Louisiana Tech University
Louisiana Tech Digital Commons

Doctoral Dissertations | Graduate School

Winter 3-3-2018

Cost-Effective Use of Follow-Up Colonoscopies and Fecal Immunochemical Tests in Colorectal Cancer Screening

Grace N. Joseph
Louisiana Tech University

Follow this and additional works at: https://digitalcommons.latech.edu/dissertations

Recommended Citation
Joseph, Grace N., "" (2018). *Dissertation*. 30.
https://digitalcommons.latech.edu/dissertations/30

This Dissertation is brought to you for free and open access by the Graduate School at Louisiana Tech Digital Commons. It has been accepted for inclusion in Doctoral Dissertations by an authorized administrator of Louisiana Tech Digital Commons. For more information, please contact digitalcommons@latech.edu.

Louisiana Tech University
Louisiana Tech Digital Commons

Doctoral Dissertations | Graduate School

Winter 3-3-2018

Cost-Effective Use of Follow-Up Colonoscopies and Fecal Immunochemical Tests in Colorectal Cancer Screening

Grace N. Joseph
Louisiana Tech University

Follow this and additional works at: https://digitalcommons.latech.edu/dissertations

Recommended Citation
Joseph, Grace N., "" (2018). *Dissertation*. 30.
https://digitalcommons.latech.edu/dissertations/30

This Dissertation is brought to you for free and open access by the Graduate School at Louisiana Tech Digital Commons. It has been accepted for inclusion in Doctoral Dissertations by an authorized administrator of Louisiana Tech Digital Commons. For more information, please contact digitalcommons@latech.edu.

COST-EFFECTIVE USE OF FOLLOW-UP COLONOSCOPIES AND FECAL IMMUNOCHEMICAL TESTS IN COLORECTAL CANCER SCREENING

by

Grace Naomie Joseph, B.S.

A Dissertation Presented in Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy

COLLEGE OF ENGINEERING AND SCIENCE
LOUISIANA TECH UNIVERSITY

March 2018

LOUISIANA TECH UNIVERSITY

THE GRADUATE SCHOOL

NOVEMBER 9, 2017
Date

We hereby recommend that the dissertation prepared under our supervision by

Grace Naomie Joseph, B.S.

entitled **Cost-effective Use of Follow-up Colonoscopies and Fecal Immunochemical Tests in Colorectal Cancer Screening.**

be accepted in partial fulfillment of the requirements for the Degree of

Doctor of Philosophy in Computational Analysis and Modeling

Supervisor of Dissertation Research

Head of Department

Mathematics and Statistics
Department

Recommendation concurred in:

Advisory Committee

Approved:

Director of Graduate Studies

Dean of the College

Approved:

Dean of the Graduate School

GS Form 13
(8/10)

ABSTRACT

Colorectal cancer (CRC), if not detected early, can be costly and detrimental to one's health. Screening techniques for colorectal cancer can help find and remove adenomas in an effort to prevent future CRC. A colonoscopy has the potential of identifying CRC early as well as preventing the disease. Fecal Immunochemical Tests (FITs) is an initial non-invasive screening technique that identifies the presence of the disease, and needs to be followed by a more invasive test (like colonoscopy) if anything is detected. However, the optimal frequency for follow-up colonoscopy, and screening colonoscopy with FITs is unknown, and may vary based on findings from colonoscopy screening and patient age.

A partially observed Markov process (POMP) was used to simulate the effects of a follow-up colonoscopy, FITs, and a combination of colonoscopy and FITs on the development of CRC. The POMP uses adenoma and CRC growth models to calculate the probability of an individual having colorectal adenomas and CRC. Then, based on mortality, quality of life, and the costs associated with diagnosis, treatment, and surveillance of colorectal cancer, the overall costs and increase in quality adjusted life years are calculated for each follow-up colonoscopy, FIT and colonoscopy combination, and FIT scenario.

This study found that spending $100,000 for a quality adjusted life year (QALY) gained will produce one follow-up colonoscopy after screening at age 50 years. The

optimal follow-up is 8.5 years later which gives 84.0 QALYs gained/10,000 persons). No follow-up colonoscopy was cost-effective at the $50,000 and $75,000/QALY gained thresholds. The intervals were relatively insensitive to the findings at screening colonoscopy.

Combining screening techniques for CRC (colonoscopy and FIT) is cost-effective at all three thresholds analyzed. All screening ages tested were cost-effective with approximately an 8 year increase in QALYs from screening age 50 to screening age 75. As a result of the protocol of combining screening tests being extremely cost-effective with added benefit (QALYs gained), coupling the tests is highly recommend.

APPROVAL FOR SCHOLARLY DISSEMINATION

The author grants to the Prescott Memorial Library of Louisiana Tech University the right to reproduce, by appropriate methods, upon request, any or all portions of this Dissertation. It is understood that "proper request" consists of the agreement, on the part of the requesting party, that said reproduction is for his personal use and that subsequent reproduction will not occur without written approval of the author of this Dissertation. Further, any portions of the Dissertation used in books, papers, and other works must be appropriately referenced to this Dissertation.

Finally, the author of this Dissertation reserves the right to publish freely, in the literature, at any time, any or all portions of this Dissertation.

Author _____

Date _____

DEDICATION

To Kaejha, Mama, Julie and Tiffany.

TABLE OF CONTENTS

ABSTRACT iii

DEDICATION vi

LIST OF FIGURES xi

LIST OF TABLES xiii

ACKNOWLEDGMENTS xiv

CHAPTER 1 INTRODUCTION 1

1.1 Colorectal Cancer Background 1

1.2 Overview of Cancer 2

1.3 Colon and Rectum 3

1.4 Colorectal Cancer 4

1.5 Risk Factors of Colorectal Cancer 5

1.5.1 Uncontrollable CRC Risk Factors 6

1.5.1.1 Age 6

1.5.1.2 Family History of Cancer 6

1.5.1.3 Personal History of Inflammatory Bowel Disease 7

1.5.2 Controllable CRC Factors 7

1.6 Symptoms of CRC 7

1.7 CRC Stages 8

1.8 CRC Treatments 9

1.8.1 Local Treatments 10

1.8.2 Systemic Treatments 11

CHAPTER 2 CRC SCREENING AND SURVEILLANCE 12
2.1 Background 12
2.2 Screening 12
2.2.1 Endoscopic Test 14
2.2.2 Non-endoscopic Test 16
2.3 Complications due to Screening 18
2.4 Surveillance 18
2.5 Current Guidelines for Screening and Surveillance of Colonoscopy 18
2.6 Screening Age 21
2.7 Cost-effectiveness Analysis 22
2.8 Research Need 24
CHAPTER 3 COMPUTATIONAL TECHNIQUES 26
3.1 Overview 26
3.2 Markov Process 27
3.3 Breakdown of each Component Methods 28
3.3.1 Colonic Neoplasia Growth Model 28
3.3.2 Mortality Rate Model 31
3.3.2.1 CRC-related Mortality 31
3.3.3 All-cause Mortality 34
3.3.4 Partially Observed Markov Process (POMP) 34
3.3.5 Follow-up Colonoscopy Scenarios 35
3.3.5.1 Control Groups 36
3.3.5.1.1 Control Group 1: Screening only 36
3.3.6 Outcomes of Partially Observed Markov Process 36
3.3.6.1 Costs 36

3.3.6.2 Discounting 39

3.3.6.3 Quality-Adjusted Life-Years (QALYs) 40

3.4 Cost-effectiveness Analysis 42

3.5 Sensitivity Analysis 43

CHAPTER 4 ANALYSIS OF SIMULATION PROTOCOLS FOR COLONOSCOPY FOLLOW-UP 45

4.1 Introduction 45

4.2 Follow-up Colonoscopy based on Patient Age and Screening 45

4.2.1 Age 50 45

4.2.2 Age 55 49

4.3 Cost-effective Interval that Maximizes Patient's QALYs Gained by Age and Screening Results 52

4.3.1 Results for Control Group 1 52

4.3.2 Age 50 53

4.3.3 Age of final colonoscopy 56

4.4 Sensitivity Analysis 57

4.4.1 Low Screening Colonoscopy Costs 59

4.4.2 High Cancer Cost 62

4.4.3 Zero Percent Discount Rate 63

CHAPTER 5 COST-EFFECTIVENESS OF FECAL IMMUNOCHEMICAL TESTS (FITs) 64

5.1 Introduction 64

5.2 Overview of simulation process for FIT 65

5.2.1 POMP Model for FIT 65

5.2.2 FIT Protocol 66

5.2.3 Costs 66

5.2.4 QALYs 67

5.2.5 Cost-effectiveness Analysis 67

5.2.5.1 Control Group: No screening from age 0 until death or age 100 68

5.2.6 Results from FIT only Protocol 69

5.2.7 Combination of Colonoscopy and FIT Tests 71

CHAPTER 6 CONCLUSIONS AND FUTURE WORK 73

6.1 Conclusions 73

6.2 Future Work 75

6.3 Limitations of the study 76

APPENDIX A MATLAB CODE USED FOR MODELING 77

A.1 Overview 77

Bibliography 163

LIST OF FIGURES

Figure 11: Diagram of the colon and rectum. 4

Figure 12: Diagram showing healthy colon vs unhealthy colon. 5

Figure 13: Diagram showing before and after a resection surgery of the colon 10

Figure 21: Instrument used to perform a colonoscopy . 14

Figure 22: Instrument used to perform a sigmoidoscopy . 15

Figure 23: Difference in colonoscopy procedure (yellow) and sigmoidoscopy (green). 16

Figure 31: General overview of simulation process. 27

Figure 32: Adenoma growth model: Adenoma growth , CRC growth , Symptoms. 28

Figure 33: Model fit of overall CRC mortality using breakpoint model. 32

Figure 34: All-cause mortality data. 34

Figure 41: Efficiency vs Surveillance intervals at age 50 for no neoplasia finding. 46

Figure 42: Efficiency vs Surveillance intervals at age 50 for 1 to 2 polyps 47

Figure 43: Efficiency vs Surveillance intervals at age 50 for 3 plus polyps 47

Figure 44: Efficiency vs Surveillance intervals at age 50 for 1 to 2 advanced polyps only finding. 48

Figure 45: Efficiency vs Surveillance intervals at age 50 for 3 plus advanced polyps only finding. 48

Figure 46: Efficiency vs Surveillance intervals at age 55 for a general all screening results- an average of all the findings combined. 50

Figure 47: Efficiency vs Surveillance intervals at age 60 for a general all screening results- an average of all the findings combined. 50

Figure 48: Efficiency vs Surveillance intervals at age 65 for a general all screening results- an average of all the findings combined. 51

Figure 49: Efficiency vs Surveillance intervals at age 70 for a general all screening results- an average of all the findings combined. 51

Figure 410: Efficiency vs Surveillance intervals at age 75 for a general all screening results- an average of all the findings combined. 52

Figure 411: Effectiveness vs Surveillance intervals (ΔQALY) at age 50 with no neoplasia. 53

Figure 412: Effectiveness vs Surveillance (ΔQALY) at age 50 with 1 to 2 small polyps only. 54

Figure 413: Effectiveness vs Surveillance (ΔQALY) at age 50 with 3 plus small polyps only. 54

Figure 414: Effectiveness vs Surveillance (ΔQALY) at age 50 with 55

Figure 415: Effectiveness vs Surveillance (ΔQALY) at age 50 with 3 plus advanced polyps only. 55

Figure 416: Efficiency vs Surveillance intervals at age 50 with all screening results. 60

Figure 417: Efficiency vs Surveillance at age 55 with all screening results. 61

Figure 418: Efficiency vs Surveillance at age 60 with all screening results. 61

Figure 419: Efficiency vs Surveillance at age 65 with all screening results. 62

Figure 51: Overview of FIT methods. 65

Figure 52: QALYs gained for the best protocol for FIT only. 70

Figure 53: Efficiency Vs Age for the best FIT only protocol. 70

LIST OF TABLES

Table 31: Annual transition probabilities between adenoma and CRC states. 29

Table 32: Annual transition probabilities between adenoma and CRC states. 31

Table 33: Annual transition probabilities between adenoma and CRC states. 33

Table 34: Costs used in the cost-effectiveness analysis. 37

Table 35: QALYs used in the cost-effective analysis. 41

Table 41: Ranges of follow-up colonoscopies that were cost effective at age 50 for all screening findings. 49

Table 42: Inter-colonoscopy intervals that maximize QALYS gained for the $100,000 threshold. 56

Table 44: Inter-colonoscopy intervals for sensitivity analyses. 57

Table 51: FIT only Analysis. 69

Table 52: Combination of FIT and colonoscopy analysis with control group 1. 72

Table 53: Combination of FIT and colonoscopy analysis with control group 2. 72

ACKNOWLEDGMENTS

I would like to start off by thanking God for giving me the strength and patience to take on this degree. I would also like to thank him for giving me such a great family structure to fall on for support and guidance in every way possible.

To the greatest advisor any student can ask for, Dr. Eric Sherer, I would like to express my sincere gratitude and appreciation to you for taking me under your wings. I will admit I started off a bit raw but with your profound knowledge and sincere nature, I turned out pretty okay. Thank you for all the support that you provided throughout my time here and for understanding me.

I would like to thank Dr. Jinko Kanno, Dr. Sumeet Dua, Dr. Prerna Dua and Dr. Pedro Derosa for serving on my dissertation committee. Also, I would like to say a special thank you to Dr. Pedro Derosa and Dr. Bala Ramachandran, for introducing me to Dr. Sherer when I was in need of an advisor.

To my daughter, Kaejha Stewart, thank you for being the most loving, kind and sincere kid anyone could ask for. I will admit pursuing this degree and raising you to be a beautiful, intelligent, strong and powerful little lady was a bit daunting at times but I wouldn't trade it for anything. You taught me so much there is to know about life, both ups and downs, and it was all well worth it.

I would like to thank my mom, Maryann Joseph, for being one of the main and biggest support systems throughout my journey. Though your education was cut short at

an early age due to you having to raise your siblings as a result of your parents' death, you ensured that your children received the help and guidance they needed to move way further than you did. For that I will forever be thankful. Thank you for all the prayers every minute, every second, and every day.

To my sister, Julie Joseph, thank you for believing in me and pushing me beyond my limits, and for all the support in all ways. The constant prayers and kind words to always push through even when times were tough really helped. You are truly an inspiration and the greatest big sister anyone can ask for.

I would like to thank my best friend, Tiffany Victor, for the constant support throughout our shared journey. We started this journey together and supported and encouraged each other throughout. On the days where I felt I had no idea what I was doing or why I was doing this, you constantly reminded me and encouraged me.

To my close friends Kevin Stewart, Kahla St. Marthe, Jermaine Morris, Germaine Pierre, Kahleen St, Marthe, Kerneisha Roachford, and Kazim Abbott, who helped in whatever way they could with anything I needed, I thank you from the bottom of my heart. I would like to say a big thank you to Jonas Montoute for helping me out with the formatting of this dissertation which was not much fun. He sacrificed himself right before me and passed on the good details and advice to make it easier for me. Also, I would like to thank Farid Heidarnejad for all his support and help.

Lastly, I would to thank everyone who had some impact on this journey, whether it was big or small. To Christine Davis, Nicketta Stewart, the Tamakloes, and Gretchen Jones, a big thank you!

CHAPTER 1

INTRODUCTION

1.1 Colorectal Cancer Background

Colorectal cancer (CRC), if not detected early, can be costly and detrimental to one's health. Colorectal cancer is the third most commonly diagnosed cancer, and also the third leading cause of cancer-related deaths in both men and women in the United States [1]. It is estimated that in 2017, the US will record 135,430 new cases (95,520 new cases of colon cancer and 39,910 new cases of rectal cancer) [2]. For men, the lifetime risk for developing the disease is about 4.7%, and for women it is about 4.4% [1]. The disease is expected to cause 50,260 deaths in 2017.

The death and incidence rates for colorectal cancer over decades have been declining. This could be due to several reasons including, but not limited to, the fact that screening is allowing more colorectal adenomas to be found and removed before they develop into cancers, and also more cancers are being found earlier when the disease is easier to cure.

Colorectal cancer, however, is both treatable and preventable when detected at an early stage. About 90% of CRC cases develop in persons 50 years and older [3]. Some major risks factors of the disease include age and personal history of one or more colorectal adenomas. The majority of CRCs are believed to grow from adenomatous

polyps and removing the polyps has been shown to prevent CRC [4]. If CRC is detected early, it is more likely to be cured.

Appropriate screening exams can help find and remove adenomas in an effort to prevent future CRC. Several screening techniques have emerged over decades in order to help lower CRC. The two main approaches for screening CRC are (1) assessing the stool for blood or DNA and (2) visual examinations. Some common stool-based tests which are used are guaiac-based fecal occult blood test (gFOBT) and fecal immunochemical test (FIT) and some common visual-based tests are colonoscopy and flexible sigmoidoscopy.

The motivation of this dissertation is to model screening and surveillance strategies for colorectal cancer and to assess their cost-effectiveness.

1.2 Overview of Cancer

When cells in the body abnormally grow out of control and take over the normal cells, cancer results. It can start in any part of the body with no warning and can affect any individual [5]. Healthy cells grow, divide and die appropriately whereas cancer cells are likely to proliferate uncontrolled and outlive healthy cells. As these abnormal cells grow, they can spread away from their original location through the blood and lymph systems [6].

Some types of cancers can grow and spread quicker than others depending on the part of the body where they are located. As a result, different types of treatments are needed. These treatment options may include surgery and/or the use of chemotherapeutic drugs to either remove or reduce the diseased cells.

Some cancers sometimes form a lump which is called a tumor or a growth. However, not all lumps are cancerous [6]. Doctors are responsible for removing the

lumps and testing them to find out if they are cancerous or not. Lumps that are found to be non-cancerous are considered benign. They often times resemble normal body cells although sometimes they can grow very large enabling them to inhibit normal body functions but they don't metastasize. Once benign tumors are removed they rarely return [6].

Lumps that are found to be cancerous are considered malignant and need to be dealt with as soon as they are detected. The malignant cells travel to other sites in the body and invade nearby tissue which can result in the growth and formation of new tumors. Cancers are named for the site where they began [6].

When cancers are detected it is better to start treatment sooner than later in order to increase life years.

1.3 Colon and Rectum

The colon and rectum are part of the digestive system; they make up the large intestine. The colon takes up most of the digestive system (5 feet) and the rectum occupies a small portion (6 inches). The colon has four main parts which are named by the direction the food is travelling [7]:

1. The ascending colon- extends upwards on the right side of the abdomen,
2. The traverse colon-travels across the body from right to left,
3. The descending colon- travels down on the left side of the abdomen,
4. The sigmoid colon-"S" shaped section that joins the rectum.

The ascending and traverse parts are referred to as the proximal colon collectively, and the descending and sigmoid parts are the distal colon. After the food goes through the small intestines, whatever is left, the colon absorbs salt and water from

it. Once the food goes through the colon, whatever is not needed goes to the rectum and is stored until it gets out of the body via the anus. **Figure 11** shows the digestive system with colon and rectum [7].

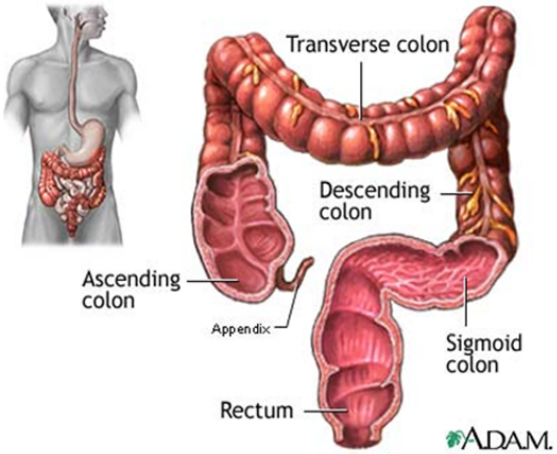

Figure 11: Diagram of the colon and rectum[8].

1.4 Colorectal Cancer

Colorectal cancer is cancer that starts in the inner lining of the colon or the rectum. They can be named colon or rectal cancer independently based on where they start. According to the American Cancer Society, because these cancers have many similar characteristics they are often grouped together as colorectal cancer. The disease evolves from a growth called a polyp. These polyps can take approximately 10 to 20 years to develop into cancer but not all result in cancer [3].

The type of polyp determines the possibility of cancer transition. According to the American Cancer Society, there are two main types of polyps: adenomatous polyps (adenomas), and hyperplastic and inflammatory polyps. The adenomas can be

precancerous, but the hyperplasic and inflammatory polyps, even though they are more common, are not [9]. The size (> 1cm) and the number found (>2) of the polyp may increase the chances of being cancerous. Once the cancer cells are in the walls of the colon, they can grow into the blood or lymph vessels then to lymph nodes and eventually to other parts of the body [6].

Early detection of the disease is the most accurate method to reduce CRC-related death. **Figure 12** shows the difference between a normal colon and an abnormal colon with cancer.

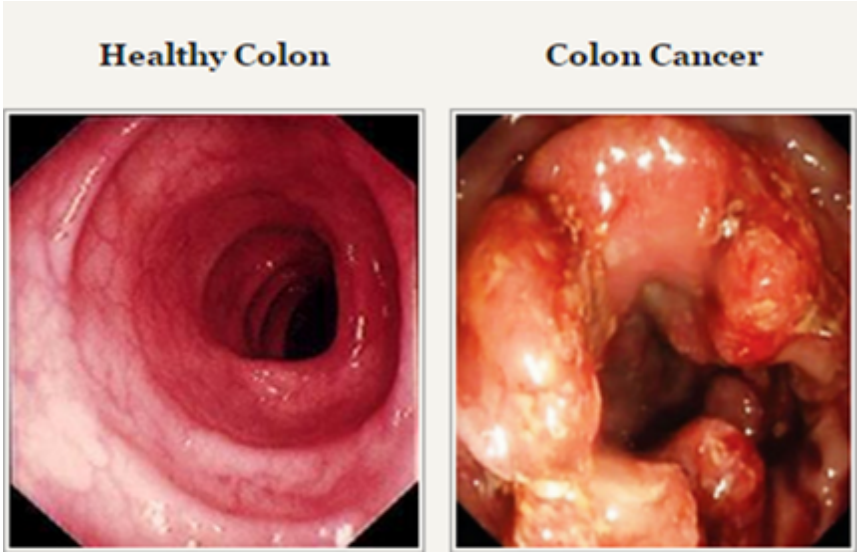

Figure 12: Diagram showing healthy colon vs unhealthy colon[10].

1.5 Risk Factors of Colorectal Cancer

According to World Health Organization, any attribute, characteristic or exposure of an individual that increases the likelihood of developing ta disease or injury is a risk factor. As with everything else, different cancers have different risks factors. Some risk

factors such as smoking can be controlled whereas familial history cannot. There is no indisputable evidence to prove what causes colorectal cancer but some researchers have found several risk factors that might increase a person's chances of getting the disease. Some of these risk factors include family history, inherited syndromes, racial and ethnic background, diet, inactive lifestyle, smoking, alcohol use, age, history of colorectal cancer or polyps, history of inflammatory bowel disease (IBD), obesity, type II diabetes, etc. [11]. Both lifestyle and genetic influences play a role in the disease development.

1.5.1 Uncontrollable CRC Risk Factors

1.5.1.1 Age

The strongest risk factor is age. As people age, they have greater chances of obtaining the disease. Approximately 90% of CRC cases develop in persons 50 years and older [3]. That does not mean that CRC cannot occur at younger ages. It can actually occur in teens in very rare cases [12-15].

1.5.1.2 Family History of Cancer

A very strong predictor of developing colorectal cancer is associated with having a first degree relative with the disease. According to the American Cancer Society 1 in 5 people who develop CRC have other family members you have had it [16]. Having one or more first-degree relatives younger than 45 years with the disease, puts you at an increased risk for the disease [17],[18].

Having family members who have had adenomatous polyps (they can become cancerous) have also been associated with increased risk of CRC. Someone with a family history of adenomatous polyps or colorectal cancer is more prone to developing the disease than others with no history [16].

1.5.1.3 Personal History of Inflammatory Bowel Disease

Any inflamed bowel disease (IBD) such as Ulcerative colitis and Crohn's disease increases the risk of CRC [19],[20]. IBD occurs when the colon is inflamed over an extended period of time. If an individual has IBD for many years, dysplasia often develops. Dysplasia describes the cells in the lining of the colon or rectum that may seem abnormal but are not cancerous. They however can evolve into cancer with time [1], [16].

1.5.2 Controllable CRC Factors

Some other possible factors that may increase the risk of developing CRC, which can be controlled by an individual, include habits such as smoking and drinking. Also having diets with foods high in fat and cholesterol and low in fiber can deteriorate your general health quicker [16],. Some studies even link increase CRC risk with working night shifts regularly [21].

1.6 Symptoms of CRC

It may take a while for CRC symptoms to appear. The symptoms depend on the stage of the cancer and where it was formed or where it is currently located. Some common symptoms associated with the disease include[1]:

- Change in bowel habits – diarrhea, constipation, narrowing of stool,
- Rectal bleeding,
- Cramping or abdominal pain,
- Weight loss and
- Weakness and fatigue.

These symptoms can be caused as a result of a different condition. Most of these symptoms are most likely due to the disease being spread to other parts of the body; the

later stage of the disease. This is why it is recommended to get screening early to possibly reduce or avoid the full development of the disease.

The symptoms of CRC depend on the location of the cancer. Cancer on the right side of the colon may go unnoticed for a very long time. People may feel a mass; have abdominal pain, fever, profuse sweating (especially at night) and anemia. If the cancer is on the left side, the main symptom that is observed is a change in bowel habits. They also present similar symptoms like abdominal pain, abdominal distention, vomiting and constipation similar to right side cancers.

1.7 CRC Stages

The extent of the cancer in the body is grouped by stages [1]. A stage is a crucial factor in deciding how to treat the disease. After CRC has been diagnosed, experts use different characteristics to determine the cancer's stage. They typically look into how far the cancer has grown in the walls of the intestine, whether it has reached any nearby structures and also if it has spread to other distant organs [1].

The data collected after diagnosis is very important to cancer registries and hospitals. Based on what their needs are, they use various staging systems [22]. Some of the major systems used to group cancer stages are (1) The American Joint Committee on Cancer's TNM System [23] (2) Surveillance, Epidemiology, and End Results (SEER) Extent of Disease (EOD) and (3) SEER Summary Staging Guide [24].

The SEER Summary Staging Guide was published in 1977 [22] and it was more site specific than the broad staging categories that were available at the time. The stage categories were defined as (1) In situ – a neoplasm is present and has all the characteristics of malignancy with the only exception that it is not invasive, (2) Localized

– an invasive malignant neoplasm is present and it is confined entirely to the organ of origin, (3) Regional – a malignant neoplasm is present and has gone past the limits of the organ of origin into nearby organs or tissues or via the lymphatic system to regional lymph nodes and (4) Distant - a malignant neoplasm is present and it has spread to other parts of the body isolated from the primary tumor to distant organs, tissues or via the lymphatic system to distant lymph nodes [22]. The five-year survival of the disease is 90% if it is diagnosed in the localized stage, 68% for the regional stage and only 10% for the distant stage [25].

The staging system most often used is The American Joint Committee on Cancer's TNM System [1]. This system is based on three important pieces of information:

1. The extent of the primary tumor (T) into the wall of the intestines and other nearby areas,
2. Whether there is a spread to nearby lymph nodes (N),
3. Whether the cancer has metastasized (M) to other organs of the body.

These letters (TNM) are normally followed by numbers or letters to give more information about each of the factors. The greater the number the more advance the cancer.

1.8 CRC Treatments

Several treatment options exist for colorectal cancer based on type and stage of the disease. American Cancer Society groups CRC treatments into two categories: local and systemic [16].

1.8.1 Local Treatments

Local treatments tend to treat just the tumor without affecting any other part of the body and are more likely it be used for earlier stage CRC. Some local treatments include surgery, radiation therapy, and ablation or embolization.

- Surgery is the primary treatment when the cancer is in its early stage. The surgery is chosen based on the stage of the cancer and its location. Some surgeries include polypectomy and local excision, colectomy, diverting colostomy, local trans anal resection, trans anal endoscopic microsurgery (TEM), lower anterior resection (LAR), and abdominoperineal resection (APR) [1],[26]. A resection surgery removes integrated sections of the colon as seen in **Figure 13**.

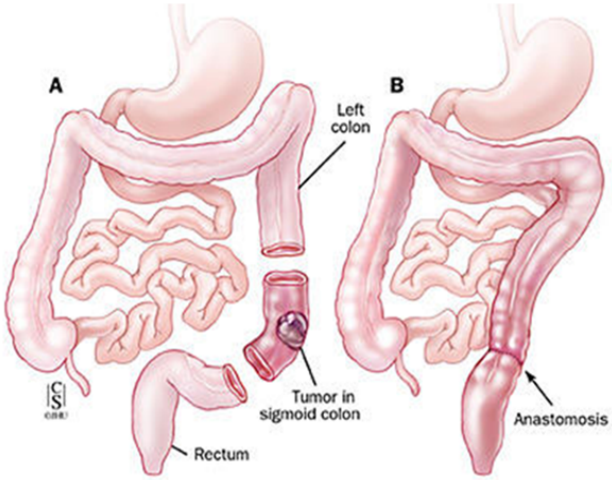

Figure 13: Diagram showing before and after a resection surgery of the colon [27].

- Radiation therapy focuses on high-energy rays to destroy cancer cells. It is sometimes paired with another treatment option (Chemotherapy) to be more effective [16],[28].

- Ablation deals with treatments that destroy the tumors without having to get rid of them. Embolization deals with injecting substances to try to reduce blood flow to cancer cells in the liver. The two treatment options can be combined [16],[29].

1.8.2 Systemic Treatments

Drugs can also aid in the treatment of CRC. They can be given orally or directly into the bloodstream. Some of these treatments include chemotherapy, targeted therapy, and immunotherapy [30],[16].

CHAPTER 2

CRC SCREENING AND SURVEILLANCE

2.1 Background

Recently computer models have been used to better identify those at risk for colorectal cancer and to help determine the best treatment for them. With the help of effective computer models, the progress and effect of CRC in terms of cost and life-years gained for screening and surveillance methods can be predicted. Without these models it would be impractical and very expensive to study the effects of the disease on people.

Colorectal cancer is a disease suitable for screening [31],[32]. Screening tests can assist in finding pre-cancerous adenomatous polyps, which can then be removed before becoming cancerous. CRC screening tests also aide in finding colorectal cancer early when it is best treated.

2.2 Screening

Colorectal cancer is both treatable and preventable when detected at an early stage. Appropriate screening exams can help find and remove adenomas in an effort to prevent future CRC. Several screening techniques have emerged over the past few decades to help lower CRC [33-36]. Screening methods for CRC differ in performance features, complication rates, suitability and costs [36-39].

Screening tests can be compared based on accuracy by how specific or sensitive they are. Sensitivity and specificity are mostly used to determine the effectiveness and quality of the test. Sensitivity measures the proportion of positives that are found in a sick population and is the capability to identify true positives. If a test records few false negatives and several true positive it is considered highly sensitive. Mathematically, sensitivity *(S)* is expressed as [40]

Eq. 21

or

Eq. 22

Specificity (*Sp*) measures the number of negatives that are accurately identified as such. If few false positives and many true negatives are generated for a screening module then that module is considered to have high specificity. Mathematically, specificity is expressed as

Eq. 23

or

Eq. 24

There are two main recognized approaches for CRC screening namely endoscopic tests (visual examinations) and non-endoscopic tests (the stool is assessed for blood or DNA).

2.2.1 Endoscopic Test

Endoscopic tests allows doctors to look at the inside lining of the organ. The two main endoscopy tests involved in CRC screening is sigmoidoscopy and colonoscopy.

- Colonoscopy- screening with the removal of adenomas is an effective strategy for reducing colorectal cancer incidence and mortality [41]. During a colonoscopy, a specialist uses a colonoscope (see **Figure 21**), which is a long, thin and flexible tube with a camera and light on the end, and inserts it in the rectum going through the entire colon. In **Figure 21**, A is the position of the colonoscope; B is the endoscopic view; and C is the detail of the colonoscope tip.

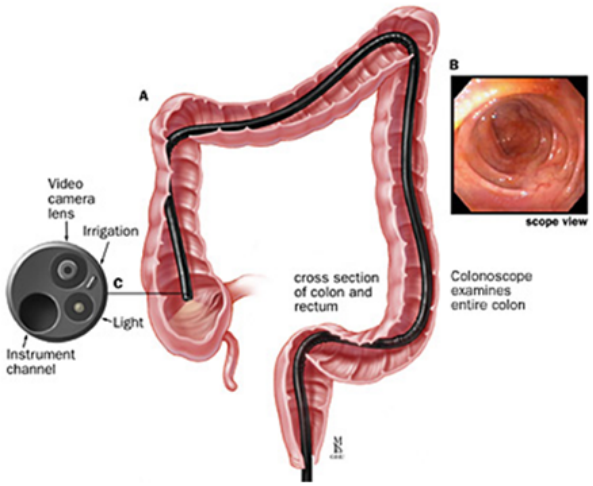

Figure 21: Instrument used to perform a colonoscopy [42].

- Sigmoidoscopy- Screening with flexible sigmoidoscopy has shown to reduce the rates of CRC diagnoses and deaths compared to no screening [43-45]. During

screening, the doctor examines only a portion of the colon and rectum using the same tool described for the colonoscopy. (See **Figure 22**). Sigmoidoscopy is often easier on patients but can miss polyps if they are in the distal colon [43].

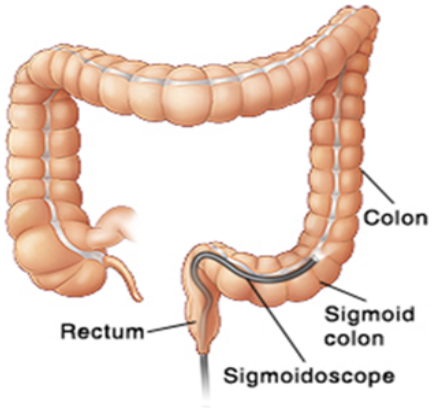

Figure 22: Instrument used to perform a sigmoidoscopy [46].

During these two procedures if some abnormal colon issue is found, it is collected and sampled. This is called a biopsy. If polyps are found during the colonoscopy or sigmoidoscopy then a polypectomy is performed. The polyp is captured and cut from the colon lining using a wire. Patients prepare for the procedures by removing all stools from the colon in order to improve visibility. The procedures are almost always performed as outpatient surgeries. **Figure 23** shows a comparison between a colonoscopy and a sigmoidoscopy.

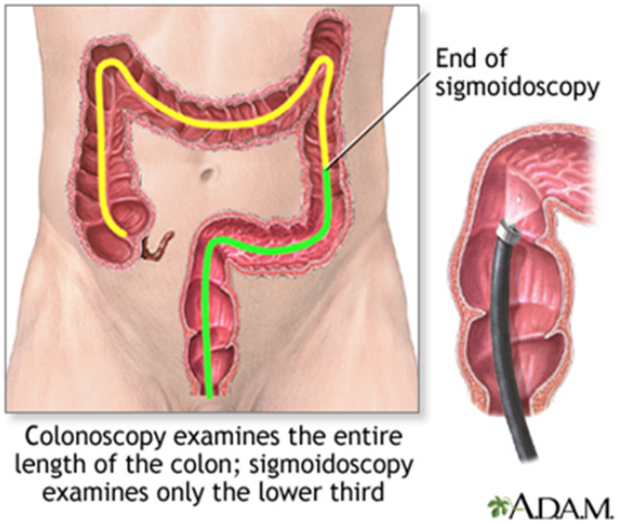

Figure 23: Difference in colonoscopy procedure (yellow) and sigmoidoscopy (green)[47].

2.2.2 Non-endoscopic Test

Fecal Immunochemical Tests (FIT) and Guaiac Fecal Occult Blood Tests (gFOBT)

Stool based screening tests are low-cost, non-invasive and is easily accessible for patients [48]. Fecal tests look for hidden blood in the stool. This could indicate an early sign of CRC. FIT and gFOBT are initial screening tests for CRC. It has been shown that testing for blood in the stool significantly reduces the incidence and death rate for CRC [48-51]. Some proof that the fecal blood tests reduce mortality was provided in some randomized trials around the 1980's [52]. CRC mortality was reduced by 15% to 33% when positive results were followed by a colonoscopy [49-51, 53].

A gFOBT uses the chemical guaiac to detect heme in the stool. Heme is an iron-containing compound of the porphyrin class that forms the non-protein part of hemoglobin and some other biological molecules [54]. During the process, hydrogen peroxide is dropped on the paper containing the stool and if blood is present, the paper will change to a blue color. The test is done with a take home kit so patients can have their privacy. From randomized trials [49-51, 53], the sensitivity of gFOBT ranges widely from 30%-90% [36], and its specificity around 78% [55]. FIT uses antibodies to detect human hemoglobin protein in the stool. The FIT procedure includes as supply kit with a collection bottle, absorbent paper, biodegradable collection paper, and a sample-mailing envelope. The kit will come will instructions on how to collect the sample. For the FIT test, only one sample needs to be collected and there are no dietary restrictions unlike the gFOBT.

The two tests are similar but FITs uses a more accurate technology in detecting blood in the stool. For that reason, studies [36], [55] show that the sensitivity of FIT is between 75% -90% with specificity about 90%. FIT has a higher sensitivity for screening relevant tumors, early stage cancers and advanced adenomas than gFOBT [36, 56, 57].

Since fecal tests have poor sensitivity to premalignant lesions, they must be repeated more often usually every 1- 2 years [48]. FIT is now considered a better alternative than gFOBT because of the better sensitivity. Since the interval for receiving fecal tests is shorter due to sensitivity and the costs of fecal tests are relatively low, combining fecal tests and with other screening techniques like sigmoidoscopy and colonoscopy may actually be more effective. Studies [58],[59],[60] have evaluated combined screening techniques. These studies focused on fecal blood test in conjunction

with sigmoidoscopy and found out that the likelihood of early detection as well as survival rates of CRC increased.

2.3 Complications due to Screening

There are some adverse effects associated with the procedures of colonoscopy. Some include, but are not limited to, death, bowel perforation, bleeding, serosal burn, reaction to sedation medicine, post-polypectomy hemorrhage, bleeding with transfusion and so on. The chances of having serious adverse effects of colonoscopy after screening are low but with increasing age they are relatively higher for follow-up colonoscopies [61].

2.4 Surveillance

Based on what was found at screening, a surveillance regimen is followed. People with prior history of colorectal adenomas or CRC should be checked more often than if nothing was found. This is because the risk of new colorectal adenomas or CRC forming is greater so a more aggressive approach needs to be implemented for such individuals. Surveillance intervals are typically shorter and it depends on the size and number of adenomas found.

2.5 Current Guidelines for Screening and Surveillance of Colonoscopy

Although in the last decade there has been an increase in the number of technologies available for CRC screening, colonoscopy screening rates are increasing while other technology rates are either declining or remain constant [62]. According to a study [63] done to determine whether Medicare reimbursement policy changes were associated with an increase in either colonoscopy use or early stage CRC diagnosis,

colonoscopy use increased by 5% each quarter during the study. The study showed that between 1993 and 2002, there was a staggering six fold increase in colonoscopy usage for detecting CRC.

Colonoscopy is thorough because it goes through the entire colon and also it is very sensitive. About 95% of cancers are detected during a colonoscopy. The National Polyp Study (NPS) found that patients who underwent a colonoscopy removing adenomas had a 76% to 90% lower incidence of CRC relative to patients without polypectomy [64]. The results of the National Polyp Study [64] revealed that colonoscopy polypectomy resulted in lower-than-expected incidence of colorectal cancer which supports the claim that adenomas grow to adenocarcinomas and also support the effectiveness of the current practice of identifying and removing adenomatous polyps [3]. As a result, recent trends in CRC incidence and mortality reveal declining rates, which have been attributed to reduce exposure to risk factors, screening effect on early detection and prevention through colonoscopy polypectomy, and improved treatments [3]. As colonoscopy rates increase, several specialty societies support colonoscopy as the ideal screening method for CRC [3].

The Microsimulation Screening Analysis (MISCAN-Colon) and Simulation Model of CRC (SimCRC) models are two models that compare strategies for screening that vary by age [65],[66],[67].

- MISCAN-Colon

This simulation model [67] was developed to examine trends in CRC due to various changes in lifestyle, improvement of treatment and application of screening approaches. It uses a Monte Carlo method to simulate all the events such as birth, death,

adenoma incidence, and transitions from one state of the disease to the other. It consists of three parts: (1) demography, (2) natural history, and (3) screening. The model combines demographic and epidemiological information from the SEER program. Individual life histories are generated from demography to form a population. Each patient consists of a date of birth and a date of death from other causes other than CRC. The model simulates a population of people where CRC and adenomatous polyps developed leading to a clinical diagnosis, treatment, and possibly death. In the natural history part, fictitious individual life histories where numerous colorectal lesions can merge are generated. Using the adenoma-carcinoma sequence of Vogelstein [68] and Morson [69], the natural history model was developed. In the screening part, some life histories will be changed. Age of screening, length of screening, the screening test and the diagnostic follow-up scheduled after a positive test is included in a screening policy. After each part the life histories are changed. The screening and natural history part are run simultaneously.

- SimCRC

The SimCRC [65] is a population-based microsimulation model that was developed in a way that it can simulate the US population from 1970 to a future year and it can also run a single birth cohort. The model is based on a state-transition Markov model designed to evaluate cost-effectiveness of screening [33]. The model consists of a natural history part, a screening part and a treatment part. The natural history follows the adenoma to carcinoma sequence as a function of age, sex, race, and risk factors. With the screening part, adenomas are detected and removed and early diagnosis of preclinical

CRC is possible. Once you have been diagnosed with CRC, then the treatment part is implemented.

2.6 Screening Age

When the disease is detected early it can be prevented thus reducing mortality rates but there is no ideal age to begin colonoscopy or to determine how often it should be done. The risk of the disease increases with age so beginning screening later will have more CRC develop while starting screening too early will likely not prevent as many cancers due to fewer adenomas having been developed. As each individual age, there is a chance that an adenomatous polyp forms and grows. One or more adenomas can happen in someone and each can develop independently into CRC [65]. The microsimulation models (MISCAN-Colon and SIMCRC) simulate colorectal disease progression in a large population of individuals from birth to death [65], [66]. These models are very useful because they allow for continued investigation of the results of varying screening age. Simulation models are sometimes used to determine if there is a protocol that is superior to existing care. They can also be used to predict the life-years gained relative to no screening, the number of colonoscopies required, the age at which to begin screening, age at which to stop screening, and screening interval [65].

Based on such simulation models and clinical evidence, the US Preventive Task Force guidelines recommend that people at average risk of colorectal cancer be screened starting at age 50 and should end at age 75 [70], [66]. People with no symptoms of the disease or personal or family history are considered average risk. They also suggest that people at average risk should undergo a colonoscopy every 10 years [66]. However, there is no formal guidance for the frequency of follow up colonoscopy after a colonoscopy in

which adenomas were found. Such patients are at higher risk for subsequent CRC [71] so the inter-colonoscopy intervals are typically shorter than 10 years. In addition, post-colonoscopy risk increases with age, but the frequency with which follow-up colonoscopy based on colonoscopy history and age should be done is unknown. This frequency will likely vary based on the risk factors for CRC at follow up.

2.7 Cost-effectiveness Analysis

Since the incidence of CRC is age-dependent, the effectiveness and cost of colonoscopy screening depend on the age at which the first examination is performed [72]. Although it has been found that colonoscopy screening is effective [71], the effectiveness comes at a significant additional cost [33]. Possible explanations for the increased cost is the need for repeated colonoscopy screening and surveillance in patients found to have adenomas on initial screening [33]. Cost-effectiveness of screening methods is often used in CRC research to compare different testing methods [73]. Cost-effectiveness analysis is considered a reasonable tool that properly compares the health and economic costs of different techniques, in turn helping decision makers to identify those that will produce the most health profits, given their resources limitations [73].

With the costs of providing these different interventions combined with the benefits associated with them, a cost-utility ratio result. This is the proportion between the cost of a health-related intervention and the benefit it produces in terms of number of years lived. This gives the incremental cost per QALY gained [74]. With the high costs associated with colonoscopy screening, well designed reviews are needed to assist decision makers in recognizing the effectiveness of the procedure in terms of QALYs gained [75]. QALY take into consideration both the quantity and the quality of life

generated by healthcare interventions. They provide a common way to assess the extent of the benefits gained in terms of health related quality of life and survival of the patient [75]. A QALY places a weight on time in different health states. A year of perfect health is valued at 1 and a year of less than perfect health is worth less than 1. Death is equal to 0; there are some health states that are considered worse than death which results in negative scores [75].

Since it has been proved that CRC screening by colonoscopy is more effective compared to other strategies [76], the economic impact has been evaluated in several cost effectiveness analyses. The majority of these analyses are based on the US population [73]. A systematic review conducted by Lansdorp-Vogelaar [73] on the cost-effectiveness of CRC screening showed that the cost-effectiveness ratios for all established screening strategies compared to no screening were less than $50,000 per life-year gained [73]. For colonoscopy screening the estimates were between $9,038 and $22,012 per life-year gained. Half of the studies found colonoscopy to be the most effective strategy. There is some variability on what is the appropriate benchmark. After over 20 decades in the US, the ratio of $50,000 per QALY gained by using a health care intervention still acts as a yardstick for value of care in the health policy system [77]. We would assume that based on inflation, economic growth and changes the yardstick would change but the benchmark still persists. Some argue that $100,000 is a better benchmark, some even argue, on the assumption of people's values and attitudes toward risk, that the threshold should be two to three times the per capita annual income, which based on the US per capita income of ~$54,000 would put the threshold at about $110,000 to $160,000 per QALY today [77]. Other societies even say a threshold of $200,000 to $300,000 per

QALY can work based on 1) the increases in health care expenditure over time and the health gains associated with those increases, 2) various tools to determine how much people are willing to pay for health gains or 3) the trade-offs people make in the workplace between pay and safety risks [78],[79]. Between 1990 and 2012, many authors have referenced different thresholds for US-Based Cost-Utility Analyses [77] with $50,000 and $100,000 per QALY still remaining the most widely used thresholds.

Several other cost-effectiveness analyses of CRC screening have been published and they generally confirm the findings of the systematic review that CRC screening is cost-effective compared to no screening but none of them has yet been found out to be most effective or have the most attractive cost-effectiveness ratio per QALY gained [73]. This is why in this study a cost effective analysis that will help to find the proper balance between life years gained and costs than what is currently recommended is performed. This work also determines the most favorable inter-colonoscopy interval.

2.8 Research Need

In the growing field of colorectal cancer, a needs area is determining the cost-effective inter-colonoscopy interval. While the MISCAN-Colon and SimCRC discussed earlier performed cost analysis of existing colorectal cancer screening protocols and evaluated the optimal age to receive a one-time colonoscopy, no work has been done to optimize the inter-colonoscopy interval. Because clinical studies have shown that post-colonoscopy CRC risk varies with age and prior colonoscopy results, it is highly likely that the cost-effective inter-colonoscopy intervals will differ from those of currently recommended for screening. Although colonoscopies are said to be effective [41], [76], the high price at which they come, can be a burden to most patients. Cost-effectiveness

analysis will not tell you what the best intervention is, but it will let you know which intervention will provide the utmost health profits, given the decision maker's willingness to pay for a unit of health [73].

Finding cost-effective use of screening procedures based on patient age and colonoscopy history will help determine the appropriate interval between colonoscopies. This is important because it can save costs. If the time interval is too long, then the risk of CRC increases leading to the need for more expensive treatments. Whereas, if the interval is too short, patients will receive unnecessary treatments and this comes with high costs.

Many studies have shown the different ages for colonoscopy screening that are more effective. In this decision analysis model [73], screening at age 40 was less cost-effective than screening at age 50. Another study found that screening at age 60 was more cost-effective than screening at age 50 or 70 [74]. The US Preventive Task Force guidelines recommend that people at average risk of colorectal cancer be screened starting at age 50 and should end at age 75 [65,], [66]. Unfortunately, currently research has not been done using a partially observed Markov process (POMP) to determine the most appropriate interval of performing a colonoscopy based on patient age and prior colonoscopy history. We intend to begin addressing this need to determine whether patients' history or age determines how soon they return for a follow-up colonoscopy.

Chapter 3 seeks to address the following questions:

- Is surveillance colonoscopy based on age and screening findings cost-effective?
- What is the optimal interval that maximizes patient QALYs?

CHAPTER 3

COMPUTATIONAL TECHNIQUES

3.1 Overview

An overview of the simulation process is shown in **Figure 31**. A partially observed Markov process (POMP) was used to simulate the effects that intervening with different follow-up colonoscopy scenarios had on the development of CRC. The POMP uses an adenoma and CRC growth model to calculate the probability of a patient having colorectal adenomas; asymptomatic local, regional, or distant CRC; and symptomatic local, regional, or distant CRC as the patient ages. Some of these adenomas and CRCs are then detected and removed during colonoscopy with the detection rate depending on the size of the neoplasia. The natural history model is coupled to a mortality rate model that calculates the probability of dying due to natural causes or CRC related mortality. Then, based on mortality, quality of life, and the costs associated with diagnosis, treatment, and surveillance of colorectal cancer, the overall costs and benefits in terms of QALYs are calculated for each follow-up colonoscopy scenario to determine its effects for the cost-effectiveness analysis. A diagram of the simulation process is available in **Figure 31**.

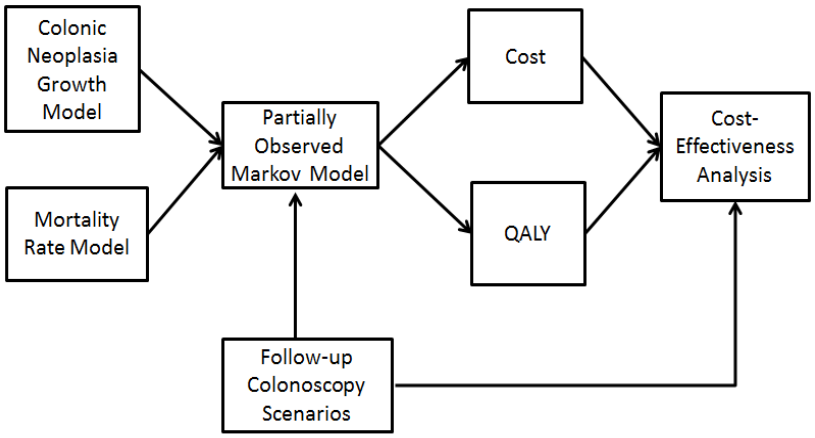

Figure 31: General overview of simulation process.

3.2 Markov Process

One of the most common and important of random processes is a Markov process. They were named after Andrei Markov. A Markov process is thought to be a random stochastic process (a sequence of events in which the outcome at any stage depends on some probability) where the number of possible outcomes or states is finite, the outcome at any stage depends solely on the outcome of the previous stage, and the probabilities remain constant over time [80]. It can be viewed by saying that the future and past of the process are independent of each other when the present is known.

A Markov process gives a more accurate solution to the problem you are addressing. A Markov process was chosen over a Monte Carlo Simulation because due to the nature of the number of simulations that needed to be run. Monte Carlo simulations also give an approximation compared to a more precise solution such as the Markov process.

3.3 Breakdown of each Component Methods

In this section, a detailed overview of each component of the proposed model will be discussed.

3.3.1 Colonic Neoplasia Growth Model

The colonic neoplasia natural history progression model combined transition rates from two studies each focusing on different phases of colonic neoplasia development: adenoma growth and CRC growth (see **Figure 32**).

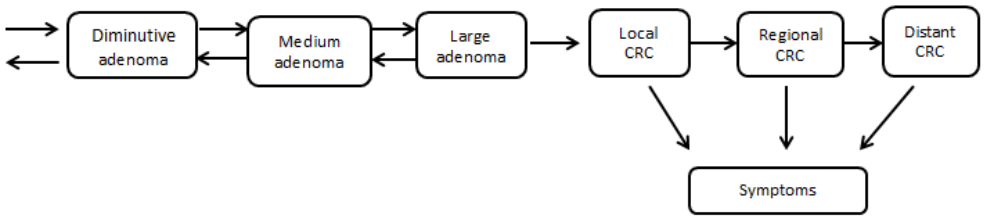

Figure 32: Adenoma growth model: Adenoma growth [81]; CRC growth [67], Symptoms [82].

To model adenomas growth, Sherer *et al.*[81] used serial colonoscopy results to identify the transition rates for the series of transition from diminutive adenoma (<5 mm) to medium adenoma (6-9 mm) to large/advanced adenoma (>10 mm) to CRC (**Figure 32**). It was assumed that multiple colorectal neoplasia can exist and grow/regress and that both the growth of each neoplasia and the appearance of new adenomas are independent of the other neoplasia. They tested whether each rate was age dependent and found that the rate of appearance of new adenomas varied with patients' age but the transitions to more advanced neoplasia were age-independent. The rates obtained from Sherer *et al.* [81] were integrated over a short, one month interval to get the monthly transition

probabilities and the monthly transition probabilities were combined to get the yearly transition probabilities (see **Table 31**).

Table 31: Annual transition probabilities between adenoma and CRC states.

Adenoma growth transition	**Yearly transition probability**
Diminutive to no adenoma	0.0181
Diminutive to medium adenoma	0.0163
Medium to diminutive adenoma	0.0716
Medium to large adenoma	0.0377
Medium adenoma to CRC	0.0025
Large to medium adenoma	0.0047
Large adenoma to local CRC	0.0028
CRC growth transition	**Yearly transition probability**
Local CRC to regional CRC	0.22
Regional CRC to distant CRC	0.50
CRC symptom transition	**Yearly transition probability**
Asymptomatic local CRC to symptomatic local CRC	0.17
Asymptomatic regional CRC to symptomatic regional CRC	0.22
Asymptomatic distant CRC to symptomatic distant CRC	0.50

To model CRC growth, the MISCAN-COLON model used SEER CRC prevalence data to identify the yearly transition probabilities between CRC stages and the probability of symptoms developing with CRC [67]. As people age, symptoms can develop as well. In the model, there are also transitions from asymptomatic to symptomatic states (which affects whether a patient receives a colonoscopy for symptoms and the neoplasia are detected) but we assume that the presence of symptoms does not affect the natural history of the neoplasia. A transition rate from asymptomatic to symptomatic [82] was used to determine probability of developing symptoms (see **Table 31**).

Each combination of adenomas and CRC defines a possible state of the colon. For example, the state, , is given by number of diminutive adenomas, number of medium adenomas, and etc. and the probability that a patient is in the state at age is . After a time period,, a patient in the state can transition to any other possible state (including remaining in the state) with a probability . Assuming no interventions, the dynamics of colonic state probability vector is the Markov Process and is giving by

Eq. 31

where, initially, there are no neoplasia. When, a person ages, the risk of CRC increases. The model mimics this behavioral pattern: each adenoma progresses naturally towards CRC and eventually death.

3.3.2 Mortality Rate Model

Patient death rates due to both CRC-related mortality and all-cause mortality were considered in the POMP model. Mathematical models for the rates of both processes were developed.

3.3.2.1 CRC-related Mortality

The CRC-related mortality rate was simultaneously fit to two data sources: the five year survival data for local, regional and distant CRC for white males diagnosed in 2003-2009 all followed through 2010 (**Table 32**) and the annual overall CRC survival rate for 10 years after diagnosis for patients diagnosed in 2003 (**Figure 33**). A least-squares objective function was used to fit every data point from both data sources: 4 data points for 5-year survival (one for each stage including an unknown stage) and 11 data points for overall CRC survival rate (annually for ten years after diagnosis).

Table 32: Annual transition probabilities between adenoma and CRC states.

CRC stage	**Prevalence**	**CDC data for 5-year survival rate**	**Model-predicted 5-year survival rate**
Local	44%	88.2%	88.1%
Regional	34%	70.1%	70.0%
Distant	18%	12.3%	12.2%
Unknown	5%	43.1%	43.1%

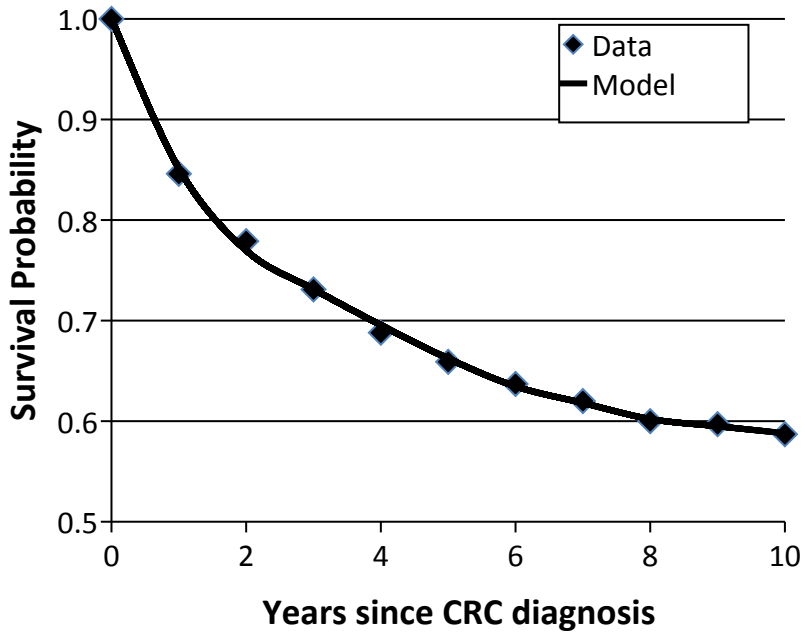

Figure 33: Model fit of overall CRC mortality using breakpoint model.

The CRC-related mortality rate varies by CRC stage so a different mortality rate was used for each CRC stage. The probability of surviving for a period of time after being diagnosed with the stage of CRC (where is either local, regional, distant, or unknown), , is described by

Eq. 32

where is the mortality rate.

With those probabilities, the overall survival probability of CRC patients with time,, was calculated by combining the survival rates for each stage weighted by the prevalence of each stage and it is given by

Eq. 33

where *rCRC* is regional CRC, *lCRC* is local CRC, *dCRC* is distant CRC, *uCRC* is the unknown CRC and subscript *s* represents survivor.

A constant mortality rate was not a good fit to the data because there was an over prediction in the earlier years since diagnosis and an under prediction in the latter years. A single breakpoint model was then applied on the mortality rates of each stage of the disease and provided an accurate fit to the data (**Figure 419** and **Table 33**). The mortality rate increased as the CRC spread and the decrease in the mortality rate after a few years matches the expectation that the mortality rate is highest immediately after CRC diagnosis. In addition, the breakpoint was early as the cancer became more distant (7.3, 5.3, and 1.6 years for local, regional, and distant CRC, respectively).

Table 33: Annual transition probabilities between adenoma and CRC states.

CRC stage	**Initial mortality rate (1/year)**	**Breakpoint (years)**	**Second mortality rate (1/year)**
Local	0.025	7.3	0.018
Regional	0.068	5.3	0.025
Distant	0.600	1.6	0.085
Unknown	0.155	4.8	2.24286E-06

3.3.3 All-cause Mortality

The all-cause mortality data was obtained from Table III in the National Vital Statistics (NVS) - Life table database, 2010[83] (see **Figure 34**). The rates from the NVS are based per 100,000 in specified age groups. The midpoint of each age group was

obtained and plotted against the death rates from the NVS – life table database. A 6th order polynomial was used to fit with the existing National Vital Statistics data.

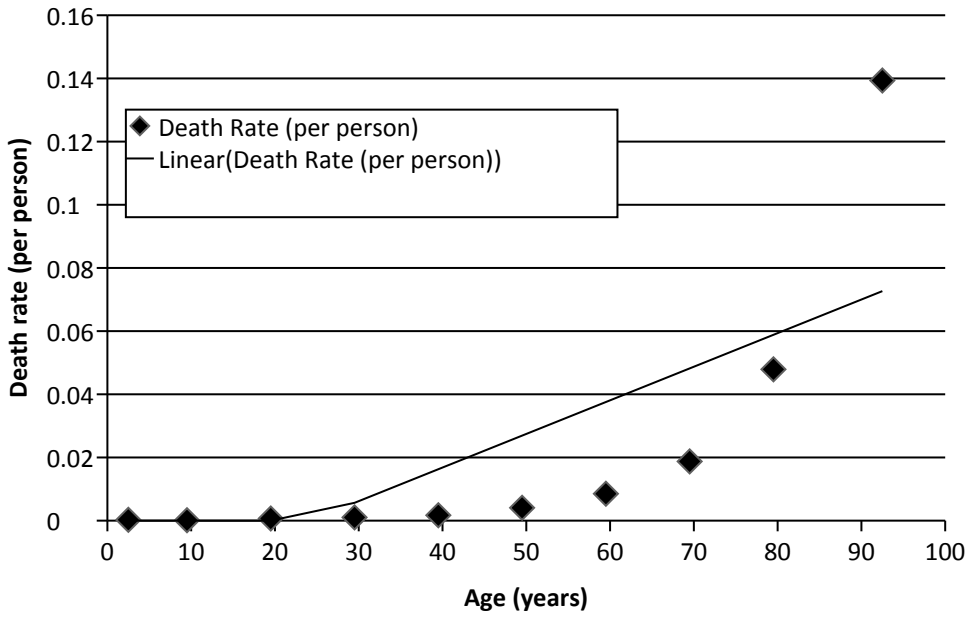

Figure 34: All-cause mortality data.

3.3.4 Partially Observed Markov Process (POMP)

Leading to the colonoscopy screening, the adenoma growth and mortality rate models are applied to the patients. A patient can die from natural causes, remain in a healthy state, develop symptoms and develop polyps or CRC. These patients are initially not in the patient pool because each hypothetical patient is considered healthy until their screening colonoscopy. To mimic the clinical classification of colonoscopy results, the probabilities of every possible combination of colonic neoplasia were used to calculated the probability of eight colonic neoplasia states: (1) no adenomas, (2) 1-2 non-advance adenomas only, (3) 3+ non-advanced adenomas only, (4) 1-2 adenomas with some

large/advanced adenomas, (5) 3+ adenomas with some large/advanced adenomas, (6) local CRC, (7) regional CRC, and (8) distant CRC.

A POMP was used to obtain the CRC predictions. Since colonoscopy is not 100% sensitive [81] the actual state is only partially observed. Sherer *et al.* [81] reported colonoscopies are more likely to be sensitive for larger adenomas (95.8%) as opposed to diminutive ones (39%). Several studies [39, 67, 81, 84-86] have shown that smaller adenomas are more commonly missed as opposed to larger ones. Sherer *et al*., in their study saw differences in patient's age for diminutive, small, large and cancerous neoplasia.

Based on the findings at the screening colonoscopy, the patients will follow a follow-up colonoscopy regimen suitable to the findings obtained. Patients can die from natural death at any point in the model and are removed from the pool of patients. The probabilities collected from the POMP are incorporated into the costs and QALYS results to perform the cost-effectiveness analysis.

3.3.5 Follow-up Colonoscopy Scenarios

Different follow-up colonoscopy protocols were applied and the associated costs and benefits (in terms of QALYs gained) calculated. One follow-up colonoscopy was evaluated to determine its effects. Scenarios were evaluated for screening colonoscopy at ages 50, 55, 60, 65, 70 or 75 years, and a single follow-up colonoscopy from 2 years until 20 years in increments of 2 years. The CRC predictions were applied to the follow-up colonoscopy scenarios and the probabilities collected were incorporated into the costs and QALYS results. The cost per QALY gained was calculated (section 3.3.6.1) and the follow-up intervals were identified by quadratic interpolation.

3.3.5.1 Control Group

Control groups are essential parts to many research designs, they allow for meaningful comparisons to be drawn. They allow researchers to minimize the effect of all variables except the independent variable.

3.3.5.1.1 Control Group: Screening only

To measure the effect of follow –up colonoscopy a control group who received a screening but no follow-up colonoscopy was used. The costs and QALYs were obtained for patients who received surveillance colonoscopies vs. those who just had a screening and no surveillance. This scenario will give the optimal intervention at each screening age.

3.3.6 Outcomes of Partially Observed Markov Process

3.3.6.1 Costs

Costs are a main factor in a cost-effective analysis. The first set of costs that is typically observed with a disease is the cost of treating the disease like hospitalization costs, medicine costs, and doctor costs. Other costs include costs of screening procedures and new treatments, cost of missing work, transportation and travel costs, and so on.

Two types of costs were considered: costs associated with CRC treatment and costs associated with receiving colonoscopy [87-91] (see **Table 34**). We assumed all other costs to be equal between patients so there would be no cost difference based on colonoscopy.

Table 34: Costs used in the cost-effectiveness analysis.

Type of treatment	Costs (Range for Sensitivity Analysis)

Costs of colonoscopy	
Colonoscopy	$1,068.59 ($303 - $2627) [87-91]
Adverse effects	$92.06 [88]
Annual cost of CRC treatment	
Local	
Initial (year 1)	$20,247.20 ($13,848 - $25,527.02) [87-91]
Surveillance (years 2-5)	$1305.04 ($425 - $2353.26) [87-91]
Regional	
Initial (year 1)	$26,007.50 ($15,398 - $37639.27) [87-91]
Surveillance (years 2-5)	$2346.72 ($1424 - $4014.69) [87-91]
Distant	
Initial (year 1)	$30,085.20 ($17,223 - $42,401) [87-91]
Surveillance (years 2-5)	$15,057 ($2702 - $26,855) [87-91]
Terminal (if CRC results in mortality)	$23,002.35 ($11,188 - $50,920) [87-91]

The cost of screening colonoscopy ranged from $300 to $2,627 [87-91]. An average US price of $1,068.59 was used. There was also an additional cost of $92.06 due to adverse events [88]. Multiplying the price of each adverse event by its rate and summing over all the adverse events calculated the cost due to adverse events. The types of adverse events incorporated were perforation, serosal burn, bleed with transfusion, bleed without transfusion, and post polypectomy hemorrhage. The two costs were combined to obtain the overall cost of colonoscopy where is the probability of receiving

a follow-up colonoscopy at age (at scheduled colonoscopies and when colonoscopies are not scheduled due to symptoms).

Eq. 34

Initial and surveillance [87-91] costs were included within the model for each of the three cancer stages (Local, Regional and Distant). A general terminal CRC cost was used because terminal costs are nearly the same for all three stages of CRC. A weighted average was calculated for each cancer stage based on the different costs. CRC is mostly characterized by stages but in our model we assumed local CRC to be the equivalent of stage 0 and stage 1 CRC combined, regional CRC to be equivalent to stage 2 and stage 3 CRC combined, and distant CRC to be equivalent to stage 4 CRC. From the different costs, an average initial cost was chosen for local, regional and distant CRC. The same rationale was applied for the surveillance costs of CRC from the different costs sources obtained. The costs were matched against projected costs for CRC for 2020 [92] and they fell within the ballpark of these projected costs.

3.3.6.2 Discounting

In order to best compare interventions with different costs and health effects, it is common practice to use a discounting in simulations. Discounting is a way of valuing rewards and events in the present more than the future. Both costs and QALYs were discounted. The overall outcome of the analysis was cost per QALY gained so both criteria had to be discounted. This prevents the problem of intertemporal inconsistencies, which are the inconsistencies that exist when people's current choices affect the options they have available in the future. All costs were discounted at an annual rate of 3%. The discounting factor at each age was calculated by

Eq. 35

where *r* was the rate and *t* was the age. The discounting factor was used in the colonoscopy costs to give an updated cost of

Eq. 36

Local, regional and distant discounted costs were calculated the same way.

For the first year, all the costs for screening and diagnosis were incorporated and multiplied by the probability of having local cancer at that age. After screening and diagnosis the patient goes in to the first year of surveillance where surveillance costs for local CRC are added to local CRC costs and multiplied by the probability of having local cancer. This calculation continued for the surveillance years with the probability of local cancer changing for each year. For local terminal costs, the calculations were similar to the surveillance but instead we used the probability of the patient dying with local cancer at each age multiplied by the probability of local CRC. Costs were calculated similarly for regional and distant CRC. Total costs were obtained by

Eq. 37

Eq. 38

where stage=local, regional, distant, and

3.3.6.3 Quality-Adjusted Life-Years (QALYs)

A QALY is a measure of the value used for quality of life. It focuses both on quantity and quality of life given by healthcare interventions. It deals with a scaled score ranging from 0 to 1, where 1 represents a utility for perfect health and zero represents a

utility for a health state close to death. With increasing age, the utilities associated with perfect health declines because several health issues arise with increasing age. In order to calculate the QALYs, the utilities were obtained from Ness *et al* [88] (see

Table 35).

Table 35: QALYs used in the cost-effective analysis.

Patient status	**Annual QALY Utility**
Healthy	0.91
Dead	0
Local CRC	0.74
Regional CRC	0.70
Distant CRC	0.25

The disease specific health state utilities were multiplied by the probability of being in that state at each given age and the results were summed up for all the health states over all ages to obtain the total QALYs:

Eq. 39

where i = healthy, dead, local, regional, distant

and

Eq. 310

where i = healthy, dead, local, regional, distant.

The QALYs were also discounted at 3% using the same discounting factor in section 3.3.6.2. The discounting factor was used in the QALYs to give updated QALYs given by

Eq. 39

3.4 Cost-effectiveness Analysis

By applying the POMP model we determined the inter-colonoscopy interval that maximizes patient's QALYS per unit cost of colon-related expenses. The primary outcome of a cost–effectiveness analysis is the incremental cost- effectiveness ratio (ICER), otherwise known as the cost per QALY. This is calculated as the difference in the expected cost of two interventions, divided by the difference in the expected QALYs produced by the two interventions. **Eq. 310** gives the formula used to calculate cost per QALY gained/10,000 persons:

Eq. 310

The outcome that yielded the most QALYs per unit cost of CRC expenses is the optimal solution. Over the years there has been an increase in articles referencing both $50,000 and $100,000 as the society's willingness to pay (WTP) threshold for a quality adjusted life year[77, 78] so this fueled our urge to use a $50,000, $75,000 and $100,000-per-QALY threshold. In the analysis, effectiveness was the change in QALYs and the efficiency referred to the change in cost per QALY.

Once the simulation for the protocols was completed, the focus was solely on the cases where the cost per QALY gained was less than or equal to the thresholds (the cost-effective scenarios). From that pool of cost-effective scenarios, the scenario with the most QALYs gained/10,000 persons was collected. This gave us our optimal interval for the varying protocols

Efficiency was assumed to be the change in cost over the change in QALYs.

Eq. 311

Effectiveness was assumed to be the change in QALYS gained by

Eq. 314

3.5 Sensitivity Analysis

Obtaining good impartial estimates of both costs and effectiveness of different protocols in a cost-effective analysis is very important. A sensitivity analysis is an easy approach used by modelers whose main goal is to support decision makers. Since the factors, values, and assumptions of any model can easily result in error and change; sensitivity analyses are needed to investigate these changes and errors and what effect they have on the model.

A main factor in the calculation is set to either the extreme low or extreme high and is recalculated. The simplest form of sensitivity analysis is a univariate analysis, only one main parameter is changed at one time, and correlations between parameters are not taken into account. The results obtained from the extreme values are compared to the original results. The difference in results will tell you how sensitive the results are to that particular parameter.

A one-way sensitivity analysis was performed to test the effect changes in various fundamental assumptions would have on the cost-effectiveness. In this study, changing the cost of colonoscopy, the cost of cancer, and the discount rate did the one-way sensitivity analysis. The ranges used in the sensitivity analysis were based on literature

review [87-91] (see **Table 34**). For the sensitivity analysis on the discount rate we tested a 0% discount rate. The entire model was analyzed using a Matlab.

CHAPTER 4

ANALYSIS OF SIMULATION PROTOCOLS FOR COLONOSCOPY FOLLOW-UP

4.1 Introduction

Chapter 3 discussed the methods needed to analyze the cost-effectiveness of follow-up colonoscopy. The goal of this section of the research was to answer two main questions:

1. Is follow-up colonoscopy based on patient age and screening colonoscopy results cost-effective?
2. What is the cost-effective interval that maximizes patients QALYs gained by age and screening results?

4.2 Follow-up Colonoscopy based on Patient Age and Screening

Is follow-up colonoscopy based on patient age and screening colonoscopy results cost-effective?

Follow-up colonoscopy was only cost-effective after screening colonoscopy at age 50 years and at the $100,000/QALY gained threshold. Follow-up colonoscopy for screening that occurs after the age of 50 years was not cost-effective and no scenario was cost-effective at the $75,000/QALY gained or the $50,000/QALY gained thresholds.

4.2.1 Age 50

At age 50, one follow-up colonoscopy was cost effective. In **Figure 41 to Figure 45** all the follow-up colonoscopies (2 to 20 years later) at age 50 for all screening findings can be seen. Looking at **Figure 41** to **Figure 45**, only the $100,000 per QALY threshold is cost effective. At screening age 50 no cost-effective follow-up colonoscopies

were recorded for the other two thresholds. There is nothing below $80,000. Figure shows the results obtained for the cases where screening age 50 was not cost-effective.

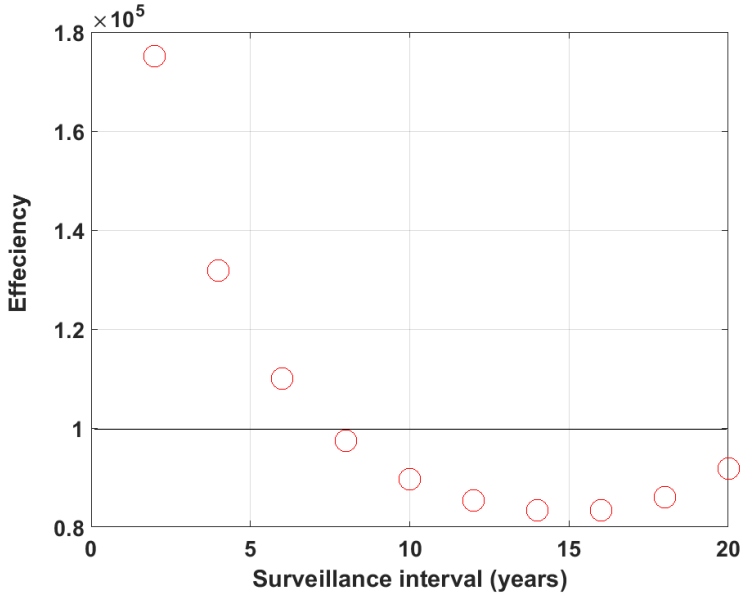

Figure 41: Efficiency vs Surveillance intervals at age 50 for no neoplasia finding.

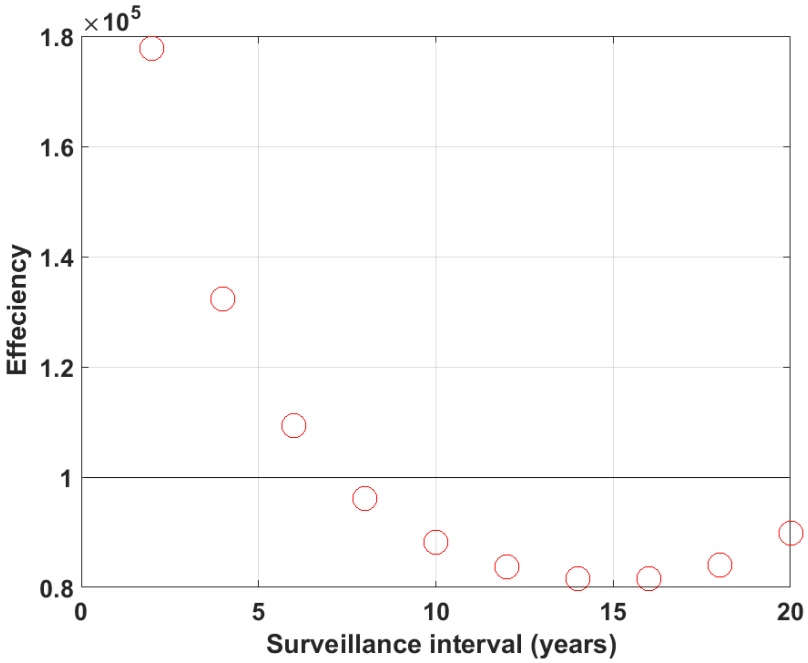

Figure 42: Efficiency vs Surveillance intervals at age 50 for 1 to 2 polyps only finding.

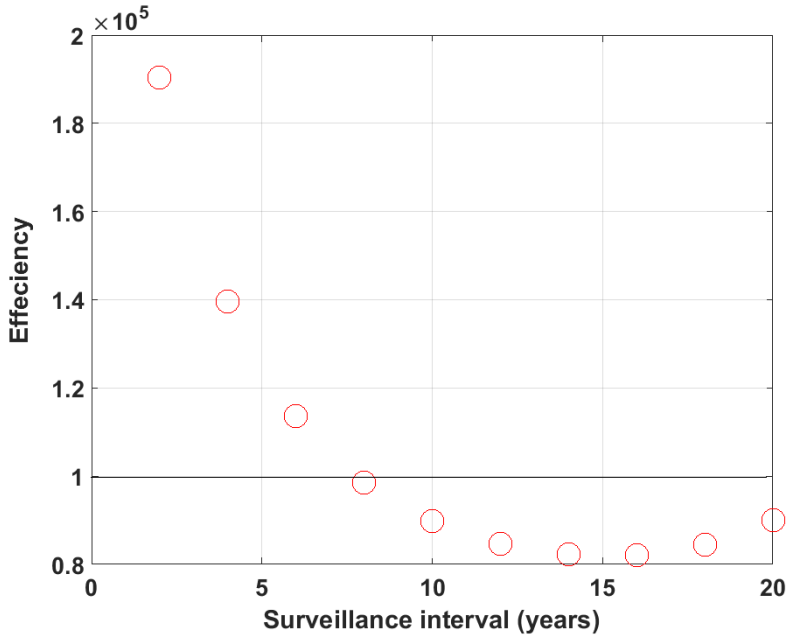

Figure 43: Efficiency vs Surveillance intervals at age 50 for 3 plus polyps only finding.

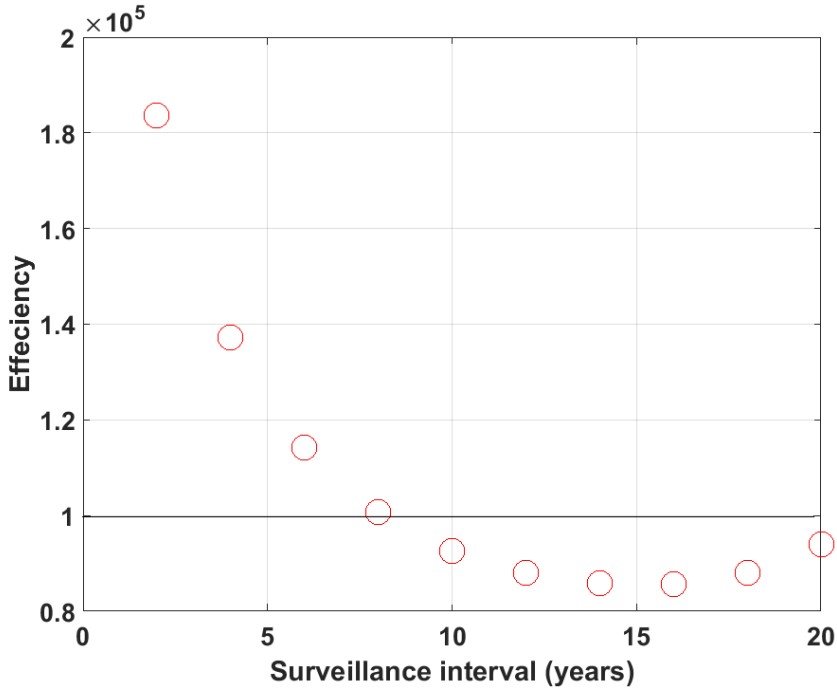

Figure 44: Efficiency vs Surveillance intervals at age 50 for 1 to 2 advanced polyps only finding.

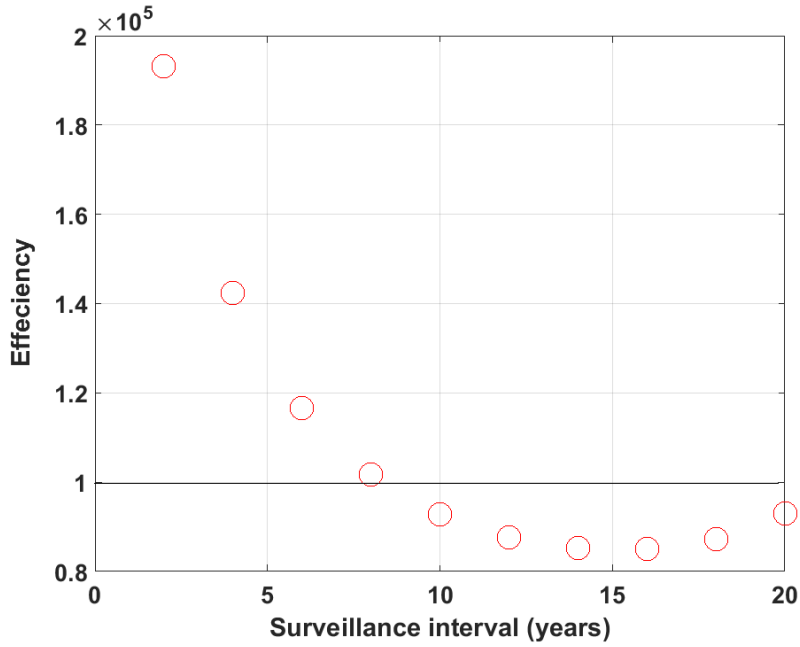

Figure 45: Efficiency vs Surveillance intervals at age 50 for 3 plus advanced polyps only finding.

Based on the results, cost-effectiveness of follow-up colonoscopy at age 50 did not vary very much with the screening findings. All the follow-up colonoscopies that were cost-effective at the different screening findings occurred between 7.7 to 20 years later. A linear interpolation was done to find the exact point where the colonoscopies became cost-effective. Because the only threshold that was cost effective was $100,000, the lower and upper intervals where this threshold fell between were used to get the most cost-effective follow-up year (see **Table 42**). **Table 4-1** shows the ranges that were cost effective for each screening finding.

Table 41: Ranges of follow-up colonoscopies that were cost effective at age 50 for all screening findings.

Age at screening colonoscopy (years)	**No Neoplasia**	**1 to 2 non-advanced adenomas only**	**3+ non-advanced adenomas only**	**1 to 2 adenomas with some advanced neoplasia**	**3+ adenomas with some advanced neoplasia**	**All stages**
50	7.6 – 20 years	7.4 – 20 years	7.8 – 20 years	8.2 – 20 years	8.4 – 20 years	7.7– 20 years

Follow-up colonoscopy was only cost-effective after screening colonoscopy at age 50 years at the $100,000/QALY gained threshold.

4.2.2 Age 55

Follow-up colonoscopy after screening at age 55, 60, 65, 70 and 75 years was not cost-effective at any of the three thresholds. Demonstrated in **Figure 46 -Figure 410** are the scenarios for the ages 55 – 75 with the general all stages finding. These instances

were not cost effective at the 3 thresholds. The follow-up colonoscopies cost more than $100,000.

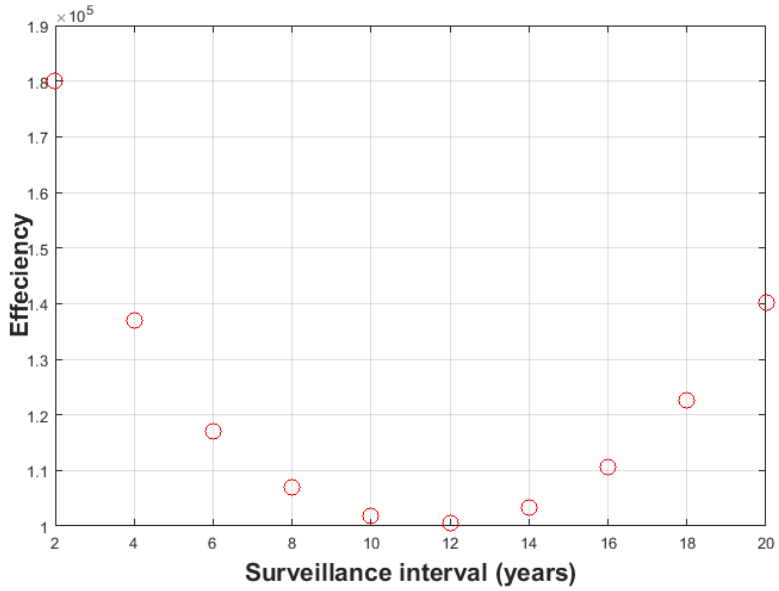

Figure 46: Efficiency vs Surveillance intervals at age 55 for a general all screening results- an average of all the findings combined.

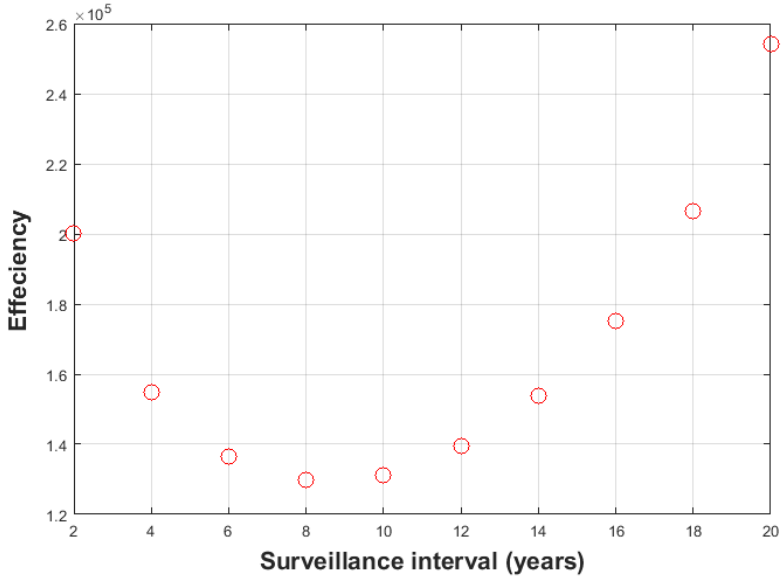

Figure 47: Efficiency vs Surveillance intervals at age 60 for a general all screening results- an average of all the findings combined.

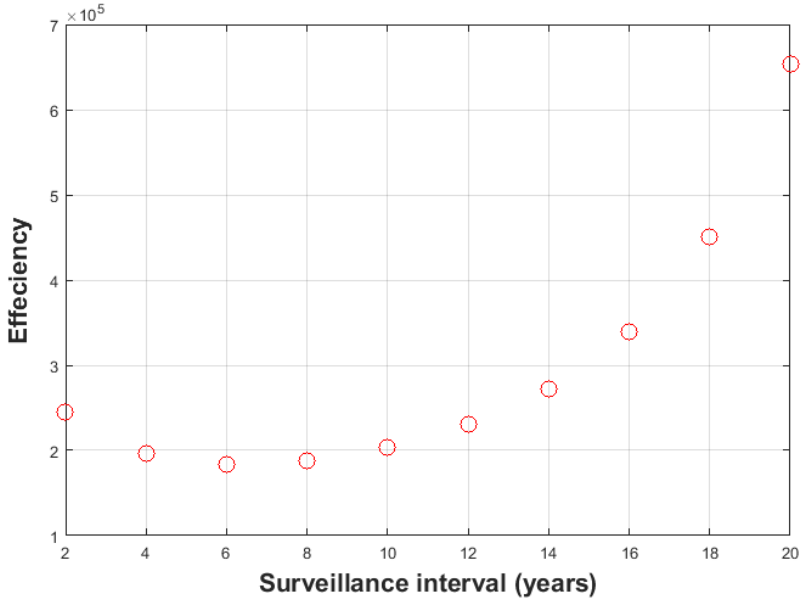

Figure 48: Efficiency vs Surveillance intervals at age 65 for a general all screening results- an average of all the findings combined.

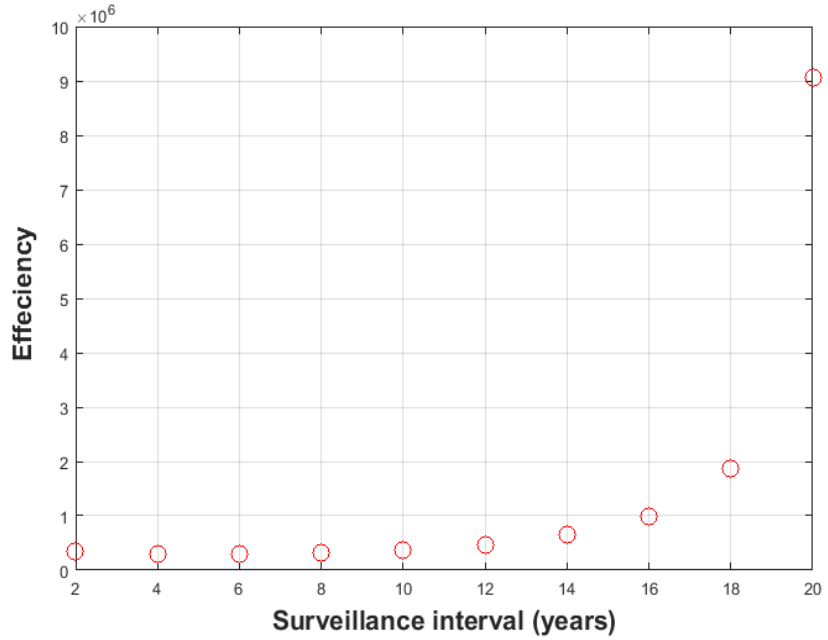

Figure 49: Efficiency vs Surveillance intervals at age 70 for a general all screening results- an average of all the findings combined.

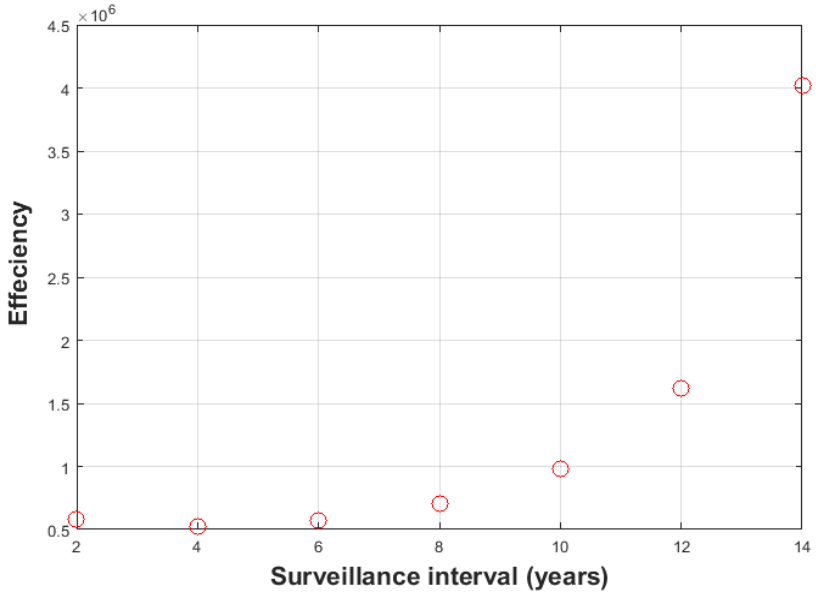

Figure 410: Efficiency vs Surveillance intervals at age 75 for a general all screening results- an average of all the findings combined.

4.3 Cost-effective Interval that Maximizes Patient's QALYs Gained by Age and Screening Results

What is the cost-effective interval that maximizes patients QALYs gained by age and screening results? Two control groups were tested to answer this question.

4.3.1 Results for Control Group 1

From the pool of colonoscopies that were cost-effective (see section 3.3.5.1.1), the one that produced the most QALYs was considered to be optimal. A quadratic interpolation was done to determine what that interval was that yielded the most QALYS.

Three points were chosen - the maximum point and the two points surrounding the maximum - and were interpolated to obtain the interval. The interpolation was done in Matlab.

4.3.2 Age 50

The cost-effective range for the $100,000 threshold for age 50 with no neoplasia was 7.6 to 20 years. Out of that range, what interval gave the highest QALYs (optimal solution)? **Figure 411** shows the QALYs-gained per 10,000 patients for the follow-up years. In the figure the three points that were used for the interpolation can be seen highlighted in the box. The maximum falls somewhere between 6 and 10 years (see **Table 42**). For all other screening findings, (see to **Figure 412** to **Figure 415),** the same procedure was used to obtain the optimal interval.

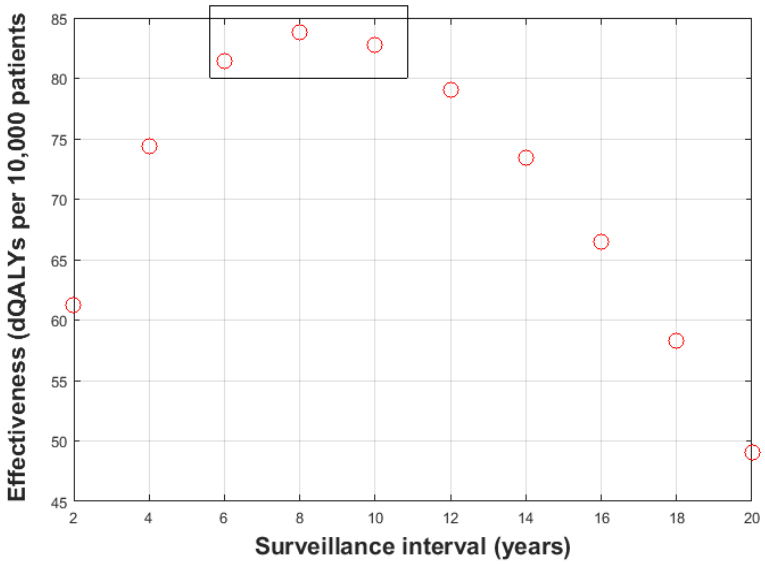

Figure 411: Effectiveness vs Surveillance intervals (ΔQALY) at age 50 with no neoplasia.

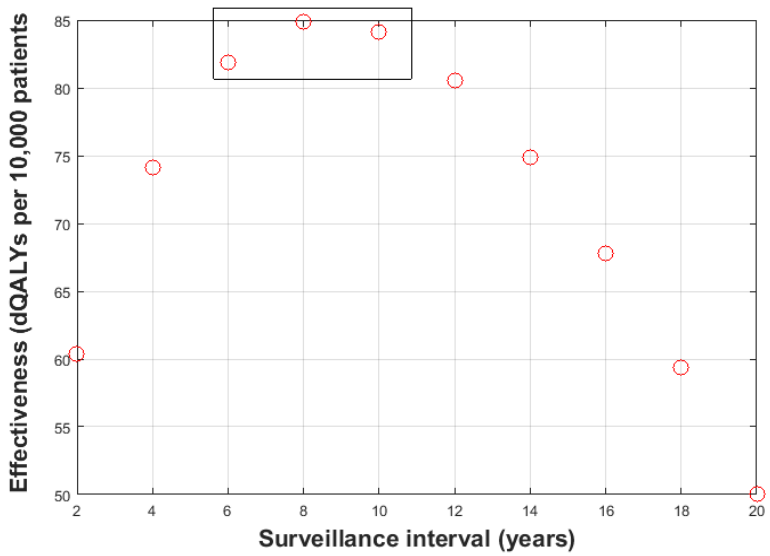

Figure 412: Effectiveness vs Surveillance (ΔQALY) at age 50 with 1 to 2 small polyps only.

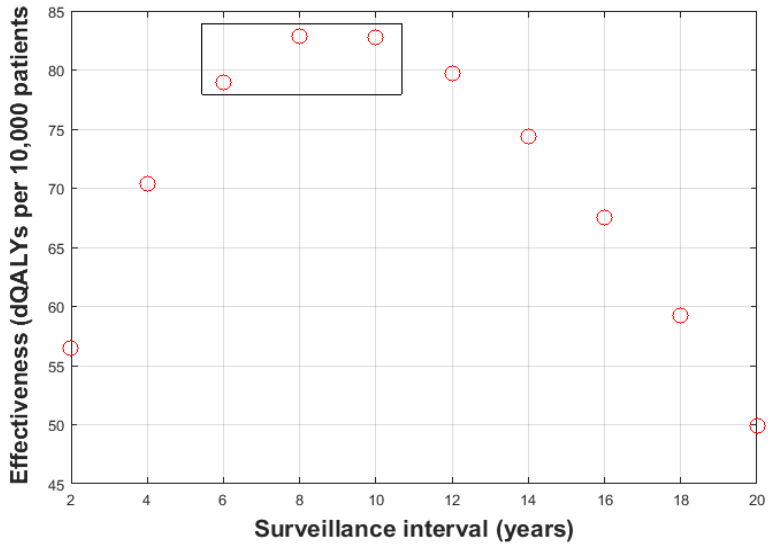

Figure 413: Effectiveness vs Surveillance (ΔQALY) at age 50 with 3 plus small polyps only.

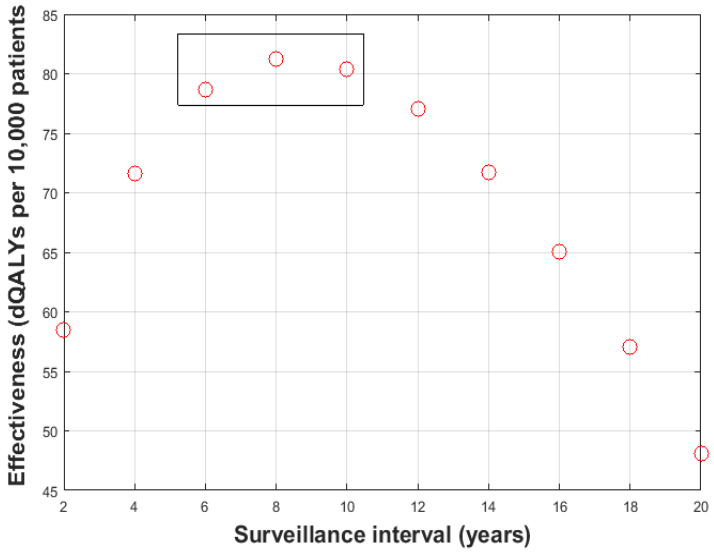

Figure 414: Effectiveness vs Surveillance (ΔQALY) at age 50 with 1 to 2 advanced polyps only.

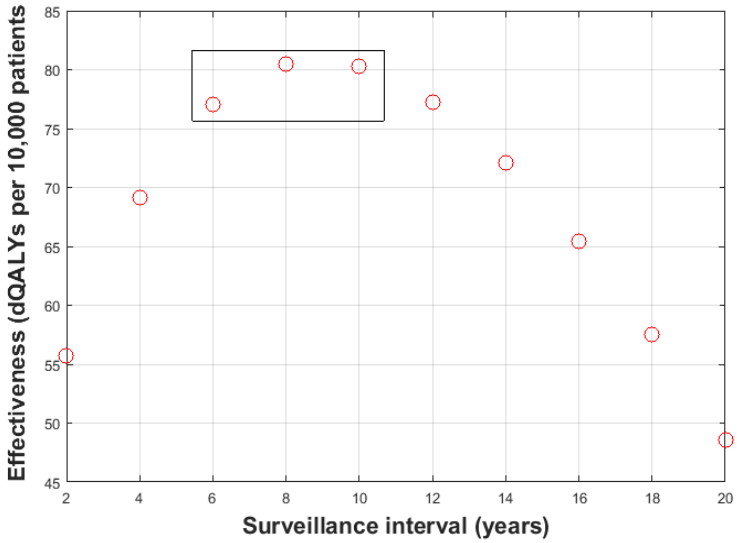

Figure 415: Effectiveness vs Surveillance (ΔQALY) at age 50 with 3 plus advanced polyps only.

The inter-colonoscopy intervals were largely insensitive to the screening colonoscopy results; inter-colonoscopy intervals stratified by the screening result were all within a 0.5-year range (see **Table 42**). Because of this insensitivity and for simplicity, the average follow-up interval is reported and the intervals stratified by screening result reported in **Table 42**.

Table 42: Inter-colonoscopy intervals that maximize QALYS gained for the $100,000 threshold.

Age at screening colonoscopy	**No Neoplasia**	**1 to 2 non-advanced adenomas only**	**3+ non-advanced adenomas only**	**1 to 2 adenomas with some advanced neoplasia**	**3+ adenomas with some advanced neoplasia**	**All stages**
50 years	8.5 years **(83.98)**	8.5 years **(84.04)**	9.0 years **(83.29)**	8.4 years **(81.25)**	8.9 years **(80.71)**	8.5 years **(83.96)**

Following screening at age 50 years the most QALYs gained at the $100,000/QALY threshold was at one follow-up colonoscopy with interval of 8.5 years. There were 83.96 QALYs gained per 10,000 people at that threshold. There were no cost-effective follow-up colonoscopies for screening at older ages. **Table 42** shows the interval where the most QALYS were gained for each finding.

4.3.3 Age of final colonoscopy

There was never a cost-effective follow-up colonoscopy after age 60 years. At the $100,000/QALY threshold, after screening at age 50 for all the stages finding, no follow-up colonoscopies were recorded after age 58.5 years.

4.4 Sensitivity Analysis

From the sensitivity analysis the model was relatively insensitive to high screening colonoscopy costs and low cancer cost. When the higher end of the colonoscopy cost was used, nothing was cost-effective at any screening age at any of the three thresholds. When using the low end of the cost of cancer, at screening age 50 years, the cost-effective window was recorded between 10 to 20 years at the $100,000 threshold, compared to 7.7 to 20 years from the original analysis. Also the recommended follow-up interval dropped from 8.5 years to 8.3 years, and the QALYS gained/10,000 persons decreased by 0.1. Nothing became cost-effective at the $75,000 or $50,000 threshold.

The model was however sensitive to lower screening colonoscopy costs, higher cancer cost and the 0% discount rate (see **Table 43**). In the table, a single number "x" represents one follow-up colonoscopy was cost-effective, two numbers "x, y" represents two follow-up colonoscopies were cost-effective and so on.

Table 43: Inter-colonoscopy intervals for sensitivity analyses.

Screen Age	Outcome	Colonoscopy Cost		Cancer Cost		Discount Rate
		Low	High	Low	High	

		($303)	($2,627)			
$100,000 / QALYs gained						
50 years	Recommended follow-up interval	8.5 years	Not cost-effective	8.3	8.5	3.9, 4.0, 4.9, 6 years (437.22)
	Range of cost-effective follow-up colonoscopy	2 – 20 years		10 – 20 years	8– 20 years	
	Gain in QALYs / 10,000 persons	84.0		83.9	84.0	
55 years	Recommended follow-up interval	6.8	Not cost-effective	Not cost-effective	5.8	3.6,4.5,5.8 years (305.52)
	Range of cost-effective follow-up colonoscopy	2 – 20 years			10– 14 years	
	Gain in QALYs / 10,000 persons	75.1			75.6	
60 years	Recommended follow-up interval	5.6 years	Not cost-effective	Not cost-effective	Not cost-effective	6.4 years (120.01)
	Range of cost-effective follow-up colonoscopy	2 – 20 years				
	Gain in QALYs / 10,000 persons	62.6				
65 years	Recommended follow-up interval	4.3 years	Not cost-effective	Not cost-effective	Not cost-effective	Not cost-effective
	Range of cost-effective follow-up colonoscopy	2 – 14 years				
	Gain in QALYs / 10,000 persons	47.6				
$75,000 / QALYs gained						
50 years		Not cost-	Not cost-	Not cost-	Not cost-	6.4, 8.1 years

		effective	effective	effective	effective	(307.30)
55 years		Not cost-effective	Not cost-effective	Not cost-effective	Not cost-effective	8.2 years (157.14)
$50,000 / QALYs gained						
50 years		Not cost-effective	Not cost-effective	Not cost-effective	Not cost-effective	10.3 years (194.12)

When the low end of the colonoscopy cost was used, more screening ages (55, 60, and 65 years) were found to be cost-effective at the $100,000 threshold and it was also observed the interval for screening in the age 50 group widened from 7.7 to 20 years to 2 to 20 years. With the screening ages that were cost-effective, the recommended follow-up intervals and number of QALYS gained/10,000 persons decreased with increasing age. With the high end of cancer cost, screening age 55 became cost effective with follow-ups 10 to 14 years later with an average 5.8 follow-up interval and 75.6 QALYS gained/10,000 persons. For screening age 50, the range closed by a mere 0.3 years with the same follow-up interval and QALYs gained from the original analysis. With the 0% discount rate showed as many as 4 follow-up colonoscopies were cost-effective at screening age 50 at the $100,000 threshold with 437.22 QALYs gained/10,000 persons. More screening ages also became cost-effective at the $50,000 and $75,000 thresholds. Based on the sensitivity analysis we can see that with increasing threshold on the societal willingness to pay for a QALY, more follow-up colonoscopies are possible with higher QALYs gained/10,000 persons.

4.4.1 Low Screening Colonoscopy Costs

After the cost of screening colonoscopy was adjusted to its ultimate low, it was observed that more screening ages became cost effective for the $100,000 threshold. From the cost of colonoscopy used in the original simulation, only age 50 was cost-effective at the $100,000 threshold. After the parameters changed, ages 50, 55, 60, and 65 became cost effective at the $75,000 and $50,000 threshold as well. With the cost of colonoscopy at its lowest we can see that follow-up colonoscopies at screening ages 50, 55, 60, and 65 being cost-effective at all the thresholds.

Figure 416 to **Figure 419** show the surveillance intervals vs. efficiency for screening at age 50, 55, 60, and 65, respectively, for the lowest screening colonoscopy cost. Below the circled area on the figures shows the region where the follow up intervals that was cost effective at the $75,000 threshold and the line shows the region where the follow up intervals that was cost effective at the $50,000 threshold.

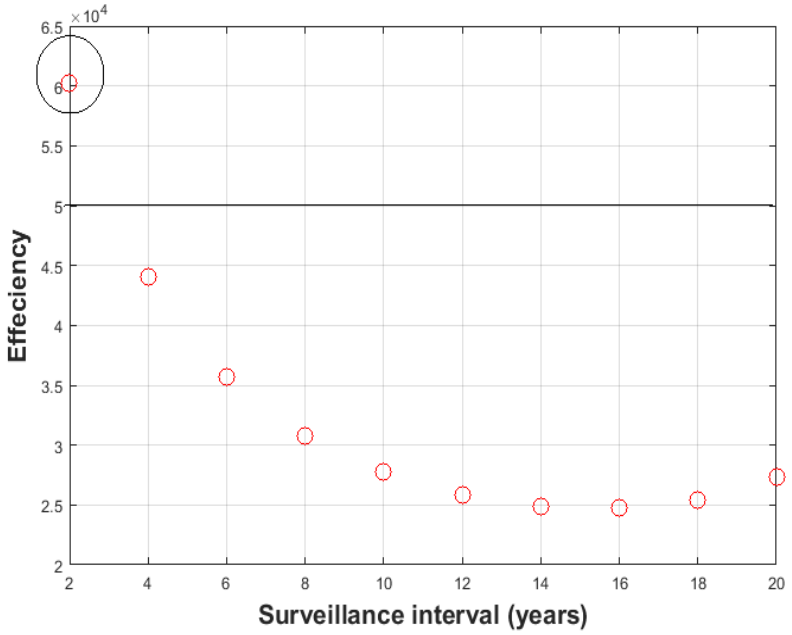

Figure 416: Efficiency vs Surveillance intervals at age 50 with all screening results.

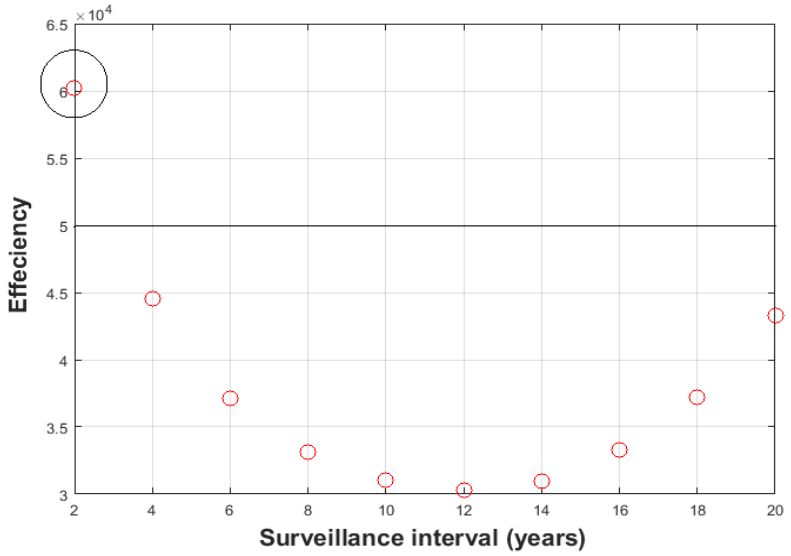

Figure 417: Efficiency vs Surveillance at age 55 with all screening results.

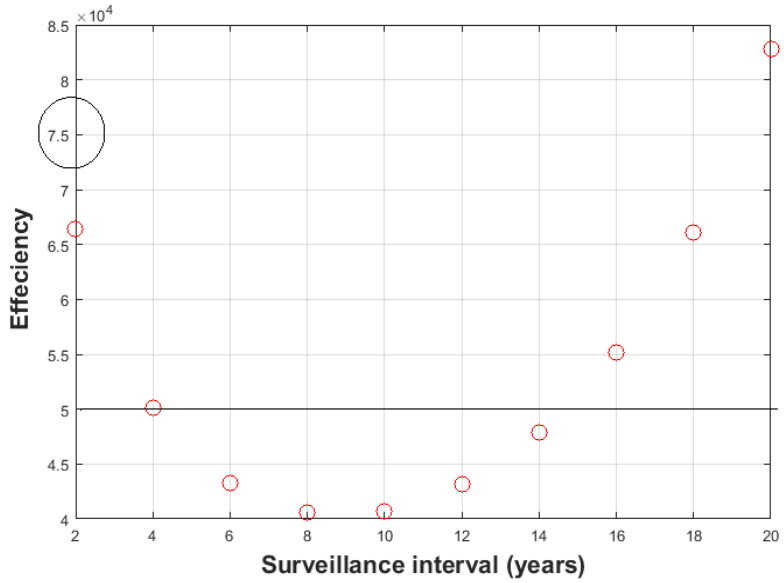

Figure 418: Efficiency vs Surveillance at age 60 with all screening results.

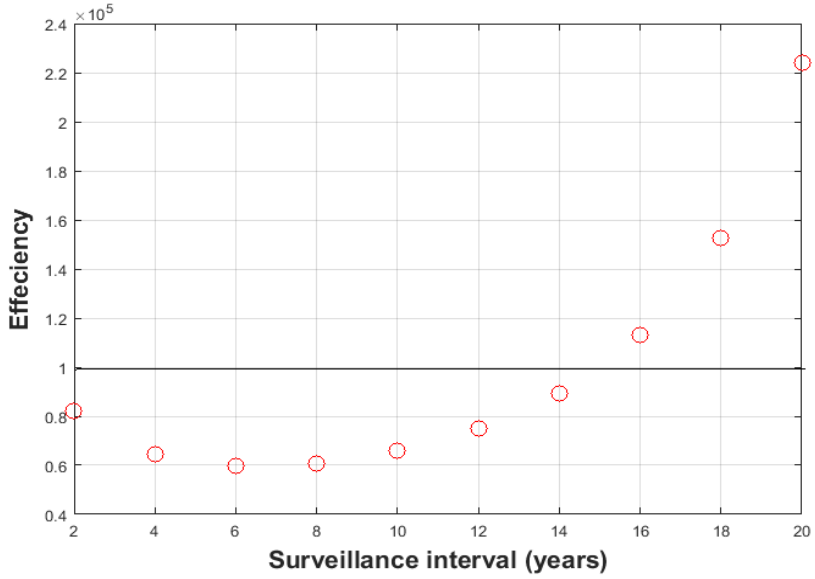

Figure 419: Efficiency vs Surveillance at age 65 with all screening results.

Older screening ages become cost effective with the lowering of the cost of colonoscopy. Also the range of cost-effectiveness widens with lower screening colonoscopy cost (as seen in **Table 43**). At screening age 65, there was a slightly smaller cost-effective range for the $100,000 and $75,000 thresholds. However, the inter-colonoscopy intervals are sensitive to age. As the screening ages increased the inter-colonoscopy interval decreases.

4.4.2 High Cancer Cost

With the high end of cancer cost, screening at age 55 was cost effective 10 to 14 years later with an average 5.8 follow-up intervals and 75.6 QALYs gained/10,000 persons. For screening age 50, the range from the original analysis (see **Table 41**)

decreased by a mere 0.3 years with the same follow-up interval and QALYs gained from the original analysis (see **Table 43**).

4.4.3 Zero Percent Discount Rate

From **Table 43**, the 0% discount rate showed as many as 4 follow-up colonoscopies were cost-effective at screening age 50 at the $100,000 threshold. A total of 437.22 QALYs were gained/10,000 persons. More screening ages also became cost-effective at the $50,000 and $75,000 thresholds.

The optimal number of follow-up colonoscopies and their timing varied based on the cost-effectiveness threshold with a trend of more colonoscopies and more frequently as the cost-effectiveness threshold increased.

The optimal number of colonoscopies following a screening colonoscopy at age 50, increased from a single follow-up colonoscopy at the $50,000/QALYs gained threshold to two follow-up colonoscopies at the $75,000/QALYs gained threshold to four follow-up colonoscopies at the $100,000/QALYs threshold. At the $50,000/QALYs gained threshold, the optimal inter-colonoscopy interval increased from 8.5 years to 10.3 years with more than double increase in QALYs gained/10,000 persons.

At the $75,000/QALYs gained threshold, we moved from nothing being cost-effective for that threshold with the 3% discount rate to 2 follow-up colonoscopies being cost-effective yielding over three times as many QALYs gained/10,000 persons compared to the $50,000 threshold. An additional screening age of 55 also becomes cost-effective at that threshold.

At the $100,000/QALYs gained threshold, we moved from nothing being cost-effective for that threshold with the 3% discount rate to 4 follow-up colonoscopies and

also additional screening ages being cost-effective yielding over four times as many QALYs gained/10,000 persons compared to the $50,000 threshold.

CHAPTER 5

COST-EFFECTIVENESS OF FECAL IMMUNOCHEMICAL TESTS (FITS)

5.1 Introduction

In section 2.2.2, non-endoscopic tests for CRC were discussed. Some acclaimed cost-effective policies for CRC in the US include colonoscopy, sigmoidoscopy and stool tests [62]. Stool based screening tests are cost effective, non-invasive and have good accessibility [48]. Fecal tests look for hidden blood in the stool. This could indicate an early sign of CRC. Since fecal tests have poor sensitivity to premalignant lesions, they must be repeated more often usually 1- 2 years [48]. Considering the shorter intervals of fecal testing required due to poor sensitivity, but enabled by the low cost of the tests; coupling this tests with colonoscopy is expected to be more cost-effective and eventually cost saving.

Fecal immunochemical testing (FIT) is a great alternative and complement to colonoscopy according to the US Multi-Society Task Force [93]. It is a non-invasive test. When used as a single application test, FIT is about 79% sensitive for detecting cancer and about 20% - 30 % sensitive for detecting advanced neoplasia [93].

For the cost-effectiveness analysis for FIT we focused on two main goals with the same concept as the colonoscopy analysis discussed in Chapter 4 (see **Figure 51**). Since

FITs are different from colonoscopies and do not have a follow-up regimen, our main goals were aimed around:

1. After a screening colonoscopy, when should FITs be administered, and
2. What is the best time to screen for FITs?

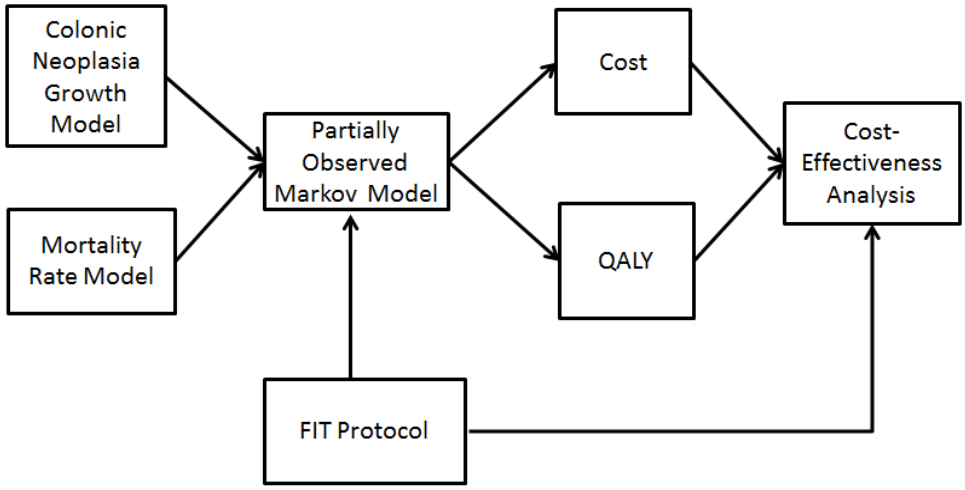

Figure 51: Overview of FIT methods.

5.2 Overview of simulation process for FIT

The colonic neoplasia growth model and mortality rate model in sections 3.3.1 and 3.3.2 were the same for the FIT simulation process.

5.2.1 POMP Model for FIT

Similar to section 3.3.3, leading to FIT screening, the adenoma growth and mortality rate models are applied to the patients. A patient can die from natural causes, remain in a healthy state, develop symptoms and develop polyps or CRC. These patients are not placed in the patient pool initially, because each hypothetical patient is considered healthy until they receive a screening FIT. A FIT test can either be positive or negative. In our model, a positive test for a FIT triggered a colonoscopy and the patient had an

interval before a next FIT was done. Similarly if a negative FIT were recorded, the patient would have an interval until the next FIT. Since a colonoscopy is done after a positive FIT, the intervals between FITs is greater when a FIT is positive than when it is negative because the colonoscopy would have possibly removed most of what was there; leaving a longer window before being tested again.

5.2.2 FIT Protocol

For the analysis we tested different start ages, stop ages and also different intervals for if the test was positive or negative. The start age to receive a FIT was set to be 50, 55, 60, 65, 70 or 75 years. The positive step, which is when to get another FIT if results were positive, was set at 4, 5 or 6 years for each screening age and the negative step, which is when to get another FIT if results are negative, was set at 2, 3 or 4 years for each screening age .The age to stop FITs was set at 70, 75, 80, 85, or 90 years. The cost per QALYs gained as a function of start age, stop age, positive interval, and negative interval were identified. The probabilities collected from the POMP model were incorporated into the costs and QALYs results to perform the cost-effectiveness analysis.

5.2.3 Costs

Since, a positive FIT triggers a colonoscopy; colonoscopy related costs (see **Table 34**) were incorporated in the FIT analysis. The cost of a FIT kit ranged from $10- $50 [94-97]. An average cost of $19.50 was used in the analysis. The cost of FIT was obtained from

Eq. 51

where is the probability of receiving a FIT at age (for scheduled FITs and when FITs are not scheduled but given due to symptoms).

The costs for FIT were added to the calculations for the total costs in section 3.3.6.1. Total costs were then obtained by

Eq. 52

The FIT costs were discounted at an annual rate of 3% and calculations were obtained in the exact manner as section 3.3.6.1 with

Eq. 53

5.2.4 QALYs

Section 3.3.6.3 explains the process that was used in calculating the QALYs.

5.2.5 Cost-effectiveness Analysis

To perform the cost-effective analysis for screening using FIT only, we run the model using the control group that was not screened. This analysis aided in answering the question of the best time for screening with just FITs.

5.2.5.1 Control Group: No screening from age 0 until death or age 100

In this case, our control group consists of patients who had no screening done. The adenoma growth model, mortality rate model, and symptoms calculations were applied to patients from age 0 to death or 100. The costs and QALYs were obtained for patients who received FITs versus those who just had symptoms, died naturally or died from CRC.

By applying the POMP model, we expected to find the most favorable start age, positive step, negative step, and stop age for FIT screening that would maximize patient's QALYs per unit cost of colon- related expenses. **Eq. 54** gives the formula used to calculate cost per QALY gained/10,000 persons.

Eq. 54

For this control group, considering start age, stop age, positive interval, and negative interval, we examined the outcome that yielded the most QALYs per unit cost of CRC expenses. The same thresholds discussed in section 3.4 were used as the societal willingness to pay (WTP) for a QALY. In the analysis, effectiveness was the change in QALYs and the efficiency referred to the change in cost per QALY.

5.2.6 Results from FIT only Protocol

Table 51: FIT only Analysis.

Recommended start age	**When to return if FIT is positive**	**When to return if FIT is negative**	**Recommended stop age**	**QALYs**
$75,000 / QALYs gained threshold				
55 years	6 years	2 years	85 years	165.3

$100,000 / QALYs gained threshold				
65 years	4 years	2 years	85 years	114.8

With the results from this analysis, since we are trying to obtain the best protocol for FIT only, we can only evaluate analysis on a single start age, negative step, positive step, and stop age at a particular time. In order to do an analysis comparing start ages, we calculated QALYs that were not discounted to obtain the actual QALYs gained.

There was no FIT only protocol that was cost-effective at the $50,000 threshold. However at the $75,000 and $100,000 thresholds there were some protocols that were cost-effective. From the cost-effective pool, the protocol that yielded the most QALYs for the threshold is the best protocol for FIT only. A Matlab function was written to obtain the protocol with the highest QALYs, from there the two surrounding points to the maximum was used to show the maximum protocol. Figure 5-2 shows the QALYs gained for each parameter tested for the best protocol for the $75,000 threshold. In Figure 5-3 shows the cost-effectiveness at the $75,000 threshold. The same technique was done for the $100,000 threshold.

From the results obtained in Table 5-1, with increasing thresholds there is an increase in start age and a decrease in frequency to return if the FIT is positive.

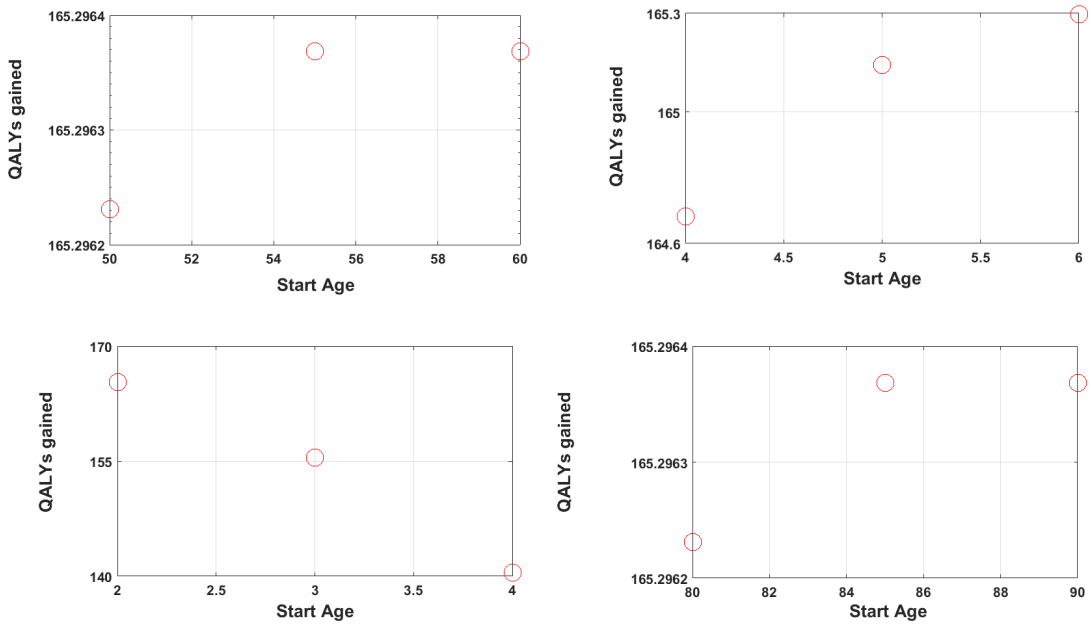

Figure 52: QALYs gained for the best protocol for FIT only.

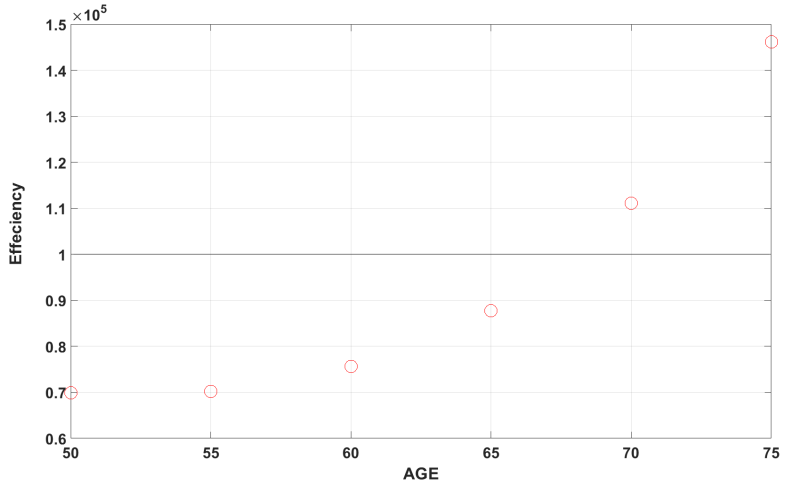

Figure 53: Efficiency Vs Age for the best FIT only protocol.

5.2.7 <u>Combination of Colonoscopy and FIT Tests</u>

In the beginning of this chapter, I discussed how coupling the two screening tests could be more cost-effective due to the cheap price of FIT and its high sensitivity. We performed a cost-effective analysis on a combination of the two tests to determine what effect coupling the tests would have. The colonoscopy and FIT combination involved patients receiving a colonoscopy at the start ages assigned and only FITs thereafter. The methods for the FITs and the colonoscopy remained the same as discussed earlier.

With this combination analysis, we had two control groups in which we analyzed to determine the effectiveness:

1. Control group 1: Screening colonoscopy only at the start age, and

2. Control group 2: No screening from age 0 until death or age 100.

With the control group where a screening colonoscopy was done at the start age, every single case was cost effective at the $50,000 threshold making it cost-effective at $75,000 and $100,000 as well. At each screening age, **Table 52** shows the recommended time to get a FIT, the frequency and when to stop. We can see FIT intervals become shorter with growing age and an increase in QALYs. We also observed that when a FIT is negative, it is recommended to come back every 2 years consistently for all age groups which justify current recommendations[48]. If a FIT comes back negative it may have missed something so we expect the intervals to be shorter.

Table 52: Combination of FIT and colonoscopy analysis with control group 1.

Recommended colonoscopy screening age	When to return if FIT is positive	When to return if FIT is negative	Stop age	QALYs gained /10,000 persons
$50,000 / QALYs gained threshold				
50 years	5 years	2 years	80 years	60.52
55 years	4 years	2 years	80 years	62.69
60 years	4 years	2 years	85 years	64.55
65 years	4 years	2 years	90 years	66.08
70 years	4 years	2 years	90 years	67.28
75 years	4 years	2 years	90 years	68.15

With the control group where no screening was done from age 0 to death or age 100, every single case was cost effective at the $50,000 threshold making it cost-effective at $75,000 and $100,000 as well. The protocol that yielded the most QALYs gained/10,000 persons (69.23) is seen in **Table 53**.

Table 53: Combination of FIT and colonoscopy analysis with control group 2.

Recommended colonoscopy screening age	When to return if FIT is positive	When to return if FIT is negative	Recommended stop age
$50,000 / QALYs gained threshold			
50 years	6 years	2 years	90 years

CHAPTER 6

CONCLUSIONS AND FUTURE WORK

6.1 Conclusions

We obtained the optimal inter-colonoscopy interval at the $100,000 threshold following a screening colonoscopy at age 50 years. The interval is approximately 8.5 years. What that means is that after a screening colonoscopy at age 50 a follow-up is recommended at age 58.5. Clinically for advanced findings (3 or more adenomas found at screening colonoscopy), the recommended interval to return is short (~3 years) [98, 99]. However, with this study, the follow-up interval observed was consistent across screening colonoscopy results for an average risk patient [62]. The shortening of clinical recommendations is based on data that advanced neoplasia are more prevalent following screening colonoscopy with advanced neoplasia [71, 98, 100]. The mathematical model also predicts a higher risk of CRC in patients with advanced neoplasia but, in the simulations, most of the patients who developed cancer got a follow-up colonoscopy due to symptoms prior to the recommended interval. Because of the inclusion of colonoscopy due to symptoms, the systematic follow-up of all patients at an earlier time is not necessarily cost-effective on the entire population level.

After screening age 50, follow-up colonoscopies are not cost effective. However, with a 0% discount rate we saw as many as four follow up colonoscopies being cost effective at the $100,000/QALY threshold. The last follow-up colonoscopy from

screening at age 50 was recorded at 68.8 years. This finding can be validated because mortality rate increases with age so there is not much time to see preventative effects because patients get old and die eventually. Studies have shown that the benefits of colonoscopies decrease with age [66, 101]. The US Preventive Task Force (USPTF) recommends screening to end at 75 years [66]. The average life expectancy in the US is approximately 79 years so the impact of CRC prevention and early detection due to colonoscopy will likely be minimal after age 75 years. In addition, after age 75 years people tend to have more health issues and undergoing colonoscopy may not be the most comfortable experience plus the rewards would not be significant as discussed earlier. From the sensitivity analysis (see **Table 43**) we also saw that with lower screening colonoscopy costs and higher cancer costs we get follow up colonoscopies at later ages.

Not surprisingly, the number of follow-up colonoscopies will increase if one is willing to pay more for a unit of health. From increased amounts in what one is willing to spend, we can see that more colonoscopies can occur leading to shorter inter-colonoscopy intervals. For decades $50,000 has been used as a benchmark for the cost of a unit of health [77-79]. Using the benchmark of $50,000 per QALY gained may be somewhat outdated due to inflation and economic growth [77].It is a reasonable enough cost but based on our study that makes the necessary treatment not cost-effective. By spending more you can receive more benefit. It should be noted that some people would spend more than $100,000 to ensure better health. The threshold used, is solely based on people's values and how they approach risk.

More benefit would mean more QALYs gained from more colonoscopies. The more tests one can get the more information that can be gathered to aide in preventing or

reducing CRC incidence [41, 64]. Cost and benefit are directly proportional as shown in the study. More people are getting screening colonoscopy and will have a lifetime of potential follow-up colonoscopy. Early follow-up colonoscopy in patients who are high risk is extremely crucial[102].

Our results indicates that people should receive a follow-up colonoscopies a little sooner than 10 years and we did obtain data quantifying those intervals based on age at screening and also based on the findings at that screening. With advancing technology and medical improvements, spending a little more for a unit of life if you can is not a bad idea. Based on the study continuing screening after the age of 75 years is not recommended. Follow-up colonoscopies may give more years to live given the appropriate protocol based on age and findings from screening.

Combining FITs and colonoscopy turned out to be very cost-effective. Each of the screening ages tested was cost effective with the combination producing more QALYs with increasing age. From the obtained results, coupling the two screening strategies will be the best cost-effective outcome.

The current study on follow-up colonoscopy is the first to quantitatively analyze the frequency of follow-up colonoscopies based on age and findings from screening results.

6.2 Future Work

With this research we focused on rate of development of CRC in a general aspect. In the future, the focus on the development of the disease will be specified by location in the colon (distal or proximal colon). Critical data will have to be obtained on cancer in the distal vs proximal colon. A recent study shows that younger patients get more

cancers in the distal colon but they may take longer to develop, while older patients are more prone to proximal cancers [103]. This study also showed trends with an increase in diagnosis of CRC within adult less than 55 years. This can open opportunities for investigating the younger birth cohorts primarily focusing on site of the disease. The rate at which CRCs develop in the distal or proximal colon may influence the use of screening techniques for the disease.

Also, since the study is limited to Veteran Affairs (VA) data, which is predominantly white males, a next direction would be to look into databases with populations that are more inclusive of gender and other races and apply the model to see what the effect would be on these populations. We can test the model on different populations to compare results from different populations. If we can obtain data to include a population of different races and different sexes, it may make a stronger argument as to recommendations for an entire population as opposed to part of a population. Obtaining adequate diverse data from the VA may pose a bit of difficulty but it may help understand greatly the other populations not covered by the VA data.

6.3 Limitations of the study

A limitation of the study is that the results rely on an adenoma growth model developed using data from a single Veterans Affairs (VA) hospital. While this model is accurate for this population, the population consisted of few female and non-white patients. Outside of the VA, the results obtained may not be applied in a broad aspect but the methodology and model basis can be applied to data sets with similar characteristics.

APPENDIX A

MATLAB CODE USED FOR MODELING

A.1 Overview

This entire research focused on cost-effectiveness of two different screening techniques for colorectal cancer and a combination of the two. We used Matlab to simulate colonoscopies and FITs in hypothetocal patients. The code required to run the model and the protocols tested will be presented here in the Appendix. A total of 5 main scenarios were analysed for the cost-effectiveness of this project:

1. Given a screening colonoscopy when to have follow-up colonoscopies,
2. Best time for colonoscopy screening,
3. Best time for FIT screening,
4. Given a screening colonoscopy when to have follow-up FITs,
5. Best time for screening colonoscopy and FIT.

Each scenario had a main function and subroutines to run that main function. The subroutines varied for each scenario. However, some subroutines were constant for all scenarios. I will go over the code needed to run the combination of colonoscopy and FIT protocols. The code can be tailored to do colonoscopy only or FIT only.

A.1.1 Given a screening colonoscopy when do you have follow-up FITs

For the main function for the combination of screening tests, before cost and /or QALYs are calculated, the following are subroutines that will need to run.

This is the main function that gives the cost and QALYs output. Withinin this main function there a several smaller functions, which will be discussed below. Below is a list of the functions that are needed to run the main function:

1. STATE_DEFINITIONS
2. K_MARKOV_MOD
3. P_F_A
4. COLONOSCOPY
5. STATE_GROUP
6. P_HEALTHY_DEATH
7. P_HEALTHY_CRC
8. P_CRC_DEATH
9. STATE_DEFINITIONS
10. STATE_TRANSITIONS
11. TRANSITION_RATES
12. TREATMENT_DEFINTIONS
13. TREATMENT_GROUP
14. P_PATIENT_COLON_FIT_COMBO
15. TOTAL_QALYS_DISCOUNTING_FIT
16. TOTAL_COSTS_FIT_ DISCOUNTING _RATE

1. STATE_DEFINITIONS:

This function gives each combination of adenomas and CRC to determine the possible state of the colon. This function gives a total 924 states.

2. K_MARKOV_MOD:

This function identifies the transition rates for the series of transition from diminutive adenoma (<5 mm) to medium adenoma (6-9 mm) to large/advanced adenoma (>10 mm) to CRC. These rates are used to obtain the colonic state probability vector

3. P_F_A

This function calculates the probability of finding an actual state during a colonoscopy.

4. COLONOSCOPY_6

The colonoscopy function goes through each state and sees when a colonoscopy should be performed. It also removes any abnormalities found during a colonoscopy.

5. STATE_GROUP

The state group function regroups the 924 states from **STATE_DEFINITIONS** into the 8 findings categories: (1) no adenomas, (2) 1-2 non-advance adenomas only, (3) 3+ non-advanced adenomas only, (4) 1-2 adenomas with some large/advanced adenomas, (5) 3+ adenomas with some large/advanced adenomas, (6) local CRC, (7) regional CRC, and, (8) distant CRC.

6. P_HEALTHY_DEATH

In this function the probability of a healthy patient dying from non CRC reasons is calculated.

7. P_CRC_DEATH

In this function the probability of dying from the disease is given.

8. P_HEALTHY_CRC

In this function the probability of a healthy patient getting CRC is calculated. This function calculates the colon state as a person ages, adjusts the colon state when there is a colonoscopy and calculates the probability of developing cancer.

9. STATE_DEFINITIONS

This function gives all the combination of states.

10. TRANSITION_RATES

In this function the rate at which adenoma forms and progresses is calculated. Symptom development rates are also developed in this function.

11. TREATMENT_DEFINITIONS

This function gives the combination of positive and negative FITs. With FITs order matters. There are a total of 127 FIT treatments.

12. P_Patient_COLON_FIT_COMBO

This function calculates the probabilities from age 0 to death or age 100. This function has a series of blocks computing different probabilities. It calculates healthy mortality for the year, cancer related mortality, colon state as a person ages, and the probability of colonoscopy based on symptom development. In this function is where patients get a screening colonoscopy then followed by a FIT follow-up. It also calculates the yearly probabilities at each block.

13. TOTAL_COSTS_FIT_DISCOUNTING

This function calculates the total costs at each time step.

14. TOTAL_QALYs_DISCOUNTING_FIT

This function calculates the total QALYs at each time step.

15. FIT_MATRIX ()

This function creates a matrix to know when a positive interval and a negative interval for a FIT are taken for each treatment.

16. FIT_AGE (start_age, positive_step, negative_step)

This function gives you all the combinations for the age of each positive and negative interval.

MAIN FUNCTION

```
global n_states max_state state_list states
n_states = 6;
[states, state_list, max_state] = STATE_DEFINITIONS_6()
global K_markov
[K_markov] = K_markov_mod();
global  dt age_max total_ages age_min
age_min=0;
age_max=100;
dt=1;
total_ages= (age_max-age_min)/dt +1;
global Initial_Local_CRC_costs Surveillance_Local_CRC_costs
Initial_Regional_CRC_costs Surveillance_Regional_CRC_costs
Initial_Distant_CRC_costs Surveillance_Distant_CRC_costs
Terminal_CRC_costs Cost_of_colonoscopy  Cost_Adverse_effects Cost_of_FIT
Initial_Local_CRC_costs=20247.2;
Surveillance_Local_CRC_costs=1305.04;
Initial_Regional_CRC_costs=26007.5;
Surveillance_Regional_CRC_costs=2346.72;
Initial_Distant_CRC_costs=30085.2;
Surveillance_Distant_CRC_costs=15057;
Terminal_CRC_costs=23002.35;
Cost_of_colonoscopy=1068.59;
```

```
Cost_Adverse_effects=141.79;
Cost_of_FIT=19.5;
global QALYs_healthy QALYs_dead QALYs_Local_CRC
QALYs_Regional_CRC QALYs_Distant_CRC
QALYs_healthy = 0.91;
QALYs_dead = 0;
QALYs_Local_CRC = 0.74;
QALYs_Regional_CRC = 0.70;
QALYs_Distant_CRC = 0.25;
global p_f_a colonoscopy state_group
[p_f_a] = P_F_A_6();
[colonoscopy] = COLONOSCOPY_6();
[state_group] = STATE_GROUP_6();
global P_local_death P_regional_death P_distant_death
[P_local_death,P_regional_death,P_distant_death] = P_CRC_DEATH;
global P_healthy_death
P_healthy_death=P_HEALTHY_DEATH();
Cost_matrix = zeros(6,1);
QALY_matrix = zeros (6,1);
Cost_matrix_ref= zeros(6,1);
QALY_matrix_ref= zeros(6,1);
Actual_QALYs_matrix = zeros(6,1);
Delta_Cost_Qaly_matrix = zeros(6,1);
```

```
i = 0;
for start_age=50:5:75
    i = i + 1;
    j = 0;
    for positive_step=4:6%:10
        j = j + 1;
        k = 0;
        for negative_step=2:4%:10
            k = k + 1;
            l=0;
             for stop_age=70:5:90
                l = l+1;
            %%%%%%%%Do nothing reference case%%%%%
            [P_death, P_Asymptomatic, P_local, P_regional, P_distant,
P_colonoscopy] = P_Patient_FIT_ref_max_1();
            total_costs_ref = TOTAL_COSTS_FIT_discoutning(P_local, P_regional,
P_distant, P_colonoscopy,zeros(101,1),start_age);
            total_qalys_ref = TOTAL_QALYs_discounting_FIT (P_local, P_regional,
P_distant, P_death, P_Asymptomatic,start_age);
            Cost_Qalys_ref = total_costs_ref / total_qalys_ref;
            Cost_matrix_ref= total_costs_ref;
            QALY_matrix_ref = total_qalys_ref;
```

```
P_death_ref = P_death;
P_Asymptomatic_ref = P_Asymptomatic;
P_local_ref = P_local;
P_regional_ref = P_regional;
P_distant_ref = P_distant;
P_colonoscopy_ref = P_colonoscopy;

%%%%%%%Colonoscopy then FIT scenario%%%%%%%
[P_death, P_Asymptomatic, P_local, P_regional, P_distant,
P_colonoscopy,P_FIT ] = P_Patient_COLON_FIT_combo(start_age, positive_step,
negative_step,stop_age);
total_costs = TOTAL_COSTS_FIT_discoutning(P_local, P_regional,
P_distant, P_colonoscopy,P_FIT,start_age);
total_qalys = TOTAL_QALYs_discounting_FIT (P_local, P_regional,
P_distant, P_death, P_Asymptomatic,start_age);
Actual_QALYS = TOTAL_QALYs(P_local, P_regional, P_distant,
P_death, P_Asymptomatic);
Cost_Qalys = total_costs / total_qalys;
Cost_matrix(i,j,k,l) = total_costs;
QALY_matrix(i,j,k,l) = total_qalys;
Actual_QALYs_matrix (i,j,k,l) =  Actual_QALYS;
Toc
```

```
Delta_Cost_Qaly_matrix(i,j,k,l) = (Cost_matrix(i,j,k,l) - Cost_matrix_ref) /
(QALY_matrix(i,j,k,l) - QALY_matrix_ref);
toc
end
end
end
end
```

Here I will go into the smaller functions that are needed within the main function.

17. STATE_DEFINITIONS ()

This function gives each combination of adenomas and CRC to determine the possible state of the colon. This function gives a total 924 states.

```
function [states, state_list, max_state] = STATE_DEFINITIONS()


global n_states
states =
zeros(n_states+1,n_states+1,n_states+1,n_states+1,n_states+1,n_states+1);
state = 0;
for i1=0:n_states
   for i2=0:n_states
      for i3=0:n_states
         for i4=0:n_states
            for i5=0:n_states
               for i6=0:n_states
                              if (i1>=i2 && i2>=i3 && i3>=i4 && i4>=i5 &&
                              i5>=i6)
                     state = state + 1;
                     states(i1+1,i2+1,i3+1,i4+1,i5+1,i6+1) = state;
                                    state_list(state,:) = [state i1 i2 i3 i4 i5 i6];
                  end
```

```
                end
            end
        end
    end
  end
end
max_state = state;
```

18. K_markov_mod()

This function identifies the transition rates for the series of transition from diminutive adenoma (<5 mm) to medium adenoma (6-9 mm) to large/advanced adenoma (>10 mm) to CRC. These rates are used to obtain the colonic state probability vector.

```
function [K_markov_new] = K_markov_mod()
global max_state
global state_list
global states
load K_markov

K_markov_new = zeros (max_state, max_state,101);

for start_state=1:max_state
   count_4_start = 0;
   count_5_start = 0;
   count_6_start = 0;
   for i=1:6
      if state_list(start_state,i+1)==4
         count_4_start = count_4_start + 1;
      end
      if state_list(start_state,i+1)==5
         count_5_start = count_5_start + 1;
```

```
    end
    if state_list(start_state,i+1)==6
        count_6_start = count_6_start + 1;
    end
end
for finish_state=1:max_state
    count_4_finish = 0;
    count_5_finish = 0;
    count_6_finish = 0;
    for i=1:6
        if state_list(finish_state,i+1)==4
            count_4_finish = count_4_finish + 1;
        end
        if state_list(finish_state,i+1)==5
            count_5_finish = count_5_finish + 1;
        end
        if state_list(finish_state,i+1)==6
            count_6_finish = count_6_finish + 1;
        end
    end
    equiv_start_1 = 1 + min(4,state_list(start_state,2));
    equiv_start_2 = 1 + min(4,state_list(start_state,3));
    equiv_start_3 = 1 + min(4,state_list(start_state,4));
    equiv_start_4 = 1 + min(4,state_list(start_state,5));
```

```
equiv_start_5 = 1 + min(4,state_list(start_state,6));
equiv_start_6 = 1 + min(4,state_list(start_state,7));
equiv_start =
states(equiv_start_1,equiv_start_2,equiv_start_3,equiv_start_4,equiv_start_5,equiv_start_6);
if count_5_start==count_5_finish && count_6_start==count_6_finish
  equiv_finish_1 = 1 + min(4,state_list(finish_state,2));
  equiv_finish_2 = 1 + min(4,state_list(finish_state,3));
  equiv_finish_3 = 1 + min(4,state_list(finish_state,4));
  equiv_finish_4 = 1 + min(4,state_list(finish_state,5));
  equiv_finish_5 = 1 + min(4,state_list(finish_state,6));
  equiv_finish_6 = 1 + min(4,state_list(finish_state,7));
  equiv_finish =
states(equiv_finish_1,equiv_finish_2,equiv_finish_3,equiv_finish_4,equiv_finish_5,equi
v_finish_6);
  for age=1:101
    K_markov_new(finish_state,start_state,age) =
K_markov(equiv_finish,equiv_start,age);
  end
else
  diff = zeros(1,6);
  diff(1) = abs(state_list(finish_state,2)-state_list(start_state,2));
  diff(2) = abs(state_list(finish_state,3)-state_list(start_state,3));
  diff(3) = abs(state_list(finish_state,4)-state_list(start_state,4));
  diff(4) = abs(state_list(finish_state,5)-state_list(start_state,5));
  diff(5) = abs(state_list(finish_state,6)-state_list(start_state,6));
```

```
                diff(6) = abs(state_list(finish_state,7)-state_list(start_state,7));
                if (sum(diff))==1 && finish_state>start_state
                  for i=1:6
                    if diff(i)==1
                      change = state_list(start_state,i+1);
                      if change==4
                        P = 0.22;
                      elseif change==5
                        P = 0.50;
                      end
                    end
                  end
                  for age=1:101
                    dP = P * K_markov_new(start_state,start_state,age);
                    K_markov_new(start_state,start_state,age) =
K_markov_new(start_state,start_state,age) - dP;
                    K_markov_new(finish_state,start_state,age) =
K_markov_new(finish_state,start_state,age) + dP;
                  end
                end
              end
            end
          end
```

19. P_F_A()

This function calcualtes the probability of finding an actual state during a colonoscopy.

```
function [p_f_a] = P_F_A()

global max_state
global state_list
global states

n_trajectories = 6;
sen_s = 1.4627;
sen_m = 1.8833;
sen_l = 3.1216;
sen_c = 3.1216;
sen_a_f = -1.9947;
sen_p = -2.8670;

n_preps = 2;

p_f_a = zeros(max_state,max_state,n_preps);
for prep = 1:2
```

```
if prep == 1
    sen_prep = sen_a_f;
else
    sen_prep = sen_p;
end
for i=1:max_state
    A1 = state_list(i,2);
    A2 = state_list(i,3);
    A3 = state_list(i,4);
    A4 = state_list(i,5);
    A5 = state_list(i,6);
    A6 = state_list(i,7);
    for i1=0:1
        if i1==1
            f1 = state_list(i,2);
        else
            f1 = 0;
        end
        for i2=0:1
            if i2==1
                f2 = state_list(i,3);
            else
                f2 = 0;
```

```
end
for i3=0:1
    if i3==1
        f3 = state_list(i,4);
    else
        f3 = 0;
    end
    for i4=0:1
        if i4==1
            f4 = state_list(i,5);
        else
            f4 = 0;
        end
        for i5=0:1
            if i5==1
                f5 = state_list(i,6);
            else
                f5 = 0;
            end
            for i6=0:1
                if i6==1
                    f6 = state_list(i,7);
                else
```

```
    f6 = 0;
end
actual = [A1 A2 A3 A4 A5 A6];
found =  [f1 f2 f3 f4 f5 f6];
X = sort([f1 f2 f3 f4 f5 f6],'descend');
F1 = X(1);  F2 = X(2);  F3 = X(3);  F4 = X(4);  F5 = X(5);  F6
= X(6);
found_state = states(F1+1,F2+1,F3+1,F4+1,F5+1,F6+1);
p_f_a_temp = 1;
for j=1:n_trajectories
    if actual(j)==1
        sen_size = sen_s;
        sen_year_temp = 0;
        sen_prep_temp = sen_prep;
    elseif actual(j)==2
        sen_size = sen_m;
        sen_year_temp = 0;
        sen_prep_temp = sen_prep;
    elseif actual(j)==3
        sen_size = sen_l;
        sen_year_temp = 0;
        sen_prep_temp = 0;
    else
```

```
                    sen_size = sen_c;
                    sen_year_temp = 0;
                    sen_prep_temp = 0;
                end
                if actual(j)==0
                    sen = 1;
                elseif actual(j)==found(j)
                    sen = sen_size + sen_prep_temp + sen_year_temp;
                    sen = exp(sen) / (1+exp(sen));
                else
                    sen = sen_size + sen_prep_temp + sen_year_temp;
                    sen = exp(sen) / (1+exp(sen));
                    sen = 1 - sen;
                end
                p_f_a_temp = p_f_a_temp * sen;
            end
            p_f_a(found_state,i,prep) = p_f_a(found_state,i,prep) +
p_f_a_temp;
        end
    end
  end
 end
end
```

```
    end
    p_f_a(:,i,prep) = p_f_a(:,i,prep) / sum(p_f_a(:,i,prep));
end
```

20. COLONOSCOPY_6()

The colonoscopy function goes through each state and sees when a colonoscopy should be performed. It also removes any abnormalities found during a colonoscopy.

```
function [colonoscopy] = COLONOSCOPY_6()
global max_state state_list states
colonoscopy = zeros(max_state,max_state);
for i=1:max_state
    for i1=0:1
        if i1==0
            j1 = state_list(i,2) + 1;
            k1 = 1;
        else
            j1 = 1;
            k1 = state_list(i,2) + 1;
        end
        for i2=0:1
            if i2==0
                j2 = state_list(i,3) + 1;
                k2 = 1;
            else
                j2 = 1;
                k2 = state_list(i,3) + 1;
```

```
end
for i3=0:1
    if i3==0
        j3 = state_list(i,4) + 1;
        k3 = 1;
    else
        j3 = 1;
        k3 = state_list(i,4) + 1;
    end
    for i4=0:1
        if i4==0
            j4 = state_list(i,5) + 1;
            k4 = 1;
        else
            j4 = 1;
            k4 = state_list(i,5) + 1;
        end
        for i5=0:1
            if i5==0
                j5 = state_list(i,6) + 1;
                k5 = 1;
            else
                j5 = 1;
```

```
                k5 = state_list(i,6) + 1;
            end
            for i6=0:1
                if i6==0
                    j6 = state_list(i,7) + 1;
                    k6 = 1;
                else
                    j6 = 1;
                    k6 = state_list(i,7) + 1;
                end
                K = sort([k6 k5 k4 k3 k2 k1],'descend');
                J = sort([j6 j5 j4 j3 j2 j1],'descend');
K1 = K(1);  K2 = K(2);  K3 = K(3);  K4 = K(4);  K5 = K(5);  K6 =K(6);
                J1 = J(1);  J2 = J(2);  J3 = J(3);  J4 = J(4);  J5 = J(5);  J6 = J(6);
                remove = states(K1,K2,K3,K4,K5,K6);
                remain = states(J1,J2,J3,J4,J5,J6);
                colonoscopy(i,remove) = remain;
            end
        end
    end
  end
end
```

21. STATE_GROUP( )

The state group function regroups the 924 states from **STATE_DEFINITIONS** into the 8 findings categories: (1) no adenomas, (2) 1-2 non-advance adenomas only, (3) 3+ non-advanced adenomas only, (4) 1-2 adenomas with some large/advanced adenomas, (5) 3+ adenomas with some large/advanced adenomas, (6) local CRC, (7) regional CRC, and, (8) distant CRC.

```
function [state_group] = STATE_GROUP()


global max_state state_list n_states
max_group = 8 ;


% STATE_GROUP
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
state_group = zeros(max_state,2);
for i=1:max_state
   state_group(i,1) = state_list(i,1);
   i1 = state_list(i,2);
   i2 = state_list(i,3);
   i3 = state_list(i,4);
   i4 = state_list(i,5);
   i5 = state_list(i,6);
   i6 = state_list(i,7);
   sm1 = 0;    sm2 = 0;    sm3 = 0;    sm4 = 0;    sm5 = 0;    sm6 = 0;
```

```
ad1 = 0;    ad2 = 0;    ad3 = 0;    ad4 = 0;    ad5 = 0;    ad6 = 0;
if i1==1 || i1==2
    sm1 = 1;
end
if i2==1 || i2==2
    sm2 = 1;
end
if i3==1 || i3==2
    sm3 = 1;
end
if i4==1 || i4==2
    sm4 = 1;
end
if i5==1 || i5==2
    sm5 = 1;
end
if i6==1 || i6==2
    sm6 = 1;
end
sm = sm1 + sm2 + sm3 + sm4 + sm5 + sm6;
if i1==1 || i1==2 || i1==3
    ad1 = 1;
end
```

```
    if i2==1 || i2==2 || i2==3
        ad2 = 1;
    end
    if i3==1 || i3==2 || i3==3
        ad3 = 1;
    end
    if i4==1 || i4==2 || i4==3
        ad4 = 1;
    end
    if i5==1 || i5==2 || i5==3
        ad5 = 1;
    end
    if i6==1 || i6==2 || i6==3
        ad6 = 1;
    end
    ad = ad1 + ad2 + ad3 + ad4 + ad5 + ad6;
    if i1==n_states || i2==n_states || i3==n_states || i4==n_states || i5==n_states ||
i6==n_states
        state_group(i,2) = 8;
    elseif i1==(n_states-1) || i2==(n_states-1) || i3==(n_states-1) || i4==(n_states-1) ||
i5==(n_states-1) || i6==(n_states-1)
        state_group(i,2) = 7;
```

```
    elseif i1==(n_states-2) || i2==(n_states-2) || i3==(n_states-2) || i4==(n_states-2) ||
i5==(n_states-2) || i6==(n_states-2)
        state_group(i,2) = 6;
    elseif i1==3 || i2==3 || i3==3 || i4==3 || i5==3 || i6==3
        if ad>=3
            state_group(i,2) = 5;
        else
            state_group(i,2) = 4;
        end
    elseif i1==0 && i2==0 && i3==0 && i4==0 && i5==0 && i6==0
        state_group(i,2) = 1;
    elseif sm<3
        state_group(i,2) = 2;
    else
        state_group(i,2) = 3;
    end
end
```

22. P_HEALTHY_DEATH ( )

In this function the probability of a healthy patient dying from non CRC reasons is calculated.

```
function [P_healthy_death] = P_HEALTHY_DEATH()
 global age_min age_max dt
% mortality data
data_ages = [2.5,7,12,17,22,25,32,37,42,47,52,57,62,67,72,77,82];
data_deaths =
[29.6,12.8,16.3,69.6,126.4,135.7,147.7,175.4,248.4,401,613.5,911.2,1269.2,1871.
3,2831.9,4493.7,7358.2];
data_deaths = data_deaths / 100000;

% interpolate to get mortality probabilities
interp_ages = age_min:dt:age_max;
P_healthy_death = spline(data_ages,data_deaths,interp_ages);
```

23. P_CRC_DEATH ()

In this function the probability of dying from the disease is given.

```
function [P_local_death,P_regional_death,P_distant_death] =
P_CRC_DEATH()
P_local_death(1) = 0.025120148;
P_local_death(2) = 0.025120148;
P_local_death(3) = 0.025120148;
P_local_death(4) = 0.025120148;
P_local_death(5) = 0.025120148;


P_regional_death(1) = 0.068866867;
P_regional_death(2) = 0.068866867;
P_regional_death(3) = 0.068866867;
P_regional_death(4) = 0.068866867;
P_regional_death(5) = 0.068866867;

P_distant_death(1) = 0.600507798;
P_distant_death(2) = 0.600507798;
P_distant_death(3) = 0.600507798;
P_distant_death(4) = 0.600507798;
P_distant_death(5) = 0.600507798;
```

24. P_HEALTHY_CRC ( )

In this function the probability of a healthy patient getting CRC is calculated. This function calculates the colon state as a person ages, adjusts the colon state when there is a colonoscopy and calculates the probability of developing cancer.

```
function [P_healthy_CRC] = P_HEALTHY_CRC(N_ages,age_start)

P_healthy_CRC = zeros(N_ages,1);

[N_rows,N_cols,N_times] = size(K_markov);
N_states = N_rows;
P_state_current = zeros(N_rows,1);
P_state_current(1,1) = 1;
P_state = zeros(N_rows,N_times);
P_state(:,1) = P_state_current;
P_group_current = zeros(6,1);
P_group_current(1,1) = 1;
P_group = zeros(6,N_times);
P_group(:,1) = P_group_current;
for T=2:N_times
   % calculate colon state as a person ages
   P_state_next = zeros(N_rows,1);
   P_transition = K_markov(:,:,T);
```

```
        for Finish_state=1:N_rows
            for Start_state=1:N_cols
                P_state_next(Finish_state) = P_state_next(Finish_state) +
P_transition(Finish_state,Start_state) * P_state_current(Start_state);
            end
        end
        P_state(:,T) = P_state_next;
        P_state_current = P_state_next;
        P_group_current = zeros(6,1);
        for State=1:N_states
            Group = state_group(State,2);
            P_group_current(Group) = P_group_current(Group) +
P_state_current(State);
        end
        P_group(:,T) = P_group_current;
        % adjust colon state when there is a colonoscopy
        if T==age_start
            P_state_observed = zeros(N_rows,1);
            P_group_observed=zeros(6,1);
            for Observed_state=1:N_rows
                for Actual_state=1:N_cols
                    P_state_observed(Observed_state) = P_state_observed(Observed_state)
+ p_f_a(Observed_state,Actual_state,2,10) * P_state(Actual_state,T);
```

```
            end
        end
        for State=1:N_states
            Group = state_group(State,2);
            P_group_observed(Group) = P_group_observed(Group) +
P_state_observed(State);
        end
        Post_colonoscopy=zeros(N_rows,1);
        for Actual_state=1:N_rows
            for Observed_state=1:N_cols
                Resulting_state = colonoscopy(Actual_state,Observed_state);
                if Resulting_state~=0
                    P_actual_state = P_state(Actual_state,T);
                    P_observed_state = p_f_a(Observed_state,Actual_state,2,10);
                    Post_colonoscopy(Resulting_state) =
Post_colonoscopy(Resulting_state) + P_actual_state * P_observed_state;
                end
            end
        end
        P_state_current = Post_colonoscopy;
    end
    % probability of developing cancer
    if T==(age_start+1)
```

```
        P_healthy_CRC(T) = P_group(6,T);
    elseif T>(age_start+1)
        P_healthy_CRC(T) = P_group(6,T) - P_group(6,T-1);
    end
end
```

25. STATE_TRANSITIONS ( )

```
function [state_transitions X_diff] = STATE_TRANSITIONS()

global n_trajectories
global state_list
global max_state

state_transitions = zeros(max_state, max_state);
X_diff = zeros(max_state, max_state);
for state_start = 1:max_state
    for state_finish = 1:max_state
        if state_start~=state_finish
            n_diff = 0;
            n_diff_1 = 0;
            n_diff_24 = 0;
            n_diff_30 = 0;
            n_diff_20 = 0;
            n_diff_10 = 0;
            for i=1:n_trajectories
                I = i + 1;
                if state_list(state_start,I)~=state_list(state_finish,I)
                    n_diff = n_diff + 1;
```

```
if state_list(state_start,I)+1==state_list(state_finish,I)
    n_diff_1 = n_diff_1 + 1;
    I_diff = I;
    x_diff = 1;
    y_diff = 1;
    if state_list(state_start,I)>0
        x_diff = x_diff - 1;
        for j=1:n_trajectories
            J = j + 1;
            if state_list(state_start,J)==state_list(state_start,I)
                x_diff = x_diff + 1;
            end
        end
    end
    if state_list(state_finish,I)>0
        y_diff = y_diff - 1;
        for j=1:n_trajectories
            J = j + 1;
            if state_list(state_finish,J)==state_list(state_finish,I)
                y_diff = y_diff + 1;
            end
        end
    end
```

```
                elseif state_list(state_start,I)==2 && state_list(state_finish,I)==4
                    n_diff_24 = n_diff_24 + 1;
                    I_diff = I;
                    x_diff = 1;
                    y_diff = 1;
                    if state_list(state_start,I)>0
                        x_diff = x_diff - 1;
                        for j=1:n_trajectories
                            J = j + 1;
                            if state_list(state_start,J)==state_list(state_start,I)
                                x_diff = x_diff + 1;
                            end
                        end
                    end
                elseif state_list(state_start,I)==3 &&
state_list(state_finish,n_trajectories+1)==0
                    go = 0;
                    if I==2 &&
sum(state_list(state_start,I+1:n_trajectories+1)==state_list(state_finish,I:n_traject
ories))/length(I:n_trajectories)==1
                        go = 1;
                    elseif I==n_trajectories+1 && sum(state_list(state_start,2:I-
1)==state_list(state_finish,2:I-1))/length(2:I-1)==1
```

```
                go = 1;
            elseif sum(state_list(state_start,2:I-1)==state_list(state_finish,2:I-
1))/length(2:I-1)==1 &&
sum(state_list(state_start,I+1:n_trajectories+1)==state_list(state_finish,I:n_trajectories))/l
ength(I:n_trajectories)==1
                go = 1;
            end
            if go==1
                n_diff_30 = n_diff_30 + 1;
                if n_diff_30==1
                    I_diff = I;
                    x_diff = 1;
                    y_diff = 1;
                    if state_list(state_start,I)>0
                        x_diff = x_diff - 1;
                        for j=1:n_trajectories
                            J = j + 1;
                            if state_list(state_start,J)==state_list(state_start,I)
                                x_diff = x_diff + 1;
                            end
                        end
                    end
                end
```

```
                end
            elseif state_list(state_start,I)==2 &&
state_list(state_finish,n_trajectories+1)==0
                go = 0;
                if I==2 &&
sum(state_list(state_start,I+1:n_trajectories+1)==state_list(state_finish,I:n_traject
ories))/length(I:n_trajectories)==1
                    go = 1;
                elseif I==n_trajectories+1 && sum(state_list(state_start,2:I-
1)==state_list(state_finish,2:I-1))/length(2:I-1)==1
                    go = 1;
                elseif sum(state_list(state_start,2:I-1)==state_list(state_finish,2:I-
1))/length(2:I-1)==1 &&
sum(state_list(state_start,I+1:n_trajectories+1)==state_list(state_finish,I:n_trajectories))/l
ength(I:n_trajectories)==1
                    go = 1;
                end
                if go==1
                    n_diff_20 = n_diff_20 + 1;
                    if n_diff_20==1
                        I_diff = I;
                        x_diff = 1;
                        y_diff = 1;
```

```
                    if state_list(state_start,I)>0
                        x_diff = x_diff - 1;
                        for j=1:n_trajectories
                            J = j + 1;
                            if state_list(state_start,J)==state_list(state_start,I)
                                x_diff = x_diff + 1;
                            end
                        end
                    end
                end
            end
        elseif state_list(state_start,I)==1 &&
state_list(state_finish,n_trajectories+1)==0
            go = 0;
            if I==2 &&
sum(state_list(state_start,I+1:n_trajectories+1)==state_list(state_finish,I:n_traject
ories))/length(I:n_trajectories)==1
                go = 1;
            elseif I==n_trajectories+1 && sum(state_list(state_start,2:I-
1)==state_list(state_finish,2:I-1))/length(2:I-1)==1
                go = 1;
            elseif sum(state_list(state_start,2:I-1)==state_list(state_finish,2:I-
1))/length(2:I-1)==1 &&
```

```
sum(state_list(state_start,I+1:n_trajectories+1)==state_list(state_finish,I:n_trajectories))/l
ength(I:n_trajectories)==1
                go = 1;
            end
            if go==1
                n_diff_10 = n_diff_10 + 1;
                if n_diff_10==1
                    I_diff = I;
                    x_diff = 1;
                    y_diff = 1;
                    if state_list(state_start,I)>0
                        x_diff = x_diff - 1;
                        for j=1:n_trajectories
                            J = j + 1;
                            if state_list(state_start,J)==state_list(state_start,I)
                                x_diff = x_diff + 1;
                            end
                        end
                    end
                end
            end
        end
    end
```

```
            end
            if n_diff_30>=1
                state_transitions(state_finish,state_start) = 30;
                X_diff(state_finish,state_start) = x_diff;
            elseif n_diff_20>=1
                state_transitions(state_finish,state_start) = 20;
                X_diff(state_finish,state_start) = x_diff;
            elseif n_diff_10>=1
                state_transitions(state_finish,state_start) = 10;
                X_diff(state_finish,state_start) = x_diff;
            elseif n_diff==1 && n_diff_24==1 && state_list(state_start,I_diff)==2
&& state_list(state_finish,I_diff)==4
                state_transitions(state_finish,state_start) = 24;
                X_diff(state_finish,state_start) = x_diff;
            elseif n_diff==1 && n_diff_1==1
                if state_list(state_start,I_diff)==0
                    state_transitions(state_finish,state_start) = 1;
                    X_diff(state_finish,state_start) = x_diff;
                elseif state_list(state_start,I_diff)==1
                    state_transitions(state_finish,state_start) = 12;
                    X_diff(state_finish,state_start) = x_diff;
                    state_transitions(state_start,state_finish) = 21;
                    X_diff(state_start,state_finish) = y_diff;
```

```
            elseif state_list(state_start,I_diff)==2
                state_transitions(state_finish,state_start) = 23;
                X_diff(state_finish,state_start) = x_diff;
                state_transitions(state_start,state_finish) = 32;
                X_diff(state_start,state_finish) = y_diff;
            elseif state_list(state_start,I_diff)==3
                state_transitions(state_finish,state_start) = 34;
                X_diff(state_finish,state_start) = x_diff;
            end
        end
    end
  end
end
```

26. STATE_DEFINITIONS ( )

This function gives all the combination of states.

```
function [states, state_list, max_state] = STATE_DEFINITIONS()


global n_states


states =
zeros(n_states+1,n_states+1,n_states+1,n_states+1,n_states+1,n_states+1);
state = 0;
for i1=0:n_states
    for i2=0:n_states
        for i3=0:n_states
            for i4=0:n_states
                for i5=0:n_states
                    for i6=0:n_states
                        if (i1>=i2 && i2>=i3 && i3>=i4 && i4>=i5 && i5>=i6)
                            state = state + 1;
                            states(i1+1,i2+1,i3+1,i4+1,i5+1,i6+1) = state;
                            state_list(state,:) = [state i1 i2 i3 i4 i5 i6];
                end
    end
end
max_state = state
```

27. TRANSITION_RATES

In this function the rate at which adenoma forms and progresses is calculated. Symptom development rates are also developed in this function.

```
function [gammas] = TRANSITION_RATES(ks)

global n_ts
global n_transitions
global dtau t_max

gammas = zeros(n_ts,n_transitions+1);

% adenoma formation
taus = 0:dtau:t_max;
gammas(:,1) = max(0,spline(0:10:t_max,[0 ks(1,:)],taus));
% adenoma progression
for i = 2:n_transitions
    gammas(:,i) = max(0,spline(0:10:t_max,[0 ks(i,:)],taus));
end
% symptom development
gammas(:,n_transitions+1) = max(0,spline(0:10:t_max,[0
ks(n_transitions+1,:)],taus));
```

```
gammas(:,n_transitions+2) = max(0,spline(0:10:t_max,[0
ks(n_transitions+2,:)],taus));
gammas(:,n_transitions+3) = max(0,spline(0:10:t_max,[0
ks(n_transitions+3,:)],taus));
```

28. TREATMENT_DEFINITIONS

This function gives the combination of positive and negative FITs. With FITs order matters. There are a total of 127 FIT treatments.

```
function [treatments, treatment_list, max_treatment] =
TREATMENT_DEFINITIONS_7()

treatments = zeros(3,3,3,3,3,3,3,3);
treatment = 0;
for i7=0:2
    for i6=0:2
        for i5=0:2
            for i4=0:2
                for i3=0:2
                    for i2=0:2
                        for i1=0:2
                            if i1==2
                                i1_temp = -1;
                            else
                                i1_temp = i1;
                            end
                            if i2==2
                                i2_temp = -1;
                            else
                                i2_temp = i2;
                            end
                            if i3==2
                                i3_temp = -1;
                            else
                                i3_temp = i3;
                            end
                            if i4==2
                                i4_temp = -1;
                            else
                                i4_temp = i4;
                            end
                            if i5==2
                                i5_temp = -1;
                            else
                                i5_temp = i5;
                            end
                            if i6==2
                                i6_temp = -1;
                            else
```

```
                    i6_temp = i6;
                end
                if i7==2
                    i7_temp = -1;
                else
                    i7_temp = i7;
                end

                if (abs(i1_temp)>=abs(i2_temp) && abs(i2_temp)>=abs(i3_temp)
&& abs(i3_temp)>=abs(i4_temp) && abs(i4_temp)>=abs(i5_temp)&&
abs(i5_temp)>=abs(i6_temp)&& abs(i6_temp)>=abs(i7_temp))

                    treatment = treatment + 1;
treatments(i1_temp+2,i2_temp+2,i3_temp+2,i4_temp+2,i5_temp+2,i6_temp+2,i7_temp+
2) = treatment;
                    treatment_list(treatment,:) = [treatment i1_temp i2_temp i3_temp
i4_temp i5_temp i6_temp i7_temp];
                end
            end
        end
    end
  end
end
max_treatment = treatment;
```

29. P_Patient_COLON_FIT_combo

This function calculates the probabilities from age 0 to death or age 100. This function has a series of blocks computing different probabilities. It calculates healthy mortality for the year, cancer related mortality, colon state as a person ages, and the proabaiblity of colonscocpy based on synmptom development. In this function is where patients get a screening colonoscopy then followed by a FIT follow-up. It also calculates the yearly probabilities at each block.

P_Patient_COLON_FIT_combo(T1,positive_step,negative_step,stop_age)

```
function [P_death, P_Asymptomatic, P_local, P_regional, P_distant,
P_colonoscopy, P_FIT] =
P_Patient_COLON_FIT_combo(T1,positive_step,negative_step,stop_age)

global total_ages
global K_markov
global P_local_death P_regional_death P_distant_death
global P_healthy_death
global state_list max_state
global p_f_a colonoscopy state_group


max_treatment = 255;
```

```
start_age = T1;

[FIT_AGE_matrix] = FIT_AGE (start_age, positive_step, negative_step);

[fit_matrix] = FIT_MATRIX ();


FIT_AGE_matrix(:,2) = FIT_AGE_matrix(:,2) + positive_step;

P_colonoscopy = zeros(total_ages,1);

P_FIT = zeros(total_ages,1);

P_Asymptomatic = zeros(total_ages,1);

P_Asymptomatic(1) = 1;

P_local = zeros(total_ages,5);

P_regional = zeros(total_ages,5);

P_distant = zeros(total_ages,5);

P_death = zeros(total_ages,1);


[N_rows,N_cols,N_times] = size(K_markov);

P_state = zeros(N_rows,max_treatment);

P_state(1,1) = 1;

P_state_local = zeros(N_rows,5,max_treatment);

P_state_regional = zeros(N_rows,5,max_treatment);

P_state_distant = zeros(N_rows,5,max_treatment);
```

```
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
% 1st block (time for loop)
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
    for T=2:(T1+1)
        age = T - 1;
        current_treatment = 1;
        age_index = T ;
        P_death(age_index) = P_death(age_index-1);

        % healthy mortality during the year
        for state=1:N_rows
            P_death(age_index) = P_death(age_index) + P_healthy_death(age_index) *
P_state(state,current_treatment);
            P_state(state,current_treatment) = P_state(state,current_treatment) -
P_healthy_death(age_index) * P_state(state,current_treatment);
        end

        % cancer related mortality during the year
        for i=1:5
            P_death(age_index) = P_death(age_index) + max(P_local_death(i),
P_healthy_death(age_index)) * sum(P_state_local(:,i,current_treatment));
```

```
            P_state_local(:,i,current_treatment) = P_state_local(:,i,current_treatment) -
max(P_local_death(i), P_healthy_death(age_index)) *
P_state_local(:,i,current_treatment);
            P_death(age_index) = P_death(age_index) + max(P_regional_death(i),
P_healthy_death(age_index)) * sum(P_state_regional(:,i,current_treatment));
            P_state_regional(:,i,current_treatment) =
P_state_regional(:,i,current_treatment) - max(P_regional_death(i),
P_healthy_death(age_index)) * P_state_regional(:,i,current_treatment);
            P_death(age_index) = P_death(age_index) + max(P_distant_death(i),
P_healthy_death(age_index)) * sum(P_state_distant(:,i,current_treatment));
            P_state_distant(:,i,current_treatment) = P_state_distant(:,i,current_treatment)
- max(P_distant_death(i), P_healthy_death(age_index)) *
P_state_distant(:,i,current_treatment);
        end

        % calculate colon state as a person ages
        P_state_next = zeros(N_rows,1);
        P_state_next_local = zeros(N_rows,5);
        P_state_next_regional = zeros(N_rows,5);
        P_state_next_distant = zeros(N_rows,5);
        P_transition = K_markov(:,:,age_index);
        for Finish_state=1:N_rows
            for Start_state=1:N_cols
```

```
                P_state_next(Finish_state) = P_state_next(Finish_state) +
P_transition(Finish_state,Start_state) * P_state(Start_state, current_treatment);
                for i=1:5
                  P_state_next_local(Finish_state,i) = P_state_next_local(Finish_state,i)
+ P_transition(Finish_state,Start_state) * P_state_local(Start_state,i,current_treatment);
                  P_state_next_regional(Finish_state,i) =
P_state_next_regional(Finish_state,i) + P_transition(Finish_state,Start_state) *
P_state_regional(Start_state,i,current_treatment);
                  P_state_next_distant(Finish_state,i) =
P_state_next_distant(Finish_state,i) + P_transition(Finish_state,Start_state) *
P_state_distant(Start_state,i,current_treatment);
                end
              end
            end
            for i=1:4
              P_state_local(:,i+1,current_treatment) = P_state_next_local(:,i);
              P_state_regional(:,i+1,current_treatment) = P_state_next_regional(:,i);
              P_state_distant(:,i+1,current_treatment) = P_state_next_distant(:,i);
            end
            P_state(:,current_treatment) = P_state_next + P_state_next_local(:,5) +
P_state_next_regional(:,5) + P_state_next_distant(:,5);

            % colonoscopy for symptoms
```

```
P_state_post = P_state(:,current_treatment);
P_state_local(:,1,current_treatment) = zeros(N_rows,1,1);
P_state_regional(:,1,current_treatment) = zeros(N_rows,1,1);
P_state_distant(:,1,current_treatment) = zeros(N_rows,1,1);
for Actual_state=1:N_rows
    P_asym_sym = 0;
    for i=6:-1:1
        if state_list(Actual_state,i+1)==4
            P_asym_sym = 0.17;
        elseif state_list(Actual_state,i+1)==5
            P_asym_sym = 0.22;
        elseif state_list(Actual_state,i+1)==6
            P_asym_sym = 0.50;
        end
    end
    P_colonoscopy(age_index) = P_colonoscopy(age_index) + P_asym_sym *
P_state(Actual_state,current_treatment);
    for Observed_state=1:N_rows
        Group = state_group(Observed_state,2);
        Resulting_state = colonoscopy(Actual_state,Observed_state);
        if Resulting_state~=0
            if Group==6
```

```
                P_state_local(Resulting_state,1,current_treatment) =
P_state_local(Resulting_state,1,current_treatment) + P_asym_sym *
p_f_a(Observed_state,Actual_state,2) * P_state(Actual_state,current_treatment);
                P_state_post(Actual_state) = P_state_post(Actual_state) -
P_asym_sym * p_f_a(Observed_state,Actual_state,2) *
P_state(Actual_state,current_treatment);
            elseif Group==7
                P_state_regional(Resulting_state,1,current_treatment) =
P_state_regional(Resulting_state,1,current_treatment) + P_asym_sym *
p_f_a(Observed_state,Actual_state,2) * P_state(Actual_state,current_treatment);
                P_state_post(Actual_state) = P_state_post(Actual_state) -
P_asym_sym * p_f_a(Observed_state,Actual_state,2) *
P_state(Actual_state,current_treatment);
            elseif Group==8
                P_state_distant(Resulting_state,1,current_treatment) =
P_state_distant(Resulting_state,1,current_treatment) + P_asym_sym *
p_f_a(Observed_state,Actual_state,2) * P_state(Actual_state,current_treatment);
                P_state_post(Actual_state) = P_state_post(Actual_state) -
P_asym_sym * p_f_a(Observed_state,Actual_state,2) *
P_state(Actual_state,current_treatment);
            else
```

```
                    P_state_post(Resulting_state) = P_state_post(Resulting_state) +
P_asym_sym * p_f_a(Observed_state,Actual_state,2) *
P_state(Actual_state,current_treatment);
                    P_state_post(Actual_state) = P_state_post(Actual_state) -
P_asym_sym * p_f_a(Observed_state,Actual_state,2) *
P_state(Actual_state,current_treatment);
                end
            end
        end
    end
    P_state(:,current_treatment) = P_state_post;


    % yearly probabilities
    P_Asymptomatic(age_index) = sum(sum(P_state));
    for i=1:5
        P_local(age_index,i) = sum(sum(P_state_local(:,i,:)));
        P_regional(age_index,i) = sum(sum(P_state_regional(:,i,:)));
        P_distant(age_index,i) = sum(sum(P_state_distant(:,i,:)));
    end
    if T~=(T+1)
        age
```

```
                100 * (P_death(age_index) + P_Asymptomatic(age_index) +
sum(P_local(age_index,:)) + sum(P_regional(age_index,:)) +
sum(P_distant(age_index,:)))
                100 * [P_death(age_index); P_Asymptomatic(age_index);
sum(P_local(age_index,:)); sum(P_regional(age_index,:)); sum(P_distant(age_index,:));
P_colonoscopy(age_index); P_FIT(age_index)]
            end
        end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
% 2nd block - screening colonoscopy
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
        P_colonoscopy(age_index) = sum(P_state(:,current_treatment));
        P_state_post = P_state(:,current_treatment);
        for Observed_state=1:N_rows
            Group = state_group(Observed_state,2);
            for Actual_state=1:N_cols
                Resulting_state = colonoscopy(Actual_state,Observed_state);
                if Resulting_state~=0
                    if Group==6
                        P_state_local(Resulting_state,1,current_treatment) =
P_state_local(Resulting_state,1,current_treatment) + P_asym_sym *
p_f_a(Observed_state,Actual_state,2) * P_state(Actual_state,current_treatment);
```

```
                P_state_post(Actual_state) = P_state_post(Actual_state) - P_asym_sym
* p_f_a(Observed_state,Actual_state,2) * P_state(Actual_state,current_treatment);
            elseif Group==7
                P_state_regional(Resulting_state,1,current_treatment) =
P_state_regional(Resulting_state,1,current_treatment) + P_asym_sym *
p_f_a(Observed_state,Actual_state,2) * P_state(Actual_state,current_treatment);
                P_state_post(Actual_state) = P_state_post(Actual_state) - P_asym_sym
* p_f_a(Observed_state,Actual_state,2) * P_state(Actual_state,current_treatment);
            elseif Group==8
                P_state_distant(Resulting_state,1,current_treatment) =
P_state_distant(Resulting_state,1,current_treatment) + P_asym_sym *
p_f_a(Observed_state,Actual_state,2) * P_state(Actual_state,current_treatment);
                P_state_post(Actual_state) = P_state_post(Actual_state) - P_asym_sym
* p_f_a(Observed_state,Actual_state,2) * P_state(Actual_state,current_treatment);
            else
                P_state_post(Resulting_state) = P_state_post(Resulting_state) +
P_asym_sym * p_f_a(Observed_state,Actual_state,2) *
P_state(Actual_state,current_treatment);
                P_state_post(Actual_state) = P_state_post(Actual_state) - P_asym_sym
* p_f_a(Observed_state,Actual_state,2) * P_state(Actual_state,current_treatment);
            end
          end
        end
```

```
        end
        P_state(:,current_treatment) = P_state_post;
        % yearly probabilities
        P_Asymptomatic(age_index) = sum(sum(P_state));
        for i=1:5
            P_local(age_index,i) = sum(sum(P_state_local(:,i,:)));
            P_regional(age_index,i) = sum(sum(P_state_regional(:,i,:)));
            P_distant(age_index,i) = sum(sum(P_state_distant(:,i,:)));
        end

        age
        100 * (P_death(age_index) + P_Asymptomatic(age_index) +
sum(P_local(age_index,:)) + sum(P_regional(age_index,:)) +
sum(P_distant(age_index,:)))
        100 * [P_death(age_index); P_Asymptomatic(age_index);
sum(P_local(age_index,:)); sum(P_regional(age_index,:)); sum(P_distant(age_index,:));
P_colonoscopy(age_index); P_FIT(age_index)]


% 3rd block - FIT after colonoscopy %%%
        % FIT after colonoscopy
        for  T=(T1+2):N_times
            age = T - 1;
```

```
age_index = T;
P_death(age_index) = P_death(age_index-1);

for current_treatment=max_treatment:-1:1
   if sum(P_state(:,current_treatment)) > 0

      % healthy mortality during the year

      for state=1:N_rows
         P_death(age_index) = P_death(age_index) +
P_healthy_death(age_index) * P_state(state,current_treatment);
         P_state(state,current_treatment) = P_state(state,current_treatment) -
P_healthy_death(age_index) * P_state(state,current_treatment);
      end

      % cancer related mortality during the year
      for i=1:5
         P_death(age_index) = P_death(age_index) + max(P_local_death(i),
P_healthy_death(age_index)) * sum(P_state_local(:,i,current_treatment));
         P_state_local(:,i,current_treatment) =
P_state_local(:,i,current_treatment) - max(P_local_death(i), P_healthy_death(age_index))
* P_state_local(:,i,current_treatment);
```

```
                P_death(age_index) = P_death(age_index) + max(P_regional_death(i),
P_healthy_death(age_index)) * sum(P_state_regional(:,i,current_treatment));
                P_state_regional(:,i,current_treatment) =
P_state_regional(:,i,current_treatment) - max(P_regional_death(i),
P_healthy_death(age_index)) * P_state_regional(:,i,current_treatment);
                P_death(age_index) = P_death(age_index) + max(P_distant_death(i),
P_healthy_death(age_index)) * sum(P_state_distant(:,i,current_treatment));
                P_state_distant(:,i,current_treatment) =
P_state_distant(:,i,current_treatment) - max(P_distant_death(i),
P_healthy_death(age_index)) * P_state_distant(:,i,current_treatment);
            End
 % calculate colon state as a person ages
            P_state_next = zeros(N_rows,1);
            P_state_next_local = zeros(N_rows,5);
            P_state_next_regional = zeros(N_rows,5);
            P_state_next_distant = zeros(N_rows,5);
            P_transition = K_markov(:,:,age_index);
            for Finish_state=1:N_rows
                for Start_state=1:N_cols
                    P_state_next(Finish_state) = P_state_next(Finish_state) +
P_transition(Finish_state,Start_state) * P_state(Start_state, current_treatment);
                    for i=1:5
```

```
                    P_state_next_local(Finish_state,i) =
P_state_next_local(Finish_state,i) + P_transition(Finish_state,Start_state) *
P_state_local(Start_state,i,current_treatment);
                    P_state_next_regional(Finish_state,i) =
P_state_next_regional(Finish_state,i) + P_transition(Finish_state,Start_state) *
P_state_regional(Start_state,i,current_treatment);
                    P_state_next_distant(Finish_state,i) =
P_state_next_distant(Finish_state,i) + P_transition(Finish_state,Start_state) *
P_state_distant(Start_state,i,current_treatment);
                  end
                end
              end
              for i=1:4
                P_state_local(:,i+1,current_treatment) = P_state_next_local(:,i);
                P_state_regional(:,i+1,current_treatment) = P_state_next_regional(:,i);
                P_state_distant(:,i+1,current_treatment) = P_state_next_distant(:,i);
              end
              P_state(:,current_treatment) = P_state_next + P_state_next_local(:,5) +
P_state_next_regional(:,5) + P_state_next_distant(:,5);


              % colonoscopy for symptoms
              P_state_post = P_state(:,current_treatment);
              P_state_local(:,1,current_treatment) = zeros(N_rows,1,1);
```

```
P_state_regional(:,1,current_treatment) = zeros(N_rows,1,1);
P_state_distant(:,1,current_treatment) = zeros(N_rows,1,1);
for Actual_state=1:N_rows
   P_asym_sym = 0;
   for i=6:-1:1
      if state_list(Actual_state,i+1)==4
         P_asym_sym = 0.17;
      elseif state_list(Actual_state,i+1)==5
         P_asym_sym = 0.22;
      elseif state_list(Actual_state,i+1)==6
         P_asym_sym = 0.50;
      end
   end
   P_colonoscopy(age_index) = P_colonoscopy(age_index) +
P_asym_sym * P_state(Actual_state,current_treatment);
   for Observed_state=1:N_rows
      Group = state_group(Observed_state,2);
      Resulting_state = colonoscopy(Actual_state,Observed_state);
      if Resulting_state~=0
         if Group==6
            P_state_local(Resulting_state,1,current_treatment) =
P_state_local(Resulting_state,1,current_treatment) + P_asym_sym *
p_f_a(Observed_state,Actual_state,2) * P_state(Actual_state,current_treatment);
```

```
                    P_state_post(Actual_state) = P_state_post(Actual_state) -
P_asym_sym * p_f_a(Observed_state,Actual_state,2) *
P_state(Actual_state,current_treatment);
                elseif Group==7
                    P_state_regional(Resulting_state,1,current_treatment) =
P_state_regional(Resulting_state,1,current_treatment) + P_asym_sym *
p_f_a(Observed_state,Actual_state,2) * P_state(Actual_state,current_treatment);
                    P_state_post(Actual_state) = P_state_post(Actual_state) -
P_asym_sym * p_f_a(Observed_state,Actual_state,2) *
P_state(Actual_state,current_treatment);
                elseif Group==8
                    P_state_distant(Resulting_state,1,current_treatment) =
P_state_distant(Resulting_state,1,current_treatment) + P_asym_sym *
p_f_a(Observed_state,Actual_state,2) * P_state(Actual_state,current_treatment);
                    P_state_post(Actual_state) = P_state_post(Actual_state) -
P_asym_sym * p_f_a(Observed_state,Actual_state,2) *
P_state(Actual_state,current_treatment);
                else
                    P_state_post(Resulting_state) = P_state_post(Resulting_state) +
P_asym_sym * p_f_a(Observed_state,Actual_state,2) *
P_state(Actual_state,current_treatment);
```

```
                    P_state_post(Actual_state) = P_state_post(Actual_state) -
P_asym_sym * p_f_a(Observed_state,Actual_state,2) *
P_state(Actual_state,current_treatment);
                    end
                end
            end
        end
        P_state(:,current_treatment) = P_state_post;

        % FIT
        if FIT_AGE_matrix(current_treatment,2) == age && current_treatment <
((max_treatment+1)/2)-1 && age <= stop_age
            P_FIT(age_index) = P_FIT(age_index) +
sum(P_state(:,current_treatment));
            P_negative = 0;
            P_positive = 0;
            for i=1:max_state
                N_small = 0;
                N_medium = 0;
                N_large = 0;
                N_CRC = 0;
                for j=1:6
                    adenoma = state_list(i,j+1);
```

```
                if adenoma==1
                    N_small = N_small + 1;
                elseif adenoma==2
                    N_medium = N_medium + 1;
                elseif adenoma==3
                    N_large = N_large + 1;
                elseif adenoma==4 || adenoma==5 || adenoma==6
                    N_CRC = N_CRC + 1;
                end
            end
            P_negative = P_negative + P_state(i,current_treatment) /
sum(P_state(:,current_treatment)) * ((1-0.05)^N_small * (1-0.101)^N_medium * (1-
0.22)^N_large * (1-0.7)^(N_CRC));
            P_positive = P_positive + P_state(i,current_treatment) /
sum(P_state(:,current_treatment)) * (1 - ((1-0.05)^N_small * (1-0.101)^N_medium * (1-
0.22)^N_large * (1-0.7)^(N_CRC)));
        end

        negative_treatment = fit_matrix(current_treatment,2);
        positive_treatment = fit_matrix(current_treatment,3);

        P_state(:,negative_treatment) = P_negative *
P_state(:,current_treatment);
```

```
P_state_local(:,:,negative_treatment) = P_negative *
P_state_local(:,:,current_treatment);
P_state_regional(:,:,negative_treatment) = P_negative *
P_state_regional(:,:,current_treatment);
P_state_distant(:,:,negative_treatment) = P_negative *
P_state_distant(:,:,current_treatment);

P_state(:,positive_treatment) = P_positive *
P_state(:,current_treatment);
P_state_local(:,:,positive_treatment) = P_positive *
P_state_local(:,:,current_treatment);
P_state_regional(:,:,positive_treatment) = P_positive *
P_state_regional(:,:,current_treatment);
P_state_distant(:,:,positive_treatment) = P_positive *
P_state_distant(:,:,current_treatment);

P_state(:,current_treatment) = zeros(N_rows,1);
P_state_local(:,:,current_treatment) = zeros(N_rows,5,1);
P_state_regional(:,:,current_treatment) = zeros(N_rows,5,1);
P_state_distant(:,:,current_treatment) = zeros(N_rows,5,1);

% colonoscopy for positive FIT
P_state_post = P_state(:,positive_treatment);
```

```
for Actual_state=1:N_rows
    P_colonoscopy(age_index) = P_colonoscopy(age_index) +
P_state(Actual_state,positive_treatment);
    for Observed_state=1:N_rows
        Group = state_group(Observed_state,2);
        Resulting_state = colonoscopy(Actual_state,Observed_state);
        if Resulting_state~=0
            if Group==6
                P_state_local(Resulting_state,1,positive_treatment) =
P_state_local(Resulting_state,1,positive_treatment) +
p_f_a(Observed_state,Actual_state,2) * P_state(Actual_state,positive_treatment);
                P_state_post(Actual_state) = P_state_post(Actual_state) -
p_f_a(Observed_state,Actual_state,2) * P_state(Actual_state,positive_treatment);
            elseif Group==7
                P_state_regional(Resulting_state,1,positive_treatment) =
P_state_regional(Resulting_state,1,positive_treatment) +
p_f_a(Observed_state,Actual_state,2) * P_state(Actual_state,positive_treatment);
                P_state_post(Actual_state) = P_state_post(Actual_state) -
p_f_a(Observed_state,Actual_state,2) * P_state(Actual_state,positive_treatment);
            elseif Group==8
                P_state_distant(Resulting_state,1,positive_treatment) =
P_state_distant(Resulting_state,1,positive_treatment) +
p_f_a(Observed_state,Actual_state,2) * P_state(Actual_state,positive_treatment);
```

```
                    P_state_post(Actual_state) = P_state_post(Actual_state) -
p_f_a(Observed_state,Actual_state,2) * P_state(Actual_state,positive_treatment);
                else
                    P_state_post(Resulting_state) = P_state_post(Resulting_state)
+ p_f_a(Observed_state,Actual_state,2) * P_state(Actual_state,positive_treatment);
                    P_state_post(Actual_state) = P_state_post(Actual_state) -
p_f_a(Observed_state,Actual_state,2) * P_state(Actual_segment,positive_treatment);
                end
            end
        end
    end
    P_state(:,positive_treatment) = P_state_post;
  end
 end
end
% yearly probabilities
P_Asymptomatic(age_index) = sum(sum(P_state));
 for i=1:5
  P_local(age_index,i) = sum(sum(P_state_local(:,i,:)));
  P_regional(age_index,i) = sum(sum(P_state_regional(:,i,:)));
  P_distant(age_index,i) = sum(sum(P_state_distant(:,i,:)));
 end
age
```

```
        100 * (P_death(age_index) + P_Asymptomatic(age_index) +
sum(P_local(age_index,:)) + sum(P_regional(age_index,:)) +
sum(P_distant(age_index,:)))
        100 * [P_death(age_index); P_Asymptomatic(age_index);
sum(P_local(age_index,:)); sum(P_regional(age_index,:)); sum(P_distant(age_index,:));
P_colonoscopy(age_index); P_FIT(age_index)]
    end
    end
```

30. TOTAL_COSTS_FIT_discounting

This function calculates the total costs at each time step.

TOTAL_COSTS_FIT_discounting(P_local,P_regional, P_distant, P_colonoscopy, P_FIT, T1)

```
function [total_costs] = TOTAL_COSTS_FIT_discoutning(P_local, P_regional, P_distant,P_colonoscopy,P_FIT,T1)

global Initial_Local_CRC_costs Surveillance_Local_CRC_costs Initial_Regional_CRC_costs Surveillance_Regional_CRC_costs Initial_Distant_CRC_costs Surveillance_Distant_CRC_costs Terminal_CRC_costs Cost_of_colonoscopy Cost_Adverse_effects Cost_of_FIT
global dt age_max total_ages age_min
global P_local_death P_regional_death P_distant_death
 t_0 = T1;
r = 0.03;

Local_CRC_costs=zeros(total_ages,1);
Regional_CRC_costs=zeros(total_ages,1);
Distant_CRC_costs=zeros(total_ages,1);
Colonoscopy_Costs=zeros(total_ages,1);
FIT_Costs=zeros(total_ages,1);
Z=zeros(total_ages,1);
```

```
for age=age_min:dt:age_max
    T=(age-age_min)/dt +1;
    t_1 = age-t_0;

     if age<t_0
        Z(T) = 0;
    else
        Z(T) = r * (1/(r*exp(r*0)) - 1/(r*exp(r*t_1)));
    end

    Colonoscopy_Costs(T) = (Cost_of_colonoscopy + Cost_Adverse_effects) *
P_colonoscopy(T);
    FIT_Costs(T) = Cost_of_FIT * P_FIT(T);

    Local_CRC_costs(T)= Initial_Local_CRC_costs * P_local(T,1);
    Local_CRC_costs(T)=Local_CRC_costs(T)+Surveillance_Local_CRC_costs *
P_local(T,2);
    Local_CRC_costs(T)=Local_CRC_costs(T)+Surveillance_Local_CRC_costs *
P_local(T,3);
    Local_CRC_costs(T)=Local_CRC_costs(T)+Surveillance_Local_CRC_costs *
P_local(T,4);
```

Local_CRC_costs(T)=Local_CRC_costs(T)+Surveillance_Local_CRC_costs * P_local(T,5);

Local_CRC_costs(T)=Local_CRC_costs(T)+Terminal_CRC_costs * P_local(T,1)*P_local_death(1);

Local_CRC_costs(T)=Local_CRC_costs(T)+Terminal_CRC_costs * P_local(T,2)*P_local_death(2);

Local_CRC_costs(T)=Local_CRC_costs(T)+Terminal_CRC_costs * P_local(T,3)*P_local_death(3);

Local_CRC_costs(T)=Local_CRC_costs(T)+Terminal_CRC_costs * P_local(T,4)*P_local_death(4);

Local_CRC_costs(T)=Local_CRC_costs(T)+Terminal_CRC_costs * P_local(T,5)*P_local_death(5);

Regional_CRC_costs(T)= (Initial_Regional_CRC_costs) * P_regional(T,1);
Regional_CRC_costs(T)=Regional_CRC_costs(T)+Surveillance_Regional_CRC_costs * P_regional(T,2);
Regional_CRC_costs(T)=Regional_CRC_costs(T)+Surveillance_Regional_CRC_costs * P_regional(T,3);
Regional_CRC_costs(T)=Regional_CRC_costs(T)+Surveillance_Regional_CRC_costs * P_regional(T,4);
Regional_CRC_costs(T)=Regional_CRC_costs(T)+Surveillance_Regional_CRC_costs * P_regional(T,5);

Regional_CRC_costs(T)=Regional_CRC_costs(T)+Terminal_CRC_costs * P_regional(T,1)*P_regional_death(1);

Regional_CRC_costs(T)=Regional_CRC_costs(T)+Terminal_CRC_costs * P_regional(T,2)*P_regional_death(2);

Regional_CRC_costs(T)=Regional_CRC_costs(T)+Terminal_CRC_costs * P_regional(T,3)*P_regional_death(3);

Regional_CRC_costs(T)=Regional_CRC_costs(T)+Terminal_CRC_costs * P_regional(T,4)*P_regional_death(4);

Regional_CRC_costs(T)=Regional_CRC_costs(T)+Terminal_CRC_costs * P_regional(T,5)*P_regional_death(5);

Distant_CRC_costs(T)= (Initial_Distant_CRC_costs) * P_distant(T,1);

Distant_CRC_costs(T)=Distant_CRC_costs(T)+Surveillance_Distant_CRC_costs * P_distant(T,2);

Distant_CRC_costs(T)=Distant_CRC_costs(T)+Surveillance_Distant_CRC_costs * P_distant(T,3);

Distant_CRC_costs(T)=Distant_CRC_costs(T)+Surveillance_Distant_CRC_costs * P_distant(T,4);

Distant_CRC_costs(T)=Distant_CRC_costs(T)+Surveillance_Distant_CRC_costs * P_distant(T,5);

Distant_CRC_costs(T)=Distant_CRC_costs(T)+Terminal_CRC_costs * P_distant(T,1)*P_distant_death(1);

```
            Distant_CRC_costs(T)=Distant_CRC_costs(T)+Terminal_CRC_costs *
P_distant(T,2)*P_distant_death(2);
            Distant_CRC_costs(T)=Distant_CRC_costs(T)+Terminal_CRC_costs *
P_distant(T,3)*P_distant_death(3);
            Distant_CRC_costs(T)=Distant_CRC_costs(T)+Terminal_CRC_costs *
P_distant(T,4)*P_distant_death(4);
            Distant_CRC_costs(T)=Distant_CRC_costs(T)+Terminal_CRC_costs *
P_distant(T,5)*P_distant_death(5);



        end

        Colonoscopy_Costs = Colonoscopy_Costs - (Colonoscopy_Costs.*Z);
        FIT_Costs = FIT_Costs - (FIT_Costs.*Z);

         Local_CRC_costs = Local_CRC_costs - (Local_CRC_costs.*Z);
         Regional_CRC_costs = Regional_CRC_costs - (Regional_CRC_costs.*Z);
         Distant_CRC_costs = Distant_CRC_costs - (Distant_CRC_costs.*Z);

        total_costs = sum(Colonoscopy_Costs + Local_CRC_costs +
Regional_CRC_costs + Distant_CRC_costs + FIT_Costs);
```

```
end
```

31. TOTAL_QALYs_discounting_FIT

This function calculates the total QALYs at each time step.

TOTAL_QALYs_discounting_FIT (P_local, P_regional, P_distant, P_death, P_Asymptomatic,T1)

```
function [total_qalys] = TOTAL_QALYs_discounting_FIT (P_local, P_regional,
P_distant, P_death, P_Asymptomatic,T1)
```

```
global QALYs_healthy QALYs_dead QALYs_Local_CRC
QALYs_Regional_CRC QALYs_Distant_CRC
global dt age_max total_ages age_min

t_0 = T1;
r=0.03;

QALYs = zeros(total_ages,1);
Z=zeros(total_ages,1);

for age=age_min:dt:age_max
   T = (age - age_min) / dt + 1;
   t_1 = age-t_0;
   if age<=t_0
      Z(T) = 0;
   else
      Z(T) = r * (1/(r*exp(r*0)) - 1/(r*exp(r*t_1)));
   end
   QALYs(T) = QALYs(T) + QALYs_healthy * P_Asymptomatic(T);
   QALYs(T) = QALYs(T) + QALYs_dead * P_death(T);
   QALYs(T) = QALYs(T) + QALYs_Local_CRC * sum(P_local(T,:));
   QALYs(T) = QALYs(T) + QALYs_Regional_CRC * sum(P_regional(T,:));
```

```
    QALYs(T) = QALYs(T) + QALYs_Distant_CRC * sum(P_distant(T,:));
end
QALYs = QALYs-(QALYs.*Z);
total_qalys = sum(QALYs);

end
```

32. FIT_MATRIX ()

This function creates a matrix to know when a positive interval and a negative interval for a FIT are taken for each treatment.

```
function [fit_matrix] = FIT_MATRIX ()
[treatments, treatment_list, max_treatment] =
TREATMENT_DEFINITIONS_7();

fit_matrix = zeros(127,3);
```

```
for current_treatment=1:127

    i = 0;
    while treatment_list(current_treatment,i+1)~=0
        i = i + 1;
    end

    for j=1:7
        if j==i
            negative_treatment(i) = 1;
            positive_treatment(i) = 3;
        else
            negative_treatment(j) = treatment_list(current_treatment,j+1) + 2;
            positive_treatment(j) = treatment_list(current_treatment,j+1) + 2;
        end
    end

    negative_number = treatments(negative_treatment(1), negative_treatment(2),
negative_treatment(3), negative_treatment(4), negative_treatment(5),
negative_treatment(6), negative_treatment(7));
    positive_number = treatments(positive_treatment(1), positive_treatment(2),
positive_treatment(3), positive_treatment(4), positive_treatment(5),
positive_treatment(6), positive_treatment(7));
```

```
        fit_matrix(current_treatment,:) = [current_treatment, negative_number,
positive_number];

    end
```

33. FIT_AGE (start_age, positive_step, negative_step)

This function gives you all the combinations for the age of each positive and negative interval.

```
    function [FIT_AGE_matrix] = FIT_AGE (start_age, positive_step, negative_step)

    [treatments, treatment_list, max_treatment] =
TREATMENT_DEFINITIONS_7();
    FIT_AGE_matrix=zeros(255,2);
```

```
for treatment = 1:255
   FIT_AGE = start_age;
   for j= 2:6
      if treatment_list(treatment,j) == 1 ;
           FIT_AGE = FIT_AGE + positive_step;
      elseif  treatment_list( treatment,j) == -1;
           FIT_AGE = FIT_AGE + negative_step;
      end
   end
     FIT_AGE_matrix(treatment, 1) = treatment;
     FIT_AGE_matrix(treatment, 2) = FIT_AGE;
end
```

BIBLIOGRAPHY

[1] American Cancer Society. Cancer Facts & Figures 2017 [Online]. Available: https://www.cancer.org/cancer/colon-rectal-cancer/about.html

[2] R. L. Siegel, K. D. Miller, S. A. Fedewa, D. J. Ahnen, R. G. S. Meester, A. Barzi, *et al.*, "Colorectal cancer statistics, 2017," *CA Cancer J Clin,* vol. 67, pp. 177-193, May 06 2017.

[3] P. Varkey, *Mayo Clinic Preventive Medicine and Public Health Board Review.* Oxford,UK: Oxford University Press, 2010.

[4] T. Muto, H. J. Bussey, and B. C. Morson, "The evolution of cancer of the colon and rectum," *Cancer,* vol. 36, pp. 2251-70, Dec 1975.

[5] A. Sudhakar, "History of Cancer, Ancient and Modern Treatment Methods," *J Cancer Sci Ther,* vol. 1, pp. 1-4, Dec 01 2009.

[6] C. GM, *The Cell: A Molecular Aprroach*, 2nd ed. Sunderland, MA: Sinauer Associates, 2000.

[7] M. H. Irving and B. Catchpole, "ABC of colorectal diseases. Anatomy and physiology of the colon, rectum, and anus," *BMJ,* vol. 304, pp. 1106-8, Apr 25 1992.

[8] T. Gersten. (2017). *Colon Cancer*. Available: http://eclinicalworks.adam.com/content.aspx?productId=39&pid=1&gid=000262

[9] P. M. Colucci, S. H. Yale, and C. J. Rall, "Colorectal polyps," *Clin Med Res,* vol. 1, pp. 261-2, Jul 2003.

[10] J. Sison. (2015). *The Difference between Colon Cancer and Ulcerative Colitis*. Available: http://www.differencebetween.net/science/health/the-difference-between-colon-cancer-and-ulcerative-colitis/

[11] F. Amersi, M. Agustin, and C. Y. Ko, "Colorectal cancer: epidemiology, risk factors, and health services," *Clin Colon Rectal Surg,* vol. 18, pp. 133-40, Aug 2005.

[12] A. Shankar, A. J. Renaut, J. Whelan, and I. Taylor, "Colorectal cancer in adolescents," *Ann R Coll Surg Engl,* vol. 81, pp. 100-4, Mar 1999.

[13] J. F. Goldthorn, D. Powars, and D. M. Hays, "Adenocarcinoma of the colon and rectum in the adolescent," *Surgery,* vol. 93, pp. 409-14, Mar 1983.

[14] M. J. Janower, J. R. Dreyfuss, and A. L. Weber, "Cancer of the gastrointestinal tract in young people," *Radiol Clin North Am,* vol. 7, pp. 121-30, Apr 1969.

[15] B. N. Rao, C. B. Pratt, I. D. Fleming, R. A. Dilawari, A. A. Green, and B. A. Austin, "Colon carcinoma in children and adolescents. A review of 30 cases," *Cancer,* vol. 55, pp. 1322-6, Mar 15 1985.

[16] (2017, May 10). Available: https://www.cancer.org/cancer/colon-rectal-cancer.html

[17] P. A. Wark, K. Wu, P. van 't Veer, C. F. Fuchs, and E. L. Giovannucci, "Family history of colorectal cancer: a determinant of advanced adenoma stage or adenoma multiplicity?," *Int J Cancer,* vol. 125, pp. 413-20, Jul 15 2009.

[18] M. L. Slattery, T. R. Levin, K. Ma, D. Goldgar, R. Holubkov, and S. Edwards, "Family history and colorectal cancer: predictors of risk," *Cancer Causes Control,* vol. 14, pp. 879-87, Nov 2003.

[19] E. R. Kim and D. K. Chang, "Colorectal cancer in inflammatory bowel disease: the risk, pathogenesis, prevention and diagnosis," *World J Gastroenterol,* vol. 20, pp. 9872-81, Aug 07 2014.

[20] J. K. Triantafillidis, G. Nasioulas, and P. A. Kosmidis, "Colorectal cancer and inflammatory bowel disease: epidemiology, risk factors, mechanisms of carcinogenesis and prevention strategies," *Anticancer Res,* vol. 29, pp. 2727-37, Jul 2009.

[21] J. Brudnowska and B. Peplonska, "[Night shift work and cancer risk: a literature review]," *Med Pr,* vol. 62, pp. 323-38, 2011.

[22] E. Shambaugh, M. Weiss, L. Gloeckler, V. Holten, M. Kruse, J. Cunningham*, et al.*, "SEER PROGRAM: COMPARATIVE STAGING GUIDE," 1993.

[23] (2017). *Cancer Staging System*. Available: https://cancerstaging.org/references-tools/Pages/What-is-Cancer-Staging.aspx

[24] (July 10). *SEER Training Modules: Staging Systems*. Available: https://training.seer.cancer.gov/staging/systems/

[25] R. LAG, M. D, M. Krapcho, A. Mariotto, M. BA, E. J. Feuer*, et al.*, "SEER Cancer Statistics Review, 1975-2004, National Cancer Institute. ," 2007.

[26] C. Taylor, A. Richardson, and S. Cowley, "Restoring embodied control following surgical treatment for colorectal cancer: a longitudinal qualitative study," *Int J Nurs Stud,* vol. 47, pp. 946-56, Aug 2010.

[27] I. h. Help. *Colon resection surgery*. Available: http://www.indiahealthhelp.com/procedure/colon-cancer-treatment/

[28] A. Takeda, N. Sanuki, and E. Kunieda, "Role of stereotactic body radiotherapy for oligometastasis from colorectal cancer," *World J Gastroenterol,* vol. 20, pp. 4220-9, Apr 21 2014.

[29] K. K. Tanabe and Y. Kulu, "Radiofrequency Ablation for Colon and Rectal Carcinoma Liver Metastases: What's Missing?," *Gastrointest Cancer Res,* vol. 1, pp. S42-6, 2007.

[30] J. A. Meyerhardt and R. J. Mayer, "Systemic therapy for colorectal cancer," *N Engl J Med,* vol. 352, pp. 476-87, Feb 3 2005.

[31] M. Pignone, M. Rich, S. M. Teutsch, A. O. Berg, and K. N. Lohr, "Screening for colorectal cancer in adults at average risk: a summary of the evidence for the U.S. Preventive Services Task Force," *Ann Intern Med,* vol. 137, pp. 132-41, Jul 16 2002.

[32] M. Pignone and B. Levin, "Recent developments in colorectal cancer screening and prevention," *Am Fam Physician,* vol. 66, pp. 297-302, Jul 15 2002.

[33] A. L. Frazier, G. A. Colditz, C. S. Fuchs, and K. M. Kuntz, "Cost-effectiveness of screening for colorectal cancer in the general population," *JAMA,* vol. 284, pp. 1954-61, Oct 18 2000.

[34] N. Khakimov, G. Khasanova, K. Ershova, L. Gibadullina, T. Vetkina, G. Lobisheva*, et al.*, "Screening for colon cancer: A test for occult blood," *Int J Risk Saf Med,* vol. 27 Suppl 1, pp. S110-1, 2015.

[35] J. S. Lin, M. A. Piper, L. A. Perdue, C. M. Rutter, E. M. Webber, E. O'Connor*, et al.*, "Screening for Colorectal Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force," *JAMA,* vol. 315, pp. 2576-94, Jun 21 2016.

[36] H. Strul and N. Arber, "Screening techniques for prevention and early detection of colorectal cancer in the average-risk population," *Gastrointest Cancer Res,* vol. 1, pp. 98-106, May 2007.

[37] E. P. Whitlock, J. S. Lin, E. Liles, T. L. Beil, and R. Fu, "Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force," *Ann Intern Med,* vol. 149, pp. 638-58, Nov 4 2008.

[38] I. Lansdorp-Vogelaar, S. L. Goede, L. J. W. Bosch, V. Melotte, B. Carvalho, M. van Engeland*, et al.*, "Cost-effectiveness of High-performance Biomarker Tests vs Fecal Immunochemical Test for Noninvasive Colorectal Cancer Screening," *Clin Gastroenterol Hepatol,* Jul 18 2017.

[39] D. K. Rex, C. J. Kahi, B. Levin, R. A. Smith, J. H. Bond, D. Brooks*, et al.*, "Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and US Multi-Society Task Force on Colorectal Cancer," *CA Cancer J Clin,* vol. 56, pp. 160-7; quiz 185-6, May-Jun 2006.

[40] J. Springer, J. Loeffler, W. Heinz, H. Schlossnagel, M. Lehmann, O. Morton*, et al.*, "Pathogen-specific DNA enrichment does not increase sensitivity of PCR for diagnosis of invasive aspergillosis in neutropenic patients," *J Clin Microbiol,* vol. 49, pp. 1267-73, Apr 2011.

[41] S. J. Winawer, A. G. Zauber, M. N. Ho, M. J. O'Brien, L. S. Gottlieb, S. S. Sternberg*, et al.*, "Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup," *N Engl J Med,* vol. 329, pp. 1977-81, Dec 30 1993.

[42] (May 5). *Colonoscopy*. Available: https://www.hopkinsmedicine.org/gastroenterology_hepatology/clinical_services/basic_endoscopy/colonoscopy.html

[43] O. Holme, M. Loberg, M. Kalager, M. Bretthauer, M. A. Hernan, E. Aas*, et al.*, "Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial," *JAMA,* vol. 312, pp. 606-15, Aug 13 2014.

[44] A. S. Brett, "Flexible sigmoidoscopy for colorectal cancer screening: more evidence, persistent ironies," *JAMA,* vol. 312, pp. 601-2, Aug 13 2014.

[45] A. W. Swartz, "Colorectal cancer and the effect of flexible sigmoidoscopy screening," *JAMA,* vol. 312, p. 2411, Dec 10 2014.

[46] (2000). *When Your Child Needs a Colonosocpy or Sigmoidoscopy*. Available: https://www.fairview.org/patient-education/88609

[47] (2017). *Colon Cancer Screening*. Available: https://medlineplus.gov/ency/article/002071.htm

[48] M. Mousavinezhad, R. Majdzadeh, A. Akbari Sari, A. Delavari, and F. Mohtasham, "The effectiveness of FOBT vs. FIT: A meta-analysis on colorectal cancer screening test," *Med J Islam Repub Iran,* vol. 30, p. 366, 2016.

[49] J. D. Hardcastle, J. O. Chamberlain, M. H. Robinson, S. M. Moss, S. S. Amar, T. W. Balfour*, et al.*, "Randomised controlled trial of faecal-occult-blood screening for colorectal cancer," *Lancet,* vol. 348, pp. 1472-7, Nov 30 1996.

[50] O. Kronborg, C. Fenger, J. Olsen, O. D. Jorgensen, and O. Sondergaard, "Randomised study of screening for colorectal cancer with faecal-occult-blood test," *Lancet,* vol. 348, pp. 1467-71, Nov 30 1996.

[51] J. S. Mandel, J. H. Bond, T. R. Church, D. C. Snover, G. M. Bradley, L. M. Schuman*, et al.*, "Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study," *N Engl J Med,* vol. 328, pp. 1365-71, May 13 1993.

[52] F. Ederer, T. R. Church, and J. S. Mandel, "Fecal occult blood screening in the Minnesota study: role of chance detection of lesions," *J Natl Cancer Inst,* vol. 89, pp. 1423-8, Oct 1 1997.

[53] J. S. Mandel, T. R. Church, F. Ederer, and J. H. Bond, "Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood," *J Natl Cancer Inst,* vol. 91, pp. 434-7, Mar 03 1999.

[54] T. e. o. E. Britannica, "Hemoglobin," ed, 2017.

[55] S. H. Elsafi, N. I. Alqahtani, N. Y. Zakary, and E. M. Al Zahrani, "The sensitivity, specificity, predictive values, and likelihood ratios of fecal occult blood test for the detection of colorectal cancer in hospital settings," *Clin Exp Gastroenterol,* vol. 8, pp. 279-84, 2015.

[56] J. E. Allison, I. S. Tekawa, L. J. Ransom, and A. L. Adrain, "A comparison of fecal occult-blood tests for colorectal-cancer screening," *N Engl J Med,* vol. 334, pp. 155-9, Jan 18 1996.

[57] F. A. Oort, S. T. van Turenhout, V. M. Coupe, R. W. van der Hulst, E. I. Wesdorp, J. S. Terhaar sive Droste*, et al.*, "Double sampling of a faecal immunochemical test is not superior to single sampling for detection of colorectal neoplasia: a colonoscopy controlled prospective cohort study," *BMC Cancer,* vol. 11, p. 434, Oct 10 2011.

[58] S. J. Winawer, B. J. Flehinger, D. Schottenfeld, and D. G. Miller, "Screening for colorectal cancer with fecal occult blood testing and sigmoidoscopy," *J Natl Cancer Inst,* vol. 85, pp. 1311-8, Aug 18 1993.

[59] D. P. Berry, P. Clarke, J. D. Hardcastle, and K. D. Vellacott, "Randomized trial of the addition of flexible sigmoidoscopy to faecal occult blood testing for colorectal neoplasia population screening," *Br J Surg,* vol. 84, pp. 1274-6, Sep 1997.

[60] M. Rasmussen, O. Kronborg, C. Fenger, and O. D. Jorgensen, "Possible advantages and drawbacks of adding flexible sigmoidoscopy to hemoccult-II in screening for colorectal cancer. A randomized study," *Scand J Gastroenterol,* vol. 34, pp. 73-8, Jan 1999.

[61] C. M. Rutter, E. Johnson, D. L. Miglioretti, M. T. Mandelson, J. Inadomi, and D. S. Buist, "Adverse events after screening and follow-up colonoscopy," *Cancer Causes Control,* vol. 23, pp. 289-96, Feb 2012.

[62] B. Levin, D. A. Lieberman, B. McFarland, K. S. Andrews, D. Brooks, J. Bond*, et al.*, "Screening and surveillance for the early detection of colorectal cancer and

adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology," *Gastroenterology,* vol. 134, pp. 1570-95, May 2008.

[63] C. P. Gross, M. S. Andersen, H. M. Krumholz, G. J. McAvay, D. Proctor, and M. E. Tinetti, "Relation between Medicare screening reimbursement and stage at diagnosis for older patients with colon cancer," *JAMA,* vol. 296, pp. 2815-22, Dec 20 2006.

[64] F. Loeve, R. Boer, A. G. Zauber, M. Van Ballegooijen, G. J. Van Oortmarssen, S. J. Winawer*, et al.*, "National Polyp Study data: evidence for regression of adenomas," *Int J Cancer,* vol. 111, pp. 633-9, Sep 10 2004.

[65] (Febraury 6). *CISNET Cancer Model profiles*. Available: https://cisnet.cancer.gov/colorectal/profiles.html

[66] A. G. Zauber, I. Lansdorp-Vogelaar, A. B. Knudsen, J. Wilschut, M. van Ballegooijen, and K. M. Kuntz, "Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force," *Ann Intern Med,* vol. 149, pp. 659-69, Nov 04 2008.

[67] F. Loeve, R. Boer, G. J. van Oortmarssen, M. van Ballegooijen, and J. D. Habbema, "The MISCAN-COLON simulation model for the evaluation of colorectal cancer screening," *Comput Biomed Res,* vol. 32, pp. 13-33, Feb 1999.

[68] B. Vogelstein, E. R. Fearon, S. R. Hamilton, S. E. Kern, A. C. Preisinger, M. Leppert*, et al.*, "Genetic alterations during colorectal-tumor development," *N Engl J Med,* vol. 319, pp. 525-32, Sep 01 1988.

[69] B. Morson, "President's address. The polyp-cancer sequence in the large bowel," *Proc R Soc Med,* vol. 67, pp. 451-7, Jun 1974.

[70] "Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement," *Ann Intern Med,* vol. 149, pp. 627-37, Nov 04 2008.

[71] M. E. Martinez, J. A. Baron, D. A. Lieberman, A. Schatzkin, E. Lanza, S. J. Winawer*, et al.*, "A pooled analysis of advanced colorectal neoplasia diagnoses after colonoscopic polypectomy," *Gastroenterology,* vol. 136, pp. 832-41, Mar 2009.

[72] T. J. Eide, "The age-, sex-, and site-specific occurrence of adenomas and carcinomas of the large intestine within a defined population," *Scand J Gastroenterol,* vol. 21, pp. 1083-8, Nov 1986.

[73] I. Lansdorp-Vogelaar, A. B. Knudsen, and H. Brenner, "Cost-effectiveness of colorectal cancer screening - an overview," *Best Pract Res Clin Gastroenterol,* vol. 24, pp. 439-49, Aug 2010.

[74] S. J. Goldie, "Chapter 15: Public health policy and cost-effectiveness analysis," *J Natl Cancer Inst Monogr,* pp. 102-10, 2003.

[75] F. L, "What is QALY?," Hayward Medical Communications, London2009.

[76] H. I. Meissner, N. Breen, C. N. Klabunde, and S. W. Vernon, "Patterns of colorectal cancer screening uptake among men and women in the United States," *Cancer Epidemiol Biomarkers Prev,* vol. 15, pp. 389-94, Feb 2006.

[77] P. J. Neumann, J. T. Cohen, and M. C. Weinstein, "Updating cost-effectiveness--the curious resilience of the $50,000-per-QALY threshold," *N Engl J Med,* vol. 371, pp. 796-7, Aug 28 2014.

[78] R. S. Braithwaite, D. O. Meltzer, J. T. King, Jr., D. Leslie, and M. S. Roberts, "What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule?," *Med Care,* vol. 46, pp. 349-56, Apr 2008.

[79] R. A. Hirth, M. E. Chernew, E. Miller, A. M. Fendrick, and W. G. Weissert, "Willingness to pay for a quality-adjusted life year: in search of a standard," *Med Decis Making,* vol. 20, pp. 332-42, Jul-Sep 2000.

[80] OSU. *Markov Processes*. Available: https://people.math.osu.edu/husen.1/teaching/571/markov_1.pdf

[81] E. A. Sherer, S. Ambedkar, S. Perng, Y. Yih, and T. F. Imperiale, "A predictive model of longitudinal, patient-specific colonoscopy results," *Comput Methods Programs Biomed,* vol. 112, pp. 563-79, Dec 2013.

[82] N. Phillips and A. Coldman, "Computer simulation of the effect of different colorectal cancer screening strategies for British Columbia.," *BCMJ,* vol. 45, pp. 254-258, 2003.

[83] S. L. Murphy, J. Xu, and K. D. Kochanek, "Deaths: final data for 2010," *Natl Vital Stat Rep,* vol. 61, pp. 1-117, May 08 2013.

[84] D. Heresbach, T. Barrioz, M. G. Lapalus, D. Coumaros, P. Bauret, P. Potier*, et al.*, "Miss rate for colorectal neoplastic polyps: a prospective multicenter study of back-to-back video colonoscopies," *Endoscopy,* vol. 40, pp. 284-90, Apr 2008.

[85] K. M. Kuntz, I. Lansdorp-Vogelaar, C. M. Rutter, A. B. Knudsen, M. van Ballegooijen, J. E. Savarino*, et al.*, "A systematic comparison of microsimulation models of colorectal cancer: the role of assumptions about adenoma progression," *Med Decis Making,* vol. 31, pp. 530-9, Jul-Aug 2011.

[86] D. K. Rex, "Colonoscopy: a review of its yield for cancers and adenomas by indication," *Am J Gastroenterol,* vol. 90, pp. 353-65, Mar 1995.

[87] K. Lang, L. M. Lines, D. W. Lee, J. R. Korn, C. C. Earle, and J. Menzin, "Lifetime and treatment-phase costs associated with colorectal cancer: evidence from SEER-Medicare data," *Clin Gastroenterol Hepatol,* vol. 7, pp. 198-204, Feb 2009.

[88] R. M. Ness, A. M. Holmes, R. Klein, and R. Dittus, "Cost-utility of one-time colonoscopic screening for colorectal cancer at various ages," *Am J Gastroenterol,* vol. 95, pp. 1800-11, Jul 2000.

[89] A. Tafazzoli, S. Roberts, R. Klein, R. Ness, and R. Dittus, "Probabilistic cost-effectiveness comparison of screening strategies for colorectal cancer," *ACM Transactions on Modeling and Computer Simulation,* vol. 19, pp. 1-29, 2009.

[90] S. H. Taplin, W. Barlow, N. Urban, M. T. Mandelson, D. J. Timlin, L. Ichikawa*, et al.*, "Stage, age, comorbidity, and direct costs of colon, prostate, and breast cancer care," *J Natl Cancer Inst,* vol. 87, pp. 417-26, Mar 15 1995.

[91] A. G. Zauber, "Cost-effectiveness of colonoscopy," *Gastrointest Endosc Clin N Am,* vol. 20, pp. 751-70, Oct 2010.

[92] A. B. Mariotto, K. R. Yabroff, Y. Shao, E. J. Feuer, and M. L. Brown, "Projections of the cost of cancer care in the United States: 2010-2020," *J Natl Cancer Inst,* vol. 103, pp. 117-28, Jan 19 2011.

[93] D. J. Robertson, J. K. Lee, C. R. Boland, J. A. Dominitz, F. M. Giardiello, D. A. Johnson*, et al.*, "Recommendations on Fecal Immunochemical Testing to Screen for Colorectal Neoplasia: A Consensus Statement by the US Multi-Society Task

Force on Colorectal Cancer," *Gastroenterology,* vol. 152, pp. 1217-1237 e3, Apr 2017.

[94] M. C. Wong, J. Y. Ching, V. C. Chan, and J. J. Sung, "The comparative cost-effectiveness of colorectal cancer screening using faecal immunochemical test vs. colonoscopy," *Sci Rep,* vol. 5, p. 13568, Sep 04 2015.

[95] L. L. Song and Y. M. Li, "Current noninvasive tests for colorectal cancer screening: An overview of colorectal cancer screening tests," *World J Gastrointest Oncol,* vol. 8, pp. 793-800, Nov 15 2016.

[96] J. Kingsley, S. Karanth, F. L. Revere, and D. Agrawal, "Cost Effectiveness of Screening Colonoscopy Depends on Adequate Bowel Preparation Rates - A Modeling Study," *PLoS One,* vol. 11, p. e0167452, 2016.

[97] G. P. Guy, Jr., L. C. Richardson, M. P. Pignone, and M. Plescia, "Costs and benefits of an organized fecal immunochemical test-based colorectal cancer screening program in the United States," *Cancer,* vol. 120, pp. 2308-15, Aug 01 2014.

[98] S. N. Bonnington and M. D. Rutter, "Surveillance of colonic polyps: Are we getting it right?," *World J Gastroenterol,* vol. 22, pp. 1925-34, Feb 14 2016.

[99] M. W. Short, M. C. Layton, B. N. Teer, and J. E. Domagalski, "Colorectal cancer screening and surveillance," *Am Fam Physician,* vol. 91, pp. 93-100, Jan 15 2015.

[100] W. S. Atkin, B. C. Morson, and J. Cuzick, "Long-term risk of colorectal cancer after excision of rectosigmoid adenomas," *N Engl J Med,* vol. 326, pp. 658-62, Mar 05 1992.

[101] J. A. Wilson, "Colon cancer screening in the elderly: when do we stop?," *Trans Am Clin Climatol Assoc,* vol. 121, pp. 94-103, 2010.

[102] S. T. Jung, D. K. Sohn, C. W. Hong, B. C. Kim, J. W. Park, K. S. Han*, et al.*, "Importance of Early Follow-up Colonoscopy in Patients at High Risk for Colorectal Polyps," *Ann Coloproctol,* vol. 29, pp. 243-7, Dec 2013.

[103] R. L. Siegel, S. A. Fedewa, W. F. Anderson, K. D. Miller, J. Ma, P. S. Rosenberg*, et al.*, "Colorectal Cancer Incidence Patterns in the United States, 1974-2013," *J Natl Cancer Inst,* vol. 109, Aug 01 2017.