Optimizing Hepatitis C Birth-Cohort Screening and Treatment Allocation Strategy

Yuankun Li

A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Science
in Industrial Engineering

University of Washington

2015

Committee:

Shan Liu, Chair

Zelda B. Zabinsky

Shi Chen

Program Authorized to Offer Degree:

Industrial & Systems Engineering

University of Washington

Abstract

Optimizing Hepatitis C Birth-Cohort Screening and Treatment Allocation Strategy

Yuankun Li

Chair of the Supervisory Committee:
Assistant Professor Shan Liu
Department of Industrial & Systems Engineering

Chronic hepatitis C (HCV) is a significant public health problem affecting 2.7-3.9 million Americans. The U.S. healthcare systems are ramping up combined HCV screening and treatment efforts, but screening and treatment programs are very costly. We design optimal HCV screening and treatment allocation strategies in the next 10 years under yearly budget constraint from a national societal perspective. The methods include a two-stage simulation and a rule-based exhaustive search.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my advisor Professor Shan Liu for her immense academic guidance, continuous support, enthusiastic motivation and utter patience. I could not have imagined finishing this thesis without her.

I am also very grateful for Professor Zelda Zabinsky, who has provided insightful guidance for the research. Her dedication to the revision process has lead to an invaluable learning experience for me.

My deep appreciation also goes to Professor Shi Chen for his effort of reviewing the thesis and his valuable comments.

I would also like to thank my colleague Hao Huang here in the ISE department, whose kind help has bettered my research.

Finally I would like to thank my parents, who have selflessly supported me through my whole life. Their love and dedication encourage me to always chase my dreams and strive to be better.

DEDICATION

To my loving parents

Chapter 1. INTRODUCTION

Chronic hepatitis C virus (HCV) infection is one of the most important clinical and public health problems facing modern medicine, and the most common blood-borne infection in the United States [20]. Approximately 2.7 million [1] Americans are HCV infected. Among them, an estimated 2 million [2] are unaware of their HCV infection due to the fact the disease is often asymptomatic or accompanied by mild flu-like symptoms. Without diagnosis and timely treatment, infected individuals are at risk for liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC). HCV screening can help identify infected individuals with higher treatment priority and consequently allow better allocation of treatment resource, thus increase population health and lower morbidity. Yet the cost of HCV screening and treatment can be very expensive. The objective of this research is to determine the optimal HCV birth-cohort screening and treatment allocation strategies on the national level HCV care system under societal spending budget constraints.

In recent years, with the approval of many novel HCV drugs such as Daklinza, Harvoni and the AbbVie Combo Hepatitis C treatment (Viekira Pak: ombitasvir, paritaprevir and ritonavir tablets co-packaged with dasabuvir tablets), up to 95% of patients with most genotypes of HCV infection going through treatment now can achieve sustained virologic response (SVR) [11]. The Centers for Disease Control and Prevention (CDC) and the U.S. Preventive Services Task Force (USPSTF) both shifted their stances on HCV screening, recommending physicians to offer screening tests to high-risk adults and adults born between 1945 and 1965 [12], due to the new evidence showing that people born during 1945 to 1965 account for approximately 75% of all HCV infections and 73% HCV associated mortality in the U.S. [13].

1.1 SYSTEM DESCRIPTION

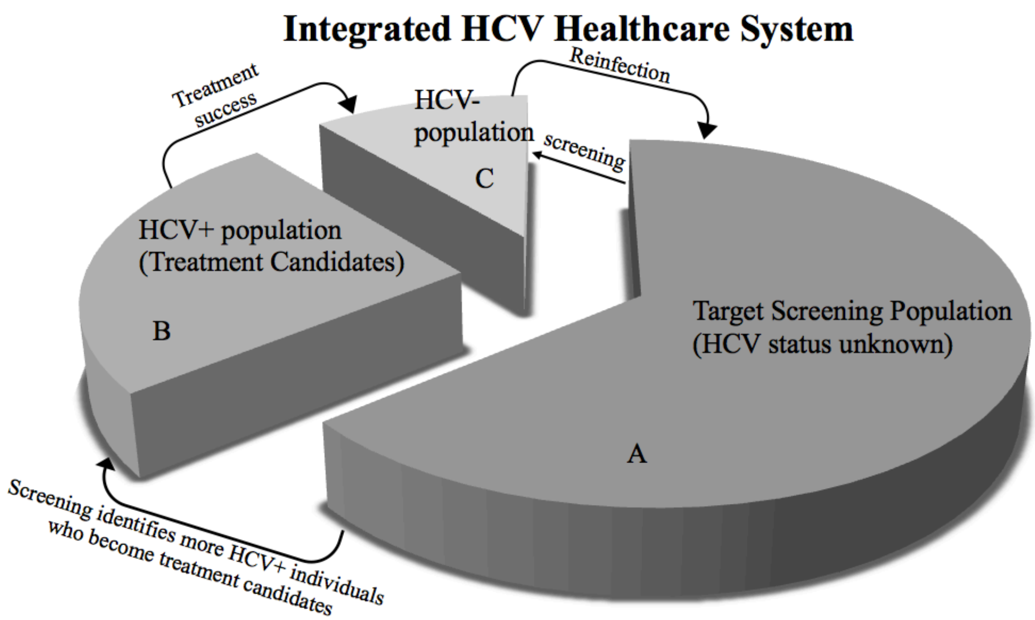

Figure 1.1 Model schematic of HCV care management system

Figure 1.1. shows various components of the HCV healthcare management system. The main component of the system is formed by the target screening population whose HCV status are unknown. The treatment candidates form the identified HCV+ portion of the system. The HCV- portion is formed by people who know they are either not HCV infected through screening or cleared of infections through treatments or spontaneous viral clearance. Through different types of screening programs, we can identify additional HCV+ individuals who become treatment candidates. For each time period, treatment candidates are required to either wait or to get treated for the infection. Patients from HCV+ group who are successfully treated will join the HCV- group. Successful treatment does not guarantee immunity against HCV. Once reinfected or uncertain about HCV status, individuals again join the target screening group.

1.2 RESEARCH APPROACH

We set the planning horizon to be 10 years with yearly budget planning cycle. The goal is to maximize the overall quality-adjusted life years (QALYs) for the population. The decision variables are the proportion of the HCV status unknown population to screen in each time period, age category and gender; and the proportion of HCV+ population to treat in each time period, age category, gender and health condition (i.e., severity of liver damage). Budget constraints ensure only a moderate proportion of treatment candidates will receive treatment per period. Although HCV screening is going to take some resources away from HCV treatment, screening may be able to identify patients with higher treatment priorities thus achieving higher QALYs for the population.

The mathematical model for this study is non-linear, non-quadratic and dynamic, which most existing optimization methods are unable to solve. We are proposing a two-stage simulation approach, where we build a simulation model to produce outcomes with given set of decision variables, and observe the outcomes of pre-defined input strategies. Once we identify feasible regions of optimal screening and treatment strategies, we conduct an exhaustive direct search for the optimal strategies.

Chapter 2. LITERATURE REVIEW

2.1 Hepatitis C Policy Modeling

As mentioned in the introduction, many new drugs and treatments for chronic hepatitis C infection have been recently approved by the FDA. While these new drugs have significantly shortened the treatment durations and improved the rate of sustainable virological response, they are also substantially more expensive than the old standard care of interferon-based therapies. There have been many studies such as Liu et al. [3], Najafzadeh et al. [7] and Chhatwal et al. [8] looking into the cost effectiveness of these new treatments. The simulation models designed vary: Liu et al. [3] used a decision-analytic Markov model, Najafzadeh et al. [7] used discrete event simulation and Chhatwal et al. [8] used HCV infection natural history microsimulation. Due to the differences of the drugs' characteristics, these studies also focus on different target patient populations differentiated by their HCV genotypes and whether they have previously received HCV treatments. All three studies measure the benefit of the new drugs by Quality-adjusted Life-years (QALYs), which is also adopted in our study. Both studies of Liu et al. [3] and Najafzadeh et al. [7] show support for the new HCV treatment, but Liu et al. [3] requires the least-expensive protease inhibitor being used for patients with advanced fibrosis and Najafzadeh et al. [7] points out that the new treatments are not cost effective for patients with HCV of genotype 2. Chhatwal et al. [8] not only support the new HCV treatment by claiming they are cost-effective for most patients, but they also point out that additional resources and value-based patient prioritization are needed to manage HCV infected patients.

Another cost-effectiveness analysis by Liu et al. [2] also addresses the issue of risk factor guided screening versus one-time birth cohort screening under different treatment strategies using a Markov model. The conclusion is supportive for the shift of stances of CDC and USPSTF on HCV screening policies, by showing that the cost-effectiveness of one-time birth-cohort HCV screening for 40-64 years olds is comparable to other screening programs, given that the healthcare system has sufficient capacity to provide treatment and follow-on care for the newly identified HCV infected individuals through screening.

Based on these findings, our research is going to further explore how can we provide sufficient treatment with new HCV drugs while conduct birth-cohort screening under budget constraints to improve the total quality-adjusted life-years for the age 40-69 years-old U.S. population under a societal perspective.

2.2 OPTIMIZATION FOR RESOURCE ALLOCATION

The optimization model of this study is a resource allocation problem due to the budgetary constraints. For most healthcare management systems, the series of decisions are made ahead of budgetary planning cycle consists of multiple discretized time periods, and the decision of the previous time period will have effects on how the system behave for the next time period. There are many studies modeling the healthcare system from a dynamic view. For example, Deo et al. [4] studies the planning problem for HIV screening and care providing for the Greater Los Angeles Veterans Health Administration station using a non-linear dynamic programming model. Rauner et al. [9] develops a dynamic resource allocation policy model addressing general chronic disease, and the model is illustrated by a numerical example of breast cancer. Both of these two studies comprise chronic disease progression and budgetary constraints, and both of them focus on the trade off of screening and treatment.

Due to the complex nature of the dynamic resource allocation problems, the traditional solution of knapsack problem is no longer applicable. Many heuristic methods have been developed to achieve computationally tractable and managerially intuitive results. Deo et al. [4]

proposed two heuristics with a series of relaxations on the constraints to simplify the model, while Rauner et al. [9] used a meta-heuristic based Pareto ant colony optimization (P-ACO) algorithm for their multi-objective combinatorial problem. We also see many studies of simulation optimization method that can be applied in our research. For example, Huang and Zabinsky [10] proposed a probabilistic branch and bound with confidence intervals algorithm that can provide a level set of solutions with a user specified quantile for general deterministic or noisy problems. But to achieve a reasonable computational time and meaningful results, the algorithm requires the decision variable to have lower dimensions and the objective function to not have flat structures in their feasible regions.

Chapter 3. METHOD

3.1 HEALTHCARE SYSTEM

Based on the previous system description and Figure 1.1, we divide the population in the HCV care management system into three parts:

A: target screening population, candidates whose HCV statuses are unknown;

B: HCV+ population, patients who know they are HCV+ and are potential treatment candidates and patients who are under-going treatment;

C: HCV- population, patients who have been cured of HCV or patients who know they are not HCV infected through screening.

To better describe the system according to budget periods as well as disease progression periods, let $\tau \in T = \{1, 2, \dots, 10\}$ denote the budget periods each corresponding to a year, and let $t \in Q_\tau = \{1 + 4(\tau - 1), \dots, 4\tau\}$ for $\tau \in T$ denote the disease progression periods each corresponding to three months (a quarter) within each budget periods.

3.2 PATIENT HEALTH STATES

Similar to earlier work in modeling the progression of chronic HCV infection, the patient's health states are evaluated through their liver conditions. The progression through fibrosis stages is indicated by the Metavir score, with possible transitions occurring every 3 months [3]. As is demonstrated by Figure 2, the health states include: healthy without HCV (H), no fibrosis (F0), portal fibrosis with no septa (F1), portal fibrosis with few septa (F2), numerous septa without cirrhosis (F3), compensated cirrhosis (F4), decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), liver transplant (LT), after liver transplant (ALT) and dead (M). There are also three recovered health states, namely recovered with history of mild fibrosis (R1), recovered with history of moderate fibrosis (R2) and recovered with history of advanced fibrosis (R3). Spontaneous virus clearance and returning to the healthy state is only possible from F0. With effective treatment, there is a chance that patients' health states can progress to corresponding recovered states. Even achieving SVR and going back to recovered health states, the patients are still stratified by prior fibrosis damage severity. A proportion of patients with decompensated cirrhosis and HCC can receive liver transplantation based on their priority. Individuals can go to the dead state from any other health states [3].

People with different health states can exist in different groups indicated in Figure 1.1. For example, people with health states H, F0, F1, F2, F3, F4, HCC, DC, LT, ALT can be in group A, the target screening population; people with health states F0, F1, F2, F3, F4, HCC, DC, LT, ALT can be in group B, the HCV+ population, and people with health states H, R1, R2, R3 can be in group C, the HCV- population.

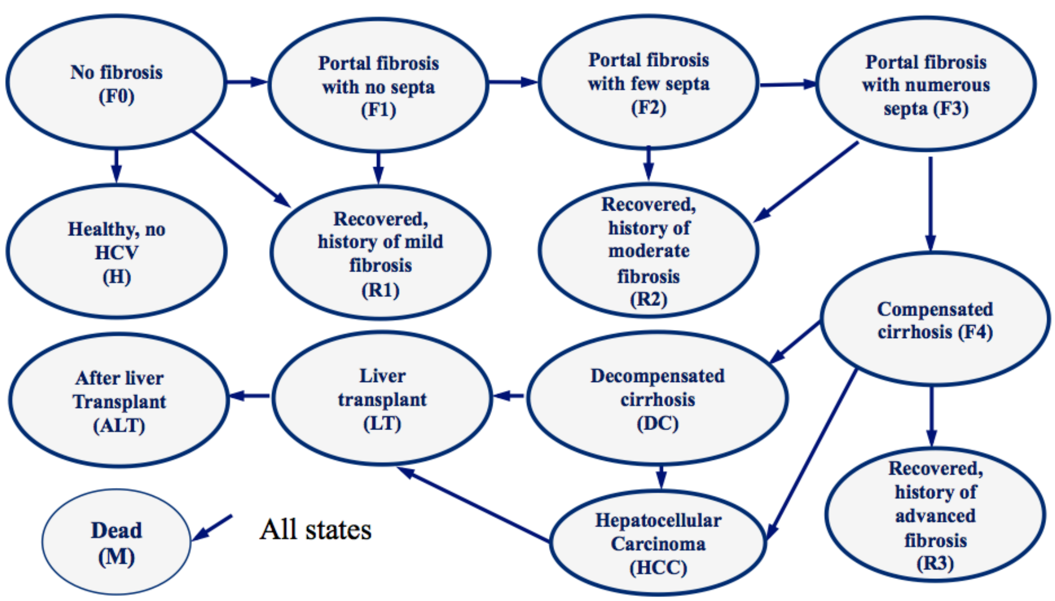

Figure 3.1 Various health states of chronic HCV progression [3]

The rates of HCV disease progression depend on age, gender [5] and whether the patients are currently being treated or not. So we let $\theta^{ij}_{a,g,CTC}$ denote the deterministic fraction of patient population of age $a \in A = \{40\sim49, 50\sim59, 60\sim69\}$, gender $g \in G = \{male, female\}$ and current treatment condition $CTC \in \{ongoing, waiting\}$, who move from health state i to health state j in one time period. Here "ongoing" refers to currently being treated while "waiting" refers to currently not undergoing treatment.

3.3 System Dynamics

Similar to recent research in policy modeling of HIV screening, diagnostics and treatment [4], we combine the disease progression and patient flow to show how individuals move between the three parts in a general HCV care population model. These transitions over time also act as constraints in the model. Let $A^i_{t,a,g}, B^i_{t,a,g}, C^i_{t,a,g}$ denote the number of patients or candidates of age a, gender g and health state i during time period t for population part A, B and C in the system.

We first look at part A, the target screening population. Assume among the candidates, fraction α go to a healthcare provider, and fraction $S_{t,a,g}$ are offered HCV screening tests, and fraction β accepted the tests. Then the number of candidates in part A for the next time period should be the combination of candidates that remain unscreened from last period and the HCV- candidates in part C from last period who become not sure about their HCV infection status. We also denote γ as the rate of people becoming unsure of their HCV infection status. Then we have:

$$A^i_{t+1,a,g} = \sum_j \theta^{ji}_{a,g,waiting} \left(1 - \alpha\, S_{t,a,g}\beta\right) A^j_{t,a,g} + C^i_{t,a,g}\gamma \quad \forall t, a, g, i \neq M \qquad (3.3.1)$$

where M (mortality) is the dead state.

For part B, the HCV+ population, we assume that for each time period, there are fraction $W^i_{t,a,g,}$ of the total number of people who choose not to treat or to wait for treatment until later due to the budget constraints. So these patients will remain in part B in the next time period. And new patients tested HCV+ through screening will join this population. Patients who failed their treatment will also remain in this part in next time period. Then we have:

$$B^i_{t+1,a,g} = \sum_j \theta^{ji}_{a,g,waiting}\, \alpha\, S_{t,a,g}\, \beta\, A^j_{t,a,g} + \sum_j \theta^{ji}_{a,g,waiting}\, W^j_{t,a,g} B^j_{t,a,g}$$

$$+ \sum_j \theta^{ji}_{a,g,ongoing} (1 - W^j_{t,a,g}) B^j_{t,a,g} \qquad \forall t, a, g, i \notin \{R1, R2, R3, H, M\} \qquad (3.3.2)$$

where R1, R2, R3 are the recovered states, H is the healthy state and M is the dead state.

For part C, candidates can go from HCV status unknown to C by screening. Patients who are cured of the HCV infection or experience spontaneous viral clearance from the HCV+ group can also join group C. Fraction $(1-\gamma)$ of the population of group C from last time period will stay in this group. Then we have:

$$C^{i}_{t+1,a,g} = \sum_{j} \theta^{ji}_{a,g,waiting}\, \alpha\, S_{t,a,g}\, \beta\, A^{j}_{t,a,g} + \sum_{j} \theta^{ji}_{a,g,waiting}\, W^{j}_{t,a,g} B^{j}_{t,a,g}$$

$$+ \sum_{j} \theta^{ji}_{a,g,ongoing} (1 - W^{j}_{t,a,g}) B^{j}_{t,a,g} + C^{i}_{t,a,g}(1-\gamma) \quad \forall a, g, i \in \{R1, R2, R3, H\} \quad (3.3.3)$$

where R1, R2, R3 are the recovered states and H is the healthy state.

Here for all the constraints, $0 \le S_{t,a,g} \le 1$ and $0 \le W^{i}_{t,a,g} \le 1$ for $\forall t, a, g, i$.

3.4 Optimization Model

The goal of the optimization model is to maximize the overall QALYs for the population during ten years of budget planning under the birth-cohorts' lifetime horizon. In order to capture the future benefit of our policy, we need to take account of the number of people in each part of the healthcare system from the end of the tenth year until everyone in the system is dead (i.e., over 100 years old). During this post budget planning time period, all screening and treatment activity will stop, meaning screening probability will be 0 and waiting probability will be 1 uniformly. We denote $\mathrm{utility}^{i}$ as the health utility multipliers corresponding to each health state. We also denote the quarterly discount rate as δ_q. Our objective function is as follows:

$$\text{Maximize} \qquad \sum_t \sum_a \sum_g \sum_i \mathrm{utility}^{i} (A^{i}_{t,a,g} + B^{i}_{t,a,g} + C^{i}_{t,a,g}) \times (1+\delta_q)^{-t} \qquad (3.1.4)$$

where t ranges from quarter 1 to quarter 240.

We denote the cost for screening associated with health state i as CS^{i}, denote the cost for treatment associated with health state i as CT^{i}. Also we denote the budget for year τ as $\mathrm{Budget}(\tau)$, and denote the annual discount rate as δ_y. The budget constraint is:

$$\sum_{i,t \in Q_\tau, a, g} CS^{i}\, \alpha\, S_{t,a,g} \beta A^{i}_{t,a,g} \times (1+\delta_q)^{-t} + \sum_{i,t \in Q_\tau, a, g} CT^{i}\, (1 - W^{i}_{t,a,g}) B^{i}_{t,a,g} \times (1+\delta_q)^{-t} + \le$$

$$\mathrm{Budget}(\tau) \times (1+\delta_y)^{-\tau} \qquad \forall \tau \qquad (3.3.5)$$

Table 3.1 shows the list of coefficients and variables used in the model.

Table 3.1 Coefficients and variables list

index	
i, j	Health states including:
	healthy (no HCV), no fibrosis (F0), portal fibrosis with no septa (F1), portal fibrosis with few septa (F2), numerous septa without cirrhosis (F3), compensated cirrhosis (F4), decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), liver transplant (LT), after liver transplant (ALT), dead (M), recovered, history of mild fibrosis (R1), recovered, history of moderate fibrosis (R2), recovered, history of severe fibrosis (R3)
τ	the budget periods each corresponding to a year, $\tau \in T=\{1,2,\ldots,10\}$
t	the disease progression periods each corresponding to three months (a quarter) within each budget periods, $t \in Q\tau = \{1+4(\tau-1),\ldots,4\tau\}$, and $\tau = 1,2,\ldots,10$
a	age a∈{40~49,50~59, 60~69}
g	gender g∈{male, female}
parameters	
$\theta^{ij}_{a,g,waiting}$	the deterministic fraction of patients population of age a and gender g who are not going through treatment and move from health state i to health state j
$\theta^{ij}_{a,g,ongoing}$	the deterministic fraction of patients population of age a and gender g who are going through treatments and move from health state i to health state j
α	fraction of candidates in part A who go to healthcare provider
β	fraction of candidates in part A who accept the tests
γ	the probability of people becoming unsure of their HCV infection status
$utility^i$	the quality adjusted life years corresponding to health state i
CS^i	the cost for screening associated with health state i
CT^i	the cost for treatment associated with health state i
$Budget(\tau)$	the budget for year τ
intermediate variables	
$A^i_{t,a,g}$	the number of patients or candidates of age a, gender g and health state i during time period t for part A in the system.
$B^i_{t,a,g}$	the number of patients or candidates of age a, gender g and health state i during time period t for part B in the system.
$C^i_{t,a,g}$	the number of patients or candidates of age a, gender g and health state i during time period t for part C in the system.

decision variables	
$S_{t,a,g}$	fraction of candidates in part A who are offered HCV screening tests
$W^{i}_{t,a,g}$	fraction of patients in part B who choose not to treat or to wait for treatment until later due to the budget constraints

3.5 SOLUTION METHOD

As mentioned in the research approach, because of the non-linear, non-quadratic and dynamic property of the model, we adopt a two-stage simulation approach, where we build a simulation model to compute QALYs with given set of the decision variables, identify a few feasible regions of optimal treatment strategies, and conduct exhaustive direct search for the optimal input combinations of these strategies.

It is obvious that the amount of computation effort for the exhaustive search relies heavily on the number of dimension d of the input variables. In order to achieve a reasonable run time of the program, we reduce the dimension of input variable to 20. We define the input variable as $x = [S, W]$, where S represents the vector containing all the $S_{t,a,g}$: screen percentage for each time period, age and gender, and W represents the vector containing all the $W^{i}_{t,a,g}$: waiting percentage for each time period, age, gender and health state. We also denote d_i as the dimension of the variable i, then we have:

$$d_x = d_S + d_W = n_{time\_period} \times n_{age} \times n_{gender} + n_{time\_period} \times n_{age} \times n_{gender} \times n_{health\_state}$$

where n_{time_period} is the number of time period, n_{age} is the number of age groups, n_{gender} is the number of gender and n_{health_state} is the number of health states. Considering the real life cases, it may not be feasible to discriminate by gender and age. So we decide to adopt the same screening and waiting percentages between two genders, so $n_{gender} = 1$. Also we decouple the problem by taking out the age subscript and dividing the budget according to the population of three different age groups, so $n_{age} = 1$. For the time period dimensions, there is really no need to change the policy every quarter, and in fact most healthcare policy change yearly or every two years. In this case we decide that the policy should only change every two years, so $n_{time\_period} = 5$. For the health state dimensions, due to the similarity in the severity of adjacent health states and the fact that patients will not get HCV treatment once their liver condition progress beyond F4, we can combine health state F0 with F1, F2 with F3, so $n_{health\_state} = 3$. After the simplification, we have $d_x = d_S + d_W = 5 \times 1 \times 1 + 5 \times 1 \times 1 \times 3 = 20$. To better adjust to this simplification, we denote the screening percentages as $\mathrm{S_t}$ for $t = 1,2, \dots ,5$ and $\mathrm{W_t^i}$ for $t = 1,2, \dots ,5$ and $i = 1,2,3$.

We design the QALYs computation model based on these simplifications. The algorithm and the code are attached in Appendix A.

3.5.1 *Initial Grid Search*

The purpose of the initial grid search is to get a sense of the feasible region. Because all three decoupled age group have the same model structure, we chose age group 50~59 as the base case. We ran the search under the resource constraint of total yearly budget $\{0,2,4, \dots ,20\}$ billion dollars, with the budget for each age group allocated according to their population weight. All the screening percentages over the years were set to be the same, so were all the waiting percentages over the years and across different health states.

The initial grid search indicates the feasible area for this model is quite small, considering the high dimensions of the input variable.

When yearly budget is within the range of 4~8 billion dollars, screening percentages for the feasible solutions can be as high as 1, meaning the system can afford to screen everyone, but the waiting percentages for these feasible solutions can only be 1, meaning no one can get treatment. When yearly budget is within the range of 10~20 billion dollars, the screening percentages for the feasible solutions can be in the range of $[0, 1]$, while most of the waiting percentages can be in the range of $[0.95, 1]$. The higher the yearly budget is, the more feasible solutions we can get. This result reflects the fact that the cost for screening is much lower than the cost for treatment, thus we can only afford to treat a limited amount of treatment candidates under various yearly budget limits. The result details are included in section 5.1.

3.5.2 *Basic Policy Scenario Analyses*

Based on the observations of the initial grid search, we decide to try out and compare some of the basic policies with all the screening percentages in the range of $[0, 1]$ and waiting percentages in the range of $[0.95, 1]$. Because we decoupled the age groups in the simplification, and different yearly budget limit can have different effect on the outcome, here the policies are tried out for 6 scenarios with different age groups and different yearly budgets, namely

Scenario 1: age group of 40∼49 with total yearly budget of 5 billion dollars

Scenario 2: age group of 50∼59 with total yearly budget of 5 billion dollars

Scenario 3: age group of 60∼69 with total yearly budget of 5 billion dollars

Scenario 4: age group of 40∼49 with total yearly budget of 10 billion dollars

Scenario 5: age group of 50∼59 with total yearly budget of 10 billion dollars

Scenario 6: age group of 60∼69 with total yearly budget of 10 billion dollars.

The total yearly budget is divided according to the population weight of the corresponding age group. The policies we tried are listed below:

Policy 1: High screening percentages with each S_t close to 1, high waiting percentages with each W_t^i close to 1

Policy 2: Low screening percentages with each S_t lower than 0.5, low waiting percentages with each W_t^i close to 0.98

Policy 3: Only spend money on treatment until the population in group B is very small, with parallel waiting percentages for patients with different fibrosis stage, then start screening

Policy 4: Only spend money on treatment until the population in group B is very small, with treatment priority for F4, then start screening

Policy 5: Only spend money on treatment until the population in group B is very small, with treatment priority for F2-F3, then start screening

Policy 6: Only spend money on treatment until the population in group B is very small, with treatment priority for F0-F1, then start screening

For each policy, we tried many combinations of S_t and W_t^i manually for the six different scenarios of different age and budget combinations. From the comparison of the results of different policies for each scenario shown in section 5.2, we can see that the more HCV+ patients we treat, the higher the QALYs we can achieve; spending more money on screening is not as beneficial as spending money on treatment; giving treatment priority to people who are F4 or F0-F1 can result in higher QALYs. These observations suggest that we should give more priority to treat patients with either F4 or F0-F1 health states, and conduct screening when the population size of group B is small. Also, due to the structure of the model, any money left at the end of the year will not be counted in the budget for the next year, so the closer we push to the budget limit each year, the better result we can get.

3.5.3 *Rule Based Exhaustive Search*

Based on the last observation of the basic policy scenario analyses, we decide to remodel the problem by making sure we spend the entire budget each year. Because treatment has more priority over screening, the question of the new model becomes when should we screen and how much money should be allocated toward screening. We change the decision variables to percentage of budget to be allocated to screening per two years. The remaining budget will be spent on treatment first following two different rules:

Rule 1: treating patients with F4 health states first, then patients with F2-F3 health states, then patients with F0-F1 health states

Rule 2: treating patients with F0-F1 health states first, then patients with F2-F3 health states, then patients with F4 health states.

Any money left from treatment during each time period will be spent on screening in addition to the original screening budget to find more HCV+ treatment candidates. The percentages of people in group A to screen and the percentages of people in group B to treat will be calculated accordingly to adapt to the previous model. The new model can affect the population size in group A, B and C by only changing the money allocation percentages.

Similarly, we have 6 scenarios with age groups 40-49, 50-59 and 60-69 under yearly budget 5 billion dollars and 10 billion dollars. From the result of the grid search on the decision variable and monotonicity checks in section 5.3, we observed that for 4 scenarios the best solutions are to set screening budget percentage to 0, and wait for the spare money from treatment. Following Rule 1, treating the sickest patients first can result in better QALYs.

Chapter 4. DATA PROCESSING

4.1 PROGRESSION MATRIX

The progression parameters $\theta^{ij}_{a,g,waiting}$ and $\theta^{ij}_{a,g,ongoing}$ describe how individuals' conditions progress through the 14 health states previously defined in Figure 3.4.1. The matrices of

$\theta^{ij}_{a,g,waiting}$ and $\theta^{ij}_{a,g,ongoing}$ consist of static probabilities of an individual within an age cohort and gender to move between two health states in the time period of one quarter. Since patient from certain HCV+ states are only allowed to progress to adjacent HCV+ states, corresponding recovered states or dead state, the progression matrices will be sparse for any age, gender and current treatment status.

4.1.1 *HCV Natural History Model*

The probability parameters of patients progressing from HCV+ health states to adjacent HCV+ health states are sourced from [2]. The fibrosis progression probabilities (probability of patients moving through F0 and F4) depend on age and gender. Once a patient's condition advances past F4, the progression is no longer age and gender dependent. The original data from [2] was yearly progression probabilities. The following functions are used to convert them into quarterly probabilities. We denote p_y as yearly probability, p_q as quarterly probabilities, r as yearly rate. Then we have:

$$p_q = 1 - e^{-rt} \qquad (4.1.1.1)$$

$$p_y = 1 - e^{-r*4t} \qquad (4.1.1.2)$$

$$p_q = 1 - (1 - p_y)^{1/4} \qquad (4.1.1.3)$$

4.1.2 *Mortality*

The mortality is the probability of going from all other health states to the dead state in the time period of one quarter. We compute these values from the data in US life table 2010 [14] and US CENSUS 2010 [15]. We take the probabilities of dying for single year of age from both genders, and calculate the weighted average by the US population for single year of age from both genders to get the death probabilities for different age groups belongs to $a \in D =${40-49, 50-59, 60-69, 70-79, 80-89, 90-99}. Denote $p_{x,g}$ as the probability that a person dies between age x and $x + 1$ for gender g. Denote $n_{x,g}$ as the population in the U.S. between age x and $x + 1$ for gender g, then we have:

$$\theta^{H,M}_{a,g} = \frac{\sum_{x \in a} p_{x,g} \cdot n_{x,g}}{\sum_{x \in a} n_{x,g}} \qquad \forall a, g \qquad (4.1.2.1)$$

Because in the model we need a stopping condition, we set the death probability for age group {100-109} to be 1, making sure that no one lives past 100 years old in the system.

The death probabilities from different fibrosis stage (F0 through F4) are adjusted by the non-liver related mortality hazard ratio of chronic HCV infection [16]. The death probabilities for health states past F4 are sourced from reference [21]. The death probabilities of recovered states are adjusted by reduction factor on background mortality after successful treatment based on the death probabilities of corresponding health states.

All the above death probabilities are converted into quarterly probabilities according to function (4.1.1.3) in the model.

4.1.3 *Treatment Effectiveness*

Treatment effectiveness refers to the probability of patients going from different fibrosis stages (F0 to F4) to corresponding recovered states (R1 to R3). The values are mainly dependent on the genotype (genotype 1, 2, 3 & 4) of the HCV infection, which are not the primary concern in this study. So we decide to use the weighted average of treatment effectiveness based on the prevalence of different genotypes of HCV. Denote the treatment effectiveness of genotype i as $effectiveness_i$, the prevalence of genotype i as $prevalence_i$, we have:

$$weighted\ effectiveness = \sum_i effectiveness_i \cdot prevalence_i.$$

4.1.4 *Infection and Reinfection*

In a traditional compartmental model in epidemiology（i.e., the Susceptible-Infected-Recovered (SIR) model), the rate of susceptible population getting infected depends on the size of infected population. But in our model, because we are only considering certain age cohorts instead of the whole population and the cure of HCV does not guarantee immunity, we simplify the factor of infection and reinfection as a constant probability of people becoming unsure of their HCV infection status, here denoted as γ.

4.1.5 *Progression Matrix Calculation*

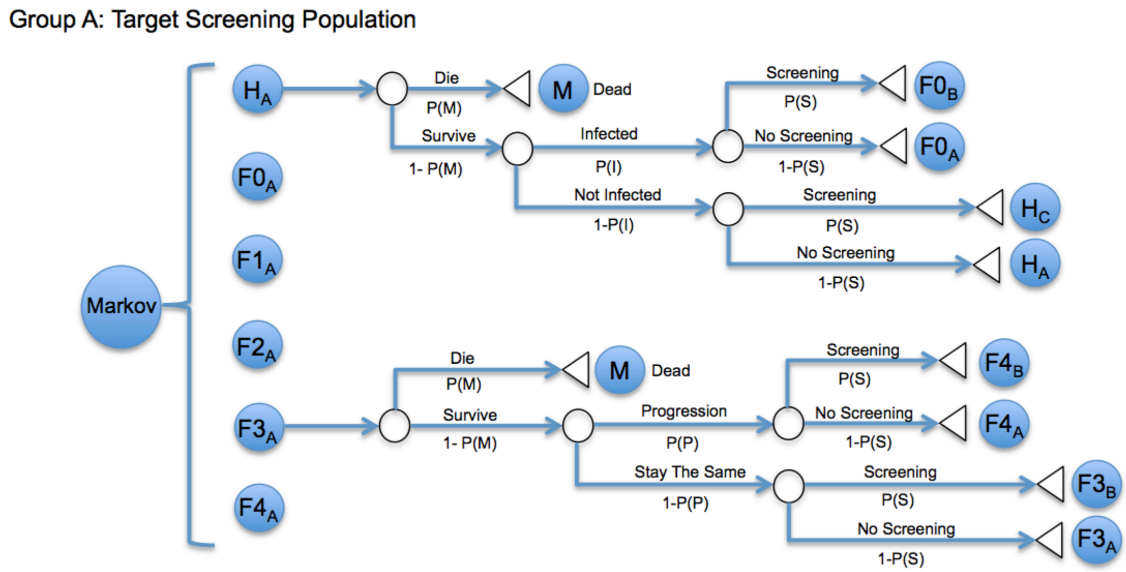

Figure 4.1 Markov decision tree for the HCV progression in group A

In Figure 4.1 we only demonstrate how patients with F3 in group A progress because patients with F0, F1, F2 and F4 in group A have similar progression process.

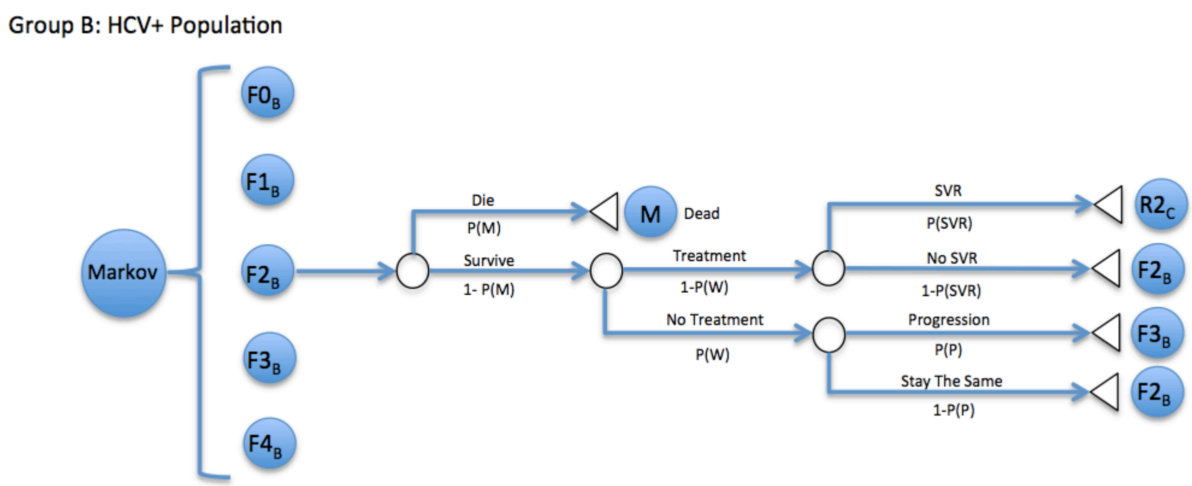

Figure 4.2 Markov decision tree for the HCV progression in group B

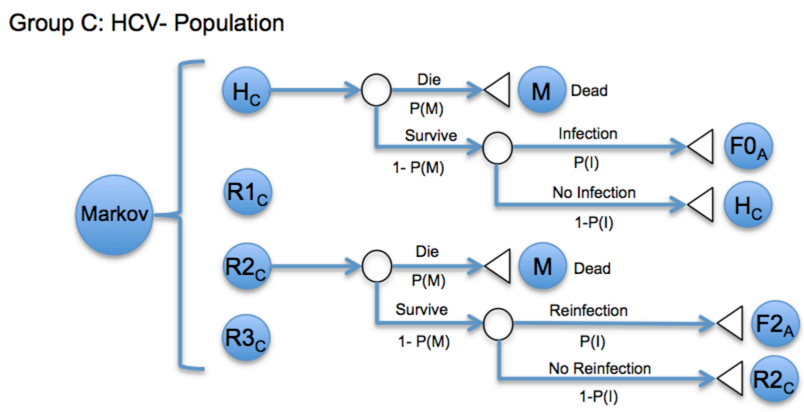

Figure 4.3 Markov decision tree for the HCV progression in group C

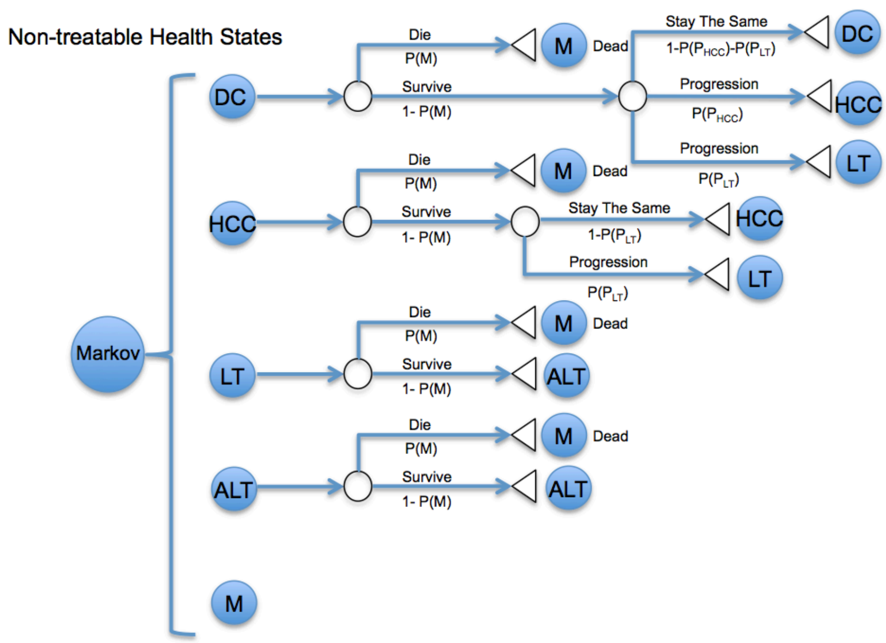

Figure 4.4 Markov decision tree for the HCV progression for non-treatable health states

Figures 4.1, 4.2, 4.3 and 4.4 show all the health states in each part of the HCV healthcare system and how they transition to other groups. The subscript for each health state node indicates which group the node can be in. In all figures, M stands for mortality state, which is the dead state. In Figure 4.4, health states DC, HCC, LT and ALT can be in both group A and group B. We calculated our HCV progression matrix for different age groups, gender and treatment status according to these four figures, using all the data from previous sections in this chapter.

Examples of progression matrices are attached in Appendix B. For the same age group and gender, the difference of $\theta^{ij}_{a,g,ongoing}$ from $\theta^{ij}_{a,g,waiting}$ is the probabilities of going from various fibrosis states to the corresponding recovered states are not 0. Compared to the matrices from younger age group, the death probabilities of all health states increase in the older age group. For the same age group, the death probability of females is lower than that of males. All the progression matrices are sparse.

4.2 Population Initialization

As indicated in the model, in order to calculate the population for the coming quarters, we need to know the initial population distribution across the A-C groups and health states. In this study, we are using national level data to gain a better understanding of the U.S. HCV screening and treatment efforts as a whole.

The HCV infection awareness is estimated at 50% right now in the U.S. [22], so this means up to half of the HCV infected population for each fibrosis state should be in group B, leaving the unaware half in A. From the paper of Alison et. al [23], we can obtain the initial fibrosis stage distribution for different age group, race and gender. We weight-averaged these numbers to combine different age group and race. The population number used in the weighted computation is from U.S. CENSUS from year 2013 [17]. The number of people with HCV across age and gender are direct input from National Health and Nutrition Examination Survey (NHANES) [22]. Combined together with the weighted fibrosis distribution, we have the number of HCV infected people for each fibrosis stage, age group and gender.

The number of people with no HCV in group A should be the target screening population in the U.S. minus the sum of corresponding HCV infected population of all fibrosis stage in group A.

4.3 Costs, Utilities and Other Parameters

The costs are divided into different categories: screening cost, treatment cost, care cost and recovered cost. The screening costs should be the same for all HCV chronic patients regardless of their fibrosis stage, and for healthy people with no HCV, the screening cost is far less. The treatment costs are also the same across different fibrosis state, and we do not treat anyone past F4 state, meaning the treatment costs for other states are zeros.

As mentioned in the modeling section, we denote $utility^i$ as the utility multiplier corresponding to each health state. These parameters are from reference [2].

Table 4.1. and Table 4.2. show the values and ranges of the parameters used in the model.

Table 4.1 Model parameters and ranges

Variable	**Base Case (Range)**	**Reference**
Model assumptions		[2]
Quarterly discount rate	0.076 (0.00-0.0127)	
HCV natural history (quarterly)		[2]
Quarterly probability of spontaneous remission from no fibrosis (F0) health state	0.003 (0.0018-0.0043)	
Fibrosis progression (quarterly probability)		
Males		
Age 40-49 y	0.0127 (0.0076-0.0233)	
Age 50-59 y	0.0315 (0.018-0.037)	
Age 60-69 y	0.0543 (0.0315-0.0853)	
Females		
Age 40-49 y	0.0076 (0.0025-0.0153)	
Age 50-59 y	0.0153 (0.0076-0.0287)	
Age 60-69 y	0.0287 (0.0102-0.0572)	
Cirrhosis to decompensated cirrhosis	0.0102 (0.0076-0.0127)	
Cirrhosis (both F4 and decompensated cirrhosis) to HCC	0.005 (0.0043-0.0076)	
Liver transplant (quarterly probability)		
Decompensated cirrhosis to liver transplant	0.0127 (0.00-0.1199)	
HCC to liver transplant	0.0398 (0.0127-0.1199)	
Reduction factor on background mortality after successful treatment	0.9 (0.3-1)	
Liver related mortality (quarterly probability)		
Liver transplant	0.037 (0.0353-0.0398)	
After liver transplant	0.0127 (0.125-0.013)	
Decompensated cirrhosis	0.0725 (0.0315-0.0953)	
HCC		
First year	0.2726 (0.195-0.3313)	
Subsequent year	0.0694 (0.0427-0.0853)	
Utility parameters		[2]
HCV specific weights		
HCV mild fibrosis (F0, F1, R1)	0.98 (0.70-1.00)	
SVR after mild fibrosis	1.00 (0.74-1.00)	
HCV moderate fibrosis (F2, F3, R2)	0.85 (0.66-1.00)	
Compensated cirrhosis (F4, R3)	0.79 (0.46-1.00)	
Decompensated cirrhosis, HCC	0.72 (0.257-0.913)	
Liver transplant, post-liver transplant	0.825 (0.636-1.00)	
Healthy	1.00 (1.00-1.00)	
Dead	0 (0-0)	

Quarterly Cost		
Screening		
HCV anti-body screening (ELISA)	20 (10-31)	
Diagnosis (2 confirmatory ELISA, RIBA, and RNA test)	210 (105-315)	
HCV genotyping	369 (184-553)	
Liver biopsy	1340 (990-1650)	
FibroTest	240 (102-300)	
Treatment (drug and medical care)		
SOF+Ledipasvir (Harvoni), 12-weeks Average Whole Sale Price, 50% discount	47250 (37800-94500)	
Treatment effectiveness		
genotype 1&4	0.97	
genotype 2	0.97	
genotype 3	0.94	
Genotype prevalence		
genotype 1&4	0.69	
genotype 2	0.12	
genotype 3	0.19	
Mortality Hazzard ratio		
non-liver related, chronic	3.12 (1.76-5.53)	[18]
Reinfection probability (quarterly)	0.00080096 (0.00025009-0.0099)	[19]

Table 4.2 Cohort characteristics

Cohort Characteristics						Reference
U.S. population						US CENSUS [15]
	Male	Female				
40-49	21603062	21996493				
50-59	20456922	21506008				
60-69	13930047	15323140				
Number of people with HCV						NHANES [22]
	Male	Female				
40-49	463300	365550				
50-59	1094026	549716				
60-69	399016	144492				
Fibrosis Distribution						[23]
male	F0	F1	F2	F3	F4	
40-44	0.33	0.35	0.18	0.12	0.02	
45-49	0.25	0.34	0.22	0.14	0.05	
50-54	0.20	0.32	0.25	0.17	0.07	
55-59	0.11	0.25	0.28	0.22	0.13	
60-64	0.07	0.19	0.28	0.27	0.20	
65-69	0.03	0.12	0.23	0.31	0.31	
female	F0	F1	F2	F3	F4	
40-44	0.33	0.35	0.18	0.12	0.02	
45-49	0.29	0.34	0.20	0.13	0.04	
50-54	0.25	0.34	0.22	0.14	0.05	
55-59	0.19	0.31	0.25	0.17	0.08	
60-64	0.14	0.28	0.27	0.20	0.11	
65-69	0.08	0.22	0.28	0.25	0.17	
U.S. population by age and race						US CENSUS [15]
	white male	white female	black male	black female		
40-45	8234026	8107290	1301039	1450544		
45-50	9030996	9071931	1367345	1533878		
50-55	8921642	9086671	1290098	1463073		
55-60	7905694	8237780	1030244	1215926		
60-65	6841051	7247819	771632	943572		
65-70	5023639	5540089	512310	668427		

Chapter 5. RESULTS AND ANALYSIS

5.1 INITIAL GRID SEARCH

We denote the screening percentages per quarter as S and the waiting percentages per quarter as W. For the base case scenario of age group 50~59 under total yearly budget of $\{0,2,4,\dots,20\}$ billion dollars allocated according to its group population weight, we set the searching ranges for both S and W as $[0, 1]$, and the searching steps for both are set to 0.05. We rank these different combinations by their QALYs, and mark the feasible ones with 1, otherwise 0. The result shows that when total yearly budget is equal to or less than 8 billion dollars, the only feasible solutions are when the waiting percentages $W = 1$, meaning we can treat no one but only conduct screening. When total yearly budget is in the range of 8 to 16 billion dollars, for various screening percentages, the waiting percentage of 0.95 is feasible, meaning we can treat a small proportion of the HCV+ population. When total yearly budget is 18 or 20 billion dollars, when the screening percentages are in the range of [0, 0.05], the waiting percentages of 0.9 are also feasible. We can conclude that the feasible region for screening percentages is within range of [0, 1], while for waiting percentages, the feasible region is mostly within range of [0.95, 1]. So we narrow the searching range to $S \in [0, 1]$ and $W \in [0.95, 1]$ with steps of 0.05 for S and 0.01 for W. We evaluated 1386 possible combinations of S, W and total year budget, only 629 of them are feasible. Table 5.1 illustrates the number of feasible solutions under various total yearly budgets for the second search with narrowed ranges of S and W.

Table 5.1 Number of feasible solutions for different total yearly budgets

Total yearly budget	Number of feasible solutions
0	1
2	6
4	22
6	25
8	46
10	49
12	70
14	75
16	98
18	113

20	124

5.2 Basic Policy Scenario Analyses

As mentioned in section 3.5, we tried multiple combinations of input for 6 scenarios following 6 specific policies listed below, with the screening percentages in the range of $[0, 1]$ and waiting percentages in the range of $[0.95, 1]$.

Policy 1: High screening percentages with each S_t close to 1, high waiting percentages with each W_t^i close to 1

Policy 2: Low screening percentages with each S_t lower than 0.5, low waiting percentages with each W_t^i close to 0.98

Policy 3: Only spend money on treatment until the population in group B is very small, with parallel waiting percentages for patients with different fibrosis stage, then start screening

Policy 4: Only spend money on treatment until the population in group B is very small, with treatment priority for F4, then start screening

Policy 5: Only spend money on treatment until the population in group B is very small, with treatment priority for F2-F3, then start screening

Policy 6: Only spend money on treatment until the population in group B is very small, with treatment priority for F0-F1, then start screening.

We picked the combinations with the highest QALYs for each scenario and listed them in Table 5.2 with their policy number. A more detailed list with 1 combination tried for each policy for all 6 scenarios is attached in Appendix C. For scenarios 4 and 6 when the total yearly budget is 10 billion dollars and the age group is 40~49 and 60~69, because the money is enough to achieve 0.95 waiting percentages for all the health states, we do not have to put priority among different health states any more. For these scenarios, polices 4, 5 and 6 do not apply. For the convenience of comparison, we calculated the percentage of improvement of each result compared to the base case QALYs of each age group where screening percentages are 0 and waiting percentages are 1.

Table 5.2 Best simulation results tried for each scenario

Scenario Number		Total number of people screened	Total number of people treated	Total cost (discounted)	Total QALYs (discounted)	% of improvement compared to base case QALYs	Policy number
				5 billion dollars per year			
1	40-49	4,102,006	350,200	$14,753,215,764	3,839,400,155	0.0396	4
2	50-59	0	350,753	$14,298,870,512	3,183,645,763	0.0581	4
3	60-69	7,038,334	237,397	$9,974,154,819	1,801,182,824	0.035	4
				10 billion dollars per year			
4	40-49	26,444,926	715,868	$ 30,219,558,842	3,839,956,242	0.054	3
5	50-59	9,744,361	697,030	$ 28,882,956,622	3,184,717,751	0.0918	4
6	60-69	22,892,359	468,097	$ 20,019,631,312	1,801,600,784	0.0582	3

The graphs comparing discounted yearly costs with budgets, number of people screened and treated are attached in Appendix D. The input variables of screening percentages and waiting percentages associated the graph and the results listed in Table 5.2 are also included in Appendix D. They can further illustrate the impact of these different input combinations. For the sake of clarity, screening percentages are written as $S = [S_1, S_2, S_3, S_4, S_5]$ where S_t represents the screening percentages for each quarter of year $\{2t-1, 2t\}, \forall t = 1, \dots, 5$. Waiting percentages are written as $W = \begin{bmatrix} W_1^1 & \cdots & W_5^1 \\ \vdots & \ddots & \vdots \\ W_1^3 & \cdots & W_5^3 \end{bmatrix}$ where W_t^i represents the waiting percentages for each quarter of year $\{2t-1, 2t\}, \forall t = 1, \dots, 5$ and corresponding health states i. When $i = 1$, the corresponding health states are F0-F1; when $i = 2$, the corresponding health states are F2-F3; when $i = 3$, the corresponding health state is F4).

We can conclude from the result that when the budget is limited, it is better to treat patients first and put priority to patients with F4 fibrosis stage. When the budget is sufficient, we can treat patients with each health state equally, but treatment should still be put first compared to screening. For the age group 50~59, the ratio of HCV chronic patients to the whole population is higher than the other two age groups. This is the reason we can not screen anyone with limited total yearly budget of 5 billion dollars, and the reason we can not treat every patient equally regardless of health states with total yearly budget of 10 billion dollars.

5.3 RULE BASED EXHAUSTIVE SEARCH

The rules for the exhaustive grid search are:

Rule 1: treating patients with F4 health states first, then patients with F2-F3 health states, then patients with F0-F1 health states

Rule 2: treating patients with F0-F1 health states first, then patients with F2-F3 health states, then patients with F4 health states.

Rule 1 is the same with Policy 4 in the basic policy scenario analyses, and Rule 2 is the same with Policy 6 in the basic policy scenario analyses.

The decision variable is screening budget percentages for each two consecutive years, written as $Screen\_per = [SP_1, SP_2, SP_3, SP_4, SP_5]$ where SP_i represents the budget percentages for each quarter allocated for screening for year $\{2j-1, 2j\}, \forall j = 1, \ldots, 5$. The searching range for each SP_i is [0,1] with step size of 0.2. We conducted the exhaustive search for each scenario, the result is as follows:

Scenario 1 (age group 40-49, yearly budget 5 billion dollars): for rule 1 and 2, the best results are when $Screen\_per = [0,0,0,0,0]$;

Scenario 2 (age group 50-59, yearly budget 5 billion dollars): for rule 1 and 2, the best results are when $Screen\_per = [0,0,0,0,0]$;

Scenario 3 (age group 60-69, yearly budget 5 billion dollars): for rule 1 and 2, the best results are when $Screen\_per = [0,0,0,0,0]$;

Scenario 4 (age group 40-49, yearly budget 10 billion dollars): for rule 1, the best result is when $Screen\_per = [0,0,0.8,0.4,0]$, and the QALYs is 3,840,719,181; for rule 2, the best result is when $Screen\_per = [0,0,0,0,0.4]$, and the QALYs is 3,840,370,773. The difference in QALYs for rule 1 when $Screen\_per = [0,0,0,0,0]$ is 94,146, and the difference in QALYs for rule 2 when $Screen\_per = [0,0,0,0,0]$ is 12,085;

Scenario 5 (age group 50-59, yearly budget 10 billion dollars): for rule 1 and 2, the best results are when $Screen\_per = [0,0,0,0,0]$;

Scenario 6 (age group 60-69, yearly budget 10 billion dollars): for rule 1, the best result is when $Screen\_per = [0,0,0,0.6,0]$, and the QALYs is 1,801,652,714; for rule 2, the best result is when $Screen\_per = [0,0,0,0.4,0]$, and the QALYs is 1,801,523,772. The difference in QALYs for rule 1 when $Screen\_per = [0,0,0,0,0]$ is 6,463, and the difference in QALYs for rule 2 when $Screen\_per = [0,0,0,0,0]$ is 647.

We can see the optimality gap for scenario 4 and 6 when $Screen\_per = [0,0,0,0,0]$ is quite small, so we assume that for most cases, it is more beneficial to allocate all the budget to treatment first, and only screen with leftover money. To further confirm our assumption, we did a series of monotonicity checks, where we draw a line fixing 4 dimensions of the input variable and only allowing changes along the other dimension. Lumping all possible combinations for each dimension, we can get the monotonicity graphs (Figures 5.1-5.3). We find that the model does not always have monotone property under all 6 scenarios and along each dimension of the input variable.

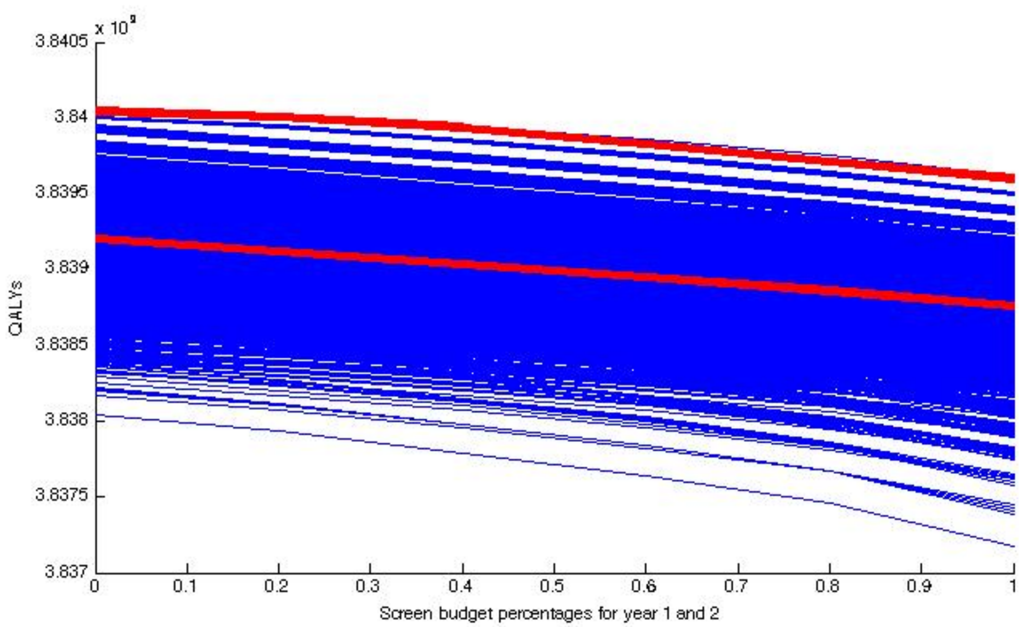

Figure 5.1 Monotonicity check for scenario 1 along dimension 1 of input, with values of dimension 2,3,4,5 from the set of {0, 0.2, 0.4, 0.6, 0.8, 1}

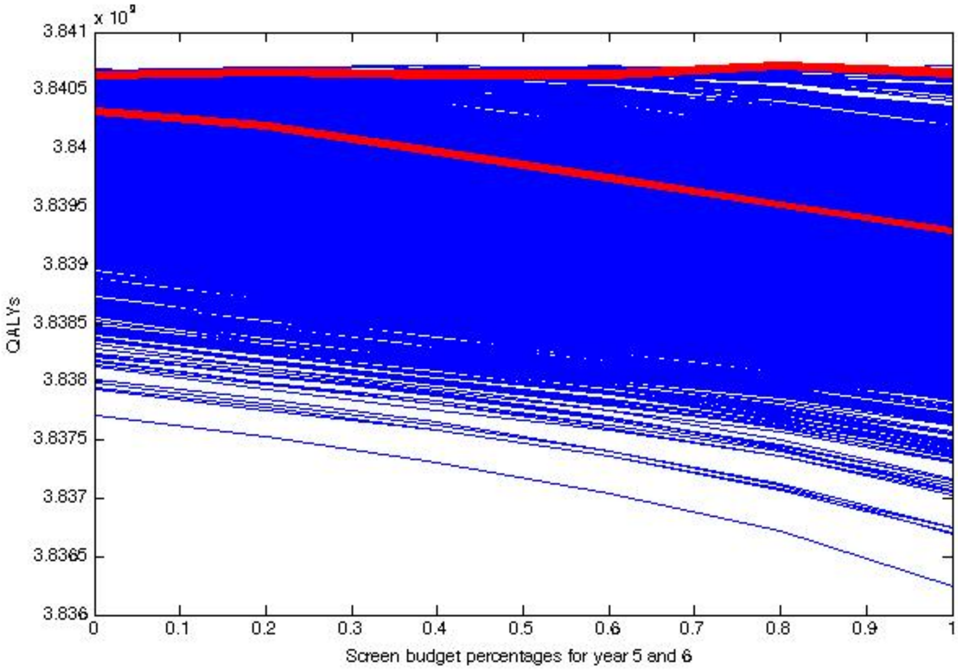

Figure 5.2 Monotonicity check for scenario 4 along dimension 3 of input, with values of dimension 1,2,4,5 from the set of {0, 0.2, 0.4, 0.6, 0.8, 1}

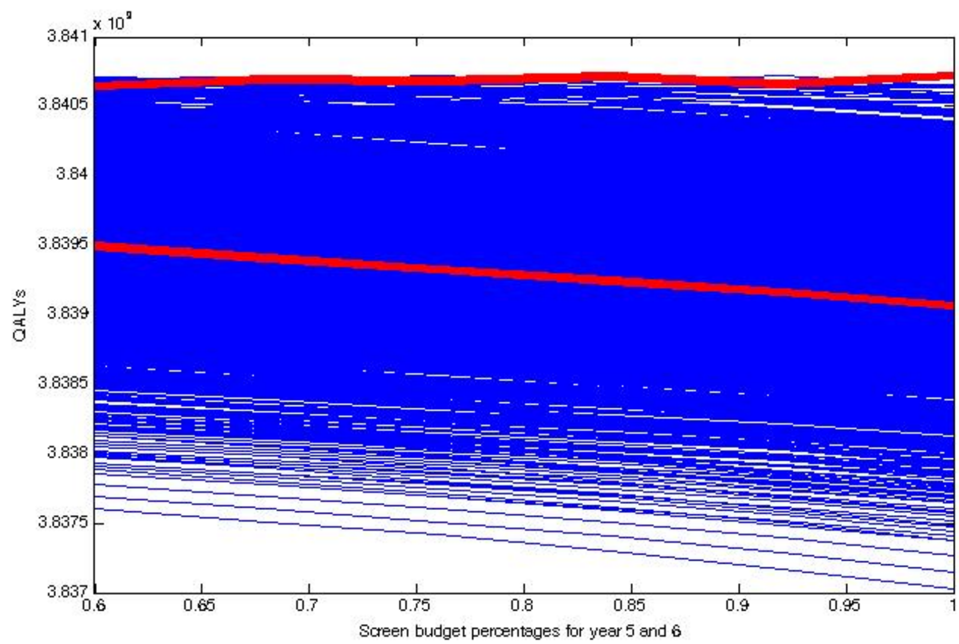

Figure 5.3 Monotonicity check for scenario 4 along dimension 3 of input with smaller searching step of 0.08 in the range of [0.6, 1], and the value of dimension 1,2,5 from the set [0, 0.2, 0.4, 0.6, 0.8, 1], value of dimension 4 from the set {0.2, 0.28, 0.36, 0.44, 0.52, 0.6}

Figures 5.1, 5.2 and 5.3 are examples of the monotonicity checks that we conducted, with red lines as highlights of what single line may look like. We can see from Figure 5.1 that in scenario 1 along dimension 1, the model is monotonically decreasing, and the optimal point is $Screen\_per = [0,0,0,0,0]$. While Figure 5.2 does not illustrate monotone property, we decide to conduct a further search with step size of 0.08 and searching range of [0.6, 1], focusing near the optimal point. Figure 5.3 is the graphic monotonicity check for this search with smaller intervals. We can see that the model does not have monotone property.

Table 5.3 and 5.4 show the QALYs gained and other results for all scenarios when $Screen\_per = [0,0,0,0,0]$. We can see that rule 1 of treating sickest patients first can achieve better QALYs than rule 2 in all the scenarios.

Table 5.3 Results of rule 1 when treat F3-F4 patients first and only screen with leftover money from treatment

Scenario Number		**Total number of people screened**	**Total number of people treated**	**Total QALYs (discounted)**	**% of improvement compared to base case QALYs**	**Rule number**
				5 billion dollars per year		
1	40-49	254,857	390,044	3,840,043,724	0.0563	1
2	50-59	0	386,720	3,184,127,430	0.0732	1
3	60-69	807,666	232,459	1,801,289,988	0.041	1
				10 billion dollars per year		
4	40-49	4,230,927	609,056	3,840,625,035	0.0715	1
5	50-59	1,297,142	713,794	3,185,361,666	0.112	1
6	60-69	3,623,835	372,555	1,801,646,251	0.0608	1

Table 5.4 Results of rule 2 when treat F0-F1 patients first and only screen with leftover money from treatment

Scenario Number		Total number of people screened	Total number of people treated	Total QALYs (discounted)	% of improvement compared to base case QALYs	Rule number
				5 billion dollars per year		
1	40-49	251,345	390,205	3,839,558,644	0.0437	2
2	50-59	0	386,720	3,183,053,133	0.0394	2
3	60-69	933,414	226,676	1,801,147,684	0.0331	2
				10 billion dollars per year		
4	40-49	4,223,711	609,389	3,840,358,688	0.0645	2
5	50-59	1,331,978	712,191	3,184,480,992	0.0843	2
6	60-69	3,757,969	366,387	1,801,523,125	0.0539	2

The graphs of number of people screened and treated each quarter for all 6 scenarios are attached in Appendix E. Similar to section 5.2, we can see that total yearly budget of 5 billion dollars is not enough for age group 50~59 to conduct screening and treat patients equally regardless of their fibrosis stage. When the total yearly budget is limited like in scenarios 1, 2, 3 and 5, it is optimal to spend the entire budget on treatment and only conduct screening with left over money each quarter. When the total yearly budget is sufficient, it is better to spend all the money on treatment first in earlier years, and conduct screening in later years combined with timely treatment.

Chapter 6. SUMMARY AND FUTURE RESEARCH

6.1 Conclusion

Chronic hepatitis C virus (HCV) infection has already become one of the most important clinical and public health problems facing modern medicine. With 2 million [1] HCV positive Americans unaware of their infection, and many among them been infected over 30 years, the public's health level is at great risk of HCV infection as well as massive amount of liver fibrosis progression. Birth-cohort HCV screening for people who are between 40 and 69 can help identify infected individuals with sever liver conditions, prevent further progression and encourage responsible behavior thus decrease the chance of infection. In this study, we design a simulation model to mimic the national level HCV healthcare system, and analyze the model using a two-stage simulation and a rule-based exhaustive search to find the optimal HCV screening and treatment budget allocation strategy in the next 10 years under yearly budget constraint.

Through careful basic policy scenario analysis and the rule based exhaustive search, we find that for all the age groups and no matter if the budget is sufficient or limited, it is always more beneficial to treat the patients in the system first and only conduct screening when there is no one left to treat. Without timely treatment, the contribution of screening alone is very limited. This finding is in accordance with the premise of Liu et al. [2]'s conclusion, where sufficient capacity to deliver prompt treatment and appropriate follow-on care to the newly screen-detected individuals are required of the HCV care system. Screening should serve as a supplement to treatment, and can only happen when we are capable to provide treatment for both the patients on hand and the new patients to be found by screening in the near future.

We also find that when the budget is limited, patients with worse liver condition (F4) should have treatment priority over patients with better liver conditions (F0-F1). This finding is especially true for the age group of 50~59. When the total yearly budget is 5 billion dollars, the other age groups of 40~49 and 60~69 can both afford to conduct some low percentages of screening, while for age group 50~59, no screening can be afforded. This indicates that the resources are relatively short compare to other two age groups, due to the higher ratio of HCV chronic patients to the age group population. So when allocating the budget for HCV care, the HCV chronic population size and distribution in different age group should also be taken into consideration. We hope this finding can provide insights for HCV care management at large healthcare systems with treatment prioritization guidance in effort to achieve better societal health benefits.

Our study has a few limitations. Because we failed to account in other benefits of screening such as improving the awareness of HCV and inducing responsible behaviors of individuals through screening, the model underestimates the benefit of screening, thus leading to the conclusion that emphasizes less on screening and more on treatment. Also the model only take yearly budget into consideration, and neglect the capacity constraints of the HCV healthcare system to deliver the services required in the model, such as available doctors appointment time, available HCV drugs etc. Incorporation these capacity constraints can further decrease the feasible regions of the model, and result in more practical conclusions.

6.2 FUTURE RESEARCH

Although the exhaustive search conducted in the research is quite efficient and requires little computational efforts, it cannot guarantee optimality. We need to better adapt our model for a more complex optimization method such as probabilistic branch and bound with confidence intervals algorithm by Huang and Zabinsky [10]. Another interesting angle is to remodel the problem as a control system with feedback signals and solve the problem from a theoretical way.

It is indicated by many trial run of the basic policy analyses that spending more money in the early planning years may bring more benefit. We can also remodel the problem with input variables of flexible budget allocation during the 10 years of planning.

One of the simplifications of our model is changing the infection and reinfection of a traditional SIR model into a constant probability of people becoming uncertain about their HCV infection status. We need to conduct further sensitivity analysis on this probability to check if our model is robust. If not, we may need to change the reinfection modeling part of our study.

BIBLIOGRAPHY

[1] Salomon, Joshua A., Milton C. Weinstein, James K. Hammitt, and Sue J. Goldie. "Empirically calibrated model of hepatitis C virus infection in the United States." American Journal of Epidemiology 156, no. 8 (2002): 761-773.

[2] Liu, Shan, Lauren E. Cipriano, Mark Holodniy, and Jeremy D. Goldhaber-Fiebert. "Cost-effectiveness analysis of risk-factor guided and birth-cohort screening for chronic hepatitis C infection in the United States." PLoS One 8, no. 3 (2013): e58975.

[3] Liu, Shan, Lauren E. Cipriano, Mark Holodniy, Douglas K. Owens, and Jeremy D. Goldhaber-Fiebert. "New protease inhibitors for the treatment of chronic hepatitis C: a cost-effectiveness analysis." Annals of internal medicine 156, no. 4 (2012): 279-290.

[4] Deo, Sarang, Kumar Rajaram, Sandeep Rath, Uday S. Karmarkar, and Matthew B. Goetz. "Planning for HIV Screening, Testing, and Care at the Veterans Health Administration." Operations Research 62, no. 2 (2015): 287-304.

[5] Allison, Robert D., Cathy Conry-Cantilena, Deloris Koziol, Cathy Schechterly, Paul Ness, Joan Gibble, David E. Kleiner, Marc G. Ghany, and Harvey J. Alter. "A 25-year study of the clinical and histologic outcomes of hepatitis C virus infection and its modes of transmission in a cohort of initially asymptomatic blood donors." Journal of Infectious Diseases 206, no. 5 (2012): 654-661.

[6] Liu S, Decision Analytics and Optimization in Disease Prevention and Treatment (under review.)

[7] Najafzadeh, Mehdi, Karin Andersson, William H. Shrank, Alexis A. Krumme, Olga S. Matlin, Troyen Brennan, Jerry Avorn, and Niteesh K. Choudhry. "Cost-effectiveness of novel regimens for the treatment of hepatitis C virus." Annals of internal medicine 162, no. 6 (2015): 407-419.

[8] Chhatwal, Jagpreet, Fasiha Kanwal, Mark S. Roberts, and Michael A. Dunn. "Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States." Annals of internal medicine 162, no. 6 (2015): 397-406.

[9] Rauner, Marion S., Walter J. Gutjahr, Kurt Heidenberger, Joachim Wagner, and Joseph Pasia. "Dynamic policy modeling for chronic diseases: metaheuristic-based identification of pareto-optimal screening strategies." Operations research 58, no. 5 (2010): 1269-1286.

[10] Huang, Hao, and Zelda B. Zabinsky. "Adaptive probabilistic branch and bound with confidence intervals for level set approximation." Proceedings of the 2013 Winter Simulation Conference: Simulation: Making Decisions in a Complex World. IEEE Press, 2013.

[11] Hepatitis C New Drug Research and Liver Health:
http://hepatitiscnewdrugresearch.com/can-hepatitis-c-be-cured.html

[12] USPSTF, CDC Advise Screening Baby Boomer Birth Cohort for Hepatitis C:

http://www.aafp.org/news/health-of-the-public/20130625uspstf-hep-c-final-rec.html

[13] Morbidity and Mortality Weekly Report (MMWR):

http://www.hepatitisc.uw.edu/level3.php?level3=10

[14] US life table 2010

[15] US CENSUS 2010

[16] El-Kamary, Samer S., Ravi Jhaveri, and Michelle D. Shardell. "All-cause, liver-related, and non–liver-related mortality among HCV-infected individuals in the general US population." Clinical infectious diseases 53.2 (2011): 150-157.

[17] U.S. CENSUS 2013

[18] El-Kamary, Samer S., Ravi Jhaveri, and Michelle D. Shardell. "All-cause, liver-related, and non–liver-related mortality among HCV-infected individuals in the general US population." Clinical infectious diseases 53.2 (2011): 150-157.

[19] Liu, Shan, et al. "Sofosbuvir-based treatment regimens for chronic, genotype 1 hepatitis C virus infection in us Incarcerated populations: a cost-effectiveness analysis." Annals of internal medicine 161.8 (2014): 546-553.

[20] Alter, Miriam J. "Hepatitis C virus infection in the United States." Journal of hepatology 31 (1999): 88-91.

[21] Salomon JA, Weinstein MC, Hammitt JK, Goldie SJ (2003) Cost-effectiveness of treatment for chronic hepatitis C infection in an evolving patient population. Jama-Journal of the American Medical Association 290: 228–237.

[22] NHANES 2001–2008

APPENDIX A

QALYS COMPUTATION MODEL: ALGORITHM AND CODE

Algorithm:

Step 1 Reading in values of decision variables from input and parameters from excel sheet.

Step 2 Computing the number of population for different groups and tie periods using the system dynamic functions iteratively, store the values in a pre-defined matrix.

Step 3 Computing the cost for each year under the corresponding input condition

Step 4 Incorporating future benefits by computing populations beyond the budget planning years where screening proportions are 0 and waiting proportions are 1.

Step 5 Checking the feasibility by comparing the discounted costs each year to the discounted budgets, if the costs are smaller or equal to the budgets, compute and return the overall discounted QALYs accordingly; otherwise, return the QALYs as -100.

Code:

```
function [ QALYs ] = QALYs_computation2(S,W)
health_state=14;
group=3;
time_period=40;
age_catagory=2;
gender=2;
CTC=2;
year=10;
decade=6;
discount_y=xlsread('Parameter List v3.xlsx','Parameter other than mortality','D2');
discount_q=xlsread('Parameter List v3.xlsx','Parameter other than mortality','D3');
screen=zeros(time_period,gender);
wait=zeros(health_state,time_period,gender);
for g=1:gender
  for t= 1:5
    screen(8*t-7:8*t,g)=S(t);
```

```
        wait(1,8*t-7:8*t,g)=W(1,t);
        wait(2,8*t-7:8*t,g)=W(1,t);
        wait(3,8*t-7:8*t,g)=W(2,t);
        wait(4,8*t-7:8*t,g)=W(2,t);
        wait(5,8*t-7:8*t,g)=W(3,t);
    end
end
population=zeros(health_state,group,decade*time_period,gender);
population(:,:,1,1)=transpose(xlsread('Parameter List v3.xlsx','population','B16:O18'));
population(:,:,1,2)=transpose(xlsread('Parameter List v3.xlsx','population','B21:O23'));
progression=zeros(health_state,health_state,decade,gender,CTC);
progression(:,:,1,1,1)=xlsread('Parameter List v3.xlsx','progression matrix','R3:AE16');
progression(:,:,1,2,1)=xlsread('Parameter List v3.xlsx','progression matrix','R20:AE33');
progression(:,:,1,1,2)=xlsread('Parameter List v3.xlsx','progression matrix','B3:O16');
progression(:,:,1,2,2)=xlsread('Parameter List v3.xlsx','progression matrix','B20:O33');
progression(:,:,2,1,1)=xlsread('Parameter List v3.xlsx','progression matrix','R37:AE50');
progression(:,:,2,2,1)=xlsread('Parameter List v3.xlsx','progression matrix','R54:AE67');
progression(:,:,2,1,2)=xlsread('Parameter List v3.xlsx','progression matrix','B37:O50');
progression(:,:,2,2,2)=xlsread('Parameter List v3.xlsx','progression matrix','B54:O67');
progression(:,:,3,1,1)=xlsread('Parameter List v3.xlsx','progression matrix','R71:AE84');
progression(:,:,3,2,1)=xlsread('Parameter List v3.xlsx','progression matrix','R88:AE101');
progression(:,:,3,1,2)=xlsread('Parameter List v3.xlsx','progression matrix','B71:O84');
progression(:,:,3,2,2)=xlsread('Parameter List v3.xlsx','progression matrix','B88:O101');
progression(:,:,4,1,1)=xlsread('Parameter List v3.xlsx','progression matrix','R105:AE118');
progression(:,:,4,2,1)=xlsread('Parameter List v3.xlsx','progression matrix','R122:AE135');
progression(:,:,5,1,1)=xlsread('Parameter List v3.xlsx','progression matrix','R139:AE152');
progression(:,:,5,2,1)=xlsread('Parameter List v3.xlsx','progression matrix','R156:AE169');
progression(:,:,6,1,1)=xlsread('Parameter List v3.xlsx','progression matrix','R173:AE186');
progression(:,:,6,2,1)=xlsread('Parameter List v3.xlsx','progression matrix','R190:AE203');
alpha=0.7;
beta=0.9;
```

```
utility=zeros(health_state,1);
utility(:)=transpose(xlsread('Parameter List v3.xlsx','costs','B10:O10'));
CS=zeros(health_state,1);
CS(:)=transpose(xlsread('Parameter List v3.xlsx','costs','B2:O2'));
CT=zeros(health_state,1);
CT(:)=transpose(xlsread('Parameter List v3.xlsx','costs','B3:O3'));
CR=zeros(health_state,1);
CR(:)=transpose(xlsread('Parameter List v3.xlsx','costs','B5:O5'));
CC=zeros(health_state,1);
CC(:)=transpose(xlsread('Parameter List v3.xlsx','costs','B4:O4'));
budget=ones(year,1);
budget(:)=transpose(xlsread('Parameter List v3.xlsx','costs','B12:K12'));
temp1=zeros(health_state,time_period,gender);
temp2=zeros(health_state,time_period,gender);
for t=1:time_period
  for g=1:gender
    for j=1:health_state
      temp1(j,t,g)=wait(j,t,g)*population(j,2,t,g);
      temp2(j,t,g)=(1-wait(j,t,g))*population(j,2,t,g);
  end
    for i=1:5
      population(i,1,t+1,g)=(1-
alpha*beta*screen(t,g))*dot(population(:,1,t,g),progression(:,i,age_catagory,g,1))+dot(populatio
n(:,3,t,g),progression(:,i,age_catagory,g,1));
    end
    for i=6:(health_state-1)
      population(i,1,t+1,g)=(1-
alpha*beta*screen(t,g))*dot(population(:,1,t,g),progression(:,i,age_catagory,g,1));
    end
    for i=1:9
```

```
population(i,2,t+1,g)=alpha*beta*screen(t,g)*dot(population(:,1,t,g),progression(:,i,age_catagory,g,1))+dot(temp1(:,t,g),progression(:,i,age_catagory,g,1))+dot(temp2(:,t,g),progression(:,i,age_catagory,g,2));
            end
            for i=10:(health_state-1)

population(i,3,t+1,g)=alpha*beta*screen(t,g)*dot(population(:,1,t,g),progression(:,i,age_catagory,g,1))+dot(temp1(:,t,g),progression(:,i,age_catagory,g,1))+dot(temp2(:,t,g),progression(:,i,age_catagory,g,2))+dot(population(:,3,t,g),progression(:,i,age_catagory,g,1));
            end
         end
      end
      cost=zeros(year,1);
      for tau=1:year
        for t=(1+4*(tau-1)):4*tau
           for g=1:gender

cost(tau,1)=cost(tau,1)+alpha*beta*screen(t,g)*dot(CS,population(:,1,t,g))*(1+discount_q)^(-t)+dot(CT,temp2(:,t,g))*(1+discount_q)^(-t)+dot(CR,population(:,3,t,g))*(1+discount_q)^(-t)+dot(CC,(temp1(:,t,g)+population(:,1,t,g)))*(1+discount_q)^(-t);
           end
        end
       end
      for decade=2:(7-age_catagory)
         for t=(decade-1)*time_period+1:decade*time_period
            for g=1:gender
               for i=1:5
                  population(i,1,t+1,g)=dot(population(:,1,t,g),progression(:,i,age_catagory+decade-1,g,1))+dot(population(:,3,t,g),progression(:,i,age_catagory+decade-1,g,1));
               end
```

```
            for i=6:(health_state-1)
               population(i,1,t+1,g)=dot(population(:,1,t,g),progression(:,i,age_catagory+decade-
1,g,1));
            end
            for i=1:9
               population(i,2,t+1,g)=dot(population(:,2,t,g),progression(:,i,age_catagory+decade-
1,g,1));
            end
            for i=10:(health_state-1)
               population(i,3,t+1,g)=dot(population(:,3,t,g),progression(:,i,age_catagory+decade-
1,g,1));
            end
         end
      end
   end
   QALYs=0;
   tao=1;
   while (cost(tao,1)<=budget(tao)*(1+discount_y)^(-tao) && tao<=year-1)
      tao=tao+1;
   end
   if (tao==year)
      for t=1:decade*time_period
            for g=1:gender
               for i=1:health_state
                  QALYs=QALYs+utility(i)*sum(population(i,:,t,g))*(1+discount_q)^(-t);
               end
            end
         end
      else
         QALYs=-100;
      end
```

end

APPENDIX B

EXAMPLES OF PROGRESSION MATRICES

progression	40-49	female	on going											
health_state	F0:1	F1:2	F2:3	F3:4	F4:5	Decompensa	HCC:7	liver transpla	liver transpla	no HCV:10	R1:11	R2:12	R3:13	dead:14
F0:1	0.0352471	0.0002707	0	0	0	0	0	0	0	0.0001069	0.9622677	0	0	0.0021075
F1:2	0	0.035354	0.0002707	0	0	0	0	0	0	0	0.9622677	0	0	0.0021075
F2:3	0	0	0.035354	0.0002707	0	0	0	0	0	0	0	0.9622677	0	0.0021075
F3:4	0	0	0	0.035354	0.0002707	0	0	0	0	0	0	0.9622677	0	0.0021075
F4:5	0	0	0	0	0.0350833	0.0003634	0.0001781	0	0	0	0	0	0.9622677	0.0021075
Decompensated cir	0	0	0	0	0	0.9106201	0.0046351	0.0117733	0	0	0	0	0	0.0729715
HCC:7	0	0	0	0	0	0	0.6980944	0.0289358	0	0	0	0	0	0.2729698
liver transplant 1st	0	0	0	0	0	0	0	0	0.9625104	0	0	0	0	0.0374896
liver transplant sub	0	0	0	0	0	0	0	0	0.9867981	0	0	0	0	0.0132019
no HCV:10	0	0	0	0	0	0	0	0	0	0.9994916	0	0	0	0.0005084
R1:11	0	0	0	0	0	0	0	0	0	0	0.9980524	0	0	0.0019476
R2:12	0	0	0	0	0	0	0	0	0	0	0	0.9980524	0	0.0019476
R3:13	0	0	0	0	0	0	0	0	0	0	0	0	0.9980524	0.0019476
dead:14	0	0	0	0	0	0	0	0	0	0	0	0	0	1

Figure B.1 Progression matrix for female of age group 40-49 undergoing treatment

progression	40-49	female	waiting											
health_state	F0:1	F1:2	F2:3	F3:4	F4:5	Decompensa	HCC:7	liver transpla	liver transpla	no HCV:10	R1:11	R2:12	R3:13	dead:14
F0:1	0.9873148	0.007584	0	0	0	0	0	0	0	0.0029937	0	0	0	0.0021075
F1:2	0	0.9903085	0.007584	0	0	0	0	0	0	0	0	0	0	0.0021075
F2:3	0	0	0.9903085	0.007584	0	0	0	0	0	0	0	0	0	0.0021075
F3:4	0	0	0	0.9903085	0.007584	0	0	0	0	0	0	0	0	0.0021075
F4:5	0	0	0	0	0.9827245	0.0101785	0.0049895	0	0	0	0	0	0	0.0021075
Decompensa	0	0	0	0	0	0.9106201	0.0046351	0.0117733	0	0	0	0	0	0.0729715
HCC:7	0	0	0	0	0	0	0.6980944	0.0289358	0	0	0	0	0	0.2729698
liver transpla	0	0	0	0	0	0	0	0	0.9625104	0	0	0	0	0.0374896
liver transpla	0	0	0	0	0	0	0	0	0.9867981	0	0	0	0	0.0132019
no HCV:10	0.0008006	0	0	0	0	0	0	0	0	0.9986911	0	0	0	0.0005084
R1:11	0.0007994	0	0	0	0	0	0	0	0	0	0.997253	0	0	0.0019476
R2:12	0	0	0.0007994	0	0	0	0	0	0	0	0	0.997253	0	0.0019476
R3:13	0	0	0	0	0.0007994	0	0	0	0	0	0	0	0.997253	0.0019476
dead:14	0	0	0	0	0	0	0	0	0	0	0	0	0	1

Figure B.2 Progression matrix for female of age group 40-49 without treatment

progression	40-49	male	waiting											
health_state	F0:1	F1:2	F2:3	F3:4	F4:5	Decompensa	HCC:7	liver transpla	liver transpla	no HCV:10	R1:11	R2:12	R3:13	dead:14
F0:1	0.9809388	0.0126566	0	0	0	0	0	0	0	0.0029898	0	0	0	0.0034148
F1:2	0	0.9839286	0.0126566	0	0	0	0	0	0	0	0	0	0	0.0034148
F2:3	0	0	0.9839286	0.0126566	0	0	0	0	0	0	0	0	0	0.0034148
F3:4	0	0	0	0.9839286	0.0126566	0	0	0	0	0	0	0	0	0.0034148
F4:5	0	0	0	0	0.9814371	0.0101652	0.0049829	0	0	0	0	0	0	0.0034148
Decompensa	0	0	0	0	0	0.910339	0.0046337	0.0117696	0	0	0	0	0	0.0732577
HCC:7	0	0	0	0	0	0	0.6978789	0.0289269	0	0	0	0	0	0.2731942
liver transpla	0	0	0	0	0	0	0	0	0.9622133	0	0	0	0	0.0377867
liver transpla	0	0	0	0	0	0	0	0	0.9864935	0	0	0	0	0.0135065
no HCV:10	0.0008003	0	0	0	0	0	0	0	0	0.9983828	0	0	0	0.0008169
R1:11	0.0007984	0	0	0	0	0	0	0	0	0	0.9960466	0	0	0.003155
R2:12	0	0	0.0007984	0	0	0	0	0	0	0	0	0.9960466	0	0.003155
R3:13	0	0	0	0	0.0007984	0	0	0	0	0	0	0	0.9960466	0.003155
dead:14	0	0	0	0	0	0	0	0	0	0	0	0	0	1

Figure B.3 Progression matrix for male of age group 40-49 without treatment

progression	50-59	female	on going											
health_state	F0:1	F1:2	F2:3	F3:4	F4:5	Decompensa	HCC:7	liver transpla	liver transpla	no HCV:10	R1:11	R2:12	R3:13	dead:14
F0:1	0.0348856	0.0005437	0	0	0	0	0	0	0	0.0001066	0.9598679	0	0	0.0045962
F1:2	0	0.0349922	0.0005437	0	0	0	0	0	0	0	0.9598679	0	0	0.0045962
F2:3	0	0	0.0349922	0.0005437	0	0	0	0	0	0	0	0.9598679	0	0.0045962
F3:4	0	0	0	0.0349922	0.0005437	0	0	0	0	0	0	0.9598679	0	0.0045962
F4:5	0	0	0	0	0.0349958	0.0003625	0.0001777	0	0	0	0	0	0.9598679	0.0045962
Decompensated cir	0	0	0	0	0	0.9100811	0.0046324	0.0117663	0	0	0	0	0	0.0735203
HCC:7	0	0	0	0	0	0	0.6976812	0.0289187	0	0	0	0	0	0.2734001
liver transplant 1st	0	0	0	0	0	0	0	0	0.9619407	0	0	0	0	0.0380593
liver transplant sub	0	0	0	0	0	0	0	0	0.986214	0	0	0	0	0.013786
no HCV:10	0	0	0	0	0	0	0	0	0	0.9989	0	0	0	0.0011
R1:11	0	0	0	0	0	0	0	0	0	0	0.9957535	0	0	0.0042465
R2:12	0	0	0	0	0	0	0	0	0	0	0	0.9957535	0	0.0042465
R3:13	0	0	0	0	0	0	0	0	0	0	0	0	0.9957535	0.0042465
dead:14	0	0	0	0	0	0	0	0	0	0	0	0	0	1

Figure B.4 Progression matrix for female of age group 50-59 undergoing treatment

APPENDIX C

BASIC POLICY ANALYSES FOR ALL SCENARIOS

The input combinations with best QALYs are highlighted in Table C.1. Screening percentages are written as $S = [S_1, S_2, S_3, S_4, S_5]$ where S_t represents the screening percentages for each quarter of year $\{2t-1, 2t\}, \forall t = 1, \ldots, 5$. Waiting percentages are written as $W = \begin{bmatrix} W_1^1 & \cdots & W_5^1 \\ \vdots & \ddots & \vdots \\ W_1^3 & \cdots & W_5^3 \end{bmatrix}$ where W_t^i represents the waiting percentages for each quarter of year $\{2t-1, 2t\}, \forall t = 1, \ldots, 5$ and corresponding health states i. When $i = 1$, the corresponding health states are F0-F1; when $i = 2$, the corresponding health states are F2-F3; when $i = 3$, the corresponding health state is F4).

Table C.1 Input combinations tried for each policy and each scenario and their outputs

		5 billion dollars per year				
Scenario Number		Policy number	S	W	Total cost (discounted)	Total QALYs (discounted, base case subtracted)
	40-49	1	[1,1,1,1,1]	$\begin{bmatrix} 0.996 & 0.99 & 0.991 & 0.992 & 0.993 \\ 1 & 1 & 1 & 1 & 1 \\ 1 & 0.98 & 1 & 1 & 1 \end{bmatrix}$	$ 14,123,743,366	3,288,031,733
		2	[0.2,0.2,0.2,0.2,0.2]	$\begin{bmatrix} 0.988 & 0.991 & 0.992 & 0.993 & 0.994 \\ 0.99 & 0.991 & 0.992 & 0.993 & 0.994 \\ 0.98 & 0.98 & 0.98 & 0.98 & 0.98 \end{bmatrix}$	$ 15,146,063,580	3,289,024,623
		3	[0,0,0,0.01,0.01]	$\begin{bmatrix} 0.975 & 0.97 & 0.96 & 0.95 & 0.95 \\ 0.98 & 0.97 & 0.96 & 0.95 & 0.95 \\ 0.98 & 0.97 & 0.96 & 0.95 & 0.95 \end{bmatrix}$	$ 14,411,806,516	3,291,993,287
		4	[0,0,0,0.01,0.01]	$\begin{bmatrix} 0.98 & 0.97 & 0.96 & 0.95 & 0.95 \\ 0.975 & 0.97 & 0.96 & 0.95 & 0.95 \\ 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \end{bmatrix}$	$ 14,753,215,764	3,292,036,661
		5	[0,0,0,0.014,0.012]	$\begin{bmatrix} 0.988 & 0.975 & 0.96 & 0.95 & 0.95 \\ 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \\ 1 & 1 & 0.98 & 0.97 & 0.96 \end{bmatrix}$	$ 14,884,250,874	3,291,916,600
1		6	[0,0,0,0.014,0.012]	$\begin{bmatrix} 0.96 & 0.955 & 0.95 & 0.95 & 0.95 \\ 1 & 0.985 & 0.968 & 0.95 & 0.95 \\ 1 & 1 & 0.98 & 0.97 & 0.96 \end{bmatrix}$	$ 14,769,534,802	3,291,861,806
	50-59	1	[0.6,1,1,1,1]	$\begin{bmatrix} 1 & 0.9955 & 0.9955 & 0.9955 & 0.9955 \\ 1 & 0.9955 & 0.9955 & 0.9955 & 0.9955 \\ 1 & 0.9955 & 0.9955 & 0.9955 & 0.9955 \end{bmatrix}$	$ 13,672,223,166	2,633,984,439
2		2	[0.1,0.1,0.1,0.1,0.1]	$\begin{bmatrix} 0.993 & 0.994 & 0.994 & 0.995 & 0.995 \\ 0.993 & 0.994 & 0.994 & 0.995 & 0.995 \\ 0.993 & 0.994 & 0.994 & 0.995 & 0.995 \end{bmatrix}$	$ 14,030,694,186	2,634,757,267

		3	[0,0,0,0,0]	$\begin{bmatrix} 0.988 & 0.984 & 0.98 & 0.98 & 0.98 \\ 0.99 & 0.99 & 0.99 & 0.985 & 0.98 \\ 0.99 & 0.98 & 0.97 & 0.96 & 0.95 \end{bmatrix}$	$ 14,202,334,811	2,636,096,565
		4	[0,0,0,0,0]	$\begin{bmatrix} 0.992 & 0.99 & 0.987 & 0.985 & 0.98 \\ 0.992 & 0.99 & 0.987 & 0.985 & 0.98 \\ 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \end{bmatrix}$	$ 14,298,870,512	2,636,282,269
		5	[0,0,0,0,0]	$\begin{bmatrix} 1 & 1 & 1 & 0.997 & 0.99 \\ 0.973 & 0.966 & 0.96 & 0.95 & 0.95 \\ 1 & 1 & 0.99 & 0.99 & 0.98 \end{bmatrix}$	$ 14,169,922,097	2,635,897,489
		6	[0,0,0,0,0]	$\begin{bmatrix} 0.974 & 0.961 & 0.95 & 0.95 & 0.95 \\ 1 & 1 & 0.997 & 0.984 & 0.976 \\ 1 & 1 & 0.99 & 0.99 & 0.98 \end{bmatrix}$	$ 13,848,784,803	2,635,849,752
	60-69	1	[1,1,1,1,1]	$\begin{bmatrix} 1 & 0.991 & 0.991 & 0.992 & 0.992 \\ 1 & 0.991 & 0.991 & 0.992 & 0.992 \\ 0.99 & 0.99 & 0.99 & 0.99 & 0.99 \end{bmatrix}$	$ 9,544,217,452	1,253,271,540
		2	[0.2,0.2,0.2,0.2,0.2]	$\begin{bmatrix} 0.98 & 0.99 & 0.99 & 0.99 & 0.99 \\ 0.99 & 0.99 & 0.99 & 0.99 & 0.99 \\ 0.99 & 0.983 & 0.985 & 0.99 & 0.99 \end{bmatrix}$	$ 10,272,177,149	1,253,467,592
		3	[0,0,0.02,0.02,0.02]	$\begin{bmatrix} 0.977 & 0.965 & 0.95 & 0.95 & 0.95 \\ 0.975 & 0.965 & 0.95 & 0.95 & 0.95 \\ 0.97 & 0.96 & 0.95 & 0.95 & 0.95 \end{bmatrix}$	$ 9,885,616,731	1,253,798,714
		4	[0,0,0.02,0.02,0.02]	$\begin{bmatrix} 0.984 & 0.972 & 0.95 & 0.95 & 0.95 \\ 0.98 & 0.965 & 0.95 & 0.95 & 0.95 \\ 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \end{bmatrix}$	$ 9,974,154,819	1,253,819,330
		5	[0,0,0.02,0.02,0.02]	$\begin{bmatrix} 1 & 0.975 & 0.95 & 0.95 & 0.95 \\ 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \\ 1 & 0.97 & 0.95 & 0.95 & 0.95 \end{bmatrix}$	$ 10,012,018,472	1,253,766,714
3		6	[0,0,0.02,0.02,0.02]	$\begin{bmatrix} 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \\ 0.98 & 0.965 & 0.95 & 0.95 & 0.95 \\ 0.99 & 0.97 & 0.95 & 0.95 & 0.95 \end{bmatrix}$	$ 9,710,919,990	1,253,771,083
		10 billion dollars per year				
		Policy number	S	W	Total cost (discounted)	Total QALYs (discounted, base case subtracted)
	40-49	1	[1,1,1,1,1]	$\begin{bmatrix} 0.98 & 0.981 & 0.982 & 0.983 & 0.984 \\ 0.99 & 0.982 & 0.987 & 0.988 & 0.989 \\ 0.98 & 0.98 & 0.98 & 0.98 & 0.98 \end{bmatrix}$	$ 30,625,788,501	3,289,981,013
		2	[0.3,0.3,0.3,0.3,0.3]	$\begin{bmatrix} 0.975 & 0.978 & 0.981 & 0.982 & 0.983 \\ 0.975 & 0.978 & 0.981 & 0.982 & 0.983 \\ 0.975 & 0.975 & 0.975 & 0.975 & 0.975 \end{bmatrix}$	$ 30,906,695,604	3,290,511,681
		3	[0,0.07,0.04,0.04,0.03	$\begin{bmatrix} 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \\ 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \\ 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \end{bmatrix}$	$ 30,219,558,842	3,292,592,748
		4				
		5				
4		6				
	50-59	1	[1,1,1,1,1]	$\begin{bmatrix} 0.995 & 0.99 & 0.99 & 0.99 & 0.99 \\ 0.993 & 0.99 & 0.99 & 0.99 & 0.99 \\ 0.99 & 0.985 & 0.985 & 0.985 & 0.985 \end{bmatrix}$	$ 28,732,702,423	2,635,626,287
5		2	[0.2,0.2,0.2,0.2,0.2]		$ 30,111,416,553	2,636,140,678

				$\begin{bmatrix} 0.987 & 0.988 & 0.988 & 0.987 & 0.987 \\ 0.987 & 0.988 & 0.988 & 0.988 & 0.988 \\ 0.983 & 0.983 & 0.983 & 0.988 & 0.99 \end{bmatrix}$		
		3	[0,0,0.01,0.02,0.02]	$\begin{bmatrix} 0.973 & 0.97 & 0.96 & 0.95 & 0.95 \\ 0.98 & 0.97 & 0.96 & 0.95 & 0.95 \\ 0.98 & 0.965 & 0.95 & 0.95 & 0.95 \end{bmatrix}$	$ 28,446,135,067	2,637,262,742
		4	[0,0,0.01,0.02,0.025]	$\begin{bmatrix} 0.98 & 0.972 & 0.96 & 0.95 & 0.95 \\ 0.978 & 0.97 & 0.96 & 0.95 & 0.95 \\ 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \end{bmatrix}$	$ 28,882,956,622	2,637,354,257
		5	[0,0,0.01,0.02,0.02]	$\begin{bmatrix} 1 & 0.985 & 0.97 & 0.955 & 0.95 \\ 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \\ 0.97 & 0.96 & 0.95 & 0.95 & 0.95 \end{bmatrix}$	$ 28,323,822,973	2,637,282,006
		6	[0,0,0.01,0.02,0.02]	$\begin{bmatrix} 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \\ 1 & 0.983 & 0.968 & 0.955 & 0.95 \\ 0.99 & 0.96 & 0.95 & 0.95 & 0.95 \end{bmatrix}$	$ 27,935,330,006	2,637,195,182
6	60-69	1	[1,1,1,1,1]	$\begin{bmatrix} 0.98 & 0.975 & 0.975 & 0.975 & 0.975 \\ 0.98 & 0.975 & 0.975 & 0.975 & 0.975 \\ 0.99 & 0.99 & 0.99 & 0.99 & 0.99 \end{bmatrix}$	$ 20,205,299,794	1,253,853,930
		2	[0.2,0.2,0.2,0.2,0.2]	$\begin{bmatrix} 0.97 & 0.97 & 0.97 & 0.97 & 0.97 \\ 0.97 & 0.97 & 0.97 & 0.97 & 0.97 \\ 0.96 & 0.97 & 0.97 & 0.97 & 0.97 \end{bmatrix}$	$ 21,062,960,156	1,254,142,946
		3	[0.01,0.11,0.063,0.07,(	$\begin{bmatrix} 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \\ 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \\ 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \end{bmatrix}$	$ 20,019,631,312	1,254,237,290
		4				
		5				
		6				

APPENDIX D

GRAPHS AND INPUT VARIABLES FOR THE BEST RESULTS OF BAISC POLICY ANALYSIS

For scenario 1 where the age group is 40-49 and yearly budget is 5 billion dollars, the best combination is $S = [0,0,0,0.01,0.01]$ and $W = \begin{bmatrix} 0.98 & 0.97 & 0.96 & 0.95 & 0.95 \\ 0.975 & 0.97 & 0.96 & 0.95 & 0.95 \\ 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \end{bmatrix}$.

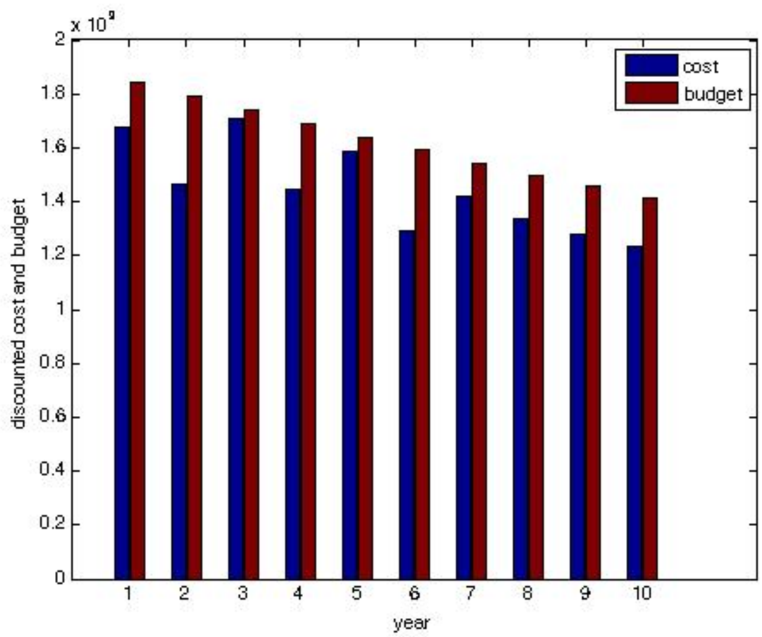

Figure D.1 Cost and budget comparison for best input of scenario 1

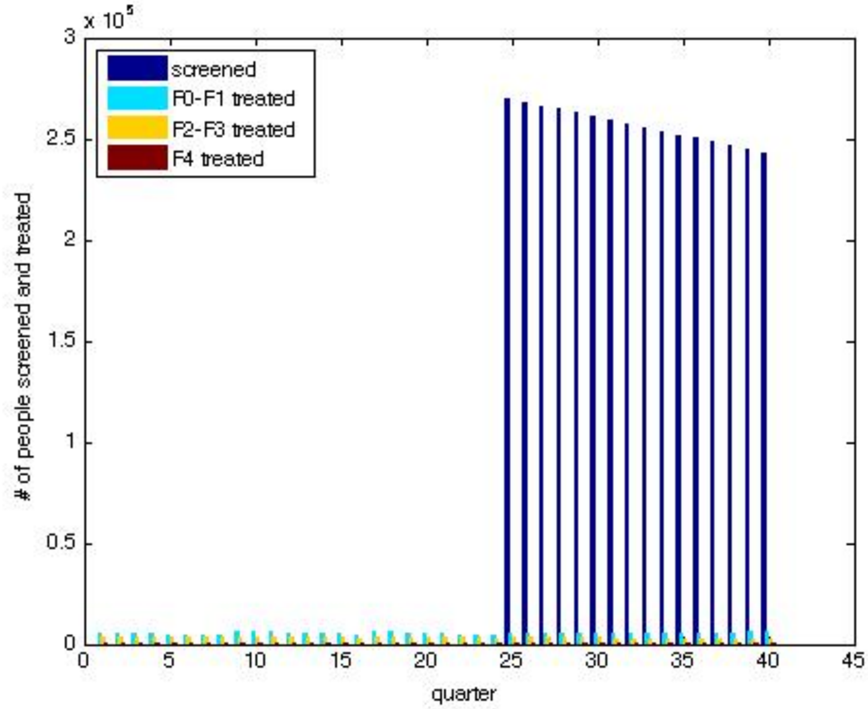

Figure D.2 Number of people screened and treated quarterly for best input of scenario 1

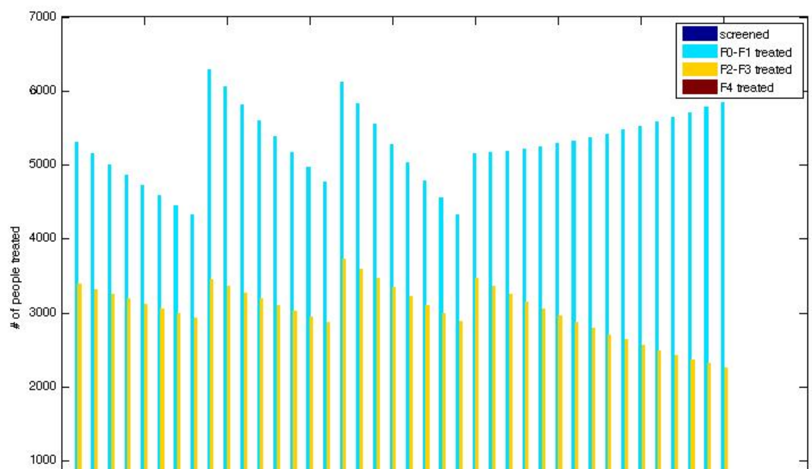

Figure D.3 Number of people treated quarterly for best input of scenario 1

For scenario 2 where the age group is 50-59 and yearly budget is 5 billion dollars, the best combination is $S = [0,0,0,0,0]$ and $W = \begin{bmatrix} 0.992 & 0.99 & 0.987 & 0.985 & 0.98 \\ 0.992 & 0.99 & 0.987 & 0.985 & 0.98 \\ 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \end{bmatrix}$.

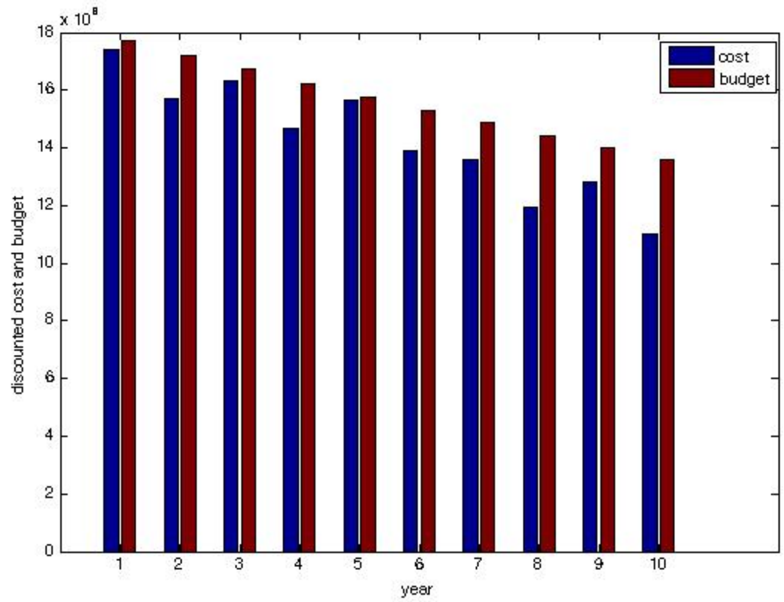

Figure D.4 Cost and budget comparison for best input of scenario 2

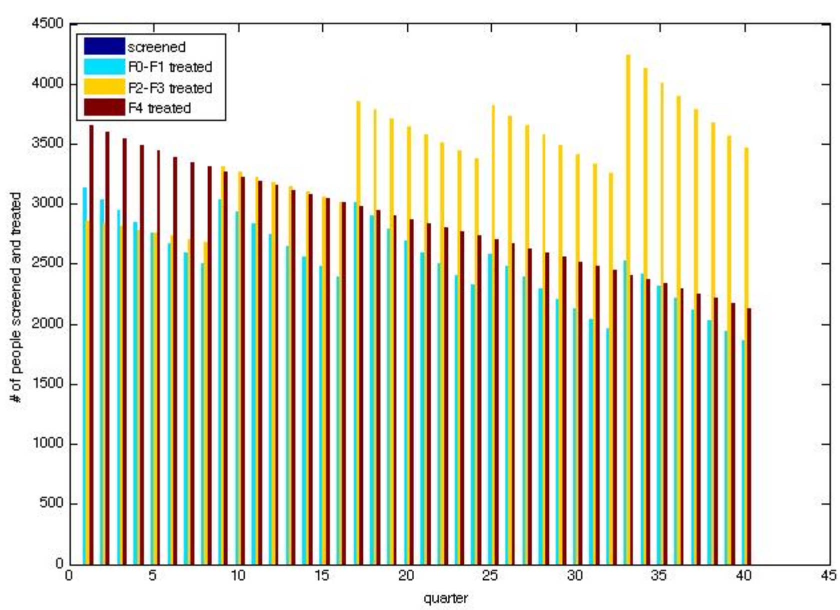

Figure D.5 Number of people screened and treated quarterly for best input of scenario 2

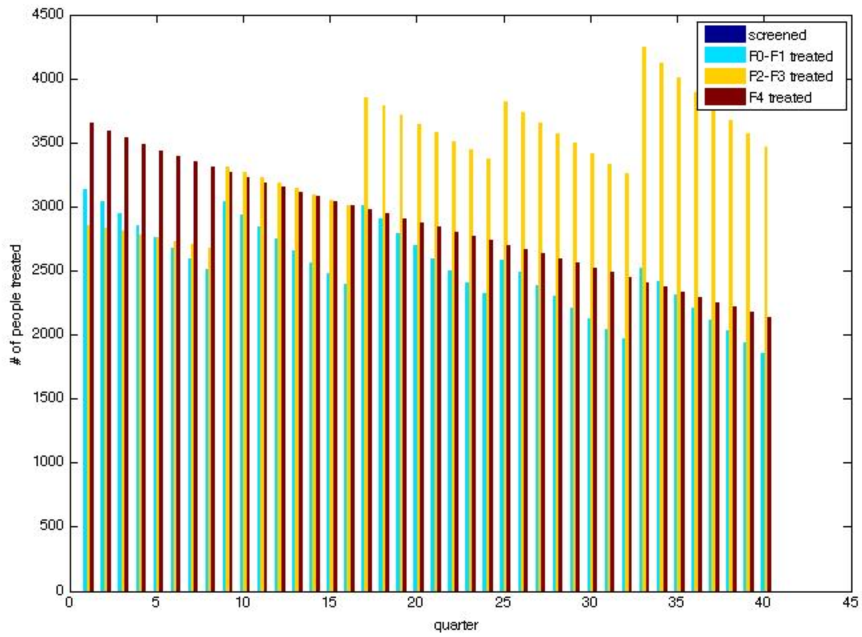

Figure D.6 Number of people treated quarterly for best input of scenario 2

For scenario 3 where the age group is 60-69 and yearly budget is 5 billion dollars, the best combination is $S = [0,0,0.02,0.02,0.02]$ and $W = \begin{bmatrix} 0.984 & 0.972 & 0.95 & 0.95 & 0.95 \\ 0.98 & 0.965 & 0.95 & 0.95 & 0.95 \\ 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \end{bmatrix}$.

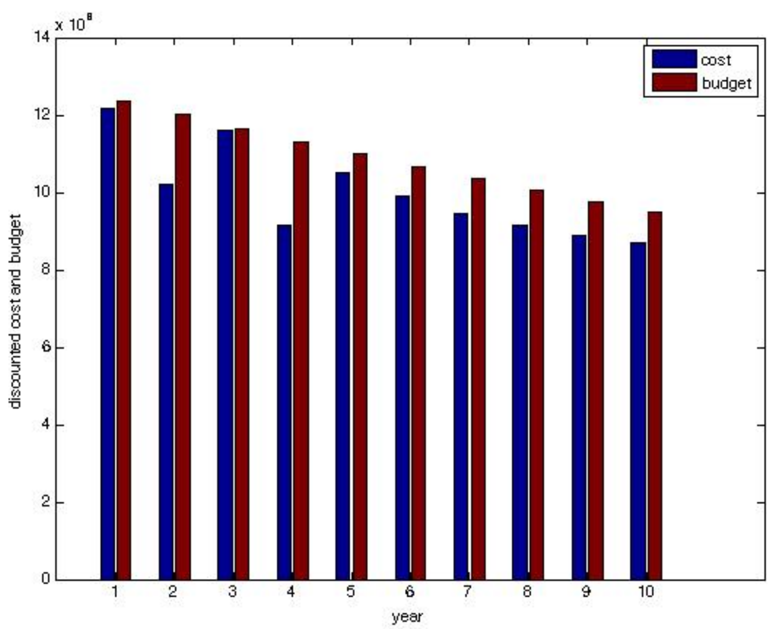

Figure D.7 Cost and budget comparison for best input of scenario 3

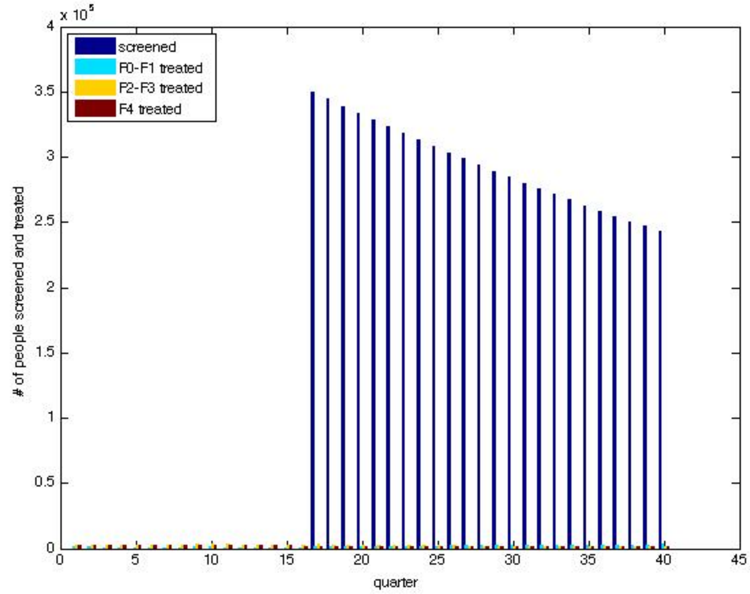

Figure D.8 Number of people screened and treated quarterly for best input of scenario 3

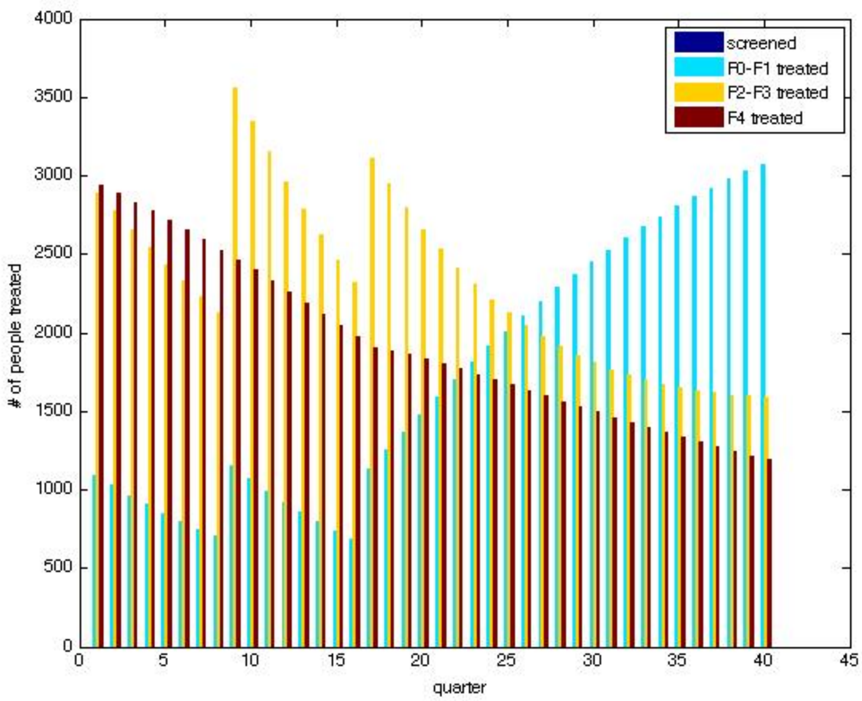

Figure D.9 Number of people treated quarterly for best input of scenario 3

For scenario 4 where the age group is 40-49 and yearly budget is 10 billion dollars, the best combination is $S = [0,0.07,0.04,0.04,0.035]$ and $W = \begin{bmatrix} 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \\ 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \\ 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \end{bmatrix}$.

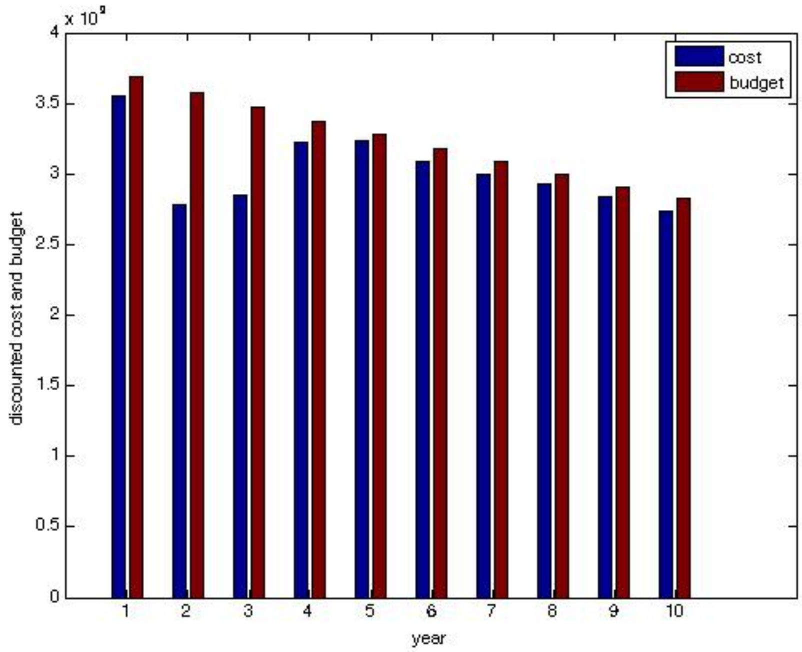

Figure D.10 Cost and budget comparison for best input of scenario 4

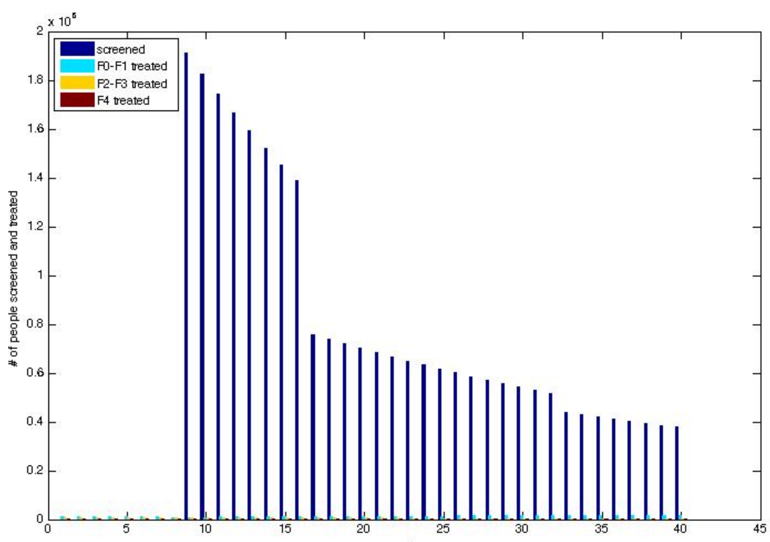

Figure D.11 Number of people screened and treated quarterly for best input of scenario 4

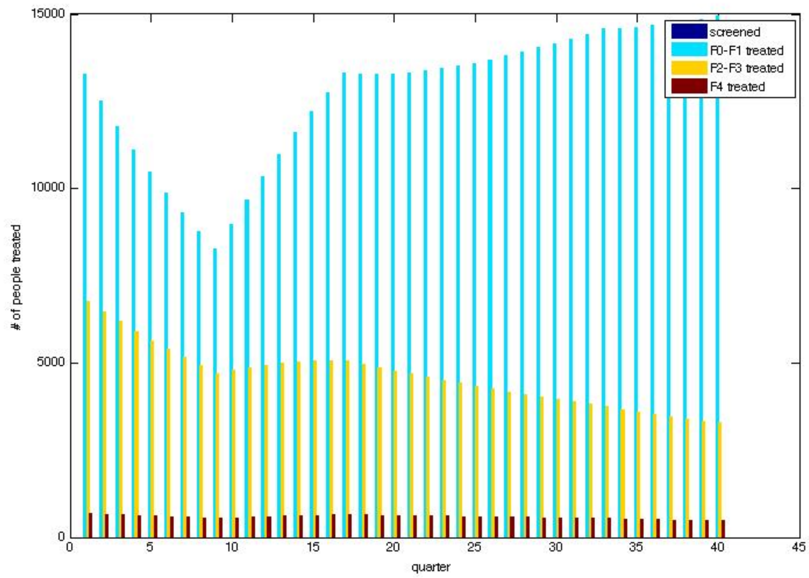

Figure D.12 Number of people treated quarterly for best input of scenario 4

For scenario 5 where the age group is 50-59 and yearly budget is 10 billion dollars, the best combination is $S = [0,0,0.01,0.02,0.025]$ and $W = \begin{bmatrix} 0.98 & 0.972 & 0.96 & 0.95 & 0.95 \\ 0.978 & 0.97 & 0.96 & 0.95 & 0.95 \\ 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \end{bmatrix}$.

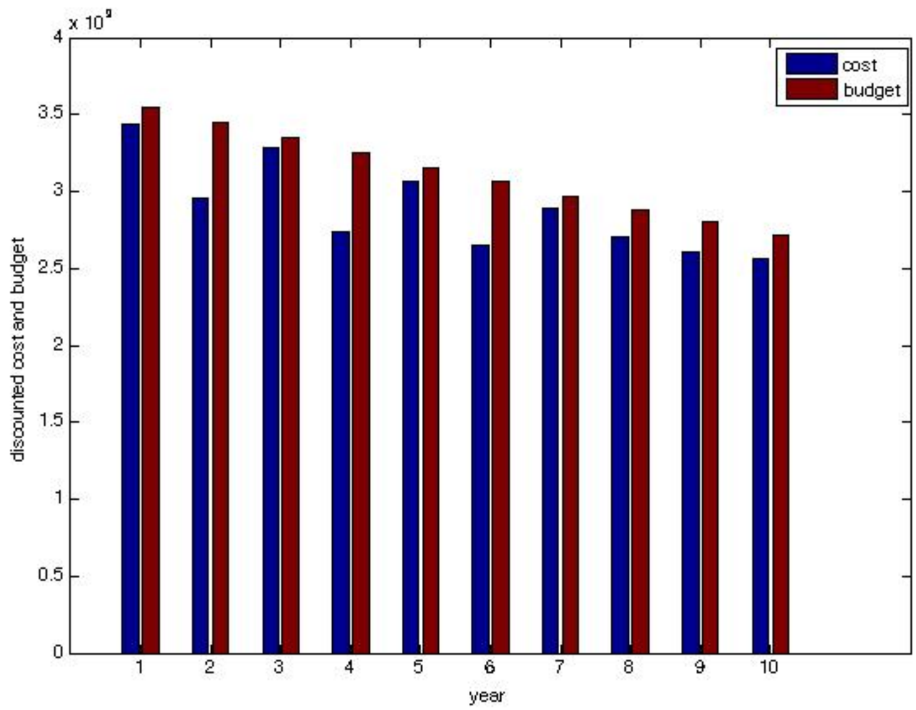

Figure D.13 Cost and budget comparison for best input of scenario 5

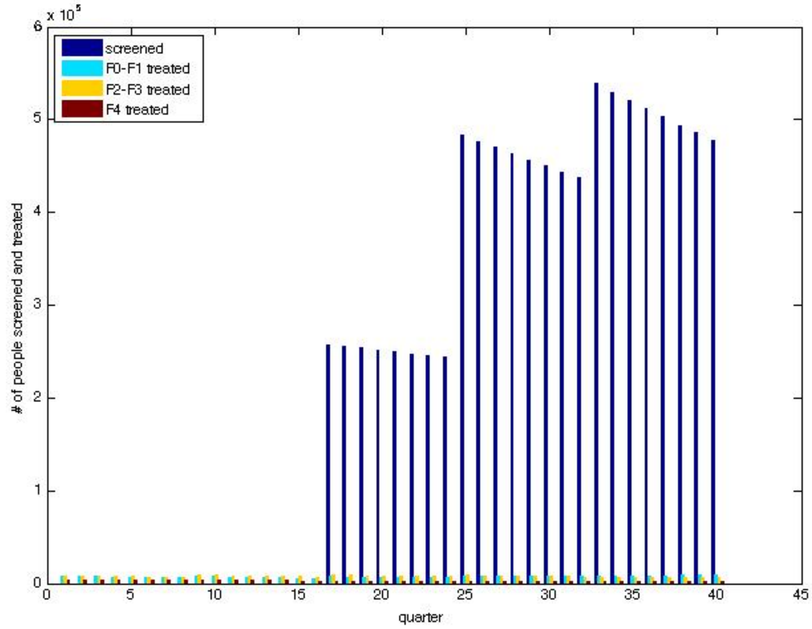

Figure D.14 Number of people screened and treated quarterly for best input of scenario 5

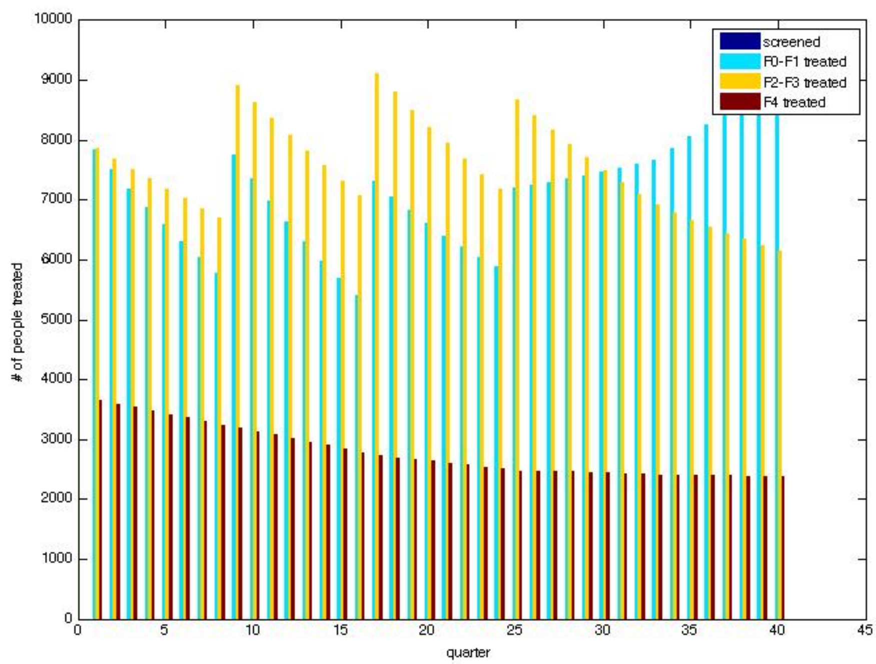

Figure D.15 Number of people treated quarterly for best input of scenario 5

For scenario 6 where the age group is 60-69 and yearly budget is 10 billion dollars, the best combination is $S = [0.01, 0.11, 0.063, 0.07, 0.08]$ and $W = \begin{bmatrix} 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \\ 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \\ 0.95 & 0.95 & 0.95 & 0.95 & 0.95 \end{bmatrix}$.

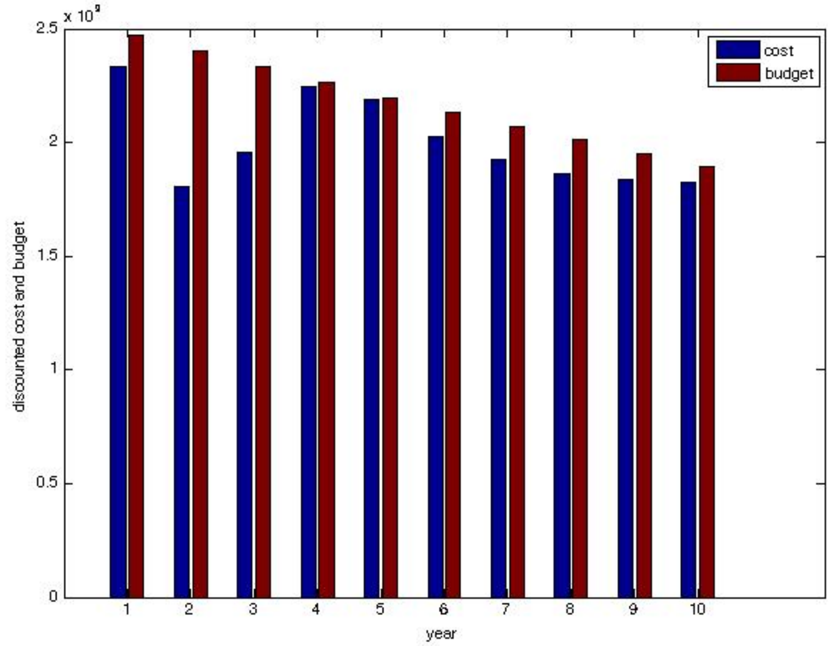

Figure D.16 Cost and budget comparison for best input of scenario 6

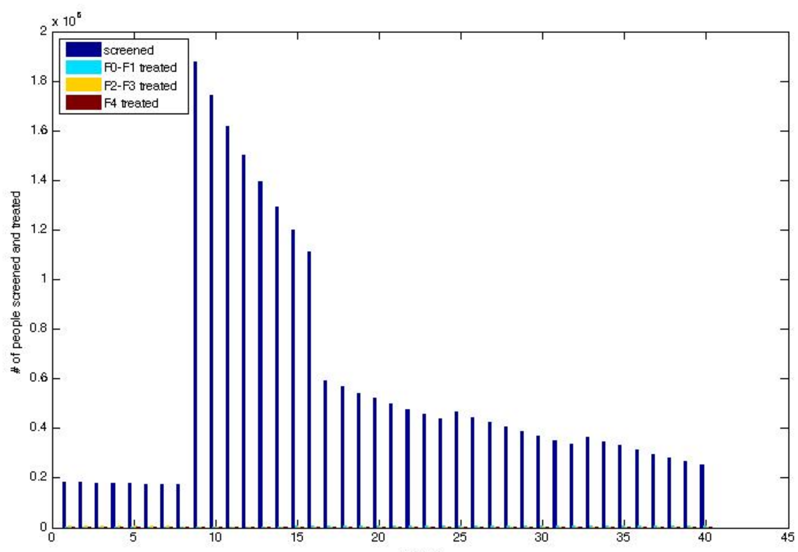

Figure D.17 Number of people screened and treated quarterly for best input of scenario 6

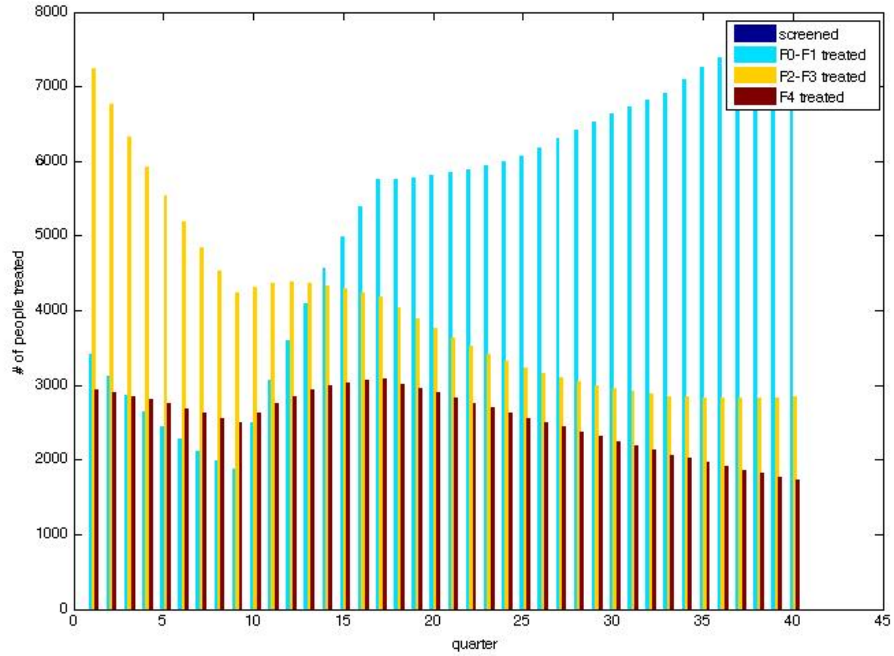

Figure D.18 Number of people treated quarterly for best input of scenario 6

APPENDIX E

GRAPHS FOR THE RULE BASED EXHAUSTIVE SEARCH

The following graphs

scenario 1: age group is 40-49, yearly budget of 5 billion dollars

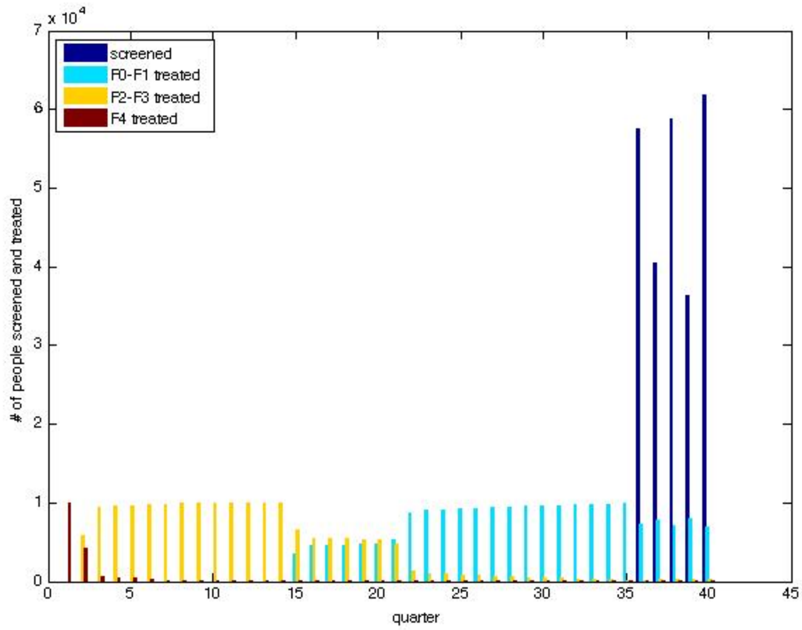

Figure E.1 Number of people screened and treated quarterly for rule 1 scenario 1

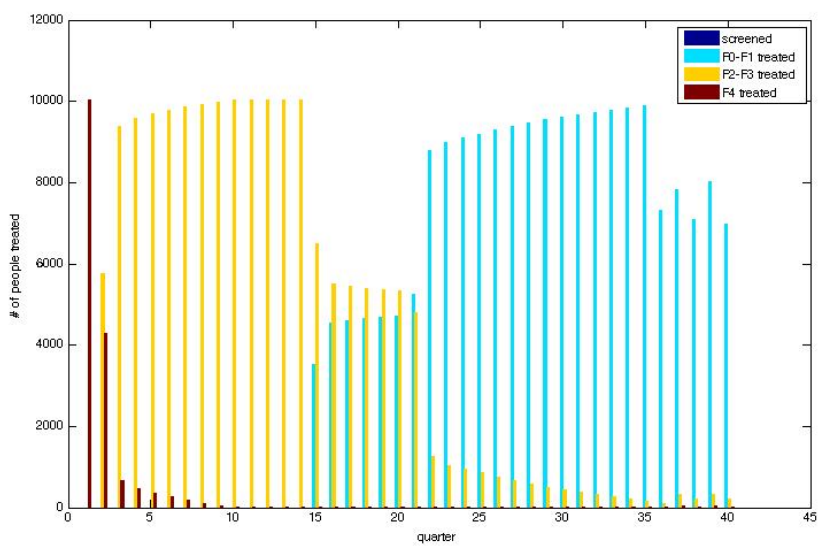

Figure E.2 Number of people treated quarterly for rule 1 scenario 1

scenario 2: age group is 50-59, yearly budget of 5 billion dollars

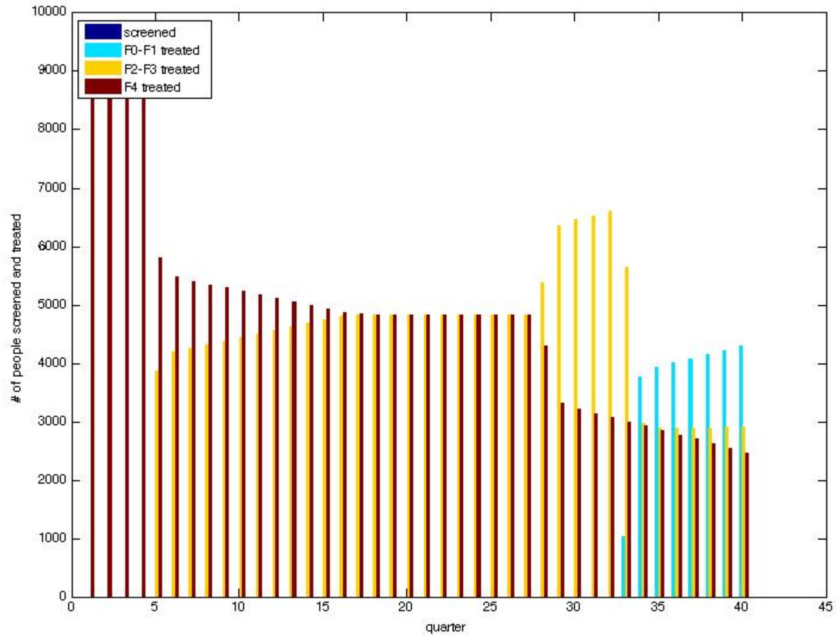

Figure E.3 Number of people screened and treated quarterly for rule 1 scenario 2

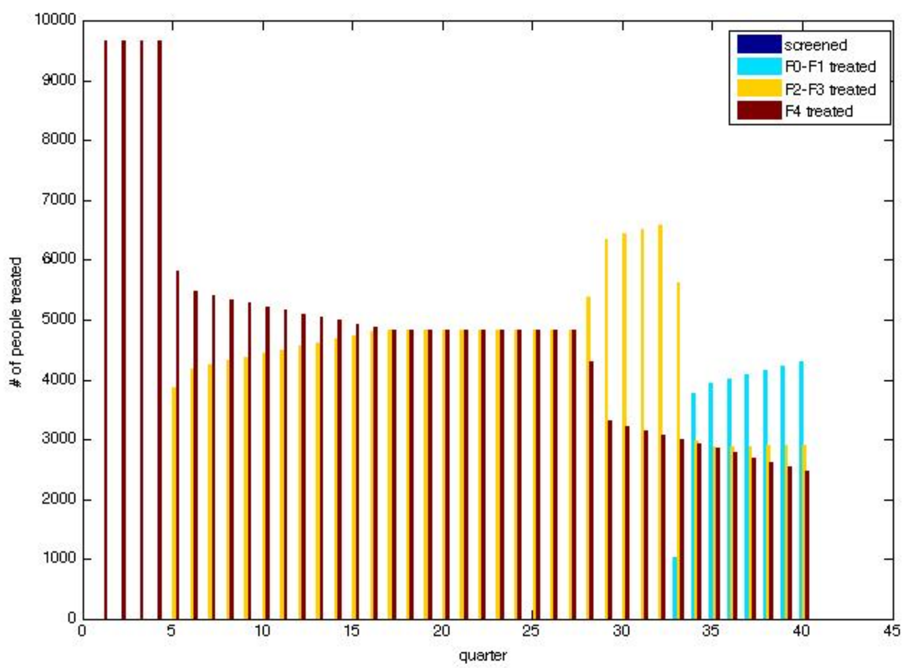

Figure E.4 Number of people treated quarterly for rule 1 scenario 2

scenario 3: age group is 60-69, yearly budget of 5 billion dollars

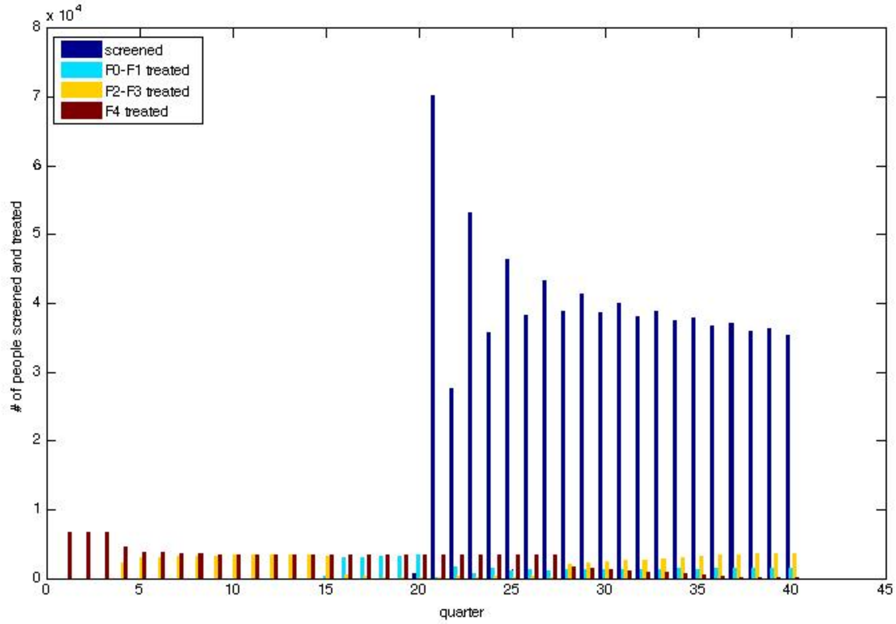

Figure E.5 Number of people screened and treated quarterly for rule 1 scenario 3

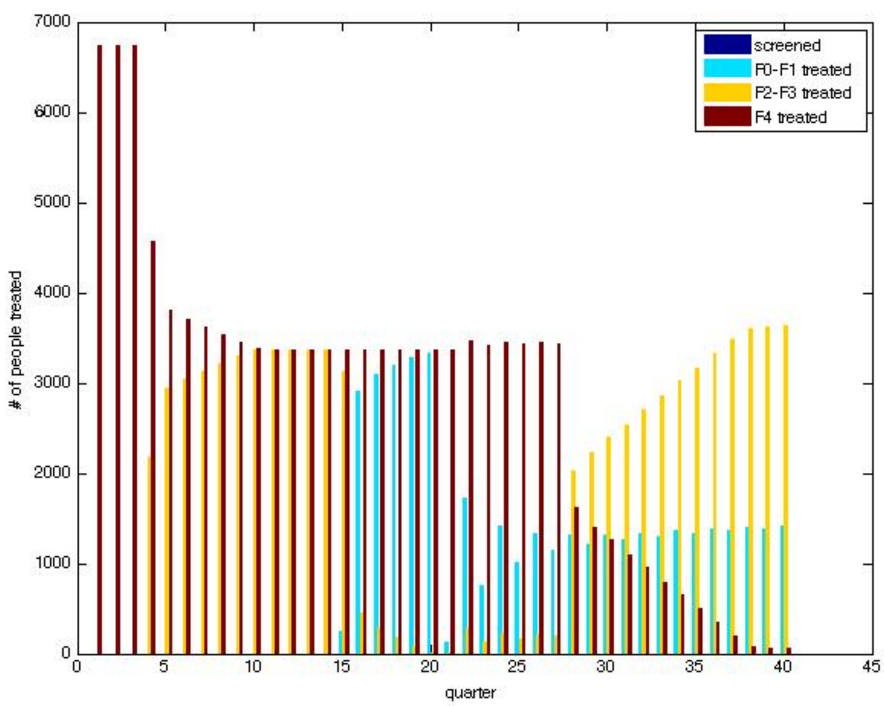

Figure E.6 Number of people treated quarterly for rule 1 scenario 3

scenario 4: age group is 40-49, yearly budget of 10 billion dollars

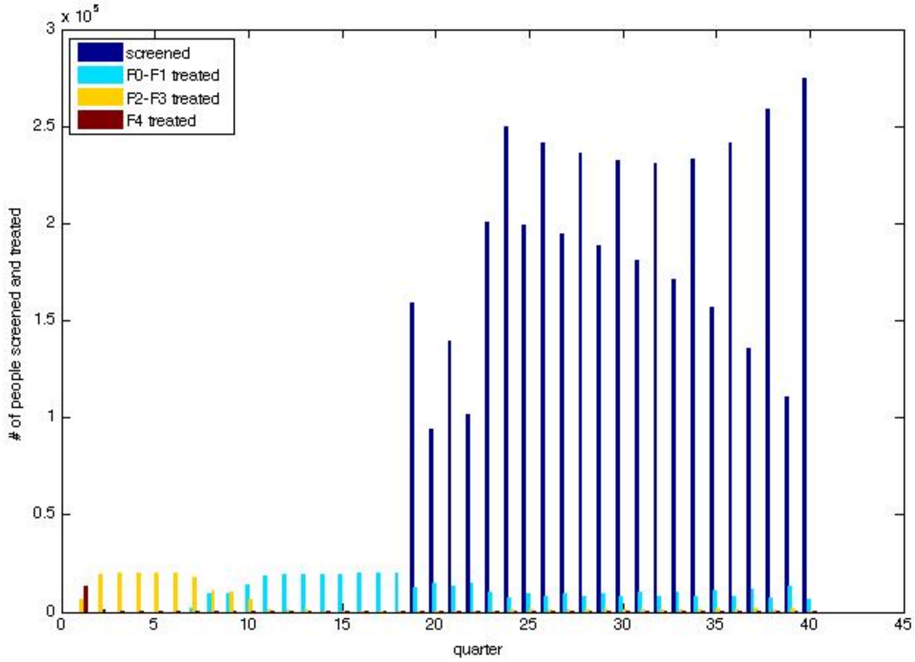

Figure E.7 Number of people screened and treated quarterly for rule 1 scenario 4

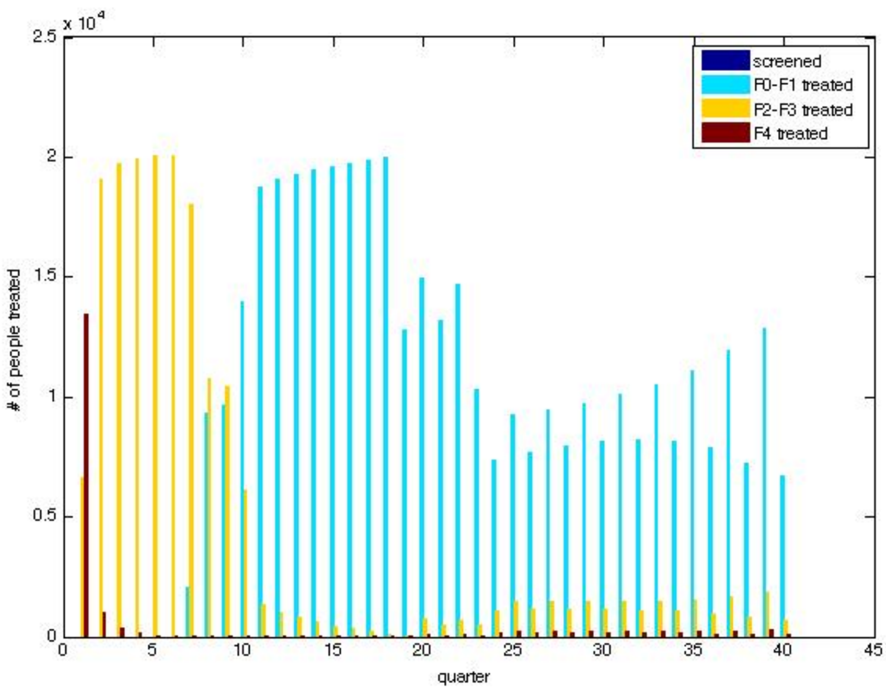

Figure E.8 Number of people treated quarterly for rule 1 scenario 4

scenario 5: age group is 50-59, yearly budget of 10 billion dollars

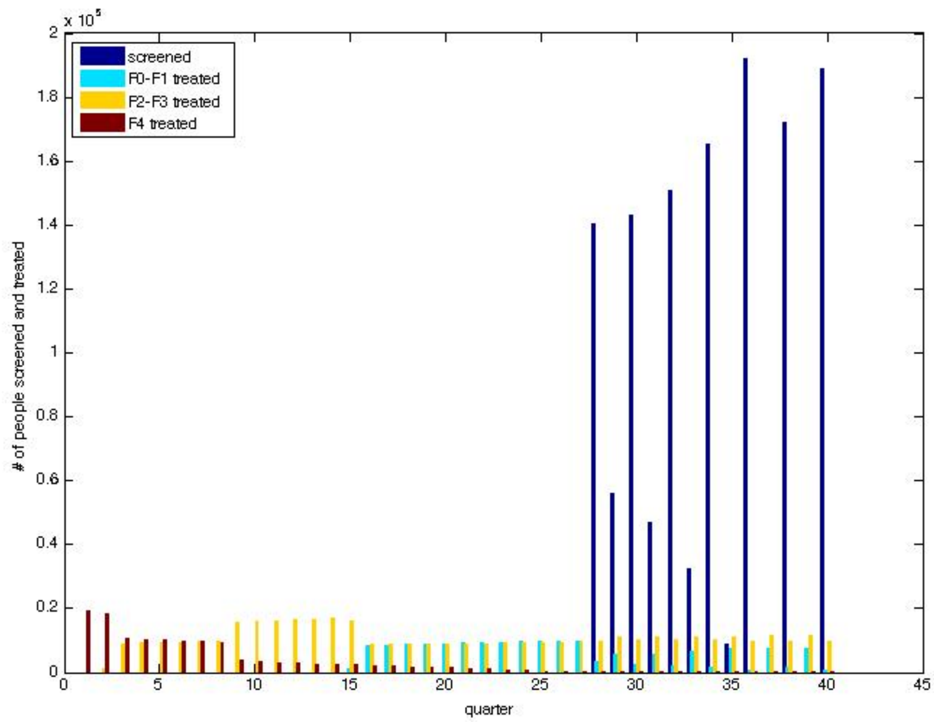

Figure E.9 Number of people screened and treated quarterly for rule 1 scenario 5

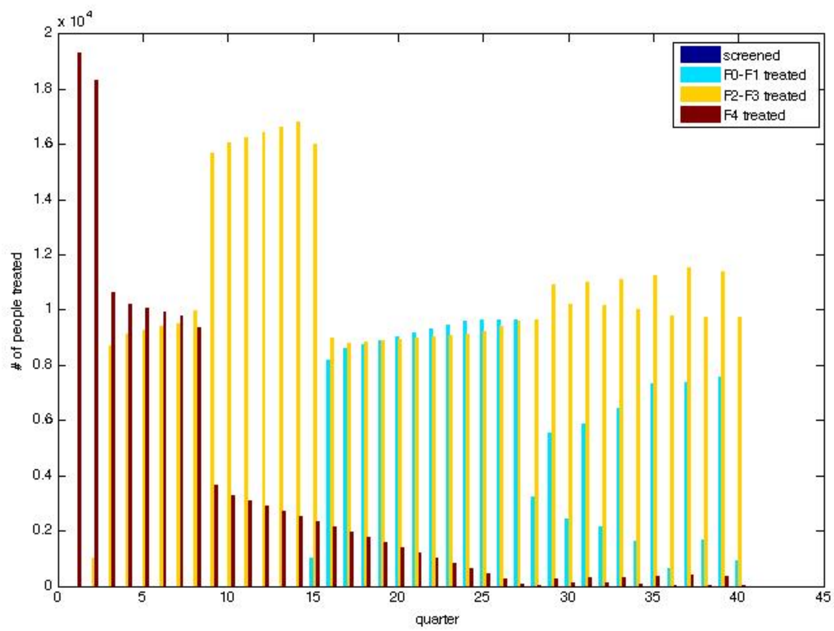

Figure E.10 Number of people treated quarterly for rule 1 scenario 5

scenario 6: age group is 60-69, yearly budget of 10 billion dollars

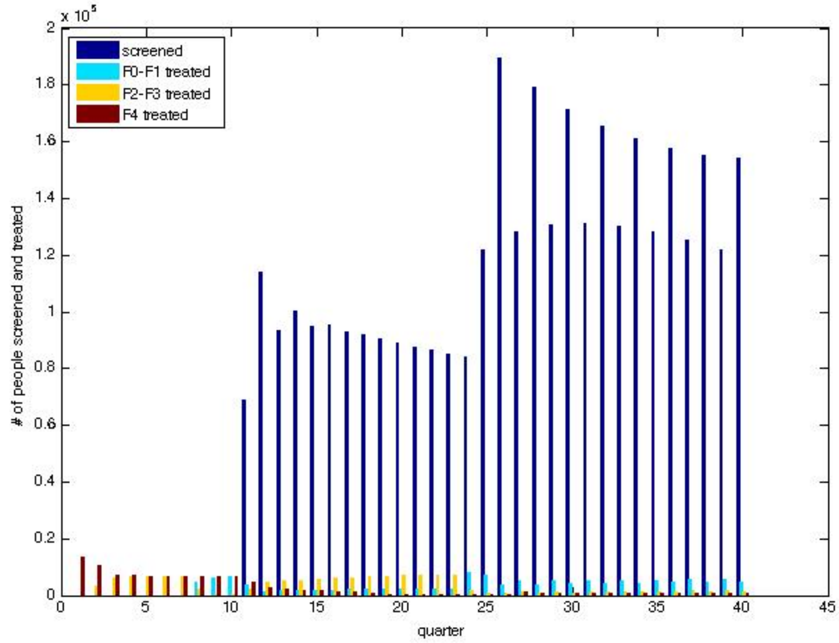

Figure E.11 Number of people screened and treated quarterly for rule 1 scenario 6

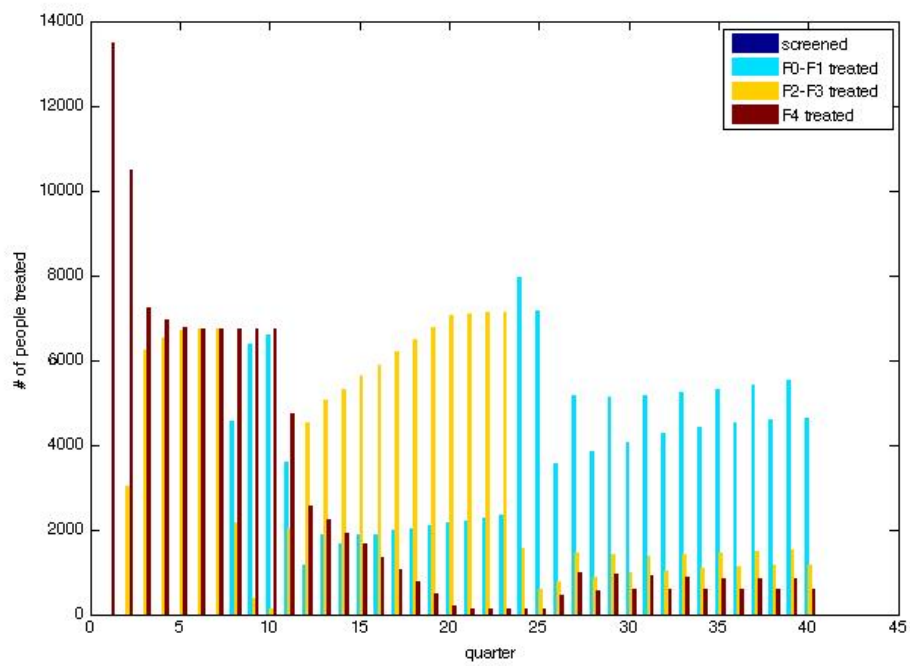

Figure E.12 Number of people treated quarterly for rule 1 scenario 6

VITA

Yuankun Li holds a Bachelor of Engineering degree in Mechanical Engineering and Automation from Tsinghua University. She's currently pursuing a MSIE degree in Industrial Engineering from University of Washington, and will graduate in December 2015.