Optimal Treatment Planning under Consideration of Patient Heterogeneity and Preparation Lead-Time

by

Mohammad Reza Skandari

B.Sc. in Industrial Engineering, Sharif University, 2007
M.Sc. in Socio-Economics Engineering, University of Tehran, 2009
M.Sc. in Industrial & Systems Engineering, The University of Florida, 2011

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

The Faculty of Graduate and Postdoctoral Studies

(Business Administration)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

August 2016

Abstract

This thesis comprises three chapters with applications of stochastic optimization models to vascular access planning for patients with chronic kidney disease (CKD). Hemodialysis (HD) is the most common treatment for patients with end-stage renal disease, the last stage of CKD. There are two primary types of vascular accesses used for HD, arteriovenous fistula (AVF), and central venous catheter (CVC). An AVF, which is created via a surgical procedure, is often considered the gold standard for delivering HD due to better patient survival and higher quality of life. However, there exists a preparation lead-time for establishing a functional AVF since it takes several months to know whether the surgery was successful, and a majority of AVF surgeries end in failure.

In this thesis, we address the question of whether and when to perform AVF surgery on patients with CKD with the aim of finding individualized policies that optimize patient outcomes. In Chapter 2, we focus on vascular access planning for HD dependent patients. Using a continuous-time dynamic programming model and under data-driven assumptions, we establish structural properties of optimal policies that maximize a patient's probability of survival and quality-adjusted life expectancy. We provide further insights for policy makers through our numerical experiments.

In Chapter 3, we develop a Monte-Carlo simulation model to address the timing of AVF preparation for progressive CKD patients who have not yet initiated HD. We consider two types of strategies based on approaches suggested in recently published guidelines. We evaluate these strategies over a range of values for each strategy, compare them with respect to different performance metrics (e.g., percentage of patients with an unnecessary AVF creation), and provide policy recommendations. Our simulation results suggest that the timing of AVF referral should be guided by the individual rate of CKD progression.

Motivated by our findings in Chapter 3, we develop a dynamic programming model in Chapter 4 that incorporates patient heterogeneity in disease progression when making clinical decisions. We then apply this modeling framework to the case of the AVF preparation timing problem introduced in Chapter 3 and provide recommendations that consider patient heterogeneity in CKD progression.

Preface

A version of Chapter 2 has been published at *Manufacturing & Service Operations Management*, 17(4): 608 - 619 (2015). A version of Chapter 3 has been published at *the American Journal of Kidney Diseases*, 63(1): 95-10 (2014).

These two papers are co-authored with Prof. Steven Shechter and Dr. Nadia Zalunardo. They were involved in the stages of problem formulation and analysis, provided feedback during the course of both research projects, and contributed to manuscript edits. I was responsible for writing the majority of these papers, developing and implementing all the models, and preparing all the numerical results.

Table of Contents

Appendices

List of Tables

List of Figures

Acknowledgments

My sincere thanks go to my supervisor, Prof. Steven Shechter at the Sauder School of Business for his invaluable help and support during my PhD studies. I am thankful to the two other members of my committee, Prof. Mahesh Nagarajan at the Sauder School of Business, and Dr. Nadia Zalunardo (MD) at the Department of Medicine for their insightful comments and suggestions.

I would also like to thank my wife Negar and my parents for their support and encouragement throughout these years which made all this possible.

To my wife, Negar.

Chapter 1

Introduction

There has been a growing interest in the application of mathematical models developed in the field of Operations Research (OR) to health-care problems. These models can help policy makers and practitioners to deliver high quality care, at a low cost, in a timely manner. Treatment planning, an active area in the field of health-care analytics, deals with complex decisions a clinician faces on a daily basis; decisions such as when to start a medication regiment, if/when to refer a patient for surgery, and how often to monitor patients with a chronic disease.

Approximately 23 million American adults have chronic kidney disease (CKD) [1] and 550,000 have end-stage renal disease (ESRD) [2]. Most ESRD patients are treated with hemodialysis (HD) [3]. In order to perform HD, patients need to have a vascular access. The preferred vascular access for HD is an arteriovenous fistula (AVF) [3] due to greater longevity and lower complication rates; however, it may take several months and more than one surgical procedure to establish a usable AVF [4, 5]. If the AVF is created too late, it may not mature in time, and a central venous catheter (CVC) may be used; however, CVCs are associated with an increased risk of morbidity and mortality [6–9]. On the other hand, creating an AVF too early is undesirable due to a small increase in risk of complications and wasting the limited lifetime of an AVF before HD is needed [10].

Existing guidelines for whether/when to refer a patient for the AVF creation surgery are inconsistent and based on expert opinion [10]. In my thesis, I investigate the vascular access planning problem for patients with CKD. One of the key features of this problem is that unlike other treatments where they can be administered whenever desired, using an AVF as the vascular access for HD requires a stochastic preparation lead-time (the time from the first AVF surgery until an functional AVF becomes available). Heterogeneity of patients with respect to the rates at which CKD progresses [11] is another feature of this problem. We develop three data-driven analytical models that incorporate these features when designing patient-specific treatment plans. In the remainder of this chapter, I briefly describe and motivate each chapter, discuss the objectives, and outline main results of our models.

1.1 Optimal Vascular Access Planning on Hemodialysis

In Chapter 2, we investigate vascular access planning for CKD patients who have started HD. Using AVF for HD is associated with better survival and quality of life in comparison with HD using a CVC [7, 12]. Nevertheless, the process of AVF creation has some disutility associated with it, which can be attributed to the surgery and post-surgery inconveniences, complications or costs. Therefore, it is not clear under what conditions an HD dependent patients should undergo the AVF creation surgery.

The purpose of this chapter is to address the following questions: 1. Whether new HD patients should undergo a surgery for AVF creation or not, and 2. Whether an AVF surgery should be performed on existing HD patients if a previous AVF fails. We develop a dynamic programming model to find individualized optimal policies that maximize a patient's probability of survival and remaining quality adjusted life expectancy considering factors such as the patient's age at the time of decision and hemodialysis onset, probability of AVF surgery success, hemodialysis related utilities, and the AVF creation disutility. We show structural properties of optimal policies under certain modeling assumption. As an extension, we consider the possibility of kidney transplant and how it affects optimal vascular access planning decisions. We provide further insights for policy makers through our numerical experiments.

1.2 Optimal Vascular Access Planning Prior to Hemodialysis

In Chapter 3, we investigate vascular access planning for CKD patients who have not yet started HD. Due to the AVF preparation lead-time (the time from the first AVF surgery until a functional AVF becomes available), guidelines recommend starting the AVF preparation process well in advance of HD need. If the AVF is created too late, it may not be ready in time, and a CVC may be used until an AVF becomes available. A late AVF is unfavorable since the risk of morbidity and mortality increases when dialyzing with a CVC [6–9]. On the other hand, creating an AVF too early is undesirable due to wasting the limited lifetime of an AVF before HD is needed. To avoid the consequences of having a functional AVF earlier or later than HD start time, it is *ideal* for the patient to have an AVF that becomes functional right at the time of HD start. Nevertheless, due to intrinsic uncertainties in the AVF preparation lead-time as well as the time of HD initiation, the ideal case is hardly achievable.

Estimated glomerular filtration rate (eGFR) is often used as the primary measure of kidney health. Nephrologists monitor eGFR progression periodically to decide

when to initiate HD as well as when to start AVF preparation. In this chapter, we develop a detailed data-driven Monte Carlo simulation model to determine the optimal timing of the AVF preparation. We evaluated 2 strategies based on approaches suggested in recently published guidelines [13–16]:

1. a "preparation window" strategy, where AVF preparation starts as soon as a patient's HD is anticipated to begin within a specific time window (e.g., the next 12 months),

2. an "eGFR threshold" strategy, where AVF preparation starts as soon as a patient's eGFR falls below a specific threshold (e.g., eGFR < 15 mL/min/1.73m^2).

We evaluate these strategies over a range of values for each strategy (preparation windows ranging between 3-18 months and eGFR thresholds ranging between 10-30 mL/min/1.73m^2) with respect to different performance metrics (e.g., a patient's life expectancy after HD initiation and percentage of patients with an unnecessary AVF creation). We also discuss how different strategies might perform when applied across a cohort of patients that vary in initial age, level of kidney function, and rate of CKD progression.

1.3 Patient Type Bayes-Adaptive Treatment Plans

Heterogeneity of patients with respect to disease progression and response to medical interventions is an important characteristic of clinical decision making problems. In Chapter 4, we formulate and analyze the problem of designing patient type Bayes-adaptive treatment plans defined as follows. We consider designing treatment plans when treatment-dependent patient outcomes vary across the population in a way that 1) we can categorize patients into distinct types, 2) we cannot perfectly identify a patient's type a priori, and 3) the patient type can be observed partially by monitoring the patient health over time. We assume a Bayesian setting in which we start with some prior belief about the patient type and update our belief by observing the patient health over time using Bayes' rule, hence the name "patient type Bayes-adaptive treatment plans". We formulate the problem as a partially observable Markov decision process (POMDP) with a two-dimensional state-space, where the state consists of the patient health and progression type. We first provide structural properties of the value-function, as well as the optimal policy for the special case of optimal stopping problems for a multi-dimensional state-space. Then, we provide conditions under which these results can be applied to our POMDP model.

Using the framework developed for designing patient type Bayes-adaptive treatment plans, we revisit the AVF preparation timing question posed in Chapter 3 by considering two types of patients, patients with slow and fast eGFR progression. We show that under data-driven assumptions, the optimal AVF preparation timing policy is monotone in a patient's current eGFR as well as our belief that the patient is a

slow progressor. Through numerical experiments we provide recommendations that consider patient heterogeneity in chronic kidney disease progression when deciding if/when to begin the AVF preparation process. We also discuss model outputs and compare the resulting policies with existing guidelines and the policy implications.

Chapter 2

Optimal Vascular Access Planning on Hemodialysis [1]

2.1 Introduction

End-stage renal disease (ESRD), the final stage of chronic kidney disease (CKD), occurs when the kidneys can no longer perform their essential task of removing waste products from the blood. Patients with ESRD require one of two interventions to stay alive: dialysis or kidney transplantation. Dialysis refers to the removal of waste and excess water from the body by circulating blood through a filter surrounded by clean fluid. While kidney transplantation yields better patient outcomes [17], the demand for organs far outstrips the available supply, and nearly 100,000 patients await a kidney transplant in the US [18]. Therefore, dialysis is the only realistic treatment option for the majority of patients with ESRD.

Hemodialysis (HD) is the most common form of dialysis, accounting for 92% of the incident dialysis cases in 2011 [19]. HD involves the circulation of blood from a patient through a dialysis machine. The blood stream is typically accessed in one of two ways: by creation of an *arteriovenous fistula* (AVF) or by insertion of a *central venous catheter* (CVC). An AVF is created by a surgical procedure in which an artery is connected to a vein in the lower or upper arm. In contrast, placing a CVC is a minor procedure in which synthetic tubing is inserted directly into a large vein, usually in the neck. The AVF is often considered the gold standard for vascular access [14] because it is associated with lower infection and mortality rates [9] and higher quality of life [7,12]. The preference for using AVFs for HD is underscored by the *Fistula First Breakthrough Initiative (FFBI)*, whose mission is "to improve the survival and quality of life of hemodialysis patients by optimizing vascular access selection - which for most patients will be an AV fistula . . . " [20]. Current guidelines reflect this by suggesting that patients on HD should be referred for an AVF surgery when possible [14, 16].

Although the benefits of an AVF over a CVC may seem clear, there are some major differences between them that deserve careful consideration before recommending one access versus the other. First, a CVC can be used immediately after placement for HD, whereas an AVF requires a lead time of approximately 3 months

[1] A version of this chapter has been published at *Manufacturing & Service Operations Management*, 17(4): 608 - 619 (2015).

from the time of surgical creation until it has matured for possible use in HD [21]. This is the time it takes for the vein used in the AVF to become thick and large enough to support the insertion of needles necessary for each HD session. However, a significant proportion of created AVFs (around 50%) do not mature to a point they can be used for HD [22, 23]. In these cases, patients and their doctors may decide to undergo a subsequent AVF surgery, provided there are still suitable vessels located elsewhere on the arms to allow for this (typically two locations on each arm may be considered). Furthermore, even if AVF creation is successful, a mature and functional AVF has a limited lifetime, with a 15% annual failure probability [24, 25]. Finally, while an AVF has quality of life and morbidity advantages relative to a CVC once it is in use for HD, it still has several disadvantages associated with it prior to that time. Since the procedure is more invasive than a CVC insertion, it brings about the usual concerns with any surgery (e.g., patient anxiety, infection, post-operative recovery). In some cases, an AVF creation might compromise the blood supply to the hand, which can lead to permanent tissue and neurological damage. Furthermore, AVFs impose physical limitations (e.g., heavy lifting with the AVF arm is not advised), and some patients find AVFs disfiguring. In summary, an AVF is superior to a CVC *conditional* on being available for *immediate use* in HD. However, that is not the decision faced by patients and their doctors. Instead, they must decide whether or not to begin the AVF creation process, with the uncertain outcomes, disutilities, and durations just described.

The renal community has recently begun debating the complexities of vascular access choice [10], raising concerns about whether "fistula first" should continue to be the treatment paradigm for all patients. [26] and [27] discuss opposing views regarding whether or not AVF is the best vascular access for HD patients, and [28] comments on this debate. The decision is especially germane for the elderly population; [29] suggests considering factors such as an elderly patient's remaining life expectancy and personal preferences when making a recommendation of vascular access. This relates to the growing momentum in the medical community to take a personalized and shared approach (between clinicians and patients) to medical decisions, rather than the one-size-fits-all approach of most clinical guidelines [30]. The need for individualized renal care has also been emphasized in [31].

The goal of this chapter is to bring a data-driven, analytical approach to investigate if and when HD patients should undergo an AVF surgery. In the spirit of patient-centered care, we focus on the patient's perspective and consider objectives related to patient lifetime and quality-adjusted lifetime. Our study is also in line with the recent emphasis in the US on the use of comparative effectiveness research (CER) for guiding evidence-based decision making in medicine [32]. The importance of CER for guiding renal disease treatments in particular is discussed in [33]. On a similar note, [29] noted the importance of future quantitative studies evaluating timing and type of vascular access to improve mortality and quality of life in elderly patients. Our work provides decision makers with both high level analytical

insights on AVF vs. CVC decisions as well as quantitative studies to guide decisions specifically for different patient types (including the elderly).

2.2 Literature Review

In this section, we review existing literature related to our research in two categories: 1. Operations Research/Management Science (OR/MS) papers on the optimal timing of medical interventions, and 2. clinical papers describing decision-analytic models of vascular access choice for renal disease patients.

2.2.1 Optimal Timing of Medical Interventions

Decisions regarding the optimal time to apply a medical treatment or screen patients for some disease have received growing attention in the OR/MS community in the past decade. For instance, [34] developed a Markov decision model to investigate the optimal timing of a living-donor liver transplant to maximize a patient's quality adjusted life expectancy (QALE). [35] addressed the question of when to initiate HIV treatment so as to maximize the expected lifetime or quality-adjusted lifetime of a patient. [36] and [37] applied partially observable Markov decision process (POMDP) models related to breast cancer treatment. [38] used a simulation-based approximate dynamic programming algorithm to derive near optimal strategies for initiation and management of dialysis therapy. [39] investigated the problem of optimal prostate biopsy referral decisions and proved the existence of a control-limit type policy that maximizes a patient's QALE. [40] studied the effect of budgetary restrictions on breast cancer diagnostic decisions by solving a mixed-integer program that maximizes a patient's total QALE under resource constraints.

2.2.2 Vascular Access Choice

A number of decision analytic models related to AVF decision making have appeared in the recent clinical literature. [41] developed a Markov model to study cost-effectiveness of different vascular access alternatives among incident HD patients. They found that the decision of whether to use AVFs or arteriovenous grafts (AVGs), another type of vascular access used in HD, for patients with incident HD depends highly on the AVF maturation failure probability, and they suggested taking this into account for individualized access planning. [42] compared two AVF creation timing policies for a 70-year-old patient with stage 4 CKD using a Markov model and reported life expectancy and quality adjusted life expectancy as the outcomes. They recommended further research on patient preference and cost implications when making AVF creation recommendations. Using a data-driven Monte-Carlo simulation model, [43] investigated policies of AVF surgery timing for CKD patients. They assessed two classes of AVF referral policies over a range of values in terms of patient expected lifetime, proportion of AVF incident HD patients, and

proportion of unused AVFs. A recent study by [44], using the framework of [41], found that a patient's characteristics such as diabetes status and gender also affect the cost-effectiveness of a vascular access choice.

2.2.3 Contributions

The purpose of this chapter is to address the following questions: 1. Whether new HD patients should undergo a surgery for AVF creation or not, and 2. Whether an AVF surgery should be performed on existing HD patients if a previous AVF fails. We aim to find individualized optimal policies that maximize a patient's probability of survival and remaining quality adjusted life expectancy, and we consider how AVF timing policies depend on patient age.

Unlike existing papers on vascular access choice for HD patients whose recommendations are simulation-based [41, 42, 44], we have tackled the problem analytically. For instance, we prove the form of optimal policy for both lifetime and QALE metrics. Also, our work provides the optimal decision for vascular access choice for the whole duration of a patient's dependency on HD, whereas existing literature only focuses on the vascular access decision at the time of HD initiation.

Existing recommendations for vascular access choice for HD-dependent patients do not appear evidence-based, and are not patient-specific. We construct an analytical, data-driven model that incorporates several key factors when making AVF surgery decisions. In particular, patient age, AVF success probabilities, hazard rate functions for patient survival on an AVF vs. CVC, and patient quality of life measures are important drivers of our model-based recommendations.

One of the key model components in determining the optimal policy, the AVF creation disutility, may be difficult to estimate and varies from patient to patient. To circumvent this issue, we introduce a dual view of the optimal policy by using the notion of a critical disutility. We prove that at each decision point, the nephrologist needs to know only if a patient's AVF creation disutility is below or above a critical factor, rather than its exact value, to make the optimal decision. This involves engaging patients in the decision making process, by assessing their individual tolerances for undergoing surgery.

Several unique features of our research contribute to the OR/MS literature on medical decision making. We model a patient's lifetime as a continuous random variable, which facilitates our consideration of a patient's treatment-based non-stationary mortality rate. One key difference between our framework and other clinical decision making papers in the literature is that we consider treatment options which require a stochastic lead-time before they are effective. Whereas the previous models can assume a mammography, transplantation, or HIV treatment can be administered whenever it is desired, an AVF cannot be created instantaneously. Moreover, there is uncertainty regarding if and when a successful AVF will be attained. This brings an interesting dynamic to the decision, because the benefit of the AVF may not be as substantial at the time it is ready, and moreover, the

patient may die beforehand.

2.3 Modeling Framework

We consider an ESRD patient already on HD with at least one unused AVF opportunity. Note that our model will answer two types of AVF creation timing questions: 1. should patients who just begin HD on a CVC undergo an AVF surgery (assuming no AVF is already in process), and 2. should patients who have an AVF fail during the course of HD undergo an AVF surgery? We assume that the patient chooses between two vascular access types: CVC, and AVF. We discuss the role of AVGs in Section 2.6. In Figure 2.1, the decision making framework is illustrated. As the decision flowchart suggests, we make the following assumption:

Assumption 2.1 (Decision points)**.** A patient can undergo an AVF surgery at any time, provided there are remaining AVF opportunities and an AVF is not under preparation or being used.

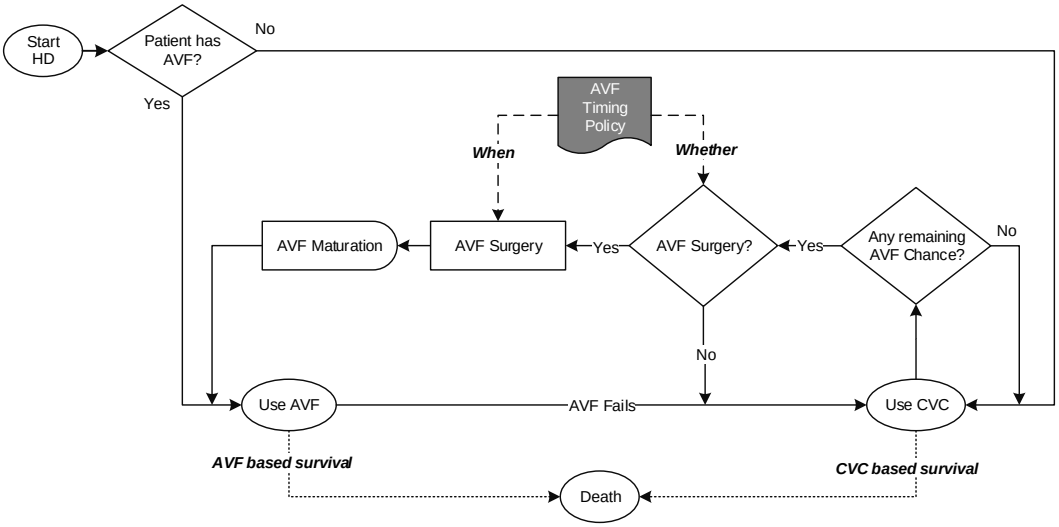

Figure 2.1: Modeling framework for vascular access dynamics (including decisions and events) for an HD-dependent patient.

The dynamics and principles of the model can be summarized as follows. A patient receives HD via an AVF as long as she has an established one. When there is no functional AVF (either when one fails or at the beginning of HD when the patient starts HD without a functional AVF) the patient dialyzes via a CVC as a bridge access. During this time, the policy determines *whether* and *when* to perform AVF surgery on the patient. If the policy recommends an AVF surgery, the patient goes

through the AVF creation process and waits until possibly attaining a functional AVF. If all AVF opportunities have been used up, or the policy recommends no further AVF creation, the patient remains on HD with a CVC until death.

We discuss clinical factors impacting the decision of whether and when to use AVF opportunities in the following sections.

2.3.1 Access-Based Patient Survival

Patient survival on HD depends on the vascular access being used [9,45]. Figure 2.2 (left), obtained from [9], shows that patients receiving HD via an AVF experience stochastically better survival than those who receive it via a CVC. Nevertheless, the survival benefit of AVF over CVC, measured by the failure rate difference, diminishes as a patient continues using HD (see Figure 2.2 (right)). In addition, a patient's failure rate on either access types increases as the HD duration increases.

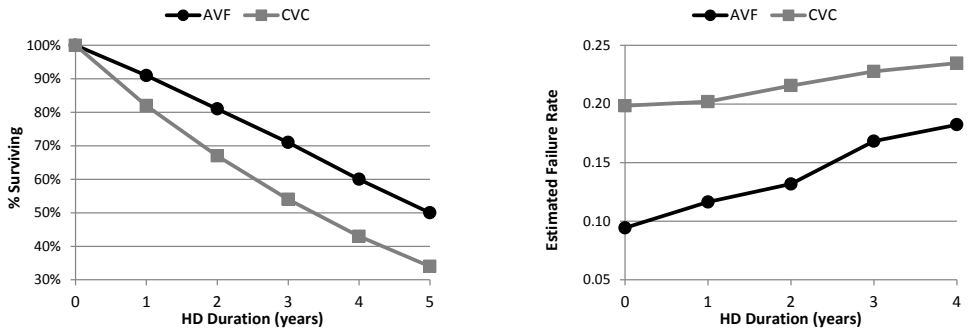

Figure 2.2: Access-based survival probability and failure rate for a 67 year old HD patient. Survival probability (left) is obtained from [9], and failure rate (right) is estimated from survival probabilities.

We use these data-driven observations to justify further assumptions below. First, we describe some notation:

- t: time since the patient started HD
- $\overline{\mathbf{F}}_{\mathbf{X}}(t)$: survival probability function of a random variable X until time t ($\overline{\mathbf{F}}_{\mathbf{X}}(t) = \mathbb{P}[X > t]$)
- $\mathbf{f}_{\mathbf{X}}(t)$: probability density function of a random variable X at time t
- $\mathbf{r}_{\mathbf{X}}(t)$: hazard rate function of a random variable X at time t
- X_t: residual lifetime of a random variable X at time t (a random variable denoting the remaining lifetime of X from time t onward conditional on survival until time t)

- $\mu(t) \in \{a, c\}$: patient's HD access type at time t (a if it is an AVF, and c, if it is a CVC).
- C: random variable denoting patient's lifetime when remaining on a CVC from HD initiation time until death.
- A: random variable denoting patient's lifetime when remaining on an AVF from HD initiation time until death.
- L: random variable denoting patient's lifetime

Note that the distributions of C and A are dependent on a patient's age at the time HD commences, but we do not denote this dependency for ease of notation.
Our next assumption describes how survival depends on HD duration and vascular access type.

Assumption 2.2 (Survival distribution)**.** A patient's remaining survival only depends on the length of time that the patient has been on HD and the ongoing mode of HD access (an AVF or a CVC).

Mathematically, Assumption 2.2 implies

$$\mathbb{P}\left(L_t \geq x \middle| \mu(t') \text{ for all } t' \leq t, \mu(s) = a \text{ for all } t \leq s \leq x + t\right) = \overline{\mathbf{F}}_{\mathbf{A_t}}(x), \tag{2.1}$$

$$\mathbb{P}\left(L_t \geq x \middle| \mu(t') \text{ for all } t' \leq t, \mu(s) = c \text{ for all } t \leq s \leq x + t\right) = \overline{\mathbf{F}}_{\mathbf{C_t}}(x). \tag{2.2}$$

We can explain Equation 2.1 (and similarly Equation 2.2) as follows. If a patient would remain on an AVF from t until $t+x$, her probability of surviving until $t+x$ is the same as a patient who has been on an AVF from HD start and has survived until t. Note that this assumption has been applied in related clinical research papers as well (see [41, 44] for instance).
The following are the definitions for common types of stochastic orders for random variables.

Definition 2.1 (Usual stochastic order)**.** We say $X \leq_{st} Y$, if and only if $\overline{\mathbf{F}}_{\mathbf{X}}(t) \leq \overline{\mathbf{F}}_{\mathbf{Y}}(t) : \forall t$.

Definition 2.2 (Hazard rate order)**.** We say $X \leq_{hr} Y$, if and only if $\mathbf{r}_{\mathbf{Y}}(t) \leq \mathbf{r}_{\mathbf{X}}(t) : \forall t$.

The following three assumptions formalize the data-driven observations of Figure 2.2 (right).

Assumption 2.3 (Relative performance)**.** The hazard rate of C is higher than or equal to the hazard rate of A, at all ages. Mathematically, we have $\mathbf{r}_{\mathbf{C}}(t) \geq \mathbf{r}_{\mathbf{A}}(t), \forall t$.

Note that Assumption 2.3 corresponds to the CVC hazard rate curve lying above the AVF hazard rate curve in Figure 2.2 (right), and is equivalent to $C \leq_{hr} A$ by definition.

Assumption 2.4 (Diminishing difference)**.** The difference between hazard rates of C and A decreases in time, i.e., $\mathbf{r_C}(t) - \mathbf{r_A}(t)$ is decreasing in t.

Note that Assumption 2.4 corresponds to the diminishing gap between the CVC hazard rate curve and the AVF hazard rate curve of Figure 2.2 (right). As we show in the Appendix A, Lemma A.3, we have that $\mathbf{r_C}(t) - \mathbf{r_A}(t)$ is decreasing in t if and only if $\frac{\overline{\mathbf{F}}_\mathbf{C}(t)}{\overline{\mathbf{F}}_\mathbf{A}(t)}$ is log-convex in t.

Finally, the following assumption states that an HD patient's mortality rate, on either access type, increases with patient age (or rather, we should more precisely say with "duration on HD").

Assumption 2.5 (Diminishing performance)**.** Random variables A and C have the increasing failure rate (IFR) property, i.e., $\mathbf{r_A}(t)$ and $\mathbf{r_C}(t)$ are increasing in t.

Assumption 2.5 is demonstrated by the fact that both curves in Figure 2.2 (right) are increasing.

We believe that assumptions posed on a patient's survival (Assumptions 2.3-2.5) are intuitive. For instance, that a patient's failure rates increase by age, or that the benefit of one intervention over another decreases with time can be justified by the aging process and increasing presence of co-morbidities as a patient ages.

2.3.2 AVF Creation Process

After a patient and her clinician decide to use an AVF for HD, she visits a vascular surgeon for AVF placement. After the surgery is performed, the AVF maturation, a process by which a fistula becomes suitable to use for HD, begins (e.g., develops adequate flow, wall thickness, and diameter). It takes approximately 3 months of AVF maturation to learn whether the AVF is usable or not for HD. However, a major issue for AVF placement is that around 50% of AVFs fail to mature [41, 46]. Furthermore, even if an AVF creation is successful, it has an annual failure probability of 15% [24, 25]. These factors are critical to the decision of whether or not a patient should undergo an AVF surgery.

We use the following notation for random variables describing the AVF creation process:

- M_i: random variable denoting the maturation time of the i^{th} AVF
- B_i: random variable denoting whether the creation of the i^{th} AVF is successful ($B_i = 1$ if successful, 0 otherwise)
- Z_i: random variable denoting the total lifetime of the i^{th} AVF given that it matures
- NF_t: number of failed AVFs creations up to time t

Note that NF_0 is not necessarily zero since the patient may have AVF creations prior to HD initiation. We make the following assumption about the AVF creation process.

Assumption 2.6 (AVF maturation and lifetime)**.** All respective random variables describing the AVF creation process are stationary. Furthermore, M_i, and Z_i are identically distributed (across subsequent creations) and independent of the history of previous AVF creations.

The stationarity of AVF creation variables is justified by the relatively short life expectancy of HD patients (average of 6.2 years [19]). To the best of our knowledge, there is no evidence in the literature on the dependence of AVF maturation time and lifetime on the history of previous creations. However, it is natural to think that patients who fail to achieve a mature AVF on one attempt are more likely to have a failed creation in future attempts, and that the failure probability increases with the number of past AVF failures.

Assumption 2.7 (AVF creation success probability)**.** The probability that an AVF matures is a decreasing function of NF, the number of previous maturation failures, i.e., $\mathbb{P}_t(B_i = 1|NF_t)$ is decreasing in NF_t for any i.

Henceforth, by "AVF surgery success", we mean achieving a functional AVF after the maturation period.

2.3.3 Objective Functions

Total Lifetime

A natural metric for comparing policies is the total lifetime of a patient. Thus, we consider maximizing a patient's total lifetime (in the usual stochastic order) as one of the objective functions.

Quality Adjusted Life Expectancy (QALE)

Using AVF for HD not only brings better survival, but also has a slightly higher quality of life for the patient, in comparison with HD using a CVC [7,12]. Nevertheless, the process of AVF creation has some disutility associated with it, which can be attributed to the surgery and post-surgery inconveniences, complications or costs. We define a patient's quality adjusted life expectancy as the quality adjusted lifetime on each vascular access minus the AVF surgery disutility for each AVF surgery performed (whether successful or not).

The following parameters are used in defining a patient's QALE:

- q_a, q_c: utility of being an HD patient who receives HD via an AVF or a CVC, respectively.

- d: AVF creation disutility

Based on the estimates in the literature [7, 12], we make the following assumption about the access-based quality of life coefficients.

Assumption 2.8 (Relative quality of life)**.** Patients experience a better quality of life dialyzing via an AVF than via a CVC, i.e., we assume $q_a \geq q_c$.

2.3.4 Dynamic Programming Formulation

To explain the dynamics of the model to optimize a patient's QALE and prove our analytical results, we formalize the decision making process with a dynamic programming model. The model components are as follows:

- **States**: The set of vectors (NF, n, t) consisting of NF, the number of previous AVF maturation failures, n, the number of AVF chances left, and t, the time since the patient started HD, corresponds to a living state, and the absorbing state Δ corresponds to the death state. Sufficiency of (NF, n, t) to represent a living state is justified by our assumptions on patient survival (Assumption 2.2) and AVF variables (Assumption 2.6). The choice of these variables to represent a patient's state will become clear when we discuss state transitions.

- **Actions**: At each state $(NF, n \geq 1, t)$, one of two actions can be taken: either to perform an AVF surgery at time $t + y$ or to perform no more AVF surgeries on the patient. Note that the no more AVF action is the case of AVF surgery at $y = \infty$. Nevertheless, we keep it in the action space for clarity. When $n = 0$, the only option is to remain on CVC for the remainder of the patient's lifetime (the no more surgeries action). The choice of the next AVF surgery time to represent actions in the modeling framework is justified by Assumption 2.1 about decision times.

- **Transitions**: Based on Assumption 2.1, we only need to consider transitions between "decision states" (i.e., the subset of living states for which the patient does not have a functional or maturing AVF but has AVF opportunities remaining), the first transition to state $(NF, 0, t)$, and the transition to state Δ.

  From decision state $(NF, n \geq 1, t)$ and planning for surgery at $t+y$, the patient may transition to one of three possible states. If the AVF matures and the patient survives until $t_1 = t + y + M + Z$, she transitions to $(NF, n - 1, t_1)$. If the AVF creation fails but the patient survives until $t_2 = t + y + M$, she transitions to $(NF+1, n-1, t_2)$. Otherwise, the patient does not survive until the next decision state and transitions to Δ.

- **Immediate reward**: The immediate reward consists of a patient's QALE from time t until the next living state or death time. If the decision is to remain

on CVC until death (either because the policy in use recommends this, or the patient uses up her AVF chances), the patient receives an immediate reward equal to her CVC utility weighted remaining lifetime ($q_c\mathbb{E}C_t$). Otherwise, at state (NF, n, t) and when the surgery is planned at $t + y$, the patient's immediate reward includes her expected weighted lifetime from time t until t' (the next decision time) or death time (sometime between t and t'), and may include an AVF creation disutility (if she survives until $t + y$). The value of t' depends on whether AVF matures or not as it was discussed in the previous section.

We discuss the value function and other components of our dynamic programming model as needed in the proofs in Appendix A.

2.4 Analytical Results

In this section, we present analytical results. All of the proofs for the analytical results are given in Appendix A.

2.4.1 Total Lifetime

Our main result concerning total lifetime is that in order to maximize an HD patient's survival probability until any time t' (and as a result to maximize expected lifetime), she should undergo an AVF surgery as soon as an opportunity becomes available. We prove this in a stochastic ordering sense: an identical patient who undergoes an AVF surgery earlier than another patient lives stochastically longer than that patient.

Theorem 2.1. Under Assumptions 2.1-2.6, delaying AVF surgery stochastically decreases a patient's lifetime.

Note that the stochastic ordering result means that the immediate surgery policy maximizes the chance a patient may survive until a kidney transplant, either through a deceased or living kidney donor (see Theorem 2.6).

We have the following general result regarding the difference in mean residual lifetimes of variables A and C.

Theorem 2.2 (Mean residual lifetime difference)**.** Let A and C be any arbitrary random variables satisfying Assumptions 2.3-2.5. We have $\mathbb{E}[A_t]-\mathbb{E}[C_t]$ is decreasing in t.

We can explain Theorem 2.2 intuitively as follows. Assumptions 2.3 and 2.4 imply that the absolute difference of hazard rates of variables A and C is decreasing in time. Also, using the definition of hazard rate function, we have $\mathbf{r}_{\mathbf{X_t}}(s) = \mathbf{r}_{\mathbf{X}}(t+s)$ for any random variable X and $t, s \geq 0$. Therefore, the difference of hazard rates of random variables $A_{t'}$ and $C_{t'}$ at any arbitrary time is less than that of A_t and C_t for any $t' \geq t$.

2.4.2 QALE

In this section, we prove the optimality of a class of policies for the QALE metric that we refer to as HD duration threshold polices. Let τ denote a policy that at state $(NF, n \geq 1, t)$ recommends an AVF surgery *immediately*, if $t < \tau(NF)$, and recommends a CVC, otherwise. Then, we have:

Theorem 2.3 (Optimality of Threshold Policies)**.** Under Assumptions 2.1-2.8, there exists a threshold policy τ^* that maximizes the QALE of the patient.

Corollary 2.1. The optimal HD duration threshold, τ^*, is decreasing in NF.

Note that the optimal policy is independent of the number of remaining AVF chances. In the next proposition, we prove that the optimal threshold can be found using a binary search.

Proposition 2.1 (Binary Search)**.** An optimal threshold policy can be found using a binary search for τ^* over $[0, t_{\max}]$, where $t_{\max}$ is a reasonable upper bound for τ^*.

We can set $t_{\max}$ equal to the time at which the patient reaches the age of 100 years because patients never undergo AVF surgeries after that age.

2.4.3 Critical Disutility

The result of Theorem 2.3 assumes one already has an estimate of the patient's disutility for an AVF creation. However, this may be difficult to estimate precisely in practice. Also, the optimal HD duration threshold needs to be calculated for different values of NF. To circumvent these challenges, we introduce a dual view of the HD duration threshold policy. We show that at any time, the decision of whether to do an AVF surgery or not is determined by comparing the patient's AVF creation disutility with a critical value. Thus, in order to make a decision, we only need to know whether the AVF creation disutility is above the critical value or not, rather than require a precise estimate of the AVF disutility itself.

Theorem 2.4 (Critical Disutility)**.** Under Assumptions 2.1-2.8, for any HD duration t, there exists a non-negative critical AVF creation disutility, denoted by $d^{\text{cr}}(NF, t)$, such that the optimal decision at time t is to perform an AVF surgery immediately if the patient's AVF creation disutility is less than the critical disutility (i.e., if $d < d^{\text{cr}}(NF, t)$), and is to use a CVC for the rest of patient's life, otherwise.

The critical disutility at t is defined as the residual QALE difference between immediate AVF surgery at t before subtracting the AVF creation disutility and staying on a CVC until death for a patient with only one AVF chance. In Theorem 2.5, we show that the critical disutility is proportional to the success probability of the current AVF creation. Therefore, one can calculate the critical disutility for different values of NF by calculating it for some baseline AVF creation success probability and then multiplying it by some factor (the ratio of the current AVF success probability given NF previous failures to the baseline value).

Theorem 2.5. Under Assumptions 2.1-2.8, the critical disutility is proportional to the AVF creation success probability.

Based on the following corollary, we can use the critical disutility function to find the critical HD duration for patients with different values of AVF creation disutility $d > 0$.

Corollary 2.2 (Relationship between Critical Disutility and Critical Duration)**.** Suppose Assumptions 2.1-2.8. Then, $\tau^*(NF) = \inf\big(t : d^{cr}(NF, t) \leq d\big)$.

Note that Theorem 2.4 provides an alternative way of comparing the optimal policy for individual patients as follows: if the critical disutility for one patient is always smaller than another, then the first patient has a smaller HD duration threshold, given that both patients have the same AVF creation disutility.

2.4.4 Kidney Transplant

In this section, we investigate an extension to the basic model by considering kidney transplant as a possible renal replacement therapy (RRT) for the patient. Since kidney transplant provides the best long-term health outcomes for the patient [17], we assume that a patient's residual QALE on transplant is higher than on HD, and the patient switches to kidney transplant as their RRT as soon as she is offered a favorable donated kidney. In other words, we assume that the decision of whether to accept a kidney donation is exogenous to our model.

Let Ψ be the (stochastic) time until a favorable kidney donation becomes available. We assume that once the patient receives the donated kidney, her future survival is independent of her HD history. Then, we can easily show that Theorem 2.1 holds under the extended model as follows.

Theorem 2.6. Under Assumptions 2.1-2.6, delaying AVF surgery stochastically decreases a patient's lifetime, when the patient receives a donated kidney at time Ψ.

For the QALE metric on the other hand, the result of the basic model (optimality of threshold policies) does not necessarily extend even under a deterministic time until transplant. We show in the following example that the optimal policy can be neither immediate surgery, nor to stay on CVC forever (i.e., until transplant or death).

Consider a patient whose access-dependent lifetime on HD follows exponential distributions with means 3 and 1.5 months, for AVF and CVC access types, respectively. Assume that the patient has a living donor who can donate a kidney after 6 months (the wait time can be due to medical tests the donor and patient should undergo, the operating room and surgeon availability, etc.). If the patient survives until transplant time, she receives 16 additional QALE months. Also assume that

the maturation time is negligible, AVFs all mature and do not expire in the first 6 months, and $q_A = q_C = 1$.

In Figure 2.3, total QALE as a function of AVF surgery time for a patient with AVF disutility of 3 months is depicted. In this case, the optimal decision is to wait and perform surgery at $t = 1.5$ months. This demonstrates that the optimal policy is not of the form "perform AVF now or never."

We can explain the behavior observed in this example as follows. On the one hand, using the AVF for HD can benefit the patient by giving her a better quality of life as well as increasing her chances of survival until the transplant time. On the other hand, because of the AVF creation disutility, the AVF should not be used too early either since the patient may die well in advance of the transplant time. Therefore, the patient should use up some survival time without the AVF, to increase the chance that when the AVF is created, it bridges the patient's survival until the time of transplant (and therefore the AVF creation is not wasted).

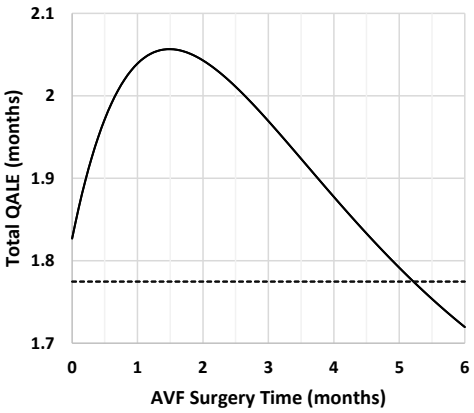

Figure 2.3: QALE plot for a patient with transplant option. Solid line depicts a patient's total QALE at $t = 0$ as a function of AVF surgery time. The dotted line shows total QALE when the patient stays on CVC until death or transplant.

Although threshold policies may be suboptimal in general, we prove their optimality under additional assumptions in the following theorem. For this result, we assume the patient has a living donor, and thus, a deterministic time until transplant seems reasonable. Also, we assume that time until transplant is short enough that AVFs, if mature, do not expire before transplant time. Finally, we allow for the possibility of transplant cancellation, for instance, if the donor changes his mind or if the donated kidney is to be found incompatible as a result of the tests.

Theorem 2.7. Suppose that the time until transplant, if it is not canceled, is deterministic, i.e., $\Psi = \psi$ for some known ψ, $\overline{\mathbf{F}}_{\mathbf{A_t}}(\psi - t) - \overline{\mathbf{F}}_{\mathbf{C_t}}(\psi - t)$ is decreasing

in t, and an AVF's lifetime, if it matures, is greater than the time until transplant with probability one. Then under Assumptions 2.1-2.8, there exists a threshold policy τ^* that maximizes the QALE of the patient.

Note that $\overline{\mathbf{F}}_{\mathbf{A_t}}(\psi - t)$ (and similarly $\overline{\mathbf{F}}_{\mathbf{C_t}}(\psi - t)$) can be interpreted as the survival probability of a patient on an AVF (CVC) until the transplant time, given her survival until t. The assumption that $\overline{\mathbf{F}}_{\mathbf{A_t}}(\psi - t) - \overline{\mathbf{F}}_{\mathbf{C_t}}(\psi - t)$ is decreasing in t is supported by the empirical data given in [9]. Also, Theorem 2.7 cannot be applied to the aforementioned example, because $\overline{\mathbf{F}}_{\mathbf{A_t}}(\psi - t) - \overline{\mathbf{F}}_{\mathbf{C_t}}(\psi - t)$ equals $e^{-\frac{1}{3}(6-t)} - e^{-\frac{1}{1.5}(6-t)}$, which is not a decreasing function.

2.5 Numerical Results

To demonstrate the results of Theorems 2.3 and 2.4, we performed a numerical study. The baseline values for different model parameters and sources used are given in Table 2.1.

Table 2.1: Baseline parameters used for calculating the critical disutility.

Variable	Value	Reference
On-HD survival (67 year old)	—	[9]
On-HD survival (82 year old)	—	[9, 45]
AVF primary failure probability (67 year old)	50%	[22, 23]
AVF primary failure probability (82 year old)	75%	[22, 23]
Yearly failure probability for a functional AVF	15%	[24, 25]
Maturation time (months)	Uniform(2,4)	[21, 22]
Utility of dialysis with AVF	0.81	[7, 12]
Utility of dialysis with CVC	0.77	[7, 12]

For patients' HD survival, we used [9], which provides only the first five years of survival outcomes for a cohort of 67 year old patients. To obtain complete survival curves, we extrapolate the hazard rate functions so that Assumptions 2.3-2.5 are satisfied. Specifically, we assume that the AVF and CVC hazard rates increase linearly after the last observed hazard rate with slopes α_A and α_C, respectively. We need to assume $\alpha_A \geq \alpha_C \geq 0$, so that Assumptions 2.4 and 2.5 are satisfied. To have Assumption 2.3 met, we modify the hazard rates for CVC such that after the point the hazard rate curves meet (if they ever meet, which is always the case when $\alpha_A > \alpha_C$), we have that $\mathbf{r_C}(t) = \mathbf{r_A}(t)$, with the slope of the line equal to α_A (see Figure 2.4 for an illustration). We calculated the average rate of increase for the AVF and CVC hazard rate functions (that is the slope connecting first and last observed hazard rates). Denoting these slopes with $\bar{\mathbf{r}}_A$ and $\bar{\mathbf{r}}_C$ respectively, we assumed $\alpha_A = \bar{\mathbf{r}}_A$ and $\alpha_C = \bar{\mathbf{r}}_C$ (below, we perform one-way sensitivity analyses by considering scenarios in which $\alpha_A = (1 \pm 25\%)\bar{\mathbf{r}}_A$ and $\alpha_C = (1 \pm 25\%)\bar{\mathbf{r}}_C$).

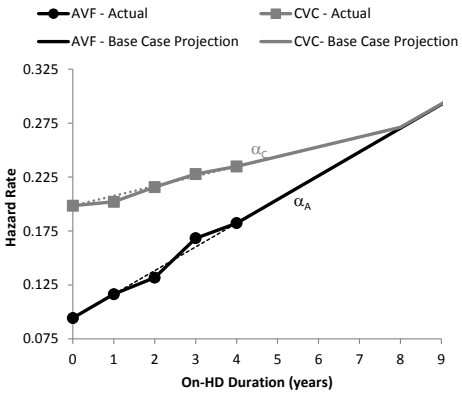

Figure 2.4: Base case hazard rate functions for a 67 year old patient's lifetime on HD.

Based on the hazard rate functions, a 67 year old patient's entire survival curve was calculated. We used the result of Theorem 2.4 to calculate the critical disutility as a function of HD-duration using Monte-Carlo simulation (see the proof of Theorem 2.4 in the online supplement). Figure 2.5 (left) shows the critical disutility under the baseline assumption for survival extrapolation. For example, a 67 year old patient who has been on HD for 2 (3) years should undergo AVF surgery provided her AVF disutility is less than 85 (65) QALE days.

Note that we assume the same probability of AVF success, regardless of NF, as the clinical literature does not yet provide this detail when discussing maturation failure rates. Nevertheless, one can easily calculate the critical disutilities as a function of NF by multiplying the function by a proper factor (see Theorem 2.5 for more details).

Recall that the motivation for the critical disutility approach was for cases in which it might be difficult to estimate precisely a patient's disutility for the AVF surgery. However, based on Corollary 2.2, Figure 2.5 (left) can also be inverted to answer questions regarding a patient for whom a precise estimate of the AVF disutility is obtained. For example, the figure also indicates that if a 67 year old patient has a disutility of 85 (65) QALE days, then she should undergo an AVF surgery as long has she has been on HD less than 2 (3) years.

To visualize the impact of age at HD initiation on the critical disutility, we have plotted the critical disutility curves for patients who start HD at ages of 67 and 82 years in Figure 2.5 (right). As the plot shows, the critical disutility of the older patient is always smaller. For instance for the time of HD initiation, a 67 year old patient should undergo AVF surgery as long as her AVF creation disutility is below 130 QALE days, while for an 82 year old patient AVF surgery is advisable only

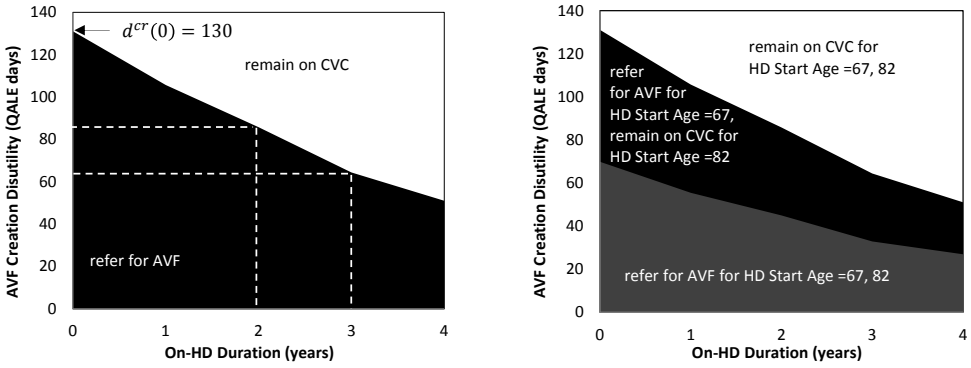

Figure 2.5: Critical disutility and HD duration for 67 and 82 year old patients.On the left, the critical HD duration for 67 year old patients with AVF creation disutility of 65 and 85 QALE days is illustrated. It also shows the critical disutility for a 67 year old who just begins HD is 130 QALE days. On the right, the critical disutility for 67 and 82 year old patients is illustrated.

when her AVF creation disutility is below 70 QALE days (Figure 2.5 (right)).

In Figure 2.6, we plot the % QALE increase from the non-optimal policy to the optimal policy as a function of the AVF creation disutility for an 82 year old patient with one AVF chance, i.e., for $n = 1$. We have compared the two policies of "no AVF surgery" and "surgery at HD initiation", as they represent two opposing opinions in the literature [26, 27], and therefore the figure indicates what can be gained if a decision maker adheres to a suboptimal policy on one side of the threshold or the other. For $d < d^{cr}(0)$, the optimal policy is to perform AVF surgery on the patient at the time of HD initiation, whereas for $d \geq d^{cr}(0)$, the optimal policy is to remain on a CVC.

2.5.1 Sensitivity Analysis

We also performed a sensitivity analysis to see how robust the results are to the changes in the input parameters. The parameters and values tested for one-way and two-way sensitivity analyses and the corresponding critical disutilities at the time of HD initiation are given in Table 2.2. For instance, the critical disutilities for patients with 60% and 20% chances of success in having a matured AVF are 223 and 76 QALE days, respectively. Since the first patient has a higher chance of surgery success, she benefits from the surgery more than the other patient, and as a result, she should be undergo AVF surgery at the time of HD initiation as long as her surgery disutility is less than 223 QALE days, while the other patient

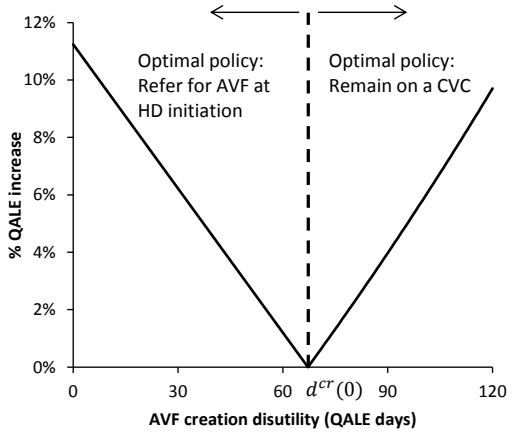

Figure 2.6: % Remaining QALE increase from the non-optimal policy to the optimal policy as a function of the AVF creation disutility. We have compared the two policies of "no AVF surgery" and "surgery at HD initiation"for an 82 year old patient with $n = 1$ (other parameters are given in Table 2.1), with the former being optimal for $d \geq d^{cr}(0)$ and the latter for $d \leq d^{cr}(0)$.

benefits from AVF surgery only when the surgery disutility is less than 76 QALE days. As the results in Table 2.2 suggest, the critical disutility is most sensitive to the AVF surgery success probability. Based on Theorem 2.5, the critical disutility is proportional to this parameter, and therefore, it can be easily adjusted by a nephrologist based on her perception of a patient's AVF surgery success probability or existing statistics in the local practice.

2.6 Conclusion

In this chapter, we considered the problem of vascular access choice between a CVC and an AVF for HD patients, with a goal of maximizing a patient's total lifetime and QALE. We analytically proved that delaying AVF surgery stochastically decreases a patient's lifetime. As a result, the policy of "use the next AVF (opportunity) as soon as a patient starts HD or when the one being used fails" maximizes a patient's survival probability. We also proved that the optimal policy to maximize a patient's QALE is of a threshold type: there is an HD duration threshold before which immediate surgery is the optimal choice, while after that time, CVC is the optimal vascular access choice for the remainder of the patient's lifetime. This threshold depends on the number of past AVF maturation failures.

The AVF creation disutility plays an essential role in determining the critical HD duration of the QALE optimal policy. Since patients may feel differently about

Table 2.2: Sensitivity analysis for the critical disutility (QALE days) of a 67 year old HD incident patient computed using Monte-Carlo simulation. The default values for each parameter are given in Table 2.1.

Parameter	**Value**	**Critical disutility**
N/A	Default	151
AVF Surgery Success Probability	0.2	76
	0.6	223
Functional AVF Annual Failure Rate	0.1	172
	0.2	134
Maturation Time (months)	Uniform [3,5]	150
	Uniform [4,6]	149
	Uniform [1,6]	150
QALE Coeff [CVC, AVF]	[0.73,0.81]	164
	[0.75,0.81]	158
	[0.81,0.81]	139
Patient's survival projection parameters $[\alpha_A, \alpha_C]$	$[\overline{\mathbf{r}}_A, 1.25 * \overline{\mathbf{r}}_C]$	151
	$[\overline{\mathbf{r}}_A, 0.75 * \overline{\mathbf{r}}_C]$	150
	$[1.25 * \overline{\mathbf{r}}_A, \overline{\mathbf{r}}_C]$	147
	$[0.75 * \overline{\mathbf{r}}_A, \overline{\mathbf{r}}_C]$	155

the disutility of AVF surgery, and also because it is not an easy parameter to elicit from a patient, our model provides an alternative way to make the optimal AVF timing decision. We showed that the decision of whether to perform an AVF surgery or not can be determined solely by comparing the patient's AVF creation disutility with a boundary value reflecting the prospective additional quality lifetime for the patient, which we refer to as the critical disutility. Thus, a nephrologist can inform the patient of the benefits and inconveniences of undergoing the AVF surgery, and then, they can collectively decide whether to do the surgery or not. Even if a rough estimate of the patient's disutility for AVF surgery indicates that it is clearly below or above the critical disutility, then it will be clear that the patient should or should not, respectively, undergo an AVF surgery. Estimates of a patient's disutilities can be obtained using standard elicitation methods in the medical decision making community, such as the standard gamble, time trade-off, and visual analog scale [47]. This also facilitates getting patients involved in the decision making process, one of the key recommendations of the Institute of Medicine's report on patient-centered care, which has been emphasized in the medical community in the past decade [48].

We also found that the possibility of receiving a kidney transplant adds new complexities to the model and optimal policy structure. Although the optimal policy under the total lifetime remains the same, the result on QALE metric (optimality

of threshold policies) does not necessarily extend, even when the time of transplant is known with certainty. Nevertheless, we provided a theorem which proves that under additional assumptions (which are supported by data), threshold policies remain optimal.

Our framework and analytical results may also be relevant to operational questions outside of health care, particularly in the area of machine maintenance and equipment reliability. For example, consider a machine with a vital component. If the component breaks down, it may be replaced with a cheap, available spare. Additionally, one may order a more expensive, higher-quality component, which involves a lead time for delivery. This is analogous to deciding whether and when to refer a patient for an AVF versus letting them continue to receive HD through a CVC. An AVF provides higher quality HD outcomes compared to a CVC, but an AVF cannot be created quickly, and it is more expensive in the sense of the surgical disutility it imposes on patients.

Chapter 3

Optimal Vascular Access Planning Prior to Hemodialysis [2]

3.1 Introduction

Approximately 23 million American adults have chronic kidney disease (CKD) [1] and 550,000 have end-stage kidney disease [2]. Most of these patients are treated with hemodialysis (HD) [3]. The preferred vascular access for HD is an arteriovenous fistula (AVF) [3] due to greater longevity and lower complication rates; however, it may take several months and more than one procedure to establish a usable AVF [4, 5]. If the AVF is created too late, it may not mature in time, and a central venous catheter (CVC) may be used; however, CVCs are associated with an increased risk of morbidity and mortality [6–9]. On the other hand, creating an AVF too early is undesirable due to a small increase in risk of complications and wasting the limited lifetime of an AVF before HD is needed [10]. In 2008 over 80% of incident HD patients in the United States used a CVC as their initial vascular access [49]. Although there are multiple reasons for this, suboptimal timing of AVF referral has contributed to low incident AVF rates [50].

Existing guidelines for AVF referral are inconsistent and based on expert opinion [10]. Over the past decade, the Kidney Disease Outcomes Quality Initiative (KDOQI) recommendations have varied from referral for AVF creation when HD is anticipated within 12 months (2000) [13], within 6 months (2006) [14], or when estimated glomerular filtration rate (eGFR) falls below 30 mL/min/1.73m^2 (2002) [15]. In 2006, the Canadian Society of Nephrology (CSN) guidelines suggested referral at an eGFR of 15-20 mL/min/1.73m^2 in patients with progressive CKD [16].

Establishing clearer guidelines may improve incident AVF rates in HD patients and thereby positively impact on patient outcomes. In this chapter, we develop a data-driven, decision-analytic model to provide an objective approach to timing AVF referral in CKD.

[2] A version of this chapter has been published at *the American Journal of Kidney Diseases*, 63(1): 95-10 (2014).

3.2 Related Literature

The existing literature related to the optimal vascular access planning for incident hemodialysis patient is discussed in Chapter 3. To my knowledge the only decision model for vascular access planning prior to hemodialysis is the study by [42]. Hiremath et al. [42] compared two AVF creation timing policies for a 70-year-old patient with stage 4 CKD using a Markov model and reported life expectancy, quality adjusted life expectancy and costs as the outcomes. Our modeling perspective differs from that of Hiremath et al. [42], who took a comparative effectiveness approach. Rather than considering only two possible strategies, we considered a wide range of possible referral policies and how they might perform when applied across a cohort of patients that vary in initial age, level of kidney function, and rate of CKD progression.

3.3 Methods

3.3.1 Study Design

We developed a Monte Carlo computer simulation model in C++ to determine the optimal timing of AVF referral in patients with CKD. We evaluated 2 AVF referral strategies based on approaches suggested in recently published guidelines [13–16]:

1. a "preparation window" strategy, where referral occurs as soon as HD is anticipated to begin within a specific time window (e.g., the next 12 months),

2. an "eGFR threshold" strategy, where patients are referred as soon as their eGFR falls below a specific threshold (e.g., eGFR < 15 mL/min/1.73m^2).

We examined both strategies over a wide range of values for their respective parameters (see Figures 3.3, 3.4).

Figure 3.1 provides an overview of the model. In each simulation replication of a given referral strategy, patients from a sample cohort enter the model, and their eGFR measurements are simulated at periodic intervals. After each eGFR measurement, the Nephrologist decides whether to refer the patient for AVF creation or not. For simulated patients who survive until HD commences, we simulate on-dialysis survival according to whether HD is delivered via AVF or CVC. After a simulated patient dies, the next patient in the cohort enters the model, and after all the patients in the cohort have gone through the model, one simulation replication is complete. For each AVF referral strategy, we run the same patient cohort through 100,000 independent replications.

Table 3.1 indicates the base-case parameters of our model, which were derived from the literature and from primary data analysis (further described below). Expert opinion was used in cases where literature-based estimates were unavailable.

3.3.2 Modeling eGFR Progression

While standard time series models (e.g., autoregressive of order one, or AR-1) can consider correlation from one observation to the next, they assume equally spaced measurements [51]. This is unsuitable for our purposes, as the timing of patient eGFR measurements is highly irregular (the average standard deviation of inter-test times is approximately one month across patients). Therefore, we applied statistical methods proposed by Erdogan et al. [52], which extend standard AR-1 models to irregularly spaced time series. Consider the following OLS linear regression model for eGFR progression:

$$eGFR(t_i) = \beta_0 + \beta_1 t_i + \epsilon_{t_i}$$

where t_i is the time of the i^{th} eGFR measurement. In the OLS model, it is assumed that the residual terms ϵ_{t_i} are mutually independent across measurements. The model proposed in [52] instead assumes a systematic correlation structure between consecutive residuals as follows:

$$\epsilon_{t_i} = \epsilon_{t_{i-1}} \theta^{(t_i - t_{i-1})} + \omega_{t_i}$$

The term $\theta^{(t_i - t_{i-1})}$ (with θ between 0 and 1) represents the correlation between consecutive residuals spaced $t_i - t_{i-1}$ time units apart, and the ω_{t_i} are independent white noise terms. This model captures commonly observed properties of residuals in longitudinal data analysis [53]. They are positively correlated, with the degree of correlation decreasing with longer separation between measurements.

We used Matlab to fit these regression models to each of the 860 patients in our cohort of patients who were enrolled in a multi-disciplinary kidney clinic at Vancouver General Hospital (VGH) between Jan 1, 1994 and Nov 9, 2010. As a validation step, we compared the goodness of fit for these two models using the coefficient of determination R^2. For the proposed model the coefficient of determination is on average 0.51, while for the OLS model it is 0.44.

Our simulation model simulates eGFR values for a given patient as follows: first at the i^{th} eGFR measurement time, t_i, the mean value of the patient's eGFR is calculated $\beta_0 + \beta_1 t_i$. Then, a residual term is added, which is calculated by multiplying the previous residual by the correlation factor that depends on the elapsed time since the last measurement ($\epsilon_{t_{i-1}} \theta^{(t_i - t_{i-1})}$). Finally, a normally distributed white noise term is added to this (ω_{t_i}).

3.3.3 AVF Creation and Long-term Patency

Once an AVF referral is made, the patient first waits for a surgical creation date and then waits for the AVF to (possibly) mature. The distribution of surgical wait times was based on 209 HD patients who had AVFs created at Vancouver General Hospital between 2005 and 2009. The median surgery wait time was 28 days, with

a maximum of 65 days. Using the distribution fitting tool of the Arena simulation software [54], we found that a Uniform (0,65) (days) distribution best represented the variability observed for this duration.

In the base case analysis, the probability of an AVF failing to mature was 0.4 if a patient had no prior CVC [4, 22, 23, 55–57] and 0.6 if HD had already started with a CVC [4, 41, 46, 55, 58]. We assumed the time it takes to determine whether an AVF is functional for HD or not (with interventions if necessary) is uniformly distributed between 2 and 4 months [21].

We assumed functional AVFs have annual failure probabilities of 0.15 or 0.075, depending on whether the AVF is being used for HD or not, respectively [24, 25]. If the AVF fails to mature, or a mature AVF fails, the patient is again referred for AVF creation. We assume a maximum of three attempts at AVF creation, with no more than two attempts occurring in the predialysis period.

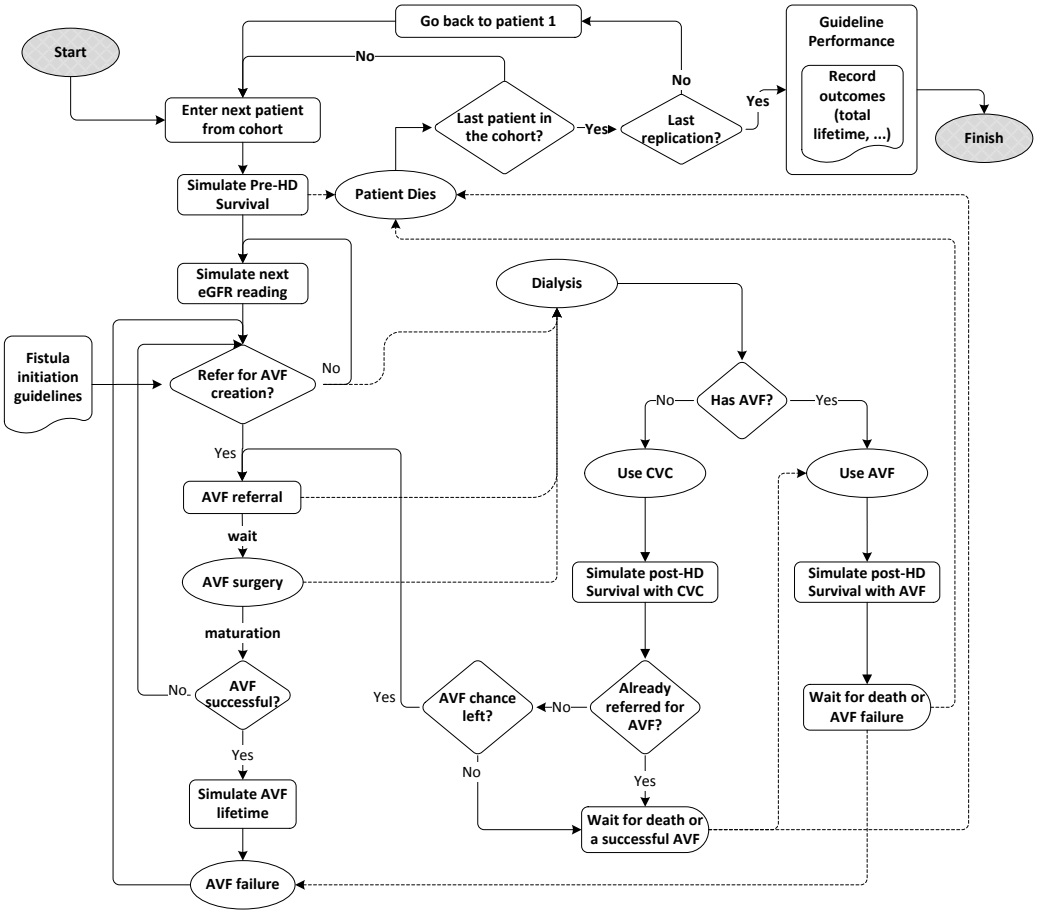

Figure 3.1: An overview of the Monte Carlo simulation model. One replication consists of all patients from the cohort going through the model one at a time, from the time they are referred to a kidney clinic, until they die. Dashed lines indicate events that can occur at any time. For example, dialysis may occur at any time between eGFR measurements, while waiting for AVF surgery, or while waiting for an AVF to mature.

Table 3.1: Baseline model parameters.

Model parameter	**Value**	**Reference**
Patient-specific eGFR progression parameters ($\beta_0, \beta_1, \sigma, \theta$)	Varies by patient	Primary data analysis*, [59, 60]
Average rate of eGFR decline (mL/min/1.73m^2 per year)	5.29	Primary data analysis, [59, 60]
eGFR level at which dialysis starts	Normal(10, 2.5) distribution	Primary data analysis
Survival for CKD predialysis	Age and gender-dependent	[61]
Survival for ESRD on dialysis	Age, gender, and access type-dependent Baseline mortality relative risk, CVC vs AVF: 1.53	[61, 62]
Time from AVF referral to surgical creation (in days)	Uniform (0, 65)	Primary data analysis, [21]
Maximum number of AVF attempts in predialysis period	2	Expert opinion†
Maximum number of AVF creation attempts in total	3	Expert opinion
Time from AVF creation to achieve an AVF usable for HD (with interventions if necessary), or AVF abandonment due to failure (in months)	Uniform (2,4)	[5, 21]
Probability patient is willing to have more than one AVF attempt	1	Baseline assumption
Probability of AVF failing to mature (without history of CVC use)	0.4	[22, 23, 55–57, 63]
Probability of AVF failing to mature (with history of CVC use)	0.6	[4, 41, 55, 58]
Probability of a functional AVF failing, per year (if used for HD)	0.15	[24, 25]
Probability of a functional AVF failing, per year (if not used for HD)	0.075	Expert opinion

*indicates parameters obtained from analysis of patients treated at the multidisciplinary kidney clinic at Vancouver General Hospital.
† indicates values provided by Dr. Nadia Zalunardo, Clinical Associate Professor at the University of British Columbia, Division of Nephrology

3.3.4 Patient Survival

Patient survival was simulated according to whether the patient is CKD not yet on HD, on HD with an AVF, or on HD with a CVC. We used survival data from the USRDS [64] to model predialysis survival, and data from the USRDS [62, 64] to model vascular access-specific survival for HD patients. To simulate survival times beyond the time horizon of the survival curves in these studies, we used complete statistical life tables [61] and estimated relative risk ratios [62] to extrapolate the survival curves.

3.3.5 AVF Referral Decision Making

We assume a patient's eGFR is measured every 3 months for Stage 3 CKD, every 2 months for Stage 4 CKD, and every month for Stage 5 CKD. After each simulated eGFR measurement, a decision is made to refer the patient for AVF creation or to wait and reevaluate after the next eGFR measurement.

The timing of AVF referral is specified by the strategy being tested. For the eGFR threshold strategy, AVF referral occurs once the simulated eGFR falls below the threshold value being tested. For the preparation window strategy, AVF referral occurs once the anticipated HD start date is within the time window being tested. In reality, a Nephrologist's recommendation to start HD is based on eGFR combined with other important factors such as uremic symptoms. However, these symptoms generally appear closer to the HD start date, and are not awaited before AVF referral. We therefore assume the Nephrologist estimates the HD start date by fitting a regression line through the patient's history of eGFR measurements, and determining when this line would fall to 10 mL/min/1.73m^2 (the mean eGFR at HD start in our CKD cohort). We assume AVF referral occurs at the start of HD if it did not occur before that.

3.3.6 Actual versus Estimated HD Start Date

The difference between the Nephrologist's estimated HD start time and the actual HD start time affects the degree to which an AVF will be ready before or after HD commences. To account for the considerable inter-patient variability in the actual eGFR at HD initiation in clinical practice, we used the Arena simulation software [54] to fit a probability distribution to the eGFR values at the start of HD for 204 HD patients in our cohort. The best fit was a Normal distribution, with a mean of 10 and a standard deviation of 2.5 mL/min/1.73m^2. We used this distribution to simulate the actual eGFR at which HD would commence for each patient.

3.3.7 Model Outcomes

The outcomes of interest were: expected remaining lifetime (measured from dialysis initiation until death), percentage of HD patients who begin dialysis with a CVC, and percentage of patients who have an unnecessary AVF creation (patients who have an AVF created and die before requiring HD, and patients who had at least one functional AVF fail before HD start). We evaluated these outcomes in the overall cohort and stratified by age (at the time of referral to the kidney clinic) in the following groups: 50-60, 60-70, 70-80, and 80-90 years old.

3.3.8 Model Validation

We compared survival curves of simulated patients who enter the clinic in Stage 3 and Stage 4 CKD with the Kaplan Meier survival curves of our kidney clinic cohort who entered in the same stages. The simulated survival curves were within the 95% confidence intervals of the actual survival curves (See Figure 3.2).

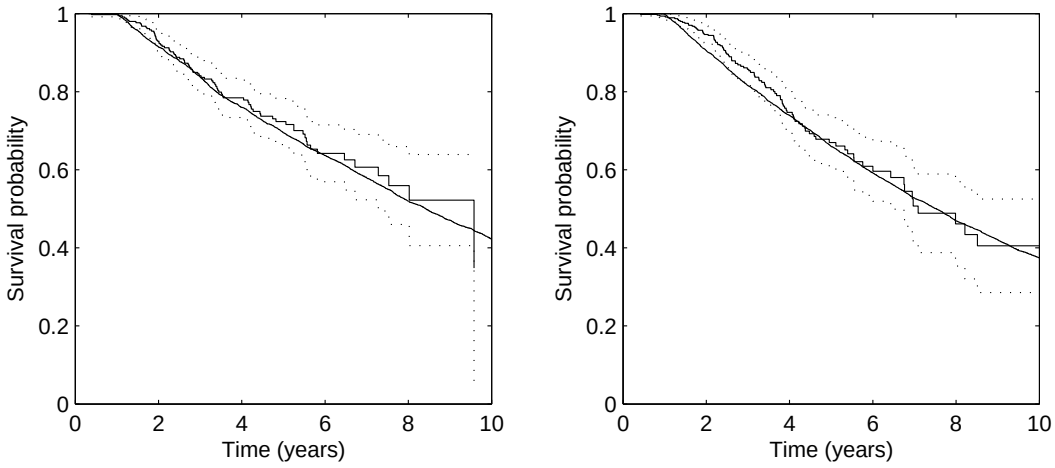

Figure 3.2: Comparison between the Kaplan-Meier survival curves of the actual cohort (the solid step function, with the 95% confidence intervals shown by the dashed step function), with the survival curves of the simulated cohort (smooth solid lines). The plot on the left shows survival, from the time patients first enter the clinic in Stage 3 CKD until their death. The plot on the right is similar, for patients who enter the clinic with Stage 4 CKD.

3.3.9 Sensitivity Analyses

We performed a variety of one-and two- way sensitivity analyses as well as a probabilistic sensitivity analyses (PSA) [65]. We compared policies based on the total

HD lifetime outcome. The parameters and values tested for one-and two-way sensitivity analyses are given in Tables 3.4 and 3.5. In each replication of the PSA, we simultaneously sampled all the parameters of the model according to a probability distribution (parameters given in Table 3.6) and then compared the lifetime obtained by applying the baseline optimal policy to the optimal policy under the set of sampled parameters.

3.4 Results

3.4.1 Incident Vascular Access Type and Percent Having an Unnecessary AVF Creation

Figure 3.3 and Tables 3.2 and 3.3 demonstrate the tradeoff that is observed for both types of strategies: as AVF referral occurred earlier (larger preparation window or higher eGFR threshold), the percentage starting HD with a CVC decreased but the percentage with an unnecessary AVF increased. Overall, referral 15 months before anticipated HD initiation resulted in 34% starting HD with a CVC and 14% having an unnecessary AVF creation. Referral windows between 12 and 18 months performed similarly.

Relative differences between referral strategies were more pronounced for threshold policies, with respect to the unnecessary AVF creation outcome in particular. For example, a referral threshold eGFR of 20 mL/min/1.73m^2 compared to 15 mL/min/1.73m^2 resulted in a doubling of the percent with an unnecessary AVF creation from 10 to 20%.

3.4.2 Life Expectancy

Figure 3.4 and Tables 3.2 and 3.3 indicate life expectancy differences for a range of strategies tested in the base case analysis. The optimal preparation window was 15 months before anticipated HD, which yielded an expected lifetime increase of 14 days over a preparation window of 6 months. However, any preparation window between 9 and 18 months performed nearly optimally. The optimal eGFR threshold strategy was 20 mL/min/1.73m^2; however, thresholds of 15 mL/min/1.73m^2 or greater performed similarly.

Figure 3.4 displays the result of a strategy where AVF referral is delayed until HD starts (with a CVC). This yields a shortened expected total lifetime of 73 days compared to referral 15 months before anticipated HD start.

3.4.3 Effects of Age

Age-stratified results for selected AVF referral strategies are also shown in tables 3.2 and 3.3. For any given strategy, aging had a greater relative effect on the percentage of patients with an unnecessary AVF creation (which increased with age mainly due

Table 3.2: Various output measures from the simulation, for both the overall cohort as well as by 10-year age ranges for preparation window policies. Age is determined at the time of kidney clinic enrollment. For the total lifetime, the average reduction from the best strategy (for preparation window and threshold strategies separately) is reported. A zero indicates that policy was optimal for that cohort. All differences reported are statistically significant at level = 0.05, using a t-test of equality of means between two policies.

Cohort	**Output Measure**	**Preparation window (months)**					
		3	**6**	**9**	**12**	**15**	**18**
Overall Cohort	Lifetime reduction (days)	37	13.8	3.8	0.3	0	1
	% Starting HD with CVC	74%	52%	41%	36%	34%	34%
	% with unnecessary AVF	3%	6%	9%	11%	14%	16%
50-60 year olds	Lifetime reduction (days)	41.9	16.5	3.4	0	0.3	1.4
	% Starting HD with CVC	75%	53%	42%	37%	35%	35%
	% with unnecessary AVF	1%	3%	5%	7%	9%	11%
60-70 year olds	Lifetime reduction (days)	36.2	13.5	3.4	0	0.2	0.9
	% Starting HD with CVC	72%	50%	39%	35%	33%	33%
	% with unnecessary AVF	3%	5%	8%	10%	13%	15%
70-80 year olds	Lifetime reduction (days)	30.5	11.7	3.2	0.4	0	0.2
	% Starting HD with CVC	73%	50%	39%	35%	33%	33%
	% with unnecessary AVF	4%	7%	11%	14%	16%	19%
80-90 year olds	Lifetime reduction (days)	27.3	10.4	3.1	0.6	0	0
	% Starting HD with CVC	74%	52%	42%	38%	37%	36%
	% with unnecessary AVF	5%	9%	13%	16%	19%	22%

to the competing risk of death before HD start) than on the percentage of HD patients starting with a CVC, which changed little. For example, with the strategy of AVF referral 15 months before anticipated HD start, the percentage of patients with an unnecessary AVF creation increased from 9% to 19% as age increased from 50-60 to 80-90 years old, whereas the percent starting HD with a CVC remained similar at 33 37%.

For the two oldest cohorts (70-80 and 80-90 years old), preparation widow strategies of 15 18 months resulted in 16 22% with an unnecessary AVF creation; any eGFR threshold strategy of 20 mL/min/1.73 m^2 or higher resulted in unnecessary AVF percentage consistently above 20%.

3.4.4 Sensitivity Analyses

Optimal policies from the base case analysis were robust across one-way sensitivity analyses. A 15 month preparation window and eGFR threshold of 20 mL/min/1.73m^2 were optimal or within 0.05% of optimal in each case. In the sensitivity analysis

Table 3.3: Various output measures from the simulation, for both the overall cohort as well as by 10-year age ranges for threshold policies. Age is determined at the time of kidney clinic enrollment. For the total lifetime, the average reduction from the best strategy (for preparation window and threshold strategies separately) is reported. A zero indicates that policy was optimal for that cohort. All differences reported are statistically significant at level $= 0.05$, using a t-test of equality of means between two policies.

Cohort	**Output Measure**	**eGFR mL/min/1.73m^2**				
		10	**15**	**20**	**25**	**30**
Overall Cohort	Lifetime reduction (days)	37.4	8.1	0	1	2.6
	% Starting HD with CVC	78%	51%	38%	36%	36%
	% with unnecessary AVF	4%	10%	20%	30%	38%
50-60 year olds	Lifetime reduction (days)	34	5.5	0	4.6	7.9
	% Starting HD with CVC	74%	49%	40%	39%	39%
	% with unnecessary AVF	4%	9%	16%	23%	28%
60-70 year olds	Lifetime reduction (days)	37.8	8.1	0	2	3.6
	% Starting HD with CVC	75%	47%	36%	35%	35%
	% with unnecessary AVF	4%	10%	18%	28%	37%
70-80 year olds	Lifetime reduction (days)	36.6	9.7	0	0.2	1
	% Starting HD with CVC	78%	49%	35%	33%	33%
	% with unnecessary AVF	5%	12%	22%	33%	41%
80-90 year olds	Lifetime reduction (days)	36.7	10.9	1.8	0	0
	% Starting HD with CVC	82%	54%	41%	37%	37%
	% with unnecessary AVF	5%	12%	24%	38%	48%

where HD begins at a mean eGFR of 7 mL/min/1.73m^2, the performance of preparation windows between 9 and 15 months was essentially identical (within 1 day of one another) as was the performance of eGFR threshold policies of 15 mL/min/1.73m^2 or greater.

Results were robust in two-way sensitivity analysis for AVF maturation failure probabilities (Table 3.5). A preparation window of 12 months performed optimally in many cases where AVF failure probabilities were lower than in the baseline case, although the absolute lifetime differences between the 12 and 15 month preparation window policies was small (less than 2 days). When the AVF maturation failure probability was equivalent before and after CVC use, later referral strategies were favored (preparation window 9 months, eGFR threshold 15 mL/min/1.73m^2).

We assessed the performance of policies for the range of average cohort CKD progression rates from 2.78 (average progression in our cohort) to 7 mL/min/1.73m^2 per year (fast progressors). To achieve a similar incident CVC percentage as the

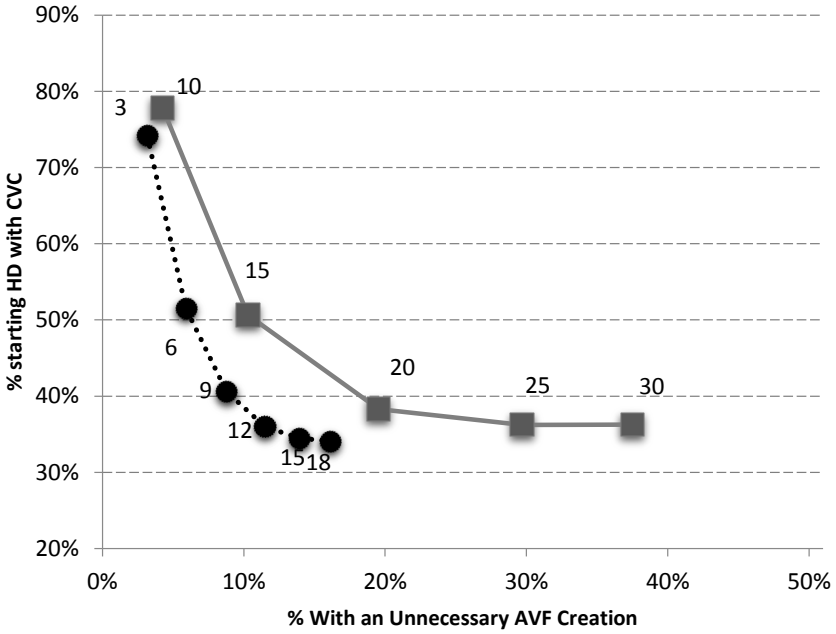

Figure 3.3: Tradeoff curve between % of hemodialysis patients who start with a CVC and % of patients who have an AVF created unnecessarily. Each point represents the value of these two measures for a given AVF referral policy. The preparation window (months) and eGFR threshold (mL/min/1.73m^2) strategies are shown by circles and squares, respectively.

9 month preparation window policy in the baseline case (about 40%), referral 15 18 months before anticipated HD start would be required for those progressing at 7 mL/min/1.73m^2 per year. For threshold policies, referral at eGFR 25 mL/min/1.73m^2 for fast progressors yielded a similar incident CVC percentage (about 40%) as referral at 20 mL/min/1.73m^2 in the baseline case. In our (more slowly progressing) cohort, similar results were achieved with referral at eGFR 15 mL/min/1.73m^2.

The relative risk (RR) of mortality on HD with CVC versus AVF is a key determinant of the absolute magnitude of the lifetime differences between policies. The downside of a late AVF referral is magnified when the relative risk of mortality is larger. For instance, the lifetime reduction of using a preparation window of 6 months instead of 15 months increases from 1 day for RR 1.05 versus 35 days for RR 2.75 (the range of RRs reported by Ravani et al. [62]).

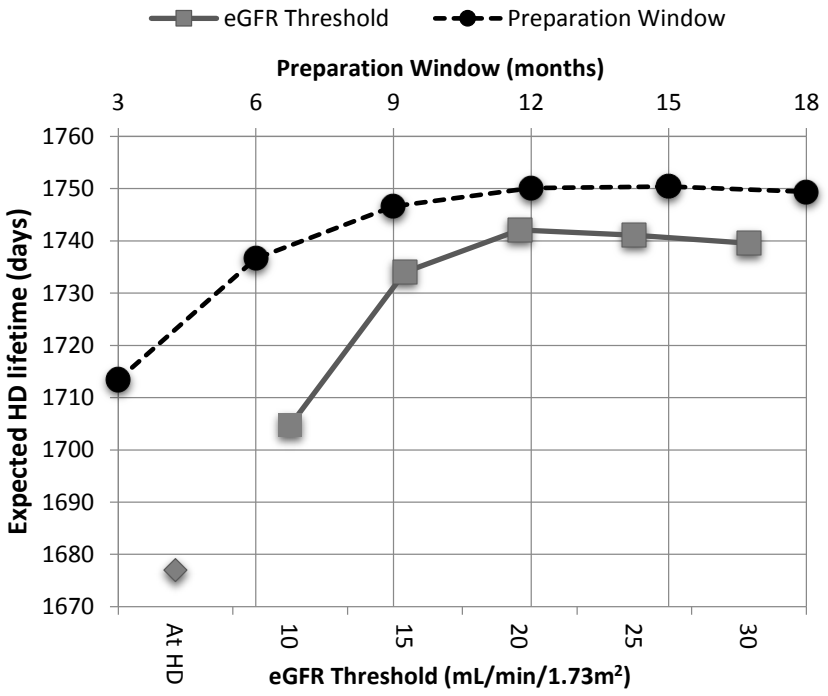

Figure 3.4: Policy comparisons with respect to expected lifetime on hemodialysis. The preparation window and eGFR threshold strategies are shown by circles and squares, respectively. The figure also shows the result of a policy that waits until dialysis begins to refer a patient for AVF (the diamond).

3.4.5 Probabilistic Sensitivity Analysis

To check the robustness of the optimal preparation window and threshold policies obtained from the baseline model, we performed a probabilistic sensitivity analysis (PSA) [65, 66]. In each replication of the PSA, we simultaneously sampled all model parameters according to a probability distribution given in Table 3.6, and then we compared the lifetime obtained by applying the baseline optimal policy, i.e. the preparation window of 15 months and eGFR threshold of 20 mL/min/1.73m^2 to the optimal policy under the set of sampled parameters. The PSA results (reported in Table 3.7) show that the baseline optimal policies are quite robust; the lifetime reduction of the optimal baseline policy from the optimal policy across all PSA samples were on average 4.1 and 2.6 days for preparation window and eGFR threshold strategies, respectively. Similar to the baseline results, any preparation windows between 9 and 15 months performed similarly in this respect, and they were optimal in 70% of all PSA samples. The eGFR threshold policies 15 to 25 also had a similar performance and they contributed to the 87% of optimal policies

Table 3.4: One-way sensitivity analysis for a set of plausible values for model parameters.

Parameter(s)	**Value(s)**
Time from AVF referral to surgical creation (in days)	Uniform (0, 30)
	Uniform (0, 120)
eGFR decline rate (mL/min/1.73m^2 per year)	2.78
	7
Time from AVF creation to achieve an AVF usable for HD or AVF abandonment due to failure (in months)	Uniform (1,3)
	Uniform (3,5)
	Uniform (4,6)
	Uniform (1,6)
Probability of AVF failing to mature (Without, With) history of CVC use	(0.2, 0.3)
	(0.3, 0.45)
	(0.4, 0.4)
	(0.4, 0.5)
	(0.5, 0.75)
Maximum number of AVF creation attempts in total	4
Probability patient is willing to have more than one AVF attempt	0.7
	0.5
Time between eGFR measurements (in months)	stage 3: Uniform (2,4)
	stage 4: Uniform (1,3)
	stage 5: Uniform (0,2)
Probability of a functional AVF failing, per year (If not used, If used) for HD	(0.15, 0.15)
	(0.115, 0.15)
	(0.05, 0.1)
	(0.1, 0.2)
Hemodialysis mortality relative risk with CVC vs. AVF	1.05
	1.41
	1.67
	2
eGFR level at which dialysis starts	Normal (7, 2.5)

Table 3.5: Two-way sensitivity analysis results on probability of AVF failing to mature with and without history of CVC use. The results in the parenthesis show the best preparation window and threshold strategies, respectively.

		Probability of AVF failing to mature with history of CVC use				
		0.3	**0.4**	**0.45**	**0.5**	**.6**
Probability of AVF failing to mature without history of CVC use	**0.2**	(12, 20)	(12, 20)	(15, 20)	(12, 20)	(15, 25)
	0.3	(9, 15)	(12, 20)	(12, 20)	(12, 20)	(15, 20)
	0.4		(9, 15)	(12, 20)	(12, 20)	(15, 20)
	0.5				(9, 15)	(12, 20)

Table 3.6: Parameters and distributions used for probabilistic sensitivity analysis.

Parameter(s)	**Distributions**
Time from AVF referral to surgical creation (in days)	Uniform (0, max), max $\sim$ Uniform(30,120)
Maximum number of AVF creation attempts in total	Sample from (1, 2, 3, 4) with probability (0.2,0. 3,0.4, 0.1)
Time from AVF creation to achieve an AVF usable for HD or AVF abandonment due to failure (in months)	Equal probability selection from Uniform (1,3), Uniform (3,5), Uniform (4,6), Uniform (1,6)
Probability of AVF failing to mature (Without, With) history of CVC use	Equal probability selection from the two way sensitivity table (see Table 3.5).
Probability of a functional AVF failing, per year (If not used, If used) for HD	Equal probability selection from {(0.05,0.1),(0.05,.015),(0.05,0.2), (0.075,0.1),(0.075,0.15),(0.075,0.2), (0.1,0.1),(0.1,0.15),(0.1,0.2), (0.115,0.15),(0.115,0.2), (0.15,0.15),(0.15,0.2)}
Time between eGFR measurements (in months)	stage 3: Uniform (2,4), stage 4: Uniform (1,3), stage 5: Uniform (0,2),

across all PSA samples.

3.5 Discussion and Conclusion

We used a simulation model to assess the performance of a range of AVF referral strategies in individuals with CKD. Except in cases where AVF referral occurred very late, the differences in expected HD lifetime between policies were modest. The effects of different strategies on incident vascular access type and the likelihood of creating an unnecessary AVF were clinically meaningful and useful as a guide to optimizing the timing of AVF referral. The results for the overall cohort suggest AVF referral about 12 months before HD is anticipated is appropriate; this supports KDOQI guidelines published in 2000 [13, 14]. An eGFR threshold for referral of 15-20 mL/min/1.73m^2, as suggested by the CSN guidelines, was also appropriate overall [16]. However, the choice of strategy should also be guided by an assessment of the individual's rate of CKD progression to avoid excessively early or late referrals in slow or rapid progressors, respectively.

Threshold strategies have the advantage of easier implementation since they do not require forecasting the anticipated HD start date; however, they fail to consider a patient's rate of CKD progression. In contrast, preparation window strategies consider the rate of CKD progression rather than just the most recent measurement; however, accurately estimating the time to HD start is a major challenge for clinicians in part because the decision to start HD is based on multiple factors in addition to the eGFR.

The lowest incident CVC percentage we observed was about 35%. The combination of AVFs failing to mature and a limited number of AVF opportunities limits how low this number can be; however, it can probably be further reduced by considering AV grafts as an option. AV grafts have the advantage of near certain short-term patency and no prolonged maturation time compared to AVFs. AV grafts can be placed nearly immediately before HD is required and in certain patients may be the preferred approach if AVF maturation is felt to be very unlikely, as suggested by Rosas et al. [67] We did not consider AV grafts in our model since there is almost no uncertainty regarding early patency. Finally, incident CVC rates are also likely to be lower where AVF maturation failure probabilities are substantially less than the 0.4 we used in our baseline model, which was based primarily on North American reports.

Dialysis planning in very elderly individuals (where the competing risk of death is high) is a challenge receiving increasing attention [68–70]. With a 15 month preparation window, 19% of AVFs created for 80-90 year olds are unnecessary compared to 9% for 50-60 year olds (age is determined at the start of kidney clinic follow-up). The increased risk of creating an unnecessary AVF in the elderly is a potentially significant source of morbidity and health care resource utilization with no benefit. A tailored approach to AVF referral based on age is therefore indicated. In our model,

referral for AVF creation 6 months before the anticipated HD start for 80-90 year olds, and 9 months for 70-80 year olds yielded a similar percentage with unnecessary AVF creations as a 12 to 15 month window for 50-60 year olds.

Our model focused on patient outcomes and did not consider system costs. While cost-effectiveness analysis (CEA) is an important analysis for health policy evaluation, we chose to perform a comparative effectiveness analysis (CER) instead. In recent years, there has been significant interest in CER, which focus on how policies compare with respect to health outcomes, rather than costs. A recent article underscored the importance and need for CER in evaluating treatments for kidney disease [33].

The strengths of our simulation model include its mimicking of the dynamic forecasting and AVF decision making process faced by Nephrologists. It explicitly factors in forecast inaccuracies when evaluating the various preparation window-based referral policies. Our model also considers a wide variety of patient types in terms of their initial eGFR and rate of disease progression. We performed a variety of sensitivity analyses, and the robustness of our results is reassuring and potentially supports the generalizability of our findings to CKD populations elsewhere.

A number of assumptions pose limitations to our model. We did not account for uncommon complications of AVF creation in our model (e.g. high output cardiac failure and limb ischemia), we did not include AV grafts, and we did not include a transition to kidney transplant. Further, there were few studies in the literature from which to obtain maturation probabilities for second AVFs and AVFs created after CVC use. However, we performed sensitivity analyses to determine the impact of this limitation. Finally, it is regrettable that the literature on the impact of vascular access and dialysis related interventions on quality of life is quite limited. Our modeling framework can easily incorporate improved quality of life data (and thereby also report on quality-adjusted life expectancy) whenever good estimates become available.

We modeled eGFR decline using linear regression, an approach which is consistent with other studies [60, 71, 72]. However, recent reports indicate that some patients do not experience a linear decline in eGFR [11, 73]. In a study by O'Hare et al. [11], 12% of patients experienced a nonlinear, rapid rate of eGFR decline in the two years before the start of dialysis. Our model did not consider patients who experience a sudden acceleration in eGFR decline, leading to a much earlier requirement for HD. Our simulated incident AVF percentage applies to a large proportion of patients stably progressing to ESRD (and who are followed in a multidisciplinary kidney clinic). Since a significant number of patients do not fall in this category, the incident AVF results we report are optimistic if applied indiscriminately to all CKD patients. Therefore, they should not be used as a specific target for incident AVF percentages in all CKD patients.

In conclusion, our results suggest that the optimal policy for AVF referral is when the estimated time to HD initiation is within about 12 months, or when eGFR falls

below 15-20 mL/min/1.73m^2. However, the choice of strategy should also be guided by an assessment of the individual's rate of CKD progression to avoid excessively early or late referrals. Since elderly CKD patients have a greater risk of having an unnecessary AVF creation due to the competing risk of death, later referral seems appropriate in this group.

Table 3.7: Results for 10,000 PSA samples. For each AVF referral strategy (preparation window and eGFR threshold) the average lifetime reduction from the optimal policy (across each PSA setting) and the percentage of times when each policy was found optimal is shown.

Policy	Preparation window (months)					
	3	6	9	12	15	18
Average lifetime reduction (day)†	25.3	9.6	3.7	3.1	4.1	5.5
Optimality percentage	3%	13%	26%	25%	19%	14%
Policy	eGFR threshold (mL/min/1.73m^2)					
	At HD	10	15	20	25	30
Average lifetime reduction (day)‡	45.6	25.1	5.9	2.6	5.4	7.5
Optimality percentage	1%	4%	29%	42%	17%	8%

† from the optimal preparation windows policy (15 months)
‡ from the optimal eGFR threshold policy (20 mL/min/1.73m^2)

Chapter 4

Patient Type Bayes-Adaptive Treatment Plans

There has been a growing interest in the application of operations research methods to treatment planning for different diseases. Due to the nature of chronic disease, patients are frequently seen by their specialist doctors, and their health status is measured periodically. The purpose of frequent follow-ups is three-fold: 1. to understand the patient's current health status, 2. to know how fast the disease is progressing, 3. to (possibly) revise the treatment plan (treatment type or intensity) based on the information learned. The periodic follow-up, uncertainty in health progression, and sequential decision making make Markov Decision Processes (MDPs) an important tool in clinical decision making of chronic diseases.

Heterogeneity of patients with respect to disease progression and response to medical interventions is an important characteristic of clinical decision making problems. There is strong evidence in the clinical literature that patient characteristics such as age, gender, race, ethnicity, and culture play an important role in determining patients' responses to treatment and intervention outcomes including their survivals. Therefore, patient-specific treatment plans are essential in achieving better patient outcomes at a lower cost.

Patient heterogeneity is observed in several areas of clinical problems, for instance, adherence to screening procedures (e.g., adherence to colorectal cancer screening [74, 75] and mammography screening [76]), adherence to medication (e.g., adherence to HIV treatment [35]), response to interventions (e.g., response to multiple sclerosis medications [77] and chemotherapy for prostate cancer patients [78]), dependence on medical devices (e.g., weekly usage of implantable cardioverter defibrillator devices [79]), and disease progression rate (e.g., chronic kidney disease progression [11]).

Although patient characteristics may inform the decision maker about a certain parameter of the clinical problem (e.g., whether the patient responds well to a certain medication) and decrease uncertainty around that parameter, they provide partial information, and variability among patients of the same sub-population still exists. Due to the long treatment horizon for chronic diseases, the decision maker has the chance to incorporate the information obtained during the course of the disease to learn about the patient disease progression profile and adjust the patient's treatment based on the learned information.

In this chapter, we develop a model that incorporates patient heterogeneity in disease progression when making clinical decisions and study structural properties of the model under certain modeling assumptions. Then, we apply this modeling framework to the case of AVF preparation timing problem introduced in Chapter 3 and provide recommendations that consider patient heterogeneity in chronic kidney disease progression when deciding if/when to begin the AVF preparation process.

4.1 Related Literature

In this section, we review existing literature related to our research in two categories: 1. methodological papers, 2. application papers.

4.1.1 Methodological Papers

We often face uncertainty in parameters that define a decision model. In MDPs, parameter uncertainty can be present in different model components including rewards and transition probability matrices. In clinical decision making models where patient heterogeneity is present, model parameters usually depend on the patient type, e.g., the utility that a patient receives from a treatment or the efficacy of treatments on slowing the progression of diseases may vary across the population.

The uncertainty in parameters that form an MDP problem can be addressed in two major ways, by solving the problem as a 1. Bayesian MDP, or a 2. Robust MDP. In the Bayesian setting, it is assumed that uncertain model parameters have prior distributions. Using Bayes' rule, a posterior distribution can be formed after information is gained through the course of the sequential decision making process. In the robust setting, model parameters are chosen by nature from an uncertainty set. When nature is modeled as an adversary, the problem can be formulated as a robust optimization problem [80].

Satia and Lave [81] considered a robust setting, where at each decision epoch, the transition matrix row for each action is chosen from an uncertainty set by the nature. They considered max-min (a robust optimization framework) and max-max criteria in expected total reward maximization problems and presented ϵ-algorithms that solve the problem in a finite number of iterations. Goh et al. [82] considered a robust optimization framework in which the uncertainty set has a row-wise structure and provide bounds on the performance of such uncertain MDPs. They provide an iterative algorithm for solving the problem under the row-wise structure and show that a slight relaxation of the structure makes the problem computationally intractable (NP-hard). They also applied their model to assess the cost-effectiveness of fecal immunochemical testing, a new screening method for colorectal cancer.

Martin wrote a seminal book on Bayesian MDPs [83] and formulated a problem in which each row of the transition probability matrix for each action has some prior distribution. Using Bayes' rule, a posterior distribution is obtained after observing

state transitions. Satia and Lave [81] considered conjugate beta distribution priors and presented a decision tree solution algorithm that solved the problem for a given prior distribution. Bayes-adaptive MDPs is an active research area in the computer science community with a focus on solution algorithms, e.g., see [84–86].

Bayesian MDPs can be cast as a partially observable Markov decision process (POMDP) [87–90]. Due to the high complexity of POMDP problems (see [91] for a complexity analysis), proving structural properties of the value function or the optimal policy of POMDPs can facilitate obtaining efficient solution algorithms and also provide managerial insights to problems. Lovejoy [92] provided sufficient conditions for monotonicity of POMDP value function in belief vectors. He also provided conditions under which the set of beliefs where an action is optimal forms a convex set [93].

4.1.2 Application Papers

Several research papers have incorporated patient heterogeneity in disease progression in their decision model. Lavieri et al. [78] studied the decision of when to switch from chemotherapy to radiation therapy for prostate cancer patients based on predictions of the time when the prostate specific antigen (PSA) level of a patient reaches its lowest point. They identified clusters of patients with respect to PSA progression parameters and formed a prior distribution on the cluster each patient belongs to, which was then updated after observing PSA levels over time. Helm et al. [94] considered the question of when to monitor a glaucoma patient and developed a model to predict the likelihood of glaucoma progression, where using a Kalman filter, a patient's disease progression parameters are learned sequentially through medical tests combined with population information. Negoescu et al. [95] addressed treatment planning for patients with chronic diseases, where a patient was either a responder or non-responder to some medication. They considered dosage between 0% and 100% as possible actions in each belief state. By continuously monitoring the health of the patient as well as observing critical health events, the likelihood of being a responder was then updated and the treatment plan revised accordingly.

POMDPs are also applicable where due to observation errors, the state of a system is partially observed. For instance, a patient's health (e.g., whether the patient has cancer or not) may not be perfectly identifiable due to diagnostic errors. Here we briefly survey such application of POMDPs in clinical decision making problems. Zhang et al. [39] addressed the prostate biopsy referral decision in a POMDP framework. They used PSA levels to update the belief on whether a patient has prostate cancer, based on which, prostate biopsy referral decision was made. Ayer et al. [96] used a POMDP model to provide personalized mammography screening policy based on a patient's screening history, where the belief on whether the patient has breast cancer was updated based on self-detection and mammography screening. Ayer et al. [76] addressed the role of patient adherence to mammography recommendations, and heterogeneity thereof, on optimal breast cancer screening policies in a

POMDP framework. Unlike the above papers, we apply the POMDP framework to incorporate the patient heterogeneity in disease progression in clinical decision making problems and develop a model that learns the patient type partially through observing health transitions.

4.1.3 Contributions & Chapter Structure

In this work, we formulate and analyze the problem of designing ongoing treatment plans for a population whose patients' response to treatments or disease progression in the absence of treatment vary from patient to patient in a way that 1) we can recognize distinct types of patients, and 2) each patient's type can be learned partially by monitoring her health over time. We formulate the problem as a two-dimensional state-space POMDP, where the state consists of the patient health and type. In our model, we assume that the patient health is observed perfectly, whereas the patient type is revealed only partially through observing health transitions.

In Section 4.2.2, we provide sufficient conditions under which the value function of an MDP with state-space $\mathbb{R}^n$ is monotone in state. This result generalizes the known result in the literature for one dimensional state spaces (e.g., see Proposition 4.7.3 in [97]). In Section 4.2.3, we provide conditions for having monotone optimal policies for optimal stopping timing problems with state-space $\mathbb{R}^n$. We then apply these result to Bayes adaptive treatment plan design problems defined and analyzed in Section 4.3. Finally, in Section 4.4, we apply the results of Section 4.3 to the AVF preparation timing problem introduced in Chapter 3.

We contribute to the OR/MS literature by providing results on the structure of multi-dimensional state-space MDPs. We also develop a framework for incorporating the heterogeneity of patient disease progression in an MDP and provide structural properties of the associated POMDP. This framework enables clinicians to dynamically adjust a patient's ongoing treatment plan based on the patient health and the belief about the patient's disease progression type. We also contribute to the clinical literature on vascular access planning for patients with chronic kidney disease by finding optimal AVF preparation timing policies that consider a patient's rate of disease progression in addition to the kidney health state.

Our framework bears similarities and differences to [95]. The authors assumed two types of patients, responders and non-responders, and used rewards gained under a certain medication as well as critical life events to partially learn the patient type. Our model differs from [95] since in our work, treatment decisions may depend on a patient's current health state in addition to our belief about the patient type. Similar to [92], we provide structural properties for POMDP problems, with a distinction that in our setting, the two-dimensional state-space consists of correlated observable (the health state) and partially observable (the patient type) components.

4.2 Monotonicity Results

In this section, we provide monotonicity results for MDPs with state-space $\mathbb{R}^n$. We first define notation that will be useful in the discussion that follows.

4.2.1 Notation

- T: planning horizon. Decisions are made for time periods $t = 1, \ldots, T$.
- $\mathcal{A}$: finite set of actions available in periods $t = 1, \ldots, T$
- x_t: random vector in $\mathbb{R}^n$ denoting the state of the system in period t
- $\tilde{x}_t^a(x)$: random vector denoting the state of the system in period $t+1$ when the system is at state x in period t and and action a is taken
- $r_t^a(x) : \mathbb{R}^n \to \mathbb{R}$: immediate reward received in period $t \leq T$, when action a is taken and the system is at state x
- $R(x) : \mathbb{R}^n \to \mathbb{R}$: terminal reward received at $t = T+1$ when the system is at state x

4.2.2 Monotone Value Functions

We consider discounted expected total reward maximization MDPs characterized by action space $\mathcal{A}$, rewards $r_t^a(x)$ and $R(x)$, and state transitions indicated by $\tilde{x}_t^a(x)$. Let $v_t(x) : \mathbb{R}^n \to \mathbb{R}$ be the period t value function. Then, by the principle of optimality $v_t(x)$ satisfies:

$$v_t(x) = \begin{cases} R(x), & t = T+1, \\ \max_{a \in \mathcal{A}} \left\{ r_t^a(x) + \beta \mathbb{E} v_{t+1}(\tilde{x}^a(x)) \right\}, & \text{o.w. }, \end{cases}$$

where β is the discount factor.

We use the usual stochastic order of random vectors defined below (see [98]). In the following definition, we use upper sets in $\mathbb{R}^n$ defined as follows. A set $U \in \mathbb{R}^n$ is called upper if $y \in U$ whenever $y \geq x$ and $x \in U$. Note that the we say $x \leq x'$, whenever $x_i \leq x'_i$ for all i, i.e., we compare vectors component-wise.

Definition 4.1 (Usual stochastic order)**.** Let X and Y be random vectors. We say X is smaller than Y in the usual stochastic order, denoted by $X \leq_{st} Y$, whenever we have $\mathbb{P}[X \in U] \leq \mathbb{P}[Y \in U]$ for all upper sets U.

Shaked and Shanthikumar [98] provide the following interpretation of the usual stochastic order of random vectors: X is said to be smaller than Y in the usual

stochastic order when X is less likely than Y to take on large values. Alternatively, [98] shows that $X \leq_{st} Y$ whenever we have $\mathbb{E}f(X) \leq \mathbb{E}f(Y)$ for all bounded increasing functions f.

Puterman [97] (Proposition 4.7.3), provides sufficient condition for the monotonicity of an MDP value function for one dimensional state spaces. We extend the result to n-dimensional spaces in Proposition 4.1. All of the proofs for the analytical results are given in Appendix B.

Proposition 4.1. (Monotonicity of Value Function)
$v_t(x)$ increases with x for all t, if we have:
(a) $r_t^a(x)$ increases with x for all $a \in \mathcal{A}$ for all t,
(b) $R(x)$ increases with x,
(c) $\tilde{x}_t^a(x) \leq_{st} \tilde{x}_t^a(x')$ for all $x \leq x'$ and $a \in \mathcal{A}$.

Assumptions (a,b) state that the immediate reward of all actions and the terminal reward increase with x, respectively, and assumption (c) states that the system is more likely to transitions to higher states in period $t+1$, when the system is at higher states in period t. The underlying transition probability structure, $\tilde{x}^a(x)$, depends on the context. We discuss the transition probability structure for Bayes adaptive treatment design problems in Section 4.3.

4.2.3 Monotone Optimal Policies

In finite horizon optimal stopping problems, for each $t \leq T$ we have a choice between two actions, continue and stop. When stop is chosen, a state-dependent lump-sum reward, $R_t(x)$ is received. If on the other hand continue is chosen, a state-dependent immediate reward $r_t(x)$ is received, the system evolves, and we face a similar decision in the next period (the choice between stop and continue). At $t = T+1$, a state-dependent terminal reward $R_{T+1}(x)$ is received.

Since the system evolution matters only under the continue action, each optimal stopping MDP can be characterized by the 3-tuple $(r_t(x), R_t(x), \tilde{x}(x))$, where $\tilde{x}(x)$ is a random vector denoting the state of the system in period $t+1$ when the system is at state x in period t, and action continue is taken.

Define the one-step benefit function $\delta_t(x)$ as the difference in the expected reward between waiting in period t and stopping in period $t+1$, and stopping in period t when the state is x, i.e., let $\delta_t(x) := r_t(x) + \beta\mathbb{E}R_{t+1}(\tilde{x}_t(x)) - R_t(x)$. Oh (2012) [99] showed that the optimal policy is monotone in x when $\delta_t(x)$ is monotone (increasing or decreasing) in x and $\tilde{x}_t(x) \leq_{st} \tilde{x}_t(x')$ for all $x \leq x'$. Here we state Proposition 2.5. in [99].

Proposition 4.2.
If for all t we have:
(a) $\delta_t(x)$ increases with x,
(b) $\tilde{x}_t(x)$ increases with x in the usual stochastic order.

then, it is optimal to stop at state x, whenever stopping is optimal at state x', for any $x \leq x'$.

Consider two optimal stopping time problems indexed by $i = 1, 2$, and characterized by the 3-tuple $(r_t^i(x), R_t^i(x), \tilde{x}_t^i(x))$. Also, let $\delta_t^i(x)$ be the one-step benefit function for problem i. We show that if the one-step benefit function is always smaller for problem 1 and the state dynamics is stochastically the same for both problems, then it is optimal to stop in problem 1 whenever stopping is optimal in problem 2. We use this result to provide comparative statics on the optimal policy of an optimal stopping time problem defined in Section 4.4.

Proposition 4.3.
If for all t we have:
(a) $\delta_t^1(x) \leq \delta_t^2(x)$ for any x,
(b) $\tilde{x}_t^2(x)$ has the same distribution as $\tilde{x}_t^1(x)$ for any x.
Then, stopping is optimal in state x in problem 1 whenever it is optimal to stop in state x in problem 2.

Similar to $\delta_t(x)$, define $\sigma_t(x)$ as the difference between the immediate reward of waiting and the lump-sum reward of stopping in period t, i.e., $\sigma_t(x) := r_t(x) - R_t(x)$. In the following proposition, we show that if $\tilde{x}(x)$ increases with x_i, the i^{th} component of x, in the usual stochastic order, the value function is increasing in x, and $\sigma_t(x)$ is increasing in x_i, then the optimal policy is monotone in x_i. Let x_{-i} denote all components of vector x except for the i^{th} component.

Proposition 4.4.
If for all t we have:
(a) $\tilde{x}_t(x)$ increases with x_i in the usual stochastic order,
(b) $v_{t+1}(x)$ increases with x,
(c) $\sigma_t(x)$ increases with x_i.
Then, it is optimal to stop at x, whenever stopping is optimal at state x', where $x_i \leq x'_i$, and $x'_{-i} = x_{-i}$.

Note that Proposition 4.1 provides sufficient conditions for assumption (b) to hold.

4.3 Bayes-adaptive Treatment Plans

4.3.1 Problem Statement

In this section, we formulate and analyze the problem of designing patient type Bayes-adaptive treatment plans defined as follows. We consider designing treatment plans when treatment-dependent patient outcomes vary across the population in a way that 1) we can categorize patients into distinct types, 2) we cannot perfectly

identify a patient's type a priori, and 3) the patient type can be observed partially by monitoring the patient health over time. One example of such case is where there are two types of patients in the population with respect to the response to a certain medication, good and bad responders, and the type of the patient cannot be identified a priori; nevertheless, whether the patient is a good responder to the medication or not can be learned (partially) by monitoring the patient's response to the medication over time. Another example is where there are two different types of "natural history" (i.e., disease progression in the absence of treatment), and the decision on if/when to administer a certain treatment plan depends on the true underlying disease progression process. We assume a Bayesian setting in which we start with some prior belief about the patient type and update our belief by observing the patient health over time using Bayes' rule, hence the name "patient type Bayes-adaptive treatment plans".

In the following section, we formulate the problem as a MDP with a two-dimensional state-space, where the state consists of the patient health and the belief about the patient type ("better" or "worse" disease progression type).

4.3.2 Notation

We first define notation that will be useful in the discussion that follows. For ease of notation, in this section we only consider stationary MDPs. The result can be easily extended to non-stationary MDPs.

- $\mathcal{C} = \{w, b\}$: set of two patient types. Types can represent differing stochastic progressions of disease (fast or slow) or response to medical interventions (responder or non-responder). Below, we will assume an ordering of the types so that type b, the *better* type, represents slower disease progression or better response to medical intervention, e.g., in terms of on-going rewards, compared to type w, the *worse* type.

- γ_m^a: random-variable denoting the per-period decrement of the patient health when patient type is m, and action a is taken. We let f_m^a denote the pdf (pmf) of γ_m^a.

- $r_m^a(e)$: immediate reward received in period $t \leq T$, when action a is taken, and patient health and type are e and m, respectively.

- $R_m(e)$: terminal reward received at $t = T + 1$, when patient health state and type are e and m, respectively.

4.3.3 MDP Formulation

- **States**: the state of the system at time t is comprised of the patient type, b or w, and health state. We assume that the health state is observed perfectly while patient type is observed only partially through health transitions, and

we assume that the health state is one-dimensional (i.e., a scalar). We denote the system state at t by $x_t = [e_t, p_t]$, where e_t represents health state, and p_t represents our belief (i.e., the probability) that the patient is of type b. We will assume an ordering of the states so that higher states represent better health conditions.

- **Transition dynamics**: We assume that the health state of patient type m evolves according to

$$e_{t+1,m} = e_{t,m} - \gamma_m^a.$$

Let $\tilde{x}^a(x_t)$ denote the state in period $t+1$ when in period t, action a is chosen, and the state is x_t. Then, we have $e_{t+1} = e_t - \gamma_{p_t}^a$, where $\gamma_{p_t}^a$ is defined as a random variable with pdf (pmf) given by $f_{p_t} = p_t f_b^a + (1-p_t) f_w^a$. After observing e_{t+1}, we update our patient type belief using Bayes' rule by $p_{t+1} := \mathcal{B}^a(e_{t+1} - e_t, p_t)$, where $\mathcal{B}^a(d,p)$ is defined by:

$$\mathcal{B}^a(d,p) := \frac{p f_b^a(d)}{p f_b^a(d) + (1-p) f_w^a(d)} = \frac{p f_b^a(d)}{f_p(d)}. \tag{4.1}$$

Therefore, $\tilde{x}$ satisfies

$$\tilde{x}^a(e,p) = \left[e - \gamma_p^a, \mathcal{B}^a(\gamma_p^a, p)\right].$$

- **Rewards**: At $t \le T$, an immediate reward $r_m^a(e)$ is received when action a is taken, and at $t = T+1$, a terminal reward $R_m(e)$ is received, when the patient health and type are m and e, respectively. Therefore, for state $x = [e,p]$ we have:

$$r^a(e,p) = p r_b^a(e) + (1-p) r_w^a(e),$$
$$R(e,p) = p R_b(e) + (1-p) R_w(e).$$

- **Optimality condition**: let $v_t(s,p)$ be the period t value function. Then, the value function satisfies:

$$v_t(e,p) = \begin{cases} \max_{a \in \mathcal{A}} \left\{ r^a(e,p) + \beta \mathbb{E} v_{t+1}(\tilde{x}^a(e,p)) \right\} & t \le T \\ R(e,p) & t = T+1. \end{cases}$$

4.3.4 Monotone Value Functions

We use the monotone likelihood ratio (MLR) defined below (see [98]):

Definition 4.2 (MLR Order)**.** Let X and Y be random variables with pdf's (pmf's) f and g, respectively. Then, we say X is smaller than Y in the monotone likelihood ratio (MLR) order, denoted by $X \leq_r Y$, whenever $g(z)/f(z)$ increases in z (here $b/0$ is taken to be equal to ∞ whenever $b > 0$).

Intuitively, X is said to be smaller than Y in the MLR order, when the likelihood ratio of taking large values to small values is higher for Y than X. Note that the MLR order implies the usual stochastic order of random variables [90].

In the following, we provide conditions under which the Bayesian update is monotone. Since we assume disease progression is slower for patient type b, a small decline of health can be a signal for slower disease progression, i.e., patient type b. The lemma compares the posterior belief for different values of health-decline and prior beliefs. More specifically, it states that when health decline is smaller for patient type b in the MLR order, the posterior belief about the patient being of type b is higher when our prior belief is higher, or when we observe smaller decline in the the patient health.

Lemma 4.1 (**Monotonicity of Bayesian Operator**)**.**
If $\gamma_b^a \leq_r \gamma_w^a$ for action a, then $\mathcal{B}^a(d, p)$ increases with p and decreases with d.

Intuitively, $\gamma_b^a \leq_r \gamma_w^a$ means that the likelihood ratio of observing higher health declines to lower health declines is higher for patient type w (the worse progressor type).

The following key result compares the random vector $\tilde{x}^a(x)$ for different values of x. It states that when the health decline is smaller for patient type b in the MLR order, transitions to higher health states and patient type beliefs are more likely when current health state and patient type belief are higher.

Lemma 4.2.
If for action a we have $\gamma_b^a \leq_r \gamma_w^a$, then for any $x \leq x'$ we have:

$$\tilde{x}^a(x) \leq_{st} \tilde{x}^a(x').$$

In the following proposition, we show that the total expected reward is higher if the patient is healthier (i.e., health state is higher) or when our belief about the patient being of the better type (type b) is higher. We use Proposition 4.1 and Lemma 4.2 to prove the result. For ease of notation, we order patient types in set $\mathcal{C}$ such that $w < b$.

Proposition 4.5. (Monotonicity of Value Function)
$v_t(e, p)$ increases with e and p for any t, if we have:
(a) For any $a \in \mathcal{A}$, $r_m^a(e)$ increases with e and is higher for $m = b$,
(b) $R_m(e)$ increases with e and is higher for $m = b$,
(c) $\gamma_b^a \leq_r \gamma_w^a$ for any $a \in \mathcal{A}$.

Assumptions (a,b) state that the immediate reward for any action and the terminal reward are higher when the patient health is higher or her type is better. Assumption (c) states that the health decline is smaller for patient type b (compared to patient type w) in the MLR order.

4.3.5 Monotone Policies in Optimal Stopping Problems

In clinical optimal stopping problems, the stop action can represent any medical intervention such as performing surgery (e.g., organ transplant) or starting a medication regiment (e.g., HIV treatment). Below, we will apply our modeling framework to the problem of timing AVF preparation for patient with progressive chronic kidney disease (defined in Chapter 3), where in each period, we face the decision of whether the patient should start the AVF preparation process, or we should wait and reconsider the decision in the subsequent period.

We simplify our notation for optimal stopping problems as follow. For each t, let $r_m(e)$, $R_m(e)$ denote the immediate reward of continuing and the terminal reward of stopping when patient health state and type are e and m, respectively. Also, since the system evolution matters only under the continue action, we let γ_m represent the health decline for patient type m under the continue action.

In what follows, define $\sigma_m(e) := r_m(e) - R_m(e)$. We can explain $\sigma_m(e)$ as the difference between the immediate reward of waiting for one period and the lump-sum reward of the intervention, when patient health state and type are e and m, respectively. In the following proposition, we show that if $\sigma_m(e)$ increases with m and e, i.e., when the incremental benefit of intervention is higher for sicker patients (patients with lower health) and for patients with faster disease progression (patients type w), and conditions of Proposition 4.5 hold, then intervention is optimal whenever it is optimal for healthier patients or when our belief that the patient is a slow progressor is higher.

Proposition 4.6.
If we have:

(a) For any $a \in \mathcal{A}$, $r_m^a(e)$ increases with e and is higher for $m = b$,
(b) $R_m(e)$ increases with e and is higher for $m = b$,
(c) $\gamma_b \leq_r \gamma_w$,
(d) $\sigma_m(e)$ increases with e and is higher for $m = b$.

then, it is optimal to stop at (e, p), whenever stopping is optimal at state (e', p') for any $e \leq e'$ and $p \leq p'$.

Note that assumptions (a-c) are the same as assumptions in Proposition 4.5 and used to obtain the monotonicity of the value function. We use Propositions 4.4 and 4.5 to prove Proposition 4.6 (in Appendix B).

Next, define $\delta_m(e) := r_m(e) + \beta \mathbb{E} R_m(e - \gamma_m) - R_m(e)$. We can explain $\delta_m(e)$ as the incremental benefit of waiting for one period and intervening in the subsequent period over intervening in the current period, when patient health state and type are

e and m, respectively. In the following proposition, we show that if $\delta_m(e)$ increases with m and e, i.e., when the incremental benefit of waiting for one period and intervening in the subsequent period over intervening in the current period is higher for sicker patients (patients with lower health) and for patients with faster disease progression (patients type w), and the health decline is smaller for patient type b in the MLR order, then intervention is optimal whenever it is optimal for healthier patients or when our belief that the patient is a slow progressor is higher. We use Proposition 4.2 and Lemma 4.2 to prove Proposition 4.7.

Proposition 4.7.
If we have:
(a) $\delta_m(e)$ increases with e and is higher for $m = b$,
(b) $\gamma_h^a \leq_r \gamma_l^a$ for any $a \in \mathcal{A}$.
Then, it is optimal to stop at (e, p), whenever stopping is optimal at state (e', p') for any $e \leq e'$ and $p \leq p'$.

It is intuitive that $\delta_m(e)$ increases with e since sicker patients, in comparison with healthier patients, gain more from medical interventions. For instance, the benefit of taking pain relief drugs is more pronounced for patients with higher pain levels. On the other hand, whether or not $\delta_m(e)$ increases with m is context-specific and not something we expect to intuitively hold in all contexts and not something we necessarily expect to hold. The following provides alternative conditions based on model primitives, to check if we can expect $\delta_m(e)$ to increase with m. We show that when patient types differ only in their disease progression rate (not in rewards they receive at different states), the terminal reward increases in the patient health, and the health decline is smaller for patient type b in the MLR order, then $\delta_m(e)$ increases with m.

Proposition 4.8.
If we have:
(a) $R_w(e) = R_b(e)$ and $r_w(e) = r_b(e)$ for all e,
(b) $R_b(e)$ increases with e,
(c) $\gamma_b \leq_{st} \gamma_w$.
Then, we have $\delta_w(e) \leq \delta_b(e)$.

4.4 Optimal Timing of AVF Preparation

In this section, we revisit the AVF preparation timing question of Chapter 3. We model the AVF preparation timing problem as an optimal stopping MDP problem. We incorporate the heterogeneity of patient disease progression in our model using the framework of Section 4.3.

4.4.1 Timing of AVF Preparation

The preferred vascular access for HD is an AVF [3] due to greater longevity and lower complication rates; however, it may take several months and more than one procedure to establish a usable AVF [4,5]. If the AVF is created too late, it may not mature in time, and a central venous catheter (CVC) may be used; however, CVCs are associated with an increased risk of morbidity and mortality [6–9]. On the other hand, creating an AVF too early is undesirable due to a small increase in risk of complications and wasting the limited lifetime of an AVF before HD is needed [10]. To avoid the consequences of having a functional AVF earlier or later than HD start time, it is *ideal* for the patient to have an AVF that becomes functional right at the time of HD start. Nevertheless, due to intrinsic uncertainties in AVF preparation lead-time (the time from the first AVF surgery until an functional AVF becomes available) as well as the time of HD start, the ideal case is hardly achievable.

Figure 4.1 depicts the costs associated with deviating from the ideal case. More specifically, it shows the differential in life-expectancy between the ideal case and the case when AVF becomes ready earlier or later than HD start time. When AVF becomes ready after HD starts (positive values on the x-axis), the patient loses an average of 1.6 of expected life-month for each 6 months of lateness, whereas an average of .88 of expected life-month is lost for each 6 months AVF is ready earlier than HD start time (negative values on the x-axis). The loss of life-expectancy for early AVFs are associated with the waste of AVF's limited lifetime before HD starts. The loss of life-expectancy for late AVFs is due to lower patient survival on a CVC (until an AVF becomes functional).

Estimated glomerular filtration rate (eGFR) is often used as the primary measure of kidney health. Nephrologists monitor eGFR progression periodically to decide when to initiate HD as well as when to start AVF preparation. HD is often initiated when a patient's eGFR falls below 10 mL/min/1.73m^2 [43]. Due to AVF preparation lead-time, CKD patients should start the AVF preparation in advance of HD start time, i.e., when eGFR is well above the HD start threshold. The Canadian Society of Nephrology (CSN) guidelines suggest starting the AVF preparation at an eGFR of 15-20 mL/min/1.73m^2 [16]. We develop a data-driven, dynamic programming approach to provide recommendations regarding if/when to begin the AVF preparation.

The eGFR value at which the AVF preparation starts as well as the rate at which eGFR deteriorates over time determine (stochastically) how much earlier or later than HD start time an AVF becomes available, and in turn, affect a patient's life-expectancy (Figure 4.1). The rates at which eGFR progresses over time varies considerably across the population. For example, O'hare et al. [11] identified four distinct types of patients with respect to eGFR progression rates (Table 4.1). Therefore, it is important to take into account the progression heterogeneity when making AVF preparation timing decisions. In Chapter 3, we used a Monte-Carlo simulation model to find the best time to start the AVF preparation. In this section, we model

the problem as an optimal stopping MDP, where in each period, we make a decision whether to start the AVF preparation (the stop action) or wait another period and reconsider the decision in the subsequent period. We use the framework of Section 4.3 to factor in the patient heterogeneity in disease progression.

Table 4.1: Heterogeneity of eGFR progression for chronic kidney disease patients. Table includes mean eGFR decline for different types of eGFR progression as well as their prevalence in the population [11].

EGFR progression type	mean eGFR decline†	Prevalence
Persistently low eGFR levels	7.7	63%
Progressive eGFR loss	16.3	25%
Accelerated eGFR loss	32.3	9%
Catastrophic eGFR loss	50.7	3%

†: mL/min/1.73 m^2 per year.

4.4.2 MDP Formulation

- **Patient Types:** we associate type b with patients that have stochastically slower decline of eGFR (compared to type w).
- **States**: the state of the system in period t is comprised of p_t, our belief about patient type, and e_t, the kidney health state measured by the eGFR value. We assume that HD starts when the eGFR value falls below e_d, a certain eGFR threshold. The time at which patient transitions to a state below the HD threshold is used as a proxy for HD start time.
- **Transition dynamics:** each month eGFR declines according to a random variable γ_m, for patient type m, i.e., we have:

  $$e_{t+1,m} = e_{t,m} - \gamma_m.$$

  After observing a decline d in the eGFR, we update our belief about patient type according to Eq. 4.1.

  Note that the constant expected eGFR decline in our eGFR progression model is consistent with other studies that model eGFR decline using linear regression [43, 60, 71, 72].
- **Decision epochs and actions:** each month, an eGFR reading is taken from the patient, and a decision whether to start AVF preparation or wait until the next period is made, provided that HD and AVF preparation processes have

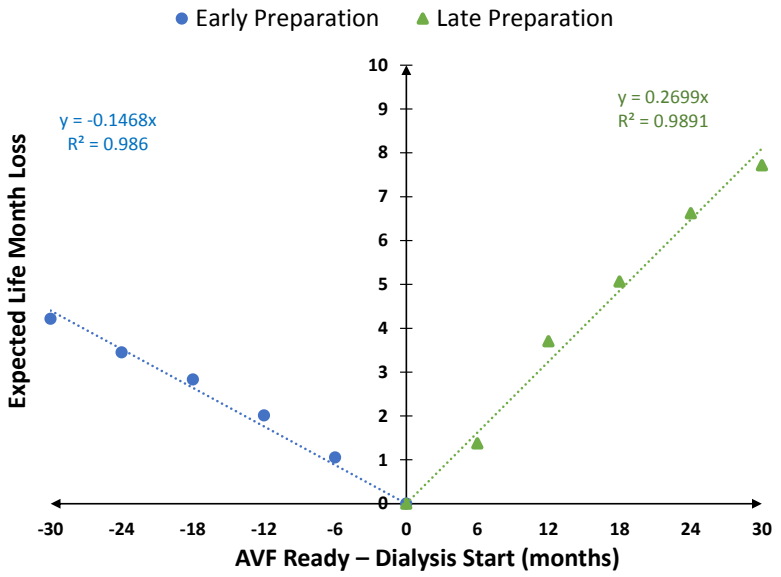

Figure 4.1: Earliness/lateness cost of AVF ready time. Plot shows a patient's expected life month loss to imperfect AVF ready time. On the x-axis, we have the difference between the time AVF is ready and HD start time. On the y-axis, we calculated the differential in life-expectancy between the ideal case (when AVF is ready at the time of HD start) and the case when AVF is ready earlier or later than HD start time for different values of *AVF Ready - Dialysis Start*. Life-expectancy for different scenarios are calculated using Monte-Carlo simulation with parameters given in Table 3.1.

not started yet. When HD starts (i.e., when the eGFR falls below the HD threshold), we start the AVF preparation if it has not already started.

- **Costs:** when we start the AVF preparation process at state (e, p), a lump-sum cost $d(e, p)$ is incurred, which is associated with AVF earliness/lateness. Let t_d and t_a denote time instants at which dialysis starts, and a functional AVF becomes available, respectively. Then, we assume that the cost under this scenario equals to $c(t_a - t_d)$ for a real-valued earliness/lateness cost function c. We fit a piece-wise linear function to data-points in Figure 4.1 to create function c. Let $d_m(e)$ be the expected earliness/lateness cost when the AVF preparation starts at eGFR e and the patient type is m. Also, let T_e^m denote the time until HD starts when eGFR is at e, and the patient type is m. Note that T_e^m is endogenous to the problem parameters. Assume that at the

beginning of month t, eGFR is at e. Then, T_e^m is defined by the following:

$$T_e^m := \min\{\tau : \sum_{i=t}^{t+\tau} \gamma_m^i \geq e - e_d\}$$

where γ_m^i denotes the decline of eGFR in month i.

Let L denote the AVF preparation lead-time. We assume that the AVF preparation is independent of patient type. Then, we have:

$$d_m(e) = \mathbb{E}_{L,T_e^m}[c(L - T_e^m)].$$

Therefore, we have $d(e,p) := pd_b(e)+(1-p)d_w(e)$. For $e \leq e_d$, we have $T_e^m = 0$ by definition. Therefore, $d_m(e) = \mathbb{E}c(L)$, and thus we have $p(e,p) = \mathbb{E}c(L)$.

We assume no immediate cost is incurred when we take the wait action, and actions do not affect the time of HD need (i.e., AVF preparation does not affect progression of chronic kidney disease).

- **Optimality condition:** let $v(e,p)$ be the value function. Then, the value function satisfies:

$$v(e,p) = \begin{cases} \mathbb{E}c(L) & e \leq e_d \\ \min\left[d(e,p), \mathbb{E}v\big(e - \gamma_p, \mathcal{B}(\gamma_p, p)\big)\right] & \text{o.w.} \end{cases}$$

In the following proposition, we show that under certain conditions, the optimal policy for starting the AVF preparation is of threshold type, i.e., it is optimal to start the AVF preparation, whenever starting is optimal for higher eGFR values (better kidney health) or for higher patient type beliefs.

Proposition 4.9. Optimal Timing of AVF Preparation
If we have:
(a) $\gamma_b \leq_r \gamma_w$,
(b) Function c is convex.
then, it is optimal to start the AVF preparation at state (e,p), whenever starting is optimal at state (e',p'), for any $e \leq e'$ and $p \leq p'$.

Assumption (a) states that the likelihood ratio of observing a higher eGFR decline to a lower eGFR decline is higher for patient type w. Note that the cost function in Figure 4.1 is approximately linear on both sides of zero. Therefore, we have $c(x) = h[-x]^+ + b[x]^+$, where $[x]^+ = \max[0,x]$. Note that c is convex for all $h, b \geq 0$, thus satisfying assumption (b) of Proposition 4.9 .

In the following proposition, we compare the optimal AVF preparation policy under different AVF preparation lead-time. We show that when the conditions of Proposition 4.9 are met, it is optimal to start the AVF preparation at any state,

whenever starting the AVF preparation is optimal under longer preparation lead-times (in the usual stochastic order).

Proposition 4.10. Comparative Statics
Consider two problem instances indexed by 1, 2, each satisfying assumptions (a) and (b) of Proposition 4.9. Assume that problems only differ in AVF preparation lead-time with $L_1 \leq_{st} L_2$. Then, it is optimal to start the AVF preparation at any state (s, p) in problem 1, whenever starting is optimal in problem 2.

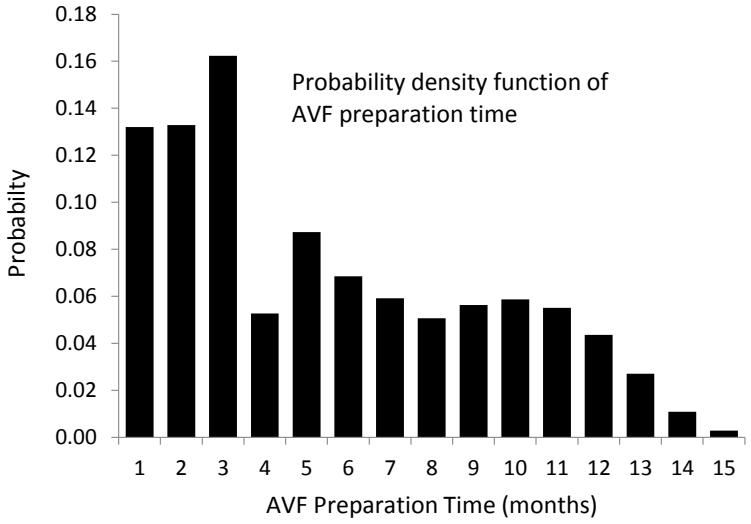

Figure 4.2: Empirical probability mass function of the AVF preparation time, generated using Monte-Carlo simulation. We considered a series of AVF surgeries performed one after the other until one surgery is successful, with at most 4 of AVF creations. The values for AVF surgery success probability and maturation times and the sources used for each parameter are given in Table 3.1.

4.4.3 Numerical Results

To demonstrate the results of Proposition 4.9, we performed a numerical study. The parameters used for the study are as follows. We used the earliness/lateness cost function depicted in Figure 4.1 and chose $c(x) = h[-x]^+ + b[x]^+$. We set $h = 26.5$ and $b = 48$ and assume $c(x)$ and x are measured in days and months, respectively. We used the patient types defined in [11] (see Table 4.1) and let types b and w represent 'persistently low eGFR' and 'progressive eGFR loss'. These two types represented 88% of the CKD population in the study by [11]. Note that the two other patient types ('accelerated eGFR loss' and 'catastrophic eGFR loss' patients) can be easily

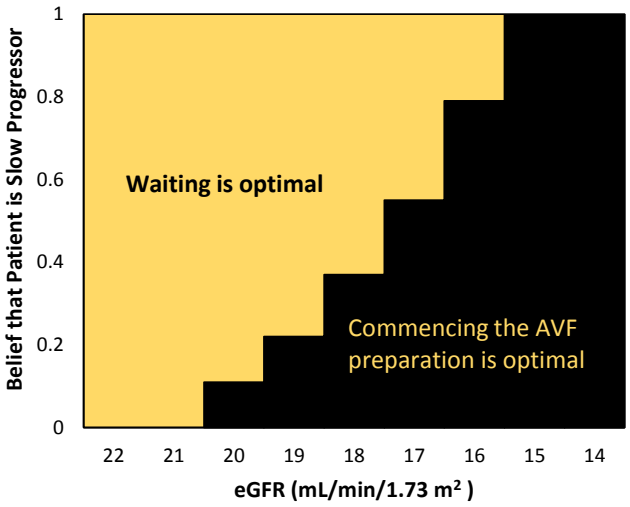

Figure 4.3: Optimal policy for AVF preparation timing. The optimal policy for different values of eGFR as well as the belief that the patient is of type b, i.e., the slow progressor, is shown. The states at which the optimal policy is 'start the AVF preparation' and 'wait' are depreciated in black and yellow, respectively. As figure suggest, the optimal policy is monotone in both state dimensions.

distinguished from the types we consider here since they have noticeably higher eGFR decline rates. We modeled eGFR monthly decrement for patient types b and w as normally distributed random variables, i.e., we assumed $\gamma_m \sim \mathcal{N}(\mu_m, \sigma_m^2)$. We used the average monthly eGFR decline given for patient types b and w in [11] and set $[\mu_w, \mu_b] = [1.4, .64]$. To calculate σ_m, we performed primary data analysis on the eGFR trajectories of 1048 patients treated at the multidisciplinary kidney clinic at Vancouver General Hospital. We found that $[\sigma_w, \sigma_b] = [1.5, 1.4]$. We assumed that HD starts when eGFR falls below 10 mL/min/1.73m^2, i.e., $e_d = 10$ [43]. We calculated the probability mass function of AVF preparation lead-time using parameters given in Table 3.1 (see Figure 4.4.2 for more details).

To solve the problem numerically, we discretize the state-space with a uniform grid, in which eGFR values are grouped in buckets of 1 mL/min/1.73m^2, and beliefs are grouped in buckets of 0.01. We have $\mathcal{N}(\mu_b, \sigma_b^2) \leq_r \mathcal{N}(\mu_w, \sigma_w^2)$ whenever $\sigma_b = \sigma_w$ and $\mu_b \leq \mu_w$ (see [100]). Although we have $\mu_b \leq \mu_w$, the condition that $\sigma_b = \sigma_w$ does not hold; nevertheless, we can show that assumption (a) of Proposition 4.9 empirically holds for our discretize state-space. Finally, assumption (b) of Proposition 4.9 holds since for all values of parameters $h, b \geq 0$, function $c(x) = h[-x]^+ + b[x]^+$ is convex. Therefore by Proposition 4.9, the optimal policy for starting the AVF preparation is of threshold type, i.e., it is optimal to start the AVF preparation, whenever starting is optimal for higher eGFR values and higher beliefs (that the

patient is a slow progressor).

Figure 4.3 depicts the optimal policy for AVF preparation timing for different eGFR values and patient type beliefs. As we expect, the optimal policy is monotone in both state dimensions. When the patient type is a slow progressor (fast progressor) with certainty, the optimal eGFR threshold beyond which starting the AVF preparation is optimal is 15 mL/min/1.73m^2 (20 mL/min/1.73m^2). This is consistent with the Canadian Society of Nephrology (CSN) guidelines which suggests starting the AVF preparation at an eGFR of between 15 and 20 mL/min/1.73m^2 [16]. Our results sharpen the guidelines by matching the lower bound of 15 with patients classified as slow progressors (mean eGFR decline of .64 mL/min/1.73m^2 per month) and the upper bound of 20 with the fast progressors (mean eGFR decline of 1.4 mL/min/1.73m^2 per month).

4.5 Conclusion

In this chapter, we analyzed the problem of designing ongoing treatment plans for a heterogeneous population with respect to disease progression and response to medical interventions. We created a model that learns the patient type by monitoring the patient health over time and updates a patient's treatment plan according to the gathered information. We formulated the problem as a two-dimensional state-space POMDP and provided structural properties of the value-function, as well as the optimal policy for the special case of optimal stopping timing problems. This framework can be extended to other contexts where an MPD is applicable and transition parameters can be learned by observing state transitions.

We also applied the framework to the AVF preparation timing question posed in Chapter 3 by considering two types of patients, patients with slow and fast eGFR progression. We showed that under data-driven assumptions, the optimal AVF preparation timing policy is monotone in a patient's current eGFR as well as our belief that the patient is a slow progressor.

Although we considered two patient types, our results can be extended to cases with multiple patient types. We also believe that the framework can be applied to other chronic diseases where heterogeneity in disease progression is present. We considered a special structure for the state dynamics of MDPs where random variables representing the difference between the states in periods t and $t+1$ for each action do not depend on the state in period t. It would be interesting to extend the result to a more general setting for state transitions. Finally, we only investigated the monotonicity of optimal policies for optimal stopping timing problems. As a direction for future research, one might consider extending the results to the case with a more general action space.

Chapter 5

Conclusions, Extensions and Further Applications

The research in this dissertation focused on the application of stochastic optimization models to vascular access planning for patients with chronic kidney disease. In this section, we provide a review of the problem, analytical models developed to address the research questions, and the main results. Furthermore, we discuss possible extensions and avenues for further research.

Hemodialysis is the most common form of renal replacement therapy. There are two primary types of vascular accesses used for HD, arteriovenous fistula (AVF), and central venous catheter (CVC). An AVF, which is created via a surgical procedure, is often considered the gold standard for delivering HD due to better patient survival and higher quality of life. However, it may take several months and more than one procedure to establish a functional AVF, whereas a CVC can be inserted via a simple procedure and used immediately after placement. In this thesis, we address the question of whether and when to perform AVF surgery on patients with CKD with the aim of finding individualized policies that optimize patient outcomes. This question is relevant in two stages of the disease, before HD commences and after.

In Chapter 2, we focused on vascular access planing for patients already on HD. Using AVF for HD not only brings better survival, but also has a slightly higher quality of life for the patient, in comparison with HD using a CVC. Nevertheless, the process of AVF creation has some disutility associated with it, which can be attributed to the surgery and post-surgery inconveniences, complications or costs. Therefore, it is not clear under what conditions an HD dependent patient should undergo the AVF creation surgery. We developed a continuous-time dynamic programming model to find optimal policies that maximize a patient's life expectancy and Quality-adjusted life expectancy (QALE).

We analytically proved that delaying AVF surgery stochastically decreases a patient's lifetime. As a result, the policy of "use the next AVF (opportunity) as soon as a patient starts HD or when the one being used fails" maximizes a patient's survival probability. We also proved that the optimal policy to maximize a patient's QALE is of a threshold type: there is an HD duration threshold before which immediate surgery is the optimal choice, while after that time, CVC is the optimal vascular access choice for the remainder of the patient's lifetime. This threshold depends on the number of past AVF maturation failures.

The AVF creation disutility plays an essential role in determining the optimal policy when maximizing QALE. Since patients may feel differently about the disutility of AVF surgery, and also because it is not an easy parameter to elicit from a patient, our model provides an alternative way to make the optimal AVF timing decision. We showed that the decision of whether to perform an AVF surgery or not can be determined solely by comparing the patient's AVF creation disutility with a boundary value reflecting the prospective additional QALE for the patient, which we refer to as the critical disutility. Thus, a nephrologist can inform the patient of the benefits and inconveniences of undergoing the AVF surgery, and then, they can collectively decide whether to do the surgery or not. Even if a rough estimate of the patient's disutility for AVF surgery indicates that it is clearly below or above the critical disutility, then it will be clear that the patient should or should not, respectively, undergo an AVF surgery.

We also found that the possibility of receiving a kidney transplant adds new complexities to the model and optimal policy structure. Although the optimal policy under the total lifetime remains the same, the result on QALE metric (optimality of threshold policies) does not necessarily extend, even when the time of transplant is known with certainty. Nevertheless, we provided a theorem which proves that under additional assumptions (which are supported by data), threshold policies remain optimal. It would be interesting to investigate how the possibility of cadaveric donations and random wait times affect the vascular access planning for ESRD patients under the QALE metric. We did not consider costs in our model and focused on patient outcomes. It would be interesting to perform a cost-effectiveness analysis and investigate whether suggested policies are cost-effective or not.

Our framework and analytical results may also be relevant to operational questions outside of health care, particularly in the area of machine maintenance and equipment reliability. For example, consider a machine with a vital component. If the component breaks down, it may be replaced with a cheap, available spare. Additionally, one may order a more expensive, higher-quality component, which involves a lead time for delivery. This is analogous to deciding whether and when to refer a patient for an AVF versus letting them continue to receive HD through a CVC. An AVF provides higher quality HD outcomes compared to a CVC, but an AVF cannot be created quickly, and it is more expensive in the sense of the surgical disutility it imposes on patients.

In Chapter 3, we developed a Monte-Carlo simulation model to address the timing of AVF preparation for progressive CKD patients who have not yet initiated HD. We considered two types of strategies based on approaches suggested in recently published guidelines: refer when hemodialysis is anticipated to begin within a certain time frame or refer when eGFR drops below a certain threshold. We evaluated these strategies over a range of values for each strategy, compared them with respect to different performance metrics (e.g., a patient's life expectancy after HD initiation and percentage of patients with an unnecessary AVF creation), and provided policy

recommendations.

Our simulation results shows that in general, AVF referral within about 12 months of the estimated time to dialysis performed best among time frame strategies, and referral at eGFR between 15 and 20 mL/min/1.73m^2 performed best among threshold strategies. Elderly patients with CKD could be referred later to reduce the risk of creating an AVF that is never used. Similar to Chapter 2, the focus in this chapter was on patients outcomes rather than costs. A future cost-effectiveness analysis can elaborate whether an early AVF referral is cost-effective, especially for the elderly who benefit the least from hemodialysis, are more frail and have multiple co-morbidities. We did not consider arteriovenous grafts (AVGs) as a vascular access choice in our model. It would be interesting to investigate how considering AVGs would affect the optimal policy structure, patient outcomes, and costs.

One of our results in Chapter 3 was that the timing of referral should be guided by the individual rate of CKD progression. In Chapter 4, motivated by this finding, we analyzed the problem of designing ongoing treatment plans for a heterogeneous population with respect to disease progression and response to medical interventions. We developed a dynamic programming model that incorporates patient heterogeneity in disease progression when making clinical decisions. The designed model learns the patient type by monitoring the patient health over time and updates a patient's treatment plan according to the gathered information. We formulated the problem as a two-dimensional state-space partially observable Markov decision process (POMDP) and provided structural properties of the value-function, as well as the optimal policy for the special case of optimal stopping problems.

We applied this framework to the AVF preparation timing question posed in Chapter 3 by considering two types of patients, patients with slow and fast eGFR progression. We showed that under data-driven conditions, the optimal policy for starting the AVF preparation is of a threshold type, i.e., it is optimal to start the AVF preparation, whenever starting is optimal for higher eGFR values (better kidney health) or when our belief that the patient is a slow processor is higher.

Our numerical results showed that when the patient type is a slow progressor (fast progressor) with certainty, the optimal eGFR threshold beyond which starting the AVF preparation is optimal is 15 mL/min/1.73m^2 (20 mL/min/1.73m^2). This is consistent with the Canadian Society of Nephrology (CSN) guidelines which suggests starting the AVF preparation at an eGFR of between 15 and 20 mL/min/1.73m^2 [16]. Our results sharpens the guidelines by matching the lower bound of 15 with patients classified as slow progressors (mean eGFR decline of .64 mL/min/1.73m^2 per month) and the upper bound of 20 with the fast progressors (mean eGFR decline of 1.4 mL/min/1.73m^2 per month).

We believe that this framework can be extended to other contexts where a Markov Decision Process (MPD) is applicable and transition parameters can be learned by observing state transitions. Although we considered two patient types in this chapter, our results can be extended to cases with multiple patient types.

We also believe that the framework can be applied to other chronic diseases where heterogeneity in disease progression is present. We considered a special structure for the state dynamics of MDPs where random variables representing the difference between the states in periods t and $t+1$ for each action do not depend on the state in period t. It would be interesting to extend the result to a more general setting for state transitions. Finally, we only investigated the monotonicity of optimal policies for optimal stopping timing problems. As a direction for future research, one might consider extending the results to the case with a more general action space.

Bibliography

[1] National Institutes of Health. Chronic kidney disease and kidney failure., 2016. Retrieved June 1, 2016, https://report.nih.gov/NIHfactsheets/ViewFactSheet.aspx?csid=34&key=C#C.

[2] National Kidney & Urologic Diseases Information Clearinghouse (NKUDIC). Kidney and urologic diseases statistics for the united states, 2016. Retrieved June 1, 2016, http://kidney.niddk.nih.gov/kudiseases/pubs/kustats/.

[3] National Kidney Foundation Vascular Access Work Group. Clinical practice guidelines for vascular access. *American Journal of Kidney Diseases*, 48(Supplement 1):S248–S273, 7 2006.

[4] Harold I Feldman, Marshall Joffe, Sylvia E Rosas, J Eileen Burns, Jill Knauss, and Kenneth Brayman. Predictors of successful arteriovenous fistula maturation. *American Journal of Kidney Diseases*, 42(5):1000–1012, 2003.

[5] Hugh C Rayner, Ronald L Pisoni, Brenda W Gillespie, David A Goodkin, Takashi Akiba, Tadao Akizawa, Akira Saito, Eric W Young, and Friedrich K Port. Creation, cannulation and survival of arteriovenous fistulae: data from the dialysis outcomes and practice patterns study. *Kidney International*, 63(1):323–330, 2003.

[6] Rajnish K Dhingra, Eric W Young, TE Hulbert-Shearon, Sean F Leavey, and Friedrich K Port. Type of vascular access and mortality in US hemodialysis patients. *Kidney International*, 60(4):1443–1451, 2001.

[7] Haimanot Wasse, Nancy Kutner, Rebecca Zhang, and Yijian Huang. Association of initial hemodialysis vascular access with patient-reported health status and quality of life. *Clinical Journal of the American Society of Nephrology*, 2(4):708–714, 2007.

[8] Eduardo Lacson, J Michael Lazarus, Jonathan Himmelfarb, T Alp Ikizler, and Raymond M Hakim. Balancing fistula first with catheters last. *American Journal of Kidney Diseases*, 50(3):379–395, 2007.

[9] Jeffrey Perl, Ron Wald, Philip McFarlane, Joanne M Bargman, Edward Vonesh, Yingbo Na, S Vanita Jassal, and Louise Moist. Hemodialysis vas-

cular access modifies the association between dialysis modality and survival. *Journal of the American Society of Nephrology*, 22(6):1113–1121, 2011.

[10] Ann M O'Hare, Michael Allon, and James S Kaufman. Whether and when to refer patients for predialysis av fistula creation: complex decision making in the face of uncertainty. *Seminars in Dialysis*, 23(5):452–455, 2010.

[11] Ann M O'Hare, Adam Batten, Nilka Ríos Burrows, Meda E Pavkov, Leslie Taylor, Indra Gupta, Jeff Todd-Stenberg, Charles Maynard, Rudolph A Rodriguez, Fliss EM Murtagh, et al. Trajectories of kidney function decline in the 2 years before initiation of long-term dialysis. *American Journal of Kidney Diseases*, 59(4):513–522, 2012.

[12] I. Gorodetskaya, S. Zenios, C. E. McCulloch, A. Bostrom, C. Hsu, A. B. Bindman, A. S. Go, and G. M. Chertow. Health-related quality of life and estimates of utility in chronic kidney disease. *Kidney International*, 68(6):2801–2808, 2005.

[13] National kidney foundation K/DOQI. Clinical practice guidelines for vascular access: Update 2000. *American Journal of Kidney Diseases*, 48(Supplement 1):S137–S181, 2000.

[14] National kidney foundation K/DOQI. Clinical practice guidelines for vascular access. *American Journal of Kidney Diseases*, 48(Supplement 1):S176–S247., 2006.

[15] Garabed Eknoyan and Nathan W. Levin. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *American Journal of Kidney Diseases*, 14(Supplement 2):S1–S246, 2002.

[16] K. Jindal, C. T. Chan, C. Deziel, D. Hirsch, S. D. Soroka, M. Tonelli, and B. F. Culleton. Hemodialysis Clinical Practice Guidelines for the Canadian Society of Nephrology: (Chapter 4) Vascular access . *Journal of the American Society of Nephrology*, 17(3 Supplement 1):S16–S23, 2006.

[17] M Tonelli, N Wiebe, G Knoll, A Bello, S Browne, D Jadhav, S Klarenbach, and J Gill. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. *American Journal of Transplantation*, 11(10):2093–2109, 2011.

[18] UNOS. United Network for Organ Sharing, 2014. Retrieved Feb 1, 2014, http://www.unos.org/.

[19] *Annual Data Report: 2013 Atlas of CKD and ESRD: United States Renal Data System*, 2013.

[20] Fistula First. Fistula first breakthrough initiative, 2014. Retrieved Feb 1, 2014, http://www.fistulafirst.org/.

[21] Jean Ethier, David C Mendelssohn, Stacey J Elder, Takeshi Hasegawa, Tadao Akizawa, Takashi Akiba, Bernard J Canaud, and Ronald L Pisoni. Vascular access use and outcomes: an international perspective from the dialysis outcomes and practice patterns study. *Nephrology Dialysis Transplantation*, 23(10):3219–3226, 2008.

[22] C. E. Lok, M. Allon, L. Moist, M. J. Oliver, H. Shah, and D. Zimmerman. Risk equation determining unsuccessful cannulation events and failure to maturation in arteriovenous fistulas. *Journal of the American Society of Nephrology*, 17(11):3204–3212, 2006.

[23] W. J. Peterson, J. Barker, and M. Allon. Disparities in fistula maturation persist despite preoperative vascular mapping. *Clinical Journal of the American Society of Nephrology*, 3(2):437–441, 2008. id: 135.

[24] Prabir Roy-Chaudhury, Vikas P Sukhatme, and Alfred K Cheung. Hemodialysis vascular access dysfunction: a cellular and molecular viewpoint. *Journal of the American Society of Nephrology*, 17(4):1112–1127, 2006.

[25] Aicha Radoui, Zineb Lyoussfi, Intissar Haddiya, Zoubair Skalli, Redouane El Idrissi, Hakima Rhou, Fatima Ezzaitouni, Naima Ouzeddoun, Abbes El Mesnaoui, Rabea Bayahia, et al. Survival of the first arteriovenous fistula in 96 patients on chronic hemodialysis. *Annals of Vascular Surgery*, 25(5):630–633, 2011.

[26] C. Basile and C. Lomonte. Pro: The arteriovenous fistula is a blessing of God. *Nephrology Dialysis Transplantation*, 27(10):3752–3756, 2012.

[27] R. Amerling. Con: On cardiovascular outcomes and the arteriovenous fistula: lesser of evils. *Nephrology Dialysis Transplantation*, 27(10):3756–3757, 2012.

[28] N. Lameire and W. Van Biesen. Moderator's view: A 'secular' view on vascular access in haemodialysis. *Nephrology Dialysis Transplantation*, 27(10):3758–3761, 2012.

[29] L. M. Moist, Charmaine E. Lok, T. J. Vachharajani, W. Xi, A. AlJaishi, K. R. Polkinghorne, M. Vazquez, and T. C. Lee. Optimal hemodialysis vascular access in the elderly patient. *Seminars in Dialysis*, 25(6):640–648, 2012.

[30] M.J. Barry and S. Edgman-Levitan. Shared decision making-the pinnacle of patient-centered care. *New England Journal of Medicine*, 366(9):780–781, 2012.

[31] M. K. Tamura, J. C. Tan, and A. M. O'Hare. Optimizing renal replacement therapy in older adults: a framework for making individualized decisions. *Kidney International*, 82(3):261–269, 2011.

[32] H.C. Sox and S. Greenfield. Comparative effectiveness research: A report from the Institute of Medicine. *Annals of Internal Medicine*, 151:203–205, 2009.

[33] L Boulware. Comparative effectiveness research in kidney disease: a national priority. *American Journal of Kidney Diseases*, 61(1):9–12, 2013.

[34] O. Alagoz, L. M. Maillart, A. J. Schaefer, and M. S. Roberts. The optimal timing of living-donor liver transplantation. *Management Science*, 50(10):1420–1430, 2004.

[35] S. M. Shechter, M. D. Bailey, A. J. Schaefer, and M. S. Roberts. The optimal time to initiate HIV therapy under ordered health states. *Operations Research*, 56(1):20–33, 2008.

[36] L. M. Maillart, J. S. Ivy, S. Ransom, and K. Diehl. Assessing dynamic breast cancer screening policies. *Operations Research*, 56(6):1411–1427, 2008.

[37] T. Ayer, O. Alagoz, and N. K. Stout. OR Forum-A POMDP approach to personalize mammography screening decisions. *Operations Research*, 60(5):1019–1034, 2012.

[38] Chris P. Lee, Glenn M. Chertow, and Stefanos A. Zenios. Optimal initiation and management of dialysis therapy. *Operations Research*, 56(6):1428–1449, 2008.

[39] Jingyu Zhang, Brian T Denton, Hari Balasubramanian, Nilay D Shah, and Brant A Inman. Optimization of prostate biopsy referral decisions. *Manufacturing & Service Operations Management*, 14(4):529–547, 2012.

[40] Mehmet US Ayvaci, Oguzhan Alagoz, and Elizabeth S Burnside. The effect of budgetary restrictions on breast cancer diagnostic decisions. *Manufacturing & Service Operations Management*, 14(4):600–617, 2012.

[41] Hui Xue, Eduardo Lacson, Weiling Wang, Gary C Curhan, and Steven M Brunelli. Choice of vascular access among incident hemodialysis patients: a decision and cost-utility analysis. *Clinical Journal of the American Society of Nephrology*, 5(12):2289–2296, 2010.

[42] Swapnil Hiremath, Greg Knoll, and Milton C Weinstein. Should the arteriovenous fistula be created before starting dialysis?: a decision analytic approach. *PloS one*, 6(12):e28453, 2011.

[43] S. M. Shechter, Skandari M. R., and N. Zalunardo. Timing of arteriovenous fistula creation in patients with CKD: A decision analysis. *American Journal of Kidney Diseases*, 63(1):95–103, 2014.

[44] D. Drew, C. Lok, J. Cohen, M. Wagner, N. Tangri, and D. Weiner. Vascular access choice in incident hemodialysis patients: A decision analysis. *Journal of the American Society of Nephrology*, 2014. Forthcoming.

[45] M. Kurella, K. E. Covinsky, A. J. Collins, and G. M. Chertow. Octogenarians and nonagenarians starting dialysis in the United States. *Annals of Internal Medicine*, 146(3):177–183, 2007.

[46] Raymond M Hakim and Jonathan Himmelfarb. Hemodialysis access failure: a call to action revisited. *Kidney international*, 76(10):1040–1048, 2009.

[47] M.R. Gold, J.E. Siegel, L.B. Russell, and M.C. Weinstein. *Cost-Effectiveness in Health and Medicine*. Oxford University Press, USA, 1996.

[48] Institute of Medicine. Insuring America's Health: Principles and Recommendations, 2004. Retrieved October 15, 2013, http://www.iom.edu/Reports/2004/Insuring-Americas-Health-Principles-and-Recommendations.aspx.

[49] Allan J Collins, Robert N Foley, David T Gilbertson, and Shu-Chen Chen. The state of chronic kidney disease, esrd, and morbidity and mortality in the first year of dialysis. *Clinical Journal of the American Society of Nephrology*, 4(Supplement 1):S5–S11, 2009.

[50] William F Owen. Patterns of care for patients with chronic kidney disease in the United States: dying for improvement. *Journal of the American Society of Nephrology*, 14(Supplement 2):S76–S80, 2003.

[51] Douglas C Montgomery, Cheryl L Jennings, and Murat Kulahci. *Introduction to time series analysis and forecasting*. John Wiley & Sons, 2015.

[52] Emre Erdogan, Sheng Ma, Alina Beygelzimer, and Irina Rish. Statistical models for unequally spaced time series. In *Proceedings of the Fifth SIAM International Conference on Data Mining*. SIAM, 2004.

[53] Garrett M Fitzmaurice, Nan M Laird, and James H Ware. *Applied longitudinal analysis*, volume 998. John Wiley & Sons, 2012.

[54] Rockwell Automated Technologies. Arena (version 10), 2010.

[55] Laura M Dember, Gerald J Beck, Michael Allon, James A Delmez, Bradley S Dixon, Arthur Greenberg, Jonathan Himmelfarb, Miguel A Vazquez, Jennifer J Gassman, Tom Greene, et al. Effect of clopidogrel on early failure of

arteriovenous fistulas for hemodialysis: a randomized controlled trial. *Jama*, 299(18):2164–2171, 2008.

[56] Wenjie Wang, Brendan Murphy, Serdar Yilmaz, Marcello Tonelli, Jennifer MacRae, and Braden J Manns. Comorbidities do not influence primary fistula success in incident hemodialysis patients: a prospective study. *Clinical Journal of the American Society of Nephrology*, 3(1):78–84, 2008.

[57] Carrie A Schinstock, Robert C Albright, Amy W Williams, John J Dillon, Eric J Bergstralh, Bernice M Jenson, James T McCarthy, and Karl A Nath. Outcomes of arteriovenous fistula creation after the fistula first initiative. *Clinical Journal of the American Society of Nephrology*, 6(8):1996–2002, 2011.

[58] Dember, Laura M., and Bradley S. Dixon. Early fistula failure: Back to basics. *American Journal of Kidney Diseases*, 50(5):696–699, 2007. id: 127.

[59] Barry M Brenner, Mark E Cooper, Dick de Zeeuw, William F Keane, William E Mitch, Hans-Henrik Parving, Giuseppe Remuzzi, Steven M Snapinn, Zhonxin Zhang, and Shahnaz Shahinfar. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *New England Journal of Medicine*, 345(12):861–869, 2001.

[60] Lawrence G Hunsicker, Sharon Adler, Arlene Caggiula, Brian K England, Tom Greene, John W Kusek, Nancy L Rogers, Paul E Teschan, Gerald Beck, Modification of Diet in Renal Disease Study Group, et al. Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study. *Kidney International*, 51(6):1908–1919, 1997.

[61] E. Arias. United states life tables. *National Vital Statistics Reports*, 58(21):1—40, 2010.

[62] Pietro Ravani, Suetonia C Palmer, Matthew J Oliver, Robert R Quinn, Jennifer M MacRae, Davina J Tai, Neesh I Pannu, Chandra Thomas, Brenda R Hemmelgarn, Jonathan C Craig, et al. Associations between hemodialysis access type and clinical outcomes: a systematic review. *Journal of the American Society of Nephrology*, 24(3):465–473, 2013.

[63] Martin Ferring, Martin Claridge, Steven A Smith, and Teun Wilmink. Routine preoperative vascular ultrasound improves patency and use of arteriovenous fistulas for hemodialysis: a randomized trial. *Clinical Journal of the American Society of Nephrology*, pages 282–310, 2010.

[64] United States Renal Data System. 2012 atlas of CKD & ESRD., 2012. Retrieved June 1, 2016, `http://www.usrds.org/atlas12.aspx`".

[65] Andrew H Briggs. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics*, 17(5):479–500, 2000.

[66] Peter Doubilet, Colin B Begg, Milton C Weinstein, Peter Braun, and Barbara J McNeil. Probabilistic sensitivity analysis using monte carlo simulation. a practical approach. *Medical Decision Making: an International Journal of the Society for Medical Decision Making*, 5(2):157–177, 1984.

[67] Sylvia E Rosas and Harold I Feldman. Synthetic vascular hemodialysis access vs native arteriovenous fistula: A cost-utility analysis. *Annals of Surgery*, 255(1):181, 2012.

[68] Manjula Kurella Tamura, Kenneth E Covinsky, Glenn M Chertow, Kristine Yaffe, C Seth Landefeld, and Charles E McCulloch. Functional status of elderly adults before and after initiation of dialysis. *New England Journal of Medicine*, 361(16):1539–1547, 2009.

[69] Lorien S Dalrymple, Ronit Katz, Bryan Kestenbaum, Michael G Shlipak, Mark J Sarnak, Catherine Stehman-Breen, Stephen Seliger, David Siscovick, Anne B Newman, and Linda Fried. Chronic kidney disease and the risk of end-stage renal disease versus death. *Journal of general internal medicine*, 26(4):379–385, 2011.

[70] Tushar J Vachharajani, Shahriar Moossavi, Jean R Jordan, Vidula Vachharajani, Barry I Freedman, and John M Burkart. Re-evaluating the fistula first initiative in octogenarians on hemodialysis. *Clinical Journal of the American Society of Nephrology*, 6(7):1663–1667, 2011.

[71] BO Eriksen and OC Ingebretsen. The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. *Kidney International*, 69(2):375–382, 2006.

[72] Adeera Levin, Ognjenka Djurdjev, Monica Beaulieu, and Lee Er. Variability and risk factors for kidney disease progression and death following attainment of stage 4 ckd in a referred cohort. *American Journal of Kidney Diseases*, 52(4):661–671, 2008.

[73] Liang Li, Brad C Astor, Julia Lewis, Bo Hu, Lawrence J Appel, Michael S Lipkowitz, Robert D Toto, Xuelei Wang, Jackson T Wright, and Tom H Greene. Longitudinal progression trajectory of gfr among patients with ckd. *American Journal of Kidney Diseases*, 59(4):504–512, 2012.

[74] Sujha Subramanian, Michelle Klosterman, Mayur M Amonkar, and Timothy L Hunt. Adherence with colorectal cancer screening guidelines: a review. *Preventive Medicine*, 38(5):536–550, 2004.

[75] John M Inadomi, Sandeep Vijan, Nancy K Janz, Angela Fagerlin, Jennifer P Thomas, Yunghui V Lin, Roxana Muñoz, Ma Somsouk, Najwa El-Nachef,

and Rodney A Hayward. Adherence to colorectal cancer screening: a randomized clinical trial of competing strategies. *Archives of internal medicine*, 172(7):575–582, 2012.

[76] Turgay Ayer, Oguzhan Alagoz, Natasha K Stout, and Elizabeth S Burnside. Heterogeneity in womens adherence and its role in optimal breast cancer screening policies. *Management Science*, 2015.

[77] M Romeo, F Martinelli-Boneschi, M Rodegher, F Esposito, V Martinelli, and G Comi. Clinical and mri predictors of response to interferon-beta and glatiramer acetate in relapsing–remitting multiple sclerosis patients. *European Journal of Neurology*, 20(7):1060–1067, 2013.

[78] Mariel S Lavieri, Martin L Puterman, Scott Tyldesley, and William J Morris. When to treat prostate cancer patients based on their psa dynamics. *IIE Transactions on Healthcare Systems Engineering*, 2(1):62–77, 2012.

[79] Anahita Khojandi, Lisa M Maillart, Oleg A Prokopyev, Mark S Roberts, Timothy Brown, and William W Barrington. Optimal Implantable Cardioverter Defibrillator (ICD) Generator Replacement. *INFORMS Journal on Computing*, 26(3):599–615, 2014.

[80] Aharon Ben-Tal and Arkadi Nemirovski. Robust convex optimization. *Mathematics of operations research*, 23(4):769–805, 1998.

[81] Jay K Satia and Roy E Lave Jr. Markovian decision processes with uncertain transition probabilities. *Operations Research*, 21(3):728–740, 1973.

[82] Joel Goh, Mohsen Bayati, Stefanos A Zenios, Sundeep Singh, and David Moore. Data uncertainty in markov chains: Application to cost-effectiveness analyses of medical innovations. *Working Paper*, 2015.

[83] James John Martin. *Bayesian Decision Problems and Markov Chains*. Wiley, 1967.

[84] Pascal Poupart, Nikos Vlassis, Jesse Hoey, and Kevin Regan. An analytic solution to discrete bayesian reinforcement learning. In *Proceedings of the 23rd international conference on Machine learning*, pages 697–704. ACM, 2006.

[85] Mauricio Araya-López, Olivier Buffet, Vincent Thomas, and François Charpillet. Active learning of MDP models. In *Recent Advances in Reinforcement Learning*, pages 42–53. Springer, 2011.

[86] Arthur Guez, David Silver, and Peter Dayan. Efficient Bayes-adaptive reinforcement learning using sample-based search. In *Advances in Neural Information Processing Systems*, pages 1025–1033, 2012.

[87] Richard D Smallwood and Edward J Sondik. The optimal control of partially observable markov processes over a finite horizon. *Operations Research*, 21(5):1071–1088, 1973.

[88] Leslie Pack Kaelbling, Michael L Littman, and Anthony R Cassandra. Planning and acting in partially observable stochastic domains. *Artificial intelligence*, 101(1):99–134, 1998.

[89] Michael O'Gordon Duff. *Optimal Learning: Computational procedures for Bayes-adaptive Markov decision processes*. PhD thesis, University of Massachusetts Amherst, 2002.

[90] Vikram Krishnamurthy. *Partially Observed Markov Decision Processes: From Filtering to Controlled Sensing*. Cambridge University Press, 2016.

[91] M. Mundhenk. *The complexity of planning with partially-observable Markov Decision Processes.* PhD thesis, Friedrich-Schiller-Universitdt., 2001.

[92] William S Lovejoy. Some monotonicity results for partially observed markov decision processes. *Operations Research*, 35(5):736–743, 1987.

[93] William S Lovejoy. Technical noteon the convexity of policy regions in partially observed systems. *Operations Research*, 35(4):619–621, 1987.

[94] Jonathan E Helm, Mariel S Lavieri, Mark P Van Oyen, Joshua D Stein, and David C Musch. Dynamic forecasting and control algorithms of glaucoma progression for clinician decision support. *Operations Research*, 63(5):979–999, 2015.

[95] Diana M Negoescu, Kostas Bimpikis, Margaret L Brandeau, and Dan A Iancu. Dynamic learning of patient response types: An application to treating chronic diseases. *Working Paper*, 2015.

[96] Turgay Ayer, Oguzhan Alagoz, and Natasha K Stout. OR Forum-A POMDP approach to personalize mammography screening decisions. *Operations Research*, 60(5):1019–1034, 2012.

[97] Martin L Puterman. *Markov Decision Processes: Discrete Stochastic Dynamic Programming*. John Wiley & Sons, 2014.

[98] M. Shaked and J. G. Shanthikumar. *Stochastic orders*. Springer Verlag, 2007.

[99] SeChan Oh. *Optimal Stopping Problems in Operations Management*. PhD thesis, Stanford University, 2010.

[100] A. Müller and D. Stoyan. *Comparison methods for stochastic models and risks*. Wiley, 2002.

[101] R. C. Gupta and D. M. Bradley. Representing the mean residual life in terms of the failure rate. *Mathematical and Computer Modelling*, 37(12-13):1271–1280, 2003.

[102] Felix Belzunce, Carolina Martinez Riquelme, and Julio Mulero. *An Introduction to Stochastic Orders*. Academic Press, 2015.

Appendix A

Chapter 2 Mathematical Proofs

Section A.1 provides some general results that are used in Section 2.4, which contains the proof of the analytical results of chapter 2.

A.1 General Results

Lemma A.1. Each of the following are equivalent to $X \leq_{hr} Y$:

1. $X_t \leq_{st} Y_t, \forall t$
2. $\dfrac{\overline{\mathbf{F}}_{\mathbf{X}}(t)}{\overline{\mathbf{F}}_{\mathbf{Y}}(t)}$ is decreasing in t.

Proof. For (1) see Equation 1.B.7 in [98]. For (2), see Theorem 1.3.3 in [100]. ■

Lemma A.2 (Closure of stochastic order under mixture)**.** Let X, Y be two random variables such that for all realizations of the random vector $\mathbf{Z}$, we have $[X|\mathbf{Z}=\mathbf{z}] \leq_{st} [Y|\mathbf{Z}=\mathbf{z}]$. Then, $X \leq_{st} Y$.

Proof. The proof directly follows Theorem 1.2.15 in [100]. ■

Lemma A.3. Assumption 2.4 is equivalent to having that $\dfrac{\overline{\mathbf{F}}_{\mathbf{C}}(t)}{\overline{\mathbf{F}}_{\mathbf{A}}(t)}$ is a log-convex function of t.

Proof. Note that $\frac{d}{dt}\ln \overline{\mathbf{F}}_{\mathbf{X}}(t) = -\mathbf{r}_{\mathbf{X}}(t)$. Since $\frac{d}{dt}\ln \dfrac{\overline{\mathbf{F}}_{\mathbf{C}}(t)}{\overline{\mathbf{F}}_{\mathbf{A}}(t)} = \frac{d}{dt}\ln \overline{\mathbf{F}}_{\mathbf{C}}(t) - \frac{d}{dt}\ln \overline{\mathbf{F}}_{\mathbf{C}}(t) = \mathbf{r}_{\mathbf{A}}(t) - \mathbf{r}_{\mathbf{C}}(t)$, the result follows from Assumption 2.4 and the fact that a differentiable function is convex if and only if its derivative is increasing. ■

Lemma A.4. Assume that g is a differentiable and log-convex function. Then, $\frac{g(x)}{g(x+a)}$ is decreasing in x for any $a \geq 0$.

Proof. It suffices to show that $\ln \frac{g(x)}{g(x+a)} = \ln g(x) - \ln g(x+a)$ is decreasing in x. Define $G := \ln g$, a convex function by assumption. Since $\frac{d}{dx}\ln \frac{g(x)}{g(x+a)} = \frac{d}{dx}G(x) - \frac{d}{dx}G(x+a) \leq 0$, based on the fact that the derivative of a convex function is increasing, we have that $\ln \frac{g(x)}{g(x+a)}$ is decreasing in x. ■

Lemma A.5. If the random variable X is IFR, then X_t is stochastically decreasing in t.

Proof. Choose $t \leq t'$ and $s \geq 0$, arbitrarily. We have $\mathbf{r}_{\mathbf{X_{t'}}}(s) = \mathbf{r}_{\mathbf{X}}(t'+s)$ and $\mathbf{r}_{\mathbf{X_t}}(s) = \mathbf{r}_{\mathbf{X}}(t+s)$. Since X has the IFR property, we have $\forall s, \mathbf{r}_{\mathbf{X_t}}(s) \leq \mathbf{r}_{\mathbf{X_{t'}}}(s)$. Thus, $X_{t'} \leq_{hr} X_t$ by definition which implies $X_{t'} \leq_{st} X_t$, because hazard rate order implies the stochastic order (see Lemma A.1). ■

Lemma A.6. If $\overline{\mathbf{F}}_{\mathbf{X}}(t)$ is differentiable, then the mean residual lifetime of a random variable X is differentiable. Moreover, we have: $\dfrac{d}{dt}\mathbb{E}X_t = \mathbf{r}_{\mathbf{X}}(t)\mathbb{E}X_t - 1$.

Proof. See [101]. ■

A.2 Analytical Results

We provide proofs in three sections. Proof of Theorem 2.1 is given in the first section. The second section includes proofs for Theorems 2.2-2.5, Corollaries 2.1-2.2, and Proposition 2.1. The final section provides proofs for Theorems 2.6 and 2.7.

A.2.1 Proof of Theorem 2.1:

We first prove a preliminary lemma that facilitates proving the main results.

Lemma A.7. Assumptions 2.3-2.5 apply to A_t and C_t as well. In other words, for all $s, t \geq 0$, we have $C_t \leq_{hr} A_t$, $\mathbf{r}_{\mathbf{C_t}}(s) - \mathbf{r}_{\mathbf{A_t}}(s)$ is decreasing in s, and $\mathbf{r}_{\mathbf{A_t}}(s)$, $\mathbf{r}_{\mathbf{C_t}}(s)$ are increasing in s.

Proof. The result follows by noting that $\mathbf{r}_{\mathbf{X_t}}(s) = \mathbf{r}_{\mathbf{X}}(t+s)$ for any random variable X, and $t, s \geq 0$. ■

In what follows, we let K_i denote the lifetime of the i^{th} AVF, i.e., $K_i = 0$, if the i^{th} AVF does not mature and $K_i = Z_i$, if otherwise.

Proof of Theorem 2.1. We prove Theorem 2.1 for all realization of M_i, and K_i for $i = 1, \ldots, N$, where N is the total number of AVF chances. Since AVF creation variables are not affected by the policy in use based on Assumption 2.6, the result generalizes using Lemma A.2 (closure of stochastic order under mixture).

Let $L(t, n)$ denote a patient's residual lifetime at t, given n remaining AVF chances, under the optimal policy (one that maximizes a patient's survival function probability for each time t). Suppose one could set the AVF use time (rather than setting the surgery time) at $t + u$. Let $L(u)$ be a patient's residual lifetime at time t when we plan to use current AVF at $t + u$ and follow the optimal policy for the subsequent $n-1$ AVF chances. We prove that $\overline{\mathbf{F}}_{\mathbf{L(u)}}(a)$ is decreasing in u (for any a). Since for y, the surgery time, we have $y = u - m_i$, this is equivalent to proving that the residual lifetime stochastically decreases in y.

→ **Base case: n=1:** Based on Assumption 2.2 on a patient's survival, we can calculate $\overline{\mathbf{F}}_{\mathbf{L(u)}}(a)$ for different values of u, a, k as follows (see Figure A.1).

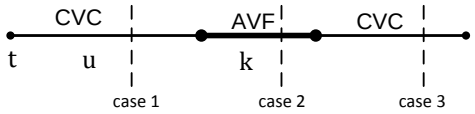

Figure A.1: Possible cases for $\overline{\mathbf{F}}_{\mathbf{L(u)}}(a)$.

- Case 1: $a \leq u$: We have $\overline{\mathbf{F}}_{\mathbf{L(u)}}(a) \overset{(*)}{=\!=} \mathbb{P}[C_t > a] = \overline{\mathbf{F}}_{\mathbf{C_t}}(a)$.
- Case 2: $[a-k]^+ \leq u \leq a$: We have

$$\begin{aligned}\overline{\mathbf{F}}_{\mathbf{L(u)}}(a) &= \mathbb{P}[C_t > u, A_{t+u} > a-u] = \mathbb{P}[C_t > u]\mathbb{P}[A_{t+u} > a-u \big| C_t > u] \\ &\overset{(*)}{=\!=} \mathbb{P}[C_t > a]\mathbb{P}[A_{t+u} > a-u] \overset{(*)}{=\!=} \mathbb{P}[C_t > u].\mathbb{P}[A_t > a | A_t > u] = \overline{\mathbf{F}}_{\mathbf{C_t}}(u)\frac{\overline{\mathbf{F}}_{\mathbf{A_t}}(a)}{\overline{\mathbf{F}}_{\mathbf{A_t}}(u)}\end{aligned}$$

- Case 3: $0 \leq u \leq [a-k]^+$: We have:

$$\begin{aligned}\overline{\mathbf{F}}_{\mathbf{L(u)}}(a) &= \mathbb{P}[C_t > u, A_{t+u} > a-u, C_{t+u+k} > a-(u+k)] \\ &= \mathbb{P}[C_t > u].\mathbb{P}[A_{u+t} > k \big| C_t > u].\mathbb{P}[C_{u+k} > a-(u+k) \big| A_{t+u} > k, C_t > u] \\ &\overset{(*)}{=\!=} \mathbb{P}[C_t > u].\mathbb{P}[A_t > k+u \big| A_t > u].\mathbb{P}[C_t > a \big| C_t > u+k] \\ &\overset{(*)}{=\!=} \overline{\mathbf{F}}_{\mathbf{C_t}}(u).\frac{\overline{\mathbf{F}}_{\mathbf{A_t}}(k+u)}{\overline{\mathbf{F}}_{\mathbf{A_t}}(u)}\frac{\overline{\mathbf{F}}_{\mathbf{C_t}}(a)}{\overline{\mathbf{F}}_{\mathbf{C_t}}(u+k)} = \overline{\mathbf{F}}_{\mathbf{C_t}}(a).\frac{\overline{\mathbf{F}}_{\mathbf{C_t}}(u)}{\overline{\mathbf{F}}_{\mathbf{A_t}}(u)} \Big/ \frac{\overline{\mathbf{F}}_{\mathbf{C_t}}(u+k)}{\overline{\mathbf{F}}_{\mathbf{A_t}}(u+k)}\end{aligned}$$

in which $(*)$ represents implication by Assumption 2.2. Note that $\overline{\mathbf{F}}_{\mathbf{L(u)}}(a)$ is continuous within each range, and its value on the boundary points coincides. Therefore, it suffices to prove that in each range, $\overline{\mathbf{F}}_{\mathbf{L(u)}}(a)$ is decreasing. In Case 1, the function is constant and thus the result holds trivially. In Case 2, since $C_t \leq_{hr} A_t$ according to Lemma A.7 (which requires Assumptions 2.3-2.5), the function is decreasing using Lemma A.1. In Case 3, Lemma A.7 and Lemma A.3 imply that $\frac{\overline{\mathbf{F}}_{\mathbf{C_t}}(u)}{\overline{\mathbf{F}}_{\mathbf{A_t}}(u)}$ is log-convex in u. Using Lemma A.4, we have that $\overline{\mathbf{F}}_{\mathbf{L(u)}}(a)$ is decreasing in u.

Let $L(t,n,u)$ be the patient's residual lifetime at t when we use the current AVF chance at $t+u$ and follow the optimal policy for the subsequent AVF chances. We now present the induction step:

$\rightarrow$ **Induction step:** Assume $L(t,n-1,u_2) \leq_{st} L(t,n-1,u_1)$, for all $u_1 \leq u_2$. We prove that if $u_1 \leq u_2$, then $L(t,n,u_2) \leq_{st} L(t,n,u_1)$.

To calculate the lifetime of the patient for the case of multiple AVF chances, we assume that AVFs are created sequentially and never in parallel (supported by Assumption 2.1). Since stochastic order is a partial order, using the transitivity property we can instead prove that $L(u_2) \leq_{st} L'$ and $L' \leq_{st} L(u_1)$, in which L' is the lifetime under a hypothetical situation similar

to $L(u_1)$ with the difference that the decision to use the subsequent AVF is delayed until u_2+k (see Figure A.2).

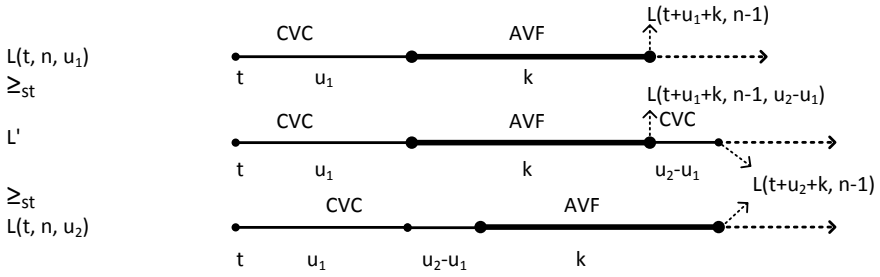

Figure A.2: Induction step and the hypothetical random variable L'.

- $L(u_2) \leq_{st} L'$: For $x \leq u_2 + k$, we have that $\overline{\mathbf{F}}_{\mathbf{L(u_2)}}(x) = \overline{\mathbf{F}}_{\mathbf{L(t,1,u_2)}}(x)$ and $\overline{\mathbf{F}}_{\mathbf{L'}}(x) = \overline{\mathbf{F}}_{\mathbf{L(t,1,u_1)}}(x)$. Thus the result follows from induction base. Otherwise, we have

$$\overline{\mathbf{F}}_{\mathbf{L(u_2)}}(x) = \overline{\mathbf{F}}_{\mathbf{L(u_2)}}(u_2+k).\overline{\mathbf{F}}_{\mathbf{L(u_2+k,n-1)}}(x-[u_2+k]),$$
$$\overline{\mathbf{F}}_{\mathbf{L'}}(x) = \overline{\mathbf{F}}_{\mathbf{L'}}(u_2+k).\overline{\mathbf{F}}_{\mathbf{L(u_2+k,n-1)}}(x-[u_2+k]).$$

  Based on the previous result, we have $\overline{\mathbf{F}}_{\mathbf{L(u_2)}}(u_2+k) \leq \overline{\mathbf{F}}_{\mathbf{L'}}(u_2+k)$, and thus we get the result.

- $L' \leq_{st} L(t,n,u_1)$. For $x \leq u_1 + k$, we have that $\overline{\mathbf{F}}_{\mathbf{L(u_1)}}(x) = \overline{\mathbf{F}}_{\mathbf{L'}}(x) = \overline{\mathbf{F}}_{\mathbf{L(t,1,u_1)}}(x)$. For $x \geq u_1 + k$,

$$\overline{\mathbf{F}}_{\mathbf{L(u_1)}}(x) = \overline{\mathbf{F}}_{\mathbf{L'}}(u_1+k).\overline{\mathbf{F}}_{\mathbf{L(u_1+k,n-1,0)}}(x-[u_1+k]),$$
$$\overline{\mathbf{F}}_{\mathbf{L'}}(x) = \overline{\mathbf{F}}_{\mathbf{L'}}(u_1+k).\overline{\mathbf{F}}_{\mathbf{L(u_1+k,n-1,u_2-u_1)}}(x-[u_1+k]).$$

  Using the induction hypothesis, we have $L(u_1+k, n-1, u_2-u_1) \leq_{st} L(u_1+k, n-1, 0)$, and thus we have the desired result.

■

A.2.2 Proofs of Theorems 2.2, 2.3-2.5, Corollaries 2.1-2.2, and Proposition 2.1:

We prove the optimality of threshold policies (Theorem 2.3) in three steps. First in Proposition A.1, we prove the existence of an optimal HD-duration threshold policy for the case $n = 1$. Next, we prove Theorems 2.4-2.5 and Corollary 2.1 for the special case $n = 1$. Finally, using these results, we prove that the same threshold policy formed in Proposition A.1 is optimal for the case $n > 1$, as well.

We use the following notations in what follows.

- $v^{\pi}(NF, n, t)$: the value function (the remaining QALE of a patient) at state (NF, n, t) under an arbitrary policy π
- $v(NF, n, t, y)$: the value function of the policy consisting of surgery planned at $t + y$ for the current AVF chance and then the optimal policy for the subsequent decisions.
- $v(NF, n, t)$: the optimal value function at state (NF, n, t).

Note that we supposed Assumptions 2.1-2.2 and 2.6 in defining the dynamic programming model (see Section 2.3.4). Let π_0 denote the policy of using CVC for the rest of the patient's life (hereafter referred to as the "no-AVF" policy). Under this policy, the patient remains on a CVC until she dies, and since her residual lifetime under this policy is C_t, her QALE is $q_c\mathbb{E}[C_t]$, i.e., we have $\forall NF, n : v^{\pi_0}(NF, n, t) = q_c\mathbb{E}C_t$. Since $v^{\pi_0}(NF, n, t) = q_c\mathbb{E}C_t$ for any NF and n, we use $v^{\pi_0}(.,.,t)$ to denote this independence.

Let s denote a general patient state. Note that the value function of an arbitrary policy π, i.e., $v^{\pi}(s)$, is the expected quality adjusted lifetime of a patient under that policy. In what follows, we let $v^{\pi}(s|\mathcal{E})$ represent the value function of the policy π conditional on an event $\mathcal{E}$. For instance, $\big(v^{\pi_1}(s) - v^{\pi_2}(s)\big|C_t \leq y\big)$ denotes the QALE difference between two arbitrary policies π_1 and π_2 conditional on the event $C_t \leq y$. We use Lemmas A.8-A.10 to prove Proposition A.1.

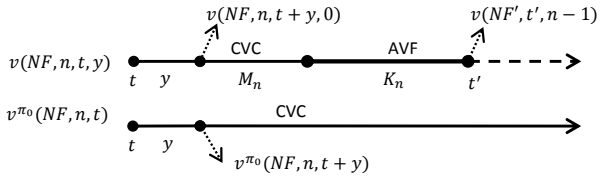

Figure A.3: Linking $v(NF, n, t, y)$, $v(NF, n, t + y, 0)$, and $v^{\pi_0}(NF, n, t + y)$.

Lemma A.8. The following equality holds for $v(NF, n, t, y)$.

$$v(NF, n, t, y) = \overline{\mathbf{F}}_{\mathbf{C_t}}(y)\Big[v(NF, n, t + y, 0) - v^{\pi_0}(.,.,t + y)\Big] + v^{\pi_0}(.,.,t)$$

Proof. Consider Figure A.3. We want to prove that the difference between the value functions of the policy consisting of surgery planned at $t + y$ for the current AVF chance and then the optimal policy for the subsequent decisions and the no-AVF policy, i.e., $v(NF, n, t, y) - v^{\pi_0}(.,.,t)$, equals $\overline{\mathbf{F}}_{\mathbf{C_t}}(y)\big[v(NF, n, t + y, 0) - v^{\pi_0}(.,.,t + y)\big]$.

If $C_t \leq y$, then the patient dies before the AVF surgery, in which case there is no difference between the two policies. If $C_t > y$, which happens with probability $\overline{\mathbf{F}}_{\mathbf{C_t}}(y)$, then the difference between the two policies equals the difference between the value function at the state $(NF, n, t+$

y) when we follow the policy consisting of immediate surgery for the current AVF chance and then the optimal policy for the subsequent decisions and that of the same state but following the no-AVF policy, i.e., $v(NF, n, t+y, 0) - v^{\pi_0}(.,.,t+y)$. Therefore, we have $v(NF, n, t, y) - v^{\pi_0}(.,.,t) = \overline{\mathbf{F}}_{\mathbf{C_t}}(y)\big[v(NF, n, t+y, 0) - v^{\pi_0}(.,.,t+y)\big]$ and thus the result. ■

For Lemma A.9, let $w(t, m, k)$ denote the residual HD utility adjusted lifetime expectancy of a patient at time t (which is the patient's QALE without subtracting the AVF creation disutility) under a scenario in which the patient undergoes the surgery at t for her only AVF chance and the AVF maturation time and AVF lifetime are deterministically set at m and k, respectively.

Based on Assumption 2.2 on a patient's survival, we can calculate $w(t, m, k)$ as follows:

$$w(t,m,k) = q_c \int_0^m x\mathbf{f}_{\mathbf{C_t}}(x)dx + \overline{\mathbf{F}}_{\mathbf{C_t}}(m)\Big[q_c m + q_a \int_0^k x\mathbf{f}_{\mathbf{A_{t+m}}}(x)dx + \overline{\mathbf{F}}_{\mathbf{A_{t+m}}}(k)\big[q_a k + q_c \mathbb{E}C_{t+m+k}\big]\Big]. \quad (A.1)$$

We can express $v(NF, 1, t, 0)$ and $v^{\pi_0}(.,.,t)$ using $w(t, m, k)$ as follows:

$$v(NF,1,t,0) = -d + \mathbb{E}_{M,K|NF}[w(t,m,k)], \quad (A.2)$$

$$v^{\pi_0}(.,.,t) = w(t,m,0) : \forall m. \quad (A.3)$$

We will use these equalities in later proofs.

Lemma A.9. Suppose Assumptions 2.2-2.5 and 2.8. We have $\frac{\partial}{\partial k} w(t, m, k)$ is non-negative and decreasing in t and m.

Proof. To have differentiability of w in k, it suffices to assume that $\overline{\mathbf{F}}_{\mathbf{A}}(x)$ and $\overline{\mathbf{F}}_{\mathbf{C}}(x)$ are differentiable at all values of x because they in turn imply that $\overline{\mathbf{F}}_{\mathbf{A_t}}(x)$ and $\overline{\mathbf{F}}_{\mathbf{C_t}}(x)$ (as a direct result) and $\mathbb{E}C_x$ (using Lemma A.6) are differentiable functions in x.

We have:

$$\frac{\partial}{\partial k} w(t,m,k) = \overline{\mathbf{F}}_{\mathbf{C_t}}(m)\Big[\frac{d}{dk} q_a \int_0^k x\mathbf{f}_{\mathbf{A_{t+m}}}(x)dx + \overline{\mathbf{F}}_{\mathbf{A_{t+m}}}(k)\frac{d}{dk}\big[q_a k + q_c \mathbb{E}C_{t+m+k}\big] + \big[\frac{d}{dk}\overline{\mathbf{F}}_{\mathbf{A_{t+m}}}(k)\big]\big[q_a k + q_c \mathbb{E}C_{t+m+k}\big]\Big] \quad (A.4)$$

$$= \overline{\mathbf{F}}_{\mathbf{C_t}}(m)\Big[q_a k \mathbf{f}_{\mathbf{A_{t+m}}}(k) + \overline{\mathbf{F}}_{\mathbf{A_{t+m}}}(k)\big\{q_a + q_c\big[\mathbf{r}_{\mathbf{C_{t+m}}}(k)\mathbb{E}C_{t+m+k} - 1\big]\big\} - \mathbf{f}_{\mathbf{A_{t+m}}}(k)[q_a k + q_c \mathbb{E}C_{t+m+k}]\Big] \quad (A.5)$$

$$= \overline{\mathbf{F}}_{\mathbf{C_t}}(m)\overline{\mathbf{F}}_{\mathbf{A_{t+m}}}(k)\Big[q_a - q_c + q_c \mathbb{E}C_{t+m+k}\big[\mathbf{r}_{\mathbf{C_t}}(m+k) - \mathbf{r}_{\mathbf{A_t}}(m+k)\big]\Big] \quad (A.6)$$

where Equation A.4 follows from Equation A.1 using the product rule in calculating the derivatives of products of two functions, Equation A.5 follows from Equation A.4 by using Lemma A.6, and finally Equation A.6 follows from Equation A.5 by rearranging terms.

We can prove that $\frac{\partial}{\partial k} w(t, m, k)$ is decreasing in t and non-negative by showing that it is a product of the following three non-negative decreasing functions:

1. $\overline{\mathbf{F}}_{\mathbf{C_t}}(m)$: This is decreasing in t, since C_t is stochastically decreasing in t based on Lemma A.5 and that C is IFR by Assumption 2.5.

2. $\overline{\mathbf{F}}_{\mathbf{A_{t+m}}}(k)$: This is decreasing in t, since A_{t+m} is stochastically decreasing in t based on Lemma A.5 and that A is IFR by Assumption 2.5.

3. $q_a - q_c + q_c \mathbb{E} C_{t+m+k} \big[\mathbf{r}_{\mathbf{C_t}}(m+k) - \mathbf{r}_{\mathbf{A_t}}(m+k)\big]$:

   - non-negative: We have that $q_a \geq q_c$ by Assumption 2.8. Also, $\mathbf{r}_{\mathbf{C_t}}(m+k) \geq \mathbf{r}_{\mathbf{A_t}}(m+k)$ based on Lemma A.7 (which requires Assumptions 2.3-2.5).
   - decreasing: $\mathbb{E} C_{t+m+k}$ is decreasing in t, because C_{t+m+k} is stochastically decreasing in t by Lemma A.5 and the fact that C is IFR by Assumption 2.5. Also, $\mathbf{r}_{\mathbf{C_t}}(m+k) - \mathbf{r}_{\mathbf{A_t}}(m+k)$ is decreasing in t based on Lemma A.7.

   Using the same logic, we can show that $\frac{\partial}{\partial k} w(t, m, k)$ is decreasing in m.

■

Lemma A.10. Suppose Assumptions 2.2-2.6 and 2.8. For any NF, we have $v(NF, 1, t, 0) - v^{\pi_0}(., ., t)$ is decreasing in t.

Proof. Choose $t_1 \leq t_2$, arbitrarily. We have that $\forall m : \frac{\partial}{\partial k}[w(t_2, m, k) - w(t_1, m, k)] \leq 0$ by the linearity of the differential operator and Lemma A.9 (which requires Assumptions 2.2-2.5 and 2.8). This implies that

$$\forall k, m : w(t_2, m, k) - w(t_1, m, k) \leq w(t_2, m, 0) - w(t_1, m, 0).$$

But by Equation A.3 we have: $\forall m, t : w(t, m, 0) = v^{\pi_0}(., ., t)$. Thus,

$$\forall k, m : w(t_2, m, k) - w(t_1, m, k) \leq v^{\pi_0}(., ., t_2) - v^{\pi_0}(., ., t_1).$$

Taking expectation from both sides with respect to $M, K | NF$ and Equation A.2 gives us:

$$v(NF, 1, t_2, 0) - v(NF, 1, t_1, 0) \leq v^{\pi_0}(., ., t_2) - v^{\pi_0}(., ., t_1).$$

Note that taking expectation is justified based on Assumption 2.6. By rearranging the terms in the above inequality, we obtain the desired result. ■

Proof of Theorem 2.2. This result is in fact a corollary to Lemma A.10. By assuming $d = 0$, $M = 0$, and $K = \infty$ with probability 1, we obtain $v(NF, 1, t, 0) = q_A \mathbb{E} A_t$. Since $v^{\pi_0}(.,.,t) = q_C \mathbb{E} C_t$ by definition, we have that $q_A \mathbb{E}[A_t] - q_C \mathbb{E}[C_t]$ is decreasing in t. The result then follows by assuming $q_A = q_C = 1$. ■

Proposition A.1 (Existence of Threshold Policies for $n = 1$)**.** Assume $n = 1$ and fix NF, arbitrarily. Under Assumptions 2.2-2.6 and 2.8, there exists a threshold policy $\tau^*(NF)$ that maximizes the QALE of the patient.

Proof. Fix t, and NF, arbitrarily. Assume that we plan the surgery at $t + y$. By Lemma A.8, we have:

$$v(NF, 1, t, y) = \overline{\mathbf{F}}_{\mathbf{C_t}}(y) \Big[v(NF, 1, t + y, 0) - v^{\pi_0}(.,.,t + y) \Big] + v^{\pi_0}(.,.,t)$$

For this decision to be an optimal action, it is necessary that surgery at $t + y$ is no worse than the no-AVF policy, i.e., $v(NF, 1, t + y, 0) \geq v^{\pi_0}(.,.,t + y)$.
Since $v(NF, 1, t + y, 0) - v^{\pi_0}(.,.,t + y)$ is decreasing in y by Lemma A.10 (which requires Assumptions 2.2-2.6 and 2.8), and $\overline{\mathbf{F}}_{\mathbf{C_t}}(y)$ is decreasing in y, then $v(NF, 1, t, y)$ is decreasing in y for all y that satisfy the necessary condition. Thus, the optimal action is to perform surgery at t if $v(NF, 1, t, 0) \geq v^{\pi_0}(.,.,t)$, and no surgeries, if otherwise.

Now, we form the policy τ^* as follows based on whether $v(NF, 1, 0, 0) \leq v^{\pi_0}(.,.,0)$ or not.

- $v(NF, 1, 0, 0) \leq v^{\pi_0}(.,.,0)$: we have that for $\forall t : v(NF, 1, 0, 0) \leq v^{\pi_0}(.,.,0)$, since $v(NF, 1, t, 0) - v^{\pi_0}(.,.,t)$ is decreasing in t by Lemma A.10. As a result, the no AVF surgery (i.e., "CVC forever") is optimal for all t. Choose $\tau^*(NF) = 0$ in this case.

- $v(NF, 1, 0, 0) > v^{\pi_0}(.,.,0)$: we have that $\exists t' \leq \infty$ such that for $t < t'$, we have $v(NF, 1, 0, 0) > v^{\pi_0}(.,.,0)$, and $v(NF, 1, 0, 0) \leq v^{\pi_0}(.,.,0)$ for $t \geq t'$ because $v(NF, 1, t, 0) - v^{\pi_0}(.,.,t)$ is decreasing in t. For $t < t'$, surgery at t is optimal, and for $t \geq t'$, the patient should remain on a CVC, i.e., the no surgery policy is optimal. Choose $\tau^*(NF) = t'$ in this case.

The policy $\tau^*(NF)$ is optimal for $n = 1$ by construction. ■

Now that we have achieved the first step in proving the optimality of threshold policies, we prove Theorems 2.4-2.5 and Corollary 2.1 for the special case $n = 1$. Once we prove the optimality of $\tau^*(NF)$ for all n in Theorem 2.3, which requires Assumptions 2.1-2.8, these results also generalize.

Proof of Theorem 2.4 for $n = 1$. Based on the way we constructed $\tau^*(NF; d)$ in Proposition A.1, we have:

$$t \geq \tau^*(NF; d) \iff v(NF, 1, t, 0; d) \leq v^{\pi_0}(.,.,t). \tag{A.7}$$

Define $d^{\text{cr}}(NT, t)$ as follows:

$$d^{\text{cr}}(NF, t) := \mathbb{E}_{M,K|NF}[w(t, m, k)] - v^{\pi_0}(., ., t). \tag{A.8}$$

Note that by Equation A.2, we have:

$$d^{\text{cr}}(NF, t) = d + v(NF, 1, t, 0) - v^{\pi_0}(., ., t). \tag{A.9}$$

By Equation A.7 and the above equality, we have:

$$t \geq \tau^*(NF) \iff d^{\text{cr}}(NF, t) \leq d \tag{A.10}$$

Thus, $d^{\text{cr}}(NF, t)$ is indeed a critical value for AVF creation disutility in determining the optimal decision. ■

Proof of Theorem 2.5 for $n = 1$. We have:

$$\begin{aligned} d^{\text{cr}}(NF, t) &= \mathbb{P}[K = 0|NF]\mathbb{E}_M[w(t, m, 0)] + \mathbb{P}[K > 0|NF]\mathbb{E}_{M,Z}[w(t, m, z)] - v^{\pi_0}(., ., t) && \text{(A.11)} \\ &= \mathbb{P}[K = 0|NF]v^{\pi_0}(., ., t) + \mathbb{P}[K > 0|NF]\mathbb{E}_{M,Z}[w(t, m, z)] - v^{\pi_0}(., ., t) && \text{(A.12)} \\ &= \mathbb{P}[B = 1|NF]\big(\mathbb{E}_{M,Z}[w(t, m, z)] - v^{\pi_0}(., ., t)\big), && \text{(A.13)} \end{aligned}$$

where Equation A.11 follows from the definition of $d^{\text{cr}}(NF, t)$ in Equation A.8, the law of total probability and definitions of K and Z, Equation A.12 follows from Equation A.11 by using the fact $v^{\pi_0}(., ., t) = w(t, m, 0)$ (see Equation A.3), and Equation A.13 follows from Equation A.12 by rearranging terms. ■

Note that we can use Equation A.13 to numerically calculate the critical disutility by calculating $\mathbb{E}_{M,Z}[w(t, m, z)]$, either by Monte-Carlo simulation or analytically, and $v^{\pi_0}(., ., t)$ using the equality $v^{\pi_0}(., ., t) = q_c\mathbb{E}C_t$.

Proof of Corollary 2.1 for $n = 1$.
By Equation A.13, we have $d^{\text{cr}}(NF, t) = \mathbb{P}[B = 1|NF]\big(\mathbb{E}_{M,Z}[w(t, m, z)] - v^{\pi_0}(., ., t)\big)$. By Assumption 2.7, the AVF surgery success probability is decreasing in NF. Therefore, we have that the critical disutility is decreasing in NF for any t.

Choose $NF_1 \leq NF_2$, arbitrarily. Let $t_i = \tau^*(NF_i)$ for $i = 1, 2$. By Equation A.10, we have $d^{\text{cr}}(NF_1, t_1) \geq d$ (substitute t_1 for t and NF_1 for NF). Since the critical disutility is decreasing in NF for any t, we have $d^{\text{cr}}(NF_2, t_1) \leq d$, as well. By Equation A.10, we have $t_2 \leq t_1$ (substitute t_2 for t and NF_2 for NF). ■

Before proving Theorem 2.3, we show the following property for τ^*.

Proposition A.2. For τ^*, we have:

1. $\forall n, NF, t : v^{\tau*}(NF, n, t) \geq v^{\pi_0}(., ., t)$,

2. $\forall n, NF : v^{\tau*}(NF, n, t) - v^{\pi_0}(., ., t)$ is decreasing in t.

Proof. Fix NF, arbitrarily. We prove the result by induction on n as follows:

- $n = 1$: We have:

$$v^{\tau*}(NF, 1, t) - v^{\pi_0}(., ., t) = \begin{cases} v(NF, 1, t, 0) - v^{\pi_0}(., ., t) & : t < \tau(NF) \\ 0 & : o.w. \end{cases}$$

  The function is decreasing for $t < \tau(NF)$ by Lemma A.10, and for $t \geq \tau(NF)$ trivially. It suffices to have that $v^{\tau*}(NF, 1, t) \geq v^{\pi_0}(., ., t)$, which follows from the fact that τ^* is optimal for $n = 1$.

- Assume the result holds for $n = 1, \ldots, l$. We prove that it holds for $n = l + 1$.

  For $t \geq \tau^*(NF)$, we have $v^{\tau*}(NF, l + 1, t) = v^{\pi_0}(., ., t)$, since the two policies coincide. For $t < \tau^*(NF)$, fix $M = m$, and $K = k$ for the current AVF chance, arbitrarily. The result generalizes by taking expectation. Let $t' = t + m + k$ and $NF' = NF + 1$, if $k = 0$, and $NF' = NF$, otherwise. We have:

$$v^{\tau*}(NF, l + 1, t) - v^{\tau*}(NF, 1, t) = S(t, t')\big[v^{\tau*}(NF', l, t') - v^{\pi_0}(., ., t')\big]. \tag{A.14}$$

  where $S(t, t')$ represent the probability of survival of the patient until time t'. We can explain Equation A.14 as follows. The difference, in terms of QALE, between the states $(NF, l + 1, t)$ and $(NF, 1, t)$ under the policy τ^* does not start until t', which is realized only if the patient survives until t' with probability $S(t, t')$. At t', the patient receives $v^{\tau*}(NF', l, t')$ for the case we start by $l + 1$ AVF chances, whereas for the case we start by one AVF chance, the patient switches to a CVC forever at t' and receives $v^{\pi_0}(., ., t')$. Therefore, we have

$$v^{\tau*}(NF, l + 1, t) \geq v^{\tau*}(NF, 1, t) \geq v^{\pi_0}(., ., t),$$

  where the first inequality results from Equation A.14 and that $v^{\tau*}(NF', l, t') \geq v^{\pi_0}(., ., t')$ by induction assumption, and the second inequality results from induction basis. This proves the first property.

  Since $v^{\tau*}(NF, 1, t) - v^{\pi_0}(., ., t)$ is decreasing in t, in order to prove the second property, it suffices to prove that the right-hand side of Equation A.14 is decreasing in t. We prove it by showing that it is the product of the following two non-negative and decreasing functions:

  1. $S(t', t)$: The probability is non-negative by definition. First we compute $S(t', t)$ as

follows:

$$\begin{aligned} S(t,t') =& \mathbb{P}[C_t > m, A_{t+m} > k] = \mathbb{P}[C_t > m]\mathbb{P}[A_{t+m} > k | C_t > m] \\ &= \overline{\mathbf{F}}_{\mathbf{C_t}}(m)\overline{\mathbf{F}}_{\mathbf{A_{t+m}}}(k), \end{aligned}$$

where the last equality follows from Assumption 2.2. Both $\overline{\mathbf{F}}_{\mathbf{C_t}}(m)$ and $\overline{\mathbf{F}}_{\mathbf{A_{t+m}}}(k)$ are decreasing in t because A_{t+x} and C_{t+x} are stochastically decreasing in t, for any $x \geq 0$ by Lemmas A.5 and A.7.

2. $v^{\tau^*}(NF', l, t') - v^{\pi_0}(.,.,t')$: This term is non-negative and decreasing in t using the induction assumption.

■

Proof of Theorem 2.3. We prove the optimality of $\tau^*(NF)$ formed in Proposition A.1 by induction on n. Note that Proposition A.1 required Assumptions 2.2-2.6 and 2.8. The proof additionally requires Assumption 2.7 to use Corollary 2.1 and Assumption 2.1 regarding decision points in the model.

- $n = 1$: The policy is optimal for $n = 1$ by construction.
- Assume the optimality of $\tau^*(NF)$ for $n = 1, \ldots, l$. We prove it for $n = l + 1$.
  Fix NF, arbitrarily. We prove the optimality of τ^* based on whether $t \geq \tau^*(NF)$ or not as follows.

  $\rightarrow t \geq \tau^*(NF)$: The policy suggests no more surgeries. We argue its optimality as follows.
  We argue that the last l AVF chances will not be used. Note that these AVFs' possible use time will be at some $t' \geq t$ and for some $NF' \geq NF$. Since τ^* is optimal for $n \leq l$, $\tau^*(NF') \geq \tau^*(NF)$ (by Corollary 2.1), and that $t' \geq t \geq \tau^*(NF) \geq \tau^*(NF')$, these AVF chances will not be used . Thus, we are left with one AVF chance. Similarly, we should not use that chance, either. Thus, the no surgery decision is optimal in this case.

  $\rightarrow t < \tau^*(NF)$: The policy suggests surgery at t. We argue that it is optimal as follows.
  Assume the surgery is planned at $t' := t + y$. Note that no surgeries should be performed later than $\tau^*(NF)$ (using the logic explained in the first case). Thus, we restrict our attention to $t' < \tau^*(NF)$. For all such t', we have that $v(NF, n, t', 0) = v^{\tau^*}(NF, n, t')$, based on the induction assumption. By this equality and Lemma A.8, we have

$$v(NF, n, t, y) = \overline{\mathbf{F}}_{\mathbf{C_t}}(y)\Big[v^{\tau^*}(NF, n, t+y) - v^{\pi_0}(.,.,t+y)\Big] + v^{\pi_0}(.,.,t)$$

We conclude the proof by showing $v(NF, n, t, y)$ is decreasing in y. Since $\overline{\mathbf{F}}_{\mathbf{C_t}}(y)$ is decreasing in y and non-negative, it suffices to have that $v^{\tau*}(NF, n, t+y) - v^{\pi_0}(.,.,t+y)$ is non-negative and decreasing in y which holds by Proposition A.2, respectively. ■

Proof of Proposition 2.1. Fix NF, arbitrarily. Based on the way the optimal policy is formed in Proposition A.1, we have that for all $t \in (0, \tau^*(NF))$, $v(NF, 1, t, 0) > v^{\pi_0}(.,.,t)$ and for all $t \in [\tau^*(NF), t_{\max}]$, we have $v(NF, 1, t, 0) \leq v^{\pi_0}(.,.,t)$. Since $v(NF, 1, t, 0) - v^{\pi_0}(.,.,t)$ is a decreasing continuous function, we can find $\tau^*(NF)$ using a binary search over $[0, t_{\max}]$. ■

Proof of Corollary 2.2. By Equation A.9 and Lemma A.10, we have that $d^{cr}(NF, t)$ is decreasing in t. The result then directly follows Equation A.10. ■

A.2.3 Proofs of Theorems 2.6, 2.7:

Proof of Theorem 2.6. Fix $\Psi = \psi$ arbitrarily. The result generalizes using Lemma A.2. Let $LT(y)$ and $L(y)$ be a patient's residual lifetime at t when the AVF surgery is planned at y with and without a potential transplant at $t = \psi$, respectively. We prove that $\overline{\mathbf{F}}_{\mathbf{LT(y)}}(a)$ is decreasing in y for any a. Let $Tr(\psi)$ be the patient's residual lifetime on transplant at ψ. We have:

$$\overline{\mathbf{F}}_{\mathbf{LT(y)}}(a) = \begin{cases} \overline{\mathbf{F}}_{\mathbf{L(y)}}(a) & : a \leq \psi \quad \text{(A.15a)} \\ \overline{\mathbf{F}}_{\mathbf{L(y)}}(\psi)\overline{\mathbf{F}}_{\mathbf{Tr}(\psi)}(a-\psi) & : \text{o.w.} \quad \text{(A.15b)} \end{cases}$$

Equation A.15a follows from the fact that transplant benefits a patient's survival after the transplant, and Equation A.15b follows our assumption that the lifetime of a patient on transplant does not depend on HD history. The result then follows by Theorem 2.1, which indicates that $\overline{\mathbf{F}}_{\mathbf{L(y)}}(x)$ is decreasing in y. ■

We use Lemma A.11 to prove Theorem 2.7.

Lemma A.11. Consider the random variable Y, a function of the continuous random variable X, defined for $X = x$ as follows:

$$Y(x) = \begin{cases} g(x) & : x \leq \theta; \\ g(\theta) + U & : x > \theta. \end{cases}$$

where g is a linear function. Then, we have $\mathbb{E}Y(X) = \mathbb{E}g(X) + \overline{\mathbf{F}}_{\mathbf{X}}(\theta)[U - \mathbb{E}g(X_\theta)]$

Proof. We have

$$\mathbb{E}[Y(X) - g(X)] = \overline{\mathbf{F}}_{\mathbf{X}}(\theta)\mathbb{E}[Y(X) - g(X)\big|X > \theta] = \overline{\mathbf{F}}_{\mathbf{X}}(\theta)\mathbb{E}[U + g(\theta) - g(\theta + X_\theta)], \quad \text{(A.16)}$$

$$= \overline{\mathbf{F}}_{\mathbf{X}}(\theta)\mathbb{E}[U + g(\theta) - g(\theta) - g(X_\theta)] = \overline{\mathbf{F}}_{\mathbf{X}}(\theta)\mathbb{E}[U - g(X_\theta)], \quad \text{(A.17)}$$

where the first equality in Equation A.16 follows the total law of probability and the fact that $Y = g$ for $X \leq \theta$, the second equality follows using the definition of Y and the identity $X|X > \theta = X_\theta + \theta$, and finally the first equality in Equation A.17 follows by the linearity of g. ■

Proof of Theorem 2.7. In order to prove the theorem, we only show that Lemma A.10 holds under the extended model as well. The rest of the proof follows similar steps taken for Proposition A.1 and Theorem 2.3, which require Assumptions 2.1-2.8.

Let $\nu(NF, 1, t, 0)$ and $\nu^{\pi_0}(., ., t)$ be the equivalents of $v(NF, 1, t, 0)$ and $v^{\pi_0}(., ., t)$, respectively, under the model with the transplant option. Since monotonicity preserves under expectation, it suffices to prove the result under all possible scenarios (i.e., we use a sample path argument). Under the scenario where the transplant is canceled, we have $v(.) = \nu(.)$ and thus the result follows using Lemma A.10. Now we consider the case of no cancellation. If the AVF does not mature, we have $\nu(NF, 1, t, 0) - \nu^{\pi_0}(., ., t) = -d$, as the only difference in QALE is the AVF creation disutility. It remains to prove the result for the case of a successful AVF creation.

Fix $M = m$ arbitrarily. Let $t' := t + m$ be the time of switching to the matured AVF, and U be the lump-sum QALE the patient receives from transplant. Using Lemma A.11 and by considering $g(x) = q_A x$, $X = A_{t'}$, and $\theta = \psi - t'$, we can show that the QALE residual at t' for a patient who is on an AVF from t' until transplant equals $q_A\mathbb{E}A_{t'} + \overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t')(U - q_A\mathbb{E}A_\psi)$. Similarly, we can show that the QALE residual at t' for a patient on the CVC equals $q_C\mathbb{E}C_{t'} + \overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')(U - q_C\mathbb{E}C_\psi)$.

We can calculate $\nu(NF, 1, t, 0) - \nu^{\pi_0}(., ., t)$ as follows:

$$\begin{aligned}\nu(NF, 1, t, 0) - \nu^{\pi_0}(., ., t) =& \overline{\mathbf{F}}_{\mathbf{C_t}}(m)\Big[\Big\{q_A\mathbb{E}A_{t'} + \overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t')(U - q_A\mathbb{E}A_\psi)\Big\} - \\ & \Big\{q_C\mathbb{E}C_{t'} + \overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')(U - q_C\mathbb{E}C_\psi)\Big\}\Big] - d \qquad \text{(A.18)}\end{aligned}$$

Equation A.18 can be explained as follows. The patient experiences a QALE difference starting from t' (AVF maturation time), but only if she survives until then. Therefore the QALE difference after t' is discounted by $\overline{\mathbf{F}}_{\mathbf{C_t}}(m)$. Since $\overline{\mathbf{F}}_{\mathbf{C_t}}(m)$ is decreasing in t (see the proof of Lemma A.9), it suffices to prove that the term in the brackets, henceforth denoted by Δ, is non-negative and decreasing in t (or equivalently t'). By rearranging terms, we obtain :

$$\Delta = \Big[q_A\mathbb{E}A_{t'} - q_C\mathbb{E}C_{t'}\Big] + \Big[\overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')q_C\mathbb{E}C_\psi - \overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t')q_A\mathbb{E}A_\psi\Big] + U\Big[\overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t') - \overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')\Big].$$

We have:

$$\begin{aligned}\Delta &\geq \Big[q_A\mathbb{E}A_{t'} - q_C\mathbb{E}C_{t'}\Big] + \Big[\overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')q_C\mathbb{E}C_\psi - \overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t')q_A\mathbb{E}A_\psi\Big] \\ &\geq \Big[q_A\mathbb{E}A_{t'} - q_C\mathbb{E}C_{t'}\Big] + \overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t')\Big[q_C\mathbb{E}C_\psi - q_A\mathbb{E}A_\psi\Big] \geq 0.\end{aligned}$$

where the first inequality follows since $U \geq 0$ and $\overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t') \geq \overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')$ as a consequence of Lemma A.7, and the second inequality follows because again $\overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t') \geq \overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')$. We have $q_A\mathbb{E}A_{t'} - q_C\mathbb{E}C_{t'} \geq \overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t')\Big[q_A\mathbb{E}A_\psi - q_C\mathbb{E}C_\psi\Big]$ and thus the last inequality, because based on Theorem 2.2, $q_A\mathbb{E}A_t - q_C\mathbb{E}C_t$ is decreasing in t, $t' \leq \psi$, and $\overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t') \leq 1$.

Finally, by rearranging terms in Δ, we can show that it equals the sum of the following decreasing functions:

- $q_A\mathbb{E}A_{t'} - q_C\mathbb{E}C_{t'}$: This term is decreasing based on Theorem 2.2.
- $-\overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')\Big[q_A\mathbb{E}A_\psi - q_C\mathbb{E}C_\psi\Big]$: Since $\overline{\mathbf{F}}_{\mathbf{C}}(t')$ is decreasing and $-\overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t') = -\frac{\overline{\mathbf{F}}_{\mathbf{C}}(\psi)}{\overline{\mathbf{F}}_{\mathbf{C}}(t')}$ by definition, we have that $-\overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')$ is decreasing. Since $C_\psi \leq_{st} A_\psi$ based on Lemma A.7, then using Assumption 2.8 we can show that $q_A\mathbb{E}A_\psi \geq q_C\mathbb{E}C_\psi$. Therefore, the term $-\overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')\Big[q_A\mathbb{E}A_\psi - q_C\mathbb{E}C_\psi\Big]$ is decreasing.
- $\Big[\overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t') - \overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')\Big](U - q_A\mathbb{E}A_\psi)$: This term is decreasing because $\overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t') - \overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')$ is decreasing based on the theorem assumption, and $U \geq q_A\mathbb{E}A_\psi$ since we assume that a patient's residual QALE on transplant is higher than on HD.

■

Appendix B

Chapter 4 Mathematical Proofs

B.1 General Results

Lemma B.1. If $v(x)$ increases with x, we have $\mathbb{E}v(X) \leq \mathbb{E}v(Y)$, for any $X \leq_{st} Y$.

Proof. See Theorem 2.2.5. in [102]. ■

Lemma B.2. Assume an increasing function f and independent random variables X_i, Y_i with $X_i \leq_{st} Y_i$. We have $f(X_1, \ldots, X_n) \leq_{st} f(Y_1, \ldots, Y_n)$.

Lemma B.3. The random vectors X and Y satisfy $X \leq_{st} Y$ if, and only if, there exist two random vectors $\hat{X}$ and $\hat{Y}$, defined on the same probability space, such that $\hat{X} =_{st} X$ and $\hat{Y} =_{st} Y$, and we have $\hat{X} \leq \hat{Y}$ with probability 1.

Proof. See Theorem 6.B.1. in [98]. ■

Lemma B.4. Let $X_1, X_2, \ldots, X_m$ be a set of independent random variables and let $Y_1, Y_2, \ldots, Y_m$ be another set of independent random variables. If $X_i \leq_{st} Y_i$ for $i = 1, \ldots, m$, then for any increasing function $\psi : \mathbb{R}^m \to \mathbb{R}$, one has $\psi(X_1, \ldots, X_m) \leq_{st} \psi(Y_1, \ldots, Y_m)$. In particular, $\sum X_i \leq_{st} \sum Y_i$.

Proof. See Theorem 1.A.3. in [98]. ■

Lemma B.5. Let X, Y be two random variables such that for all realizations of the random variable Z, we have $[X|Z = z] \leq_{st} [Y|Z = z]$. Then, $X \leq_{st} Y$.

Proof. See Theorem 1.2.15 in [100]. ■

Lemma B.6. Let X_a be a family of real-valued random variables parametrized by $a \in \mathbb{R}$ such that $X_a \leq_{st} X_{a'}$ whenever $a \leq a'$. Then, we have $X_Z \leq_{st} X_Y$ whenever $Z \leq_{st} Y$.

Proof. By Lemma B.3, there exist random variables $\tilde{Y}$ and $\tilde{Z}$ defined on the same sample space such that $\tilde{Y} =_{st} Y$, $\tilde{Z} =_{st} Z$, and $\tilde{Z} \leq \tilde{Y}$ with probability 1. We also have $X_{\tilde{Z}} \leq_{st} X_{\tilde{Y}}$ since X_a increases in a in the usual stochastic order and $\tilde{Z} \leq \tilde{Y}$ with probability 1. Therefore, we have $X_Z =_{st} X_{\tilde{Z}} \leq_{st} X_{\tilde{Y}} =_{st} X_Y$, and thus the result. ■

B.2 Analytical Results

B.2.1 Proofs of Results in Section 4.2:

Proof of Proposition 4.1.
We prove the result by induction on t. For $t = T + 1$, we have $v_t(x) = R(x)$. Therefore, the induction basis holds by assumption (b). We now show that the result holds for t, if it hold for $t + 1$. Let a^* be an optimal action under state x at t. Consider any state $x' \geq x$. We have:

$$\begin{aligned} v_t(x) &= r_t^{a*}(x) + \beta \mathbb{E} v_{t+1}(\tilde{x}_t^{a^*}(x)) \\ &\leq r_t^{a*}(x') + \beta \mathbb{E} v_{t+1}(\tilde{x}_t^{a^*}(x)) \\ &\leq r_t^{a*}(x') + \beta \mathbb{E} v_{t+1}(\tilde{x}_t^{a^*}(x')) \\ &\leq \max_{a \in \mathcal{A}} \left\{ r_t^a(x') + \beta \mathbb{E} v_{t+1}(\tilde{x}_t^a(x')) \right\} = v_t(x'), \end{aligned}$$

where the first inequality follows by assumption (a), the second inequality follows since $v_{t+1}(x)$ increases with x (by induction assumption) and $\tilde{x}_t^{a^*}(x) \leq_{st} \tilde{x}_t^{a^*}(x')$ (assumption (c)). ■

In what follows, define function $\Delta_t(x)$ for any optimal stopping problem by

$$\Delta_t(x) := r_t(x) + \beta \mathbb{E} v_{t+1}(\tilde{x}_t(x)) - R_t(x).$$

Note that in period t stopping is optimal at x if and only if we have $\Delta_t(x) \leq 0$ (for maximization problems).

Proof of Proposition 4.3:
Let $\Delta_t^i(x)$ be the $\Delta_t(x)$ function for problem i, i.e., let

$$\Delta_t^i(x) := r_t^i(x) + \beta \mathbb{E} v_{t+1}^i(\tilde{x}_t^i(x)) - R_t^i(x).$$

We can show that it suffices to prove that $\Delta_t^1(x) \leq \Delta_t^2(x)$ as follows. Assume that stopping is optimal for problem 2 at x in period t, i.e., we have $\Delta_t^2(x) \leq 0$. We then have $\Delta_t^1(x) \leq \Delta_t^2(x) \leq 0$, and therefore, stopping is optimal for problem 1 as well.

We now show that $\Delta_t^1(x) \leq \Delta_t^2(x)$. For $t = T$, we have $\Delta_t^i(x) = \delta_t^i(x)$ by the definition of one-step benefit function. Therefore, the induction basis holds by assumption (a). As shown in [99], we can show that $\Delta_t(x) = \delta_t(x) + \beta \mathbb{E} \max[0, \Delta_{t+1}(\tilde{x}_t(x))]$ as follows.

$$\begin{aligned} \Delta_t(x) =& r_t(x) + \mathbb{E} v_{t+1}(\tilde{x}_t(x)) - R_t(x) \\ =& r_t(x) - R_t(x) + \mathbb{E} \max[r_{t+1}(\tilde{x}_t(x)) + \mathbb{E} v_{t+2}(\tilde{x}_{t+1}(\tilde{x}_t(x))), R_{t+1}(\tilde{x}_t(x))] && \text{(B.1)} \\ =& r_t(x) - R_t(x) + \mathbb{E} \max[R_{t+1}(\tilde{x}_t(x)) + \Delta_{t+1}(\tilde{x}_t(x)), R_{t+1}(\tilde{x}_t(x))] && \text{(B.2)} \\ =& r_t(x) - R_t(x) + \mathbb{E} R_{t+1}(\tilde{x}_t(x)) + \mathbb{E} \max[\Delta_{t+1}(\tilde{x}_t(x)), 0] && \text{(B.3)} \\ =& \delta_t(x) + \beta \mathbb{E} \max[0, \Delta_{t+1}(\tilde{x}_t(x))]. && \text{(B.4)} \end{aligned}$$

where the Eq. B.1 follows the definition of $v_{t+1}(.)$, Eq. B.2 follows by the definition of $\Delta_{t+1}(.)$, Eq. B.3 follows by re-arranging terms, and Eq. B.4 follows by the definition of $\delta_{t+1}(.)$.

Therefore, we have:

$$\begin{aligned}\Delta_t^1(x) &= \delta_t^1(x) + \mathbb{E}\max[0, \Delta_{t+1}^1(\tilde{x}_t^1(x))] \\ &\leq \delta_t^2(x) + \mathbb{E}\max[\Delta_{t+1}^1(\tilde{x}_t^1(x)), 0] \\ &\leq \delta_t^2(x) + \mathbb{E}\max[\Delta_{t+1}^2(\tilde{x}_t^2(x)), 0] = \Delta_t^2(x),\end{aligned}$$

where the first inequality follows since $\delta_t^1(x) \leq \delta_t^2(x)$ (assumption (a)), and the second inequality follows since $\Delta_{t+1}^1(x) \leq \Delta_{t+1}^2(x)$ for any x (by induction assumption), and $\tilde{x}_t^1(x) =_{st} \tilde{x}_t^2(x)$ for any x (assumption (b)). ■

Proof of Proposition 4.4:
It suffices to show that $\Delta_t(x)$ increases in x_i. By the definitions of Δ_t and σ_t we have:

$$\Delta_t(x) = \sigma_t(x) + \beta\mathbb{E}v_{t+1}(\tilde{x}_t(x)).$$

The first term is increasing in x_i by assumption (c). The second term increases with x_i by the definition of stochastic order of random vectors since v_{t+1} increases with x (assumption (b)) and $\tilde{x}_t(x)$ increases with x_i in the usual stochastic order (assumption (a)). ■

B.2.2 Proof of Results in Section 4.3

Proof of Lemma 4.1. By re-arranging terms in Eq. 4.1, we obtain:

$$\mathcal{B}^a(d,p) = \Big[1 + \frac{1-p}{p}\frac{f_w^a(d)}{f_b^a(d)}\Big]^{-1}.$$

Since $\dfrac{1-p}{p}$ decreases with p and $\dfrac{f_w^a(d)}{f_b^a(d)}$ increases with d by the definition of the MLR order, the result follows. ■

We use the following lemma to prove Lemma 4.2.

Lemma B.7. Assume that we have $\gamma_b^a \leq_{st} \gamma_w^a$, for action a. Then, γ_p^a decreases in p in the usual stochastic order.

Proof. We have $f_p = pf_b^a + (1-p)f_w^a$. Therefore, $\mathbb{P}[\gamma_p^a \leq x] = p\mathbb{P}[\gamma_b^a \leq x] + (1-p)\mathbb{P}[\gamma_w^a \leq x]$. Since by assumption $\mathbb{P}[\gamma_w^a \leq x] \leq \mathbb{P}[\gamma_b^a \leq x]$, we have that $\mathbb{P}[\gamma_p^a \leq x]$ increase with p, and therefore, the result follows. ■

Proof of Lemma 4.2. We show that $\tilde{x}^a(e,p)$ stochastically increases with e and p as follows.

- $\tilde{x}^a(e,p) \leq_{st} \tilde{x}^a(e,p')$ for $p \leq p'$.
  Since the MLR order implies the usual stochastic order, we have $\gamma_b^a \leq_{st} \gamma_w^a$. Therefore by Lemma B.7, we have that γ_p^a decreases with p in the usual stochastic order. By Lemma B.3, there exist random variables γ and γ' defined on the same probability space such that $\gamma =_{st} \gamma_p^a$, $\gamma' =_{st} \gamma_{p'}^a$, and $\gamma' \leq \gamma$ with probability 1. Therefore, we have that the following holds with probability 1:

  $$[e-\gamma, \mathcal{B}^a(\gamma,p)] \leq [e-\gamma', \mathcal{B}^a(\gamma',p)] \leq [e-\gamma', \mathcal{B}^a(\gamma',p')], \tag{B.5}$$

  where the first and second inequalities hold since $\mathcal{B}^a(d,p)$ decreases with d and increases with p by Lemma 4.1.

  Since $\tilde{x}^a(e,p) =_{st} [e-\gamma, \mathcal{B}^a(\gamma,p)]$ and $\tilde{x}^a(e,p') =_{st} [e-\gamma', \mathcal{B}^a(\gamma',p')]$, the result follows by Lemma B.3 and Eq. B.5.

- $\tilde{x}^a(e,p) \leq_{st} \tilde{x}^a(e',p)$ for $e \leq e'$.
  We have the following:

  $$\tilde{x}^a(e,p) =_{st} [e-\gamma_p^a, \mathcal{B}^a(\gamma_p^a,p)] \leq [e'-\gamma_p^a, \mathcal{B}^a(\gamma_p^a,p)] =_{st} \tilde{x}^a(e',p). \tag{B.6}$$

  where the inequality holds with probability 1. Therefore, the result follows by Lemma B.3.

■

Proof of Proposition 4.5. We use Proposition 4.1 to show the result. By Lemma 4.2 and assumption (c), we have $\tilde{x}^a(e,p) \leq_{st} \tilde{x}^a(e',p')$, and hence assumption (c) of Proposition 4.1 holds. We have $r^a(e,p) = pr_b^a(e)+(1-p)r_w^a(e)$. Since $r_m(e)$ increases with m and e (assumption (a)), we have $r^a(e,p)$ increases with (e,p), and hence assumption (a) of Proposition 4.1 holds. Similarly using assumption (b), we can show that assumption (b) of Proposition 4.1 holds, and the result follows. ■

Proof of Proposition 4.6. We use Proposition 4.4 to prove the result. By Lemma 4.2 we have $\tilde{x}(e,p)$ increases with e and p in the usual stochastic order. Therefore, assumption (a) of Proposition 4.4 holds. Also, by Proposition 4.5 and assumptions (a,b,c), the value function increases with (e,p). Therefore, assumption (b) of Proposition 4.4 holds. We have:

$$\sigma(e,p) = p\sigma_b(e) + (1-p)\sigma_w(e)$$

Therefore, $\sigma(e,p)$ increases with p and e by assumption (d), and thus, assumption (c) of Proposition 4.4 holds. ■

Proof of Proposition 4.7. We use Proposition 4.2 to prove the result. By Lemma 4.2 we have $\tilde{x}(e,p)$ increases with e and p in the usual stochastic order. Therefore, assumption (b) of Proposition 4.2 holds.

It remains to show that assumption (a) of Proposition 4.2 holds. To that end, it suffices to show that $\delta(e,p) = p\delta_b(e) + (1-p)\delta_w(e)$, since then we have $\delta(e,p)$ increases with p and e since $\delta_m(e)$ increases with m and e (assumption (a)).

Let $[\pi_w(d,p), \pi_b(d,p)] = [1-\mathcal{B}(d,p), \mathcal{B}(d,p)]$ and $[\pi_w, \pi_b] = [1-p, p]$ be posterior and prior belief vectors. We have:

$$\begin{aligned}
\delta(e,p) &= r(e,p) + \mathbb{E}_{\gamma_p}[R(e-\gamma_p, \mathcal{B}(\gamma_p,p))] - R(e,p) && \text{(B.7)}\\
&= \sum_{m=w,b} \pi_m r_m(e) + \mathbb{E}_{\gamma_p}\Big[\sum_{m=w,b} \pi_m(\gamma_p,p) R_m(e-\gamma_p)\Big] - \sum_{m=w,b} \pi_m R_m(e) && \text{(B.8)}\\
&= \sum_{m=w,b} \pi_m [r_m(e) - R_m(e)] + \mathbb{E}_{\gamma_p}\Big[\sum_{m=w,b} \pi_m(\gamma_p,p) R_m(e-\gamma_p)\Big] && \text{(B.9)}\\
&= \sum_{m=w,b} \pi_m [r_m(e) - R_m(e)] + \int \Big[\sum_{m=w,b} \frac{\pi_m f_m(x)}{f_p(x)} R_m(e-x) f_p(x)\Big] dx && \text{(B.10)}\\
&= \sum_{m=w,b} \pi_m [r_m(e) - R_m(e)] + \int \Big[\sum_{m=w,b} \pi_m f_m(x) R_m(e-x)\Big] dx && \text{(B.11)}\\
&= \sum_{m=w,b} \pi_m [r_m(e) - R_m(e)] + \sum_{m=w,b} \pi_m \int f_m(x) R_m(e-x) dx && \text{(B.12)}\\
&= \sum_{m=w,b} \pi_m [r_m(e) - R_m(e)] + \sum_{m=w,b} \pi_m \mathbb{E} R_m(e-\gamma_m) && \text{(B.13)}\\
&= \sum_{m=w,b} \pi_m \delta_m(e), && \text{(B.14)}
\end{aligned}$$

where Eq. B.7 and Eq. B.8 follow by the definition of $\delta(x)$, Eq. B.9 follows by re-arranging terms, Eq. B.10 follows by the definition of the posterior belief, Eq. B.11 follows by re-arranging terms, Eq. B.12 follows by exchanging the order of expectation and summation, Eq. B.13 follows by the definition of expectation, and Eq. B.14 follows by the definition of $\delta_m(s)$. ■

Proof of Proposition 4.8. We have:

$$\begin{aligned}
\delta_w(e) &= r_w(e) + \mathbb{E}R_w(e-\gamma_w) - R_w(e) = r_b(e) + \mathbb{E}R_b(e-\gamma_w) - R_b(e)\\
&\leq r_b(e) + \mathbb{E}R_b(e-\gamma_b) - R_b(e) = \delta_b(e),
\end{aligned}$$

where the first and last equality follow the definition of δ, the second equality follows assumption (a,b), and the inequality follows by Lemma B.1 since $R_b(e)$ increases with e, and $e-\gamma_w \leq_{st} e-\gamma_b$ (assumption (c)). ■

B.2.3 Proof of Results in Section 4.4:

In what follows let $\delta_m(e)$ be the one-step benefit function for patient type m at health state e, i.e., let $\delta_m(e) := \mathbb{E}d_m(e-\gamma_m) - d_m(e)$. In Lemma B.9, we show that under the assumptions of Proposition 4.9, $\delta_m(e)$ decreases with e and m. We use Lemma B.8 to prove Lemma B.9.

Lemma B.8. T_e^m increases with e and m in the usual stochastic order, whenever $\gamma_b \leq_{st} \gamma_w$.

Proof. We need to show that $\mathbb{P}[T_e^m \leq t]$ decreases with e and m. Let γ_m^i be i.i.d. samples from γ_m. By definition we have:

$$\mathbb{P}[T_e^m \leq t] = \mathbb{P}\big[\sum_{i=1}^{t} \gamma_m^i \geq e - e_d\big].$$

It is trivial that $\mathbb{P}[T_e^m \leq t]$ decreases with e. By Lemma B.4, we have that $\gamma_b \leq_{st} \gamma_w$ implies $\sum_{i=1}^t \gamma_b^i \leq_{st} \sum_{i=1}^t \gamma_w^i$. Therefore, $\mathbb{P}[T_e^m \leq t]$ decreases with m, as well. ■

Lemma B.9. Assume:
(a) $\gamma_b \leq_r \gamma_w$,
(b) Function c is convex.
then, $\delta_m(e)$ decreases with e and m.

Proof. Let e' be the eGFR value in the subsequent period when the eGFR is currently at e and the decision is to continue, i.e., let $e' := e - \gamma_m$. Also, define L' as a random variable that is smaller than L (the lead time until the AVF is ready) by one month, i.e., let $L' := L - 1$. Recall that $L - T_e^m$ represents the difference between the time an AVF becomes available and when HD commences. We have $L - T_e^m =_{st} L' - T_{e'}^m$, since after one month, the eGFR has transitioned from e to e', and thus we have $T_{e'}^m$ until HD starts, and one month of the AVF preparation has passed. Therefore, we have $d_m(e) = \mathbb{E}c(L' - T_{e'}^m)$. Let $g(x) := c(x) - c(x-1)$. We have:

$$\begin{aligned}\delta_m(e) &= \mathbb{E}d_m(e-\gamma_m) - d_m(e) = \mathbb{E}c(L - T_{e-\gamma_m}^m) - \mathbb{E}c(L - 1 - T_{e-\gamma_m}^m) \\ &= \mathbb{E}g(L - T_{e-\gamma_m}^m), \end{aligned} \tag{B.15}$$

where the first follows by the definition of δ, the second equality follows by the definition of $d_m(e)$ and the observation above that $L - T_e^m =_{st} L' - T_{e'}^m$, and the last equality follows by the definition of g. Since the MLR order implies the usual stochastic order, by assumption (a) we have $\gamma_b \leq_{st} \gamma_w$, and therefore by Lemma B.8, T_e^m increases with e and m in the usual stochastic order. Also, since c is convex (assumption (b)), g increases with x.

We now prove the claim:

→ Monotonicity in e:
Choose $e \leq e'$ arbitrarily. Since T_e^m increases with e in the usual stochastic order, we

have:

$$[T^m_{e-\gamma_m}|\gamma_m = d] \leq_{st} [T^m_{e'-\gamma_m}|\gamma_m = d].$$

By Lemma B.5 , we have $T^m_{e-\gamma_m} \leq_{st} T^m_{e'-\gamma_m}$. Therefore,

$$\delta_m(e) = \mathbb{E}g(L - T^m_{e-\gamma_m}) \geq \mathbb{E}g(L - T^m_{e'-\gamma_m}) = \delta_m(e'),$$

where the inequality follows by Lemma B.1 since $L - T^m_{e-\gamma_m} \geq_{st} L - T^m_{e'-\gamma_m}$, and g increases with x.

$\rightarrow$ Monotonicity in m:
We first show $T^w_{e-\gamma_w} \leq_{st} T^b_{e-\gamma_b}$ as follow. Since T^m_e increases with e in the usual stochastic order, and $\gamma_b \leq_{st} \gamma_w$, we obtain that $T^b_{e-\gamma_w} \leq_{st} T^b_{e-\gamma_b}$ by Lemma B.6. Since for any e, $T^w_e \leq_{st} T^b_e$, we have:

$$[T^w_{e-\gamma_w}|\gamma_w = d] \leq_{st} [T^b_{e-\gamma_w}|\gamma_w = d].$$

Therefore, by Lemma B.5, we have $T^w_{e-\gamma_w} \leq_{st} T^b_{e-\gamma_w}$, and as a result, $T^w_{e-\gamma_w} \leq_{st} T^b_{e-\gamma_b}$. We have:

$$\delta_b(e) = \mathbb{E}g(L - T^b_{e-\gamma_b}) \leq \mathbb{E}g(L - T^w_{e-\gamma_w}) = \delta_w(e),$$

where the inequality follows by Lemma B.1 since $L - T^w_{e-\gamma_w} \geq_{st} L - T^b_{e-\gamma_b}$, and g increases with x.

■

We now prove Proposition 4.9.

Proof of Proposition 4.9.
By Lemma B.9 and assumptions (a,b), we have that $\delta^m(e)$ decreases with e and m. Therefore, the result follows the infinite-horizon, cost minimization version of Proposition 4.7. ■

Proof of Proposition 4.10.
We use the infinite horizon version of Proposition 4.3 to show the result. Let $\delta^i(e,p)$ be the one-step benefit function for problem i. Since $\tilde{x}^1(e,p) = \tilde{x}^2(e,p)$ by assumption, it suffices to show that $\delta^1(e,p) \leq \delta^2(e,p)$. In the proof of proposition 4.7, we show that $\delta^i(e,p) = p\delta^i_b(e) + (1-p)\delta^i_w(e)$. Therefore, it suffices to show that $\delta^1_m(e) \leq \delta^2_m(e)$. By Eq. B.15, we have $\delta^i_m(e) = \mathbb{E}g(L_i - T^m_{e-\gamma_m})$ for some increasing function g. We have:

$$\delta^1_m(e) = \mathbb{E}g(L_1 - T^m_{e-\gamma_m}) \leq \mathbb{E}g(L_2 - T^m_{e-\gamma_m}) = \delta^2_m(e),$$

where the inequality follows by Lemma B.1 since g is increasing and $L_1 \leq_{st} L_2$. ■