<=99){ #copying patient life matrix next year

      S[i+1,]<-S[i,]

      if(STF>0){
        S[i+1,9]<-S[i,9]+1 ########add one to Sojourn time counter for next year
      }
  }

 ##############Applying screening tests
  ##########Removing adenomas via clonoscopy / a person with adenoma and not cancer has colonoscopy
  if(Scenario[i]==1 & sum(S[i,(4:6)])==0){ ## removing adenomas
    SCRES[h,13]<-SCRES[h,13]+1
    for(g in c(1:3)){ #to apply the test on Dimunitive,Medium and Large Adenoma
      for(e in c(1:S[i,g])){ #to go one by one on each adenoma
        r13<-runif(1,0,1)
```

```
          if(S[i,g]>0 & r13<=TSen[g,1]){
            S[i+1,g]<-S[i+1,g]-1

            CF<-1
           }
         }
        }
      }
       ##########Removing adenomas via FS / a person with adenoma and not cancer has
FS
      if(Scenario[i]==4 & sum(S[i,(4:6)])==0){ ## removing adenomas
        for(g in c(1:3)){ #to apply the test on Dimunitive,Medium and Large Adenoma
          for(e in c(1:S[i,g])){ #to go one by one on each adenoma
            r11<-runif(1,0,1)
            r14<-runif(1,0,1)
            if(S[i,g]>0 & r14<=TSen[g,4] & r11<=.34){
              S[i+1,g]<-S[i+1,g]-1

              CF<-1
             }
           }
         }
      }
          ######### A CRC case has Screening
      r15<-runif(1,0,1)
      if((sum(S[i,c(4:6)]))>0 & Scenario[i]>0){
        if(r15<(FSF[Scenario[i]])){
        TT<-Scenario[i] #to clarify test type
        if(TT==1){
          SCRES[h,13]<-SCRES[h,13]+1 # a measure test
        }
        r8<-runif(1,0,1)
        if(r8<TSen[4,TT]){#True positive ,, terminating patient because we discover his
CRC
                  if(TT==2 | TT==3){ #deduct colonoscopy disutility and add colonoscopy
cost
          QALYs<-QALYs-Disutilities[1] #extra colonoscopy
          Costs<-Costs+Price[1]
          SCRES[h,14]<-SCRES[h,14]+1# a test measure
         }
                  S[c(i:100),7]<-i #setting the matrix life for the rest of the years to show age
at death and cause of dead
         S[c(i:100),8]<-TT
         SCRES[h,(TT+5)]<-SCRES[h,(TT+5)]+1 # a test measure
         A<-1
         # adding QALYS based on final stage of patient
```

```
        if(S[i,6]>0){ #distant
          QALYs<-QALYs+DQ[(i),3]


          Costs<-Costs+TRC[1,3]+TRC[2,3] #adding treatment costs

          AQ<-1
        }
              if(S[i,5]>0 & AQ==0){ #regional
          QALYs<-QALYs+DQ[(i),2]
          Costs<-Costs+TRC[1,2]+TRC[2,2]
          AQ<-1
        }
           if(S[i,4]>0 & AQ==0){ #localized
          QALYs<-QALYs+DQ[(i),1]
          Costs<-Costs+TRC[1,1]+TRC[2,1]

          AQ<-1
        }
       }
       #if we get False Negetive, patient will go back to system and his CRC may be
diagnosed later
     }}
     ########### A healthy patient has Screening
     if(sum(S[i,c(4:6)]==0 & Scenario[i]>0)){
      TT<-Scenario[i]
      r10<-runif(1,0,1)
      if(r10 > TSpec[TT]){ # false positive

        # colonoscopy  and biopsy discover the truth ,, True Negetive
          QALYs<-QALYs-.0027 #deducting disutility for the false positive
          if(TT==2 | TT==3){ # if patient gest the false negative from FIT or FOBT
          Costs<-Costs+Price[1] #extra colonoscopy
          QALYs<-QALYs-Disutilities[1] #extra colonoscopy
          SCRES[h,14]<-SCRES[h,14]+1 # a test measure


           if(sum(S[i,(1:3)])>0){ ## removing adenomas in case the patient has adenoma ,
(lucky patient)
             for(g in c(1:3)){ #to apply the test on Dimunitive,Medium and Large Adenoma
              for(e in c(1:S[i,g])){ #to go one by one on each adenoma
                r13<-runif(1,0,1)
                if(S[i,g]>0 & r13<=TSen[g,1]){
                  S[i+1,g]<-S[i+1,g]-1

                  CF<-1
```

```
          }
         }
        }
       }
      }
  }

  if(TT==1){ #test is colonoscopy
    SCRES[h,13]<-SCRES[h,13]+1 # a test measure
  }
}
############################## Sojourn time and self detection
if(A==0 & S[i,9]>=RST){ #if cancer becoms symptomatic
  ### we add remaining QALYs and costs based on distant stage and terminate  him
  S[c(i:100),7]<-i
  S[c(i:100),8]<-9
  SCRES[h,10]<-SCRES[h,10]+1 # a test measure
  A<-1
  DC[i]<-DC[i]+1

  # adding QALYS based on distant stage
    QALYs<-QALYs+DQ[i,3]

    Costs<-Costs+TRC[1,3]+TRC[2,3]

    AQ<-1
}


########### terminating  a CRC case before sojourn time

if(A==0 & S[i,6]>0){ #killing a distant case

  r7<-runif(1,0,1)
  if(r7<= ASDR[i,3]){

    S[c(i:100),7]<-i #updating teh life matrix
    S[c(i:100),8]<-6
    SCRES[h,11]<-SCRES[h,11]+1 #a test measure
    A<-1
    DC[i]<-DC[i]+1
    FSR[k,]<-S[i,]
    CSR[c(i:100),3]<-CSR[c(i:100),3]-1 # a test measure
  }
}
     if(A==0 & S[i,5]>0){ #terminating a regional case
```

```
        r7<-runif(1,0,1)
  if(r7<= ASDR[i,2]){

    S[c(i:100),7]<-i #updating the life matirx
    S[c(i:100),8]<-6
    SCRES[h,11]<-SCRES[h,11]+1
    A<-1
    DC[i]<-DC[i]+1
    FSR[k,]<-S[i,]
    CSR[c(i:100),2]<-CSR[c(i:100),2]-1 #a test measure
  }
}

if(A==0 & S[i,4]>0){ #killing a localized case
     r7<-runif(1,0,1)
  if(r7<= ASDR[i,1]){

    S[c(i:100),7]<-i #updating the life matrix
    S[c(i:100),8]<-6
    SCRES[h,11]<-SCRES[h,11]+1 #a test measure
    A<-1
    DC[i]<-DC[i]+1
    FSR[k,]<-S[i,]
    CSR[c(i:100),1]<-CSR[c(i:100),1]-1
  }
}

###########killing a non crc cases because of natural causes
r9<-runif(1,0,1)
if(r9<=DR[i] & A==0 & sum(S[i,(4:6)])==0){
  S[c(i:100),7]<-i # updating the life matrix
  S[c(i:100),8]<-10
  SCRES[h,12]<-SCRES[h,12]+1 # a test measure
  A<-1
  DC[i]<-DC[i]+1
}
#######adding QALYs
     if(AQ==0){#adding cost and  QALYs for the patient
  QALYs<-QALYs+Utilities[i,1]
  AQ<-1
}

if(Scenario[i]>0){
    QALYs<-QALYs - Disutilities[Scenario[i]]
    Costs<-Costs+Price[Scenario[i]]
}
```

```
      #end of adding cost and QALYs for the patient
      i<-i+1 #next year of the person's life
    } # end of simulating a person
       BQALYs[k]<-QALYs # recording this patient QALYs
      BCosts[k]<-Costs # recording this patient cost
       if(CF==1){ # a test measure
      CQALYs[k]<-QALYs
      CCosts[k]<-Costs
    }
    for (ab in c(1:100)){#a test measure
      if (sum(S[ab,c(4:6)])>0){
        AC[ab]<-AC[ab]+1
      }
    }
    PREC[,,k]<-S # a test measure
    k<-k+1 #next person
  } #end of simulating K people
AP<-K-cumsum(DC) #Alive Population
############################################ Population Matrix
PO<-matrix(0,18,1)
for(i in c(1:16)){
  PO[i+1]<-sum(AP[(5*i):(5*i+4)])
}
PO[1]<-sum(AP[1:4])
PO[18]<-sum(AP[85:100])
############################################Cancer Cases Matrix
CCases<-matrix(0,18,1)
for(i in c(1:16)){
  CCases[i+1]<-sum(CC[(5*i):(5*i+4)])
}
CCases[1]<-sum(CC[1:4])
CCases[18]<-sum(CC[85:100])
############################################Final result
MRates<-matrix(0,18,1)
for(i in c(1:18)){
  MRates[i]<-((100000*CCases[i])/(PO[i]))
}
Temp<-t(MRates)
BIGRES[x,]<-Temp[1,]
############################################ absolute Error and Square Error
between Seer and my rates
Difference<-matrix(0,18,1)
DifferenceS<-matrix(0,18,1)
for(i in c(1:18)){
  Difference[i]<-((SEER_Males[i])-(MRates[i]))
  DifferenceS[i]<-((SEER_Males[i])-(MRates[i]))^2
```

```
}
ERROR<-sum(abs(Difference))
MSERROR<-sum(DifferenceS)
BERROR[x]<-ERROR
BMSERROR[x]<-MSERROR
BDIF[x,]<-t(Difference[,1])
############################################ gathering all row result in a matrix
and write it
Result<-cbind(AP,CC,AC)
colnames(Result)<-c("Population","New Cancer cases","Alive cancer cases")
############################################Putting final results and SEER
together
COMP<-cbind(MRates,SEER_Males)
#COMP
############################################
}#calibration ends
SCRES[h,1]<-mean(BQALYs) # patinets expected QALYs
SCRES[h,2]<-sd(BQALYs) #  QALYs standard deviation
SCRES[h,3]<-mean(BCosts) # patinets expected costs
SCRES[h,4]<-sd(BCosts) # cost standard deviation

SCRES[h,15]<-mean(CQALYs[CQALYs!=0]) # test measures
SCRES[h,16]<-sd(CQALYs[CQALYs!=0]) # test measures
SCRES[h,17]<-mean(CCosts[CCosts!=0]) # test measures
SCRES[h,18]<-sd(CCosts[CCosts!=0]) # test measures

SCRES[h,19]<-K-length(which(BQALYs==0)) # test measures
SCRES[h,20]<-K-length(which(BCosts==0)) # test measures
SCRES[h,21]<-K-length(which(CQALYs==0)) # test measures
SCRES[h,22]<-K-length(which(CCosts==0)) # test measures

write.csv(SCRES,file = "C:\\Users\\amirhosein.fouladi\\Dropbox\\LA
Tech\\Research\\Dessertation\\ACL\\Scenarios\\SCRES10-1-27-41-81.csv")
```

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