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COST EFFECTIVENESS IN SCREENING POLICIES FOR BREAST CANCER IN THE PRESENCE OF OVER-DIAGNOSIS

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ABSTRACT

Although breast cancer screening can help reduce the rate of mortality and morbidity, it can also cause harm when there is a presence of over-diagnosis. Over-diagnosis is a medical term, recently used in the healthcare field, indicating harm that is caused by screening mammography. This study aims to explore the issue of breast cancer screening policies in the presence of over-diagnosis and to determine an optimal policy in each scenario. Sensitivity analysis over a range of over-diagnosis rates between 0% and 50%, starting ages between 35 to 50, and screening intervals between 1 year and 5 years is conducted using a Markov chain and decision tree model of breast cancer screening. TreeAge Pro 2013 software was used to perform the analysis. The method incorporates Monte Carlo simulation as well as cost effectiveness analysis with the purpose of determining a recommended policy in breast cancer screening. Quality adjusted life years (QALYs), number of mammograms, and cumulative screening costs were also determined.

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Thank you for believing in me.

Chapter 1

Introduction

1.1 Introduction

This chapter provides an overview on the background on breast cancer, breast cancer screening, and over-diagnosis in mammography screening. This is followed by the thesis objective that explains the goal of the study. Finally, the outline for the organization of the thesis is discussed.

1.2 Background

Among different types of cancer, breast cancer is the second most common cause of cancer death. In 2013, an estimated 232,340 new cases of invasive breast cancer were diagnosed in women, as well as an estimated 64,640 new cases of in situ breast cancer (American Cancer Society, 2013). This means that about 1 in 8 women in the US will develop invasive breast cancer during their lifetime.

Screening programs such as mammography screening have been effective in reducing mortality as well as detecting early stage cancer. Yet, it can also pose harm to women who have been exposed to the program at an early age (National Cancer Institute, 2014). Moreover, there is no consistency among the screening policies proposed by various agencies for the length of screening interval due to variations in risk factors and differences in family medical history. The American Cancer Society recommends that women receive an annual mammogram beginning at age 40 (2013). However, the U.S. Preventive Services Task Force recommends biannual screening for women 50 years and older (Calogne et.al., 2009).

The National Breast Cancer Foundation (NBCF) categorizes breast cancer progression into four stages: stage 0, stage I, stage II, Stage III and stage IV based on the size of the tumor, number of lymph nodes affected and the invasion to other organs within the body. Stage 0 is a non-invasive cancer which is *in situ* breast cancer whereas Stage I-IV is invasive cancers (2012).

The study limits the clinical breast exam only to screening mammogram and breast biopsy test. Screening mammogram is a standard diagnosis scan that routinely x-rays the breast to detect breast cancer in women who have no apparent symptoms. Biopsy is an additional test that removes tissues or sometimes fluid from suspicious areas and examines it under a microscope to check the presence of breast cancer (The National Breast Cancer Foundation, 2012). This thesis assumes that a perfect fine-needle aspiration biopsy is done for every woman who requires a biopsy test.

One of complications for an effective screening program that may cause potential harms to women who are exposed to screening is over-diagnosis. Over-diagnosis in cancer is the detection of cancers that do not have progress to cause symptoms or lead to mortality (American Cancer Society, 2013). Two explanations can describe this phenomenon: i) the cancer never progresses (or, in fact, regresses) or ii) the cancer progresses slowly enough that the patient dies of other causes before the cancer becomes symptomatic (Welch and Black, 2010). Over-diagnosis can lead to unnecessary treatment with the possibility of low mortality rate and subsequent post-surgery psychological distress. A recent study shows that 1.3 million U.S. women were over-diagnosed in the past 30 years. Further, 70,000 women in 2008, which accounted for 31% of all breast cancers diagnosed in US women in 2008, were over-diagnosed (Bleyer and Welch, 2012).

1.3 Thesis Objective

This research will determine recommended screening intervals along with the most appropriate starting age for women for mammography screening. The study will estimate the impact of over-

diagnosis, which is one of the harms of mammography. Little research has been conducted in the area of the impact of over-diagnosis in breast cancer screening on the optimal screening intervals. Quality adjusted life years (QALYS), number of mammograms, and cumulative screening costs will be determined. The model of breast cancer screening that included an over-diagnosis state was developed using TreeAge Pro 2013 (TreeAge Software Inc.) software. A Markov model incorporating a Monte Carlo simulation was applied to a decision tree to examine the impact of various screening policies over a lifetime. Sensitivity analysis over a range of over-diagnosis values of 0% to 50%, starting age values of 35 to 50, and screening interval values of 1 to 5 were conducted. Cost effective analysis and the effect of variance were used to determine an optimal recommendation for screening.

1.4 Organization of the Thesis

The thesis is organized in the following manner. Chapter 2 presents a literature review of previous relevant work pertaining to breast cancer screening. It begins by exploring the current suggested screening policies for breast cancer and looking at how other studies evaluated the screening policy. This Chapter also discusses over-diagnosis during screening that can potentially occur. Chapter 3 presents a detailed review of the methodologies used in this study. It begins by describing the problem to be examined as well as the assumptions made in the models. It also presents how data from previous studies is used in the model we develop. Finally, we show how a Markov model can be transformed into a decision tree. Chapter 4 presents the result produced from methodology discussed in Chapter 3 and shows the results of a cost effective analysis. These results are used to define an optimal policy for breast cancer screening. Finally, Chapter 5 summarizes the main results, conclusions, and suggestions for further research.

Chapter 2

Literature Review

2.1 Introduction

The literature review will begin by exploring the current policy for breast cancer screening and the basic foundation for cancer along with the definition of over-diagnosis. It presents previous studies that suggest the presence of over-diagnosis in breast cancer screening. This chapter also gives an introduction to a measurement that will be used for the effectiveness of breast cancer screening – quality adjusted life years (QALY). Furthermore it includes basic discussion about cost effectiveness analysis and finishes with an example of previous studies on how to model a Markov chain for screening.

2.2 Over-diagnosis

Welch and Black describe the phenomenon of cancer diagnosis is "the diagnosis of a *cancer* that would otherwise not go on to cause symptoms or death. We describe the two prerequisites for cancer over-diagnosis to occur: the existence of a silent disease reservoir and activities leading to its detection (particularly cancer screening)" (2010). The presence of over-diagnosis has changed the definition of cancer contained in medical dictionary – "a neoplastic disease the natural course which is fatal" (Dorland, 1994). The word "cancer" now encompasses cellular abnormalities with widely variable natural courses: fast growing, slow growing, very slow growing, and non-progressive growing. In the case of over-diagnosis, it occurs when either non-progressive cancers or very slow growing cancer are detected (Welch and Black, 2010).

Figure 1 represents the heterogeneity of cancer progression. “Fast” represents a cancer that quickly leads to symptoms and to death. “Slow” represents a slow growing cancer that leads to symptoms and death but take several years. “Very slow” represents a cancer that never causes problems because the patient will die of some other cause before the cancer is large enough to produce symptoms. “Non-progressive” represents cellular abnormalities that meet the pathological definition of cancer but never grow to causes symptoms; sometime they may grow and then regress (Welch and Black, 2010).

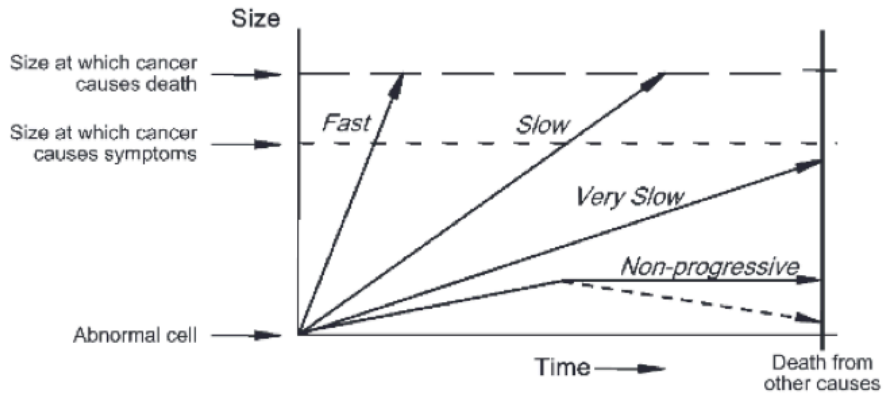


Figure 1 : Heterogeneity of cancer progression (Welch and Black, 2010)

Welch and Black also studied the long-term follow-up after a randomized trial of screening. They determined that the risk that a mammography-detected cancer represents over-diagnosis is about 24 % (Welch and Black, 2010).

2.3 The Suggestion on the Presence of Over-diagnosis in Breast Cancer Screening

The study done by Bleyer and Welch suggests that in order to reduce mortality, screening must detect life-threatening diseases at an earlier stage. Therefore, effective cancer screening programs must both increase the incidence of cancer detection at an early stage and decrease the incidence of cancer presenting at a late stage. The analysis on data collected over three decades, from 1976 to 2008, shows

that the number of cases of early stage breast cancer that are detected each year increased by 122 cases per 100,000 women while the number of cases of late stage cancer decreased by 8 cases per 100,000 women. The conclusion from the author's study shows that the imbalance in number suggests that there is a substantial over-diagnosis accounting for nearly a third of all newly diagnosed breast cancer with an estimation of cancer over-diagnosis in 1.3 million US women in the past 30 years which accounts for over-diagnosis rate of 31% of all breast cancer diagnosis. Bleyer and Welch also conclude that the decreasing mortality in breast cancer must largely be the result of improved treatment, not screening (2012).

Kalager et al. (2012) seek to quantify the percentage of over-diagnosis in breast cancer attributable to mammography screening. They believe that "mammography screening increases breast cancer incidence owing to early detection of cancer that would otherwise have been diagnosed later in life and to over-diagnosis of cancer that would not have been identified clinically in a lifetime." The study made a comparison of invasive breast cancer with and without screening based on information of nationwide mammography screening program in Norway between women aged 50 and 69 years. They estimate that the rate of over-diagnosis due to screening program is between 15% and 25%. This study shows that with the presence of over-diagnosis in the screening, it creates a substantial ethical dilemma, which burdens both patient and health care service.

However, a study done by the Independent UK Panel on Breast cancer screening suggests that the frequency of over-diagnosis was roughly 11% from the population perspective and around 19% from the perspective of the UK woman invited to screening (Marmot et. al., 2012). The studies focused on the UK setting, where women aged 50-70 years were invited to screening every 3 years. Although the study showed that there is over-diagnosis from cancer screening, they concluded that further investigation is needed to determine the balance of benefit to harm of breast cancer screening to women younger than 50 years and those older than 60 years.

2.4 Quality-Adjusted Life years (QALYs)

Quality adjusted life year (QALY) is widely used to as a measurement of health effectiveness. The use of QALYs assumes that health can be measured or valued based on amounts of time spent in various health states. Milton et al. explained that "the core concept of the conventional QALY is grounded in decision science and expected utility theory…Health, which is what we are seeking to maximize, is defined as the value-weighted time – life-years weighted by their quality – accumulated over the relevant time horizon to yield QALYs" (Milton et al., 2009). This means that health states must be valued on a scale between 0 and 1; 0 represents the death state and 1 represents a perfect health state. When using QALYS in the analysis, the assumption is typically made that the objective of the study is to maximize QALYs, which is maximizing health effectiveness. This measurement of Quality adjusted life year (QALYs) will be used as a main measurement to see how effectiveness of the suggested policies done in this thesis's study.

2.5 Cost Effectiveness Analysis on Breast Cancer Screening policy

Cost effectiveness analysis allows policy makers to compare the relative costs and health outcomes in of alternative intervention policies. There are studies that have done cost effective analysis on other cancer screening, but a limited amount has been done on breast cancer screening considering the effect of over-diagnosis and using QALYs as a health effective measurement. A study done by Melnikow et al. analyzes the effectiveness of two different screening strategies, biennial and annual, between women aged 40 and 64 years. They found that biennial film mammography beginning at age 50 years was the least expensive cost effective option; at $18,999 per additional life-year while the current policy of biennial film mammography beginning at age 40 was at $84,607 per additional life-year (2013). However the method does not take into the consideration the presence of over-diagnosis.

2.6 Modeling using Markov Chains

A Markov chain model is a technique that allows the analysis of random process over time when the time horizon is long and the tree involves multiplicity of health states. Because Markov chains involve a process of simulating progression and recursive disease, it allows the model to handle complicated conditions of disease management, which is very difficult to simulate in a simple decision tree (Xin, 2007).

Markovian indicates that the process is stochastic and that the behavior of the model in one time period does not depend on the previous time period. Xin explains the principal of Markov modeling where the disease of interest is divided into discrete states, by which the progression of disease falls, within a stochastic manner, over a certain amount of defined time (termed 'Markov cycle') (2007). The examples of Markov modeling of the treatment and the hypothetical decision tree on HBeAGg+ chronic hepatitis B can be seen in Figure 2 and Figure 3.

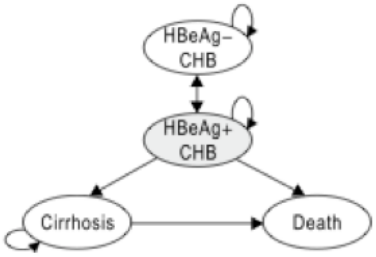


Figure 2: Markov modeling of a treatment for HBeAg+ CHB (Xin, 2007)

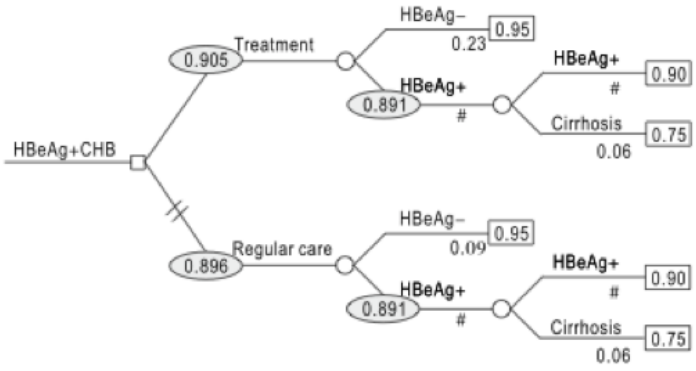


Figure 3: Decision tree on treatment for HBeAg+ CHB (Xin, 2007)

Many studies have tried to formulate the progression of Breast cancer using a Markov Chain model. Maillart et al. adjusted and divided the breast cancer progression using in their screening model into the following five states: no breast cancer (state 0), early breast cancer (state 1), late/advanced breast cancer (state 2), breast cancer induced death (state 3), and non-breast cancer induced death (state 4). As can be seen in Figure 4, patient of age α years has $p_{j,j+1}(\alpha)$ as a transition probability from stage j to state $j+1$, where j = 0, 1 ,2, or $p_{j,j+1}(\alpha) = p_{j,4}(\alpha)$ from stage j to state 4. The authors restrict the assumption that the patients would never develop symptoms during the transitional process which equivalently means that if a patient develops symptoms, the earliest that patient can be diagnosed is at the time of the next screening (2008).

Maillart et al. also discuss that if the patient is in state j, the result can either be "abnormal" with probability $a_j(\alpha)$ or "normal" with probability $1 - a_j(\alpha)$. These parameters correspond to the probability of a true positive, a false positive, a true negative, or a false negative, depending on the underlying disease state. The authors made a further assumption for the model that if the screening mammogram result is abnormal; a "perfect" test such as diagnostic mammogram and biopsy is performed. If a reveal of "perfect" test results in false abnormal, the patient would return to state 0 with probability of one. If it results in true abnormal, the patient exits the state, enters treatment, and is eventually absorbed into state 3 or state 4 with the probability of r_i and 1- r_i, respectively (2008).

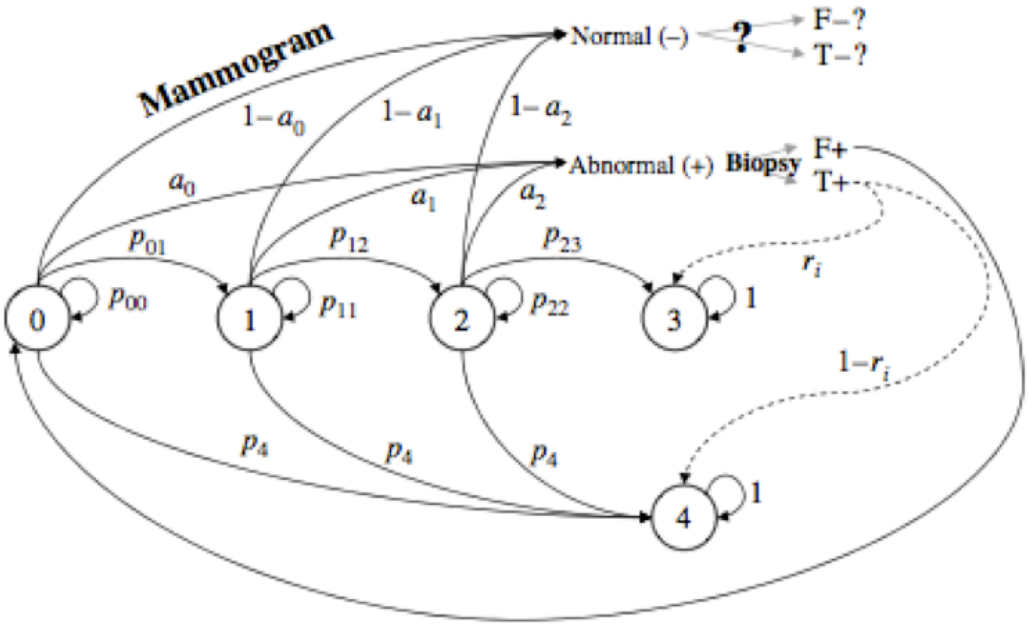


Figure 4 : Partially observed Markov chain diagram (Millart et al., 2008)

Although the Markov model developed by Millart et al. can be used to model age-based dynamics, the model fails to take into a consideration of an existence of over-diagnosis in breast cancer screening. Griffin and Zhang extended the study of from Maillart et al. and included the effect of an over-diagnosis with sensitivity analysis over a range of over-diagnosis values of 0% to 50% (2013). Figure 5 represents the diagram of the Markov chain with state 1' as an additional state, which indicates the over-diagnosis state.

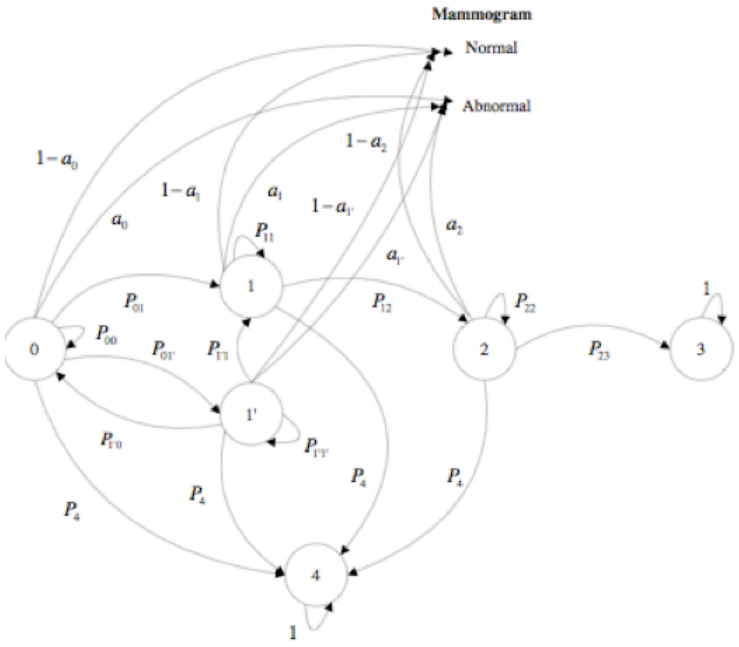


Figure 5: Markov chain transition diagram (Griffin and Zhang, 2013)

Griffin and Zhang also assume that a mammogram may be prescribed at the beginning of each period. The transitional probability between states also follows the initial idea from Millart et al. with an additional state 1'. Since the over-diagnosis state occurs in early state breast cancer (state 1), the fraction of original state 0 to state 1 is the transitional probabilities from state 0 to state 1'. This work, similar to Millart et al., categorizes the result of mammograms into a true positive, a false positive, a true negative, or a false negative, depending on the patient's true disease status with an additional constraint of having only biopsy as a reliable procedure for perfect test. If the result is negative (normal), no further procedures will be conducted to reveal the true status of the patient. If the result is positive (abnormally), biopsy will be subsequently conducted to reveal the true state of the patient (2013). The suggested policies from this study can be seen in Table 1, which characterized screening policies into five elements: starting age, first screening interval, switching age, second screening interval and ending age. This thesis will adopt the Markov chain diagram from Griffin and Zhang to develop a one-time policy for breast

cancer screening with the presence of over-diagnosis with no switching age in between, and taken into an account of variance of QALYs and cost effectiveness.

Table 1: Efficient policy for various levels of over-diagnosis (Griffin and Zhang, 2013)

Rate of Over-diagnosis	Starting Age	Screening Interval	Switching Age	Screening Interval	Ending Age	Expected Number Mammograms under Lifetime
0%	35	3	40	2	90	22.4
10%	35	3	40	2	90	22.4
20%	35	3	50	2	85	19.6
30%	35	3	50	2	85	19.5
40%	35	3	(none)	3	90	15.4
50%	35	4	50	3	90	14.4

Chapter 3

Methodology

3.1 Introduction

This chapter contains the methodology of the thesis. The organization of this chapter begins with the description of the Markov model from the previous study that will be translated into a decision tree using TreeAge Pro software considering mean and variance of the cost effectiveness. It will be followed by model formation, assumptions that are made in this study along with data and parameter input from different sources.

3.2 Model

This thesis adopted the idea of the presence of over-diagnosis in the screening using a discrete Markov Chain diagram from the study done by Griffin and Zhang as shown in Figure 5 (2013). Figure 5 shows that with the presence of over-diagnosis, six cancer states can be formulated into the diagram. State 0 represents cancer free state, state 1 represents an early stage invasive breast cancer, state 1' (or state 1p as appears in a decision tree model in Appendix A) represents the over-diagnosis state, state 2 represents an advanced stage of breast cancer, state 3 represents breast cancer stage that induced death and state 4 represents any other causes or incidences that induce death before the death happens by state 3. Transition probability between states and within the state itself, represent by $p_{j,\,j+1}\,(\alpha)$ where j is the current state and α as a patient of that particular age.

The study used a sensitivity analysis of over-diagnosis rate (%ODR) between 0% and 50% with a 10% interval and starting screening age of 30, 35, 40, 45, and 50 with ending age of 100. Because of the

presence of over-diagnosis, we adopt a transition probability matrix from Maillart et al (2008) and adjusted the probability associated with state 1' (or 1p). In this study, the summation of transition probability from state 0 to state 1 and the from state 0 to stat 1' (or 1p) is equivalent to transition probability from state 0 to state 1 as shown in Maillart et al. This indicates that transition probability from state 0 to state 1 is (1 - %ODR) of original transition probability and transitional probability from state 0 to state 1' (or 1p) is %ODR of original transition probability. Appendix B represents the value of each transition probability for each interval of particular age α as used in Maillart et al.

The following shows an example of how to calculate a new matrix for six states including over-diagnosis state using transition probabilities from Millart et al. For instance, between ages 40 – 44 with an over-diagnosis rate of 30% the following matrix will be used:

$P(\alpha)$ =

$$\begin{pmatrix} 0.99858 & 0.00060193*(1-0.3) & 0.00060193*(0.3) & 0 & 0 & 0.00081799 \\ 0 & 0.79085 & 0 & 0.20833 & 0 & 0.00081799 \\ 0 & 0 & 1-0.00081799 & 0 & 0 & 0.00081799 \\ 0 & 0 & 0 & 0.87870 & 0.12048 & 0.00081799 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

The study also assumes that a mammogram is prescribed at the beginning of a given period and if a patient develops cancer symptoms during the time between periods, that patient would not find out about the cancer until the next mammogram screening. Once the mammogram screening has been prescribed, the result can be either abnormal (positive) with a probability $a_j(\alpha)$ or normal (negative) with a probability of 1- $a_j(\alpha)$. These probabilities correspond to patient's true disease state, which includes a true positive, a false positive, a true negative or a false negative. If a screening mammogram results in abnormal (positive), a biopsy will be performed as a perfect test to reveal a true state of the patient. This

means that if a patient truly has cancer (true positive), the patient will be given a perfect treatment to cure the disease and exit the model. However if a patient has a false positive, the patient will returns to state 0 with probability of 1. If a screening mammogram results in normal (negative), both true negative and false negative, no further procedures will be conducted to reveal the true state of the patient and the patient will follow the probability transition into another state. Since over-diagnosis is presence in the study, the assumption that the same probability in state 1 and state 1' (or 1p) will be assume when a patient find out from screening result. The following are the example of probability when the result is abnormal (positive) for a patient between the ages 40 – 44 with an over-diagnosis rate of 30%:

$$a(\alpha) = \begin{pmatrix} 0.078156 & 0.75033 & 0.75033 & 0.81860 \end{pmatrix}$$

Appendix B represents the value of the transition probabilities as well as the probability when the screening result is abnormal according to the study of Maillart et al (2008).

3.3 Parameter Input

As mentioned previously, six states of cancer will be formulated in the model. This includes state 0, 1, 1p (or 1'), 2, 3, and 4. Furthermore, when we model a decision tree, an additional *exit state* will also be created. The *exit state* represents a situation when a patient truly has cancer and receives perfect treatment to cure the disease before receiving a lump sum QALYs (refer to Appendix C). This model does not take into consideration the treatment costs, hence, there are only two associated costs as shown in the example of the decision tree model in Appendix A – mammography screening cost and a perfect biopsy cost. According to MetroHealth.net, the average annual screening mammogram is approximately $212.90 and the average cost of a fine needle biopsy is approximately $1681.84 (2014).

The study also considers half cycle correction when calculating the intermediate QALY reward for each cycle. For example, in a case of a one year cycle, an individual would receive a QALY of 0.5 for

living half a year in a healthy state. However if an individual dies, he or she would receive QALY of 0.25 due to the assumption that the individual lived on average the midpoint of the interval (3 months). According to the study from Griffin and Zhang (2013), the formulation of intermediate QAYL reward with half year correction is 0.5*P (live through current period | current state is j)
+ 0.25*P (die in current period | current state is j).

Furthermore, there are three intermediate costs of QALY associated with the result for each mammogram screening. If mammogram result is a false positive, the intermediate cost of a QALY is 0.1538. If the mammogram result is a true positive, the intermediate cost of a QALY is 0.0769. If the mammogram result is either a true negative or a false negative, the intermediate cost of a QALY is 0.0027. These values were obtained from a study done by Ayer and Stout (2012) stating that the disutility for a false positive mammogram is four weeks, which yields 4/26 = 0.1538; for a true positive a mammogram is two weeks, which yields 2/26 = 0.0769; and for a negative mammogram is 0.5 days, which yield 0.5/365 = 0.0027.

3.4 Monte Carlo Simulation and CE Analysis

This thesis incorporates Monte Carlo Simulation with an additional cost effectiveness analysis. Random independent trials of 1000 simulations were conducted to determine stable average results for each screening scenario. This will result in both an estimate of the mean and variance for each scenario that will be used to determine the suggested policy for breast cancer screening. Sensitivity analysis of over-diagnosis rates between 0% and 50% will be conducted with a 10% interval. In addition, a starting age of 30 to 50 with a 5 years intervals and ending age of 100 will also be considered to determine the best policy in each circumstance.

Chapter 4

Results and Analysis

4.1 Introduction

This chapter will present the result after simulating the model using TreeAge Pro 2013. The results will be divided into six scenarios which represent different levels of over-diagnosis rate (%ODR). The sensitivity analysis includes the case of no over-diagnosis rate, 10% ODR, 20% ODR, 30% ODR, 40% ODR, and 50% ODR. Mean and variance of cost and quality adjusted life years will be presented for each scenario. Furthermore, the number of average screenings will also be presented.

4.2 Scope of Results

Due to the difficulty of determining the presence of the over-diagnosis rate in breast cancer screening, six scenarios of the over-diagnosis rate were considered. The results will be divided into 6 circumstances: no presence of over-diagnosis rate, 10% ODR, 20% ODR, 30% ODR, 40% ODR, and 50% ODR. Starting age begins at age 30 up to age 50 with an interval of five years and screening interval can range from annual screening to 5 year interval screening. For example, policy 35_2 represents a screening starting age 35 with biannual screening. Each circumstance will be compared using cost effectiveness analysis to determine the optimum policy in each circumstance.

4.3. Results on No Presence of Over-diagnosis Rate (0% ODR)

Table 2 indicates the mean value and 95% confident interval of cost and QALY of specific policies. It also displays the number of total screenings that a patient would receive. For instance, a screening cost for policy 35_4 is $3442.95 with confidence interval of 28.46. The same policy also yields QALY of 95.468558 with confidence interval of 0.505577 and total number of screenings of 16. In the case of no presence of over-diagnosis rate (0% ODR), policy 50_5, 50_4 and 35_4 dominates the other policies as appears in Tables 3 and 4.

The incremental cost effectiveness ratio (ICER) and average cost effectiveness (C/E) are also displayed in Tables 3 and 4. ICER is the ratio of mean incremental cost and mean incremental effectiveness that compares the strategy to the previous less costly strategy on the cost effectiveness frontier. Lower and positive ICERs correspond to better values (lower cost per unit of additional effectiveness). The C/E value indicates an average cost effectiveness, which is cost, divided by effectives for the strategy. For example, policy 45_5 has ICER = 220.48/ 0.011912 = 18508.60 with an average cost-effective of 24.36.

The three policies, policy 50_5, 50_4 and 35_4, form an efficient frontier (i.e., no other policy dominates them), which can be seen in Figure 5. Figure 6 displays error bars of policies that are close to efficient frontier, which confirm that policy 50_5, 50_4 and 35_4 dominate other policies.

4.3.1 Statistical Results

Table 2: Statistical Results in 0% ODR

0% ODR					
Policy	Cost	Cost CI	QALY	QALY CI	# Screening
30_1	12120.88	170.39	86.025880	0.733548	56
30_2	6732.79	69.26	91.060315	0.617793	31
30_3	4771.09	42.39	93.924976	0.562350	22
30_4	3664.52	26.98	94.414066	0.471966	17
30_5	2882.81	20.43	92.417270	0.434451	13
35_1	11194.28	165.23	86.668276	0.720124	52
35_2	6247.08	70.86	91.597578	0.620492	29
35_3	4373.54	40.06	93.226929	0.537362	20
35_4	3442.95	28.46	95.468558	0.505577	16
35_5	2671.74	20.04	92.394401	0.432581	12
40_1	10091.75	164.45	86.777514	0.693282	47
40_2	5695.69	68.25	91.420191	0.607520	27
40_3	3965.79	38.46	92.620660	0.509866	18
40_4	3062.54	24.29	93.222740	0.433050	14
40_5	2454.61	20.31	92.332933	0.427238	11
45_1	9131.34	156.14	87.084687	0.678055	42
45_2	5231.70	67.07	92.026750	0.605192	24
45_3	3738.42	38.72	94.450496	0.522003	17
45_4	2826.29	25.48	93.840730	0.450734	13
45_5	2249.05	20.64	92.320531	0.409401	10
50_1	8089.86	150.56	87.070357	0.672581	38
50_2	4653.82	63.05	91.602149	0.567835	22
50_3	3326.18	37.22	93.636383	0.506355	15
50_4	2596.27	26.54	94.459843	0.469256	12
50_5	2028.57	20.11	92.308619	0.404478	9

4.3.2 Cost Effectiveness Analysis

Table 3: Cost Effectiveness Analysis Excluding Dominated Strategies in 0% ODR

Excluding Dominated							
Policy	Cost	Incr Cost	Eff	Incr Eff	ICER	C/E	
50_5	2028.57	0.00	92.308619	0.000000	0.00	21.98	undominated
50_4	2596.27	567.70	94.459843	2.151224	263.90	27.49	undominated
35_4	3442.95	846.68	95.468558	1.008716	839.37	36.06	undominated

Table 4: Cost Effectiveness Analysis with All Strategies in 0% ODR

All Strategies							
Policy	Cost	Incr Cost	Eff	Incr Eff	ICER	C/E	
50_5	2028.57	0.00	92.308619	0.000000	0.00	21.98	undominated
45_5	2249.05	220.48	92.320531	0.011912	18508.60	24.36	ext. dominated
40_5	2454.61	205.56	92.332933	0.012402	16574.36	26.58	ext. dominated
50_4	2596.27	567.70	94.459843	2.151224	263.90	27.49	undominated
35_5	2671.74	75.47	92.394401	-2.065442	-36.54	28.92	abs. dominated
45_4	2826.29	230.02	93.840730	-0.619113	-371.53	30.12	abs. dominated
30_5	2882.81	286.54	92.417270	-2.042573	-140.29	31.19	abs. dominated
40_4	3062.54	466.27	93.222740	-1.237103	-376.91	32.85	abs. dominated
50_3	3326.18	729.91	93.636383	-0.823460	-886.39	35.52	abs. dominated
35_4	3442.95	846.68	95.468558	1.008716	839.37	36.06	undominated
30_4	3664.52	221.56	94.414066	-1.054493	-210.11	38.81	abs. dominated
45_3	3738.42	295.46	94.450496	-1.018063	-290.22	39.58	abs. dominated
40_3	3965.79	522.84	92.620660	-2.847898	-183.59	42.82	abs. dominated
35_3	4373.54	930.58	93.226929	-2.241629	-415.14	46.91	abs. dominated
50_2	4653.82	1210.87	91.602149	-3.866410	-313.18	50.80	abs. dominated
30_3	4771.09	1328.13	93.924976	-1.543583	-860.42	50.80	abs. dominated
45_2	5231.70	1788.74	92.026749	-3.441809	-519.71	56.85	abs. dominated
40_2	5695.69	2252.74	91.420191	-4.048368	-556.46	62.30	abs. dominated
35_2	6247.08	2804.13	91.597578	-3.870980	-724.40	68.20	abs. dominated
30_2	6732.79	3289.84	91.060315	-4.408244	-746.29	73.94	abs. dominated
50_1	8089.86	4646.90	87.070357	-8.398201	-553.32	92.91	abs. dominated
45_1	9131.34	5688.39	87.084687	-8.383871	-678.49	104.86	abs. dominated
40_1	10091.75	6648.80	86.777514	-8.691045	-765.02	116.29	abs. dominated
35_1	11194.28	7751.32	86.668276	-8.800282	-880.80	129.16	abs. dominated
30_1	12120.88	8677.93	86.025880	-9.442678	-919.01	140.90	abs. dominated

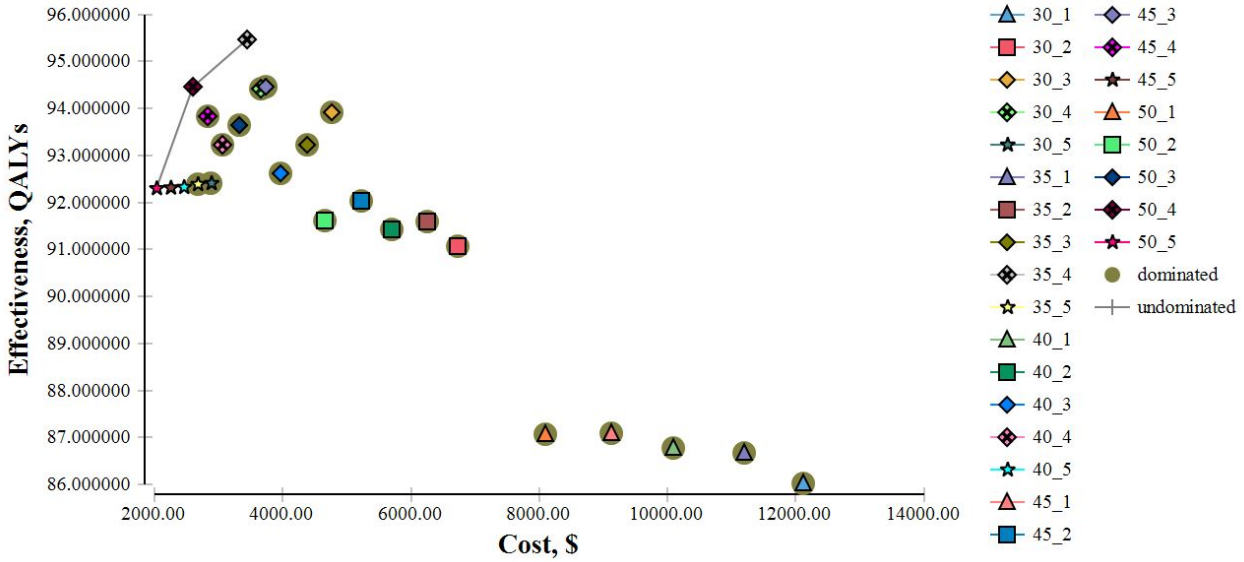


Figure 6: Cost Effectiveness Analysis in 0% ODR without Variance

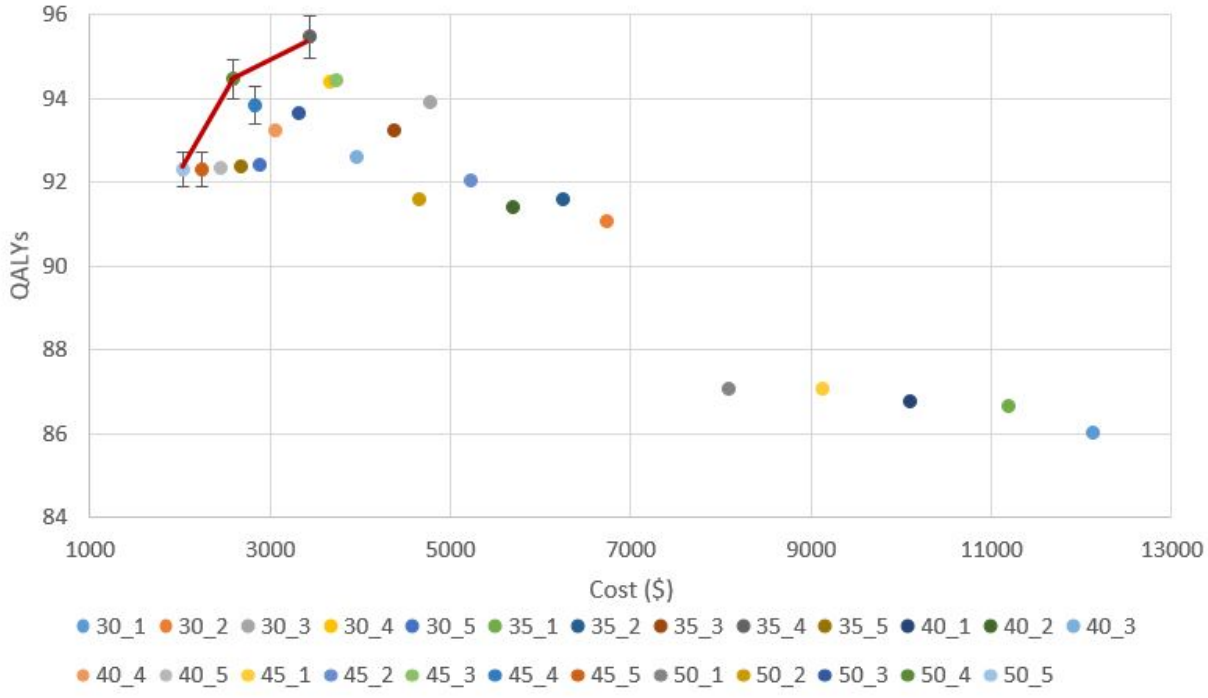


Figure 7: Cost Effectiveness Analysis in 0% ODR with Variance

4.4 Results on 10% Over-diagnosis Rate (10% ODR)

In the presence of 10% over-diagnosis rate, policy 50_5, 50_4 and 35_4 are the dominant policies. Table 5 represents the statistical results for each policy. Table 6 and Table 7 indicate the cost effectiveness analysis by showing the dominance of each policy whereas Figure 8 and Figure 9 represent the graphical version of cost effectiveness analysis.

4.4.1 Statistical Results

Table 5: Statistical Results in 10% ODR

	Cost	Cost CI	QAYL	QALY CI	# Screening
30_1	12059.57	166.41	85.845611	0.710161	56
30_2	6750.95	67.50	91.108540	0.600269	31
30_3	4789.59	40.48	93.970046	0.533008	22
30_4	3673.18	23.58	94.708219	0.416935	17
30_5	2898.12	17.17	92.590155	0.348062	13
35_1	11050.82	162.70	86.190390	0.690033	51
35_2	6286.53	69.13	91.801061	0.613591	29
35_3	4391.02	37.33	93.390756	0.479896	20
35_4	3447.55	24.63	95.391573	0.437140	16
35_5	2680.84	18.18	92.553716	0.378891	12
40_1	9982.39	159.35	86.117176	0.689413	46
40_2	5702.52	64.19	91.407000	0.567350	26
40_3	3978.25	35.06	92.784391	0.459370	18
40_4	3072.27	22.72	93.320086	0.384543	14
40_5	2463.76	18.91	92.552726	0.395851	11
45_1	9003.24	152.93	86.505465	0.664852	42
45_2	5213.51	63.71	91.748091	0.564638	24
45_3	3740.67	36.71	94.439784	0.499682	17
45_4	2825.20	24.75	93.802340	0.427164	13
45_5	2259.31	19.80	92.585023	0.382847	10
50_1	8084.92	146.48	87.041307	0.649095	37
50_2	4691.78	60.44	91.798773	0.534909	22
50_3	3324.13	35.64	93.614905	0.479679	15
50_4	2612.09	24.82	94.783841	0.430136	12
50_5	2049.40	19.01	92.680545	0.364895	9

4.4.2 Cost Effectiveness Analysis

Table 6: Cost Effectiveness Analysis Excluding Dominated Strategies in 10% ODR

Excluding Dominated							
Strategy	**Cost**	**Incr Cost**	**Eff**	**Incr Eff**	**ICER**	**C/E**	
50_5	2049.40	0.00	92.680545	0.000000	0.00	22.11	undominated
50_4	2612.09	562.69	94.783841	2.103295	267.53	27.56	undominated
35_4	3447.55	835.46	95.391573	0.607733	1374.72	35.14	undominated

Table 7: Cost Effectiveness Analysis with All Strategies in 10% ODR

All Strategies							
Strategy	**Cost**	**Incr Cost**	**Eff**	**Incr Eff**	**ICER**	**C/E**	
50_5	2049.40	0.00	92.680545	0.000000	0.00	22.11	undominated
45_5	2259.31	209.92	92.585023	-0.095522	-2197.59	24.40	abs. dominated
40_5	2463.76	414.37	92.552726	-0.127819	-3241.83	26.62	abs. dominated
50_4	2612.09	562.69	94.783841	2.103295	267.53	27.56	undominated
35_5	2680.84	68.75	92.553716	-2.230124	-30.83	28.97	abs. dominated
45_4	2825.20	213.11	93.802340	-0.981501	-217.13	30.12	abs. dominated
30_5	2898.12	286.03	92.590155	-2.193686	-130.39	31.30	abs. dominated
40_4	3072.27	460.18	93.320086	-1.463755	-314.39	32.92	abs. dominated
50_3	3324.13	712.04	93.614905	-1.168936	-609.14	35.51	abs. dominated
35_4	3447.55	835.46	95.391573	0.607733	1374.72	35.14	undominated
30_4	3673.18	225.63	94.708219	-0.683354	-330.18	38.78	abs. dominated
45_3	3740.67	293.12	94.439784	-0.951789	-307.97	39.61	abs. dominated
40_3	3978.25	530.70	92.784391	-2.607182	-203.55	42.88	abs. dominated
35_3	4391.02	943.47	93.390756	-2.000817	-471.54	47.02	abs. dominated
50_2	4691.78	1244.23	91.798773	-3.592800	-346.31	51.11	abs. dominated
30_3	4789.59	1342.04	93.970046	-1.421527	-944.08	50.97	abs. dominated
45_2	5213.51	1765.96	91.748091	-3.643482	-484.69	56.82	abs. dominated
40_2	5702.52	2254.97	91.407000	-3.984573	-565.93	62.39	abs. dominated
35_2	6286.53	2838.98	91.801061	-3.590513	-790.69	68.48	abs. dominated
30_2	6750.95	3303.40	91.108540	-4.283033	-771.28	74.10	abs. dominated
50_1	8084.92	4637.36	87.041307	-8.350266	-555.36	92.89	abs. dominated
45_1	9003.24	5555.69	86.505465	-8.886108	-625.21	104.08	abs. dominated
40_1	9982.39	6534.83	86.117176	-9.274397	-704.61	115.92	abs. dominated
35_1	11050.82	7603.27	86.190390	-9.201183	-826.34	128.21	abs. dominated
30_1	12059.57	8612.01	85.845611	-9.545962	-902.16	140.48	abs. dominated

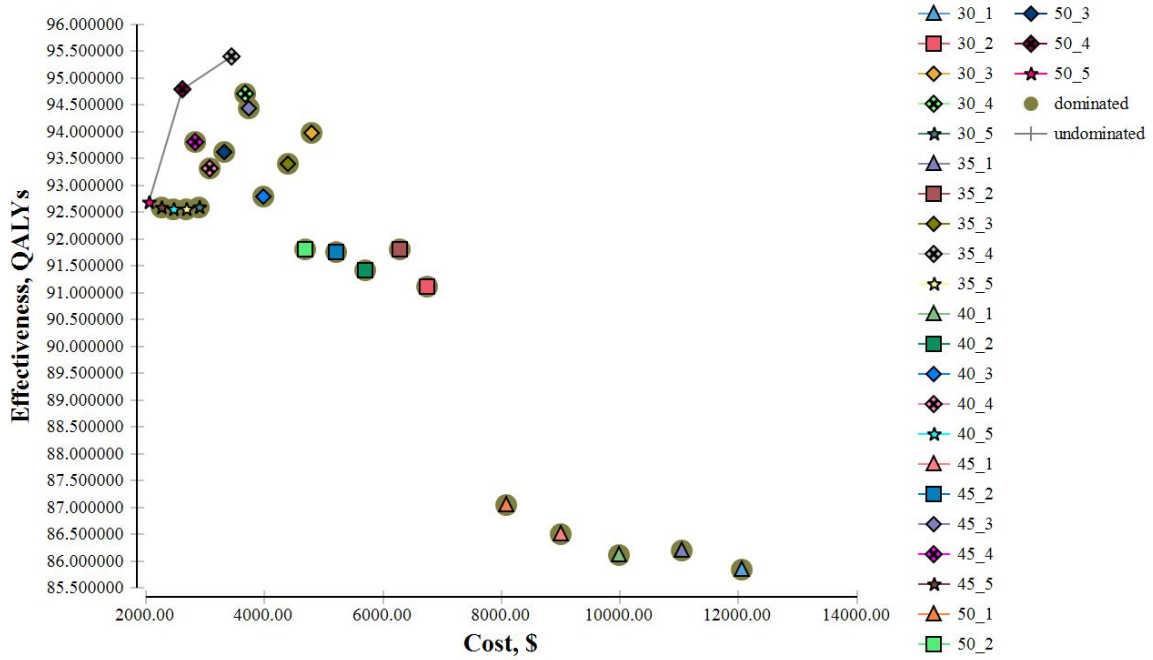


Figure 8: Cost Effectiveness Analysis in 10% ODR

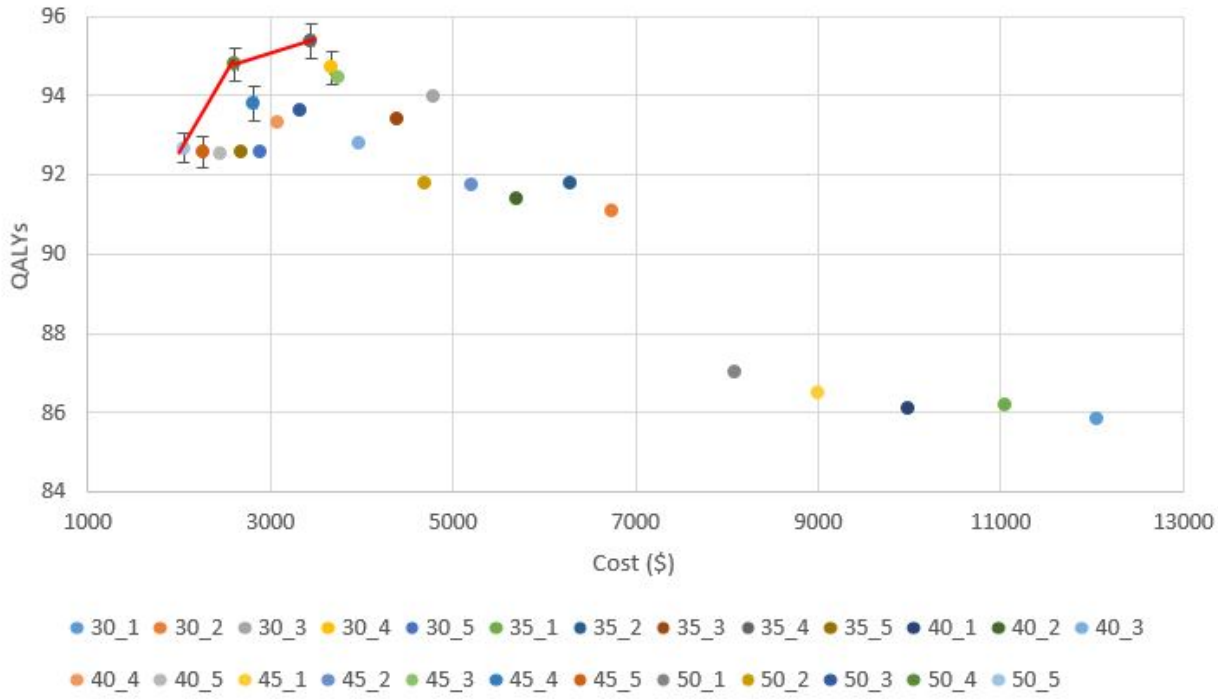


Figure 9: Cost Effectiveness Analysis in 10% ODR with Variance Close to Efficient Frontier

4.5 Results on 20% Over-diagnosis Rate (20% ODR)

In the presence of 20% over-diagnosis rate, policy 50_5, 50_4 and 35_4 are the dominant policies. Table 8 represents the statistical results for each policy. Table 9 and Table 10 indicate the cost effectiveness analysis by showing the dominance of each policy whereas Figure 10 and Figure 11 represent the graphical version of cost effectiveness analysis.

4.5.1 Statistical Results

Table 8: Statistical Results in 20% ODR

	Cost	Cost CI	QAYL	QALY CI	# Screening
30_1	12140.11	165.46	86.139216	0.722671	56
30_2	6722.42	69.98	90.847609	0.629735	31
30_3	4761.78	41.81	93.762889	0.564535	22
30_4	3650.11	27.29	94.191037	0.469892	17
30_5	2880.20	19.39	92.362547	0.416323	13
35_1	11001.69	164.53	86.125974	0.696506	51
35_2	6187.62	70.59	90.929252	0.629504	29
35_3	4368.64	39.15	93.210497	0.517484	20
35_4	3429.39	27.15	94.982738	0.476713	16
35_5	2673.28	20.05	92.296814	0.415325	12
40_1	10042.81	158.67	86.251565	0.703193	47
40_2	5636.65	67.04	90.845036	0.592999	26
40_3	3968.43	37.63	92.503360	0.492785	18
40_4	3050.15	24.82	93.017786	0.441600	14
40_5	2457.65	22.26	92.157695	0.443924	11
45_1	9001.53	154.20	86.724790	0.658713	42
45_2	5178.32	66.26	91.526229	0.592432	24
45_3	3698.39	40.23	93.749384	0.538924	17
45_4	2808.11	26.77	93.435673	0.469388	13
45_5	2237.28	21.14	92.283083	0.423829	10
50_1	8013.98	148.12	86.837776	0.652473	37
50_2	4676.56	61.65	91.741257	0.552235	22
50_3	3291.47	37.94	93.155953	0.513584	15
50_4	2591.80	27.54	94.334945	0.468152	12
50_5	2037.18	19.29	92.613015	0.388422	9

4.5.2 Cost Effectiveness Analysis

Table 9: Cost Effectiveness Analysis Excluding Dominated Strategies in 20% ODR

Excluding Dominated							
Strategy	**Cost**	**Incr Cost**	**Eff**	**Incr Eff**	**ICER**	**C/E**	
50_5	2037.18	0.00	92.613015	0.000000	0.00	22.00	undominated
50_4	2591.80	554.63	94.334945	1.721929	322.10	27.47	undominated
35_4	3429.39	837.59	94.982738	0.647793	1292.99	36.11	undominated

Table 10: Cost Effectiveness Analysis with All Strategies in 20% ODR

All Strategies							
Strategy	**Cost**	**Incr Cost**	**Eff**	**Incr Eff**	**ICER**	**C/E**	
50_5	2037.18	0.00	92.613015	0.000000	0.00	22.00	undominated
45_5	2237.28	200.10	92.283083	-0.329932	-606.50	24.24	abs. dominated
40_5	2457.65	420.48	92.157695	-0.455320	-923.48	26.67	abs. dominated
50_4	2591.80	554.63	94.334945	1.721929	322.10	27.47	undominated
35_5	2673.28	81.48	92.296814	-2.038131	-39.98	28.96	abs. dominated
45_4	2808.11	216.31	93.435673	-0.899272	-240.54	30.05	abs. dominated
30_5	2880.20	288.39	92.362547	-1.972398	-146.22	31.18	abs. dominated
40_4	3050.15	458.35	93.017786	-1.317159	-347.99	32.79	abs. dominated
50_3	3291.47	699.67	93.155953	-1.178992	-593.45	35.33	abs. dominated
35_4	3429.39	837.59	94.982738	0.647793	1292.99	36.11	undominated
30_4	3650.11	220.71	94.191037	-0.791700	-278.78	38.75	abs. dominated
45_3	3698.39	269.00	93.749384	-1.233354	-218.10	39.45	abs. dominated
40_3	3968.43	539.04	92.503360	-2.479378	-217.41	42.90	abs. dominated
35_3	4368.64	939.25	93.210497	-1.772241	-529.98	46.87	abs. dominated
50_2	4676.56	1247.17	91.741257	-3.241480	-384.75	50.98	abs. dominated
30_3	4761.78	1332.39	93.762889	-1.219849	-1092.26	50.79	abs. dominated
45_2	5178.32	1748.93	91.526229	-3.456508	-505.98	56.58	abs. dominated
40_2	5636.65	2207.26	90.845036	-4.137701	-533.45	62.05	abs. dominated
35_2	6187.62	2758.22	90.929252	-4.053486	-680.46	68.05	abs. dominated
30_2	6722.42	3293.03	90.847609	-4.135128	-796.35	74.00	abs. dominated
50_1	8013.98	4584.59	86.837776	-8.144962	-562.87	92.29	abs. dominated
45_1	9001.53	5572.14	86.724790	-8.257948	-674.76	103.79	abs. dominated
40_1	10042.81	6613.42	86.251565	-8.731172	-757.45	116.44	abs. dominated
35_1	11001.69	7572.29	86.125974	-8.856763	-854.97	127.74	abs. dominated
30_1	12140.11	8710.71	86.139216	-8.843521	-984.98	140.94	abs. dominated

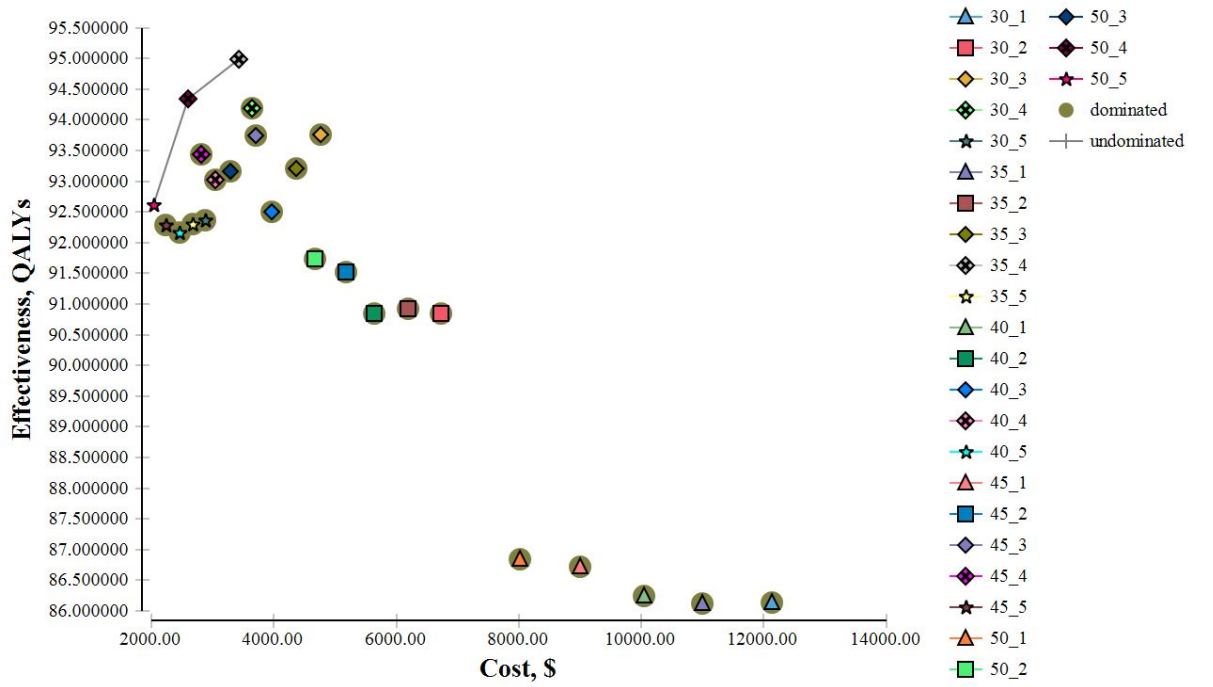


Figure 10: Cost Effectivenss Analysis in 20% ODR

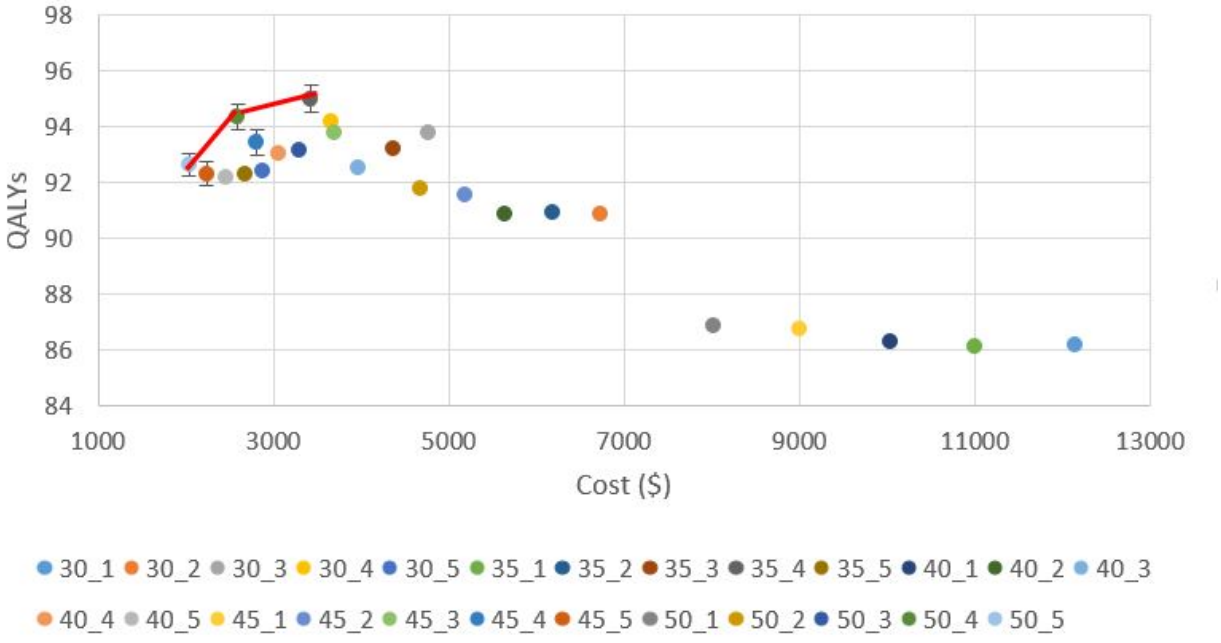


Figure 11: Cost Effectiveness Analysis in 20% ODR with Variance Close to Efficient Frontier

4.6 Results on 30% Over-diagnosis Rate (30% ODR)

In the presence of 30% over-diagnosis rate, policy 50_5, 50_4 and 35_4 are the dominant policies. Table 11 represents the statistical results for each policy. Table 12 and Table 13 cost effectiveness analysis by showing the dominance of each policy whereas Figure 12 and Figure 13 represent the graphical version of cost effectiveness analysis.

4.6.1 Statistical Results

Table 11: Statistical Results in 30% ODR

	Cost	Cost CI	QAYL	QALY CI	# Screening
30_1	12346.32	155.26	86.979689	0.671108	57
30_2	6764.15	65.11	91.246639	0.580671	31
30_3	4777.81	39.48	94.075305	0.536491	22
30_4	3665.41	26.62	94.417478	0.460890	17
30_5	2886.41	19.24	92.513414	0.405322	13
35_1	11323.49	151.37	87.253398	0.655141	53
35_2	6260.53	66.33	91.599654	0.588732	29
35_3	4373.73	37.48	93.387219	0.503797	20
35_4	3442.12	27.20	95.296807	0.469907	16
35_5	2673.49	17.93	92.541763	0.390461	12
40_1	10196.33	149.44	87.112013	0.638720	47
40_2	5678.27	64.11	91.209934	0.569102	26
40_3	3967.60	35.66	92.605965	0.475993	18
40_4	3072.87	24.85	93.253425	0.408398	14
40_5	2458.08	19.35	92.486583	0.400508	11
45_1	9182.31	146.25	87.383778	0.630335	43
45_2	5242.30	63.56	92.076083	0.571868	24
45_3	3728.18	37.98	94.281197	0.508629	17
45_4	2821.48	24.93	93.835253	0.431367	13
45_5	2258.55	19.13	92.687817	0.372842	10
50_1	8166.73	141.96	87.533344	0.624023	38
50_2	4653.82	60.15	91.600420	0.543309	22
50_3	3336.23	35.96	93.717165	0.471544	15
50_4	2601.53	24.29	94.701994	0.426521	12
50_5	2035.86	17.34	92.568784	0.356198	9

4.6.2 Cost Effectiveness Analysis

Table 12: Cost Effectiveness Analysis Excluding Dominated Strategies in 30% ODR

Excluding Dominated							
Strategy	**Cost**	**Incr Cost**	**Eff**	**Incr Eff**	**ICER**	**C/E**	
50_5	2035.86	0.00	92.568784	0.000000	0.00	21.99	undominated
50_4	2601.53	565.68	94.701994	2.133210	265.18	27.47	undominated
35_4	3442.12	840.59	95.296807	0.594813	1413.21	36.12	undominated

Table 13: Cost Effectiveness Analysis with All Strategies in 30% ODR

All Strategies							
Strategy	**Cost**	**Incr Cost**	**Eff**	**Incr Eff**	**ICER**	**C/E**	
50_5	2035.86	0.00	92.568784	0.000000	0.00	21.99	undominated
45_5	2258.55	222.69	92.687817	0.119032	1870.86	24.37	ext. dominated
40_5	2458.08	199.53	92.486583	-0.201234	-991.53	26.58	abs. dominated
50_4	2601.53	565.68	94.701994	2.133210	265.18	27.47	undominated
35_5	2673.49	71.96	92.541763	-2.160231	-33.31	28.89	abs. dominated
45_4	2821.48	219.95	93.835253	-0.866741	-253.76	30.07	abs. dominated
30_5	2886.41	284.88	92.513414	-2.188580	-130.17	31.20	abs. dominated
40_4	3072.87	471.34	93.253425	-1.448569	-325.38	32.95	abs. dominated
50_3	3336.23	734.70	93.717165	-0.984828	-746.01	35.60	abs. dominated
35_4	3442.12	840.59	95.296807	0.594813	1413.21	36.12	undominated
30_4	3665.41	223.29	94.417478	-0.879329	-253.93	38.82	abs. dominated
45_3	3728.18	286.05	94.281197	-1.015610	-281.66	39.54	abs. dominated
40_3	3967.60	525.48	92.605965	-2.690842	-195.28	42.84	abs. dominated
35_3	4373.73	931.61	93.387219	-1.909587	-487.86	46.83	abs. dominated
50_2	4653.82	1211.70	91.600420	-3.696386	-327.81	50.81	abs. dominated
30_3	4777.81	1335.69	94.075305	-1.221502	-1093.48	50.79	abs. dominated
45_2	5242.30	1800.17	92.076083	-3.220724	-558.93	56.93	abs. dominated
40_2	5678.27	2236.15	91.209934	-4.086873	-547.15	62.26	abs. dominated
35_2	6260.53	2818.41	91.599654	-3.697153	-762.32	68.35	abs. dominated
30_2	6764.15	3322.03	91.246639	-4.050168	-820.22	74.13	abs. dominated
50_1	8166.73	4724.61	87.533344	-7.763462	-608.57	93.30	abs. dominated
45_1	9182.31	5740.18	87.383778	-7.913028	-725.41	105.08	abs. dominated
40_1	10196.33	6754.21	87.112013	-8.184794	-825.21	117.05	abs. dominated
35_1	11323.49	7881.36	87.253398	-8.043408	-979.85	129.78	abs. dominated
30_1	12346.32	8904.20	86.979689	-8.317118	-1070.59	141.94	abs. dominated

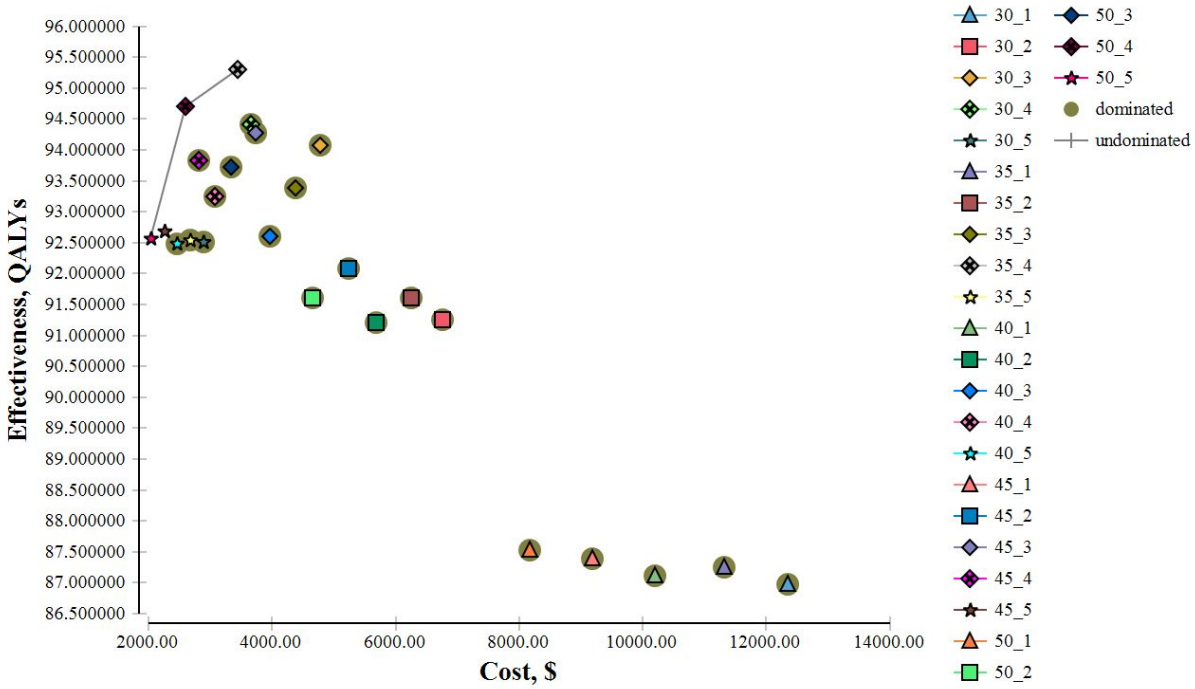


Figure 12: Cost Effectiveness Analysis in 30% ODR

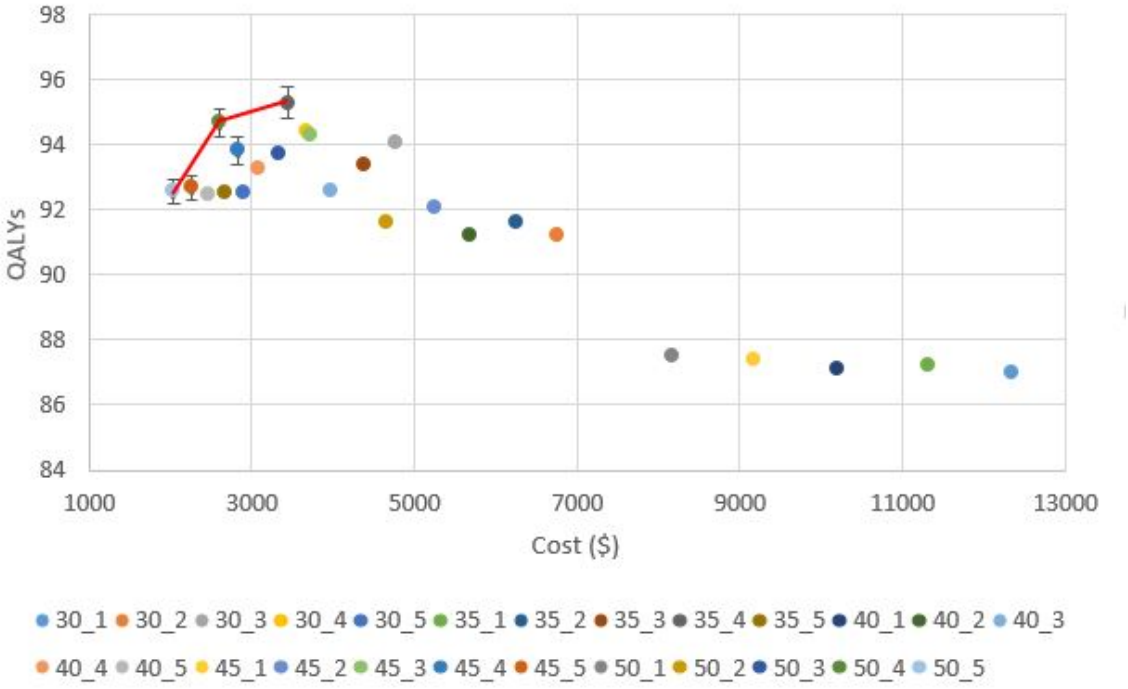


Figure 13: Cost Effectiveness Analysis in 30% ODR with Variance Close to Efficient Frontier

4.7 Results on 40% Over-diagnosis Rate (40% ODR)

In the presence of 40% over-diagnosis rate, policy 50_5, 50_4 and 35_4 are the dominant policies. Table 14 represents the statistical results for each policy. Table 15 and Table 16 cost effectiveness analysis by showing the dominance of each policy whereas Figure 14 and Figure 15 represent the graphical version of cost effectiveness analysis.

4.7.1 Statistical Results

Table 14: Statistical Results in 40% ODR

	Cost	Cost CI	QALY	QALY CI	# Screening
30_1	12032.04	164.59	85.862648	0.702237	56
30_2	6776.20	66.25	91.411682	0.595338	31
30_3	4787.48	39.74	94.141179	0.535752	22
30_4	3664.77	27.13	94.420779	0.470716	17
30_5	2871.51	19.78	92.213846	0.421338	13
35_1	11033.47	162.16	85.947025	0.713158	51
35_2	6259.36	69.11	91.609854	0.621278	29
35_3	4389.29	38.71	93.442751	0.515630	20
35_4	3448.66	27.71	95.139310	0.489073	16
35_5	2667.66	19.32	92.275856	0.408245	12
40_1	10079.53	154.77	86.504248	0.679293	47
40_2	5694.86	63.90	91.342302	0.569128	26
40_3	3981.99	35.87	92.755430	0.481486	18
40_4	3048.49	25.87	92.920754	0.438402	14
40_5	2460.27	21.03	92.287555	0.414297	11
45_1	9075.18	149.40	86.835051	0.654200	42
45_2	5207.40	64.92	91.755829	0.581331	24
45_3	3720.74	39.20	94.060808	0.530607	17
45_4	2807.34	26.13	93.482301	0.452292	13
45_5	2251.03	19.70	92.455657	0.383357	10
50_1	8068.56	144.37	87.280314	0.625380	37
50_2	4685.61	60.28	91.816713	0.543443	22
50_3	3316.51	37.59	93.512884	0.499576	15
50_4	2603.49	25.82	94.516850	0.439194	12
50_5	2033.39	17.39	92.616082	0.356945	9

4.7.2 Cost Effectiveness Analysis

Table 15: Cost Effectiveness Analysis Excluding Dominated Strategies in 40% ODR

Excluding Dominated							
Strategy	**Cost**	**Incr Cost**	**Eff**	**Incr Eff**	**ICER**	**C/E**	
50_5	2033.39	0.00	92.616082	0.000000	0.00	21.95	undominated
50_4	2603.49	570.10	94.516850	1.900768	299.93	27.55	undominated
35_4	3448.66	845.17	95.139310	0.622460	1357.79	36.25	undominated

Table 16: Cost Effectiveness Analysis with All Strategies in 40% ODR

All Strategies							
Strategy	**Cost**	**Incr Cost**	**Eff**	**Incr Eff**	**ICER**	**C/E**	
50_5	2033.39	0.00	92.616082	0.000000	0.00	21.95	undominated
45_5	2251.03	217.65	92.455657	-0.160426	-1356.69	24.35	abs. dominated
40_5	2460.27	426.89	92.287555	-0.328527	-1299.39	26.66	abs. dominated
50_4	2603.49	570.10	94.516850	1.900768	299.93	27.55	undominated
35_5	2667.66	64.17	92.275856	-2.240994	-28.63	28.91	abs. dominated
45_4	2807.34	203.85	93.482301	-1.034549	-197.04	30.03	abs. dominated
30_5	2871.51	268.02	92.213846	-2.303004	-116.38	31.14	abs. dominated
40_4	3048.49	445.00	92.920754	-1.596096	-278.81	32.81	abs. dominated
50_3	3316.51	713.02	93.512884	-1.003966	-710.21	35.47	abs. dominated
35_4	3448.66	845.17	95.139310	0.622460	1357.79	36.25	undominated
30_4	3664.77	216.12	94.420779	-0.718531	-300.77	38.81	abs. dominated
45_3	3720.74	272.09	94.060808	-1.078502	-252.28	39.56	abs. dominated
40_3	3981.99	533.34	92.755430	-2.383880	-223.73	42.93	abs. dominated
35_3	4389.29	940.63	93.442751	-1.696559	-554.44	46.97	abs. dominated
50_2	4685.61	1236.95	91.816713	-3.322597	-372.28	51.03	abs. dominated
30_3	4787.48	1338.82	94.141179	-0.998131	-1341.33	50.85	abs. dominated
45_2	5207.40	1758.74	91.755829	-3.383481	-519.80	56.75	abs. dominated
40_2	5694.86	2246.20	91.342302	-3.797008	-591.57	62.35	abs. dominated
35_2	6259.36	2810.71	91.609854	-3.529456	-796.36	68.33	abs. dominated
30_2	6776.20	3327.54	91.411682	-3.727628	-892.67	74.13	abs. dominated
50_1	8068.56	4619.91	87.280314	-7.858996	-587.85	92.44	abs. dominated
45_1	9075.18	5626.52	86.835051	-8.304259	-677.55	104.51	abs. dominated
40_1	10079.53	6630.87	86.504248	-8.635062	-767.90	116.52	abs. dominated
35_1	11033.47	7584.82	85.947025	-9.192285	-825.13	128.38	abs. dominated
30_1	12032.04	8583.38	85.862648	-9.276662	-925.27	140.13	abs. dominated

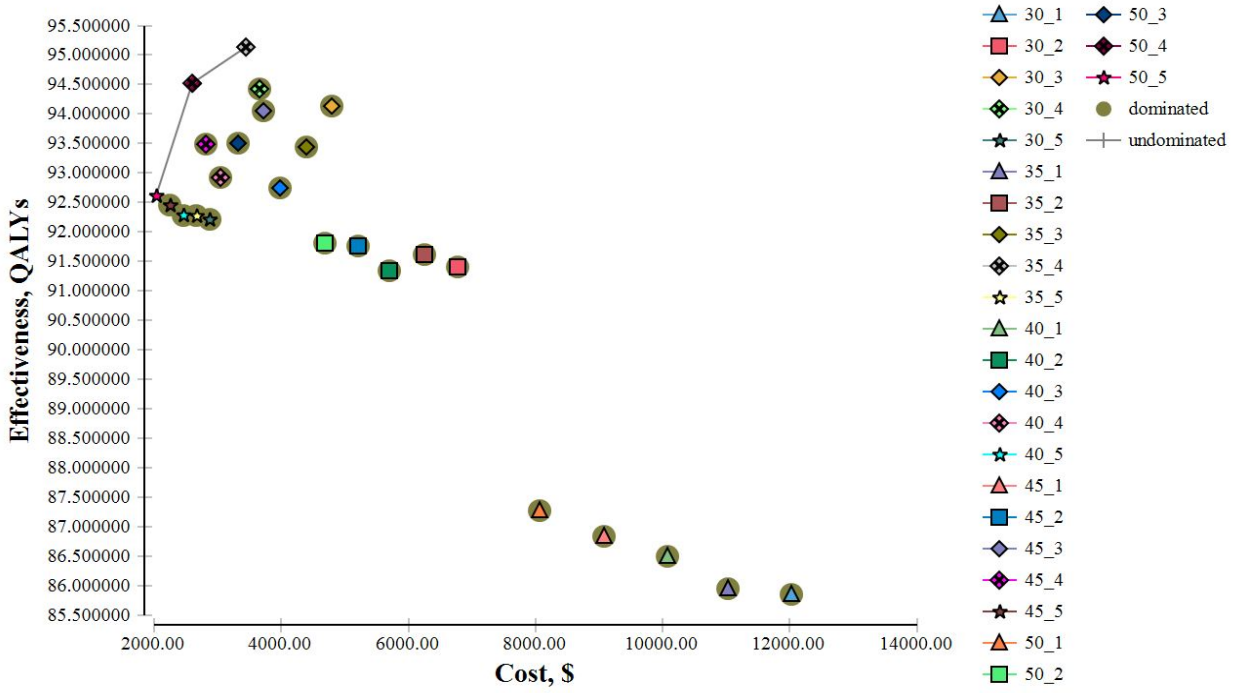


Figure 14: Cost Effectiveness analysis in 40% ODR

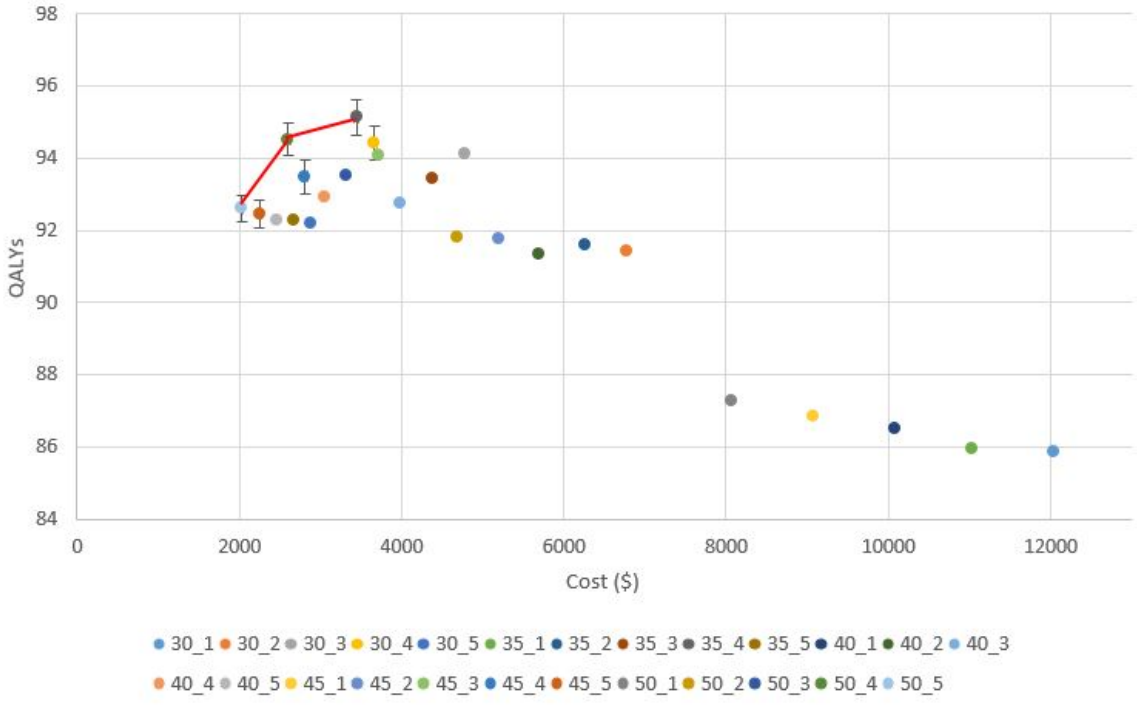


Figure 15: Cost Effectiveness Analysis in 40% ODR with Variance Close to Efficient Frontier

4.8 Results on 50% Over-diagnosis Rate (50% ODR)

In the presence of 50% over-diagnosis rate, policy 50_5, 50_4 and 35_4 are the dominant policies. Table 17 represents the statistical results for each policy. Table 18 and Table 19 cost effectiveness analysis by showing the dominance of each policy whereas Figure 16 and Figure 17 represent the graphical version of cost effectiveness analysis.

4.8.1 Statistical Results

Table 17: Statistical Results in 50% ODR

50% ODR					
	Cost	Cost CI	QAYL	QAYL CI	# Screening
30_1	12020.31	178.75	85.607068	0.774183	56
30_2	6731.30	73.09	90.992500	0.649535	31
30_3	4766.68	42.79	93.746182	0.577035	22
30_4	3659.49	28.81	94.328913	0.495690	17
30_5	2891.65	19.63	92.569163	0.418536	13
35_1	11066.45	172.09	85.932666	0.764858	51
35_2	6235.94	73.90	91.349637	0.658815	29
35_3	4350.95	43.08	93.066220	0.567204	20
35_4	3428.92	29.57	95.100325	0.512950	16
35_5	2681.41	21.05	92.427939	0.430463	12
40_1	10026.97	166.72	86.339646	0.720798	47
40_2	5675.53	68.72	91.148732	0.606435	26
40_3	3950.49	39.39	92.461662	0.522811	18
40_4	3056.37	24.75	93.142337	0.436714	14
40_5	2452.67	21.44	92.248979	0.440077	11
45_1	9063.94	158.49	86.741278	0.696052	42
45_2	5164.38	70.96	91.401255	0.633624	24
45_3	3716.55	41.05	94.042427	0.545267	17
45_4	2820.41	27.67	93.584899	0.474089	13
45_5	2242.54	21.01	92.304089	0.426645	10
50_1	8045.10	150.76	86.948370	0.666937	37
50_2	4661.00	65.17	91.619483	0.585406	22
50_3	3308.34	38.49	93.383441	0.517523	15
50_4	2593.14	27.56	94.439811	0.477440	12
50_5	2029.26	21.26	92.329509	0.418114	9

4.8.2 Cost Effectiveness Analysis

Table 18: Cost Effectiveness Analysis Excluding Dominated Strategies in 50% ODR

Excluding Dominated							
Strategy	**Cost**	**Incr Cost**	**Eff**	**Incr Eff**	**ICER**	**C/E**	
50_5	2,029.26	0.00	92.329509	0.000000	0.00	21.98	undominated
50_4	2,593.14	563.89	94.439811	2.110302	267.21	27.46	undominated
35_4	3,428.92	835.78	95.100325	0.660514	1,265.35	36.06	undominated

Table 19: Cost Effectiveness Analysis with All Strategies in 50% ODR

All Strategies							
Strategy	**Cost**	**Incr Cost**	**Eff**	**Incr Eff**	**ICER**	**C/E**	
50_5	2,029.26	0.00	92.329509	0.000000	0.00	21.98	undominated
45_5	2,242.54	213.28	92.304089	-0.025420	-8,390.41	24.30	abs. dominated
40_5	2,452.67	423.42	92.248979	-0.080530	-5,257.88	26.59	abs. dominated
50_4	2,593.14	563.89	94.439811	2.110302	267.21	27.46	undominated
35_5	2,681.41	88.27	92.427939	-2.011871	-43.87	29.01	abs. dominated
45_4	2,820.41	227.27	93.584899	-0.854912	-265.84	30.14	abs. dominated
30_5	2,891.65	298.51	92.569163	-1.870648	-159.57	31.24	abs. dominated
40_4	3,056.37	463.23	93.142337	-1.297474	-357.02	32.81	abs. dominated
50_3	3,308.34	715.19	93.383441	-1.056370	-677.03	35.43	abs. dominated
35_4	3,428.92	835.78	95.100325	0.660514	1,265.35	36.06	undominated
30_4	3,659.49	230.57	94.328913	-0.771412	-298.89	38.80	abs. dominated
45_3	3,716.55	287.63	94.042427	-1.057898	-271.89	39.52	abs. dominated
40_3	3,950.49	521.56	92.461662	-2.638663	-197.66	42.73	abs. dominated
35_3	4,350.95	922.03	93.066220	-2.034105	-453.28	46.75	abs. dominated
50_2	4,661.00	1,232.07	91.619483	-3.480841	-353.96	50.87	abs. dominated
30_3	4,766.68	1,337.76	93.746182	-1.354143	-987.90	50.85	abs. dominated
45_2	5,164.38	1,735.45	91.401255	-3.699070	-469.16	56.50	abs. dominated
40_2	5,675.53	2,246.60	91.148732	-3.951593	-568.53	62.27	abs. dominated
35_2	6,235.94	2,807.02	91.349637	-3.750688	-748.40	68.26	abs. dominated
30_2	6,731.30	3,302.38	90.992500	-4.107825	-803.92	73.98	abs. dominated
50_1	8,045.10	4,616.18	86.948370	-8.151955	-566.27	92.53	abs. dominated
45_1	9,063.94	5,635.01	86.741278	-8.359047	-674.12	104.49	abs. dominated
40_1	10,026.97	6,598.04	86.339646	-8.760679	-753.14	116.13	abs. dominated
35_1	11,066.45	7,637.53	85.932666	-9.167659	-833.09	128.78	abs. dominated
30_1	12,020.31	8,591.38	85.607068	-9.493257	-905.00	140.41	abs. dominated

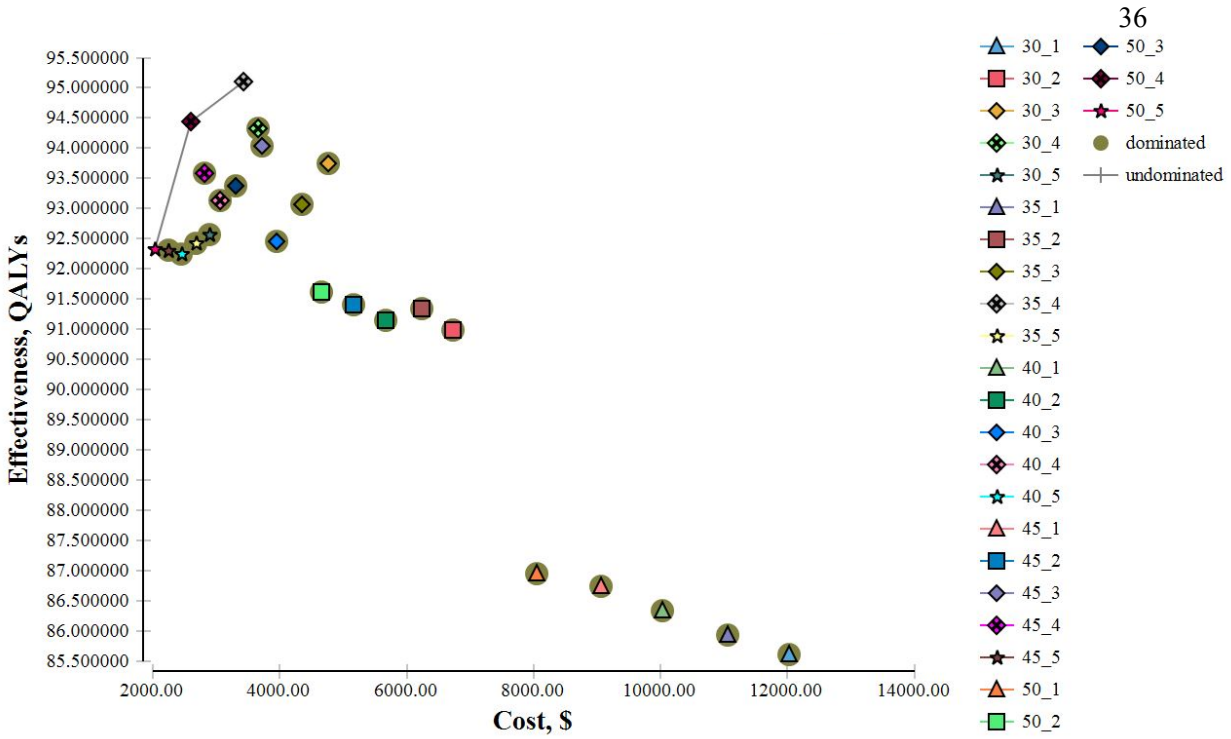


Figure 16: Cost Effectiveness Analysis in 50% ODR

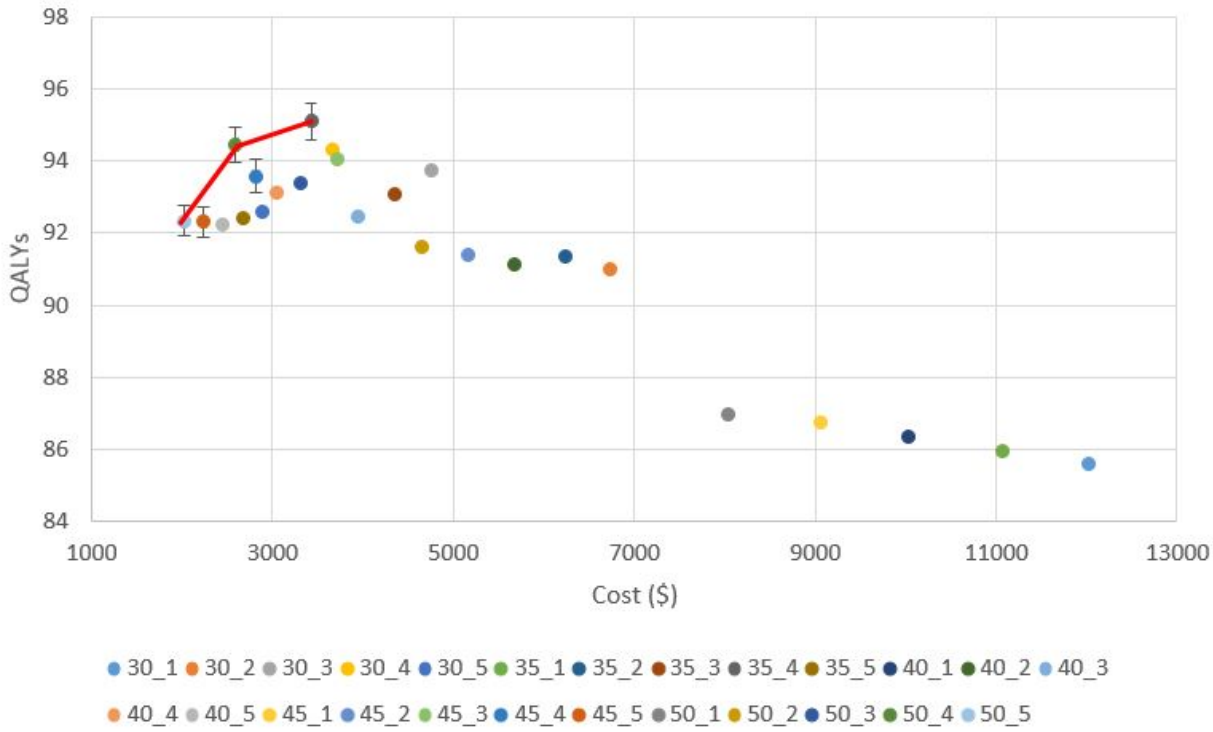


Figure 17: Cost Effectiveness Analysis in 50% ODR with Variance Close to Efficient Frontier

Chapter 5

Summary, Conclusions, and Further Research

5.1 Summary and Conclusions

Although the research has taken into consideration the variance, the study found that the presence of over-diagnosis rate does not affect the suggested policy for breast cancer screening based on it. The case of no presence of over-diagnosis rate (0% ODR), 10% ODR, 20% ODR, 30% ODR, 40% ODR and 50 % ODR suggested three optimal policies which are starting screening age 35 with a 4 year screening interval, starting screening age 50 with 4 years screening interval, or starting screening age 50 with 5 years screening interval. Table 20 shows the details for each suggested policy under the six different scenarios of the presence of over-diagnosis rate.

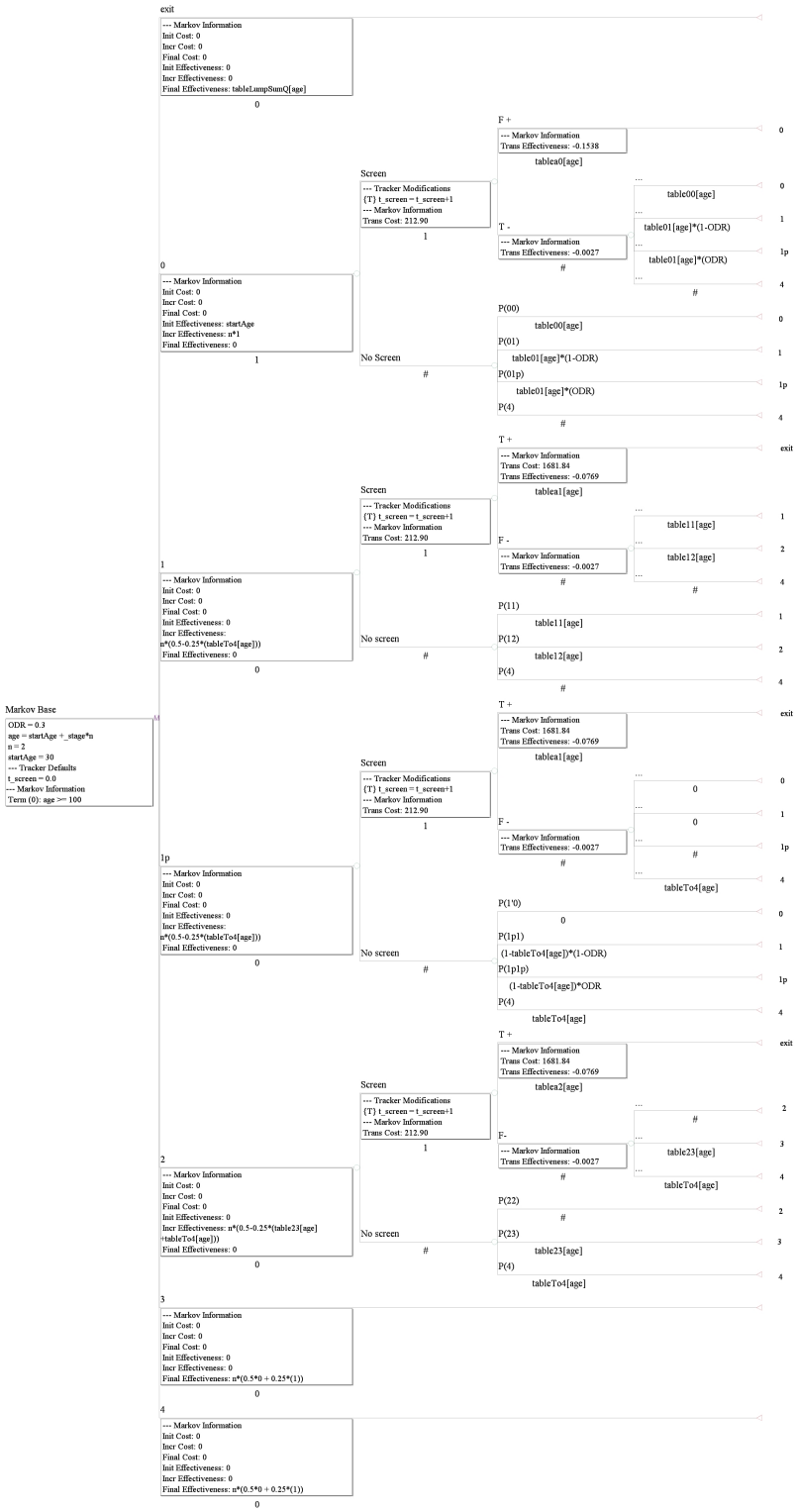
Table 20: Optimum Policy Suggested in Different Over-diagnosis Rate

Over-diagnosis Rate	Strategy	Cost	Cost CI	QALY	QALY CI	C/E	# Screening
0%	50_5	2028.57	20.11	92.308619	0.404478	21.98	9
	50_4	2596.27	26.54	94.459843	0.469256	27.49	12
	35_4	3442.95	28.46	95.468558	0.505577	36.06	16
10%	50_5	2049.40	19.01	92.680545	0.364895	22.11	9
	50_4	2612.09	24.82	94.783841	0.430136	27.56	12
	35_4	3447.55	24.63	95.391573	0.437140	35.14	16
20%	50_5	2037.18	19.29	92.613015	0.388422	22.00	9
	50_4	2591.80	27.54	94.334945	0.468152	27.47	12
	35_4	3429.39	27.15	94.982738	0.476713	36.11	16
30%	50_5	2035.86	17.34	92.568784	0.356198	21.99	9
	50_4	2601.53	24.29	94.701994	0.426521	27.47	12
	35_4	3442.12	17.93	95.296807	0.390461	36.12	16
40%	50_5	2033.39	17.39	92.616082	0.356945	21.95	9
	50_4	2603.49	25.82	94.516850	0.439194	27.55	12
	35_4	3448.66	27.71	95.139310	0.489073	36.25	16
50%	50_5	2029.26	21.26	92.329509	0.418114	21.98	9
	50_4	2593.14	27.56	94.439811	0.477440	27.46	12
	35_4	3428.92	29.57	95.100325	0.512950	36.06	16

5.2 Future Research

There are limitations in this research mostly due to the assumptions made in order to simulate the model. First, due to the difficulty of directly measuring an over-diagnosis rate of screening, the assumption that the fraction of original state 0 to state 1 was assumed to equal the probability of state 0 to the over-diagnosis state. Furthermore, the model also excluded the cost of after-screening-diagnosis such as cancer treatment cost, cancer cost therapy, making doctor appointments etc. The thesis assumes that if a patient found that the screening result is a true positive, the patient would be forced to exit the model by receiving a perfect treatment (without taking into a consideration of aftermath-cost) and receive a lump sum quality adjusted life year. Moreover, there is also limitation on the assumption of breast cancer progression. In reality, there are many stages that could represent cancer processions, thus an additional cancer stages should be added in order to obtain more accurately result.

APPENDIX A: Example of Decision Tree Model with the Presence of 30% ODR



APPENDIX B: Transitional Probability between Cancer Stages (adopted from Maillart et al., 2008)

$\alpha \in [25, 29]$

$$p_\alpha = \begin{pmatrix} 0.99970 & 0.000038010 & 0 & 0 & 0.00026405 \\ 0 & 0.79140 & 0.20833 & 0 & 0.00026405 \\ 0 & 0 & 0.85369 & 0.14604 & 0.00026405 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$a_\alpha = [0.078156 \quad 0.75033 \quad 0.81860]$

$\alpha \in [30, 34]$

$$P_\alpha = \begin{pmatrix} 0.99952 & 0.00013403 & 0 & 0 & 0.00034808 \\ 0 & 0.79132 & 0.20833 & 0 & 0.00034808 \\ 0 & 0 & 0.85369 & 0.14596 & 0.00034808 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$a_\alpha = [0.078156 \quad 0.75033 \quad 0.81860]$

$\alpha \in [35, 39]$

$$P_\alpha = \begin{pmatrix} 0.99915 & 0.00030863 & 0 & 0 & 0.00053717 \\ 0 & 0.79113 & 0.20833 & 0 & 0.00053717 \\ 0 & 0 & 0.85370 & 0.14577 & 0.00053717 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$a_\alpha = [0.078156 \quad 0.75033 \quad 0.81860]$

$\alpha \in [40, 44]$

$$P_\alpha = \begin{pmatrix} 0.99858 & 0.00060193 & 0 & 0 & 0.00081799 \\ 0 & 0.79085 & 0.20833 & 0 & 0.00081799 \\ 0 & 0 & 0.87870 & 0.12048 & 0.00081799 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$a_\alpha = [0.078156 \quad 0.75033 \quad 0.81860]$

$\alpha \in [45, 49]$

$$P_\alpha = \begin{pmatrix} 0.99784 & 0.00097505 & 0 & 0 & 0.0011804 \\ 0 & 0.79049 & 0.20833 & 0 & 0.0011804 \\ 0 & 0 & 0.87870 & 0.12011 & 0.0011804 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$a_\alpha = [0.078156 \quad 0.75033 \quad 0.81860]$

$\alpha \in [50, 54]$

$$P_\alpha = \begin{pmatrix} 0.99703 & 0.0012814 & 0 & 0 & 0.0016911 \\ 0 & 0.86317 & 0.13514 & 0 & 0.0016911 \\ 0 & 0 & 0.85732 & 0.14099 & 0.0016911 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$a_\alpha = [0.073921 \quad 0.85449 \quad 0.93224]$

$\alpha \in [55, 59]$

$$P_\alpha = \begin{pmatrix} 0.99563 & 0.0016822 & 0 & 0 & 0.0026897 \\ 0 & 0.86218 & 0.13514 & 0 & 0.0026897 \\ 0 & 0 & 0.85732 & 0.13999 & 0.0026897 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$a_\alpha = [0.073921 \quad 0.85449 \quad 0.93224]$

$\alpha \in [60, 64]$

$$P_\alpha = \begin{pmatrix} 0.99371 & 0.0019797 & 0 & 0 & 0.0043137 \\ 0 & 0.87664 & 0.11905 & 0 & 0.0043137 \\ 0 & 0 & 0.89090 & 0.10479 & 0.0043137 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$a_\alpha = [0.052669 \quad 0.85449 \quad 0.93224]$

$\alpha \in [65, 69]$

$$P_\alpha = \begin{pmatrix} 0.99086 & 0.0022136 & 0 & 0 & 0.0069270 \\ 0 & 0.87402 & 0.11905 & 0 & 0.0069270 \\ 0 & 0 & 0.89090 & 0.10217 & 0.0069270 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$a_\alpha = [0.052669 \quad 0.85449 \quad 0.93224]$

$\alpha \in [70, 74]$

$$P_\alpha = \begin{pmatrix} 0.98656 & 0.0023770 & 0 & 0 & 0.011064 \\ 0 & 0.86394 & 0.12500 & 0 & 0.011064 \\ 0 & 0 & 0.86253 & 0.12641 & 0.011064 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$a_\alpha = [0.044040 \quad 0.85449 \quad 0.93224]$

$\alpha \in [75, 79]$

$$P_\alpha = \begin{pmatrix} 0.97945 & 0.0025088 & 0 & 0 & 0.018045 \\ 0 & 0.85695 & 0.12500 & 0 & 0.018045 \\ 0 & 0 & 0.86253 & 0.11942 & 0.018045 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$$a_\alpha = [0.044040 \quad 0.85449 \quad 0.93224]$$

$\alpha \in [80, 84]$

$$P_\alpha = \begin{pmatrix} 0.96702 & 0.0023996 & 0 & 0 & 0.030581 \\ 0 & 0.84442 & 0.12500 & 0 & 0.030581 \\ 0 & 0 & 0.86253 & 0.10689 & 0.030581 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$$a_\alpha = [0.044040 \quad 0.85449 \quad 0.93224]$$

$\alpha \in [85, 100]$

$$P_\alpha = \begin{pmatrix} 0.92519 & 0.0020751 & 0 & 0 & 0.072740 \\ 0 & 0.80226 & 0.12500 & 0 & 0.072740 \\ 0 & 0 & 0.86253 & 0.064729 & 0.072740 \\ 0 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$$a_\alpha = [0.044040 \quad 0.85449 \quad 0.93224]$$

APPENDIX C: Lump Sum Quality Adjusted Life years (adopted from Arias, 2006)

Age	All races		
	Total	Male	Female
0	77.4	74.7	80.0
1	77.0	74.3	79.5
5	73.1	70.4	75.6
10	68.1	65.5	70.6
15	63.2	60.5	65.7
20	58.4	55.8	60.8
25	53.6	51.2	56.0
30	48.9	46.5	51.1
35	44.1	41.8	46.3
40	39.5	37.2	41.5
45	34.9	32.8	36.9
50	30.5	28.5	32.3
55	26.2	24.3	27.9
60	22.2	20.4	23.7
65	18.4	16.8	19.7
70	14.8	13.4	15.9
75	11.7	10.5	12.5
80	8.9	7.9	9.5
85	6.6	5.9	7.0
90	4.8	4.3	5.0
95	3.5	3.1	3.5
100	2.5	2.2	2.5

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Retail Business Solution (RBS Design) **Bangkok, Thailand**
Management Trainee in International Department May 2013-Jun. 2013

- Assisted in the calculation of optimum shelves arrangement for the turned key project
- Reviewed, updated and placed the number of items for each layout of convenient store plan
- Carried out a client care during client visitations includes clients from Malaysia, Myanmar and Japan
- Conducted research on Myanmar, Laos and Cambodia convenience store markets to seek potential clients
- Reorganized the visual presentation and visual tool on manufacturing facility

Bangkok Bank **Bangkok, Thailand**
Student Internship Program Jul. 2013-Aug. 2013

- Partook in one-month internship program that emphasized business skills in finance, banking and investment
- Investigated the Thai commercial bank structure and its role in the national economy
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Management Intern Jun. 2012-Aug. 2012

- Assisted in analyzing company's key activities to improved project management of residential real estate
- Conducted qualitative analysis on customers' satisfaction to improve quality of company's projects
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