ABSTRACT

TAFAZZOLI YAZDI, ALI. A COMPARISON OF SCREENING METHODS FOR COLORECTAL CANCER. (Under the direction of Dr. Stephen D. Roberts.)

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States. This cancer has a very long asymptomatic phase and most patients are not aware of its presence until it grows into an advanced stage when the survival chance is very low. Evidence from several studies suggests that screening for detecting and removing colorectal cancer and precancerous adenomatous polyps can reduce the incidence of CRC and colorectal cancer-related mortality. There are a number of screening methods designed for this purpose, which vary considerably in terms of their performance characteristics and cost. However, because of the long latency of CRC and time needed for clinical trials, it is not practical to provide clinical trials of all the screening strategies for CRC. Simulation models offer an alternative means to evaluate and compare screening strategies.

The primary goal of this thesis was to add a screening structure onto an existing discrete-event simulation model of the natural history of the CRC. The enhanced model is capable of simulating various screening interventions. It is the only model that can simulate all the screening strategies recommended by the American Gastroenterological Association clinical guidelines.

In order to compare the screening strategies in these guidelines, a deterministic cost-effectiveness analysis (CEA) was first performed. CEA is considered the most appropriate method of evaluating preventive health services from an economic perspective. The model provides the discounted cost and effectiveness of each of the screening strategies which are the key inputs for CEA.

Adopting a Bayesian approach, an appropriate distribution was assigned to strategic and economic parameters of the model to compare the screening strategies under the uncertainty. A probabilistic sensitivity analysis was performed for this purpose and the empirical distributions for average cost-effectiveness (CE) ratio of screening methods along with their 95% confidence intervals were developed on the CE plane.

Finally, the cost-effectiveness acceptability curves (CEAC) were derived from the CE planes. These curves present the probability that a screening strategy is cost-effective for different ceiling ratios, which is the money society is willing to pay to gain a year of life. Examining the CEAC for all the populations (average and high risk), fecal occult blood test (FOBT), combined sigmoidoscopy & FOBT, and colonoscopy were three screening strategies showing higher probabilities to be the most cost-effective strategy for different ceiling ratios. In general, CEAC provide a probabilistic comparison between screening strategies, which can be used by medical policy makers for guideline development and health-care resource allocation. This thesis is the first effort to compare multiple number of CRC screening strategies by using CEAC.

A Comparison of Screening Methods for Colorectal Cancer

By

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Biography

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1. Introduction to Colorectal Cancer

Colorectal Cancer (CRC) is the fourth most common malignant disease diagnosed each year and the second leading cause of cancer death in persons living in the United States. In 2004, an estimated 146,940 new cases of colorectal cancer will be diagnosed, and 56,730 Americans are expected to die of colorectal cancer this year. Eighty to 90 million Americans (approximately 20 percent of the US population) are considered at risk because of age or other factors (Jemal et al. 2003).

Screening for CRC remains the cornerstone of CRC prevention and control efforts around the world. The efficacy of CRC screening is believed to rest in the ability of the employed screening modality to identify colorectal adenomas and asymptomatic early-stage CRC. In general, identification of colorectal cancer at an earlier stage leads to improved survival (from <http://www.cancer.org>):

- Over 90% of those diagnosed when the cancer is found at a local stage (confined to colon or rectum) survive more than five years.
- Once the cancer is diagnosed at a regional stage (spread to surrounding tissue) that rate drops to 66%.
- When the cancer has also spread to distant sites, only 8.5% of those diagnosed will reach the five year survival milestone.

Unfortunately, the majority of colorectal cancers are not found early:

- 37% of colorectal cancers are found while the cancer is found at a local stage (confined to colon or rectum).
- 37% of colorectal cancers are found after the cancer is diagnosed at a regional stage (spread to surrounding tissue).
- Over 20% of colorectal cancers are found after the disease has spread to distant organs.

CRC is principally a disease of Western industrialized nations, where it generally ranks second or third in cancer mortality. Many have hypothesized that this increased

incidence of CRC is attributable to the high rate of red meat and fat consumption and low rate of fruit and vegetable consumption in these countries. In the United States, CRC incidence is significantly higher in males than in females. CRC incidence and mortality is also higher in African Americans compared to Caucasian Americans.

The purpose of this thesis is to model different screening and surveillance strategies for colorectal cancer and to evaluate and compare their costs and effectiveness. However, it is necessary to become familiar with natural course of CRC and common screening modalities that are used to reduce the risk of developing this disease.

1.1. Cancer

Cancer is an abnormal, uncontrolled growth of cells. Normally, cells in the body grow, divide and die in an orderly fashion. During the early years of a person's life, normal cells divide more rapidly until the person becomes an adult. After that, new cells are formed, at a steady pace, to replace an equal number of "worn-out" cells or to repair injuries.

With cancer, cells proliferate out of control. Instead of dying, the cancerous cells outlive normal cells and continue to form new abnormal cells. The proliferation of cancer cells can then spread from its location of origin to other parts of the body through the blood and lymph systems.

Cancer cells develop because of damage to DNA. This damage is replicated in all newly formed cells and directly affects their activities. Most of the time when DNA becomes damaged the body is able to repair it. When cancer cells survive, the damaged DNA is not repaired.

Abnormal growths of cancerous cells form tumors, which can cause other body tissues to be destroyed. Not all tumors are cancerous. A benign tumor is not cancerous. The cells in a benign tumor look like normal body cells. Although benign tumors can grow large enough to interfere with normal body functions, they do not spread to other parts of the body. Benign tumors that are removed rarely return.

Cancerous or malignant tumors can invade surrounding tissue. Through a process known as metastasis, malignant cells travel to distant sites in the body, where the cells can multiply again and form tumors or metastases. Regardless of where a cancer may spread, however, it is always named for the place it began.

The risk of developing most types of cancer can be reduced by changes in a person's lifestyle, for example, by quitting smoking and eating a better diet. Furthermore, the sooner a cancer is found and treatment begins, the better are the chances for living for many years.

1.2. Colon and Rectum

The colon and rectum are parts of the digestive system. They form a long, muscular tube called the large intestine. It is elastic, flexible and can expand and move. The colon is about 3 inches in diameter. It is the first 4 to 5 feet of the large intestine, and the rectum is the last 4 to 5 inches. The colon is divided into four main sections that go up (the ascending colon), across (the transverse colon), down (the descending colon), and then curve into an "S" shaped segment (the sigmoid colon) before joining to the rectum. Figure 1 shows the anatomy of the abdomen, including the colon and rectum.

Figure 1: Diagram of the colon and rectum

Almost fully digested food enters the colon from the small intestine. The colon removes water and some specific nutrients from the chyme and stores the rest as waste. The waste passes from the colon into the rectum and then out of the body through the anus.

1.3. Colorectal Cancer

Although the exact cause of colorectal cancer is not fully understood, based on an increasing body of evidence, most (if not all) types of colorectal cancer are adenocarcinomas. This designation means that the cancer arises from adenomas (adenomatous polyps), which are the unusual collection of cells lining the inside wall of the colon and rectum forming a precancerous growth of tissue. Figure 2 shows how a normal colon might look on examination and how a colonic polyp might appear.

Figure 2: The lining of the colon A: Normal colon B: Colonic polyp

In general, the larger the size of the adenoma, the greater the probability that it harbors cancer cells. Adenomas that are larger than 2 cm in diameter have up to a 40% chance of being cancerous. The likelihood of developing colorectal cancer also increases with the number of adenomas that are present. The risk of malignancy is also associated with adenoma histology and degree of villous characteristics. Adenoma histology, which is the microscopic structure of the adenoma, is classified based on the proportion of villous versus tubular architecture.

Figure 3 shows the different anatomical areas of the colon and the distribution of polyps and cancers that develop in these areas. The numbers shown in each figure refer to the percentage of polyps and cancers that may develop in that particular anatomic section of the colon.

Figure 3: Areas of Distribution of adenomatous polyps (right) and cancers (left)

If an adenoma develops and is not removed, it may become cancerous. Once a cancer develops it begins to invade the intestinal wall and may spread to nearby lymph nodes. Lymph nodes are part of the lymphatic system, which carries special filtered fluids throughout the body. Through the lymphatic system, cancer cells may also be carried to areas of the body far from the original tumor location.

The spread of cancer may also occur via the blood stream. Colon and rectal cancers that metastasize through the blood stream will travel first to the liver. There the cancerous cells may continue to grow and develop new tumors.

1.4. Colorectal Cancer Risk Factors

The exact causes of colorectal cancer are still largely unknown, but certain factors are known to increase the risk of developing this disease. Still other factors are suspected of increasing the risk of colorectal cancer, but the evidence is not as well established. The disease appears to be caused by both inherited and lifestyle factors. It is known that about 75% of all new cases of colon cancer occur in people with no known inherited risk factors for the disease (Lieberman et al. 2003).

1.4.1. Known Risk Factors

Everyone has some risk of developing CRC. The following factors are known to increase the risk of developing colorectal cancer.

- **Age:** As people get older they are more likely to develop colorectal cancer. Approximately 90% of colorectal cancers occur in people over the age of 50. The average age at diagnosis is in the mid-60s. However, colorectal cancer can occur at younger ages and, in rare cases, in the teens. (almost always in patients with cancer syndromes)
- **Personal History of Adenomatous Polyps:** Individuals with a history of adenomatous polyps develop colorectal cancer more often than those without these polyps.
- **Family History of Cancer:** Having a family history of colorectal neoplasia, apart from one of the identified inherited syndromes, has been shown to be a strong predictor of developing colorectal neoplasia. Studies have consistently shown a two to four-fold increase in the risk for developing CRC in patients with a first-degree (parents, siblings, and children) relative diagnosed with either CRC or adenomatous polyps. Other studies have shown an increased risk of colorectal adenomas in patients who have a first-degree relative with CRC. Most of these studies have reported that the increased risk of colorectal neoplasia posed by an affected first-degree relative is dependent on the age of that relative at initial diagnosis, with younger age posing a higher risk.
- **Inflammatory Bowel Disease:** Diseases that cause inflammation of the bowel, such as ulcerative colitis and Crohn's disease increase the risk of colorectal cancer. The risk is greater for those with ulcerative colitis than for those with Crohn's disease, and it is directly related to how widespread and severe the disease is in the colon of an affected individual. Increasing the risk even more is how long an individual has had ulcerative colitis. Individuals who have had ulcerative colitis for 30 or more years have more than a 30% risk of developing colorectal cancer. Areas of the colon affected by colitis often give rise to dysplastic cells (abnormally developed), and from these arise cancer cells.

- ***Prior Personal History of Cancer:*** A person who has already been treated for colorectal cancer has a significantly greater risk for developing another colorectal cancer. Women who have had breast, ovarian, or uterine cancer also have an increased chance of developing colorectal cancer.

1.4.2. Other Possible Risk Factors

Other possible factors that may increase the risk of developing CRC are:

- ***Lifestyle:*** such as cigarette smoking, a sedentary lifestyle, and obesity.
- ***Diet:*** Diets high in fat and Cholesterol and low in fiber or folates.

1.5. Symptoms Associated with CRC

The symptoms of colorectal cancer depend upon the stage of the disease and the area of the colon that is involved. During the early stage of colorectal cancer, some people may not have symptoms. Others may complain of different kinds of problems such as:

- Rectal bleeding
- Melena (dark-tarry stools caused by proximal bleeding source)
- A change in bowel habits, especially in the shape of the stool (e.g., narrow like a pencil)
- General abdominal discomfort (frequent gas pains, bloating, fullness, and/or cramps)
- Weight loss with no known reason
- Constant fatigue.

Most of these symptoms are associated with late-stage disease and thus limited survival.

These symptoms depend on where in the colon or rectum the cancer is located. Colorectal cancer involving the person's right side of the colon can cause vague abdominal aching, and a mass on the right side of the abdomen. Blood loss can cause anemia, a reduction in red blood cells that can cause weakness and fatigue. Colorectal cancer involving the left side of the colon can cause cramping, abdominal pain, nausea

and vomiting, or alternating constipation and diarrhea. Periodic rectal bleeding can also occur. Persons whose cancer involves the rectum may experience a feeling of rectal fullness, rectal bleeding, painful spasms, change in bowel movements, and change in the diameter of stools. Disease metastatic to the liver or lungs is often associated with fatigue and unexplained weight loss

1.6. Colorectal Cancer Stages

Determining the extent of a cancer is called “staging.” Usually, the *stage* of a cancer is based on factors such as the size of the tumor, and whether the cancer has spread into the lymph nodes or to more distant sites. In colorectal cancer, however, how deeply the tumor has invaded into the wall of the bowel plays a more important role in staging than does the size of the tumor.

There are different methods of staging, the most common being the Modified Astler-Coller Duke’s classification and the TNM system of staging. A combination of these is given below, along with their typical treatment (from <http://www.cancer.org>).

Stage 0

In stage 0, the cancer is found in the epithelium, innermost lining of the colon, and has not grown beyond that. All that is needed is to do surgical resection to take out the cancer. If detected early, colon cancer is highly curable and has a low risk of recurrence. Stage 0 cancer is also called carcinoma *in situ* or high-grade dysplasia.

Stage I

In stage I, cancer has spread beyond the epithelium and into the lamina propria, muscularis mucosa, which together with the epithelium form the mucosa, and perhaps the submucosa, but it has not spread into the muscularis propria, the main muscular layer, adventitia, outer wall of the colon, or beyond the colon. Surgical resection to remove the section of the colon containing the cancer is the standard treatment. Generally there is no need for any additional therapy. Stage I is also curable, with a low risk for recurrence. It is comparable to Dukes' A colon cancer.

Stage II

In stage II, cancer has spread into or through the muscular layers of the colon but is still limited to the colonic wall. Surgical resection is usually the only treatment needed. If the doctor thinks the cancer is likely to come back because of its appearance under the microscope or because it was growing into other tissues, radiation (only for rectal) and/or chemotherapy may be recommended. Radiation can be directed to the local area of the abdomen where the cancer was growing. Chemotherapy is not standard treatment for this stage of colon cancer and should only be given as part of a clinical trial. Stage II colon cancer is comparable to Dukes' B colon cancer.

Stage III

In stage III, cancer has spread to nearby lymph nodes, but it has not spread to other parts of the body. Surgical resection is the first treatment. The person should then receive chemotherapy with 5-FU and leucovorin with or without the addition of newer active agents. Also the person may need radiation therapy if the cancer is rectal. Studies have shown that the number of regional lymph nodes involved affects the outcome. Patients with 1-3 nodes involved have significantly greater survival rates than those with 4 or more nodes involved. Stage III colon cancer is comparable to Dukes' C colon cancer.

Stage IV

In stage IV, cancer has spread to other parts of the body, such as the liver or lungs. The goal of surgery (segmental resection or diverting colostomy) in this stage is usually to relieve or prevent blockage of the colon and to prevent other local complications. In some patients with extensive metastases, blockage can be prevented or managed by inserting a tube through the tumor (stent) during colonoscopy so that surgery can be avoided. If the cancer is small and the patient is in poor health, surgery may not be recommended. Generally the primary tumor is resected for palliation to prevent future bowel obstruction. New chemotherapy regimens have been shown to extend life up 15-18 months. Stage IV colon cancer is sometimes called Dukes' D colon cancer.

1.7. Colorectal Cancer Treatments

The three main types of treatment for colorectal cancer are resection surgery, chemotherapy, and radiation therapy. Depending on the stage of the cancer, two or more types of treatment may be used at the same time, or one after the other.

1.7.1. Resection Surgery

The primary treatment for colorectal cancer is surgery, with resection or removal of the involved segment of colon and the draining lymph nodes. The feasibility and type of surgery for colorectal cancer depends on a number of factors, including the size of the tumor, whether it is attached to the surrounding tissues, and whether the muscles of the anus can be spared. Resection surgery removes “modular” sections of the colon as it is shown in Figure 4.

Figure 4: Cancer Resection Diagram

1.7.2. Chemotherapy

The use of drugs for the purpose of eliminating cancer cells is called chemotherapy. Some patients with stage II and most patients with stage III or IV disease will need some form of chemotherapy after surgery. Chemotherapy is employed because cancer cells can remain in the body even after a tumor has been removed. If not eliminated, these remaining cancer cells can multiply, grow, and spread, either at the site where they were

originally or other sites reached by traveling through blood and lymph vessels. Therapies based on 5-fluorouracil (5FU) and leukovorin have been the mainstay of adjuvant chemotherapy for the last 15 years. More recently, the addition of oxaloplatin to 5FU leukovorin, had led to even greater survival among patients with stage III disease. Palliative or non-curative-intent chemotherapy regimens are also changing as newer drugs offer patients longer survival.

1.7.3. Radiation Therapy

Radiation therapy is often used in the treatment of stage II and III rectal cancer . In rectal cancer, radiation to the pelvis can be used before surgery to shrink the tumor, after surgery to prevent local recurrence, or in the treatment of a local pelvic recurrence. Unlike systemic chemotherapy, radiation therapy cannot control the recurrence of cancer outside the area that was irradiated.

1.8. Modeling CRC Screening Methods and Organization of This Thesis

Because CRC directly affects individuals, it is not economically feasible or morally justified to arbitrarily intervene in the lives of people who might become victims of CRC. Thus, using computer models to study various means to identify and treat people for CRC is an attractive alternative to direct experimentation. With valid models it may be possible to predict the course and outcome, in terms of costs and life-years gained, of screening, surveillance, and treatment methods.

A discrete simulation model was employed in this thesis to perform a comparison of the cost-effectiveness of popular CRC screening strategies to provide insight for developers of CRC screening guidelines. The work in this thesis is supported from a grant to Vanderbilt University from the Department of Health and Human Services, National Institute of Health, National Cancer Institute, grant number 1 R01 CA92653 01A1, titled “Simulation Modeling of Colorectal Cancer.” More specifically, a subcontract from Vanderbilt to North Carolina State University, named “Simulation Model for Colorectal Cancer,” grant number VUMC CA#9195 supported the work for this thesis.

The organization of this thesis is as follows:

Chapter 2 presents a brief review of literature related to the methods of CRC screening. Cost-effectiveness is discussed as a proper method used in comparing different medical interventions, along with sensitivity analysis which is a common method of evaluating medical models under uncertainty.

Chapter 3 gives a careful delineation of the modeling assumptions. It describes the objects and events used in the simulation, along with their relationships and pathways. Chapter 3 also describes the data sources for the model construction and details the parameters which were used in probabilistic sensitivity analysis and their distributions.

Chapter 4 of this thesis focuses on the analysis of the model. This chapter contains the usual simulation concerns of verification and validation. The cost-effectiveness results of comparing different screening strategies in populations with different CRC development risks are presented in this chapter

Chapter 5 provides conclusions and recommendations for further study. Here is stated the recommendations for screening based on cost-effectiveness.

2. CRC Screening and Surveillance Strategies

Colorectal cancer, with its high incidence and mortality, constitutes a serious public health burden in most industrialized countries. In the US, there has been an extensive effort in recent years to reduce the prevalence of this disease by different organizations like the National Cancer Institute and the American Gastroenterological Association.

Evidence from the several studies showed that colorectal cancer fulfils the criteria of a disease ideal for screening (Pignone, Teutsch, and Breg 2002). They have concluded that screening could help by identifying and removing the adenomatous polyps which are the precursors of CRC, and since such a person is always at risk of developing new adenomas, that person should be under a continuous surveillance.

The screening methods that are currently available vary considerably in terms of their performance characteristics, complication rates, acceptability, and cost (Frazier et al. 2000). Despite multiple studies comparing alternative screening strategies, there is no consensus as to which is the most effective strategy. Furthermore, the emergence of new screening modalities and improvements in existing screening and surveillance strategies add to an already complicated issue.

In this chapter we will first introduce the notion of screening and surveillance and offer a brief review of different screening modalities. Then screening and surveillance strategies are explained in the context of clinical guidelines. Compliance and its critical role in colorectal screening are discussed afterwards. At the end of this chapter the necessity of cost-effectiveness analysis in medical decision studies and the concept of probabilistic sensitivity analysis are presented.

2.1. Screening

Since CRC has a long asymptomatic phase, screening can substantially reduce colorectal cancer mortality by detecting disease in early stages, when it is often curable. Screening tests are administered to asymptomatic individuals, but who are at risk for developing colorectal cancer. The tests are used to detect colorectal polyps or cancer. In many cases, these tests can find colorectal cancers at an early stage and greatly improve

the chances of successful treatment. Some screening tests can also help prevent cancers by allowing doctors to find and remove polyps that might become cancer.

The accuracy of each screening modality is judged by its sensitivity and specificity characteristics. These two measures are used to characterize the effectiveness and quality of a screening test.

Sensitivity of a test is its ability to identify true disease, which in the present case refers to colorectal adenoma or cancer. A screening test is highly sensitive if it has few false negatives (missing of an existing adenomatous polyp) and many true positives (detecting of an existing adenomatous polyp) in its results. Sensitivity is computed by dividing the number of true positives by the sum of true positive plus false negatives.

Specificity is the test's ability to determine there is no disease. High specificity for a screening test means that it generates few false positives ("detecting" a non-existing adenomatous polyp) and many true negatives (detecting no adenomatous polyp in a normal colon). Specificity is computed by dividing the number of true negatives by the sum of true negatives plus false positives.

Generally, screening tests fall into two categories: endoscopic and non-endoscopic tests. Endoscopic tests employ methods of direct observation of the colon. Non-endoscopic methods rely on consequences of adenoma or cancer presence in the colon (from <http://www.cancer.org>).

2.1.1. Endoscopic Tests

Endoscopic tests are the ones that provide the physician with direct views of the lining of the colon. The two types of endoscopy employed in CRC screening include sigmoidoscopy and colonoscopy.

Both tests employ endoscopes, which are flexible tubes about the thickness of a finger with controlled deflection at the tip. The endoscopes are attached to a light source and have digital viewing components present at the tip. In colorectal endoscopy, the endoscope is inserted into the anus and advanced under direct visualization (digital perspectives projected on a monitor) to the cecum, the most proximal colonic segment. On withdrawal, a complete and thorough evaluation of the visual appearance of the

mucosal lining is performed. This is made possible by a pre-procedure purging of the colonic contents using certain oral laxatives and air insufflations (Figures 5).

FIGURE 3 Flexible sigmoidoscope. Photograph courtesy of Olympus.

FIGURE 4 Colonoscope. Photograph courtesy of Olympus.

Figure 5: Sigmoidoscope (up) and Colonoscope (down)

About two feet in length, the sigmoidoscope can visualize much of the colon (rectum and sigmoid reliably, descending colon in about 50% of cases), but cannot examine the entire colon. The colonoscope can visualize the entire colon and can therefore detect cancers located in the upper colon. Figure 6 depicts the areas of the colon viewed on sigmoidoscopy and colonoscopy.

Figure 6: The “Reach” of Sigmoidoscopy (blue part) and Colonoscopy (total area)

During a sigmoidoscopy or colonoscopy, small pieces of identified abnormal colon tissue can be sampled. This process is called “biopsy”. These specimens can then be sent to pathology to be microscopically examined for abnormalities indicating pathology. Polyps can be totally removed during colonoscopy using a technique called polypectomy, wherein a wire is fitted over a polyp and used to cut and cauterize the polyp from the surrounding normal mucosa.

To obtain the accurate results, both tests are performed after the patient has prepared for the procedure by following directions designed to remove all stool from the colon, so the mucosa (colon linings) can be better seen. This recommendation usually involves limiting food intake on the day before the procedure and drinking a laxative that promotes emptying of the bowel.

Both sigmoidoscopy and colonoscopy are performed as outpatient procedures that do not require overnight hospitalization. Sigmoidoscopy is often done within the doctor’s office as sedating analgesic medications are generally not given. Because colonoscopy

usually requires both sedation and analgesia, it is generally performed in a hospital-based endoscopy suite or freestanding surgical center.

Because colonic endoscopies are invasive procedures, they do carry some small risk of bowel perforation, bleeding, and reaction to sedating medications. There is a very low risk that a patient dies during colonoscopy or sigmoidoscopy unless the perforations and bleedings are very serious. In experienced hands, these risks should be minimal.

A positive result for an endoscopic test is one where a pathologic lesion is identified. Such a test result should always be valid because pathologic confirmation is available through the submission of biopsy and polypectomy specimens. An endoscopic test result is negative when the test outcome suggests that the colon is normal and no adenomatous polyps have been found in the screened sections. But these results might be incorrect since it is possible that the physician misses a polyp because of the irregular surface of the colon.

2.1.2. Non-Endoscopic Tests

Non-Endoscopic tests fall into two groups. The first group consists of screening tests like the fecal occult blood test (FOBT) and fecal DNA which indirectly check the colon through examination of the stool. The second group includes non-endoscopic imaging tests, like virtual colonoscopy and double contrast barium enema (DCBE) which apply techniques such as tomography to take indirect images from the lining of colon.

- ***Fecal Occult Blood Test (FOBT)***

FOBT uses a chemical-impregnated card to detect the presence of small amounts of blood in the stool that cannot be seen with the naked eye. Although the presence of blood in the stool does not necessarily mean an individual has colorectal cancer, the guaiac test identifies individuals who should be further screened for the disease. The FOBT is relatively inexpensive and painless, but its sensitivity is low (15-50%). The probability of a false positive result is around 5-10%.

Since bleeding does not always occur at the time of testing, some polyps and colorectal cancers are not detected by this test. Just 50% of cancers and 10% of polyps

bleed enough to be detected. Therefore, the observed mortality reduction is fairly low for this test (15-33%).

- ***Double Contrast Barium Enema (DCBE)***

A DCBE provides a relatively sensitive indirect view of the lining of the colon. Barium and air are used as a double contrast to detect abnormal areas that may indicate colon polyps or cancers. Unlike colonoscopy, DCBE does not allow tissue samples to be removed at the time of the test. The patient requires the use of laxatives the night before the exam and an enema the morning of the exam.

- ***Virtual colonoscopy***

Virtual colonoscopy uses a high-definition computed tomography (CT or CAT scan) of the abdomen, which allows radiologists to create virtual views of the colon that look similar to those seen by conventional colonoscopy. Patients need a cleansing preparation of their bowel prior to the test. In some protocols, oral contrast agents are employed. A small flexible rubber tube is always placed in the rectum during the procedure to allow the insufflation of air that is used as a contrast agent. A CAT scan is then performed. The total time required for the study is approximately 10-20 minutes. Because sedation is not required, patients are free to leave the CT suite immediately without the need for recovery. Radiologists analyze the CT data to detect colon polyps or cancers. The test sensitivity has been high for colorectal neoplasia in most studies.

- ***DNA Stool Test***

Colorectal cancer is a disease in which many DNA mutations associated with the process of carcinogenesis have been characterized. This characterization makes it potentially valuable to examine the stool for the presence of DNA with these different mutations as indicators of both pre-clinical and clinical disease. Using multiple indicators is important since no single mutation has been found that is expressed in all colorectal cancers. Further, research has shown DNA to be a good marker. It is stable in the stool; it is shed continuously; and, through the use of amplification tests, such as polymerase chain reaction, it can be detected in minute amounts. Early clinical studies in a small number of patients with a multi-target DNA-based stool assay approach suggest high

sensitivity for both colorectal cancer and premalignant adenomatous polyps while maintaining high specificity.

After any positive non-endoscopic test, a diagnostic colonoscopy needs to be performed to scope the colon and find and remove the probable existing polyps or cancers. This procedure is needed even after a positive sigmoidoscopy test, since the sigmoidoscopy is not capable of performing polypectomy.

A non-endoscopic screening test result is negative whenever the outcome suggests that the colon is normal, e.g. in FOBT no blood is detected in the impregnated cards. Although just because a test is negative, a low test specificity (false negative rate) means there is always a chance that a test may miss an existing adenomatous polyp or cancer.

2.2. Screening Complications

Perforation and bleeding are two possible complications associated with these screening tests. These complications can happen during any colonoscopy and sigmoidoscopy tests when the endoscope perforates the lining of the colon. It rarely happens, but it can be a deadly event. Colonic perforation usually happens in one in 500 to 1000 cases of colonoscopy tests. As it was mentioned, the probability of dying while being screened is very low, about one in 2000 to 5000 perforations (Orsoni et al. 1997). Abnormal bleeding is generally associated with a previous endoscopic biopsy or polypectomy.

2.3. Surveillance

CRC surveillance refers to the regular examination of the colon in patients with a prior history of colorectal adenoma or cancer history. Because a history of colorectal adenomas or cancer is a risk factor for future colonic neoplasia, surveillance regimens are more aggressive than standard screening strategies. Therefore the frequency of the screening tests should be increased for a person under surveillance. This increase is directly associated with the size and number of adenomas discovered in colon.

2.4. CRC Screening and Surveillance Strategy

Since the advent of CRC screening tests in the 1970s numerous clinical guidelines have been published by professional medical organizations. Although knowledge is limited about the exact course of CRC disease and the effectiveness of different screening modalities is unknown, the guidelines have been continuously under change. New improvements in existing screening techniques, as well as newly emerged screening methods, are incorporated into new guidelines. Results from conducted randomized screening studies also have informed better screening strategies.

Generally, in any screening strategy the following factors should be addressed for any member of a population at risk: the appropriate screening tests (could be more than one), the screening start age, and the frequency of screening examinations. A strategy must be designed to balance the costs and risks of screening with the benefits people receive from being screened. Clearly, doing more frequent screenings for high risk people (with CRC family history) can improve their chance of cancer survival. Frequent screening has a higher screening cost, but the cancer costs are consequently reduced or eliminated, and also the person's quality of life may increase.

Decreasing the screening start age or increasing the screening frequencies may not be beneficial to the average risk (with no family history) population. For that reason clinical strategies have first classified the people based on their CRC level of risk and then have created separate guidelines for each group. As explained in Section 1.4.1, age, personal, and family history are three major factors that influence the person's CRC risk. The polyp incidence is age-dependent and its risk of recurrence is positively correlated with personal history. Beside these, studies have shown that patients who have a first-degree relative with CRC are at higher risk of developing colorectal cancer.

An instance of risk stratification which was presented in a recent screening guideline is shown in Figure 7. By following the branches of this tree each person is screened according to their risk (Winawer et al. 2003).

Figure 7: Algorithm for colorectal cancer screening according to Risk

There is no doubt that any of the screening tests described in Section 2.1 reduces the risk of CRC morbidity and mortality in some extent. Although despite all the research done on the effectiveness of various screening modalities, no single test has shown clear superiority in terms of effectiveness, risk, and cost. Thus the guidelines have recommended that people at average risk of developing CRC should be offered all the reliable screening tests, and should be given an opportunity to apply their own preferences in selecting how they should be screened. A believed benefit of this approach is to increase the patient's compliance to screening (the likelihood that screening will occur). The notion of compliance and its important role will be discussed in the following section.

Current guidelines have recommended more aggressive screening strategies for those with a family history of colorectal neoplasia. These recommendations may vary based on the number of first-degree and second-degree relatives previously affected by colorectal

cancer. Most of the guidelines employ colonoscopic screening in this high-risk population because of the modalities high sensitivity for colorectal neoplasms of all sizes.

The most recent updated guideline for colorectal cancer screening and surveillance strategies was released in 2003 by the American Gastroenterological Association (Winawer et al. 2003). Based on new evidence and experienced judgment, they have presented a clinical guideline that includes varying recommendations for people at average and increased risk. The screening recommendations of this guideline for different risk groups are described and tabulated in the following.

1. Average Risk Group:

- No factors place these people at increased risk.
- All procedures should begin at age 50.
- The options listed below are all acceptable choices for colorectal cancer screening in average-risk individuals.
- All positive tests should be followed up with colonoscopy.

Procedure	Beginning at	When to repeat
Combined FOBT & Sig	Age 50	FOBT every year + Sig every 5 years
FOBT	Age 50	Every year
Flexible sigmoidoscopy	Age 50	Every 5 years
DCBE	Age 50	Every 5 years
Colonoscopy	Age 50	Every 10 years

Table 1: Guideline screening recommendations to Average risk group

2. High Risk Group:

People with a first-degree relative (parent, sibling, or child) with colon cancer or adenomatous polyps diagnosed at age <60 years or two first degree relatives diagnosed with colorectal cancer at any age should be advised to have screening colonoscopy. This colonoscopy should start at age 40 years or 10 years younger than the earliest diagnosis in their family, whichever comes first and should be repeated every 5 years.

3. Surveillance Strategy

People with a history of adenomatous polyps or colorectal cancer should be screened based on the following table:

Procedure	Risk category	When to begin	Follow-up
Colonoscopy	Patient with advanced adenomas (Large or Villous) or 3 or more non-advanced adenomas	3 years after the initial colonoscopy	If exam is normal, repeat procedure in 5 years
Colonoscopy	Patient with single non-advanced adenomas (has one or two small(<1 cm) tubular adenomas)	5 years after the initial colonoscopy	If exam is normal, repeat procedure in 5 years
Colonoscopy	Patient with history of resection of colorectal cancer	Within 1 year of cancer resection	If exam is normal, repeat in 3 years. If still normal, repeat in 5 years

Table 2: Guideline Surveillance recommendations

2.5. Compliance

In healthcare, compliance is defined as willingness to follow a prescribed course of treatment. It encompasses the patient's active participation in his/her own healthcare correctly and on time; seeking medical advice, keeping appointments, following recommendations concerning lifestyle, as well as following medical regimens.

CRC screening compliance is defined as a criterion that expresses an individual person's potential willingness over his/her lifetime to adhere to a screening strategy. Although compliance is often viewed as patient behavior, it can also encompass physician behavior, since there is a need to offer proper guidance to patients, consistent with current screening and surveillance recommendations.

Despite the recommendations of expert groups that all Americans age 50 years and older should be screened, screening rates remain low. In a national survey of U.S. residents with age>50 years in 1999, only 20.6% had a home FOBT within 1 year, and 33.6% had undergone sigmoidoscopy or colonoscopy within 5 years. Compliance rates have increased in recent years, but only 1%-3% between 1997 and 1999 (Vijan, Hwang, and Hofer 2001).

The most commonly cited reasons for noncompliance are:

- Low public awareness about colorectal cancer
- Relatively recent emergence of a consensus on the need for screening
- Implementation barriers
- Complexity of screening guidelines

The patient's rate of compliance for different screening modalities is also variable. Evidence has shown that characteristics of a test like efficacy, invasiveness, frequency, accessibility, and cost can affect the compliance level of a patient.

2.6. Cost-Effectiveness Analysis

All the screening and surveillance strategies that are recommended in the clinical guidelines are proposed based on the results of various cost-effectiveness analysis studies that have been done using different screening interventions. Cost-effectiveness analysis (CEA) is considered the most appropriate method of comparing preventive health services from an economic point of view (Gold et al. 1996). The basic purpose of CEA is to assess the cost of healthcare resources dedicated to a health-care intervention relative to the health-care benefits that are produced by that same intervention.

The central measure in CEA of health-care interventions is the cost-effectiveness ratio. It is the difference in costs of two comparing alternatives divided by the difference in their effectiveness. In other words, the CE ratio is essentially the incremental price of obtaining a unit health effect from a given health intervention when compared with an alternative. In case the intervention under study is both less costly and more effective than the alternative, it is said to dominate the alternative and there is no need to calculate a CE ratio. Therefore, CE analysis is just performed in circumstances where the intervention is both more costly and more effective than the alternative. Interventions that have a relatively low ratio would typically have high priority for resources.

CEA can also show tradeoffs involved in choosing among various interventions. In this situation the CE ratios should compare each intervention to the next most effective option, after eliminating options that are dominated to obtain incremental cost-

effectiveness ratios. Similarly, options can be ruled out by extended dominance, i.e., when a linear combination of other options can produce greater benefits at lower costs.

2.7. Modeling

The effectiveness and imposed cost of a screening strategy cannot be evaluated unless its performance has been studied in a sample population or within a valid computer model. Three popular methods that are usually used to study and compare different screening strategies are randomized trials, case-control studies, and computer models.

2.7.1. Clinical Trials

Perhaps the most widely accepted way to evaluate performance of screening strategies is to conduct a randomized, controlled clinical trial on a targeted population. This approach has the advantage that it demonstrates the benefits of screening in a real population. The major problem in implementing a clinical trial of a screening method is that it requires a very large number of subjects, a long duration, or both to detect reductions in mortality from cancer. Furthermore, a clinical trial can also be hampered by noncompliance and dropouts by studied subjects. Moreover people who are willing to participate in randomized trials are probably not representative of a general population.

Clinical trials have not been done (and may never be done) for variants of screening, diagnostic and surveillance modalities, time intervals, and age ranges that are proposed for specific screening programs. This limitation restricts the study of even minor changes in the strategy decision variables (sensitivity analysis). The characteristics of the screened population and the health-care delivery setting also may differ between past trials and current proposed screening programs.

At the present time only the effectiveness of the every year FOBT strategy has been established by randomized clinical trial (Mandel et al. 2000) and no other screening method has yet been studied in a randomized population.

2.7.2. Case-Control Study

The case-control approach is another method that has been suggested as an efficient alternative design for the evaluation of screening tests. In this process, to test the effect of

screening on mortality from cancer, previous exposure to the screening test is compared in subjects who died of cancer (case) to those in a general population sample (control). A lower frequency of death in the screening group provides evidence in support of a protective influence of screening on mortality.

This method along with randomized trials can just be applied to very limited screening strategies that have already been practiced by a large group of people for a considerable period of time. A case-control study also relies on consistent personal and medical data about the case and control subjects. It is important that information be used to identify controls that exactly match the case subjects.

A few sigmoidoscopy case-control studies have been done indicating that regular flexible sigmoidoscopy may result in a reduced incidence of invasive and advanced-stage cancers (Selby et al. 1992).

2.7.3. Computer Models

Another approach that is increasingly popular is to design computer models to study different screening interventions. With new generations of computer software and hardware systems, it is possible to model a very large population of patients and test the efficiency of different screening strategies on them. The critical issue in this approach is designing a model that appropriately imitates the actual course of CRC disease and the screening performance characteristics. In addition all the input variables must be estimated and calibrated including their random distributions, which are necessary for a realistic representation.

Computer models are also very efficient for purposes of developing new strategies for newly emerging screening tests. They have the flexibility to run different potential strategies for a test and also to model combinations of other screening strategies together with new ones.

For all of these reasons, modeling tools may be useful in extending and extrapolating the results of existing clinical trial data and in estimating the probable cost-effectiveness of protocols for which evidence is less definitive in clinical trial data.

2.8. Examining Outcomes

Developers of clinical guidelines tend to employ a set of outcome measures that presents the societal perspective in the evaluation of the effect of various interventions. This perspective implies that the examined outcomes should not be measured from the viewpoint of particular agents in society. Both benefits and losses of patients and health maintenance organizations should be involved in computation of outputs (Gold et al. 1996).

Usually a CEA done from the societal perspective uses a diversity of components that contribute to costs and health effects. It is important in cost-effectiveness analysis to give an exact definition of the examining outcomes.

1. Quality-Adjusted Life-Years (QALY)

The QALY is a measure of the effectiveness adjusted for quality of life. A person's utility for a specific outcome is a measure of its relative preference to other possible health outcomes. It usually consists of a scaled score ranging from 0 to 1 where a weight of 1 corresponds to perfect health and a weight of 0 corresponds to a health state equivalent to death.

The utility of life tends to fall as people age due to declining health. For example, a patient who is bedridden has a lower utility than a completely healthy patient. These utilities may be determined by the use of the "standard gamble" instrument which measures a person's willingness to sacrifice additional years of life for the relief of the ailments associated with the disease (Gold et al. 1996).

QALYs are computed by multiplying a life-year by its utility. So the time spent bedridden is multiplied by the lower utility to compute the QALY for the patient. The total QALYs for a person is simply the sum of all quality-adjusted life-years. The multiplication is an approximation to calculating the integral of the utility function over time. This simplification is acceptable if the utility is assumed to change at discrete time intervals. Using this measure tends to make the benefits of reducing or eliminating a disease more pronounced because, in addition to life years gained, the measure also includes improvements in quality of life associated with treatment. This approach makes

it possible to compare interventions that extend life expectancy but may result in some decrease in the quality of life to others that improve the quality of life without extending life expectancy. QALYs can also simultaneously capture gains from reduced morbidity (quality gains) and reduced mortality (quantity gains), and integrate these into a single measure.

2. Cost

Since an objective of most medical decision models is to direct policy of disease treatment or screening or to better understand the impact of a disease, actual costs are a main factor in a cost-effectiveness analysis. The cost most properly reported is the societal cost of the disease (Gold et al. 1996). The first key component of this cost is the cost of treating the disease including hospitalization costs, medicine costs, and doctor costs. Secondary costs include the costs of screening procedures and new treatments. Any new treatment or screening must prove that it is more cost-effective than existing procedures if it hopes to be implemented by Health Maintenance Organizations (HMO) or as public policy. Tertiary costs, which include the costs of missed work and other time, can be even larger than the secondary costs. Depending on your perspective some of these costs do not necessarily apply. Loss of work is of concern if the perspective is that of a large company looking at treatment recommendations for employees, but is of little concern if the perspective is that of an HMO. Again, the most traditional approach for medical modeling considers all costs because it considers these costs from the perspective of the whole society.

3. Discounted QALY and Cost

In order to compare interventions with different temporal distributions of costs and health effects, it is a standard practice in cost-effectiveness analysis to employ discounting.

Discounting is a means of valuing earlier events and rewards more than later ones. Within discounting there are two methods of discounting, continuous and discrete. Discrete discounting is the simplest method to understand. An analogy is financial compounding, when a bank gives interest on a deposit at the end of every year. A similar

method is used for medical models, where the discount on the QALYs or cost is calculated at end of the year. The formula for discrete discounting is shown below.

$$P = F(1 + i)^{-n}$$

P = Present Worth

F = Future Worth

i = Discount Rate

n = Number of Years

The other form of discounting is continuous discounting. Again using a financial analogy, consider a bank that charges you 5% interest on a loan, but they compute the interest owed every day. Now extend that scenario to re-computing interest all the time, and it is continuous compounding. While in some cases appropriate, in medical decision models there are usually discrete costs, so continuous compounding is not as applicable.

The issue of discounting in medical decision-making is more troublesome since both costs and QALYs are being considered. One possible way to combine costs and QALYs into a single cost-effectiveness measure is to compute a cost per quality-adjusted life year. The discounting of cost streams for purposes of comparison is commonly accepted. While slightly less intuitive, this discounting can also be applied to QALYs (Nord 1999). The currently recommended discount rate in modeling medical decisions is 3% for both costs and QALYs (Gold et al. 1996). Using the same discount rate for both costs and QALYs avoids the problem of having different discount rates change the cost-effectiveness in different years (called “intertemporal inconsistencies”).

In order to compare different interventions in cost-effectiveness analysis, costs and QALYs are required to be discounted from the date decisions about these interventions are being made. This date is considered as the reference point for discounting. In case of CRC screening, costs and QALYs should be discounted to the initial screening age, which is age 40 or 50, based on the CRC risk of the population being studied.

2.9. Sensitivity Analysis

In conducting CEA to evaluate the desirability of a prevention method, it is important to obtain good unbiased estimates of costs and effectiveness of different comparable alternatives. These core outcome values are in turn functions of many elemental parameters in the model. Investigators might have a very good sense of what the true values are for many of these parameters based on clinical trials and observational studies in the literature, or experience. Yet for some aspects of the study, knowledge might be limited regarding the exact value and behavior of some parameters. These imperfections can cause a level of uncertainty in the estimated results for CE ratios.

Sensitivity analysis (SA) is a standard methodology which has been suggested to study the effect of uncertainty in the model parameters on the output measures. In SA some critical component(s) in the calculation is/are changed by a meaningful amount or varied from worst case to best case, and the CE ratio is recalculated. The resulting difference in the ratio provides some indication of how sensitive the results might be to that parameter. If the major results are insensitive to reasonable variation in a parameter, then the analyst can be relatively sure that the conclusions are insensitive to the working assumptions about that parameter. However, if the main results are sensitive to a plausible range of values of a parameter, then the conclusions are not robust. If the results are sensitive to some variable over part of its plausible range, but not over other parts of the range, then the analysis should provide some evidence about when the analyst should be concerned about the value for that parameter. If more precise data are not readily available, then the study can't be definitive. But often SA is useful to focus attention to critical variables and thus to pose the question of whether the issues are sufficiently critical such that better or more data are needed.

In SA approach, concerned input parameters can be either varied systematically from baseline (one, two or N at a time) or simultaneously, as in a probabilistic sensitivity analysis. In any case, the purpose of any uncertainty analysis for decision makers is to know how much confidence they should place on the results of an analysis.

2.9.1. Univariate Sensitivity Analysis

Univariate sensitivity analysis, which examines one variable of interest at a time, has been the most common approach to sensitivity analysis. In this method the CE ratio is computed for both high and low values of each key variable in the analysis, as well as their best estimate of that parameter. To determine a plausible range of variation for key parameters, some have employed the 95% confidence intervals; some altered the values of these parameters by plus or minus one standard deviation, where some others have advocated the use of a clinically meaningful range.

Univariate or one-at-a-time sensitivity analyses are not always adequate, because looking just at one source of uncertainty at a time in the model provides an incomplete estimate of how uncertain the estimated overall cost-effectiveness ratio actually is. The results from univariate SA usually understate the overall uncertainty in the CE ratio. One reason is that the incremental cost and effectiveness usually depend on multiple parameters. Additionally, the interaction of certain factors may imply that the total effect is something quite different from the simple sum of individual contributions.

2.9.2. Probabilistic Sensitivity Analysis

In this method the uncertain parameters are assumed to follow certain distributions that are specified in terms of mean, standard deviation, median, or other statistics. If the estimates of the parameters are independent of each other, then the outcome can be simulated by taking random draws from each distribution and calculating the outcome variables, such as CE ratios.

Distributions for uncertain parameters in the model can be determined, using the bootstrap method, Bayesian method, or from expert opinions. Once the distributions have been specified, the overall distribution of the cost-effectiveness ratio can be determined by simulation. In case the distributions of parameters of interest are not independent, the form of dependence is needed, usually specified by a correlation.

2.10. Summery of Chapter 2

This chapter began with a brief overview of different CRC screening methods and their characteristics. The necessity of developing different guidelines for people with different CRC risk was presented. The major factors that should be considered in a screening guideline are the screening start age and frequency of a test. Then, the importance of cost-effectiveness analysis for medical decision making was discussed. Popular methods which are used to study and compare different screening strategies were reviewed. Common outcomes used for many medical decision models were described later. In the end the necessity of performing a sensitivity analysis when uncertainty is present in a model was explained.

3. Simulation of the CRC Screening and Surveillance

A primary simulation goal of this thesis is to add a screening structure onto an existing discrete-event simulation model of the natural history of the CRC, called the “Vanderbilt-NC State” model. The CRC natural history simulation model was developed by Dan Cubbage in his master’s thesis (Cubbage 2004) as a successor to the “Vanderbilt” model developed earlier (Ness et al. 2000). By equipping the Vanderbilt-NC State (V/NCS) model with the most recent screening technologies, this enhanced model can provide an opportunity to simulate the effects of various screening and surveillance interventions to lessen morbidity and mortality in the US general population. However, the main purpose of this thesis is to examine the cost-effectiveness of screening and surveillance strategies recommended to the US population in the most recent clinical guideline provided by American Gastroenterological Association in year 2003 (Winawer et al. 2003).

This chapter will first review the basic design of the V/NCS simulation model and the structure of the natural history model. Then the enhanced screening model will be discussed in detail, including all its main objects and events. The input modeling and the user interface environment are presented next. Finally, parameters considered for probabilistic sensitivity analysis are described.

3.1. Basic Design of the Model

The V/NCS model is an object-oriented, discrete-event simulation built in the Visual Studio.NET 2003 programming platform. Other than the code for the random number generator which is written in Visual C++.NET, the rest of the code is developed in the Visual Basic.NET programming language.

In object-oriented programming, the inheritance feature can be employed to share the attributes and operations of classes based on a hierarchical relationship. Therefore, a basic class can be defined and then specialized in its subclasses.

The V/NCS model takes advantage of the inheritance feature to modularize the discrete-event simulation structure. Modules are defined in two separate levels. The lower level includes the general modules needed for a simulation program that define

basic classes like event calendar, simulation event, simulation entity, and other classes required for collecting observation-based and time-persistent statistics. The higher level consists of the modules related to the CRC natural history along with the added screening and surveillance procedures.

3.2. Basic Objects

Using the object-oriented methodology within the programming platform, objects are the main elements of the model. Each object has its own variables and methods which replicate the real world states and their behaviors.

In the V/NCS model, the central object is an individual person which is instantiated from the person class. In each replication of the simulation, a person object is created and follows in its own pathway between events till the person dies. Each person has his/her own personal characteristics which are sampled from the population variables that are to be studied.

The other important class of objects associated with each individual in this model is adenomas for that person. Each adenoma is capable of progressing from a small polyp to a cancerous tumor. At the very first moment an adenoma is created, characteristics will be assigned to it and then it would go through various stages in its lifetime that can end as a cancer. Obviously, an adenoma's life is terminated by its host's death or after a polypectomy process. In this model each adenoma has a separate event calendar that stores all the future events associated with it. This design is a key to efficient simulation with screening options, since when an adenoma is removed, without any search, all the related events to that adenoma can be omitted by eliminating its particular event calendar. Although this approach makes finding the next event more difficult, the simulation time update mechanism is expanded to include the earliest adenoma event along with earliest general simulation event. However the total efficiency gained from this change in the executing model is considerable.

The scenario is another object which is instantiated from the scenario class just one time at the beginning of the simulation run to define the characteristics of the cohort that is going to be studied. Parameters for each random variate generator are assigned based

on scenario definitions. Parameters for each scenario are stored and retrieved from a database, which also stores the calibrated information for the natural history simulation, along with screening and surveillance information (explained in Section 3.6).

3.2.1. Scenario object

The V/NCS model is a cohort model which may be used to study a homogenous group of people to determine the effect of different screening interventions. This study group can have specific levels of detail which have been delineated under the scenario object in this model.

A scenario is defined by the following characteristics:

- Reference Year: The current year of the simulation. This year is used to determine the birth year of the examining population.
- Initial Screening Age: This characteristic is the age at which the CRC statistics for an individual begin to be collected. Persons who die before this age are excluded from the study.
- Race: Black or white
- Gender: Male or Female
- Family History: This characteristic is a Boolean variable denoting the presence or absence of CRC in a first-degree relative.
- Screening Strategy: This determines the method of screening and the surveillance strategy for the population under study. The following eight screening strategies are investigated in V/NCS model:
 1. No Screening
 2. Sigmoidoscopy
 3. FOBT
 4. Combined FOBT and sigmoidoscopy
 5. DCBE

6. Colonoscopy
7. Virtual Colonoscopy
8. Fecal DNA

Random seeds and parameters of all the required lifetime and screening variables are initialized in this object before the simulation instantiates the first person in the cohort. This structure in the design of the simulation has been used to explore the sensitivity of the desired outputs to uncertainty in the input data.

3.2.2. Person Object

Each person possesses certain object properties that are unique to that individual and are obtained by sampling from random variate generators or gained by following the simulation pathway. In the following sections, the main person properties are described under five major groups of variables.

General Variables:

- ID: An identification number that is unique to each person. It is used to track an individual during the simulation steps
- Natural Death: It is the expected lifetime of a person without CRC.
Distribution for this comes from the modified Berkeley Mortality Database (Wilmoth 2003)
- Overall risk: Estimated risk of developing CRC in a person
- Compliance: It denotes the person's level of adherence to different screening tests

Neoplasm Variables:

- Number of Neoplasm: It is a collection that keeps the track of all adenomas and CRCs formed in a person
- Health State: It is a person's health state as determined by neoplasm status, described by the following states:

No CRC neoplasm

Known adenoma(s): Diagnosed by a colonoscopy or sigmoidoscopy

Known cancer(s): Has shown symptoms or has been diagnosed by a colonoscopy or sigmoidoscopy

- Cancer State: It reflects the extend of a cancer growth using the following states:

Local cancer: Stages 0 and I

Regional cancer: Stages II and III

Distant cancer: Stage IV

- Resection: This shows if any part of a person's colon or rectum has been removed, so no new adenoma can anymore form in that area
- Symptomatic: This indicates whether or not the person has symptoms related to CRC.

Cost Variables:

- Accumulated Cancer Care Cost: It tracks the total discounted and undiscounted costs associated with CRC treatment to date for a person. It is a function of the person's cancer stage and length of treatment period. It can consist of the following costs:

Initial costs: It is the initial six months of care cost for cancer treatment

Continuing costs: cost of treatment per year of living with cancer before the cancer becomes terminal

Terminal costs: The expenses during the last six months of a patient's life during which has no hope of survival because of the severe conditions of disease.

- Accumulated Screening Cost: It tracks the total discounted and undiscounted costs associated with the performance of a diagnostic test, pathology on a biopsy or polypectomy specimen, and treatment of test complications.

Utility Variables:

- Utility: It is a quality of life measurement associated with the current CRC-related health states and the person's age. Utility is a numerical value.
- Accumulated quality of life: It denotes the total discounted quality-adjusted life-years for an individual, as affected by CRC.

Screening variables:

- Compliance: It is the person's maximum adherence rate with any specific screening test. It will be discussed in Section 3.4.1.
- Screening strategy: Denotes the screening strategy being employed.
- Diagnostic: Indicates whether or not the person is awaiting diagnostic colonoscopy (for symptoms or to follow-up a positive screening test).
- Surveillance: Denotes whether or not the patient is in post-polypectomy or post-CRC resection surveillance.

3.2.3. Adenoma Object

Each adenoma object holds the following characteristics:

- ID: A unique number associated to each adenoma in a colon. It is used to keep track of adenomas and their states when performing screening tests and treatment.
- Progression Type: It denotes whether an adenoma is immediately progressive to CRC, progressive to CRC, or non-progressive.
- Location: Indicates the place of the adenoma growth in the colon. An adenoma can be in one of the following locations: Left Colon, Right Colon, Sigmoid, Upper Rectum, and Lower Rectum. These designations are defined from the view point of screening and treatment and are different from the general medical partitioning of colon described in Chapter 1 (shown in Figure 8).

Figure 8: Locations within the Colon

- **Histology:** Indicates the microscopic structure and size of the neoplasm within the colon. The categories of histology in this model are: Non-advanced adenoma , advanced adenoma, and cancer. All adenomas begin as non-advanced adenomas and then if they are progressive they can grow into advanced adenoma and finally into a cancerous one. An advanced adenoma is defined as one that is larger than one cm in diameter and/or has tubulovillous or villous histology.

3.3. A Brief Review of Natural History of CRC Model

To better understand the modeling contributions of this thesis, it is helpful to review the model of the natural course of CRC disease and its assumptions. This section is mostly acquired from the thesis done by Dan Cubbage (Cubbage 2004) whose work focused on the natural course of CRC absent any screening.

Each person has a risk of developing a colon cancer in his lifetime. Between all the factors affecting the CRC incidence risk, apparently family history has the most powerful influence. Other factors like race, gender, and age also affect the risk to a lesser degree.

Because the body's repair mechanism wears down as the person ages, the ability of the body to deal with the abnormal cells begins to decrease. As a result the person's risk of developing an adenoma will increase by the age. Also the percent of adenomas that are progressive will rise as the person ages.

This personal risk influences the rate of adenoma appearance and the progression of the adenoma to cancer differently in each individual. There are three modes by which risk can affect these two influences in an individual. It can affect only the adenoma incidence, which means people with higher risk have a higher chance of developing adenomas than a person with a lower risk. It also can just affect the adenoma progression rate, which is the time between the stages of the adenoma growth and cancer incidence. The third and the most complicated case is when risk affects both the overall adenoma incidence and progression time.

Although a colon cancer can appear spontaneously, there is growing biomedical evidence that most of the colon cancers are developed from benign adenomas that are not visible by standard endoscopy. These not visible adenomas may transition into three other states. It can become a non-progressive adenoma that has no chance to develop into cancer but can progress to an advanced state, transition to a progressive adenoma that eventually will become cancer, or transition immediately to cancer. Progressive adenomas are considered to account for 85% of the cancer incidences. These adenomas may take between 0 to 60 years to develop into cancer. The remaining 15% of cancer incidences are caused by not visible adenomas that transition directly to CRC.

An adenoma's location in a colon is dependent on the a person's age, gender, and race. Based on these factors, a person has different chances of developing adenomas in the five sections of colon, identified earlier.

Cancer is initially local, but it can metastasize to regional and distant cancer during its lifetime. It is not necessary for a cancer to become regional before it transitions to distant. Also progression through stages of cancer is independent of other variables like risk.

There is a time between cancer incidence and the cancer symptomatic event. A cancer symptomatic event is the time the disease starts showing symptoms, and these events are independent of the cancer stage progression. Since in the absence of screening, treatment

cannot begin until symptoms are detected, the cancer stage at the time of cancer diagnosis determines the proper treatment and the potential survival associated with the cancer.

3.4. Assumptions

The screening model was developed employing certain assumptions regarding the course of CRC disease, screening methods procedures and effectiveness, and general US population dissemination/adherence to screening. These assumptions are made based on the available knowledge found regarding these issues in the literature and also from the data supplied by medical experts. Below are described the main assumptions about screening and compliance.

3.4.1. Compliance Assumptions:

Patient compliance has been treated differently in its application to screening modeling. Some models have supposed that compliance to recommended screening strategies is either a completely random event (Frazier et al. 2000) or an “all or nothing” process (Sonnenberg, Delco, and Inadomi 2000). Modeling compliance using either of these simplifications may bias results for (completely random event) or against (“all or nothing” process) screening strategies that employ frequent testing. In the V/NCS model the compliance is considered a process wherein defined subpopulations of each cohort were assigned different modality-specific, maximum-acceptable screening frequencies. This design provides flexibility to better simulate variable rates of compliance for different screening modalities.

The following assumptions were made regarding patient compliance, using community modality-specific compliance rates (Schoen et al. 2002; Winawer et al. 2003):

1. Compliance is considered to be independent of age, gender, race and family history of a person.

Evidence that any of the above mentioned factors have direct effect on screening compliance is weak and inconsistent.

2. Almost 30% of people never comply with any screening test during their lifetime.
3. For any specific screening modality, the fraction of the population that undergoes any screening is set at 70%.
4. Compliance is a unique person-specific characteristic that determines the maximum acceptable screening frequency for any given screening modality. The model uses a discrete distribution to assign a value to the compliance variable. This variable governs whether or not the person is adherent with the given screening test and, if adherent, at what maximum frequency (e.g. a person may be compliant to FOBT but only at a maximum frequency of one time in three years). An individual can have one of the following compliance rates:

Never compliant

One-Time compliant

Every 1, 2, 3,... year(s) compliant

5. An individual compliance rate is constant during his/her lifetime. The screening diagnosis does not influence the person's compliance rate for a screening test.
6. A person's maximum compliance rate to different modalities is negatively correlated with the test invasiveness. The more invasive a test is the less compliant a person is to that test.
7. 100% compliance is assumed for post-cancer diagnostic tests.
8. About 80% of one-time compliant individuals are adherent to surveillance.
9. Almost 70% of people will accept a diagnostic colonoscopy test after a post-positive FOBT or fecal DNA test.
10. Around 80% of people will accept a diagnostic colonoscopy test after a post-positive sigmoidoscopy and DCBE test.

3.4.2. Screening Assumptions

1. Screening tests have associated sensitivity and specificity for adenomas and CRC based on adenoma histology (non-advanced adenoma, advanced adenoma, cancer) at the time of the procedure. All test characteristics are assigned values based on the current literature and defined for each screening method.
2. In a colonoscopy test, any scoped (found) polyp should be removed through a polypectomy and submitted to pathology for diagnosis. It is still impossible to determine how often an adenomatous polyp evolves into cancer, because the natural history of adenomatous polyps and their sequence of developing to cancer are not totally understood (Schoen 2003). Thus, the latest screening guidelines have recommended removal of all the scoped polyps from the colon to decrease the risk of cancer to as low as possible.
3. In a sigmoidoscopy test, all suspicious growths in a colon are biopsied and sent to the pathologist for further investigation.
4. All the patients have a colonoscopy immediately after their cancer becomes symptomatic.
5. Surveillance tests halt after the cancer goes into a terminal stage.

3.4.3. Cost Assumptions

1. Cancer Care Cost: After cancer is diagnosed, there is a one-time charge for treatments associated with the first part of cancer care, which might include the cost for resection surgery. Then there is an annual continuing care cost for follow-up treatment associated with the cancer. This cost continues until the patient dies of CRC, or survives for five years. Lastly, there is a larger one-time cost associated with the last six months of terminal CRC.
2. Screening Strategy Cost: Based on compliance to a screening strategy and their CRC health conditions, people can incur costs associated with performing different screening or surveillance tests, as well as costs required for doing pathology on biopsy and polypectomy specimens.

3.4.4. Utility Assumptions

1. Utility changes are associated with age

The quality of life diminishes as someone gets older. Based on the information provided by the expert panel associated with this project, the average utility perceived for an American population during their life time is as follows :

Age	Utility
0-44	0.99
45-54	0.93
55-64	0.92
64-74	0.89
75+	0.87

Table 3: Utility change over age

Each time a person moves into a higher age interval, his/her utility is lowered based on above table.

2. Utility change relates to a person's CRC health state

The utility further changes upon detection of CRC. If the cancer is diagnosed at the early stages, there is a chance that the disease can be fully treated and the patient gets back to its normal utility. In most cases, based on stage of the diagnosed cancer, a person might have a resection surgery or experience another sort of treatment like chemotherapy that lowers the patient's quality of life.

3. Some screening tests might cause a temporal utility change

Inconvenience preceding some screening tests like colonoscopy, as well as complications associated with them can cause a drop in the patient's utility for a short period of time.

3.5. Event Modeling

System evolution over time is represented by variables that change instantaneously at discrete points over time called events. A discrete-event simulation model moves forward through time by advancing from one event to the next. Therefore, in each simulation model all actions are centered on events.

The original V/NCS model is enhanced by the addition of three new events. Each of these events has a fairly complicated structure since people may encounter various specific screening pathways based on their CRC health conditions. Generally each screening event consists of two steps. The primary step is to diagnose potential cancers or adenomas which may be present in the colon. The second step is to schedule the necessary follow-up events after the test result is determined. There are many factors besides test outcome, such as compliance to screening, family history and neoplasm history of a person that can affect the appropriate response. For example in some cases screening may be halted because of a patient's non-compliance, or in some other cases a switch into more precise screening tests is needed for further study of the colon.

An event graph of the model is shown in Figure 9. The event graph portrays all events in the simulation and, when relevant, what conditions are required for an event to be scheduled. If no conditions are stated, the event is always scheduled.

Figure 9: Event Graph of the V/NCS model

In Appendix A, a series of flowcharts are offered to better illustrate the logical sequence of tasks in various screening strategies. The basic logic of those charts are all derived exactly from the screening recommendations provided in American Gastroenterological Association latest guideline discussed in Chapter 2. In some special situations, the guideline has not provided the necessary recommendations and the proper pathway in the flowchart was not clear. Appropriate additions given by Dr. Reid Ness of Vanderbilt University were implemented into the flowcharts for these conditions.

3.5.1. Screening Event

Description: This event checks the CRC related health conditions of the colon based on the characteristics of the chosen screening test. Even though in reality each screening test employs a specific method of diagnosis (endoscopic or non-endoscopic), by taking advantage of sensitivity and specificity properties, screening events in this model have been designed in a manner that all of them follow identical steps for diagnosis purposes.

As a primary step, each neoplasm in the adenoma collection of a person is checked based on the screening test's sensitivity for that special neoplasm histology. Then the chance for the false positive test result is observed by obtaining a sample from a discrete distribution where its parameters are assigned based on the specification characteristics of the test. In the next step, the possibility of a test complication is examined by using the same procedure explained for specificity check. Finally, this event checks the overall test result in order to schedule the proper response event.

Predecessor: This screening event can be initially scheduled in the person creation event. In addition, a screening event reschedules itself after any negative screening test result. The recommended time of the initial and follow-up screening tests are drawn from the clinical guidelines and then are adjusted based on each patient's compliance. For example if a guideline recommends a follow-up FOBT in one year, but the person is compliant to this test every two years, next FOBT will be scheduled in two years, which is the maximum of these two numbers.

Events Scheduled: The successor of this event can be either another follow-up screening event or a diagnostic colonoscopy event. Negative results lead to the former

event and a positive result leads to the later event. In case of any perforation or hemorrhage, a utility change event is scheduled.

Statistics Collected: Statistics are collected on screening, pathology and complication costs. In addition, the number of screening tests, polypectomies, biopsies and test complications are counted.

3.5.2. Diagnostic Colonoscopy Event

Description: This event inspects the validity of the screening event results by performing a colonoscopy test. It scans the entire colon again, specifically the suspicious sections and removes the probable existing neoplasm in order to prevent the CRC. In that case, all events associated with the removed adenomas are deleted.

Predecessor: This event is triggered after any positive screening test other than colonoscopy, as well as after a cancer symptomatic event

Events Scheduled: A surveillance event is scheduled after a positive diagnostic colonoscopy test. In case of a negative test result, a patient will be switched back to his/her previous screening strategy by being scheduled for a screening event. A utility change event is also scheduled if a complication happens during the process of colonoscopy.

Statistics Collected: Total number of diagnostic tests, polypectomies, and complications are accumulated together with their costs.

3.5.3. Surveillance Event

Description: This event schedules and performs colonoscopy tests on people with a history of adenoma or cancer. The recommended frequency of colonoscopy tests are higher under a surveillance strategy than a screening strategy because the risk of adenoma recurrence is higher in the surveillance group. The adenoma histology and number of discovered adenomas are the two main criteria which are used to determine the proper time of the follow-up surveillance event. This event is removed from the event calendar, when a person moves into a terminal stage of CRC.

Predecessor: This event is scheduled in follow up to a positive diagnostic colonoscopy event.

Events Scheduled: This event schedules the follow-up surveillance test based on the number and type of neoplasms discovered in the colon. It also schedules a utility change event if a complication occurs during the surveillance procedure.

Statistics Collected: Same statistics as diagnostic colonoscopy event

3.5.4. Utility Change Event

Description: This event reflects the transition to a slightly lower quality of life based upon reaching a more advanced age or because of being affected by colorectal cancer. A screening complication can also lower the person's utility for a short period of time.

Predecessor: This event can be scheduled by a Person Creation Event, Screening Event, Surveillance Event, or Diagnostic Colonoscopy Event.

Events Scheduled: None

Statistics Collected: QALYs are computed, by multiplying the utility of each period times the period length.

3.5.5. Cancer Symptomatic Event

It is at this event that the person first becomes aware of the cancer and seeks treatment. A colonoscopy is performed to determine the extent of the cancer, and treatment of the cancer begins. Affected sections of the colon are resected in most cases, and chemotherapy is given to all patients who have regional or distant cancer.

The first event scheduled is a Colonoscopy Diagnosis Event. This event determines the extent of the damage to the colon and treatment options. If surgery proves to be necessary, some sections of the colon are resected, thus eliminating all adenomas in those sections (and any that would have occurred in that section). As with the adenomas removed by screening, all events associated with those adenomas are removed from their event calendars. This event along with other CRC natural history events are explicitly described in the thesis by Dan Cubbage.

3.6. Role of Data in the Simulation

One of the benefits of the V/NCS model is that the simulation code is isolated from the input data. All the data regarding the natural history of disease and screening methods are saved into a Microsoft Access database. Thus, the model first retrieves the values for the input variables from the database and then runs the simulation.

3.6.1. Input Data

All the variables and their specifications together with their possible values and distribution parameters are stored in three major database tables. These three tables are the Input Variables table, InputVariableValuations table, and SAVariableValuations table.

The InputVariables table (partially shown in Figure 10 below) stores the variable name and ID along with a unique random number seed for all the natural history and screening variables. From the simulation point of view, a unique seed is required to be assigned to each variable in order to employ the concept of “common random numbers” to minimize the potential error due to randomization (Law and Kelton 2000). These common random numbers mean that multiple screening scenarios can be run on the same population, and the same random numbers will be assigned to each random variate. So each person will have the same natural life in all scenarios and have the same numbers sent to the adenoma incidence generators, and so on. This is very important in comparing alternative screening strategies, since comparisons should be done on identical populations.

Additionally, InputVariables stores the category and measure of the variable. The category groups the variables into related clinical categories such as adenoma progression, utilities, compliance, or costs. Measure is a unit-specific breakdown that is chosen from a dropdown menu. These describe the type of distribution associated with the variable and can specify if the variable is a probability, time distribution, or risk distribution among other choices.

InputVariables : Table									
CategoryName	Variable	Measure	VariableID	Sensitivity Analysis	Seed1	Seed2	Seed3	Seed4	Seed5
Utilities	Utility of known adenoma	Percentage	225		0.3446225690	835741554	2195834023	1297741021	3357053382
Utilities	Utility of local colon	Percentage	226		26.3984477137	1.268E+09	3770063761	216527865	1568537936
Utilities	Utility of local rectal (stage I)	Percentage	227		27.2503334853	3.18E+09	2080184241	2881517721	3611607237
Utilities	Utility of local high rectal (stage II)	Percentage	228		28.2784301963	3.004E+09	4065265451	2351994899	1824839263
Utilities	Utility of local low rectal (stage II)	Percentage	229		29.3645411182	1.391E+09	3995023402	536114258	1376034799
Utilities	Utility of regional colon (chemoRx complications)	Percentage	230		30.4205039797	2.988E+09	2737381050	2060484144	21123025
Utilities	Utility of regional colon (no chemoRx complications)	Percentage	231		31.1708138263	1.103E+09	3131738563	354874525	1462105562
Utilities	Utility of regional high rectal	Percentage	232		32.1762624356	3.339E+09	1869672149	2420033342	3823777008
Utilities	Utility of regional low rectal	Percentage	233		33.1406960847	2.69E+09	2086754669	1479781266	4277003072
Utilities	Utility of distant/terminal (within 18 months of cancer)	Percentage	234		34.3217706054	3.908E+09	3316415646	934936431	1155310743
Cost	Cost of initial Local CRC	Dollar	235		35.2996242632	2.506E+09	1182520337	938957435	3286002927
Cost	Cost of initial regional CRC	Dollar	236		35.3757057907	1.335E+09	1509001838	991499602	1502864996
Cost	Cost of initial distant CRC	Dollar	237		35.3728532268	988545039	1631700325	1143954198	2209269908
Cost	Cost of continuing local CRC	Dollar	238		35.3294123071	1.465E+09	3721431761	2693241183	1754954480
Cost	Cost of continuing regional CRC	Dollar	239		35.131824893	3.189E+09	1376082626	2419937722	2563475034
Cost	Cost of continuing distant CRC	Dollar	240		35.3770164700	4.029E+09	1104720217	3496143152	735265587
Cost	Cost of terminal CRC	Dollar	241		35.2131062045	2.456E+09	789218840	1151705419	286383816
Colonoscopy	Colonoscopy - Sensitivity for CA (%)	Percentage	242		42.2053528341	4.170E+09	3515474899	98091789	1000335891
Colonoscopy	Colonoscopy - Sensitivity non-advanced adenomas (%)	Percentage	243		42.2469807084	9172128	3362394154	4021928081	2651348937
Colonoscopy	Colonoscopy - Sensitivity for advanced adenomas (%)	Percentage	244		42.794136241	1.327E+09	1423309168	588827532	1370684418
Colonoscopy	Colonoscopy - Specificity for adenomas/CRC	Percentage	245		42.2866999578	1.918E+09	3899143652	2905238681	3298551408
Colonoscopy	Colonoscopy - Overall mortality rate (%)	Percentage	246		46.3040095656	1.207E+09	780501254	597456198	1004013014
Colonoscopy	Colonoscopy - Perforation rate (%)	Percentage	247		47.3970659565	2.744E+09	4070166570	141329301	2711190398
Colonoscopy	Colonoscopy - Post-polypectomy hemorrhage rate (%)	Percentage	248		48.216582539	3.263E+09	1880572884	3722908253	287018188
Utilities	Utility of Colonoscopy complication (6 weeks)	Percentage	249		49.4258459985	1.892E+09	2510345890	2935846613	1134826799
Utilities	Utility of Colonoscopy performance (2 days)	Percentage	250		0.578737695	119907309	1233642926	4159114509	3946997940
Cost	Cost of Screening Colonoscopy	Dollar	251		35.2479155365	4.125E+09	170057196	2546874696	2945959743

Figure 10: Screenshot of InputVariables Table

All constant variables associated with the simulation are also clearly labeled and stored within the InputVariables table. This design is very beneficial, since in order to do a deterministic sensitivity analysis, it is important to be able to easily change any values associated with the simulation without changing the actual simulation code. Furthermore, keeping constants out of the code eliminates any “magic numbers” whose interpretation depends on the coded value. The InputVariables table also has a “sensitivity analysis” column which stores a link to the distribution of constant variables chosen for probabilistic sensitivity analysis.

InputVariableValuations (see Figure 11 for a portion of this table) is the table that specifies the values for the variables in the InputVariables table. For example if variable 196 is described by a Beta distribution, the first 4 columns of this table are the variable ID along with the race, gender, and family history of the population to which the valuations apply. Using these columns allows different populations to have their own valuations for each variable if necessary. For example, individual risk is dependent on race, gender, and family history; and will have 8 sets of valuations within the table (2 races* 2 genders * 2 family histories = 8 valuations). Next is the distribution name, which in the case of variable 196, is a Beta. The next column is the parameter name, followed by its valuation. Since the Beta distribution has four parameters associated with it, each of these valuations have four rows; one for each parameter, Minimum, Maximum, Alpha

and Beta. Based upon the distribution type, the simulation knows which parameters to look for and finds the valuations associated with each of the parameter key words.

InputVariableValuations : Table							
	VariableID	Gender	Race	Family History	Input Distribution	Parameter Name	Valuation
	195	All	All	All	Beta	Beta	4.384
	196	All	All	All	Beta	Minimum	0.6808
	196	All	All	All	Beta	Maximum	0.92
	196	All	All	All	Beta	Alpha	2.197
	196	All	All	All	Beta	Beta	4.641
	197	All	All	All	Beta	Minimum	0.6586
	197	All	All	All	Beta	Maximum	0.89
	197	All	All	All	Beta	Alpha	2.955
	197	All	All	All	Beta	Beta	4.603
	198	All	All	All	Beta	Minimum	0.6438
	198	All	All	All	Beta	Maximum	0.87
	198	All	All	All	Beta	Alpha	3.504
	198	All	All	All	Beta	Beta	4.384
	201	Female	All	First Degree	JohnsonSB	delta	0.816
	201	Female	All	First Degree	JohnsonSB	gamma	2.226
	201	Female	All	First Degree	JohnsonSB	maximum	1
	201	Female	All	First Degree	JohnsonSB	minimum	0
	201	Female	All	None	JohnsonSB	delta	0.661
	201	Female	All	None	JohnsonSB	gamma	2.6
	201	Female	All	None	JohnsonSB	maximum	1
	201	Female	All	None	JohnsonSB	minimum	0

Figure 11: Screenshot of InputVariableValuations Table

SAVariableValuations table has exactly the same columns as the InputVariableValuations table. This table contains the probabilistic distribution for the parameters which are selected for a probabilistic sensitivity analysis. Constant variables such as “colonoscopy sensitivity for cancer” which are represented by a point estimate (0.95) are the potential candidates for probabilistic studies.

These three tables are created and modified by the database administrator and the simulation user has read-only access to their data. Any change to the valuation of input variables should be arranged by the recommendations of expert panels and applied by the database administrator.

Once a new scenario is created in the user interface, the cohort information together with screening setups is stored into two tables in the database. These two tables are the PopulationAtRisk table and ScreeningOptions table.

The PopulationAtRisk table (shown in Figure 12 below) stores a scenario ID and the description of the scenario. Along with this information are columns identifying the race, gender, and family history of the population to be studied in the scenario. There is a

population size column that specifies how many people it is to simulate. In addition to these, there are seven screening columns that each specifies whether a screening strategy is arranged to be studied in a scenario or not. For example, Scenario 19, is defined to examine the effect of FOBT and Sigmoidoscopy screening strategies on a population of 80,000 white males that are born in year 1953 (2003-50), from age 50 until they die.

PopulationAtRisk : Table												
	Scenario	Scenario Name	Reference Year	Age	Gender	Race	Family History	Population Size	FOBT	Colonoscopy	Sigmoidoscopy	DCBE
	+	19 CRC A	2003	50	Male	White	None	80000	☒	☐	☒	☐
	+	22 CRC G	2003	40	Female	White	First Degree	80000	☒	☐	☒	☒
	+	23 CRC H	2003	50	Female	White	None	80000	☐	☒	☒	☒
	+	24 CRC B	2003	50	Female	Black	None	80000	☒	☐	☒	☐
	+	25 CRC N	2003	50	Male	Black	None	80000	☐	☒	☐	☒
	*	0 Base Case	2003	50	Female	Black	First Degree	10000	☐	☐	☐	☐

Figure 12: Screenshot of PopulationAtRisk Table

The ScreeningOptions table stores the screening variables for each screening strategy (see Figure 13). Screening variables can be edited from within the user interface, to set the starting screening age, follow-up screening intervals and surveillance frequencies for an average risk population, a high risk population or people with CRC history. This table stores a variable ID together with its variable name in a descriptive form such as “Follow-up colonoscopy for patients with advanced adenomas”. In addition, the category column indicates the screening strategy attached to this variable. Measure and value of a variable are the contents of two other columns in this table. The measure column specifies the unit of time for a variable.

ScreeningOptions : Table					
Screening ID	Description	CategoryName	Measure	Value	
1001	First (One-time) FOBT for average risk person	FOBT	Year	50	
1002	First (One-time) FOBT for person with one first-degree relative with CRC at age > 60 years	FOBT	Year	40	
1003	First (One-time) FOBT for increased risk person	FOBT	Year	40	
1004	Years younger than the earliest diagnosis for FOBT for increased risk person	FOBT	Year	10	
1005	Follow-up FOBT for person with no history of adenoma or CRC	FOBT	Year	1	
1006	Follow-up FOBT after a negative colonoscopy test for a person with no history of adenoma or CRC	FOBT	Year	5	
1007	Follow-up colonoscopy for patient with non-advanced adenoma	FOBT	Year	5	
1008	Follow-up colonoscopy for patient with advanced adenomas	FOBT	Year	3	
1009	First follow-up colonoscopy after resection surgery	FOBT	Year	1	
1010	Second follow-up colonoscopy after first resection surgery	FOBT	Year	3	
1011	Next Follow-up colonoscopy if the test is normal after resection surgery	FOBT	Year	5	
1012	Next Follow-up colonoscopy if the test is not normal after resection surgery	FOBT	Year	3	
1013	First (One-time) Sigmoidoscopy for average risk person	Sigmoidoscopy	Year	50	
1014	First (One-time) Sigmoidoscopy for person with one first-degree relative with CRC at age > 60 years	Sigmoidoscopy	Year	40	
1015	First (One-time) Sigmoidoscopy for increased risk person	Sigmoidoscopy	Year	40	
1016	Years younger than the earliest diagnosis for Sigmoidoscopy for increased risk person	Sigmoidoscopy	Year	10	
1017	Follow-up Sigmoidoscopy for person with no history of adenoma or CRC	Sigmoidoscopy	Year	5	

Figure 13: Screenshot of ScreeningOptions Table

Once all inputs have been retrieved, all the necessary valuations from related variables are written into the ScenarioInputs table. This table cannot be changed since it represents a complete scenario. Once a simulation is run for the first time, the valuations for it are retrieved from the InputVariables table and written to the ScenarioInputs table. Every time that scenario is run, the valuations are retrieved from the ScenarioInputs table. This switch of data sources provides two benefits. First, it permits scenarios to be repeated exactly. Furthermore, having two source methods allows the database administrator to update valuations as new information becomes available without the fear of changing the values used to simulate a prior scenario. If a new study using new information is desired, the user needs only define a new scenario to see the effect of the new valuations.

3.6.2. Data Sources for the Simulation

All of the distributions and constants that are stored in the database that composes the simulation run must have a reference source. Within this simulation, there are two primary sources.

First, there are distributions and constants with values based upon medical studies, or a standard value agreed upon by an organization such as the National Cancer Institute (National Cancer Institute 2003). If set by such an organization, there are predefined ranges of valuations that are agreed upon, such as colonoscopy sensitivity values. This range defines the possible values for sensitivity analysis and also allows for standardization between different simulation models of CRC. The other alternative for this type of data is data that have a clinical research background. Different studies may observe slightly different results when studying the same phenomenon. This information provides a range for future sensitivity analysis. This information was compiled and provided to the simulation team by Dr. Ness after a thorough literature review.

3.7. User Interface

A graphical user interface is built into the V/NCS model to provide the user an interactive environment to define and run CRC screening scenarios. The primary form that appears when the V/NCS model is opened is the “Run Simulation” form (See Figure 14 below). At the upper part of this form there is a DataGrid object which lists all the

scenarios defined previously along with their cohort specifications. Once you click on a scenario in the DataGrid, all the screening strategies assigned within that scenario along with list of all input variables related to that scenario will appear in two Listboxes provided under the DataGrid. Two buttons are located at the upper right side of the form to enable the user to remove an old scenario or create a new one.

1. Select a Scenario from following listbox:

Scenario	Scenario Na	Gender	Race	Family Histor	Age	Reference Ye	Population Si
19	A	Male	White	None	50	2003	80000
22	G	Female	White	First Degree	40	2003	80000
23	H	Female	White	None	50	2003	80000
24	H	Female	Black	None	50	2003	80000
25	N	Male	Black	None	50	2003	80000

2. Check the Simulations you want to run:

- ☒ No Screening
- ☒ Colonoscopy
- ☐ Combined Sig and FOBT
- ☒ DCBE
- ☐ Fecal DNA
- ☒ FOBT
- ☐ Sigmoidoscopy
- ☐ Virtual Colonoscopy

Selected Screening Modality Variables:

First (One-time) Colonoscopy for average risk person

Value of the Selected Variables: 50

Input Variables

Variable Name:

305 -- Probability of death from local Cancer

306 -- Probability of death from Regional Cancer

307 -- Probability of death from Distant Cancer

308 -- Screening compliance rate - Endoscopy/D

309 -- Screening compliance rate - FOBT

310 -- Screening compliance rate - Fecal DNA

311 -- Surveillance compliance rate

Distribution Name: Discrete

Parameters and Valuations:

X	Y
0	0.6069
1	0.3931

Figure 14: Screenshot of “Run Simulation” Form

At the “New Scenario” form (shown in Figure 15), in order to define the cohort population the user has to specify the gender, race and family history, as well as the reference year and population size and screening strategies that are to run on the cohort. To set the screening and surveillance setups for the selected screening strategies the user clicks the “Set Screening Variables” button.

Enter New Scenario Name:

New Scenario:

Gender:

Race:

Family History:

Age:

Reference Year:

Population Size:

Screening Type

- ☒ Colonoscopy
- ☐ Combined Sig and FOBT
- ☒ DCBE
- ☐ Fecal DNA
- ☒ FOBT
- ☐ Sigmoidoscopy
- ☐ Virtual Colonoscopy

Input Variables

Variable Name

- 21 -- SAProbability of chemotherapy side-effects
- 23 -- SAProbability of local rectal CA is Stage I
- 26 -- SAUtility of local colon
- 27 -- SAUtility of local rectal (stage I)
- 28 -- SAUtility of local high rectal (stage II)
- 29 -- SAUtility of local low rectal (stage II)

Distribution Name:

Parameters and Valuations

Parameter Na	Valuation
Minimum	0.4
Maximum	0.8
Alpha	2.2
Beta	4.6

Figure 15: Screenshot of “New Scenario” Form

At the “Screening Setup” form (see Figure 16), the user can specify any sort of screening and surveillance strategy based on personal and family history of the person. For example, it is possible to set the initial screening time for an average risk person with no adenoma history and so on. By clicking on different tabs provided at the top of the form the user can switch between different screening methods and set each of them independently.

Screening Setup

Colonoscopy | Combined Sig and FOBT | DCBE | Fecal DNA | FOBT | Sigmoidoscopy | Virtual Colonoscopy

Person With No Adenoma History

Average Risk Person

First Colonoscopy or One-Time Colonoscopy at age:

Follow-up colonoscopy for this person with no history of adenoma or CRC is in: years

Increased Risk Person

First Colonoscopy or One-time Colonoscopy for person with one first-degree relative with CRC at age > 60 years at age:

Follow-up colonoscopy for this Person with no history of adenoma or CRC is in: years

First Colonoscopy or One-time Colonoscopy for person with one first-degree relative with CRC at age < 60 years or two or more first-degree relative with CRC is at age: or years younger than the earliest diagnosis in their family.

Follow-up colonoscopy for this person with no history of adenoma or CRC is in: years

Person With Adenoma History

Average and Increased Risk

Follow-up colonoscopy for patient with non-advanced adenoma (has one or two small (<1 cm) tubular adenomas) in: years

Follow-up colonoscopy for patient with advanced adenomas (Large or villous) or multiple (more than two) non-advanced adenomas in: years

Person With CRC History

Average and Increased Risk

First follow-up colonoscopy after resection surgery in: years

Second follow-up colonoscopy after resection surgery in: years from first one.

Follow-up colonoscopy in: years if the test is normal

Follow-up colonoscopy in: years if the test is not normal

Figure 16: Screenshot of “Screening Setup” Form

3.8. Simulation Output

After the completion of each simulation run, all the statistics accumulated are previewed into a series of Excel spreadsheets. At the same time, outputs are saved into a table of MS Access database; therefore the user can reload the simulation outputs in future without rerunning the model.

As shown in Figure 17, many worksheets are designed to provide beneficial reports for users with different research orientations.

Figure 17: Screenshot of Simulation Excel Report

This report generates the discounted cost and QALYs which were used for the cost-effectiveness analysis.

3.9. Probabilistic Sensitivity Analysis

The main objective of doing a probabilistic sensitivity analysis using the V/NCS model was to examine the impact of uncertainty in a set of input parameters on the cost-effectiveness ratios of various screening strategies. In order to empower the model to do this analysis, some enhancements were made to the database table structures (explained in Section 3.6.1) and to the random variate sampling procedures.

In the enhanced design, the user chooses parameters for probabilistic sensitivity analysis (PSA) in the database and the simulation will automatically generate a random sample from each parameter's distribution for each replication of a screening strategy.

3.9.1. Candidate Parameters

In the V/NCS model there are three types of model parameters that can be subjected to sensitivity analysis:

- 1) Structural parameters used in the creation of the natural history model (e.g. the distribution of the lifetime CRC risk within a population)
- 2) Cancer control strategy parameters (e.g. colonoscopy test characteristics)
- 3) Economic parameters used in the analysis (e.g. cancer care costs)

All the structural parameters are intimately linked to the calibration of the model as described in the Dan Cabbage thesis. Although easily accomplished, alternation of these parameters would result in a new CRC natural history model that would need to be calibrated again. Therefore structural parameters should not be included in the PSA.

Strategic and economic parameters are good candidates for PSA since most often their values are not known with certainty. A single point estimate of these parameters is usually given along with their range of variation (95% intervals) which can be used to do a one-way or multi-way sensitivity analysis.

In PSA, instead of assigning an estimated value to a strategic or economic parameter, it is assumed that each uncertain parameter can best be described by a probability distribution. This description is done by assigning a prior probability distribution to each of these input parameters. These prior distributions reflect all available information and prior beliefs about the parameters' true values. So, for example, if cost data are available for the colonoscopy test, the mean and standard deviation of this sample could be used to define a proper distribution. Essentially this is a Bayesian approach, with the model parameters being treated as random variables (Briggs, Brien, and Blackhouse 2002).

In the V/NCS model the only available statistics on the parameters of interest were mode, lower and upper bounds which were provided by literature review done by Dr. Ness. Using these data along with recommendations given by the V/NCS model's expert panel, the prior distributions were developed. If more data become available on these parameters, the likelihood function of these parameters can be used to derive a better posterior distribution applying the Bayesian method.

The list of all strategic and economic parameters that were used for the PSA analysis, together with their assigned distributions is available in Appendix B. In the following section the reasons for selection of assigned distributions for selected parameters are explicitly described.

1. Cost Parameters

In probabilistic sensitivity analysis (PSA), different cost variables were sampled from different Beta distributions. Beta distribution was appropriate for cost variables because there existed information about a minimum value, a maximum value, and most likely value for these variables. The standard deviation of the distribution was estimated from the assumption that it was one-sixth of the range. The main issue was that according to the expert panel opinion different costs for a typical person are positively correlated. The expert panel decided to use 0.5 as the value of correlation coefficients between all pairs of cost variables. This choice was made because 0.5 shows the minimum amount of bias towards existence or absence of correlation and the expert panel did not have any reason to be biased towards any of them.

To apply the concept of correlation, the capability of generating random variates from multivariate distributions with a given correlation matrix was added to the code. Multivariate normal distributions with a given correlation matrix are the core of this generator. Generating random vectors from a multivariate normal distribution is relatively simple. Pre-multiplication of a random vector of independent standard normal variables by the Cholesky factorization of the correlation matrix generates a random vector of the multivariate normal with that correlation matrix (Devroye 1986). Then the values of inverse cdf's of the marginal normals are used to get a vector of correlated uniform random variables between zero and one. This vector is then fed into the generator of the desired distribution (here Beta) to get a vector of correlated random variables from that distribution. Although the correlation matrix of these new variables is not necessarily the same, the difference will not be very significant.

2. Screening Characteristics Parameters

Sensitivity and specificity parameters of all screening modalities along with complication parameters associated with them were also considered in the probabilistic analysis. Using literature available on characteristics of screening tests and results from medical trials, the expert panel suggested a range of variation for each of these parameters, as well as a most likely value.

All these parameters provide the model a true or false response. As in the case of complication parameters, they either show a complication such as hemorrhage, after a screening test or not. Therefore they can be considered as independent Bernoulli trials leading to a binomial form of the data likelihood. With such data, it is natural to use the proportion of the true responses as the estimate of the corresponding probability in the model.

Fortunately, Bayesian methods provide a straightforward method for assigning prior knowledge to the parameter of the binomial likelihood. The Beta distribution is a continuous distribution on the interval 0-1 and is a conjugate family for the binomial likelihood. Hence, the ease of updating the Beta prior to a Beta posterior when supplied with additional data, is one of the main advantages of using a Beta prior for the parameter of the binomial distribution (Gelman et al. 2004).

For this reason prior Beta distributions were fitted to these parameters based on existing statistics. The advantage of this distribution is that by varying its two shape parameters, a wide variety of possible shapes to the distribution over the interval can be obtained.

Based on recommendations of the expert panel, a correlation coefficient of +1 was used between all the pairs of sensitivity variables of a screening test, since they are fully correlated. Also between the specificity and each of the sensitivity parameters of the screening tests, a correlation coefficient of -1 was specified. The reason for this specification is that specificity and sensitivity of a test inversely affect each other and as one decreases the other will certainly increase. The same procedure is followed for the cost parameters to implement the concept of correlation between test characteristic parameters.

3. Utility Parameters

Unfortunately, except for a point estimate, very little is known regarding the exact behavior of CRC utility parameters. Based on what information was available, the expert panel recommended a skewed Beta distribution for these parameters. The maximum utility was set to the age-utility the person would have in the absence of cancer (when the person is healthy). The minimum was obtained by multiplying the estimated utility value with the cause by the maximum utility value. The mode is then the estimated utility value with the cause. The standard deviation of the Beta distribution was assumed to be one sixth of the utility range ($STDEV = \frac{Max - Min}{6}$). Thus, the Beta distribution is highly skewed toward the maximum value, since the minimum value usually was very close to the mode.

This distribution of the utilities is apparently similar to what happens in reality, based on the opinion of the expert panel. As an example, the procedure for computing these statistics for utility of a 54-64 years old person, diagnosed with regional low cancer is demonstrated. The age-utility for this person without cancer is 0.92, and the estimated utility after this cancer is 0.59. Therefore the Maximum should be equal to 0.92.

Minimum is $0.59 \times 0.92 = 0.54$ and STDEV is equal to $\frac{0.92 - 0.54}{6} = 0.063$.

4. Compliance Parameters

As explained in the model assumptions, there are different levels of compliance for a screening modality like never-compliant, one-time compliant, etc. For a particular modality, a typical person may have one of these compliance levels with a specific probability. Therefore, in general, if there are k levels of compliance, a multinomial distribution with parameters $p_1, p_2, \dots, p_k$ is a reasonable distribution to model the compliance level of a person, where p_i is the probability that the person has compliance level i .

In probabilistic sensitivity analysis, it was decided to assign probability distributions to parameters of this multinomial distribution, i.e. $p_1, p_2, \dots, p_k$. It should be noted that

since the sum of these probabilities must be equal to 1, they are not independent and as a result, it is not possible to assign independent distributions to each of them. In Bayesian theory there is a straightforward conjugate family for the multinomial distribution, namely the Dirichlet distribution. This distribution was used in sensitivity analysis to draw samples for $p_1, p_2, \dots, p_k$. The Dirichlet distribution is, in fact, a multidimensional beta distribution:

$$f(p_1, p_2, \dots, p_k) = \frac{\Gamma(a_1 + a_2 + \dots + a_k)}{\prod_{i=1}^k \Gamma(a_i)} p_1^{a_1} p_2^{a_2} \dots p_k^{a_k} \quad p_i > 0, \sum_{i=1}^k p_i = 1$$

If we define $a_0 = \sum a_i$, the means of the marginal distributions are $E(p_i) = \frac{a_i}{a_0}$ and

their variances are $Var(p_i) = \frac{a_i(a_0 - a_i)}{a_0^2(a_0 + 1)}$. To choose the value of parameters of the

Dirichlet distribution, i.e. $a_1, a_2, \dots, a_k$, moment matching was used. In other words, the means of the marginal distributions, i.e. $E(p_1), E(p_2), \dots, E(p_k)$, were set equal to the values suggested by the expert panel. Values to match with $Var(p_1), Var(p_2), \dots, Var(p_k)$ were chosen so as to get a reasonable variation around $E(p_i)$'s. To be more precise, from the form of the marginal variance, it can be observed that the largest value of the variance belongs to the p_i which has the closest value of $\frac{a_i}{a_0}$ to 0.5. As a result, we set three times the standard deviation of the p_i with the closest $E(p_i)$ to 0.5 equal to 0.07. The value of 0.07 seems to be a reasonable half-width regarding the values of estimates for $E(p_i)$'s and their differences.

In this way, the necessary set of independent equations were derived to solve for the values of $a_0, a_1, a_2, \dots, a_k$ and hence the Dirichlet distribution will be completely defined. As an example, the procedure for the case of compliance for endoscopic screenings is illustrated. There are three levels of compliance for endoscopic strategies, level 0 or never-compliant, level 1 or one-time compliant, level 2 or every-5-years compliant.

According to the expert panel, the mean probabilities of being in one of these compliance groups for a person are 0.30, 0.17 and 0.53 respectively. Therefore it was known

$$\text{that: } \frac{a_1}{a_0} = 0.30, \frac{a_2}{a_0} = 0.17, \frac{a_3}{a_0} = 0.53.$$

The closest of these three to 0.5 was 0.53 which was for p_3 . Thus it is determined that:

$$0.07 = 3 \sqrt{\frac{a_3(a_0 - a_3)}{a_0^2(a_0 + 1)}} = 3 \sqrt{\frac{0.53a_0(a_0 - 0.53a_0)}{a_0^2(a_0 + 1)}},$$

from which $a_0 = 454$ and hence $a_1 = 136, a_2 = 77, a_3 = 241$. Therefore Dirichlet (136, 77, 241) was the distribution for the parameters of the endoscopic screening compliance multinomial distribution.

It should be noted that one of the main advantages of using the Dirichlet distribution for $p_1, p_2, \dots, p_k$ is that it is a conjugate family for the multinomial. As a result, if a posteriori data on the multinomial distribution are obtained, the prior Dirichlet used here based on expert opinions can be easily updated to a Dirichlet posterior.

Drawing samples from a Dirichlet distribution is a simple procedure. Each sample is produced using k independent samples from Gamma distributions with parameters which depend upon the parameters of the Dirichlet (Devroye 1986). This generator was added to the code.

It should be mentioned that the parameters for each Beta distribution were derived using the VIM program (Roberts 2004). This program allows users to fit a desired distribution to certain statistical characteristics such as mode and standard deviation. For instance Figure 18 shows the output reported by the VIM program, after being provided the following information for the statistical characteristics of the “Diagnostic Colonoscopy cost”: Mode = \$661, STDEV = \$59, Min = \$ 529, Max = \$1,058

Figure 18: Screenshot of VIM Program Output

Above Figure shows a Beta (4.316, 10.972) distribution for the studied parameter.

3.10. Summary of Chapter 3

This chapter describes the simulation of the CRC screening methods. The main objects used in the simulation were reviewed, as well as the way they interact with the model. Key assumptions were explained. Simulation events were identified. In the process of creating this description, the pathways of these objects were discussed along with the events that affect them. The input database structure was discussed to provide a framework for the inputs that are needed for each simulation run. The model user interface was explained as a flexible feature that enables a user to apply screening setups in an interactive interface. Finally the parameters in model which were chosen to be studied in a probabilistic sensitivity analysis and their assigned distributions were reviewed.

4. Cost-Effectiveness Analysis Using Probabilistic Sensitivity Analysis

With the completion of the model construction explained in Chapter 3, the next step was to verify and validate the model, and then analyze the results. The verification actions were to ensure that all portions of the model worked as expected. The validation included the task of making sure that the model outputs matched targets obtained from the medical literature. The analysis involved performing a cost-effectiveness analysis on the eight candidate CRC screening strategies using the probabilistic sensitivity analysis method.

4.1. Model Verification

The main purpose of the verification was to ensure that the screening and surveillance models worked according to the screening flowcharts given in Appendix A. The screening model is programmed in Microsoft Visual Studio.NET 2003, which provides a very strong development environment for constructing, compiling, testing and executing code. Taking advantages of these tools and other techniques, two methods were employed to verify the model:

- 1) Stepping through the screening source code line-by-line and routine-by-routine to verify the general program flow, while watching the key variables
- 2) Creating and examining an output trace file

4.1.1. General Flow Verification

General flow analysis was the primary step used to verify the general program flow and insure the correct execution of the code and the behavior of the event calendars. Several people were processed through each of the screening strategies using the Visual Studio.NET “debug” feature to watch the processing of the simulation from within the code. One intention was to insure that the correct distributions were being retrieved from the database and sampled properly. The next step was to look at the program flow and make sure that people were moving through the screening process correctly and following the expected decisions at each event.

The most comprehensive verification occurred when the Visual Studio debugger was used to check the key variables, which were discounted cost and QALYs. The reason was that, validation of these two values is critical to the cost-effectiveness analysis. Therefore exact verification was done to check whether cost and utility are collected and discounted properly. All discounting calculations were also performed by hand to check their computational correctness.

4.1.2. Trace Output Analysis

Trace statements have been added to the code. They were placed at every event so that they reveal the event time and the action the code is taking relative to that event. The trace statements are written to an external text file (see example of trace file in Figure 19) whose content is then examined for discrepancies. Since the general flow of the model has usually been verified, the trace provides a summary of experience that is more easily seen as a whole, such as time between screening events and response to cancer or adenoma diagnosis.

```
Trace - Notepad
File Edit Format View Help

PERSON 2
Screening Strategy: FOBT
White Female
No Family History
Birth Year: 1953
Natural Life = 77.35
Risk = 0.04
Personal risk = 0.62
Time to first adenoma = 72.45
This person is Every 2 Years compliant to FOBT.
At Time = 44.000
Person 2's utility is lowered to 0.93 due to age
At Time = 50.000
Person 2 is screened: FOBT
FOBT result is Positive.
Patient is Compliant to the follow-up colonoscopy.
At Time = 50.000
Person 2 is screened: Colonoscopy
Screening test result is Negative. The colon is Normal.
Next FOBT scheduled 5 years from now
At Time = 54.000
Person 2's utility is lowered to 0.92 due to age
At Time = 55.000
Person 2 is screened: FOBT
FOBT result is Negative.
Next FOBT scheduled 2 years from now
At Time = 57.000
Person 2 is screened: FOBT
FOBT result is Negative.
Next FOBT scheduled 2 years from now
At Time = 59.000
Person 2 is screened: FOBT
FOBT result is Negative.
Next FOBT scheduled 2 years from now
At Time = 61.000
Person 2 is screened: FOBT
FOBT result is Negative.
Next FOBT scheduled 2 years from now
At Time = 63.000
Person 2 is screened: FOBT
FOBT result is Negative.
Next FOBT scheduled 2 years from now
At Time = 64.000
Person 2's utility is lowered to 0.89 due to age
At Time = 65.000
```

Figure 19: Screenshot of Trace Report

Looking over trace output was a tremendous help in verifying correct implementation of screening and surveillance scheduling. The trace was sent regularly to the V/NCS model medical expert panel during the event development process to be verified from their points of view.

4.2. Model Validation

To validate the ability of the V/NCS model to simulate screening strategies over a specific period of time, a comparison of the Minnesota Colon Cancer Control Study was made to a simulation of that population. The Minnesota study was performed with the goal to compare the effectiveness of annual and biennial FOBT screening strategies in reducing CRC mortality to no screening program (Mandel et al. 1993). The reason for choosing this trial was that it is a well-known study within the medical literature and many other models have already used it for validation purposes. The other reason was that in comparison with other randomized trials done, it has provided more comprehensive outputs, which are essential inputs to a simulation model.

The Minnesota study was initiated by recruiting 46,551 men and women volunteers 50 to 80 years of age from 1975 through 1977 and randomly assigning them to three groups: annual screening, biennial screening and control (no Screening). The participants in these three groups were studied until 1991 when that study ended. During this interval the CRC incidence and mortality were accumulated for all three groups. The final report of this randomized trial revealed a 33 % decrease of mortality within the annual FOBT screening group in comparison with the control group.

The original V/NCS model was not capable of modeling the Minnesota study because of its specific characteristics. However by making some assumptions and applying some changes to the classes within the simulation code, the modified V/NCS model was altered to replicate the Minnesota study. The most difficult part of this modification process was to generate a population with the same characteristics based on age, gender and family history in simulation model as was observed in Minnesota trial. The difficulty occurred because the V/NCS model was primarily designed to model a homogeneous cohort and it did not have this ability to simulate a mixed cohort population.

The following assumptions were made in the simulation model based on information provided by the Minnesota study papers:

1. The Minnesota study did provide the sample population by age in ten year increments. It was assumed that nineteen percent of the sample had a family history of CRC.

2. Although the Minnesota study began in 1975, the panel of patients did not fill until later. Also the Minnesota study was stopped in 1982, but resumed in 1985 when more data were needed. Thus the simulation was initiated in 1977, stopped in 1982, re-initiated in 1985 and continued until 1991. In the simulation eleven FOBT screening tests were scheduled for the annual screening group, versus 6 FOBT tests for the biennial group. Data from the actual study was unclear regarding the actual number of FOBT tests per group.

3. The Minnesota study only gave a range of 50 to 80 for the ages of the persons in the study. To generate the sample population for the simulation, a birth cohort based on a common age for each 10 year increment was assumed:

- age 50 to 60, birth-year 1922 (55 years old in 1977)
- age 60 to 70, birth-year 1913 (64 years old in 1977)
- age 70 to 80, birth-year 1904 (73 years old in 1977)

4. Compliance with screening tests was calculated based on the rates reported in the Minnesota Study paper.

5. In the simulation, it was assumed that modeled persons are adherent with their first FOBT (other than never compliant group) and then, based on the total number of positive adherence episodes assigned, randomly adherent with a set number of future FOBTs. No FOBT is scheduled during the non-screening gap.

6. None of the FOBT slides collected prior to 1985 was rehydrated, whereas all of the FOBT slides collected after 1985 were rehydrated. In the simulation model, all unrehydrated FOBT was assigned a sensitivity of 29% for cancer and specificity of 95% while rehydrated FOBT was given a sensitivity of 40% for cancer and specificity of 90%.

An extensive effort to verify all aspects of the simulated model was made and a thorough check of procedures was used to be sure they conformed to the practices in the Minnesota trial. Since the papers which were written about this study have not provided all the necessary information (e.g. the exact sensitivity and specificity of the FOBT test is not mentioned), a complete verification/validation was not possible.

The results generated from V/NCS model are shown in Table 4. The CRC mortality in the control and annual groups of the simulation model were observed to be very close to what happened in actual study as it is shown in Table 4. All simulation outcomes (CRC incidence and mortality) were somewhat lower than the actual trial. This may reflect a lower risk for CRC in the modeled population compared to the actual population in the trial. However, the percent decrease in CRC mortality, comparing the actual and simulated outcomes, was identical (~33%). This result adds substantial validation to the V/NCS model.

Strategy	CRC Incidence		CRC Mortality	
	Actual	Simulation	Actual	Simulation
Control Group	356	331	121	116
Annual Group	323	294	82	81

Table 4: Modeled versus Actual CRC Outcomes for the Minnesota Study

Figure 20 compares the cumulative CRC mortality during the study years between the actual trial and simulated model. It is easily seen from these curves that both the annual and control group's mortality curves in simulated model are similar to the actual trial.

Figure 20: Comparison of Actual and Simulated CRC Mortality for the Minnesota Study

4.3. Deterministic Cost-Effectiveness Analysis

Initially, a deterministic cost-effectiveness analysis was performed to quantitatively compare the expected outcomes of competing screening alternatives when the best estimates of model parameters were applied (base-case analysis).

4.3.1. Model Assumptions

The following assumptions were made in cost-effectiveness analysis:

- The analysis was done separately on eight populations that can be defined according to various gender, race and family history combinations.

Populations	
White Male NF*	White Male F**
White Female NF	White Female F
Black Male NF	Black Male NF
Black Female NF	Black Female F
* NF: No Family History	
** F: With Family History	

Table 5: Defined Populations

Each of these eight groups has its own response toward different screening strategies, since all of the factors used in population definition (gender, race and family history) are major known aspects influencing the CRC

development risk. This classification of scenarios can provide valuable information on CRC screening cost-effectiveness outcome of each specific scenario and consequently be used by policy makers to develop specific screening recommendations for each population.

- The screening strategies studied on average risk (no family history) populations were the ones recommended in most of the recent screening guidelines, including the one explained in Chapter 2. The capabilities of two newly proposed screening strategies, virtual colonoscopy and fecal DNA tests, were also examined to compare them with current strategies. Specifically, the strategies are summarized as:.

- 1) FOBT every year
- 2) DCBE every five years
- 3) Sigmoidoscopy every five years
- 4) FOBT every year and sigmoidoscopy every 5 years (Sig & FOBT strategy)
- 5) Colonoscopy every 10 years (Colon 10)
- 6) Virtual Colonoscopy every 10 years (VColon)
- 7) Fecal DNA every 3 years

For the high risk population (with family history), the only recommendation in CRC clinical guidelines is to perform a colonoscopy test every 5 years (Colon 5). Therefore for high risk group this strategy was also studied along with all the ones mentioned above. This approach would give a good estimate of how proper had been this unique recommendation of medical policy makers for high risk population, and if any other strategies have this potential to be added to the guidelines.

Using the “screening option” form in the User Interface, all the necessary setup information required for each of the above strategies were applied. As explained in Section 3.8, this form has the potential to specify any kind of screening strategy on the provided screening tests in the V/NCS model.

- Reference year was set to year 2003 (the year the latest American Gastroenterological Association guideline was released).
- Screening for populations with no family history started at age 50 and Cost and QALYs were discounted to this age with a 3% discounting rate. For people with family history starting and discounting age were set to 40.
- Cost effectiveness ratios for each screening strategy indicates the average cost a person incurs for following that intervention to gain a quality adjusted year of life. Therefore to compute this ratio, cost and QALYs results of a screening strategy should be compared to the cost and QALYs of the situation where no screening is present. For this reason all the populations were also simulated under a no-screening strategy.
- Persons in the population whose lifetimes were less than the initial screening age, or the ones who were diagnosed with symptomatic cancer before initial screening age, were irrelevant to the cost-effectiveness analysis model and eliminated from the population.

4.3.2. Population Size

After observing several simulation outputs, it was determined that the mean estimates of QALYs have much closer values than cost values in different screening strategies. The magnitude of the difference in QALYs was in the thousandths. This result comes from the fact that cost of screening changes considerably among different strategies, while the average QALYs provided by each of these strategies for the total population is very limited.

Therefore to obtain a valid result, the variance of QALYs should be lowered to an extent that their confidence intervals do not overlap when comparing any two strategies. By achieving the desired amount of precision on QALYs, the necessary precision for cost would certainly be provided (Al, Van Hout, and Michel 1998).

Applying the concept of “common random numbers” to V/NCS model, it was possible to simulate different screening strategies on a uniform population with the same characteristics. Therefore differences in mean performances, such as cost and QALYs,

between various screening strategies are estimated more precisely than absolute mean performances of an individual strategy (Kelton, Sadowski, and Sturrock 2004).

To estimate the proper model size, first a sample population of size 20,000 was simulated under Colon 10 and Sig & FOBT strategies and the 3% discounted QALYs for each person was saved into an Excel file (partially shown in Table 6 below).

Person #	QALYS 3%		Difference
	Colon 10	Sig & FOBT	
1	15.7906	19.4897	-3.6991
2	19.5216	19.5216	0.0000
3	8.0333	8.0333	0.0000
4	15.7210	15.5308	0.1902
5	14.0518	14.0518	0.0000
6	13.0026	13.0026	0.0000
7	15.9987	15.9987	0.0000
8	17.4993	18.5555	-1.0562
9	16.5292	18.3374	-1.8082
10	11.2656	11.2656	0.0000
11	11.2676	11.2676	0.0000
12	22.7044	22.7044	0.0000
13	15.0578	14.5872	0.4706
14	19.6495	19.6495	0.0000
15	23.4535	23.4535	0.0000
16	21.5817	21.8460	-0.2642
17	19.6456	19.6456	0.0000
18	16.1279	18.0505	-1.9226
19	10.0237	10.0237	0.0000
20	16.8917	16.8917	0.0000
21	10.0351	10.0351	0.0000
...	...	...	...
Mean(Difference) = -0.00667			
STDEV(Difference) = 0.977001			

Table 6: QALYs of each Person under Colon 10 and Sig & FOBT strategies

The 95% confidence interval on the average difference in QALYs were computed as following:

$$\bar{y} \pm t_{1-\alpha/2, n-1} \frac{s_y}{\sqrt{n}} = -.00667 \pm 1.96 \frac{0.977}{\sqrt{20000}} = [-0.0202, 0.0068]$$

The half-width of the difference in QALYs for a population of size 20,000 was about $H_0 = 0.0135$ years. Although the margin error of ± 0.005 years (less than 2 days) with 95% confidence interval was decided to be enough to satisfy our required precision. The total population necessary to be simulated to achieve the assigned precision was therefore computed as follows:

$$n \cong n_0 \frac{H_0^2}{H_{desired}^2} = 20000 \frac{0.0135^2}{0.005^2} = 145,800$$

Based on this output, a population size of 150,000 was assigned for each replication of the screening strategies.

4.4. Cost-effectiveness results

Considering all the assumptions mentioned in Section 4.3, discounted cost and QALYs were computed for different populations and variations of the interventions (shown in Tables 7, 8). For example, in Table 7, the computed discounted cost for applying FOBT strategy on “White Male NF” population is \$1,274 and 3% discounted QALYs is 15.8421 years beyond age 50. Note that for the family history scenarios shown in Table 8, costs and QALYs are accumulated beyond age 40.

Population		White Male NF	White Female NF	Black Male NF	Black Female NF
No Screening	Cost 3%	1,003	904	748	716
	QALS 3%	15.8125	17.8116	14.2894	16.0513
FOBT	Cost 3%	1,274	1,232	1,082	1,037
	QALS 3%	15.8421	17.8357	14.2982	16.0726
DCBE	Cost 3%	1,548	1,499	1,278	1,293
	QALS 3%	15.8443	17.8347	14.3069	16.0697
Sigmoidoscopy	Cost 3%	1,591	1,513	1,317	1,313
	QALS 3%	15.8536	17.8490	14.3133	16.0783
Sig & FOBT	Cost 3%	1,728	1,693	1,468	1,450
	QALS 3%	15.8569	17.8443	14.3163	16.0834
VColon	Cost 3%	1,936	1,917	1,655	1,657
	QALS 3%	15.8388	17.8273	14.3039	16.0720
Colono 10	Cost 3%	1,989	2,007	1,739	1,758
	QALS 3%	15.8643	17.8516	14.3191	16.0841
Fecal DNA	Cost 3%	2,333	2,359	1,957	2,039
	QALS 3%	15.8312	17.8278	14.3006	16.0716

Table 7: Discounted Cost and QALYs for each Screening Test for all 4 “no family history” Populations

Population		White Male F	White Female F	Black Male F	Black Female F
No Screening	Cost 3%	1,830	1,734	1,380	1,346
	QALS 3%	20.7199	22.4688	19.5770	21.1341
FOBT	Cost 3%	2,211	2,129	1,778	1,773
	QALS 3%	20.7710	22.5157	19.6250	21.1832
DCBE	Cost 3%	2,518	2,465	2,097	2,099
	QALS 3%	20.7742	22.5186	19.6235	21.1755
Sigmoidoscopy	Cost 3%	2,616	2,479	2,122	2,106
	QALS 3%	20.7775	22.5268	19.6334	21.1880
Sig & FOBT	Cost 3%	2,737	2,685	2,297	2,282
	QALS 3%	20.7883	22.5381	19.6411	21.1985
VColon	Cost 3%	2,975	2,886	2,502	2,493
	QALS 3%	20.7619	22.5141	19.6170	21.1750
Colon 10	Cost 3%	3,064	3,000	2,570	2,621
	QALS 3%	20.7861	22.5350	19.6448	21.1971
Fecal DNA	Cost 3%	3,407	3,407	2,877	2,992
	QALS 3%	20.7571	22.5070	19.6139	21.1727
Colon 5	Cost 3%	3,521	3,605	3,094	3,232
	QALS 3%	20.8052	22.5560	19.6560	21.2109

Table 8: Discounted Cost and QALYs for each Screening Test for all 4 “with family history” Populations

Although these tables show that every CRC screening strategy provide higher QALYs (extended life expectancy) than “no screening”, some of these strategies are more cost-effective as indicated by a lower cost per life-year saved than for the alternatives. In order to identify these strategies, a cost-effectiveness analysis was implemented.

First, all of the different populations were examined to determine whether any strategies were simply dominated by other strategies having lower costs and greater effectiveness (QALYs). Second, the principle of extended dominance (i.e., whether linear combinations of other strategies can produce greater benefit at lower cost) was applied to all strategies. Third, among the non-dominated screening strategies, the incremental cost-effectiveness ratios (ICER) were calculated by comparing each strategy to the next more costly and more effective intervention. This process produces an “efficiency frontier” of increasingly more costly and more effective strategies. Finally, the results of analysis for each population are presented on a cost-effectiveness plane, together with the efficiency frontier line for non-dominated strategies within a population (Gold et al. 1996).

The CE plane is a two-dimensional space with the x-axis being the average difference (treatment – control) in effectiveness (ΔE) and the y-axis being the average difference in cost (ΔC). The axes are unbounded from positive to negative infinity, and the origin represents the control group because scales are in difference form.

The cost-effectiveness calculations are only illustrated for one of the populations in this chapter. The necessary tables and graphs for the rest of populations are presented in Appendix C. The following table shows the cost-effectiveness analysis for the “White Male NF” population.

Rank	Strategy	Lifetime Cost 3%	QALYS 3% Discounted	ICER \$ per Life-Year Gained
	No Screening	1003	15.8125	...
1	FOBT	1274	15.8421	9,165
	DCBE	1548	15.8443	Dominated
2	SIG	1591	15.8536	27,436
	SIG & FOBT	1728	15.8569	Dominated
	VColon	1936	15.8388	Dominated
3	Colon 10	1989	15.8643	37,062
	Fecal DNA	2333	15.8312	Dominated

Table 9: ICER of Different Screening Strategies for a “White Male NF” Population

Closer examination of this table reveals that DCBE, Sig & FOBT, VColon and Fecal DNA strategies can be eliminated by either simple or extended dominance. For example, since the Fecal DNA strategy has both higher cost and less effectiveness in comparison with other strategies, it can be rejected by the simple dominance principle.

An ICER is also computed in Table 9 for each non-dominated strategy. For instance, the ICER of the sigmoidoscopy strategy in comparison with FOBT strategy is as follows:

$$ICER_{(FOBT-Sig)} = \frac{Cost_{(Sig)} - Cost_{(FOBT)}}{QALYs_{(Sig)} - QALYs_{(FOBT)}} = \frac{1591 - 1274}{15.8536 - 15.8421} = 27,436 \text{ \$ / year}$$

Table 9 also indicates that FOBT strategy results in incremental CE ratio of \$9,165 per life-year saved. The sigmoidoscopy strategy had a CE ratio of \$ 27,436 per QALY gained in comparison with the FOBT strategy. “Colonoscopy every 10 years” strategy was the most effective CRC screening strategy, resulting in an incremental CE ratio of \$37,062 per QALY compared with the sigmoidoscopy strategy. In the other words, this incremental CE ratio indicates that switching from sigmoidoscopy to colonoscopy strategy is only cost-effective in case the decision maker is willing to pay at least \$37,062 for a QALY.

Comparing each screening strategy to the no-screening strategy, the following CE plane was developed (Figure 21). In this figure the x-axis shows the average difference in

cost between each screening strategy and no-screening strategy and y-axis demonstrate the average difference in QALYs. Note that the origin represents the no-screening strategy.

Figure 21: CE Plane and Frontier Line for a “White Male NF” Population

The efficiency frontier in this figure is given by the lines joining no-screening, FOBT, Sigmoidoscopy and Colon 10 strategies. DCBE and Sig & FOBT strategies are internal to this frontier, indicating that they also can be ruled out through the principle of extended dominance (i.e., a linear combination of FOBT and sigmoidoscopy strategies would strongly dominate the DCBE strategy). The slope of the frontier at any point reflects incremental cost-effectiveness, i.e., the additional cost at which additional QALYs can be purchased.

Overall, this analysis showed that three strategies (FOBT, Sigmoidoscopy, Colonoscopy) are more appropriate to be considered in recommendations of healthcare policy makers. The Incremental CE ratios for these strategies ranged from \$9,165 per QALY gained to \$37,062.

Reviewing the results of this analysis a couple of questions may arise, such as how robust are these conclusions and how much the uncertainty in parameters has influenced

these results? Or is it consistent for medical decision makers to simply rule out the dominated strategies?

Taking a careful look at the cost-effectiveness planes and the efficiency frontiers, it was perceived that in several situations the dominated strategies might have formed a part of frontier line if their cost or effectiveness was slightly decreased or increased. For instance, the Sig & FOBT strategy in Figure 21, is very close to the frontier line and it wouldn't be wise to reject this strategy knowing that uncertainty exists in the perceived values of many cost and effectiveness parameters of this model. Therefore, these point estimates for the cost-effectiveness ratio of different screening strategies, should be used just in the primary analysis. On the whole, these observations justify the necessity for a probabilistic cost-effectiveness analysis on screening strategies.

4.5. Probabilistic Analysis

Confidence intervals for cost effectiveness ratios are a valid approach to addressing uncertainty in cost-effectiveness analysis. However, as a ratio statistic, the solution to confidence interval estimation is not straightforward. The intuition behind this problem is that where there is non-negligible probability that the denominator of the ratio takes a zero value, the ICER becomes unstable since for a zero denominator the ICER would be infinite. For a positive cost difference (the numerator of the ICER) as the effect difference approached zero from the positive direction, the ICER tends to positive infinity. As the effect difference approaches zero from the negative direction, the ICER tends to negative infinity. For negative cost differences the ICER signs are reversed. This discontinuity about the zero effect difference causes statistical problems for estimating confidence limits. For example, there is no mathematically tractable formula for the variance of the statistic. Even where the effect difference is significantly different from zero, it would be inappropriate to assume that the ICER's sampling distribution followed a normal distribution (Briggs, Brien, and Blackhouse 2002).

Two main approaches have been proposed for the purpose of estimating the confidence interval for incremental CE ratios: the parametric method introduced by Fieller (Fieller 1954) and the nonparametric approach of bootstrapping (Fenn, McGuire,

and Backhouse 1996). In this thesis the bootstrapping method was applied in the context of the PSA approach to generate the confidence intervals.

4.6. Probabilistic Sensitivity Analysis

Having specified distributions for all the relevant parameters of the model, the probabilistic analysis was done by randomly sampling from each of the parameter distributions and calculating the discounted expected cost and discounted expected QALYs for that combination of parameter values. This process formed a single replication of the model results for a specific screening strategy within a population. A total of 100 replications were performed in order to examine the distributions of the resulting costs and outcomes for each screening strategy (available time limited the number of replications that could practically be completed).

The results of the probabilistic analysis for all 100 replications of a specific screening strategy were saved into an Excel worksheet (partially shown is Figure 22 below). Each replication of the strategy is contained in a row of the worksheet.

	A	B	C	D	E	F	G	H	I	J	K	L	M
1	PSA Analysis												
2	Colonoscopy Test												
3	White Male NF												
4	Replication #	Population Risk	Colonoscopy Tests	Polypectomies	Bleeds	Perforations	Screening Deaths	Costs	Costs(3% disc.)	QALYs	QALYs(3% disc.)	Life Years	Life Expectancy
5	1	0.821	154485	27566	1261	235	13	\$3,289.58	\$2,158.13	20.7962	15.8615	0	73.14
6	2	0.821	150574	26404	1140	259	13	\$3,276.33	\$2,150.18	20.7887	15.8545	0	73.14
7	3	0.821	147984	26413	1095	191	11	\$3,014.75	\$2,003.93	20.7926	15.8561	0	73.14
8	4	0.821	154291	27375	1206	264	8	\$3,311.29	\$2,191.26	20.8001	15.8624	0	73.14
9	5	0.821	145495	26002	1163	254	16	\$3,056.49	\$2,005.76	20.7916	15.8583	0	73.14
10	6	0.821	152358	27347	1225	184	11	\$3,003.36	\$1,999.62	20.7921	15.8589	0	73.14
11	7	0.821	145330	25994	1184	203	12	\$3,213.50	\$2,114.38	20.7940	15.8589	0	73.14
12	8	0.821	148818	26614	1142	259	11	\$3,135.92	\$2,076.91	20.7970	15.8610	0	73.14
13	9	0.821	148525	26527	1234	261	10	\$2,903.24	\$1,904.45	20.8012	15.8628	0	73.14
14	10	0.821	146994	26202	1161	235	12	\$3,185.92	\$2,066.00	20.7806	15.8526	0	73.14
15	11	0.821	146707	26218	931	253	14	\$3,167.31	\$2,071.69	20.7968	15.8592	0	73.14
16	12	0.821	146627	26375	927	263	12	\$3,012.52	\$1,985.34	20.7994	15.8618	0	73.14
17	13	0.821	155757	27592	1291	262	10	\$2,955.01	\$1,930.66	20.7870	15.8573	0	73.14
18	14	0.821	151321	26939	1263	205	11	\$2,736.31	\$1,794.14	20.7956	15.8605	0	73.14
19	15	0.821	142863	25971	877	247	13	\$2,932.63	\$1,924.01	20.7890	15.8534	0	73.14

Figure 22: Screenshot of Cost and QALYs Excel sheet Report for 100 Replications of Colonoscopy Strategy for the “White Male NF” Population

After simulating all the screening strategies for a population, discounted cost and QALYs results were saved into another Excel worksheet for further computations (Figure 23).

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q
1	Male White	No Screening		FOBT		DCBE		Sigmoidoscopy		Sig & FOBT		VColon		Colonoscopy		Fecal DNA	
2	No Family History	Cost 3%	QALY 3%	Cost 3%	QALY 3%	Cost 3%	QALY 3%	Cost 3%	QALY 3%	Cost 3%	QALY 3%	Cost 3%	QALY 3%	Cost 3%	QALY 3%	Cost 3%	QALY 3%
3	Base Case	1003	15.8125	1274	15.8421	1548	15.8443	1591	15.8536	1728	15.8569	1936	15.8388	1989	15.8643	2333	15.8312
4	1	1141	15.8166	1397	15.8497	1735	15.8495	1768	15.8567	1947	15.8556	2148	15.8403	2158	15.8615	2564	15.8421
5	2	1119	15.8163	1349	15.8377	1666	15.8395	1765	15.8489	1876	15.8569	1991	15.8390	2150	15.8545	2557	15.8324
6	3	1017	15.8169	1312	15.8401	1599	15.8485	1637	15.8493	1741	15.8538	1849	15.8382	2004	15.8561	2326	15.8426
7	4	1109	15.8163	1475	15.8483	1669	15.8453	1698	15.8546	1861	15.8610	2108	15.8455	2191	15.8624	2609	15.8396
8	5	1038	15.8216	1360	15.8474	1581	15.8507	1608	15.8530	1761	15.8573	1889	15.8434	2006	15.8583	2370	15.8388
9	6	1002	15.8156	1396	15.8534	1540	15.8442	1619	15.8519	1786	15.8555	1991	15.8398	2000	15.8589	2260	15.8398
10	7	1073	15.8115	1414	15.8473	1586	15.8495	1640	15.8513	1835	15.8586	1920	15.8459	2114	15.8589	2427	15.8388
11	8	1078	15.8133	1361	15.8462	1567	15.8514	1701	15.8525	1846	15.8624	1952	15.8403	2077	15.8610	2550	15.8388
12	9	1032	15.8192	1233	15.8458	1474	15.8552	1507	15.8504	1604	15.8589	1960	15.8428	1904	15.8628	2208	15.8422
13	10	1080	15.8212	1497	15.8504	1668	15.8494	1681	15.8547	1900	15.8590	2023	15.8438	2066	15.8526	2468	15.8432
14	11	1130	15.8218	1335	15.8519	1606	15.8526	1611	15.8492	1687	15.8592	2024	15.8429	2072	15.8592	2711	15.8417
15	12	996	15.8200	1201	15.8484	1475	15.8479	1526	15.8537	1630	15.8594	1826	15.8461	1985	15.8618	2286	15.8384
16	13	1009	15.8140	1243	15.8463	1489	15.8468	1527	15.8497	1651	15.8572	1817	15.8450	1931	15.8573	2262	15.8365
17	14	930	15.8147	1101	15.8403	1369	15.8475	1458	15.8488	1533	15.8529	1680	15.8478	1794	15.8605	2047	15.8343
18	15	1048	15.8164	1380	15.8439	1528	15.8402	1569	15.8447	1758	15.8487	1823	15.8378	1924	15.8534	2320	15.8389
19	16	934	15.8176	1173	15.8447	1384	15.8480	1409	15.8540	1530	15.8540	1772	15.8416	1827	15.8595	2299	15.8402
20	17	958	15.8149	1285	15.8492	1491	15.8445	1535	15.8515	1682	15.8560	1829	15.8430	1906	15.8618	2238	15.8421

Figure 23: Screenshot of Cost and QALYs Excel sheet Report for 100 Replications of all the screening strategies for the “White Male NF” Population

Figure 24 shows the results of these 100 replications plus the base-case (i.e., the deterministic cost-effectiveness analysis) on the CE plane for the “White Male NF” population, together with the efficiency frontier of the base-case (Briggs, Blackhouse, and O'Brien 2002). For the other seven populations this CE plane is provided in the Appendix C.

Figure 24: CE Plane for 100 Replications of Screening strategies for “White Male NF” Population

This figure shows how it may not be possible to rule out Sig & FOBT and DCBE strategies, since they potentially form part of the frontier in many replications. However, it is not possible to gain a clear view from Figure 24 as to how often these two strategies

form part of the frontier because there can be substantial correlation between simulations plotted in this figure.

The above figure also shows the empirical distribution of cost-effectiveness for different screening strategies. Confidence limits for each strategy was obtained by selecting the 3rd and 97th percentile of the 100 replicates (which excludes 2 (or 2.5%) of the observations from either end of the empirical distribution). The following table (Table 10) shows the lower and upper 95% confidence limits for cost-effectiveness of different strategies relative to “no screening”.

Strategy	Lower Limit	Upper Limit
FOBT	\$7032/QALY	\$12,919/QALY
Sigmoidoscopy	\$13,082/QALY	\$19,144/QALY
DCBE	\$13,514/QALY	\$23,240/QALY
Sig & FOBT	\$17,649/QALY	\$22,430/QALY
Colon 10	\$18,862/QALY	\$28,576/QALY
Vcolon	\$24,668/QALY	\$53,484/QALY
Fecal DNA	\$38,727/QALY	\$92,517/QALY

Table 10: CI for CE Ratios of Different Screening Strategies for “White Male NF” Population

As a result, 95% of the estimated joint density falls within the wedge on the cost-effectiveness plane defined by the confidence limits. This wedge is shown for FOBT, DCBE and Colonoscopy strategies in Figure 25.

Figure 25: CI of FOBT (Blue wedge), DCBE (Brown wedge), and Colonoscopy (Yellow Wedge) Strategies for “White Male NF” Population

These confidence limits also support the conjecture that DCBE and Sig & FOBT strategies should not be ruled out from screening choices, since their confidence intervals overlap with confidence intervals of the strategies that formed the frontier line in the base-case analysis (i.e., Colonoscopy and Sigmoidoscopy strategies). Although these results are valuable, they cannot provide proper recommendations for medical decision makers regarding comparison of different screening strategies.

As the next step of the analysis, in order to figure out how often screening strategies form parts of the frontier line a Macro was written in MS Excel. This macro was applied to each replication of a population and chosen strategies were saved into a table like below (Table 11).

	A	B	C	D	E	F	G	H
1		FOBT	DCBE	Sigmoidoscopy	Sig & FOBT	VColon	Colonoscopy	Fecal DNA
2	Base Case	1		1			1	
3	1	1		1			1	
4	2	1			1			
5	3	1	1		1		1	
6	4	1		1	1		1	
7	5	1		1	1		1	
8	6	1					1	
9	7	1			1		1	
10	8	1			1			
11	9	1	1		1		1	
12	10	1		1	1			
13	11	1			1			
14	12	1			1		1	
15	13	1			1		1	
16	14	1	1		1		1	
17	15	1					1	
18	16	1		1			1	
19	17	1					1	
20	18	1					1	

Table 11: Screening Strategies formed part of Frontier Line for each Replication for “White Male NF” Population

Summing up each column of the above table and dividing that number by total numbers of replications (100 replications + base case = 101), the proportion of replications each strategy formed part of the cost-effectiveness frontier was computed. Tables 12, 13 show these proportions for all the populations.

Strategy	Percentage of Time Formed Part of the Frontier			
	White Male NF	White Female NF	Black Male NF	Black Female NF
FOBT	100%	100%	94%	99%
DCBE	7%	10%	17%	15%
Sigmoidoscopy	46%	22%	36%	36%
Sig & FOBT	74%	74%	58%	67%
Vcolon	0%	0%	0%	0%
Colon 10	75%	75%	82%	94%
Fecal DNA	0%	0%	0%	0%

Table 12: Percentage of Time each Screening Strategy formed part of the Frontier Line for “no family history” Populations

Strategy	Percentage of Time Forms Part of Frontier			
	White Male F	White Female F	Black Male F	Black Female F
FOBT	100	100	100	100
DCBE	3	4	3	1
Sigmoidoscopy	8	12	10	10
Sig & FOBT	82	86	65	74
Vcolon	0	0	0	0
Colon 10	2	10	6	15
Fecal DNA	0	0	0	0
Colon 5	97	100	98	100

Table 13: Percentage of Time each Screening Strategy formed part of the Frontier Line for “with family history” Populations

As an example, in the “White Male NF” population, it is clear from Table 12 that VColon and fecal DNA strategies can be ruled out, since they appeared zero times on the frontier. By contrast, it turned out that DCBE formed part of frontier in 7% of simulations and Sig & FOBT also formed part of frontier in 74% of simulations. However, even knowing the proportion of times a strategy forms part of the efficient frontier, it is not clear how this result could be interpreted by medical decision makers.

If the shadow price for an extra QALY (the maximum willingness to pay or “ceiling ratio”) were known, it would be possible to choose between all of the screening strategies, not just identify those that form the efficient frontier. Therefore, conditional upon knowing the ceiling ratio, in each replication there is only one strategy of choice from eight screening strategies under evaluation. The proportion of times that an intervention is the strategy of choice from the 100 replications of each population gives the strength of evidence in favor of that strategy.

Unfortunately, the shadow price of an extra QALY is not known, although it might be compared to the shadow price of other medical interventions. For that reason by plotting

all possible values of the ceiling ratio, the proportion of times an intervention is the strategy of choice was determined (explained in next Section).

4.6.1. Cost-Effectiveness Acceptability Curves

Decision-making in health care is certainly undertaken in a context of uncertainty concerning the effectiveness and costs of health care interventions. One method that has been suggested to represent this uncertainty uses cost-effectiveness acceptability curves (CEACs). These curves present the probability that each competing alternative is optimal for each value of the cost-effectiveness threshold (Lothgren and Zethraues 2000).

For this purpose, the value of the ceiling ratio was varied from zero to infinity to figure out how the evidence in favor of cost-effectiveness of different screening strategies varies with this value. It should be mentioned that fecal DNA and virtual colonoscopy strategies were not considered in the analysis in this section, since they did not appear to be cost-effective in comparison with other strategies.

In the first step of this analysis, the cost-effectiveness ratios for each replication were sorted in ascending order. The resulting order yields an inequality for the sample replication illustrated as follows:

$$CE_{FOBT} \leq CE_{Sigmoidoscopy} \leq CE_{Sig\&FOBT} \leq CE_{Colonoscopy} \leq CE_{DCBI}$$

FOBT has had the lowest ratio in this example and it also has a higher efficiency than the no-screening strategy (see Figure 26), thus it would be the strategy to replace the no-screening strategy when the ceiling ratio is being increased.

Figure 26: Sample CE Plane Describing the issue of Dominance in Context of CEAC

This process of determining the relative cost-effectiveness can also be illustrated within a CE plane. The slope of a line, related to the y-axis of a CE plane, corresponds to a certain ceiling ratio value. Therefore, rotating a line around the origin point (clockwise) is the same as varying the ceiling ratio from zero to infinity. In Figure 26, the FOBT point would be the first point on the CE plane to fall up and to the left of an imaginary ceiling ratio line, rotated around the origin clockwise.

The sigmoidoscopy strategy will replace the FOBT strategy in next stage as the ceiling ratio line rotates around. Next Sig & FOBT replaces sigmoidoscopy and at last Colonoscopy replaces the Sig and FOBT strategy as ceiling ratio increases. Although DCBE has a higher CE ratio than colonoscopy, it will not replace this strategy even when the ceiling ratio is high enough. The reason is that it is not wise to switch from a strategy with higher efficiency to one with lower efficiency.

Therefore, sorting CE ratios in ascending order does not provide enough information alone for developing an acceptability curve. In order to avoid this potential switch to a less effective strategy, the screening strategies should be checked for dominance, whether simply dominated or by the principle of extended dominance. The simply dominated

strategies should be immediately rejected, since it is never beneficial to replace a non-dominated strategy by any of them (e.g., DCBE strategy in Figure 26).

In case a strategy is dominated by the principle of extended dominance (e.g., sigmoidoscopy strategy in Figure 26), two situations can occur which are shown in the triangle with red and black areas in Figure 26. The triangle is an area which can be drawn between any two strategies which are not simply dominated. Two ceiling ratio lines which cross these two strategies, divide that triangle into two parts. If any other strategy falls into this triangle, it would be dominated by the principle of extended dominance (i.e., linear combinations of two other strategies produce greater benefit at lower cost). If this dominated strategy is found in the red area (see Figure 26), it could become cost-effective, since its ceiling value is between the ceiling ratios of two other strategies which dominate it. But when it is in the black area it can not be cost-effective for any ceiling ratio, since the ceiling ratio value of the line which crosses it is higher than one of the strategies that shape the triangle.

By applying the above procedure to all the 100 replications for each ceiling ratio, only one screening strategy was chosen within each population. Figure 27 shows the acceptability curves generated for the “White Male NF” population. For other populations this figure is given in Appendix C.

Figure 27: Acceptability Curve for “White Male NF” Population

The curves become parallel to the x-axis after a certain value of the ceiling ratio. This occurs because these strategies are unable to provide a CE ratio higher than that certain ceiling ratio.

The acceptability curves in Figure 27 clearly shows the initial concern that DCBE strategy might form part of the frontier and might be a cost-effectiveness choice in some situations was unwarranted. In fact, the conditions necessary for DCBE strategy to be considered the most cost-effective option never arose in the 101 simulations. Based on the acceptability curves FOBT, sigmoidoscopy, Sig & FOBT and Colon 10 are the strategies that had the highest cost-effectiveness probability within certain ranges of ceiling ratios (Table 14).

Strategy	Ceiling ratio value	
	Min	Max
No-Screening	\$0	\$9,782
FOBT	\$9,783	\$16,040
Sigmoidoscopy	\$16,041	\$17,555
Sig & FOBT	\$17,556	\$22,700
Colonoscopy	\$22,701	\$29,012

Table 14: Ceiling Ratio Range which a Strategy has the Highest Probability to be Cost-Effective

For instance, for a ceiling ratio of \$20,000/QALY gained, Sig & FOBT strategy is the best choice since it is the top most curve in comparison with other screening curves.

These figures can be easily used by decision makers in providing new CRC clinical recommendations based on money society is willing to pay to gain a QALY.

4.7. Summery of Chapter 4

This chapter described the verification and validation of the model. The results from a deterministic cost-effectiveness analysis were also provided along with rationale for why these results may not be dependable. A probabilistic sensitivity analysis was performed subsequently to study CE ratios of screening strategies under uncertainty. Finally the cost-effectiveness acceptability curves were developed to determine the probability that a screening test is cost-effective for different ceiling ratios.

5. Conclusions and Recommendations

Since CRC is the second leading cause of cancer death among both males and females, the prevention and treatment of CRC is an important component of national healthcare policy and medical decision making. Before a rational policy can be set however, some method of evaluating alternative treatment and screening strategies is necessary. A discrete event simulation of the CRC screening methods such as the model in this thesis is fundamental to exploring alternative medical interventions. Because of the huge expense, the long length of time between interventions and results, and questionable ethics in performing large scale screening trials of medical interventions in real life, a simulated model of the screening methods is an important tool that allows the examination of alternative hypotheses.

The V/NCS model is a “grand hypothesis” that was built on an object-oriented platform and based on a series of assumptions identified from an extensive review of the medical literature and from the expert panel associated with the project. These assumptions were translated into a series of objects and events describing screening and surveillance strategies for CRC. This model is able to examine various interventions on cohorts with specific CRC risks and generates customized reports.

Some key factors that make this model successful are:

- The object-oriented approach makes the simulation more flexible and easy to change.
- The database interface within the simulation is an excellent method of storing the data in a convenient and easily manageable location, while providing the users the ability to apply deterministic and probabilistic sensitivity analysis on selected parameters.
- The model was designed in a manner which allows for many potential extensions to screening methods; to incorporate test characteristics for future screening tests that may not have been developed or tested yet.

- The screening model was validated against the Minnesota Trial, a well-known actual randomized trial, which helped to establish the validity of the cost-effectiveness analysis done later on.
- The output Excel file provides the discounted costs and QALYs for any screening strategies, which are the core inputs for any cost-effectiveness analysis.
- By applying different techniques during and after the simulation construction an extensive verification was performed to ensure the simulation is accurately and correctly modeled.
- This model can be used to study various screening interventions under uncertainty by applying a probabilistic sensitivity analysis on selected parameters.
- A Bayesian approach was adopted in the choice of distributions for the parameters encountered in the probabilistic cost-effectiveness analysis.
- This model provides a unique basis to compare all the screening strategies that the American Gastroenterological Association's newest guideline recommends for different risk populations for the first time ever.

The major accomplishments of the analysis presented in this thesis are:

- The analysis showed that introducing uncertainty into the model can provide a stronger basis for decisions by medical decision makers.
- The developed cost-effectiveness acceptability curves (CEAC) can be widely used by medical policy makers in development of new screening clinical guidelines and health-care resource allocation.
- Considering the CEAC for all the populations (average and high risk), FOBT, Sig & FOBT, and Colonoscopy were three screening strategies showing higher probabilities to be the most cost-effective strategy for different ceiling ratios.

- For each risk population under consideration, CEAC were developed, which can be used by medical decision makers to provide appropriate recommendations for each specific group.
- The literature to date has largely confined itself to discussing CEAC in the context of decisions involving two interventions. This is due to complexities associated with the stochastic analysis of incremental cost-effectiveness ratios for decisions involving multiple options. This thesis is the first effort to compare multiple numbers of CRC screening strategies by using CEAC.

5.1. Recommendations for Future Study

One possible area for future research is to conduct a factor analysis on the parameters subjected to the probabilistic sensitivity analysis. This would clarify the effect of each parameter on the output measures, such as cost and effectiveness. Verifying the main factors with higher effects could lead us to improve the estimates of those parameters.

Another area for future research is to consider a population basis instead of a cohort basis. The simulation model in this thesis takes a homogeneous group of people and runs them through the simulation. Some medical policy makers would like to be able to simulate a diverse group of many different birth years, races and genders, as well as different screening strategies in various population subgroups. This requires a fundamental change in the way the inputs are acquired and people are created and one which has recently been added to the V/NCS model

Another interesting topic for future research can be the optimization of the screening strategies for CRC. Values for many parameters are not determined by experience in the screening strategies, such as initial screening age and screening frequencies. Applying a heuristic optimizing method to this model might aid in optimizing the cost-effectiveness of screening programs in terms of screening age ranges, screening schedules, risk group selection, and choosing the most efficient diagnostic, follow-up, and surveillance protocols. Finding a optimal stopping age for screening is one of the issues of interest to many policy makers.

One other potential future study could be the application of a net-benefit framework methodology to compare screening strategies. Net-benefit is a new framework for the analysis of uncertainty in stochastic cost-effectiveness analysis. Basically, it is a simple rearrangement of the cost-effectiveness decision rule to overcome the problems associated with incremental CE ratios (Stinnett and Mullahy 1998).

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Appendices

Appendix A: Screening Flowcharts

CRC Risk Assessment

FOBT Strategy

Colonoscopy Strategy

Note: A box is colored in grey if a sort of cost incurred in it

Sigmoidoscopy Strategy

Sigmoidoscopy Strategy (One-Time Compliant)

Note: A box is colored in grey if a sort of cost incurred in it

Combined FOBT & Sig Strategy

Combined FOBT & Sig Strategy (One-Time Compliant)

DCBE Strategy

Virtual Colonoscopy Strategy

Surveillance Strategy (Adenoma History)

Surveillance Strategy (CRC History)

Appendix B: Parameter Distribution Tables

Cost	Dis Type	Mode	Min	Max	SD	Alpha	Beta	Correlation
cancer: initial local (within 6 months of CRC diagnosis)	MVBeta	\$20,323	\$16,258	\$32,517	\$1,829	4.261	10.781	All Cost Variables are + 0.5 Correlated
cancer: initial regional (within 6 months of CRC diagnosis)	MVBeta	\$23,368	\$18,694	\$37,389	\$2,103	4.261	10.781	
cancer: initial distant (within 6 months of CRC diagnosis)	MVBeta	\$26,708	\$21,366	\$42,733	\$2,404	4.261	10.781	
cancer: continuing local/year	MVBeta	\$539	\$431	\$862	\$49	4.261	10.781	
cancer: continuing regional/year	MVBeta	\$2,461	\$1,969	\$3,938	\$221	4.261	10.781	
cancer: continuing distant/year	MVBeta	\$26,855	\$21,484	\$42,968	\$2,417	4.261	10.781	
cancer: terminal (within 6 months of scheduled cancer death)	MVBeta	\$21,172	\$16,938	\$33,875	\$1,905	4.261	10.781	
screening colonoscopy (G0121)	MVBeta	\$614	\$491	\$982	\$55	4.261	10.781	
diagnostic colonoscopy (45378)	MVBeta	\$661	\$529	\$1,058	\$59	4.261	10.781	
colonoscopy with polypectomy (45835)	MVBeta	\$745	\$596	\$1,192	\$67	4.261	10.781	
post-polypectomy hemorrhage	MVBeta	\$16,088	\$12,870	\$25,741	\$1,448	4.261	10.781	
screening sigmoidoscopy (G0104)	MVBeta	\$210	\$168	\$336	\$19	4.261	10.781	
diagnostic sigmoidoscopy (45330)	MVBeta	\$276	\$221	\$442	\$25	4.261	10.781	
perforation: Colonoscopy	MVBeta	5,004	\$4,003	\$8,006	\$450	4.261	10.781	
perforation: Sigmoidoscopy, DCBE, V-Colon	MVBeta	5,004	\$4,003	\$8,006	\$450	4.261	10.781	
pathology per polypectomy	MVBeta	\$67	\$54	\$107	\$6	4.261	10.781	
pathology per Biopsy	MVBeta	\$67	\$54	\$107	\$6	4.261	10.781	
sigmoidoscopy with biopsy (45331)	MVBeta	\$288	\$230	\$461	\$26	4.261	10.781	
post-biopsy hemorrhage	MVBeta	\$16,088	\$12,870	\$25,741	\$1,448	4.261	10.781	
Fecal DNA test	MVBeta	\$400	\$320	\$640	\$36	4.261	10.781	
FOBT (G0103)	MVBeta	\$4.54	\$4	\$7	\$0	4.261	10.781	
DCBE (G0106)	MVBeta	\$192	\$154	\$307	\$17	4.261	10.781	
CT colonography	MVBeta	\$614	\$491	\$982	\$55	4.261	10.781	

Distribution of Cost Parameters

Colonoscopy test characteristics	Dis Type	Mode	Min	Max	SD	Alpha	Beta	242	243	244	245
sensitivity for CA	MVBeta	0.95	0.9	1	0.0167	3.982	3.982	1	1	1	-1
Non-advanced adenoma sensitivity	MVBeta	0.77	0.7	0.8	0.0167	4.65	2.564		1	1	-1
Advanced adenoma sensitivity	MVBeta	0.84	0.8	0.9	0.0167	3.307	4.46			1	-1
Neoplasia specificity†	MVBeta	0.79	0.74	0.87	0.0217	3.196	4.514				1
mortality rate (5% prob death given perf)	Beta	0.0001	0.000025	0.0001	0.0000125	3.871	1				
perforation rate	Beta	0.002	0.0005	0.002	0.00025	3.872	1				
post-polypectomy hemorrhage rate	Beta	0.009	0.0045	0.009	0.00075	3.872	1				
Sigmoidoscopy test characteristics	Dis Type	Mode	Min	Max	SD	Alpha	Beta	256	257	258	259
sensitivity for CA (in segments traversed)	MVBeta	0.95	0.9	1	0.0167	3.982	3.982	1	1	1	-1
Non-advanced adenoma sensitivity (in segments traversed)	MVBeta	0.77	0.7	0.8	0.0167	4.65	2.564		1	1	-1
Advanced adenoma sensitivity (in segments traversed)	MVBeta	0.84	0.8	0.9	0.0167	3.307	4.46			1	-1
Neoplasia specificity†	MVBeta	0.83	0.79	0.89	0.0167	3.307	4.46				1
mortality rate (5% prob death given perf)	Beta	0.000045	0.000025	0.00005	0.000004	4.984	1.995				
perforation rate	Beta	0.0009	0.0005	0.001	0.000083	4.604	1.901				
post-biopsy hemorrhage rate	Beta	0									
DCBE test characteristics	Dis Type	Mode	Min	Max	SD	Alpha	Beta	319	320	321	322
sensitivity for CA	MVBeta	0.85	0.75	0.95	0.0333	4.091	4.091	1	1	1	-1
Non-advanced adenoma sensitivity	MVBeta	0.3	0.2	0.5	0.0500	2.821	4.643		1	1	-1
Advanced adenoma sensitivity	MVBeta	0.45	0.4	0.7	0.0500	1.695	4.477			1	-1
Neoplasia specificity†	MVBeta	0.78	0.75	0.85	0.016666667	2.485	4.464				1
mortality rate (5% prob death given perf)	Beta	0.000003	0.000003	0.00003	0.0000045	1.001	3.879				
perforation rate	Beta	0.00006	0.00006	0.0006	0.00009	1	3.872				
Fecal DNA test characteristics	Dis Type	Mode	Min	Max	SD	Alpha	Beta	270	271	272	273
Colorectal cancer sensitivity	MVBeta	0.65	0.5	0.9	0.0667	3.011	4.352	1	1	1	-1
Non-advanced adenoma sensitivity	MVBeta	0.08	0.05	0.15	0.0167	2.485	4.464		1	1	-1
Advanced adenoma sensitivity	MVBeta	0.15	0.1	0.3	0.0333	2.15	4.45			1	-1
Neoplasia specificity†	MVBeta	0.94	0.9	0.97	0.0117	4.999	4				1
FOBT Characteristics	Dis Type	Mode	Min	Max	SD	Alpha	Beta	275	276	277	278
Colorectal cancer sensitivity	MVBeta	0.29	0.15	0.5	0.0583	5.156	5.593	1	1	1	-1
Non-advanced adenoma sensitivity	MVBeta	0.06	0.05	0.15	0.0167	1.399	4.593		1	1	-1
Advanced adenoma sensitivity	MVBeta	0.15	0.1	0.3	0.0333	2.365	5.094			1	-1
Neoplasia specificity†	MVBeta	0.95	0.9	0.98	0.0133	4.584	3.15				1
Virtual Colonoscopy Characteristics	Dis Type	Mode	Min	Max	SD	Alpha	Beta	334	335	336	337
sensitivity for CA (%)	MVBeta	1	0.9	1	0.0167	3.86	1	1	1	1	-1
Non-advanced adenoma sensitivity	MVBeta	0.45	0.43	0.49	0.0100	2.821	4.643		1	1	-1
Advanced adenoma sensitivity	MVBeta	0.89	0.81	0.95	0.0233	4.384	3.538			1	-1
Neoplasia specificity†	MVBeta	0.81	0.77	0.82	0.0083	4.605	1.901				1
mortality rate (%) (5% prob death given perf)	Beta	0.000003	0.000003	0.00003	0.0000045	1.001	3.879				
perforation rate (%)	Beta	0.00006	0.00006	0.0006	0.00009	1	3.872				

Distribution of Screening Characteristic Parameters

Utilities	Dis Type	Mode	Min	Max	SD	Alpha	Beta
local colon (44-54)	Beta	0.74	0.6882	0.93	0.0403	1.98	4.596
local colon (54-64)	Beta	0.74	0.6808	0.92	0.0399	2.197	4.641
local colon (64-74)	Beta	0.74	0.6586	0.89	0.0386	2.955	4.603
local colon (74+)	Beta	0.74	0.6438	0.87	0.0377	3.504	4.384
local rectal (44-54)	Beta	0.74	0.6882	0.93	0.0403	1.98	4.596
local rectal (54-64)	Beta	0.74	0.6808	0.92	0.0399	2.197	4.641
local rectal (64-74)	Beta	0.74	0.6586	0.89	0.0386	2.955	4.603
local rectal (74+)	Beta	0.74	0.6438	0.87	0.0377	3.504	4.384
local high rectal (stage II)(44-54)	Beta	0.59	0.5487	0.93	0.0636	1.392	4.224
local high rectal (stage II)(54-64)	Beta	0.59	0.5428	0.92	0.0629	1.475	4.324
local high rectal (stage II)(64-74)	Beta	0.59	0.5251	0.89	0.0608	1.76	4.511
local high rectal (stage II)(74+)	Beta	0.59	0.5133	0.87	0.0595	1.983	4.589
local low rectal (stage II)(44-54)	Beta	0.5	0.465	0.93	0.0775	1.253	4.11
local low rectal (stage II)(54-64)	Beta	0.5	0.46	0.92	0.0767	1.262	4.149
local low rectal (stage II)(64-74)	Beta	0.5	0.445	0.89	0.0742	1.473	4.356
local low rectal (stage II) (74+)	Beta	0.5	0.435	0.87	0.0725	1.601	4.424
regional colon (no chemoRx complications)(44-54)	Beta	0.7	0.651	0.93	0.0465	1.746	4.503
regional colon (no chemoRx complications)(54-64)	Beta	0.7	0.644	0.92	0.0460	1.909	4.572
regional colon (no chemoRx complications)(64-74)	Beta	0.7	0.623	0.89	0.0445	2.489	4.674
regional colon (no chemoRx complications) (74+)	Beta	0.7	0.609	0.87	0.0435	2.937	4.618
regional colon (chemoRx complications)(44-54)	Beta	0.63	0.5859	0.93	0.0574	1.492	4.345
regional colon (chemoRx complications)(54-64)	Beta	0.63	0.5796	0.92	0.0567	1.595	4.425
regional colon (chemoRx complications)(64-74)	Beta	0.63	0.5607	0.89	0.0549	1.956	4.585
regional colon (chemoRx complications) (74+)	Beta	0.63	0.5481	0.87	0.0537	2.245	4.647
regional high rectal(44-54)	Beta	0.59	0.5487	0.93	0.0636	1.392	4.224
regional high rectal(54-64)	Beta	0.59	0.5428	0.92	0.0629	1.475	4.324
regional high rectal(64-74)	Beta	0.59	0.5251	0.89	0.0608	1.76	4.511
regional high rectal (74+)	Beta	0.59	0.5133	0.87	0.0595	1.983	4.589
regional low rectal(44-54)	Beta	0.5	0.465	0.93	0.0775	1.253	4.11
regional low rectal(54-64)	Beta	0.5	0.46	0.92	0.0767	1.262	4.149
regional low rectal(64-74)	Beta	0.5	0.445	0.89	0.0742	1.473	4.356
regional low rectal (74+)	Beta	0.5	0.435	0.87	0.0725	1.601	4.424
distant/terminal (within 18 months of scheduled cancer death)(44-54)	Beta	0.25	0.2325	0.93	0.1163	1.076	3.964
distant/terminal (within 18 months of scheduled cancer death)(54-64)	Beta	0.25	0.23	0.92	0.1150	1.089	3.982
distant/terminal (within 18 months of scheduled cancer death)(64-74)	Beta	0.25	0.2225	0.89	0.1113	1.13	4.026
distant/terminal (within 18 months of scheduled cancer death) (74+)	Beta	0.25	0.2175	0.87	0.1088	1.16	4.058
colonoscopy complication (6 weeks)(44-54)	Beta	0.74	0.6882	0.93	0.0403	1.98	4.596
colonoscopy complication (6 weeks)(54-64)	Beta	0.74	0.6808	0.92	0.0399	2.197	4.641
colonoscopy complication (6 weeks)(64-74)	Beta	0.74	0.6586	0.89	0.0386	2.955	4.603
colonoscopy complication (6 weeks) (74+)	Beta	0.74	0.6438	0.87	0.0377	3.504	4.384
Sigmoidoscopy complication (6 weeks)(44-54)	Beta	0.74	0.6882	0.93	0.0403	1.98	4.596
Sigmoidoscopy complication (6 weeks)(54-64)	Beta	0.74	0.6808	0.92	0.0399	2.197	4.641
Sigmoidoscopy complication (6 weeks)(64-74)	Beta	0.74	0.6586	0.89	0.0386	2.955	4.603
Sigmoidoscopy complication (6 weeks) (74+)	Beta	0.74	0.6438	0.87	0.0377	3.504	4.384

Distribution of Utility Parameters

Compliance	Dis Type		Parameter	Value			
Screening compliance rate – Endoscopy/DCBE/CTC	Dirichlet	every 5 yrs - 53%	0	136			
		one time -17%	1	77			
		never – 30%	2	241			
Screening compliance rate – FOBT	Dirichlet	every 1 yrs - 35%	0	125			
		every 2 yrs - 14%	1	42			
		every 5 yrs - 11%	2	146			
		one time -10%	3	58			
		never – 30%	4	46			
Screening compliance rate – Fecal DNA	Dirichlet	every 3 yrs - 48%	0	137			
		every 5 yrs - 11%	1	50			
		one time - 11%	2	219			
		never – 30%	3	50			
Compliance	Dis Type	Mode	Min	Max	SD	Alpha	Beta
Surveillance compliance rate	Beta	0.8	0.8	1	0.0333	1	3.935
post-positive FOBT compliance rate (%)	Beta	0.7	0.7	1	0.0500	1	3.872
post-positive Fecal DNA compliance rate (%)	Beta	0.7	0.7	1	0.0500	1	3.872
post-positive Sig compliance rate (%)	Beta	0.8	0.8	1	0.0333	1	3.935
post-positive DCBE compliance rate (%)	Beta	0.8	0.8	1	0.0333	1	3.935
post-positive V-Colon compliance rate (%)	Beta	0.8	0.8	1	0.0333	1	3.935

Distribution of Compliance Parameters

Appendix C: Probabilistic Cost-Effectiveness Results

1. White Female NF

CE Plane for 100 Replications of Screening strategies, and Frontier Line for Base-Case

Acceptability Curves

Strategy	Ceiling Ratio Value	
	Min	Max
No Screening	\$0	\$13,363
FOBT	\$13,364	\$20,571
Sig & FOBT	\$20,571	\$26,683
Colon 10	\$26,684	\$34,212

Ceiling Ratio Range which a Strategy has the Highest Probability to be Cost-Effective

2. Black Male NF

CE Plane for 100 Replications of Screening strategies, and Frontier Line for Base-Case

Acceptability Curves

Strategy	Ceiling Ratio Value	
	Min	Max
No Screening	\$0	\$16,730
FOBT	\$16,731	\$24,417
Sig & FOBT	\$24,418	\$30,660
Colon 10	\$30,661	\$43,511

Ceiling Ratio Range which a Strategy has the Highest Probability to be Cost-Effective

3. Black Female NF

CE Plane for 100 Replications of Screening strategies, and Frontier Line for Base-Case

Acceptability Curves

Strategy	Ceiling Ratio Value	
	Min	Max
No Screening	\$0	\$14,811
FOBT	\$14,812	\$23,511
Sig & FOBT	\$23,512	\$28,300
Colon 10	\$28,301	\$37,883

Ceiling Ratio Range which a Strategy has the Highest Probability to be Cost-Effective

4. White Male F

CE Plane for 100 Replications of Screening strategies, and Frontier Line for Base-Case

Acceptability Curves

Strategy	Ceiling Ratio Value	
	Min	Max
No Screening	\$0	\$7,290
FOBT	\$7,291	\$13,073
Sig & FOBT	\$13,074	\$20,591
Colon 5	\$20,592	\$25,383

Ceiling Ratio Range which a Strategy has the Highest Probability to be Cost-Effective

5. White Female F

CE Plane for 100 Replications of Screening strategies, and Frontier Line for Base-Case

Acceptability Curves

Strategy	Ceiling Ratio Value	
	Min	Max
No Screening	\$0	\$7,776
FOBT	\$7,777	\$13,329
Sig & FOBT	\$13,330	\$21,309
Colon 5	\$21,310	\$29,225

Ceiling Ratio Range which a Strategy has the Highest Probability to be Cost-Effective

6. Black Male F

CE Plane for 100 Replications of Screening strategies, and Frontier Line for Base-Case

Acceptability Curves

Strategy	Ceiling Ratio Value	
	Min	Max
No Screening	\$0	\$8,868
FOBT	\$8,869	\$16,244
Sig & FOBT	\$16,245	\$22,751
Colon 5	\$22,752	\$33,212

Ceiling Ratio Range which a Strategy has the Highest Probability to be Cost-Effective

7. Black Female F

CE Plane for 100 Replications of Screening strategies, and Frontier Line for Base-Case

Acceptability Curves

Strategy	Ceiling Ratio Value	
	Min	Max
No Screening	\$0	\$9,809
FOBT	\$9,810	\$17,047
Sig & FOBT	\$17,048	\$25,456
Colon 5	\$25,457	\$33,753

Ceiling Ratio Range which a Strategy has the Highest Probability to be Cost-Effective