DYNAMIC DECISION MODELS FOR MANAGING THE MAJOR COMPLICATIONS OF DIABETES

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Diabetes is the sixth-leading cause of death and a major cause of cardiovascular and renal diseases in the U.S. In this dissertation, we consider the major complications of diabetes and develop dynamic decision models for two important timing problems: Transplantation in prearranged paired kidney exchanges (PKEs) and statin initiation.

Transplantation is the most viable renal replacement therapy for end-stage renal disease (ESRD) patients, but there is a severe disparity between the demand and supply of kidneys for transplantation. PKE, a cross-exchange of kidneys between incompatible patient-donor pairs, overcomes many difficulties in matching patients with incompatible donors. In a typical PKE, transplantation surgeries take place simultaneously so that no donor may renege after her intended recipient receives the kidney. We consider two autonomous patients with probabilistically evolving health statuses in a PKE and model their transplant timing decisions as a discrete-time non-zero-sum stochastic game. We explore necessary and sufficient conditions for patients' decisions to form a stationary-perfect equilibrium, and formulate a mixed-integer linear programming (MIP) representation of equilibrium constraints to characterize a socially optimal stationary-perfect equilibrium. We calibrate our model using large scale clinical data. We quantify the social welfare loss due to patient autonomy and demonstrate that the objective of maximizing the number of transplants may be undesirable.

Patients with Type 2 diabetes have higher risk of heart attack and stroke, and if not treated these risks are confounded by lipid abnormalities. Statins can be used to treat such abnormalities, but their use may lead to adverse outcomes. We consider the question of when

to initiate statin therapy for patients with Type 2 diabetes. We formulate a Markov decision process (MDP) to maximize the patient's quality-adjusted life years (QALYs) prior to the first heart attack or stroke. We derive sufficient conditions for the optimality of control-limit policies with respect to patient's lipid-ratio (LR) levels and age, and parameterize our model using clinical data. We compute the optimal treatment policies and illustrate the importance of individualized treatment factors by comparing their performance to those of the guidelines in use in the U.S.

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in memory of Dr. Seth Bonder...

to my parents...

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1.0 INTRODUCTION

Healthcare is the largest single industry in the U.S. Elevated healthcare costs pose major social and economic problems in the U.S. and force several cost-saving measures by state and private agencies. Total national health expenditures accounted for 17.6% of the Gross Domestic Product in 2010 and this share is expected to grow to 19.8% by 2020 [34]. National health expenditure per person of the U.S., which exceeded $8,000 in 2009, is the highest among all member states of the World Health Organization [233], and is expected to be around $14,000 by 2020 with the aging population [34].

Increasing healthcare costs and economic challenges have received considerable attention from academics and the media, and motivated a significant amount of research over the last two decades. Operations Research (OR) techniques have found a variety of applications in healthcare. These applications help develop new methodologies while improving the state of the art in modeling and optimization techniques. They also inform practitioners on how to make use of raw data to make better decisions and to address public policy concerns. Examples of OR applications in healthcare include demand forecasting, hospital capacity planning, patient and workforce scheduling, staffing emergency departments, locating emergency service facilities, immunization and vaccine selection, organ allocation, and cancer treatment planning, among several others. Earlier and more recent surveys summarize the vast literature of OR applications in healthcare and highlight contemporary issues at the intersection of OR and healthcare along with current challenges and emerging research activities [24, 52, 68, 85, 110, 116, 127, 145, 147, 154, 162, 190].

1.1 CHRONIC AND END-STAGE RENAL DISEASES (ESRD)

In a healthy patient, kidneys perform key functions such as monitoring and regulating body fluids, balancing electrolytes and filtering the blood. Chronic kidney disease (CKD) is the progressive and irreversible loss of renal functionality over a period of months or years and divided into five stages of severity [207].

ESRD, the last stage of CKD, typically occurs when the kidneys' functionality is less than 10 % of normal. It is the ninth-leading cause of death in the U.S. and has grown alarmingly in the last decade [207]. Currently, more than 500,000 Americans have ESRD and more than 26 million Americans are at increased risk of developing the disease [41]. The size of the ESRD population is projected to grow to 2.24 million by 2030 and each year more than 100,000 people experience a kidney failure in the U.S. [203, 210]. The total cost of ESRD in the U.S. was around $30 billion in 2009 [209].

ESRD can result in death if not treated. There are three viable treatment alternatives for ESRD patients: Hemodialysis, peritoneal dialysis and transplantation. Hemodialysis is the most common renal replacement therapy and typically requires a patient to visit a clinical center several times a week to have her blood cleaned. Although the procedure is safe, several complications such as hypotension, cardiac arrhythmias and muscle cramps can occur during the process of filtering blood [44].

In peritoneal dialysis, a filtering fluid is embedded into the patient's body [150]. Peritoneal dialysis is cheaper than hemodialysis but yields almost equal survival rates as hemodialysis. Especially for nondiabetic and young diabetic ESRD patients, it may have a lower risk of death because of its superior preservation of residual kidney functionality. Despite such advantages, the use of peritoneal dialysis is less common compared to hemodialysis [115, 128].

Due to insufficient supply of kidneys for transplantation, dialysis is a common intermediary step for ESRD patients. However, transplantation is the preferred choice of treatment as it allows patients resume their regular activities with a higher quality of life than dialysis by providing improved long-term survival rates [112, 228, 229].

In the U.S., an ESRD patient must join a waiting list administered by the United Network for Organ Sharing (UNOS), a scientific and educational nonprofit organization, to be eligible for a cadaveric kidney transplantation [215]. The current policy has been active for more than two decades and prioritizes patients based on a scoring rule which takes several factors into account, including the waiting time on the list and the quality of the match. Details for the current cadaveric kidney allocation policy can be found in Organ Procurement and Transplantation Network (OPTN) website [160]. As clear from Figure 1.1, the supply of kidneys for transplantation is far below the waiting list additions. Currently, more than 90,000 patients in the U.S. are awaiting a kidney transplant, but in 2010, 4850 patients died while waiting on the list and only 16,900 patients received transplants, 6,200 of which were from living-donors [216].

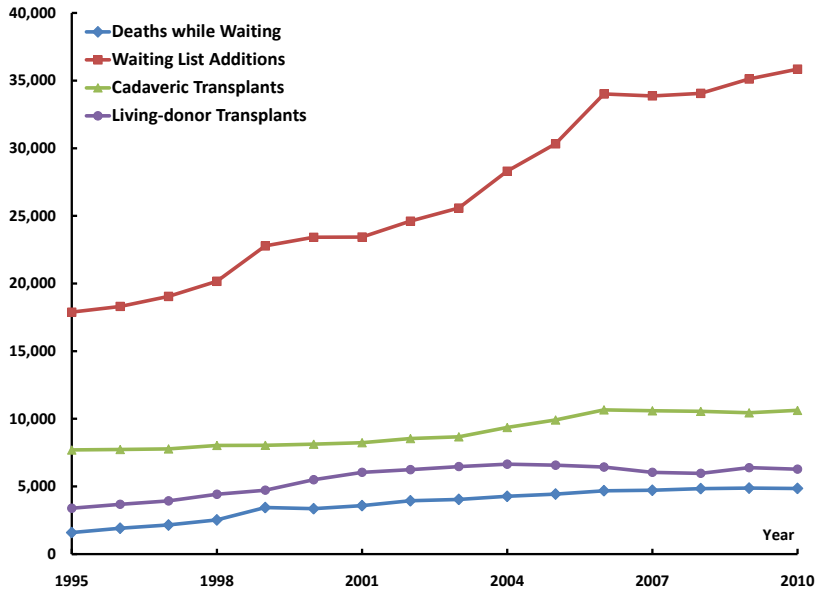

Figure 1.1: Recent trend in demand and supply of kidneys for transplantation in the U.S. [216].

Because people can function normally on only one kidney, it is also possible for an ESRD patient to receive an organ from a living-donor and transplants from such donors generally yield better survival outcomes than those from cadaveric transplants (see Figure

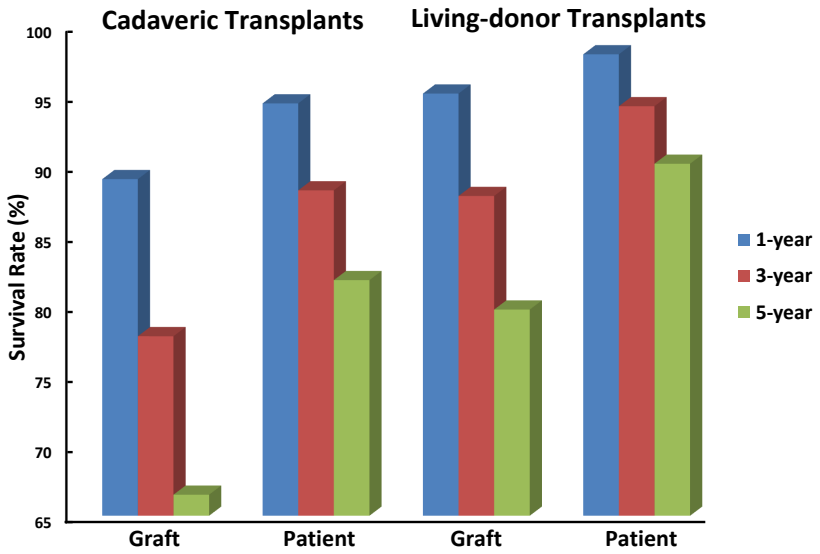

Figure 1.2: Graft and patient survival rates from kidney transplantation [216].

1.2). In fact there is a universal agreement in the transplant community that a living-donor kidney transplant is the preferred course of treatment for ESRD patients [80, 205]. A kidney transplanted from a living-donor is much preferred to a cadaveric kidney. In general, a cadaveric kidney transplant may be subject to some degree of trauma and this trauma may negatively affect the time between the moment the kidney stops functioning in the donor and begins functioning in the transplant recipient. In some extreme cases, it may take a few weeks for a cadaveric kidney transplant to function properly and the patient may need dialysis until then. There are additional benefits of living-donor transplants, too. A living kidney donation from a close relative, such as a sister or a brother, can yield an excellent tissue-type match for the recipient thereby reducing the risk of kidney rejection. Also, a living kidney donation gives the patient, donor, and possibly their families the flexibility to plan the timing of surgery conveniently [208].

Despite the flexibility provided to ESRD patients by living-donor transplants, blood type and antigen incompatibilities make kidneys difficult to match. Human leukocyte antigens (HLA) are protein molecules that are located on the surface of the white blood cells and other tissues in the body. There are three classes of HLA: HLA-A, HLA-B and HLA-DR, and each of these classes include different number of specific HLA proteins with a variety of numerical designations. A *positive crossmatch*, often referred to as "HLA incompatibility," is a strong indication against transplant between a patient-donor pair. This occurs if the patient develops in her serum antibody that causes cell damage to the donor by attacking her HLA. Specifically, Panel-Reactive Antibodies (PRA) are defined as the number of reactions that a patient's blood serum shows against a panel of blood donors and commonly used to estimate the probability that the patient will have a negative reaction to a particular donor.

With recent advances in desensitization, immunosuppressive therapies enable transplants between blood-type incompatible patient and donor pairs by decreasing the strength of the immune system; however, excessive level of antibodies in patient serum following transplantation can still render such transplants impractical. Furthermore, long-term graft and patient survival results of various immunosuppressants are still uncertain [197].

Although transplantation is regarded as the most viable renal replacement therapy, most ESRD patients undergo transplantation after a period of dialysis [79]. A *preemptive living-donor renal transplantation* occurs before dialysis, and such a transplant appears to be more cost effective [19, 97, 102]. It provides better long-term survival rates than the conventional post-dialysis transplantation and higher quality of life by avoiding the morbidities and complications associated with dialysis [57, 119, 120].

While living donation has nearly tripled in the last decade, every year more than 2000 donor/recipient pairs are excluded from transplantation because of blood type or HLA incompatibility [76]. The disparity between the demand and supply of kidneys for transplantation also yields significantly long waiting times. The national median waiting time on the transplant list is approaching 5 years, and in some states including New York patients may wait up to 7 years prior to receiving a transplant [157]. As can be seen from Figure 1.3, median waiting times vary significantly with respect to patient's blood type. Note that the list has not been cleared from the patients who were registered on after 2002.

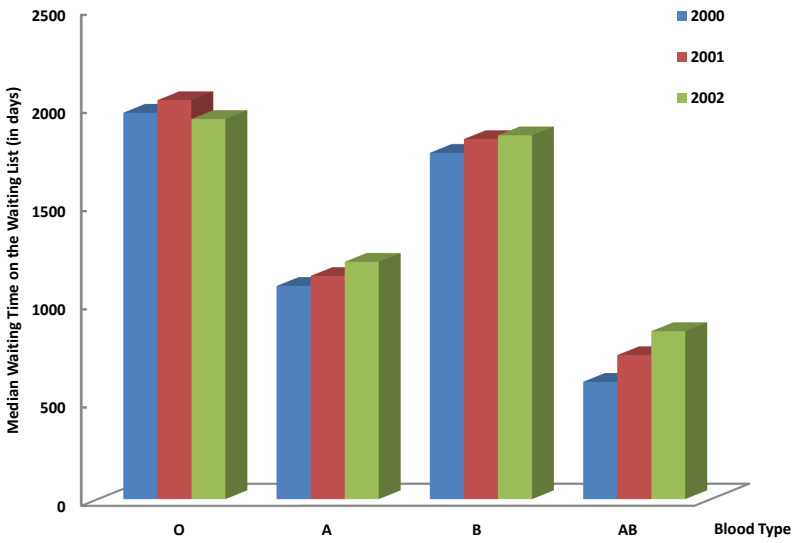

Figure 1.3: Average median times on the waiting list with respect to blood-type [216].

Because the sale and acquisition of organs are illegal under the National Organ Transplant Act of 1984 and the Uniform Anatomical Gift Act of 1987 [50], the difficulties in matching patient-donor pairs motivated new clinical strategies to alleviate the shortage of kidneys and to reduce the productivity losses due to long waiting times on dialysis [131, 144, 179, 232].

1.2 DIABETES

Diabetes mellitus, usually called diabetes, is the sixth-leading cause of death and a major underlying cause of cardiovascular complications in the U.S. [134]. According to American Diabetes Association (ADA), there are currently more than 20 million Americans with diabetes [15], and this number is expected to grow to 39 million by 2050 [91].

There are two types of diabetes: Type 1 and Type 2. Type 1 diabetes, also known as insulin-dependent diabetes, occurs when pancreas produces very little or no insulin. On the other hand, Type 2 diabetes, which is also called non insulin-dependent diabetes, occurs with insulin resistance combined with relative insulin deficiency. In Type 2 diabetes although pancreas produces insulin, body cannot use it properly. Because of this inefficiency, patients often have difficulty in maintaining their blood glucose levels within healthy ranges. While Type 1 diabetes usually occurs in children, Type 2 diabetes is more common among adults, especially those over 40. In the U.S., approximately 90% of the diabetes cases are of Type 2 [16].

Type 2 diabetes has several significant complications, including coronary heart disease (CHD), stroke, kidney failure, amputation, and blindness, all of which can result in disabilities and work losses leading to poor productivity levels [143, 163]. These complications not only affect the patients' health-related quality of life but also account for a sizable portion of the total healthcare costs to society [42, 206]. Of these complications, CHD and stroke represent the leading causes of diabetic deaths in the U.S. [15]. Because Type 2 diabetes can increase the patient's CHD and stroke risks by a factor of five, they carry significant importance for physicians in making treatment decisions [22, 106, 121, 196].

Lipid abnormalities increase the risk of CHD and stroke in patients with Type 2 diabetes [108, 218]. The cholesterol profile of a patient is usually assessed by her triglycerides and three types of cholesterol: Total cholesterol (TC), low-density lipoproteins (LDL) and high-density lipoproteins (HDL). Among these, triglycerides are the main form of fat in bloodstream and considered to be a positive risk factor for CHD. Elevated TC and LDL, which is the main source of artery clogging plaque and referred to as "bad cholesterol," increase the overall risk of CHD and stroke. In contrast, HDL, which is also called "good cholesterol," works to extract cholesterol from the artery walls and dispose them through the liver. Therefore, high levels of HDL are more desirable to reduce the risk of CHD. Elevated TC and depressed HDL have been reported in clinical trials to increase the overall risk of CHD and stroke. The ratio of TC to HDL, defined as the "lipid ratio" (LR), is a strong predictor of CHD and stroke risks, but this ratio can vary significantly and unpredictably over time [75, 222, 226].

Several published risk models try to predict CHD and stroke probabilities for patients with Type 2 diabetes based on their cholesterol levels and other risk factors. The most widely used of these models was calibrated on data from the United Kingdom Prospective Diabetes Study (UKPDS) [107, 198, 213]. The UKPDS model is based on a 20-year surveillance of over 5,000 patients in the U.K and it predicts CHD and stroke probabilities over time using several risk factors, including age, gender, ethnicity, smoking status, cholesterol, systolic blood pressure (SBP) and glycated hemoglobin (HbA1c) levels. While other predictive models have been developed, e.g. the Framingham model [17] and the Archimedes model [60, 61], the UKPDS model is unique in proposing risk equations specific to patients with Type 2 diabetes.

Clinical trials have shown that cholesterol management using statins reduces CHD and stroke risks [27, 37, 39, 40, 58]. A primary goal of managing Type 2 diabetes has been the control of blood glucose levels, however more recently the importance of cardiovascular risk has been emphasized [192, 214] and the complexity of treatment decisions has led to the development of several national treatment guidelines with differing recommendations [28, 67, 135, 136, 137, 141] (See Shah et al. [186] for a comparative effectiveness of these guidelines). For instance, current U.S. guidelines, which is also known as Adult Treatment Panel (ATP) III, and its variants [136] classify the patients with respect to their 10-year CHD risks and set a specific treatment target for LDL levels in each of these categories. Alternatively, the U.K. guidelines [28] recommend initiating lipid lowering agents such as statins when the patient's 10-year CHD risk exceeds 20%, and New Zealand guidelines [141] make the same recommendation when the patient's 5-year CHD risk exceeds 15%. Conservatively, some recent U.S. guidelines [15, 192] recommend initiating statins in all patients with Type 2 diabetes irrespective of their long-term CHD risks. Despite the effects of cholesterol build-up in the arteries on a patient's stroke risk, in addition to the differences among the guidelines' treatment policies, it is also notable that there is no guideline in practice that takes the patient's stroke risk into account for its treatment recommendations.

Although statin treatment reduces the risks of CHD and stroke, it can have serious side effects, including muscle diseases, myopathy and liver problems. Other effects have also been reported, such as headaches, nausea, fever, fatigue, shortness of breath, memory loss,

sexual dysfunction, skin problems, irritability, and effects on nervous and immunity systems [151, 152, 153, 211]. Therefore, treatment guidelines should weigh the benefits of using statins in reducing CHD and stroke risks against its side effects in making recommendations and identifying the groups that would benefit most from the treatment.

1.3 PAIRED KIDNEY EXCHANGES

A PKE [164], is a cross-exchange of kidneys between incompatible patient-donor pairs. PKEs may involve multiple patient-donor pairs and are logistically complex. A typical PKE involves two patient-donor pairs where each donor is only compatible with the intended recipient of the other, potentially leading to an exchange of organs between the pairs. Figure 1.4 illustrates a two-way kidney exchange where donors are incompatible with their intended recipients, but Donor 1 is compatible with Patient 2 and Donor 2 is compatible with Patient 1. Two-way kidney exchanges are the simplest type of PKEs and most of the social benefit is accrued by exchanges with two patients [173].

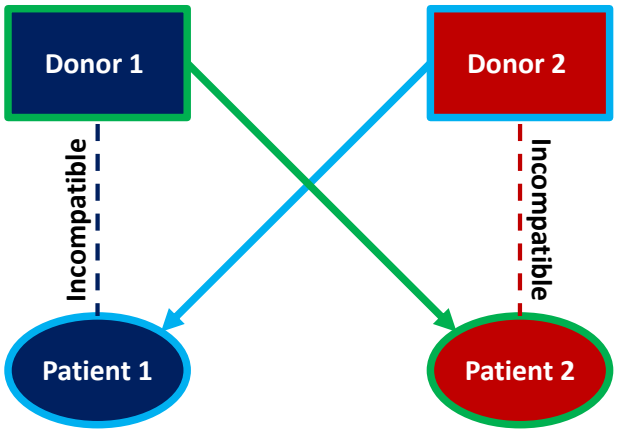

Figure 1.4: An illustration of a PKE.

PKEs typically reduce the waiting time for transplantation as well as the length of dialysis therapy, thereby reducing healthcare costs and productivity losses, leading to substantial benefits for ESRD patients [129, 130, 182, 183].

PKEs have grown rapidly over the last two decades to overcome the difficulties in matching kidneys [184] and it has been estimated that they can raise the number of transplants by up to 90 % [173].

Since their conceptual proposal in late 80s, PKEs have attracted considerable focus from media and the scientific community. The significant potential of PKEs [171, 184, 185] has led to the establishment of several regional kidney exchange clearinghouses in the U.S., Korea [148, 149] and the Netherlands [49] to organize the registry of patients and donors [13, 140]. These consortia expand the pool of living-donors and develop programs under which incompatible patient-donor pairs are identified and cross-matched to other pairs and altruistic donors [118]. Building such programs has compelled the development of advanced algorithms to match patients with donors [100, 103] and it has been estimated that including even compatible patient-donor pairs in the expansion pools can yield remarkably better matching rates [77]. More recently, a national pilot kidney exchange program joining all UNOS-approved kidney exchange clearinghouses has been launched to facilitate a more efficient network for exchanges between incompatible patient-donor pairs [158, 159]. Despite all efforts PKEs have been grossly underutilized in the U.S. [43, 184, 231].

Another approach to the kidney shortage is an indirect kidney exchange or paired list exchange [78, 133]. In such an exchange, a patient is given a higher priority on the cadaveric kidney waiting list in exchange for her donor agreeing to donate a kidney to another patient on the waiting list. There are ethical objections to indirect exchanges because of the potential harm to patients without living-donors and those with O blood type, who are in fact the hardest to match [4, 168, 169, 220, 238].

1.4 RELATION BETWEEN DIABETES, ESRD AND CARDIOVASCULAR DISEASES

Because of the vascular abnormalities, diabetes is the leading cause of ESRD in the U.S. and accounts for more than 44 % of new ESRD cases every year [33] and more than 50,000 diabetic patients in the U.S. are expected to experience ESRD eventually [32].

Kidneys contain thousands of nephrons which synthesize several proteins including albumin. In the presence of diabetes, the small blood vessels in the kidneys are injured, and high levels of blood sugar make the kidneys filter too much blood. With this extra filtering, the nephrons thicken and become scarred, and the kidneys begin releasing small quantitites of albumin into the urine. As the quantities of albumin become larger than normal, the patient develops renal disease. Diabetes can also cause difficulty in emptying the bladder and pressure resulting from a full bladder can injure the kidneys [138].

Tests can often detect signs of renal disease in the early stages and patients are recommended to have a urine test at least once a year [14]. Because the urine test seeks small quantitites of albumin in the urine, it is also called microalbuminuria test. If there is any doubt, urine test can be followed by a kidney biopsy to confirm the diagnosis; however, biopsy is not recommended as the first line of screening [86].

CKD and cardiovascular complications of diabetes are strongly related to each other in that cardiovascular diseases (CVDs) can lead to CKD, and CKD can result in cardiovascular complications. While CVDs are most effective in the early stages of CKD, majority of the ESRD patients die because of a cardiovascular complication. Several abnormalities common to ESRD also play a key role in patient's development of a CVD, high blood pressure, high blood cholesterol, excessive parathyroid hormone, to name a few [38]. Although there is no way to cure renal disease and CVDs, they are often treatable during the early stages through a systematic control of blood glucose and blood pressure. Usually, lowering blood pressure with ACE inhibitors and angiotensin receptor blockers (ARBs) is the best way of protecting kidneys from damage. Following a healthy low-fat diet and exercising regularly also help slow down the progression of CKD and CVDs [72].

Even when diabetes is controlled, it can lead to kidney failure. People with diabetes used to be excluded from dialysis and kidney transplantation, because the disease was increasing the risk of bacterial and fungal infections in transplant recipients and the damage caused by the disease was offsetting the benefits of dialysis and transplantation. Recently, with better control of diabetes, doctors do not hesitate to offer dialysis and transplantation to diabetic patients [104].

Diabetic patients who approach ESRD are not only subject to traditional cardiovascular risk factors such as high blood pressure and high blood glucose, but also kidney disease-related risk factors, such as anemia, uremia toxins, abnormal mineral metabolism, inflammation and malnutrition [224]. Combination of such risk factors may further aggravate the adverse cardiovascular risk profile. Therefore, although post-transplant graft survivals are about the same in diabetic and nondiabetic patients, diabetic patients who are eligible to receive a kidney transplant are recommended to transplant preemptively before initiating dialysis [23, 56, 194].

1.5 PROBLEM STATEMENTS AND CONTRIBUTIONS

This dissertation concentrates on the timing of prearranged PKEs for autonomous and self-interested patients with uncertain and dynamic health, and the timing of the initiation of statin therapy for patients with Type 2 diabetes.

Current practice in PKE aims to maximize only the number of transplants and favors immediate exchange. However, an early transplantation may fail to maximize the residual renal functionality. Due to ethical barriers, in a typical PKE, transplantation surgeries take place simultaneously so that no donor can withdraw her consent after her intended recipient receives the kidney from the other donor. Therefore, the timing of the exchange requires some form of an agreement between the pairs and determining proper edge weights that consider the timing aspect of the exchange requires a decision model with two self-interested patients. The optimization of the timing of a transplant for a single patient has been well studied in the literature as reviewed in Chapter 2, however the models existing in the literature do not apply to the timing of PKEs.

In Chapter 3, our contribution to the literature is two-fold. First, following current clinical practice, we assume simultaneous transplantation surgeries and develop a competitive decision model for the patients' transplant timing decisions in prearranged PKEs. Second, we analyze the resulting Nash equilibria in time-homogeneous strategies. While a complete characterization of such equilibria is computationally prohibitive, we consider the issue of

equilibrium selection from a central-decision maker's point of view and develop MIP models for a systematic computation of the socially optimal equilibria and welfare loss borne by patient autonomy.

Lipid abnormalities increase the risk of CHD and stroke in patients with Type 2 diabetes. Statins can be used to treat these abnormalities, but may have adverse side effects. Cardiovascular risk models serve as a guide to clinicians for selecting the type of intervention and the aggressiveness of treatment. However, their use in practice has focused on providing raw information about the risk of complications and there has been little direction on how to use this information to make treatment decisions that balance the trade-off between the benefits of statins in cardiovascular risk reduction with the side effects of treatment.

In Chapter 4, our contribution to the literature is two-fold. First, we address the trade-off between the benefits and side effects of statin treatment through a dynamic decision model. More precisely, we develop an MDP model to optimize the start time of a statin therapy as a function of time and the patient's LR level. The treatment policies that we provide offer individualized guidelines and may motivate the patients to adhere to prescribed treatment regimens. The implications of our model may enhance the results of various clinical trials and help physicians design more patient-focused cholesterol treatment guidelines through explicit consideration of disutility of using statins. Second, we derive sufficient conditions for the patient's optimal policy to exhibit a threshold structure, and characterize how such limits change with respect to patient's age. These conditions have two important characteristics. First, they provide analytical evidence to the structure of the treatment guidelines in practice. Second, they relax some of the strong assumptions of earlier studies that derive similar conditions to prove the existence of threshold-structured optimal policies in differing contexts. Note that much of the content in Chapter 4 originally appeared in Kurt et al. [111], and is reproduced with kind permission from the Institute of Industrial Engineers.

QALYs are commonly used for treatment evaluation and health policy investigations and in Chapters 3 and 4 we use QALYs to account for the reduction in quality of life associated with side effects from dialysis and statin treatment, respectively (For an extensive review on the use of QALYs see Gold et al. [83]).

One important feature of this dissertation is model parameterization based on clinical data. We calibrate our models using clinical data and perform extensive numerical experiments. We investigate the influence of the severity of ESRD on matching pairs with incompatible donors and the influence of the progression of a Type 2 diabetes patient's cholesterol levels on the initiation timing of statins. We also compare the welfare outcomes of our models to the practice. For PKEs, we illustrate the welfare loss due to maximizing the number of transplants rather than maximizing the total life expectancy. For Type 2 diabetes patients, we illustrate the welfare loss due to following the current ADA and ATP III guidelines rather than the policies suggested by our model.

2.0 LITERATURE REVIEW

In this chapter we review the literature related to the applications and methodologies discussed in this dissertation. Section 2.1 briefly reviews the literature on stochastic games. Section 2.2 reviews the recent applications at the crossroads of healthcare and game theory. Section 2.3 summarizes the focuses of several disciplines on PKEs. Section 2.4 summarizes the studies that approach Type 2 diabetes from an OR point of view.

2.1 STOCHASTIC GAMES

Stochastic games, also known as competitive MDPs, introduced by Shapley, represent dynamic repeated interactions between multiple players in multiple states under probabilistic transitions [188]. They fit into modeling of several economic situations and find a variety of applications in economics, biology, computer networks, admission and service control, and industrial organizations. They have also been studied by operations researchers in various contexts [191, 221]. For an extensive review of theory of stochastic games and their applications see Neyman and Sorin [142].

A stochastic game is a generalization of an MDP into multi-player domain where the play periodically moves among a set of states according to Markovian transition probabilities which are jointly controlled by the players. After each move each player gains a possibly state-specific reward which is again jointly determined by the players' action choices [65]. Stochastic games are also extension of matrix games to multiple states where each subgame in a state denotes a matrix game with the payoffs for each joint action. More precisely, similar to an MDP, a stochastic game consists of 6 sets of components: States, actions, rewards,

discount factors, transition probabilities and payoff functions, among which rewards and/or transition probabilities are coupled by the actions of the players.

Nash equilibrium is the most commonly used solution concept to analyze the outcomes of noncooperative games [69, 123, 165]. In a Nash equilibrium, each player's strategy is a best response to the others'. For instance, in a two-player game, Player 1's strategy is optimal when Player 2 keeps her strategy unchanged and Player 2's strategy is optimal when Player 1 keeps her strategy unchanged. Non-zero-sum stochastic games typically admit a large number of Nash equilibria in nonstationary strategies, which may be hard to implement in practice due to their time nonhomogeneous structure. On the other hand, stationary strategies prescribe state-contingent actions which are easier to analyze and implement as they reduce the number of parameters to be estimated and/or simulated.

Shapley [188] shows that every two-player zero-sum discounted stochastic game with finite state space has a Nash equilibirum in stationary strategies. Fink [66] and Takahashi [204] concurrently generalize this result to multiplayer games with countably many states. Rieder [166] extends Fink's result to the case of countably many players. Unfortunately, these equilibria are typically mixed, *i.e.*, has randomized strategies, where a player chooses a probability distribution over the actions. Although mixed strategies have limited acceptance in economics, pure strategy equilibria may not always exist and in such cases mixed equilibria are the only means of analyses.

While certain classes of stochastic games, such as zero-sum games and symmetric games, are easier to analyze, in general, stochastic games are extremely hard to solve [74]. Although they share similarities with single player MDPs, solution methods that are commonly employed for single player MDPs such as value iteration, policy iteration and linear programming often fail to produce an equilibrium for stochastic games. In general, equilibria of non-zero-sum discounted stochastic games with finite state/action spaces can be characterized by mathematical programs. The problem of computing an equilibrium of a finite discounted stochastic game is equivalent to finding the global optima of certain nonlinear programs with linear constraints [26, 63, 64]. The computation of the global optima of such mathematical programs requires the construction of algorithms that are free of convergence problems [25, 89, 90, 146]. However, for general non-zero-sum discounted stochastic games

there is no known way of selecting or computing a *best* equilibrium with respect to a given optimality criteria, short of enumeration. Therefore, algorithmically, characterizing an optimal equilibrium requires an elaborate modeling of equilibrium conditions that can be solved to optimality.

2.2 GAME-THEORETIC APPLICATIONS IN HEALTHCARE

Game-theoretic decision models have not been widely studied in healthcare, but have attracted some attention recently. In this section we review recent papers with competitive decision models that have found or may find applications in healthcare.

The competition between the firms on service delivery, pricing, and research and development in pharmaceutical markets have hosted several game-theoretic models. Abramson et al. [3] considers an industry with a number of firms competing in a fixed market and investigates the influence of the competitors' availability on their strategic decisions. The authors illustrate the application of the model through several experiments for a price setting game in healthcare. Lee et al. [113] examines the applicability of a dynamic competitive decision model to entry deterrence decisions in U.K. pathology services market. Arora and Ceccagnoli [18] studies the relationship between technology licensing and patent protection and presents competitive decision models for the research and development among pharmaceutical companies. In another study focusing on the competition between pharmaceutical firms in duopoly markets, Bala and Bhardwaj [20] considers the trade-off between targeting physicians and end customers, and develops game-theoretical models to help firms allocate their resources in advertising. Similarly, Ganuza et al. [73] addresses the competition between the innovations in pharmaceutical industry and develops a decision model to analyze the impact of various marketing efforts on research and development incentives. Zhang and Zenios [239] addresses information asymmetry by multiperiod principal-agent models that find numerous applications in healthcare contracts and resource allocation in drug discovery.

Problems in the context of influenza and vaccination have been approached by competitive decision models. Among these, Chick et al. [35] considers the incentives in the

coordination of influenza vaccine supply chain and formulates the hierarchical decision making process between the government and the vaccine manufacturers as a sequential game. In another closely related study, Deo and Corbett [54] proposes a two-stage oligopolistic decision model to optimize the vaccine manufacturer's entry decisions to the market and production levels under yield uncertainty. Lastly, Cho [36] studies the firms' product upgrade and production decisions so as to optimize the composition of the annual influenza vaccine in a sequential competitive setting.

Disaster planning is another area creating incentives to decision-makers with self- and collective-interests such as hospitals and countries in their preparedness tactics and have introduced several problems that can be modeled in a game-theoretic setting. Among these Adida et al. [5] considers the competition between the hospitals in their pre-disaster stockpiling decisions and develop a noncooperative strategic game to analyze the resulting policy outcomes. Sun et al. [202] considers the allocation of drug stockpiles at the onset of an international influenza pandemic and presents a game-theoretic model for the resulting problem among the countries. Similarly, Wang et al. [225] models the resource allocation decisions of self-interested countries in a competitive setting. The authors provide conditions under which competition has no effect on the number of infected people in a centralized setting.

Conflicting interests between different units of an organization in operations and purchasing processes of medical devices and service in healthcare industry have led to competitive decision models. Deo and Gurvich [55] develops a game-theoretic queueing model for the ambulance diversion of two emergency deparments and discusses the social efficiency and the stability of the equilibria they characterize through numerical experiments. Fuloria and Zenios [70] captures the conflicting objectives of the purchaser and the provider of a medical service through a dynamic principal agent model in a particular health-care delivery system and presents an illustrative application for the dialysis delivery system. Hu et al. [94] formulates two noncooperative games to answer several questions on the effects of group purchasing organizations on a single healthcare-product's supply chain.

Within the context of organ allocation, Su an Zenios [199, 200] balance the conflicting objectives of patients and the society. In these studies, the authors develop sophisticated queueing and sequential stochastic assignment models to reduce the inefficiency in kidney allocation created by organ refusals and examine the effects of patient choice on social welfare in various kidney allocation schemes.

2.3 KIDNEY EXCHANGES AND ORGAN TRANSPLANTATION

Mechanism design, a branch of game theory, seeks procedures that produce well-defined outcomes when agents autonomously reveal their preferences to the system with good incentive properties. PKEs have been on the focus of several studies mainly in the economics literature, but have been analyzed as a mechanism design problem [95, 96] to answer the question of how to match incompatible patient-donor pairs in an efficient and incentive compatible manner. Roth, Sönmez and Ünver [170] first formulates the PKE problem as a matching mechanism design problem. The underlying theory in this paper is an extension of the literature on housing markets [1, 187]. They make an analogy between the housing markets with indivisible goods and PKEs by introducing a new mechanism inspired by Gale's top trading cycles mechanism [71] and its generalization for the house allocation mechanism for student housing on college campuses. Their simulation study shows that proposed exchange mechanism can substantially increase the number of exchanges. Roth, Sönmez and Ünver [172] considers a restriction to two-way kidney exchanges by imposing 0-1 patient preferences over compatible donors. Under binary preferences, they design efficient mechanisms by analyzing the PKE problem as a maximum cardinality matching problem. They use Edmonds' matching algorithm [62] to find maximal exchanges, which were then integrated into the mechanisms they design. Roth, Sönmez and Ünver [171] also proposes the establishment of the first clearinghouse in the U.S. to implement matching mechanisms in practice. Roth, Sönmez and Ünver [173] finds that larger exchanges may be beneficial, but that when preferences are 0-1, almost all societal benefit is accrued by exchanges with no more than 4 patients. Recently, Sönmez and Ünver [195] introduces mechanisms which supersede the

earlier work with altruistic donors, and Ünver [217] formulates the PKE mechanism design problem with a dynamicly evolving patient pool. In an alternative approach, Zenios [235] addresses the dynamics of a PKE and the design of an optimal policy in a queuing framework in continuous time, but does not explicitly model the matching aspects of the problem. More recently, Abraham, Blum and Sandholm [2] develops computationally efficient and scalable online algorithms for large-scale cycle-length constrained maximum weight kidney exchange problem.

There have also been various efforts in the medical literature to weigh the relative merits and shortcomings of the current practice on PKEs. These studies not only evaluate different exchange regimes but also compare outcomes from clinical trials and simulation-based computational experiments to provide predictions on waiting times for transplantation and identify possible directions for further improvement [51, 76, 77, 132, 174, 175, 182]. Among these, in an effort to optimize the use of living donor organs in PKEs Saidman et al. [175] employs matching algorithms similar to those of Roth, Sönmez and Ünver [172], and corroborates the benefits of using such algorithms in a national kidney exchange program.

Although it is beyond the scope of this dissertation, various researchers have considered the effects of indirect kidney exchanges through simulation and queueing theory [169, 174, 236]. A common goal of these studies is to reduce the inequity borne by patients with O blood type. In the OR literature, Zenios [235] considers the optimal control of a dynamicly evolving indirect paired exchange program, but uses a stylized setting that ignores matching features of the patients. Recently, Ünver [217] considers a dynamic queueing model of exchange markets and derives optimal Markovian mechanisms to conduct kidney exchanges.

The OR literature on modeling organ allocation decisions can be classified in three main streams. Research from an individual patient's perspective focuses on how an individual patient should act within a given allocation scheme [7, 10, 11, 12, 45, 92, 93, 177, 178]. Research from the societal perspective seeks organ allocation schemes to maximize one or more societal objectives [46, 47, 167, 234, 235, 236, 237]. Lastly, the joint perspective recognizes the conflicting interests of the society and individual patients, and aims to maximize the societal welfare while providing an equity among the patients [199, 200, 201]. Among these, there are only few studies that capture the competition among the patients in organ

allocation, but there has not been any discussion of the timing of transplantation in kidney exchanges. For an extensive review of the literature on organ transplantation and allocation see Sandıkçı [176], which also provides a wide review of MDPs and their applications in healthcare.

2.4 OPERATIONS RESEARCH APPLICATIONS FOR TYPE 2 DIABETES

Although Type 2 diabetes is the sixth leading cause of death in the U.S. and a pressing health concern worldwide, it has not attracted enough focus from OR literature. Here, we provide a brief review of the few papers at the intersection of OR and Type 2 diabetes. Denton et al. [53] studies the optimal timing of statin initiation, but in contrast to patient-focused work in Chapter 4, they consider the problem from a societal perspective. Specifically, they use the monetary value of a life-year and develop a finite-horizon MDP model to minimize the total expected cost due to major cardiovascular complications of the disease and treatment. They compute the optimal treatment policies under the UKPDS, Framingham and Archimedes risk models, and discuss the influence of the risk model on the start time of the therapy. Mason et al. [126] extends the modeling framework of Denton et al. [53] to investigate the influence of suboptimal adherence to the therapy on the timing of initiation. They find that adherence can delay the optimal time to initiate statins significantly and predict the benefit of adherence-improving interventions. With a different focus than Mason et al. [126], Mason and Denton [125] develops an inverse-MDP model to estimate the monetary value of a life year for a Type 2 diabetes patient under the ATP III guidelines.

3.0 THE TIMING OF PREARRANGED PAIRED KIDNEY EXCHANGES FOR SELF-INTERESTED PATIENTS

Current literature on PKEs concentrates on maximizing the number of transplants assuming static patient health and ignores the transplant timing decisions. In this chapter, unlike the majority of the PKE literature, we consider the timing of an exchange for autonomous patients. We emphasize the timing by introducing dynamic patient health. Although our focus is on the timing rather than the matching itself, we develop a model that can be used to calculate life expectancy-based edge weights in kidney exchange pools. Specifically, we incorporate patient autonomy into the exchange process in a prearranged PKE and model the transplant timing decisions under probabilistic health transitions from self-interested patients' perspectives. We derive necessary and sufficient conditions for patients' decisions to be a stationary-perfect equilibrium of the resulting dynamic repeated game and enforce them as constraints in an MIP to compute a socially efficient stationary-perfect equilibrium. We calibrate our model using large scale clinical data to illustrate the clinical implications.

We outline the rest of this chapter as follows. In Section 3.1, we describe the model components in detail and define the patients' payoff functions. In Section 3.2, we present our equilibrium analyses and develop mathematical programming formulations for characterization and selection of equilibria. We illustrate socially efficient equilibria of the game and discuss several clinical implications in Section 3.3. We conclude the chapter in Section 3.4 by summarizing our contributions and the limitations of our model and numerical experiments.

3.1 MODEL FORMULATION

In this section, we assume the exchange surgeries between the pairs occur simultaneously and model the transplant timing decisions faced by patients in a prearranged PKE as a noncooperative stochastic game. Since patients do not share a fixed resource, the resulting game is non-zero-sum. In our model, periodically, each patient (or a physician acting on behalf of the patient) decides whether to offer to exchange or wait, as her health evolves stochastically, and an exchange occurs only if both patients offer to exchange. After making the decision, each patient receives a reward that depends on her current health status. If an exchange occurs, each patient receives a lump-sum terminal reward (e.g. quality-adjusted post-transplant survival) and terminates the process; otherwise, each patient accrues an intermediate reward and revisits the same decision subsequently. We assume the donors are not altruistic; that is, once a patient dies, her donor will not donate her kidney, rendering an exchange for the other patient infeasible. We also assume the kidney quality of each donor is static over time and patients do not receive organs from the waiting list. Therefore, if a patient dies prior to an exchange, the other patient will never receive a transplant.

We consider an infinite decision horizon with discrete, equidistant time periods (e.g. daily or weekly). We represent the set of patients in the exchange by $\mathcal{N} = \{1, 2\}$, and for each $i \in \mathcal{N}$, we let subscript $-i$ refer to $j \in \mathcal{N} \setminus \{i\}$. We denote the resulting game between the pairs by $\mathcal{G}$ and describe its components in detail as follows:

States: The state of the system is an ordered pair of the patients' individual health states, $\mathbf{s} = (s_1, s_2) \in \mathscr{S}$, where for each $i \in \mathcal{N}$, $s_i \in \Omega$ denotes the health state of Patient i, $\Omega = \{1, ..., S\}$ (with $S < \infty$) refers to the set of health states for each individual patient, and $\mathscr{S} = \Omega^2$ is the system's state space. For any patient $i \in \mathcal{N}$, $s_i = S$ refers to the (absorbing) death state and $\Phi = \Omega \setminus \{S\}$ represents the set of living states including being on dialysis. We denote the set of states in which at least one of the patients is dead by $\mathscr{D} = \mathscr{S} \setminus \Phi^2$.

Strategies: Stationary strategies restrict the patients' dynamic interactions by constraining each of them to choose her actions in a time-independent manner, and are more consistent with clinical practice. Therefore, we restrict our focus to stationary strategies only, but our equilibrium analyses also consider nonstationary deviations. In our model,

strategies or policies are defined in terms of patients' individual state-specific actions, and to allow randomization actions are their probabilities of offering to exchange. Specifically, when Patient i follows strategy $\mathbf{a}_i = \left[a_i(\mathbf{s})\right]_{\mathbf{s}\in\mathscr{S}}$, $a_i(\mathbf{s}) \in [0,1]$ refers to the probability that she offers to exchange in state $\mathbf{s} \in \mathscr{S}$ and $\mathbf{A} = (\mathbf{a}_1, \mathbf{a}_2)$ represents the resulting strategy profile.

Rewards: We have two types of rewards in our model: *Immediate rewards* and *post-transplant rewards*. We define $u_i(\mathbf{s}, 0)$ to be the *immediate reward* of Patient i (e.g quality-adjusted life days or weeks) accrued in state $\mathbf{s} \in \mathscr{S}$ given an exchange does not occur. We also define $u_i(\mathbf{s}, 1)$ as the *post-transplant reward* (e.g. expected quality-adjusted post-transplant survival) of Patient $i \in \mathcal{N}$ given an exchange occurs in $\mathbf{s} \in \mathscr{S}$. Note that for each patient $i \in \mathcal{N}$ and state $\mathbf{s} \in \mathscr{S}$, $u_i(\mathbf{s}, 1)$ is a one-time lump-sum reward, where for each $i \in \mathcal{N}$, $u_i(\mathbf{s}, 1) = 0$ for all $s \in \mathscr{D}$ as there is no possibility for an exchange in such states for the surviving patient, if there is any. Moreover, for each $\mathbf{s} \in \mathscr{D}$, $u_i(\mathbf{s}, 0) = 0$ for the dead patient(s).

Probabilities: The state of the game evolves stochastically until an exchange occurs, or at least one of the patients dies, whichever occurs sooner, where each patient's health evolves according to a discrete-time finite-state Markov chain independent of the other. Given that an exchange does not occur in state $\mathbf{s} \in \mathscr{S}$, the system moves to state $\mathbf{s}' \in \mathscr{S}$ at the next decision epoch with probability $\mathscr{P}(\mathbf{s}'|\mathbf{s})$. Since patients' health statuses evolve independently, state transitions of the system are described in terms of the product of their individual transitions; that is, for $\mathbf{s} = (s_1, s_2) \in \mathscr{S}$ and $\mathbf{s}' = (s_1', s_2') \in \mathscr{S}$, $\mathscr{P}(\mathbf{s}'|\mathbf{s}) = P_1(s_1'|s_1)P_2(s_2'|s_2)$, where $P_i(s_i'|s_i)$ denotes the probability that Patient i will be in health state $s_i' \in \Omega$ at epoch $t+1$ given she is in state $s_i \in \Omega$ at epoch t.

We assume that each patient $i \in \mathcal{N}$ discounts her future rewards by a factor $\lambda_i \in (0,1)$, but note that as long as the death state S is reachable from every other state $s \in \Omega$ for each patient, our analyses extend to the case $\lambda_i = 1$ for at least one of the patients.

Throughout this chapter, we let the terms in bold refer to a vector of $|\Omega| \times |\Omega|$ matrix, *i.e.*, $\mathbf{v}$ refers to value matrix $\left[v(\mathbf{s})\right]_{\mathbf{s}\in\mathscr{S}}$. We also represent componentwise relations between two matrices in matrix notation. For instance, given $\mathbf{v}_1$ and $\mathbf{v}_2$, $\mathbf{v}_1 = \mathbf{v}_2$ refers to $v_1(\mathbf{s}) = v_2(\mathbf{s})$ for all $\mathbf{s} \in \mathscr{S}$. Also, for convenience, we let $\mathbf{v}_1\mathbf{v}_2$ represent the sum of the componentwise

products of the matrices $\mathbf{v}_1$ and $\mathbf{v}_2$; that is, $\mathbf{v}_1\mathbf{v}_2 = \sum_{\mathbf{s}'\in\mathscr{S}} v_1(\mathbf{s}')v_2(\mathbf{s}')$. Finally, we define $\mathbf{0}$ and $\mathbf{1}$ as $|\Omega| \times |\Omega|$ matrices of 0's and 1's respectively.

For convenience, for each patient $i \in \mathcal{N}$, given a real-valued matrix $\mathbf{v}$ and state $\mathbf{s} \in \mathscr{S}$, we let $F_i(\mathbf{s}, \mathbf{v}) = u_i(\mathbf{s}, 0) + \lambda_i \sum_{\mathbf{s}'\in\mathscr{S}} \mathscr{P}(\mathbf{s}'|\mathbf{s})v(\mathbf{s}')$. We interpret $F_i(\mathbf{s}, \mathbf{v})$ as the total expected discounted reward or expected payoff-to-go of Patient i given an exchange does not occur starting in state $\mathbf{s} \in \mathscr{S}$ and the underlying strategy profile induces $\mathbf{v}$ as her expected rewards.

We assume that game $\mathcal{G}$ is of perfect recall so that each patient has a perfect memory of her previous actions and those of the other patient. We also assume that each patient has a complete knowledge of the rewards, discount factor and transition probabilities of the other patient and is assumed to behave rationally only for her self-interests during the course of the game. More explicitly, each patient seeks to maximize her own expected payoffs.

For each patient, the total expected payoff is a function of the current state of the game, her own strategy and the strategy of the other patient. We define $g_i(\mathbf{s}, \mathbf{a}_1, \mathbf{a}_2)$ as the *total expected discounted payoff* (e.g. total discounted quality-adjusted life expectancy) for Patient $i \in \mathcal{N}$ starting in state $\mathbf{s} \in \mathscr{S}$ under strategy profile $\mathbf{A} = (\mathbf{a}_1, \mathbf{a}_2)$. Recall that patients decide simultaneously and independent from each other, and an exchange occurs only if both patients offer to exchange. Therefore, the expected payoffs can be defined as a convex combination of the post-transplant rewards and the expected payoff-to-go terms where the weights are the exchange occurrence probabilities. Then, under a strategy profile $\mathbf{A} = (\mathbf{a}_1, \mathbf{a}_2)$, because an exchange occurs in state $\mathbf{s} \in \mathscr{S}$ with probability $a_1(\mathbf{s})a_2(\mathbf{s})$ and $F_i\big(\mathbf{s}, \mathbf{g}_i(\mathbf{a}_1, \mathbf{a}_2)\big)$ represents Patient i's expected payoff-to-go starting from state $\mathbf{s} \in \mathscr{S}$ when exchange does not occur, the payoffs of the game are recursively defined as follows:

$$g_i(\mathbf{s}, \mathbf{a}_1, \mathbf{a}_2) = a_1(\mathbf{s})a_2(\mathbf{s})u_i(\mathbf{s}, 1) + \big[1 - a_1(\mathbf{s})a_2(\mathbf{s})\big]F_i\big(\mathbf{s}, \mathbf{g}_i(\mathbf{a}_1, \mathbf{a}_2)\big) \quad \text{for } \mathbf{s} \in \mathscr{S},\ i \in \mathcal{N}. \quad (3.1)$$

Because $\lambda_i < 1$ for both $i \in \mathcal{N}$, for every strategy profile $\mathbf{A}$, recursion (3.1) represents a stationary, infinite-horizon Markov reward chain, and since $|\mathscr{S}| < \infty$ and rewards are nonnegative and finite, each strategy profile $\mathbf{A}$ yields a unique, nonnegative and finite payoff profile [161]. Moreover, while strategies $\mathbf{a}_1$ and $\mathbf{a}_2$ are fixed, value iteration algorithm can be applied to recursion (3.1) to successively compute $\mathbf{g}_i(\mathbf{a}_1, \mathbf{a}_2)$ with a certain precision level.

For each patient $i \in \mathcal{N}$, if we let $\mathbf{g}_i^n(\mathbf{a}_1, \mathbf{a}_2)$ be the value matrix at iteration $n \geq 0$, the value iteration algorithm for (3.1) can be described as follows:

$$g_i^{n+1}(\mathbf{s}, \mathbf{a}_1, \mathbf{a}_2) = a_1(\mathbf{s})a_2(\mathbf{s})u_i(\mathbf{s}, 1) + \big[1 - a_1(\mathbf{s})a_2(\mathbf{s})\big] F_i\big(\mathbf{s}, \mathbf{g}_i^n(\mathbf{a}_1, \mathbf{a}_2)\big) \quad \text{for } \mathbf{s} \in \mathscr{S},\ i \in \mathcal{N}. \tag{3.2}$$

For any Patient i, whenever the initial value matrix is $\mathbf{g}_i^0(\mathbf{a}_1, \mathbf{a}_2)$ is finite, the value iterates $\mathbf{g}_i^n(\mathbf{a}_1, \mathbf{a}_2)$ defined by (3.2) converge to $\mathbf{g}_i(\mathbf{a}_1, \mathbf{a}_2)$; that is $\lim_{n\to\infty} \mathbf{g}_i^n(\mathbf{a}_1, \mathbf{a}_2) = \mathbf{g}_i(\mathbf{a}_1, \mathbf{a}_2)$ [161].

3.2 EQUILIBRIUM ANALYSES

In this section, we present our analytical results for the equilibria of game $\mathcal{G}$. In our context, in a Nash equilibrium, each patient is assumed to have perfect knowledge of the equilibrium strategy of the other patient and no patient may increase life expectancy by just changing her own strategy unilaterally. Because the game between the patients may occupy different states dynamically, we consider the strategies that are Nash equilibria in all possible states of the game, which are also called *sub-game perfect equilibria* in economics literature. Moreover, because our focus is on stationary strategies we characterize such equilibria only in stationary strategies.

Definition 3.1. *A strategy profile* $\mathbf{A}$ *is a stationary equilibrium of game* $\mathcal{G}$ *if:*

$$\mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2) \geq \mathbf{g}_1(\mathbf{a}_1', \mathbf{a}_2) \ \textit{ for all } \mathbf{a}_1' \ \textit{ and } \ \mathbf{g}_2(\mathbf{a}_1, \mathbf{a}_2) \geq \mathbf{g}_2(\mathbf{a}_1, \mathbf{a}_2') \ \textit{ for all } \mathbf{a}_2'. \tag{3.3}$$

A strategy profile satisfying (3.3) is a Nash equilibrium of game $\mathcal{G}$ independent from the initial state of the game, *i.e.*, neither of the patients can be better off in any state $\mathbf{s} \in \mathscr{S}$ by only changing her strategy unilaterally. Therefore, strategy profiles satisfying (3.3) are also known as *stationary-perfect equilibria* in the economics literature [124].

It is well known that every discounted stochastic game with finite-state action pairs admits a stationary equilibrium, that is, for every discounted stochastic game with finite state/action pairs there exists a stationary best response to a stationary strategy [66, 193].

Note that this does not mean that nonstationary deviations from a stationary strategy profile are not allowed, but such deviations can be ignored [90]. In the remainder of this chapter, unless otherwise stated, we let the terms "strategy" and "equilibrium" refer to "stationary strategy" and "stationary or equivalently stationary-perfect equilibrium," respectively.

In this section, we identify necessary and sufficient conditions for a strategy profile to be an equilibrium of game $\mathcal{G}$ and refine them to characterize a pure equilibrium. Because a complete characterization of the equilibria of game $\mathcal{G}$ is computationally intractable, we also consider the issue of equilibrium selection. To compute a socially optimal equilibrium, we formulate an MIP representation of the equilibrium conditions which we further constrain to optimize over the set of pure equilibria.

In game $\mathcal{G}$, a single patient can not affect the exchange outcome in state $\mathbf{s} \in \mathscr{S}$ as long as the other patient chooses to wait in that particular state. Intuitively, for Patient i, when the strategy of Patient $-i$ is fixed, actions $\{a_{-i}(\mathbf{s})\}$ can be treated as parameters of the recursion (3.1) and the problem of maximizing expected payoffs reduces to the following optimization problem:

$$\vartheta_{i,\mathbf{a}_{-i}}(\mathbf{s}) = \max_{a_i(\mathbf{s})\in[0,1]} \left\{a_1(\mathbf{s})a_2(\mathbf{s})u_i(\mathbf{s},1) + \left[1 - a_1(\mathbf{s})a_2(\mathbf{s})\right]F_i(\mathbf{s}, \boldsymbol{\vartheta}_{i,\mathbf{a}_{-i}})\right\} \quad \text{for } \mathbf{s} \in \mathscr{S}. \tag{3.4}$$

In (3.4), $\vartheta_{i,\mathbf{a}_{-i}}(\mathbf{s})$ represents the maximum total expected payoff for Patient i in state $\mathbf{s} \in \mathscr{S}$ when Patient $-i$ follows strategy $\mathbf{a}_{-i}$. Since $\mathbf{a}_{-i}$ is fixed in (3.4) and $\mathbf{0} \leq \mathbf{a}_i \leq \mathbf{1}$, recursion (3.4) represents Bellman's optimality equations for an infinite-horizon MDP with stationary rewards and transition probabilities, where actions can be randomized between 0 and 1 in each state $\mathbf{s} \in \mathscr{S}$. Since every infinite-horizon MDP with stationary rewards and transition probabilities has a unique optimal solution and an optimal policy in deterministic strategies [161], $\boldsymbol{\vartheta}_{i,\mathbf{a}_{-i}}$ satisfies the following recursion:

$$\vartheta_{i,\mathbf{a}_{-i}}(\mathbf{s}) = \max\left\{a_{-i}(\mathbf{s})u_i(\mathbf{s},1) + \left[1 - a_{-i}(\mathbf{s})\right]F_i(\mathbf{s}, \boldsymbol{\vartheta}_{i,\mathbf{a}_{-i}}), F_i(\mathbf{s}, \boldsymbol{\vartheta}_{i,\mathbf{a}_{-i}})\right\} \quad \text{for } \mathbf{s} \in \mathscr{S}.$$

Thus, Patient i's response to strategy $\mathbf{a}_{-i}$ is best only if it yields $\boldsymbol{\vartheta}_{i,\mathbf{a}_{-i}}$. Since an equilibrium is the collection of strategies which are best response to each other, Theorem 3.1 provides necessary and sufficient conditions for a strategy profile to be an equilibrium of game $\mathcal{G}$.

Theorem 3.1. *A strategy profile* $\mathbf{A}$ *is an equilibrium of game* $\mathcal{G}$ *if and only if for all* $\mathbf{s} \in \mathscr{S}$ *and* $i \in \mathcal{N}$*:*

$$g_i(\mathbf{s}, \mathbf{a}_1, \mathbf{a}_2) = \max\Big\{a_{-i}(\mathbf{s})u_i(\mathbf{s}, 1) + \big[1 - a_{-i}(\mathbf{s})\big]F_i\big(\mathbf{s}, \mathbf{g}_i(\mathbf{a}_1, \mathbf{a}_2)\big), F_i\big(\mathbf{s}, \mathbf{g}_i(\mathbf{a}_1, \mathbf{a}_2)\big)\Big\}. \quad (3.5)$$

Proof. ($\Leftarrow$) Suppose (3.5) holds for all $\mathbf{s} \in \mathscr{S}$ and $i \in \mathcal{N}$ under the strategy profile $\mathbf{A}$. Fix $i = 1$. Let $\mathbf{a}_1^*$ be a best response to $\mathbf{a}_2$. As $\mathbf{a}_1^*$ and $\mathbf{a}_2$ are fixed, suppose we apply value iteration defined by (3.2) to $\mathbf{g}_1(\mathbf{a}_1^*, \mathbf{a}_2)$. By induction on $n \geq 0$, we will show that $\mathbf{g}_1^n(\mathbf{a}_1^*, \mathbf{a}_2) \leq \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)$ for all $n \geq 0$. Let $\mathbf{g}_1^0(\mathbf{a}_1^*, \mathbf{a}_2) = \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)$, and for some $m \geq 0$, suppose $\mathbf{g}_1^m(\mathbf{a}_1^*, \mathbf{a}_2) \leq \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)$, so that $F_1\big(\mathbf{s}, \mathbf{g}_1^m(\mathbf{a}_1^*, \mathbf{a}_2)\big) \leq F_1\big(\mathbf{s}, \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)\big)$ for all $\mathbf{s} \in \mathscr{S}$. Now, choose an arbitrary $\mathbf{s} \in \mathscr{S}$ and consider the following possible cases for $g_1^{m+1}(\mathbf{s}, \mathbf{a}_1^*, \mathbf{a}_2)$:

1. If $u_1(\mathbf{s}, 1) \leq F_1\big(\mathbf{s}, \mathbf{g}_1^m(\mathbf{a}_1^*, \mathbf{a}_2)\big)$, then

$$\begin{aligned} g_1^{m+1}(\mathbf{s}, \mathbf{a}_1^*, \mathbf{a}_2) &= a_1^*(\mathbf{s})a_2(\mathbf{s})u_1(\mathbf{s}, 1) + \big[1 - a_1^*(\mathbf{s})a_2(\mathbf{s})\big]F_1\big(\mathbf{s}, \mathbf{g}_1^m(\mathbf{a}_1^*, \mathbf{a}_2)\big) \\ &\leq F_1\big(\mathbf{s}, \mathbf{g}_1^m(\mathbf{a}_1^*, \mathbf{a}_2)\big) \leq F_1\big(\mathbf{s}, \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)\big) \leq g_1(\mathbf{s}, \mathbf{a}_1, \mathbf{a}_2), \end{aligned}$$

   where the last inequality is implied by the assumption that (3.5) holds for all $\mathbf{s} \in \mathscr{S}$ and $i \in \mathcal{N}$ under $\mathbf{A}$.

2. If $u_1(\mathbf{s}, 1) > F_1\big(\mathbf{s}, \mathbf{g}_1^m(\mathbf{a}_1^*, \mathbf{a}_2)\big)$, then

$$\begin{aligned} g_1^{m+1}(\mathbf{s},\mathbf{a}_1^*, \mathbf{a}_2) &= a_1^*(\mathbf{s})a_2(\mathbf{s})u_1(\mathbf{s}, 1) + \big[1 - a_1^*(\mathbf{s})a_2(\mathbf{s})\big]F_1\big(\mathbf{s}, \mathbf{g}_1^m(\mathbf{a}_1^*, \mathbf{a}_2)\big) \\ &\leq a_1^*(\mathbf{s})a_2(\mathbf{s})u_1(\mathbf{s}, 1) + \big[1 - a_1^*(\mathbf{s})a_2(\mathbf{s})\big]F_1\big(\mathbf{s}, \mathbf{g}_1^m(\mathbf{a}_1^*, \mathbf{a}_2)\big) \\ &\qquad + a_2(\mathbf{s})\big[1 - a_1^*(\mathbf{s})\big]\big[u_1(\mathbf{s}, 1) - F_1\big(\mathbf{s}, \mathbf{g}_1^m(\mathbf{a}_1^*, \mathbf{a}_2)\big)\big] \quad (3.6a) \\ &= a_2(\mathbf{s})u_1(\mathbf{s}, 1) + \big[1 - a_2(\mathbf{s})\big]F_1\big(\mathbf{s}, \mathbf{g}_1^m(\mathbf{a}_1^*, \mathbf{a}_2)\big) \\ &\leq a_2(\mathbf{s})u_1(\mathbf{s}, 1) + \big[1 - a_2(\mathbf{s})\big]F_1\big(\mathbf{s}, \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)\big) \leq g_1(\mathbf{s}, \mathbf{a}_1, \mathbf{a}_2), \quad (3.6b) \end{aligned}$$

   where (3.6a) is implied by $u_1(\mathbf{s}, 1) > F_1\big(\mathbf{s}, \mathbf{g}_1^m(\mathbf{a}_1^*, \mathbf{a}_2)\big)$ and $a_1^*(\mathbf{s}), a_2(\mathbf{s}) \in [0, 1]$, and the inequality in (3.6b) follows from the assumption that (3.5) holds for all $\mathbf{s} \in \mathscr{S}$ and $i \in \mathcal{N}$ under $\mathbf{A}$.

Thus, $\mathbf{g}_1^{m+1}(\mathbf{a}_1^*, \mathbf{a}_2) \leq \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)$. Then, by induction, the convergence of value iteration implies $\mathbf{g}_1(\mathbf{a}_1^*, \mathbf{a}_2) \leq \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)$. Since $\mathbf{a}_1^*$ is a best response to $\mathbf{a}_2$, $\mathbf{a}_1$ must be a best-response to $\mathbf{a}_2$.

($\Rightarrow$) The proof is similar to that of ($\Leftarrow$), and omitted. □

While Nash equilibria eliminates all possible gains by patients' unilateral deviations and a single patient can not change the transplant outcome if the other patient chooses to offer with probability 0, game $\mathcal{G}$ may admit a large number of pathological equilibria that make little or no clinical sense. For instance, when both patients offer to exchange with probability 0 in state $\mathbf{s} \in \mathscr{S}$, no unilateral deviation can change the nonoccurrence of the exchange in that particular state. Therefore, the strategy profile under which both patients offer to exchange with probability 0 in every state $\mathbf{s} \in \mathscr{S}$, *i.e.*, $(\mathbf{a}_1, \mathbf{a}_2) = (\mathbf{0}, \mathbf{0})$, denotes an equilibrium of game $\mathcal{G}$. Since $(\mathbf{a}_1, \mathbf{a}_2) = (\mathbf{0}, \mathbf{0})$ is a pure strategy profile, we also provide a formal proof of this fact to establish the existence of a pure equilibrium for game $\mathcal{G}$ by Corollary 3.1.

Corollary 3.1. *A pure equilibrium always exists for game $\mathcal{G}$.*

Proof. Let $\mathbf{A} = (\mathbf{a}_1, \mathbf{a}_2) = (\mathbf{0}, \mathbf{0})$ so that (3.1) defines the payoffs as follows;

$$g_i(\mathbf{s}, \mathbf{a}_1, \mathbf{a}_2) = F_i\big(\mathbf{s}, \mathbf{g}_i(\mathbf{a}_1, \mathbf{a}_2)\big) \text{ for all } \mathbf{s} \in \mathscr{S} \text{ and } i \in \mathcal{N}. \tag{3.7}$$

Since $\mathbf{a}_i = \mathbf{0}$ for both $i \in \mathcal{N}$,

$$F_i\big(\mathbf{s}, \mathbf{g}_i(\mathbf{a}_1, \mathbf{a}_2)\big) = a_{-i}(\mathbf{s}) u_i(\mathbf{s}, 1) + \big[1 - a_{-i}(\mathbf{s})\big] F_i\big(\mathbf{s}, \mathbf{g}_i(\mathbf{a}_1, \mathbf{a}_2)\big) \quad \text{for all } \mathbf{s} \in \mathscr{S} \text{ and } i \in \mathcal{N}. \tag{3.8}$$

By (3.7) and (3.8), (3.5) holds for all $\mathbf{s} \in \mathscr{S}$ and $i \in \mathcal{N}$. Therefore, by Theorem 3.1, $\mathbf{A}$ is an equilibrium of game $\mathcal{G}$. □

In our context, the initial state of the game, which we denote by $\widetilde{\mathbf{s}}$, may represent the patients' individual health information when they are matched to each other and different equilibria may yield different payoff outcomes across the state space depending on the initial state of the game. Because the number of strategies increase exponentially as a function of the number of states, game $\mathcal{G}$ can admit a vast number of equilibria a complete

characterization of which can be computationally prohibitive even for practical sizes of the problem. Therefore, we consider the equilibrium selection problem and motivate the following question: *Given the game starts in state* $\widetilde{\mathbf{s}} \in \mathscr{S}$*, which equilibrium maximizes the social welfare, i.e., the sum of the patients' total expected payoffs?* Specifically, we let Γ denote the set of equilibria of game $\mathcal{G}$, and seek an equilibrium of game $\mathcal{G}$ that represents an optimal solution to the following *welfare maximizing equilibrium selection problem* (WMESP): $\max_{\mathbf{A}\in\Gamma} \left[\sum_{i\in\mathcal{N}} g_i(\widetilde{\mathbf{s}}, \mathbf{a}_1, \mathbf{a}_2)\right]$. In the remainder of this chapter, we will refer to a social welfare maximizing equilibrium a "socially optimal equilibrium." Given society's wish is to maximize the sum of the patients' expected payoffs, an optimal solution to WMESP also represents an equilibrium with minimum welfare loss borne by patient autonomy among all equilibria of game $\mathcal{G}$.

Next, we will derive two key structural properties of the equilibria of game $\mathcal{G}$ to gain deeper insights into the selection of a socially optimal equilibrium. Lemma 3.1 (i) states that in an equilibrium of game $\mathcal{G}$, an exchange can not occur in a particular state $\mathbf{s} \in \mathscr{S}$ as long as there is a patient who is better off waiting in that state. Therefore, by Lemma 3.1 (ii), in an equilibrium, a patient strictly randomizes between waiting and offering to exchange in state $\mathbf{s} \in \mathscr{S}$ only when she is indifferent between her post-transplant reward and expected payoff-to-go and the other patient offers to exchange with some positive probability in that particular state.

Lemma 3.1. *Suppose* $\mathbf{A} \in \Gamma$*. Then the following hold.*
(i) *For any* $\mathbf{s} \in \mathscr{S}$*, if* $\max_{i\in\mathcal{N}} \left[g_i(\mathbf{s}, \mathbf{a}_1, \mathbf{a}_2) - u_i(\mathbf{s}, 1)\right] > 0$ *then* $a_1(\mathbf{s})a_2(\mathbf{s}) = 0$.
(ii) *For any* $\mathbf{s} \in \mathscr{S}$ *and* $i \in \mathcal{N}$*, if* $a_1(\mathbf{s})a_2(\mathbf{s}) \in (0,1)$ *and* $a_i(\mathbf{s}) \in (0,1)$*, then*

$$g_i(\mathbf{s}, \mathbf{a}_1, \mathbf{a}_2) = u_i(\mathbf{s}, 1) = F_i\big(\mathbf{s}, \mathbf{g}_i(\mathbf{a}_1, \mathbf{a}_2)\big).$$

Proof. (i): For Patient 1, suppose $g_1(\widehat{\mathbf{s}}, \mathbf{a}_1, \mathbf{a}_2) > u_1(\widehat{\mathbf{s}}, 1)$ for some $\widehat{\mathbf{s}} \in \mathscr{S}$. Then, since $a_1(\widehat{\mathbf{s}})a_2(\widehat{\mathbf{s}}) \in [0,1]$, by (3.1), $g_1(\widehat{\mathbf{s}}, \mathbf{a}_1, \mathbf{a}_2) \leq \max\left\{u_1(\widehat{\mathbf{s}}, 1), F_1\big(\widehat{\mathbf{s}}, \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)\big)\right\}$. Then, since $g_1(\widehat{\mathbf{s}}, \mathbf{a}_1, \mathbf{a}_2) > u_1(\widehat{\mathbf{s}}, 1)$, we must have $F_1\big(\widehat{\mathbf{s}}, \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)\big) > u_1(\widehat{\mathbf{s}}, 1)$. Because $\mathbf{A} \in \Gamma$, by Theorem 3.1, (3.5) is satisfied for $(\mathbf{s}, i) = (\widehat{\mathbf{s}}, j)$. These imply $g_1(\widehat{\mathbf{s}}, \mathbf{a}_1, \mathbf{a}_2) = F_1\big(\widehat{\mathbf{s}}, \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)\big) > u_1(\widehat{\mathbf{s}}, 1)$. Therefore, by (3.1), we must have $a_1(\widehat{\mathbf{s}})a_2(\widehat{\mathbf{s}}) = 0$.

(ii) First, we will show that for any $\mathbf{s} \in \mathscr{S}$ and $i \in \mathcal{N}$:

$$\text{If } u_i(\mathbf{s},1) > F_i\big(\mathbf{s}, \mathbf{g}_i(\mathbf{a}_1,\mathbf{a}_2)\big) \text{ and } a_{-i}(\mathbf{s}) > 0, \text{ then } a_i(\mathbf{s}) = 1. \tag{3.9}$$

Consider Patient 1. For some $\widehat{\mathbf{s}} \in \mathscr{S}$ with $u_1(\widehat{\mathbf{s}},1) > F_1\big(\widehat{\mathbf{s}}, \mathbf{g}_1(\mathbf{a}_1,\mathbf{a}_2)\big)$ and $a_2(\widehat{\mathbf{s}}) > 0$ suppose that $a_1(\widehat{\mathbf{s}}) < 1$. While $\mathbf{a}_2$ is fixed, suppose Patient 1 follows strategy $\mathbf{a}_1'$, where $a_1'(\widehat{\mathbf{s}}) = 1$ and $a_1'(\mathbf{s}) = a_1(\mathbf{s})$ for $\mathbf{s} \in \mathscr{S} \setminus \{\widehat{\mathbf{s}}\}$. As strategies $\mathbf{a}_1'$ and $\mathbf{a}_2$ are fixed, suppose we apply value iteration defined by (3.2) to $\mathbf{g}_1(\mathbf{a}_1',\mathbf{a}_2)$. By induction on $n \geq 0$, we will show that the following hold for all $n \geq 0$.

$$\mathbf{g}_1^n(\mathbf{a}_1',\mathbf{a}_2) \geq \mathbf{g}_1(\mathbf{a}_1,\mathbf{a}_2) \;\text{ and }\; g_1^n(\widehat{\mathbf{s}},\mathbf{a}_1',\mathbf{a}_2) > g_1(\widehat{\mathbf{s}},\mathbf{a}_1,\mathbf{a}_2). \tag{3.10}$$

For some finite $\epsilon > 0$, let $g_1^0(\mathbf{s},\mathbf{a}_1',\mathbf{a}_2) = g_1(\mathbf{s},\mathbf{a}_1,\mathbf{a}_2) + \epsilon$ for all $\mathbf{s} \in \mathscr{S}$, and suppose (3.10) holds for some $n = m \geq 0$, so that $F_1\big(\mathbf{s}, \mathbf{g}_1^m(\mathbf{a}_1',\mathbf{a}_2)\big) \geq F_1\big(\mathbf{s}, \mathbf{g}_1(\mathbf{a}_1,\mathbf{a}_2)\big)$ for all $\mathbf{s} \in \mathscr{S}$. Then, in an arbitrary state $\mathbf{s} \in \mathscr{S}$ consider the following possible cases for $g_1^{m+1}(\mathbf{s},\mathbf{a}_1',\mathbf{a}_2)$.

1. If $\mathbf{s} \neq \widehat{\mathbf{s}}$, then

$$\begin{aligned} g_1^{m+1}(\mathbf{s},\mathbf{a}_1',\mathbf{a}_2) &= a_1'(\mathbf{s})a_2(\mathbf{s})u_1(\mathbf{s},1) + \big[1 - a_1'(\mathbf{s})a_2(\mathbf{s})\big]F_1\big(\mathbf{s}, \mathbf{g}_1^m(\mathbf{a}_1',\mathbf{a}_2)\big) \\ &\geq a_1'(\mathbf{s})a_2(\mathbf{s})u_1(\mathbf{s},1) + \big[1 - a_1'(\mathbf{s})a_2(\mathbf{s})\big]F_1\big(\mathbf{s}, \mathbf{g}_1(\mathbf{a}_1,\mathbf{a}_2)\big) \\ &= a_1(\mathbf{s})a_2(\mathbf{s})u_1(\mathbf{s},1) + \big[1 - a_1(\mathbf{s})a_2(\mathbf{s})\big]F_1\big(\mathbf{s}, \mathbf{g}_1(\mathbf{a}_1,\mathbf{a}_2)\big) = g_1(\mathbf{s},\mathbf{a}_1,\mathbf{a}_2), \end{aligned}$$

   where the inequality follows from the fact that $F_1\big(\mathbf{s}, \mathbf{g}_1^m(\mathbf{a}_1',\mathbf{a}_2)\big) \geq F_1\big(\mathbf{s}, \mathbf{g}_1(\mathbf{a}_1,\mathbf{a}_2)\big)$ and the equality after that is because $a_1'(\mathbf{s}) = a_1(\mathbf{s})$.

2. If $\mathbf{s} = \widehat{\mathbf{s}}$, then

$$\begin{aligned} g_1^{m+1}(\widehat{\mathbf{s}},\mathbf{a}_1',\mathbf{a}_2) &= a_2(\widehat{\mathbf{s}})u_1(\widehat{\mathbf{s}},1) + \big[1 - a_2(\widehat{\mathbf{s}})\big]F_1\big(\widehat{\mathbf{s}}, \mathbf{g}_1^m(\mathbf{a}_1',\mathbf{a}_2)\big) \\ &\geq a_2(\widehat{\mathbf{s}})u_1(\widehat{\mathbf{s}},1) + \big[1 - a_2(\widehat{\mathbf{s}})\big]F_1\big(\widehat{\mathbf{s}}, \mathbf{g}_1(\mathbf{a}_1,\mathbf{a}_2)\big) \\ &= a_1(\widehat{\mathbf{s}})a_2(\widehat{\mathbf{s}})u_1(\widehat{\mathbf{s}},1) + \big[1 - a_1(\widehat{\mathbf{s}})\big]a_2(\widehat{\mathbf{s}})u_1(\widehat{\mathbf{s}},1) + \big[1 - a_2(\widehat{\mathbf{s}})\big]F_1\big(\widehat{\mathbf{s}}, \mathbf{g}_1(\mathbf{a}_1,\mathbf{a}_2)\big). \end{aligned} \tag{3.11}$$

   Since $u_1(\widehat{\mathbf{s}},1) > F_1\big(\widehat{\mathbf{s}}, \mathbf{g}_1(\mathbf{a}_1,\mathbf{a}_2)\big)$, $a_1(\widehat{\mathbf{s}}) < 1$ and $a_2(\widehat{\mathbf{s}}) > 0$, we have

$$\big[1 - a_1(\widehat{\mathbf{s}})\big]a_2(\widehat{\mathbf{s}})u_1(\widehat{\mathbf{s}},1) > \big[1 - a_1(\widehat{\mathbf{s}})\big]a_2(\widehat{\mathbf{s}})F_1\big(\widehat{\mathbf{s}}, \mathbf{g}_1(\mathbf{a}_1,\mathbf{a}_2)\big).$$

By (3.11) this implies:

$$g_1^{m+1}(\widehat{\mathbf{s}}, \mathbf{a}_1', \mathbf{a}_2) > a_1(\widehat{\mathbf{s}})a_2(\widehat{\mathbf{s}})u_1(\widehat{\mathbf{s}}, 1) + \Big(\big[1 - a_1(\widehat{\mathbf{s}})\big]a_2(\widehat{\mathbf{s}}) + \big[1 - a_2(\widehat{\mathbf{s}})\big]\Big)F_1\big(\widehat{\mathbf{s}}, \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)\big)$$
$$= a_1(\widehat{\mathbf{s}})a_2(\widehat{\mathbf{s}})u_1(\widehat{\mathbf{s}}, 1) + \big[1 - a_1(\widehat{\mathbf{s}})a_2(\widehat{\mathbf{s}})\big]F_1\big(\widehat{\mathbf{s}}, \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)\big) = g_1(\widehat{\mathbf{s}}, \mathbf{a}_1, \mathbf{a}_2).$$

Thus, (3.10) holds for $n = m + 1$. Then, by induction, the convergence of value iteration implies $\mathbf{g}_1(\mathbf{a}_1', \mathbf{a}_2) \geq \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)$ and $g_1(\widehat{\mathbf{s}}, \mathbf{a}_1', \mathbf{a}_2) > g_1(\widehat{\mathbf{s}}, \mathbf{a}_1, \mathbf{a}_2)$, which contradicts the assumption that $\mathbf{A} \in \Gamma$. Therefore, $a_1(\widehat{\mathbf{s}}) = 1$ and (3.9) holds in state $\widehat{\mathbf{s}}$ for Patient 1.

Next, for some $\widehat{\mathbf{s}} \in \mathscr{S}$, suppose $a_1(\widehat{\mathbf{s}})a_2(\widehat{\mathbf{s}}) \in (0, 1)$ implying the existence of a Patient j, where $a_j(\widehat{\mathbf{s}}) \in (0, 1)$. Since $a_1(\widehat{\mathbf{s}})a_2(\widehat{\mathbf{s}}) > 0$, by part (i),

$$g_j(\widehat{\mathbf{s}}, \mathbf{a}_1, \mathbf{a}_2) \leq u_j(\widehat{\mathbf{s}}, 1). \tag{3.12}$$

Also, since $a_{-j}(\widehat{\mathbf{s}}) > 0$, $a_j(\widehat{\mathbf{s}}) < 1$, by (3.9) we must have

$$u_j(\widehat{\mathbf{s}}, 1) \leq F_j\big(\widehat{\mathbf{s}}, \mathbf{g}_j(\mathbf{a}_1, \mathbf{a}_2)\big). \tag{3.13}$$

Since $\mathbf{A} \in \Gamma$, by Theorem 3.1,

$$g_j(\widehat{\mathbf{s}}, \mathbf{a}_1, \mathbf{a}_2) \geq F_j\big(\widehat{\mathbf{s}}, \mathbf{g}_j(\mathbf{a}_1, \mathbf{a}_2)\big). \tag{3.14}$$

By (3.12)-(3.14), we must have $g_j(\widehat{\mathbf{s}}, \mathbf{a}_1, \mathbf{a}_2) = F_j\big(\widehat{\mathbf{s}}, \mathbf{g}_j(\mathbf{a}_1, \mathbf{a}_2)\big) = u_j(\widehat{\mathbf{s}}, 1)$. □

Next, we present a family of MIP models to choose among equilibria. The constraints of these models represent necessary and sufficient equilibrium conditions over a set of decision variables which enable the exact computation of a socially optimal randomized or pure equilibria, but we will consider pure and randomized equilibrium selection separately. As an aside, our MIP models can also optimize over other objectives that are linear in the patients' expected payoffs. We consider another such objective in Section 3.3. Our models require the set of hypermatrices $\mathbf{V}_1$ and $\mathbf{V}_2$, where for each patient $i \in \mathcal{N}$, $V_i(\mathbf{s}) = \max\{u_i(\mathbf{s}, 1), F_i(\mathbf{s}, \mathbf{V}_i)\}$ for $\mathbf{s} \in \mathscr{S}$. The payoff matrix $\mathbf{V}_i$ represents the optimal payoff function of Patient i when the autonomy of the other patient is suppressed over the course of the game; that is, $V_i(\mathbf{s})$ denotes the maximum expected discounted reward of Patient i when she rules the game to optimize the timing of the exchange assuming Patient $-i$ will adhere to the resulting policy. Therefore it denotes an upper bound for Patient i's payoffs, which we formally state in Lemma 3.2.

Lemma 3.2. *For any $i \in \mathcal{N}$, $\mathbf{V}_i \geq \mathbf{g}_i(\mathbf{a}_1, \mathbf{a}_2)$ for all $\mathbf{A} \in \Gamma$.*

Proof. Fix $i = 1$. While strategies $\mathbf{a}_1$ and $\mathbf{a}_2$ are fixed, suppose we apply value iteration described by (3.2) to $\mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)$. By induction on $n \geq 0$, we will show that $\mathbf{g}_1^n(\mathbf{a}_1, \mathbf{a}_2) \leq \mathbf{V}_1$ for all $n \geq 0$. Let $\mathbf{g}_1^0(\mathbf{a}_1, \mathbf{a}_2) = \mathbf{V}_1$, and for some $m \geq 0$ suppose $\mathbf{g}_1^m(\mathbf{a}_1, \mathbf{a}_2) \leq \mathbf{V}_1$ implying that $F_1\big(\mathbf{s}, \mathbf{g}_1^m(\mathbf{a}_1, \mathbf{a}_2)\big) \leq F_1(\mathbf{s}, \mathbf{V}_1)$ for all $\mathbf{s} \in \mathscr{S}$. Then, for any $\mathbf{s} \in \mathscr{S}$:

$$\begin{aligned} g_1^m(\mathbf{s}, \mathbf{a}_1, \mathbf{a}_2) &= a_1(\mathbf{s})a_2(\mathbf{s})u_1(\mathbf{s}, 1) + \big[1 - a_1(\mathbf{s})a_2(\mathbf{s})\big] F_1\big(\mathbf{s}, \mathbf{g}_1^m(\mathbf{a}_1, \mathbf{a}_2)\big) \\ &\leq \max\big\{u_1(\mathbf{s}, 1), F_1\big(\mathbf{s}, \mathbf{g}_1^m(\mathbf{a}_1, \mathbf{a}_2)\big)\big\} \qquad (3.15) \\ &\leq \max\{u_1(\mathbf{s}, 1), F_1(\mathbf{s}, \mathbf{V}_1)\} = V_1(\mathbf{s}), \end{aligned}$$

where (3.15) is implied by the fact that $0 \leq a_1(\mathbf{s})a_2(\mathbf{s}) \leq 1$. Thus, $\mathbf{g}_1^{m+1}(\mathbf{a}_1, \mathbf{a}_2) \leq \mathbf{V}_1$ and by induction the result follows from the convergence of value iteration. □

For the decision variables $\mathbf{w} = \big\{\mathbf{w}_1, \mathbf{w}_2\big\}$, $\mathbf{x}$ and $\mathbf{y} = \big\{\mathbf{y}_1, \mathbf{y}_2\big\}$, we consider the following set of mixed-integer inequalities:

$$w_i(\mathbf{s}) \geq F_i(\mathbf{s}, \mathbf{w}_i) \qquad \forall \mathbf{s} \in \mathscr{S}, i \in \mathcal{N}, \qquad (3.16a)$$

$$w_i(\mathbf{s}) \leq F_i(\mathbf{s}, \mathbf{w}_i) + u_i(\mathbf{s}, 1)y_i(\mathbf{s}) \qquad \forall \mathbf{s} \in \mathscr{S}, i \in \mathcal{N}, \qquad (3.16b)$$

$$w_i(\mathbf{s}) \geq u_i(\mathbf{s}, 1)y_{-i}(\mathbf{s}) \qquad \forall \mathbf{s} \in \mathscr{S}, i \in \mathcal{N}, \qquad (3.16c)$$

$$w_i(\mathbf{s}) \leq u_i(\mathbf{s}, 1)x(\mathbf{s}) + V_i(\mathbf{s})\big[1 - x(\mathbf{s})\big] \qquad \forall \mathbf{s} \in \mathscr{S}, i \in \mathcal{N}, \qquad (3.16d)$$

$$x(\mathbf{s}) \geq y_i(\mathbf{s}) \qquad \forall \mathbf{s} \in \mathscr{S}, i \in \mathcal{N}, \qquad (3.16e)$$

$$y_i(\mathbf{s}) \in \{0, 1\} \qquad \forall \mathbf{s} \in \mathscr{S}, i \in \mathcal{N}, \qquad (3.16f)$$

$$x(\mathbf{s}) \leq 1 \qquad \forall \mathbf{s} \in \mathscr{S}, \qquad (3.16g)$$

$$w_i(\mathbf{s}) \geq 0 \qquad \forall \mathbf{s} \in \mathscr{S}, i \in \mathcal{N}. \qquad (3.16h)$$

Note that $F_i(\mathbf{s}, \mathbf{w}_i)$ is a linear function of $\mathbf{w}_i$ for all $\mathbf{s} \in \mathscr{S}$ and $i \in \mathcal{N}$. Therefore, constraints (3.16a)-(3.16h) are linear in decision variables. We define $\Lambda := \big\{(\mathbf{w}, \mathbf{x}, \mathbf{y}) | (3.16a) - (3.16h)\big\}$. Given a feasible solution $(\widehat{\mathbf{w}}, \widehat{\mathbf{x}}, \widehat{\mathbf{y}})$ to Λ, we interpret the values of the variables and their implications through constraints (3.16a)-(3.16h) as follows: The variable $\widehat{\mathbf{w}}$ denotes a payoff profile, so that $F_i(\mathbf{s}, \widehat{\mathbf{w}}_i)$ denotes the expected payoff-to-go for Patient $i \in \mathcal{N}$ starting in state $\mathbf{s} \in \mathscr{S}$. The variable $\widehat{\mathbf{y}}$ denotes statewise randomization indicators; that is, in a particular

state $\mathbf{s} \in \mathscr{S}$, $\widehat{y}_i(\mathbf{s}) = \ell$ for both $i \in \mathcal{N}$ means the exchange occurrence probability is equal to ℓ in that state. Otherwise, *i.e.*, if $\widehat{y}_1(\mathbf{s}) \neq \widehat{y}_2(\mathbf{s})$, then Patient $i \in \mathcal{N}$ with $\widehat{y}_i(\mathbf{s}) = 1$ offers to exchange with some positive probability whereas the other patient randomizes between waiting and offering to exchange. The variable $\widehat{\mathbf{x}}$ drives logical relationships between $\widehat{\mathbf{y}}_1$ and $\widehat{\mathbf{y}}_2$.

In a particular state $\mathbf{s} \in \mathscr{S}$ constraint (3.16a) ensures that no patient receives no less than her expected payoff-to-go. When $\widehat{y}_i(\mathbf{s}) = 0$ for both $i \in \mathcal{N}$, because the exchange occurrence probability is 0, constraints (3.16a)-(3.16b) ensure that each patient receives her expected payoff-to-go. When $\widehat{y}_i(\mathbf{s}) = 1$ for both $i \in \mathcal{N}$, because the exchange occurrence probability is 1, constraints (3.16a) ensure that no patient is better-off waiting, and constraints (3.16c)-(3.16e) and (3.16g) guarantee that each patient receives her post-transplant reward. When, $\widehat{y}_1(\mathbf{s}) \neq \widehat{y}_2(\mathbf{s})$ constraints (3.16a)-(3.16e) and (3.16g) ensure the patient who randomizes between waiting and offering to exchange is indifferent between her post-transplant reward and expected payoff-to-go $\big($by Lemma 3.1 $(ii)\big)$. By Theorem 3.1 and Lemma 3.1 (i), the expected reward of the patient who is offering to exchange with a positive probability should be no less than her expected payoff-to-go and no more than her post-transplant reward, which we ensure by constraints (3.16a), (3.16d), (3.16e) and (3.16g).

Theorem 3.2 (i) reveals the relationship between equilibria of game $\mathcal{G}$ and feasible solutions to Λ. Specifically, for any set of vectors $(\widehat{\mathbf{w}}, \widehat{\mathbf{x}}, \widehat{\mathbf{y}})$ satisfying constraints $(3.16a)-(3.16h)$ one can construct an equilibrium $\widehat{\mathbf{A}}$ of game $\mathcal{G}$ from $\widehat{\mathbf{w}}$ and $\widehat{\mathbf{y}}$ with a payoff profile equivalent to $\widehat{\mathbf{w}}$. Likewise, given an equilibrium $\widehat{\mathbf{A}}$ of game $\mathcal{G}$, one can construct a solution $(\widehat{\mathbf{w}}, \widehat{\mathbf{x}}, \widehat{\mathbf{y}})$ feasible to Λ from strategies $\widehat{\mathbf{a}}_1$ and $\widehat{\mathbf{a}}_2$, where $\widehat{\mathbf{w}}$ represents the payoff profile of $\widehat{\mathbf{A}}$. As a consequence of Theorem 3.2 (i), Theorem 3.2 (ii) states that an optimal equilibrium with respect to a given criteria which is linear in patients' payoffs can be exactly characterized as an optimal solution to an MIP.

In our model, exchange occurrence probabilities are sufficient to unfold the expected payoffs. If they are known in each state $\mathbf{s} \in \mathscr{S}$, then the expected payoffs can be calculated for each patient. Despite this fact, a solution $(\widehat{\mathbf{w}}, \widehat{\mathbf{x}}, \widehat{\mathbf{y}})$ to Λ involves the payoff profile of an equilibrium but not the strategies necessarily. In Theorem 3.2 (i), for a feasible solution $(\widehat{\mathbf{w}}, \widehat{\mathbf{x}}, \widehat{\mathbf{y}})$ to Λ, while $\widehat{\mathbf{w}}$ represents the payoff profile of the equilibrium that $(\widehat{\mathbf{w}}, \widehat{\mathbf{x}}, \widehat{\mathbf{y}})$ induces,

as $\widehat{\mathbf{y}}$ involve only binary values, it may not necessarily represent the strategies of the resulting equilibrium. More explicitly, a feasible solution $(\widehat{\mathbf{w}}, \widehat{\mathbf{x}}, \widehat{\mathbf{y}})$ to Λ can be transformed into possibly a randomized equilibrium of game $\mathcal{G}$ with a payoff profile equivalent to $\widehat{\mathbf{w}}$. However as such a feasible solution doesn't involve continuous variables other than $\widehat{\mathbf{w}}_1$ and $\widehat{\mathbf{w}}_2$, patients' strategies in the resulting randomized equilibrium can only be implicitly derived from the payoff matrices $\widehat{\mathbf{w}}_1$ and $\widehat{\mathbf{w}}_2$ using Theorem 3.1 and Lemma 3.1. For instance, in state $\mathbf{s} \in \mathscr{S}$, if $\widehat{y}_1(\mathbf{s}) = \widehat{y}_2(\mathbf{s})$ then an exchange occurs with probability $\widehat{y}_1(\mathbf{s})$. Otherwise, the patient for whom $\widehat{y}_i(\mathbf{s}) = 1$ offers to exchange with probability 1 while the other patient strictly randomizes between waiting and offering to exchange with probabilities $\left(\dfrac{u_i(\mathbf{s},1) - \widehat{w}_i(\mathbf{s})}{u_i(\mathbf{s},1) - F_i(\mathbf{s}, \widehat{\mathbf{w}}_i)}\right)$ and $\left(\dfrac{\widehat{w}_i(\mathbf{s}) - F_i(\mathbf{s}, \widehat{\mathbf{w}}_i)}{u_i(\mathbf{s},1) - F_i(\mathbf{s}, \widehat{\mathbf{w}}_i)}\right)$, respectively.

Theorem 3.2. *(i)* $(\widehat{\mathbf{w}}, \widehat{\mathbf{x}}, \widehat{\mathbf{y}}) \in \Lambda$ *if and only if there exists* $\widehat{\mathbf{A}} \in \Gamma$ *with* $\widehat{\mathbf{w}}_i = \mathbf{g}_i(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)$ *for both* $i \in \mathcal{N}$.

(ii) Given real-valued vectors $\mathbf{c}_1$ *and* $\mathbf{c}_2$,

$$\max_{\mathbf{A} \in \Gamma} \left[\mathbf{c}_1 \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2) + \mathbf{c}_2 \mathbf{g}_2(\mathbf{a}_1, \mathbf{a}_2)\right] = \max_{(\mathbf{w}, \mathbf{x}, \mathbf{y}) \in \Lambda} \left[\mathbf{c}_1 \mathbf{w}_1 + \mathbf{c}_2 \mathbf{w}_2\right].$$

Proof. *(i)* $(\Leftarrow)$ For convenience let $\mathscr{B}_\ell = \left\{\mathbf{s} \in \mathscr{S} | \widehat{a}_1(\mathbf{s}) \widehat{a}_2(\mathbf{s}) = \ell\right\}$ for $\ell \in \{0, 1\}$ so that $\mathscr{B}_0$ represents the set of states in which at least one of the patients offers to exchange with probability 0, $\mathscr{B}_1$ represents the set of states in which both patients offer to exchange with probability 1. Also, define $\mathscr{C} = \mathscr{S} \setminus \left(\mathscr{B}_0 \cup \mathscr{B}_1\right)$ as the set of states in which both patients offer to exchange with some positive probability and at least one of the patients strictly randomizes between waiting and offering to exchange under strategy profile $\mathbf{A}$. By the definition of $\mathscr{C}$, Lemma 3.1 *(ii)* implies that for each state $\mathbf{s} \in \mathscr{C}$ there exists $i \in \mathcal{N}$ with $g_i(\mathbf{s}, \widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) = u_i(\mathbf{s}, 1) = F_i\big(\mathbf{s}, \mathbf{g}_i(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big)$. Therefore, for $\mathbf{s} \in \mathscr{C}$, let $\tau(\mathbf{s}) = \min\left\{i \in \mathcal{N} | g_i(\mathbf{s}, \widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) = u_i(\mathbf{s}, 1) = F_i\big(\mathbf{s}, \mathbf{g}_i(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big)\right\}$. Now, we will construct a solution $(\widehat{\mathbf{w}}, \widehat{\mathbf{x}}, \widehat{\mathbf{y}})$ satisfying constraints (3.16a)-(3.16h). Let

$$\widehat{\mathbf{w}}_i = \mathbf{g}_i(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) \text{ for both } i \in \mathcal{N}. \tag{3.17}$$

As an immediate consequence of (3.17):

$$F_i\big(\mathbf{s}, \mathbf{g}_i(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big) = F_i(\mathbf{s}, \widehat{\mathbf{w}}_i) \text{ for all } \mathbf{s} \in \mathscr{S} \text{ and } i \in \mathcal{N}. \tag{3.18}$$

Also, consider $\widehat{\mathbf{x}}$ and $\widehat{\mathbf{y}}$ defined as follows:

- For $\ell \in \{0, 1\}$, $\mathbf{s} \in \mathscr{S}$ and $i \in \mathcal{N}$, let $\widehat{y}_i(\mathbf{s}) = \ell$ if $\mathbf{s} \in \mathscr{B}_\ell$;
- For $\mathbf{s} \in \mathscr{C}$, let $\widehat{y}_i(\mathbf{s}) = 0$ if $i = \tau(\mathbf{s})$, and $\widehat{y}_i(\mathbf{s}) = 1$ otherwise.
- For $\mathbf{s} \in \mathscr{S}$, let $\widehat{x}(\mathbf{s}) = 0$ if $\mathbf{s} \in \mathscr{B}_0$ and $\widehat{x}(\mathbf{s}) = 1$ otherwise.

By the construction of $\widehat{\mathbf{x}}$ and $\widehat{\mathbf{y}}$, constraints (3.16e)-(3.16g) are satisfied. Because $\widehat{\mathbf{A}} \in \Gamma$, by Theorem 3.1, $g_i(\mathbf{s}, \widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) \geq F_i\big(\mathbf{s}, \mathbf{g}_i(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big)$ for all $\mathbf{s} \in \mathscr{S}$ and $i \in \mathcal{N}$. By (3.17) and (3.18), this implies that constraints (3.16a) are satisfied. Since $\mathbf{g}_i(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) \geq \mathbf{0}$ for both $i \in \mathcal{N}$, (3.17) also imply that constraints (3.16h) are satisfied. Next, we will show that $(\widehat{\mathbf{w}}, \widehat{\mathbf{x}}, \widehat{\mathbf{y}})$ satisfy constraints (3.16b)-(3.16d). For Patient 1, consider the following possible cases for an arbitrary $\mathbf{s} \in \mathscr{S}$:

1. If $\mathbf{s} \in \mathscr{B}_0$, then since $a_1(\mathbf{s})a_2(\mathbf{s}) = 0$, by (3.1), $g_1(\mathbf{s}, \widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) = F_1\big(\mathbf{s}, \mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big)$. Therefore, by (3.17) and (3.18), $\widehat{y}_1(\mathbf{s}) = 0$ implies that constraint (3.16b) is satisfied. Because $\widehat{y}_2(\mathbf{s}) = 0$ and $\widehat{w}_1(\mathbf{s}) \geq 0$, constraint (3.16c) is satisfied. Also, since $\widehat{x}(\mathbf{s}) = 0$, by (3.17) and Lemma 3.2, constraint (3.16d) is satisfied.
2. If $\mathbf{s} \in \mathscr{B}_1$, then since $a_1(\mathbf{s})a_2(\mathbf{s}) = 1$, by (3.1), $g_1(\mathbf{s}, \widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) = u_1(\mathbf{s}, 1)$. Therefore, by (3.17), $\widehat{w}_1(\mathbf{s}) = u_1(\mathbf{s}, 1)$. Then, since $\widehat{y}_1(\mathbf{s}) = 1$ and $F_1\big(\mathbf{s}, \mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big) \geq 0$, (3.18) implies that constraint (3.16b) is satisfied. Because $\widehat{x}(\mathbf{s}) = \widehat{y}_2(\mathbf{s}) = 1$, constraints (3.16c) and (3.16d) are also satisfied by $\widehat{w}_1(\mathbf{s}) = u_1(\mathbf{s}, 1)$.
3. If $\mathbf{s} \in \mathscr{C}$, then since $a_1(\mathbf{s})a_2(\mathbf{s}) \in (0, 1)$, by Lemma 3.1 (i), $g_1(\mathbf{s}, \widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) \leq u_1(\mathbf{s}, 1)$. Therefore, by (3.17), $\widehat{w}_1(\mathbf{s}) \leq u_1(\mathbf{s}, 1)$. By definition, $V_1(\mathbf{s}) \geq u_1(\mathbf{s}, 1)$. Therefore, constraint (3.16d) is satisfied. Now, consider the following two possible cases for $\tau(\mathbf{s})$.
   a. If $\tau(\mathbf{s}) \neq 1$, then because $\widehat{y}_1(\mathbf{s}) = 1$, $\widehat{w}_1(\mathbf{s}) \leq u_1(\mathbf{s}, 1)$ and $F_1\big(\mathbf{s}, \mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big) \geq 0$, (3.18) implies that constraint (3.16b) is satisfied. Also, because $\widehat{y}_2(\mathbf{s}) = 0$ and $\widehat{w}_1(\mathbf{s}) \geq 0$, constraint (3.16c) is satisfied.

b. If $\tau(\mathbf{s}) = 1$, then since $g_1(\mathbf{s}, \widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) = u_1(\mathbf{s}, 1) = F_1\big(\mathbf{s}, \mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big)$ and $\widehat{y}_1(\mathbf{s}) = 0$, by (3.17) and (3.18), constraint (3.16b) is satisfied. Furthermore, because $\widehat{y}_2(\mathbf{s}) = 1$, by (3.17), constraint (3.16c) is also satisfied.

Thus, $(\widehat{\mathbf{w}}, \widehat{\mathbf{x}}, \widehat{\mathbf{y}}) \in \Lambda$.

($\Rightarrow$) For $\ell \in \{0, 1\}$, let $\mathscr{W}_\ell = \big\{\mathbf{s} \in \mathscr{S} | \widehat{y}_1(\mathbf{s}) = \widehat{y}_2(\mathbf{s}) = \ell\big\}$ and for $i \in \mathcal{N}$ let $\mathscr{R}_i = \big\{\mathbf{s} \in \mathscr{S} | \widehat{y}_i(\mathbf{s}) = 0, \widehat{y}_{-i}(\mathbf{s}) = 1\big\}$ and $\mathscr{Z}_i = \big\{\mathbf{s} \in \mathscr{R}_i | u_{-i}(\mathbf{s}, 1) = F_{-i}(\mathbf{s}, \widehat{\mathbf{w}}_{-i})\big\}$. Note that constraints (3.16a) hold, but in particular:

$$\text{For any } i \in \mathcal{N}\text{: } \widehat{w}_{-i}(\mathbf{s}) \geq F_{-i}(\mathbf{s}, \widehat{\mathbf{w}}_{-i}) \text{ for } \mathbf{s} \in \mathscr{R}_i. \tag{3.19}$$

Also by constraints (3.16d), (3.16e) and (3.16g)

$$\text{For any } i \in \mathcal{N}\text{: } u_{-i}(\mathbf{s}, 1) \geq w_{-i}(\mathbf{s}) \text{ for } \mathbf{s} \in \mathscr{R}_i. \tag{3.20}$$

By (3.19) and (3.20), and the definition of $\mathscr{Z}_i$:

$$\text{For any } i \in \mathcal{N}\text{: } u_{-i}(\mathbf{s}, 1) > F_{-i}(\mathbf{s}, \widehat{\mathbf{w}}_{-i}) \text{ for } \mathbf{s} \in \mathscr{R}_i \setminus \mathscr{Z}_i. \tag{3.21}$$

Thus, by (3.19)-(3.21), for any $i \in \mathcal{N}$,

$$\frac{\widehat{w}_{-i}(\mathbf{s}) - F_{-i}(\mathbf{s}, \widehat{\mathbf{w}}_{-i})}{u_{-i}(\mathbf{s}, 1) - F_{-i}(\mathbf{s}, \widehat{\mathbf{w}}_{-i})} \in [0, 1] \text{ and } \frac{u_{-i}(\mathbf{s}, 1) - \widehat{w}_{-i}(\mathbf{s})}{u_{-i}(\mathbf{s}, 1) - F_{-i}(\mathbf{s}, \widehat{\mathbf{w}}_{-i})} \in [0, 1] \quad \text{for all } \mathbf{s} \in \mathscr{R}_i \setminus \mathscr{Z}_i. \tag{3.22}$$

Now, for each $i \in \mathcal{N}$, consider the strategy $\widehat{\mathbf{a}}_i$ defined by:

$$\widehat{a}_i(\mathbf{s}) = \begin{cases} 0 & \text{for } \mathbf{s} \in \mathscr{W}_0 \cup \mathscr{Z}_i, \\ 1 & \text{for } \mathbf{s} \in \mathscr{W}_1 \cup \mathscr{R}_{-i}, \\ \dfrac{\widehat{w}_{-i}(\mathbf{s}) - F_{-i}(\mathbf{s}, \widehat{\mathbf{w}}_{-i})}{u_{-i}(\mathbf{s}, 1) - F_{-i}(\mathbf{s}, \widehat{\mathbf{w}}_{-i})} & \text{for } \mathbf{s} \in \mathscr{R}_i \setminus \mathscr{Z}_i. \end{cases} \tag{3.23}$$

By (3.23), for the product $\widehat{a}_1(\mathbf{s})\widehat{a}_2(\mathbf{s})$ we have:

$$\widehat{a}_1(\mathbf{s})\widehat{a}_2(\mathbf{s}) = \begin{cases} 0 & \text{for } \mathbf{s} \in \mathscr{W}_0 \cup \mathscr{Z}_1 \cup \mathscr{Z}_2, \\ 1 & \text{for } \mathbf{s} \in \mathscr{W}_1, \\ \dfrac{\widehat{w}_{-i}(\mathbf{s}) - F_{-i}(\mathbf{s}, \widehat{\mathbf{w}}_{-i})}{u_{-i}(\mathbf{s}, 1) - F_{-i}(\mathbf{s}, \widehat{\mathbf{w}}_{-i})} & \text{for } \mathbf{s} \in \mathscr{R}_i \setminus \mathscr{Z}_i,\ i \in \mathcal{N}. \end{cases} \tag{3.24}$$

Consider Patient 1. First, we will show that $\widehat{\mathbf{w}}_1 = \mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)$. By (3.24), (3.1) defines the payoffs $\mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)$ as:

$$g_1(\mathbf{s}, \widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) = \begin{cases} F_1\big(\mathbf{s}, \mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big) & \text{for } \mathbf{s} \in \mathscr{W}_0 \cup \mathscr{Z}_1 \cup \mathscr{Z}_2, \\ u_1(\mathbf{s}, 1) & \text{for } \mathbf{s} \in \mathscr{W}_1, \\ \left(\dfrac{\widehat{w}_2(\mathbf{s}) - F_2(\mathbf{s}, \widehat{\mathbf{w}}_2)}{u_2(\mathbf{s}, 1) - F_2(\mathbf{s}, \widehat{\mathbf{w}}_2)}\right) u_1(\mathbf{s}, 1) + \left(\dfrac{u_2(\mathbf{s}, 1) - \widehat{w}_2(\mathbf{s})}{u_2(\mathbf{s}, 1) - F_2(\mathbf{s}, \widehat{\mathbf{w}}_2)}\right) F_1\big(\mathbf{s}, \mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big) & \\ \qquad\qquad \text{for } \mathbf{s} \in \mathscr{R}_1 \setminus \mathscr{Z}_1, & \\ \left(\dfrac{\widehat{w}_1(\mathbf{s}) - F_1(\mathbf{s}, \widehat{\mathbf{w}}_1)}{u_1(\mathbf{s}, 1) - F_1(\mathbf{s}, \widehat{\mathbf{w}}_1)}\right) u_1(\mathbf{s}, 1) + \left(\dfrac{u_1(\mathbf{s}, 1) - \widehat{w}_1(\mathbf{s})}{u_1(\mathbf{s}, 1) - F_1(\mathbf{s}, \widehat{\mathbf{w}}_1)}\right) F_1\big(\mathbf{s}, \mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big) & \\ \qquad\qquad \text{for } \mathbf{s} \in \mathscr{R}_2 \setminus \mathscr{Z}_2. & \end{cases} \tag{3.25}$$

By constraints (3.16a) and (3.16b):

$$\widehat{w}_1(\mathbf{s}) = F_1(\mathbf{s}, \widehat{\mathbf{w}}_1) \text{ for } \mathbf{s} \in \mathscr{W}_0. \tag{3.26}$$

By the definition of $\mathscr{Z}_2$, $F_1(\mathbf{s}, \widehat{\mathbf{w}}_1) = u_1(\mathbf{s}, 1)$ for all $\mathbf{s} \in \mathscr{Z}_2$. Because $\mathscr{Z}_2 \subseteq \mathscr{R}_2$, by (3.19) and (3.20), this implies:

$$\widehat{w}_1(\mathbf{s}) = F_1(\mathbf{s}, \widehat{\mathbf{w}}_1) \text{ for } \mathbf{s} \in \mathscr{Z}_2. \tag{3.27}$$

By constraints (3.16a), (3.16c)-(3.16e) and (3.16g):

$$\widehat{w}_1(\mathbf{s}) = u_1(\mathbf{s}, 1) \geq F_1(\mathbf{s}, \widehat{\mathbf{w}}_1) \text{ for } \mathbf{s} \in \mathscr{W}_1. \tag{3.28}$$

Also, by constraints (3.16a)-(3.16e) and (3.16g):

$$\widehat{w}_1(\mathbf{s}) = F_1(\mathbf{s}, \widehat{\mathbf{w}}_1) = u_1(\mathbf{s}, 1) \text{ for } \mathbf{s} \in \mathscr{R}_1. \tag{3.29}$$

Then, because $\dfrac{\widehat{w}_2(\mathbf{s}) - F_2(\mathbf{s}, \widehat{\mathbf{w}}_2)}{u_2(\mathbf{s}, 1) - F_2(\mathbf{s}, \widehat{\mathbf{w}}_2)} + \dfrac{u_2(\mathbf{s}, 1) - \widehat{w}_2(\mathbf{s})}{u_2(\mathbf{s}, 1) - F_2(\mathbf{s}, \widehat{\mathbf{w}}_2)} = 1$ for all $\mathbf{s} \in \mathscr{R}_1$, by (3.22), (3.29) implies:

$$\begin{aligned} \widehat{w}_1(\mathbf{s}) = &\left(\frac{\widehat{w}_2(\mathbf{s}) - F_2(\mathbf{s}, \widehat{\mathbf{w}}_2)}{u_2(\mathbf{s}, 1) - F_2(\mathbf{s}, \widehat{\mathbf{w}}_2)}\right) u_1(\mathbf{s}, 1) \\ &+ \left(\frac{u_2(\mathbf{s}, 1) - \widehat{w}_2(\mathbf{s})}{u_2(\mathbf{s}, 1) - F_2(\mathbf{s}, \widehat{\mathbf{w}}_2)}\right) F_1(\mathbf{s}, \widehat{\mathbf{w}}_1) \text{ for all } \mathbf{s} \in \mathscr{R}_1. \end{aligned} \tag{3.30}$$

Thus, by (3.26)-(3.30), $\widehat{\mathbf{w}}_1$ satisfies the following recursion:

$$\widehat{w}_1(\mathbf{s}) = \begin{cases} F_1(\mathbf{s}, \widehat{\mathbf{w}}_1) & \text{for } \mathbf{s} \in \mathscr{W}_0 \cup \mathscr{Z}_1 \cup \mathscr{Z}_2, \\ u_1(\mathbf{s}, 1) & \text{for } \mathbf{s} \in \mathscr{W}_1, \\ \left(\dfrac{\widehat{w}_2(\mathbf{s}) - F_2(\mathbf{s}, \widehat{\mathbf{w}}_2)}{u_2(\mathbf{s}, 1) - F_2(\mathbf{s}, \widehat{\mathbf{w}}_2)}\right) u_1(\mathbf{s}, 1) + \left(\dfrac{u_2(\mathbf{s}, 1) - \widehat{w}_2(\mathbf{s})}{u_2(\mathbf{s}, 1) - F_2(\mathbf{s}, \widehat{\mathbf{w}}_2)}\right) F_1(\mathbf{s}, \widehat{\mathbf{w}}_1) & \\ \qquad\qquad \text{for } \mathbf{s} \in \mathscr{R}_1 \setminus \mathscr{Z}_1, & \\ \left(\dfrac{\widehat{w}_1(\mathbf{s}) - F_1(\mathbf{s}, \widehat{\mathbf{w}}_1)}{u_1(\mathbf{s}, 1) - F_1(\mathbf{s}, \widehat{\mathbf{w}}_1)}\right) u_1(\mathbf{s}, 1) + \left(\dfrac{u_1(\mathbf{s}, 1) - \widehat{w}_1(\mathbf{s})}{u_1(\mathbf{s}, 1) - F_1(\mathbf{s}, \widehat{\mathbf{w}}_1)}\right) F_1(\mathbf{s}, \widehat{\mathbf{w}}_1) & \\ \qquad\qquad \text{for } \mathbf{s} \in \mathscr{R}_2 \setminus \mathscr{Z}_2. & \end{cases} \tag{3.31}$$

By (3.25) and (3.31), it is clear that $\mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) = \widehat{\mathbf{w}}_1$. Next, we will prove that $\widehat{\mathbf{A}} \in \Gamma$. Since $\mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) = \widehat{\mathbf{w}}_1$ and $F_1\big(\mathbf{s}, \mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big) = F_1(\mathbf{s}, \widehat{\mathbf{w}}_1)$ for $\mathbf{s} \in \mathscr{S}$, by Theorem 3.1, it is sufficient to show that the following holds for all $\mathbf{s} \in \mathscr{S}$.

$$\widehat{w}_1(\mathbf{s}) = \max\big\{\widehat{a}_2(\mathbf{s})u_1(\mathbf{s}, 1) + \big[1 - \widehat{a}_2(\mathbf{s})\big]F_1(\mathbf{s}, \widehat{\mathbf{w}}_1), F_1(\mathbf{s}, \widehat{\mathbf{w}}_1)\big\}. \tag{3.32}$$

Choose an arbitrary $\mathbf{s} \in \mathscr{S}$ and consider the following possible cases for $\widehat{w}_1(\mathbf{s})$:

1. If $\mathbf{s} \in \mathscr{W}_0$, then by (3.26), $\widehat{w}_1(\mathbf{s}) = F_1(\mathbf{s}, \widehat{\mathbf{w}}_1)$. Then, since $\widehat{a}_2(\mathbf{s}) = 0$, (3.32) is satisfied.
2. If $\mathbf{s} \in \mathscr{W}_1 \cup \mathscr{R}_1$, then by (3.28) and (3.29), $\widehat{w}_1(\mathbf{s}) = \max\big\{u_1(\mathbf{s}, 1), F_1(\mathbf{s}, \widehat{\mathbf{w}}_1)\big\}$. Then, since $\widehat{a}_2(\mathbf{s}) = 1$, (3.32) holds.
3. If $\mathbf{s} \in \mathscr{Z}_2$, then since $u_1(\mathbf{s}, 1) = F_1(\mathbf{s}, \widehat{\mathbf{w}}_1)$, by (3.27) (3.32) is satisfied independent of the value of $\widehat{a}_2(\mathbf{s})$.
4. If $\mathbf{s} \in \mathscr{R}_2 \setminus \mathscr{Z}_2$, then since $\widehat{a}_2(\mathbf{s}) = \dfrac{\widehat{w}_1(\mathbf{s}) - F_1(\mathbf{s}, \widehat{\mathbf{w}}_1)}{u_1(\mathbf{s}, 1) - F_1(\mathbf{s}, \widehat{\mathbf{w}}_1)}$ by (3.23), we have:

$$\begin{aligned} \widehat{w}_1(\mathbf{s}) &= \left(\frac{\widehat{w}_1(\mathbf{s}) - F_1(\mathbf{s}, \widehat{\mathbf{w}}_1)}{u_1(\mathbf{s}, 1) - F_1(\mathbf{s}, \widehat{\mathbf{w}}_1)}\right) u_1(\mathbf{s}, 1) + \left(\frac{u_1(\mathbf{s}, 1) - \widehat{w}_1(\mathbf{s})}{u_1(\mathbf{s}, 1) - F_1(\mathbf{s}, \widehat{\mathbf{w}}_1)}\right) F_1(\mathbf{s}, \widehat{\mathbf{w}}_1) \\ &= \widehat{a}_2(\mathbf{s})u_1(\mathbf{s}, 1) + \big[1 - \widehat{a}_2(\mathbf{s})\big]F_1(\mathbf{s}, \widehat{\mathbf{w}}_1). \end{aligned} \tag{3.33}$$

   Since $\mathbf{s} \in \mathscr{R}_2 \setminus \mathscr{Z}_2$, by (3.21), $u_1(\mathbf{s}, 1) > F_1(\mathbf{s}, \widehat{\mathbf{w}}_1)$. By (3.33) and the fact that $\widehat{a}_2(\mathbf{s}) \in [0, 1]$, this implies that (3.32) holds.

(*ii*) The result immediately follows from part (*i*), and the proof is omitted. □

Randomized strategies introduce unpredictability into the strategies and may help patients gain from competition. However, they involve the selection of statewise probability distributions over waiting and offering to exchange and because patients may not be willing to leave the transplant outcome to chance they lack both behavioral and cognitive support. In contrast, pure strategies specify deterministic actions in each state and have a more intuitive appeal to patients and physicians.

For the remainder of this section, we switch our focus to pure strategies and pure equilibria. As a consequence of Theorem 3.1, Theorem 3.3 (i) derives necessary and sufficient conditions for a strategy profile to be a pure equilibrium of game $\mathcal{G}$. Theorem 3.3 (ii) draws on Theorem 3.2 (i) and Theorem 3.3 (i), and refines the set of solutions to the constraints (3.16a)-(3.16h) by a set of constraints to consider the issue of equilibrium selection within the class of pure equilibria. Then, Theorem 3.3 (iii) states that an optimal pure equilibrium with respect to a given criteria (which is linear in patients' expected payoffs) can be characterized as an optimal solution to this refinement. Lastly, Theorem 3.3 (iv) reveals the influence of patient autonomy on patients' payoffs in a socially optimal equilibrium. It states that in a socially optimal pure equilibrium, either an immediate exchange is optimal or at least one of the patients benefits from delaying the exchange in the initial state of the game. In the rest of this chapter, we let Π denote the set of pure equilibria of game $\mathcal{G}$, that is, $\Pi := \big\{\mathbf{A} \in \Gamma | a_i(\mathbf{s}) \in \{0,1\} \text{ for } \mathbf{s} \in \mathscr{S} \text{ and } i \in \mathcal{N}\big\}$. We also let $\Upsilon := \big\{(\mathbf{w},\mathbf{x},\mathbf{y}) \in \Lambda | \mathbf{y}_1 = \mathbf{y}_2\big\}$.

Theorem 3.3. (i) *A strategy profile* $\mathbf{A}$ *is a pure equilibrium of game* $\mathcal{G}$ *if and only if for all* $\mathbf{s} \in \mathscr{S}$ *and* $i \in \mathcal{N}$,

$$a_i(\mathbf{s}) \in \begin{cases} \{1\} & \text{if } a_{-i}(\mathbf{s}) = 1 \text{ and } u_i(\mathbf{s},1) > F_i\big(\mathbf{s}, \mathbf{g}_i(\mathbf{a}_1,\mathbf{a}_2)\big), \\ \{0\} & \text{if } a_{-i}(\mathbf{s}) = 1 \text{ and } u_i(\mathbf{s},1) < F_i\big(\mathbf{s}, \mathbf{g}_i(\mathbf{a}_1,\mathbf{a}_2)\big), \\ \{0,1\} & \text{otherwise.} \end{cases} \tag{3.34}$$

(ii) $(\widehat{\mathbf{w}},\widehat{\mathbf{x}},\widehat{\mathbf{y}}) \in \Upsilon$ *if and only if there exists* $\widehat{\mathbf{A}} \in \Pi$ *with* $\widehat{\mathbf{w}}_i = \mathbf{g}_i(\widehat{\mathbf{a}}_1,\widehat{\mathbf{a}}_2)$ *for both* $i \in \mathcal{N}$.

(iii) *Given real-valued vectors* $\mathbf{c}_1$ *and* $\mathbf{c}_2$,

$$\max_{\mathbf{A}\in\Pi} \big[\mathbf{c}_1\mathbf{g}_1(\mathbf{a}_1,\mathbf{a}_2) + \mathbf{c}_2\mathbf{g}_2(\mathbf{a}_1,\mathbf{a}_2)\big] = \max_{(\mathbf{w},\mathbf{y},\mathbf{z})\in\Upsilon} \big[\mathbf{c}_1\mathbf{w}_1 + \mathbf{c}_2\mathbf{w}_2\big].$$

(iv) Given $\widetilde{\mathbf{s}} \in \mathscr{S}$*, let* $\mathbf{A}^* \in \arg\max_{\mathbf{A}\in\Pi} \big[g_1(\widetilde{\mathbf{s}}, \mathbf{a}_1, \mathbf{a}_2) + g_2(\widetilde{\mathbf{s}}, \mathbf{a}_1, \mathbf{a}_2)\big]$*. Then, either* $g_i(\widetilde{\mathbf{s}}, \mathbf{a}_1^*, \mathbf{a}_2^*) = u_i(\widetilde{\mathbf{s}}, 1)$ *for both* $i \in \mathcal{N}$ *or* $\max_{i\in\mathcal{N}} \big[g_i(\widetilde{\mathbf{s}}, \mathbf{a}_1^*, \mathbf{a}_2^*) - u_i(\widetilde{\mathbf{s}}, 1)\big] > 0$*.*

Proof. (*i*) By Theorem 3.1, $\mathbf{A}$ is a pure equilibrium of game $\mathcal{G}$ if and only if the following holds for all $\mathbf{s} \in \mathscr{S}$ and $i \in \mathcal{N}$:

$$g_i(\mathbf{s}, \mathbf{a}_1, \mathbf{a}_2) = \begin{cases} \max\big\{u_i(\mathbf{s}, 1), F_i\big(\mathbf{s}, \mathbf{g}_i(\mathbf{a}_1, \mathbf{a}_2)\big)\big\} & \text{if } a_{-i}(\mathbf{s}) = 1, \\ F_i\big(\mathbf{s}, \mathbf{g}_i(\mathbf{a}_1, \mathbf{a}_2)\big) & \text{otherwise.} \end{cases} \tag{3.35}$$

($\Leftarrow$) Consider Patient 1. Since $a_i(\mathbf{s}) \in \{0, 1\}$ for all $\mathbf{s} \in \mathscr{S}$ and $i \in \mathcal{N}$, by (3.1), the payoffs $\mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)$ are defined as follows:

$$g_1(\mathbf{s}, \mathbf{a}_1, \mathbf{a}_2) = \begin{cases} u_1(\mathbf{s}, 1) & \text{if } a_1(\mathbf{s}) = a_2(\mathbf{s}) = 1, \\ F_1\big(\mathbf{s}, \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)\big) & \text{otherwise.} \end{cases} \tag{3.36}$$

Note that by (3.34), when $a_2(\mathbf{s}) = 1$:

$$\max\big\{u_1(\mathbf{s}, 1), F_1\big(\mathbf{s}, \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)\big)\big\} = \begin{cases} u_1(\mathbf{s}, 1) & \text{if } a_1(\mathbf{s}) = 1, \\ F_1\big(\mathbf{s}, \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)\big) & \text{if } a_1(\mathbf{s}) = 0. \end{cases} \tag{3.37}$$

By (3.36), (3.37) implies that recursion (3.35) holds for Patient 1 for all $\mathbf{s} \in \mathscr{S}$.

($\Rightarrow$) Consider Patient 1. Since $\mathbf{A} \in \Gamma$, by Theorem 3.1, (3.35) holds for all $\mathbf{s} \in \mathscr{S}$ and $i = 1$. Now, choose an arbitrary $\mathbf{s} \in \mathscr{S}$ and for the two possible cases of $a_2(\mathbf{s})$, consider $a_1(\mathbf{s})$.

1. If $a_2(\mathbf{s}) = 0$, then by (3.1) and (3.35), we must have

$$F_1\big(\mathbf{s}, \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)\big) = \big[1 - a_1(\mathbf{s})0\big] F_1\big(\mathbf{s}, \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)\big).$$

   Therefore, with no restriction, either $a_1(\mathbf{s}) = 0$ or $a_1(\mathbf{s}) = 1$.

2. If $a_2(\mathbf{s}) = 1$, then by (3.1) and (3.35), we must have

$$\max\big\{u_1(\mathbf{s}, 1), F_1\big(\mathbf{s}, \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)\big)\big\} = a_1(\mathbf{s}) u_1(\mathbf{s}, 1) + \big[1 - a_1(\mathbf{s})\big] F_1\big(\mathbf{s}, \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)\big). \tag{3.38}$$

   Since $a_1(\mathbf{s}) \in \{0, 1\}$, by (3.38), it must satisfy the following:

$$a_1(\mathbf{s}) \in \begin{cases} \{0\} & \text{if } u_1(\mathbf{s}, 1) < F_1\big(\mathbf{s}, \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)\big), \\ \{1\} & \text{if } u_1(\mathbf{s}, 1) > F_1\big(\mathbf{s}, \mathbf{g}_1(\mathbf{a}_1, \mathbf{a}_2)\big), \\ \{0, 1\} & \text{otherwise.} \end{cases}$$

Thus, for Patient 1, (3.34) is satisfied for all $\mathbf{s} \in \mathscr{S}$.

(ii) ($\Leftarrow$) Let $\widehat{\mathbf{a}}_i = \widehat{\mathbf{y}}_i$ for both $i \in \mathcal{N}$. By Theorem 3.1, it is sufficient to show that recursion (3.5) is satisfied for all $\mathbf{s} \in \mathscr{S}$ and $i \in \mathcal{N}$ under the strategy profile $\widehat{\mathbf{A}}$. Consider Patient 1. Since $\widehat{\mathbf{y}}_1 = \widehat{\mathbf{y}}_2$, $\widehat{a}_2(\mathbf{s}) = \widehat{a}_1(\mathbf{s})\widehat{a}_2(\mathbf{s})$ for all $\mathbf{s} \in \mathscr{S}$ so that the payoffs $\mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)$ are defined as follows:

$$g_1(\mathbf{s}, \widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) = \begin{cases} F_1\big(\mathbf{s}, \mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big) & \text{if } \widehat{a}_2(\mathbf{s}) = 0, \\ u_1(\mathbf{s}, 1) & \text{if } \widehat{a}_2(\mathbf{s}) = 1. \end{cases} \tag{3.39}$$

Since $\widehat{\mathbf{a}}_i = \widehat{\mathbf{y}}_i$ for both $i \in \mathcal{N}$ and $\widehat{\mathbf{y}}_1 = \widehat{\mathbf{y}}_2$, by constraints (3.16a) and (3.16b),

$$\widehat{w}_1(\mathbf{s}) = F_1(\mathbf{s}, \widehat{\mathbf{w}}_1) \text{ if } \widehat{a}_2(\mathbf{s}) = 0; \tag{3.40}$$

and, by constraints (3.16a), (3.16c)-(3.16e) and (3.16g):

$$\widehat{w}_1(\mathbf{s}) = u_1(\mathbf{s}, 1) \geq F_1(\mathbf{s}, \widehat{\mathbf{w}}_1) \text{ if } \widehat{a}_2(\mathbf{s}) = 1. \tag{3.41}$$

By (3.39) - (3.41), it is clear that $\mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) = \widehat{\mathbf{w}}_1$. Therefore, $F_1\big(\mathbf{s}, \mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big) = F_1(\mathbf{s}, \widehat{\mathbf{w}}_1)$ for all $\mathbf{s} \in \mathscr{S}$. By (3.39)-(3.41), for Patient 1, this implies that (3.5) is satisfied for all $\mathbf{s} \in \mathscr{S}$.

($\Rightarrow$) Given $\widehat{\mathbf{A}} \in \Pi$, after setting $\widehat{x}(\mathbf{s}) = \widehat{y}_i(\mathbf{s}) = \widehat{a}_1(\mathbf{s})\widehat{a}_2(\mathbf{s})$ for all $\mathbf{s} \in \mathscr{S}$ and $i \in \mathcal{N}$, and $\widehat{\mathbf{w}}_i = \mathbf{g}_i(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)$ for both $i \in \mathcal{N}$, similar to the proof of ($\Leftarrow$) it can be easily shown that $(\widehat{\mathbf{w}}, \widehat{\mathbf{x}}, \widehat{\mathbf{y}}) \in \Upsilon$.

(iii) The result immediately follows from part (ii).

(iv) We will establish the result in three steps. Let $\Gamma_{\widetilde{\mathbf{s}}} = \big\{\mathbf{A} \in \Gamma | a_1(\widetilde{\mathbf{s}})a_2(\widetilde{\mathbf{s}}) = 1\big\}$ and for each $i \in \mathcal{N}$, define $d_i(\mathbf{s}) = F_i(\mathbf{s}, \mathbf{d}_i)$ for $\mathbf{s} \in \mathscr{S}$ so that $d_i(\mathbf{s})$ represents Patient i's total expected reward starting in state $\mathbf{s} \in \mathscr{S}$ when the other patient is dead. First, we will show that

$$\text{For any } \mathbf{A} \in \Gamma: \quad \mathbf{g}_i(\mathbf{a}_1, \mathbf{a}_2) \geq \mathbf{d}_i \text{ for both } i \in \mathcal{N}. \tag{3.42}$$

Given $\widehat{\mathbf{A}} \in \Gamma$, consider Patient 1. By Theorem 3.1, recursion (3.5) holds for all $\mathbf{s} \in \mathscr{S}$ and $i = 1$ under $\widehat{\mathbf{A}}$. As strategies $\widehat{\mathbf{a}}_1$ and $\widehat{\mathbf{a}}_2$ are fixed, recursion (3.5) defines a stationary, infinite-horizon Markov reward chain. Suppose we apply value iteration to this recursion.

Let $\mathbf{g}_1^n(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)$ be the associated value matrix at iteration $n \geq 0$. More explicitly, for $n \geq 0$ and $\mathbf{s} \in \mathscr{S}$:

$$g_1^{n+1}(\mathbf{s}, \widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) = \max\left\{\widehat{a}_2(\mathbf{s})u_1(\mathbf{s}, 1) + \big[1 - \widehat{a}_2(\mathbf{s})\big]F_1\big(\mathbf{s}, \mathbf{g}_1^n(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big), F_1\big(\mathbf{s}, \mathbf{g}_1^n(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big)\right\}.$$

By induction on $n \geq 0$, we will show that $\mathbf{g}_1^n(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) \geq \mathbf{d}_1$ for all $n \geq 0$. Let $\mathbf{g}_1^0(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) = \mathbf{d}_1$, and for some $m \geq 0$, suppose $\mathbf{g}_1^m(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) \geq \mathbf{d}_1$, so that $F_1\big(\mathbf{s}, \mathbf{g}_1^m(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big) \geq F_1(\mathbf{s}, \mathbf{d}_1)$ for all $\mathbf{s} \in \mathscr{S}$. By the definition of the payoffs $\mathbf{g}_1^{m+1}(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)$ and $\mathbf{d}_1$, we also have $g_1^{m+1}(\mathbf{s}, \widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) \geq F_1\big(\mathbf{s}, \mathbf{g}_1^m(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big)$ and $d_1(\mathbf{s}) = F_1(\mathbf{s}, \mathbf{d}_1)$ for $\mathbf{s} \in \mathscr{S}$. Therefore, $\mathbf{g}_1^{m+1}(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) \geq \mathbf{d}_1$. Because the immediate rewards are finite and $\lambda_1 < 1$, $\mathbf{d}_1$ is finite implying that $\lim_{n\to\infty} \mathbf{g}_1^n(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) = \mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)$. Therefore, by induction $\mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) \geq \mathbf{d}_1$.

Secondly, we will show that if $u_i(\widetilde{\mathbf{s}}, 1) \geq d_i(\widetilde{\mathbf{s}})$ for both $i \in \mathcal{N}$ then $\Gamma_{\widetilde{\mathbf{s}}} \neq \emptyset$. Construct the strategy profile $\widehat{\mathbf{A}}$ as follows: For $\mathbf{s} \in \mathscr{S}$ and $i \in \mathcal{N}$, let $\widehat{a}_i(\mathbf{s}) = 1$ if $\mathbf{s} = \widetilde{\mathbf{s}}$, and $\widehat{a}_i(\mathbf{s}) = 0$ otherwise. By Theorem 3.1, it is sufficient to show that recursion (3.5) is satisfied for all $\mathbf{s} \in \mathscr{S}$ and $i \in \mathcal{N}$ under $\widehat{\mathbf{A}}$. Consider Patient 1. By the construction of $\widehat{\mathbf{A}}$, (3.1) defines the payoffs $\mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)$ as:

$$g_1(\mathbf{s}, \widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) = \begin{cases} u_1(\mathbf{s}, 1) & \text{if } \mathbf{s} = \widetilde{\mathbf{s}}, \\ F_1\big(\mathbf{s}, \mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big) & \text{otherwise.} \end{cases} \tag{3.43}$$

Let $\beta = u_1(\widetilde{\mathbf{s}}, 1) - d_1(\widetilde{\mathbf{s}})$. First, we will show that

$$g_1(\mathbf{s}, \widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) \in \big[d_1(\mathbf{s}), d_1(\mathbf{s}) + \beta\big] \text{ for all } \mathbf{s} \in \mathscr{S}. \tag{3.44}$$

As $\widehat{\mathbf{A}}$ is fixed, recursion (3.43) defines a stationary, infinite-horizon Markov reward chain. Now, suppose we apply value iteration to recursion (3.43). Let $\mathbf{g}_1^n(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)$ be the associated value matrix at iteration $n \geq 0$. Specifically, for $n \geq 0$ and $\mathbf{s} \in \mathscr{S}$:

$$g_1^{n+1}(\mathbf{s}, \widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) = \begin{cases} u_1(\mathbf{s}, 1) & \text{if } \mathbf{s} = \widetilde{\mathbf{s}}, \\ F_1\big(\mathbf{s}, \mathbf{g}_1^n(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big) & \text{otherwise.} \end{cases}$$

By induction on $n \geq 0$, we will show that the following holds for all $n \geq 0$.

$$g_1^n(\mathbf{s}, \widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) \in \big[d_1(\mathbf{s}), d_1(\mathbf{s}) + \beta\big] \text{ for all } \mathbf{s} \in \mathscr{S}. \tag{3.45}$$

Let $\mathbf{g}_1^0(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) = \mathbf{d}_1$. Since $\beta \geq 0$, this implies that (3.45) holds for $n = 0$. Now, suppose (3.45) holds for some $n = m \geq 0$, and for an arbitrary $\mathbf{s} \in \mathscr{S}$ consider $g_1^{m+1}(\mathbf{s}, \widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) - d_1(\mathbf{s})$.

1. If $\mathbf{s} \neq \widetilde{\mathbf{s}}$, then $g_1^{m+1}(\mathbf{s}, \widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) - d_1(\mathbf{s}) = \lambda_1 \sum_{\mathbf{s}' \in \mathscr{S}} \mathscr{P}(\mathbf{s}'|\mathbf{s}) \big[g_1^m(\mathbf{s}', \widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) - d_1(\mathbf{s}')\big]$. Since $\sum_{\mathbf{s}' \in \mathscr{S}} \mathscr{P}(\mathbf{s}'|\mathbf{s}) = 1$, $\lambda_1 < 1$ and $\beta \geq 0$, by the induction hypothesis, this implies that $\big[g_1^{m+1}(\mathbf{s}, \widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) - d_1(\mathbf{s})\big] \in \big[0, \beta\big]$.
2. If $\mathbf{s} = \widetilde{\mathbf{s}}$, then $g_1^{m+1}(\mathbf{s}, \widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) - d_1(\mathbf{s}) = u_1(\mathbf{s}, 1) - d_1(\mathbf{s}) = \beta \geq 0$.

Thus, (3.45) holds for $n = m + 1$. Since $\mathbf{d}_1$ is finite implying that $\lim_{n \to \infty} \mathbf{g}_1^n(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) = \mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)$. Therefore, by induction (3.44) holds. Next, we will show that $u_1(\widetilde{\mathbf{s}}, 1) \geq F_1\big(\widetilde{\mathbf{s}}, \mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big)$.

$$
\begin{aligned}
u_1(\widetilde{\mathbf{s}}, 1) - F_1\big(\widetilde{\mathbf{s}}, \mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big) &= u_1(\widetilde{\mathbf{s}}, 1) - F_1\big(\widetilde{\mathbf{s}}, \mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big) - d_1(\widetilde{\mathbf{s}}) + F_1(\widetilde{\mathbf{s}}, \mathbf{d}_1) \\
&= \beta - \lambda_1 \sum_{\mathbf{s}' \in \mathscr{S}} \mathscr{P}(\mathbf{s}'|\widetilde{\mathbf{s}}) \big[g_1(\mathbf{s}', \widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) - d_1(\mathbf{s}')\big] \geq \beta - \lambda_1 \sum_{\mathbf{s}' \in \mathscr{S}} \mathscr{P}(\mathbf{s}'|\widetilde{\mathbf{s}})\beta = (1 - \lambda_1)\beta \geq 0,
\end{aligned}
$$

where the first inequality follows from the fact that $g_1(\mathbf{s}', \widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) \leq d_1(\mathbf{s}') + \beta$ for all $\mathbf{s}' \in \mathscr{S}$ $\big($by (3.44)$\big)$ and the second inequality is implied by $\lambda_1 < 1$ and $\beta \geq 0$.

Thus, $u_1(\widetilde{\mathbf{s}}, 1) \geq F_1\big(\widetilde{\mathbf{s}}, \mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big)$. Then, by (3.43), the payoffs $\mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)$ can be restated as:

$$
g_1(\mathbf{s}, \widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2) = \begin{cases} \max\big\{u_1(\mathbf{s}, 1), F_1\big(\mathbf{s}, \mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big)\big\} & \text{if } \mathbf{s} = \widetilde{\mathbf{s}}, \\ F_1\big(\mathbf{s}, \mathbf{g}_1(\widehat{\mathbf{a}}_1, \widehat{\mathbf{a}}_2)\big) & \text{otherwise.} \end{cases}
$$

By the construction of $\widehat{\mathbf{A}}$, for Patient 1, this implies that recursion (3.5) is satisfied for all $\mathbf{s} \in \mathscr{S}$. Now, we will establish the main result. Consider the two possible cases for $\max_{i \in \mathcal{N}} \big[d_i(\widetilde{\mathbf{s}}) - u_i(\widetilde{\mathbf{s}}, 1)\big]$.

1. If $\max_{i \in \mathcal{N}} \big[d_i(\widetilde{\mathbf{s}}) - u_i(\widetilde{\mathbf{s}}, 1)\big] > 0$, then by (3.42), $\max_{i \in \mathcal{N}} \big[g_i(\widetilde{\mathbf{s}}, \mathbf{a}_1^*, \mathbf{a}_2^*) - u_i(\widetilde{\mathbf{s}}, 1)\big] > 0$.
2. If $\max_{i \in \mathcal{N}} \big[d_i(\widetilde{\mathbf{s}}) - u_i(\widetilde{\mathbf{s}}, 1)\big] \leq 0$, then since $\Gamma_{\widetilde{\mathbf{s}}} \neq \emptyset$, $\sum_{i \in \mathcal{N}} g_i(\widetilde{\mathbf{s}}, \mathbf{a}_1^*, \mathbf{a}_2^*) \geq \sum_{i \in \mathcal{N}} u_i(\widetilde{\mathbf{s}}, 1)$. Now, consider the following subcases:
   a. If $\sum_{i \in \mathcal{N}} g_i(\widetilde{\mathbf{s}}, \mathbf{a}_1^*, \mathbf{a}_2^*) > \sum_{i \in \mathcal{N}} u_i(\widetilde{\mathbf{s}}, 1)$, then $\max_{i \in \mathcal{N}} \big[g_i(\widetilde{\mathbf{s}}, \mathbf{a}_1^*, \mathbf{a}_2^*) - u_i(\widetilde{\mathbf{s}}, 1)\big] > 0$.
   b. If $\sum_{i \in \mathcal{N}} g_i(\widetilde{\mathbf{s}}, \mathbf{a}_1^*, \mathbf{a}_2^*) = \sum_{i \in \mathcal{N}} u_i(\widetilde{\mathbf{s}}, 1)$, then either $g_i(\widetilde{\mathbf{s}}, \mathbf{a}_1^*, \mathbf{a}_2^*) = u_i(\widetilde{\mathbf{s}}, 1)$ for both $i \in \mathcal{N}$ or $g_i(\widetilde{\mathbf{s}}, \mathbf{a}_1^*, \mathbf{a}_2^*) \neq u_i(\widetilde{\mathbf{s}}, 1)$ for some $i \in \mathcal{N}$. Because $\sum_{i \in \mathcal{N}} g_i(\widetilde{\mathbf{s}}, \mathbf{a}_1^*, \mathbf{a}_2^*) = \sum_{i \in \mathcal{N}} u_i(\widetilde{\mathbf{s}}, 1)$, in the latter case there must exist some $j \in \mathcal{N}$ with $g_j(\widetilde{\mathbf{s}}, \mathbf{a}_1^*, \mathbf{a}_2^*) > u_j(\widetilde{\mathbf{s}}, 1)$ so that $\max_{i \in \mathcal{N}} \big[g_i(\widetilde{\mathbf{s}}, \mathbf{a}_1^*, \mathbf{a}_2^*) - u_i(\widetilde{\mathbf{s}}, 1)\big] > 0$.

□

In Theorem 3.3, we can interpret (3.34) as follows. In a pure equilibrium of game $\mathcal{G}$, for Patient i there are two possible scenarios in each state $\mathbf{s} \in \mathscr{S}$: If the other patient wants to wait, then because the decision of Patient i will not affect the occurrence of the exchange, she is indifferent between waiting and offering to exchange. Otherwise, Patient i offers to exchange as well only if she benefits from the exchange, *i.e.*, her post-transplant reward exceeds her expected payoff-to-go.

In set Λ, if $y_1(\mathbf{s}) \neq y_2(\mathbf{s})$ for some $\mathbf{s} \in \mathscr{S}$, then one of the patients must be strictly randomizing between waiting and offering to exchange in that particular state. As Υ represents a refinement of Λ where binary variables $y_1(\mathbf{s})$ and $y_2(\mathbf{s})$ are not allowed to differ in value, in contrast to Λ, for any feasible solution $(\widehat{\mathbf{w}}, \widehat{\mathbf{x}}, \widehat{\mathbf{y}})$ to Υ, $\widehat{\mathbf{y}}_i$ represents the actual strategy of Patient i in the pure equilibrium that $(\widehat{\mathbf{w}}, \widehat{\mathbf{x}}, \widehat{\mathbf{y}})$ induces. In fact, in any feasible solution $(\widehat{\mathbf{w}}, \widehat{\mathbf{x}}, \widehat{\mathbf{y}})$ to Υ, for any $i \in \mathcal{N}$, $\widehat{\mathbf{y}}_i$ also represents the exchange occurrence probabilities in the equilibrium that $(\widehat{\mathbf{w}}, \widehat{\mathbf{x}}, \widehat{\mathbf{y}})$ induces.

3.3 NUMERICAL EXPERIMENTS

In this section we illustrate our model using clinical data. While maximizing the social objective, we estimate the cost of restricting our attention to pure equilibria, rather than randomized equilibria. After demonstrating that this cost appears to be negligible, we consider pure strategies for the rest of the experiments. We also compare the socially optimal equilibria to each patient's individually optimal equilibria, *i.e.*, the equilibria that maximizes the life expectancy of a particular patient. We then estimate the social welfare loss borne by patient autonomy. Finally, we provide an example that demonstrates the importance of disease severity and the timing of transplantation in kidney matching mechanisms.

3.3.1 Data Sources and Parameter Estimation

In this section, we estimate the transition probabilities and post-transplant rewards, based on clinical data. There is a broad consensus among clinicians that glomerular filtration rate

(GFR) is the best measure of remaining kidney functionality for CKD patients and can be estimated by using the patient's blood level of creatinine, age and sex. CKD is clinically defined as a GFR of less than 60 mL/min/1.73m^2 body surface area, with or without evidence of kidney damage. The stages of CKD are mainly based on measured or estimated GFR and higher GFR levels indicate healthier kidneys. ESRD represents GFR levels less than 15 mL/min/1.73m^2 [139].

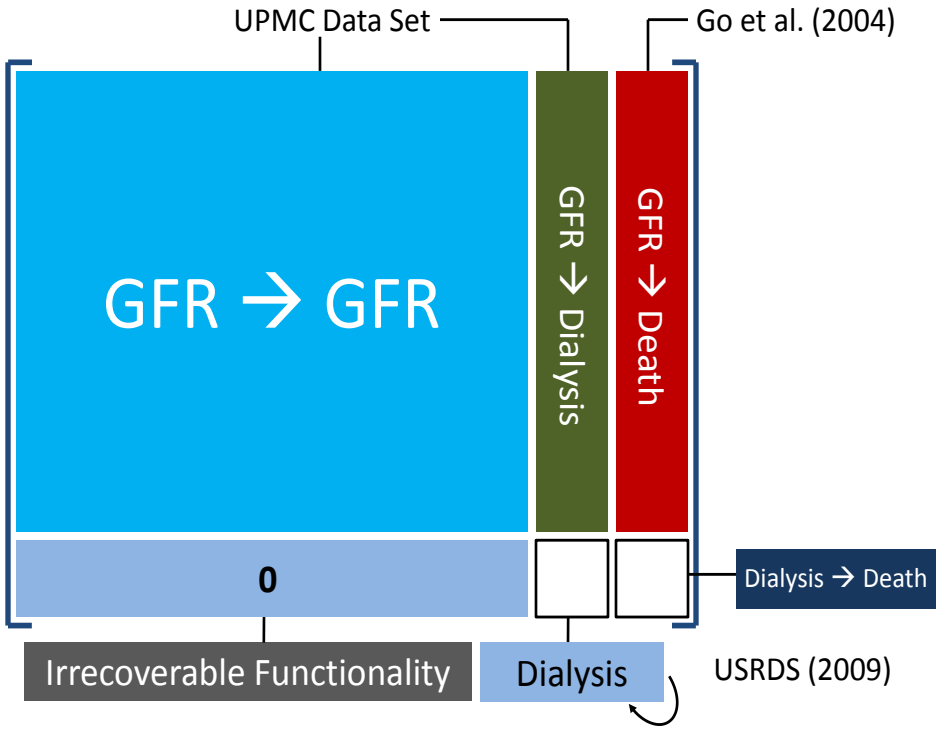

Figure 3.1: The data sources and references used in estimating daily-based health transition matrices.

It appears that no stochastic model of pre-dialysis GFR progression has been described in the literature. We use GFR levels and the patient's dialysis status to represent her health. To calibrate a Markovian progression model of pre-dialysis GFR levels, we use a data set from The Thomas E. Starzl Transplantation Institute at the University of Pittsburgh Medical Center (UPMC), one of the largest transplantation centers nationwide. This data provide a detailed set of laboratory measurements for more than 60,000 diabetic ESRD patients. Race and gender of the patient are felt to be among the most important clinical

factors in estimating the patient's post-transplant survival [210], however due to limited data availability, we restrict our focus to Caucasian and African-American patients. We discretize the continuous range of GFR levels into 10 ranges, the boundaries of which we present in Table 3.1.

Table 3.1: Boundaries of GFR ranges (in mL/min/1.73 m^2) for numerical experiments.

	GFR Range									
Boundary	1	2	3	4	5	6	7	8	9	10
Lower Bound	60	50	40	30	25	22.5	20	17.5	15	0
Upper Bound	∞	60	50	40	30	25	22.5	20	17.5	15

Consistent with national guidelines, we assume that the patient gets on dialysis whenever her GFR falls below 15 mL/min/1.73 m^2. We also assume that once the patient initiates dialysis she cannot recover her renal functionality prior to receiving a transplant [6, 117]. We add the absorbing death state to the set of GFR ranges so that $\Omega = \{1, 2, ..., 11\}$ refers to the set of health states for each individual patient. Because the UPMC data set has sparsely available GFR data, in an approach similar to Shechter [189], for each patient we use a shape-preserving piecewise Hermitian cubic spline to interpolate her missing laboratory measurements on a daily basis [98]. We let $N_s(s')$ denote the number of patients whose GFR moves from range $s \in \Phi$ into $s' \in \Phi$ on any two successive days. Then, we define $q(s'|s)$ to be the patient's probability of having a GFR in range $s' \in \Phi$ on day $h+1$ given she had a GFR in range $s \in \Phi$ on day h. Because the patient does not recover her kidney functionality after dialysis, $q(s'|S-1) = 0$ for all $s' \in \Phi \setminus \{S-1\}$ and $q(S-1|S-1) = 1$. We calculate the probability of moving from a pre-dialysis GFR range $s \in \Phi$ into GFR range $s' \in \Phi$ as $q(s'|s) = N_s(s') \left(\sum_{s' \in \Phi} N_s(s')\right)^{-1}$. Note that the UPMC data set does not have complete patient mortality information. Therefore, we caution that the probabilities $\{q(s'|s)\}_{\{s,s' \in \Phi\}}$ are conditional on the patient's survival. We denote the patient's death probability in GFR range $s \in \Phi$ by $\varphi(s)$. We use United States Renal Data System (USRDS) [210] to estimate the patient's death probability in dialysis and GFR-based mortality rates from Go et al. [81] to estimate the patient's death probabilities in pre-dialysis stage (see Figure 3.1 for a

summary of data sources and references). Then, we define the probabilities governing daily transitions among a single patient's health states as:

$$\widetilde{P}(s'|s) = \begin{cases} \varphi(s) & \text{for } s \in \Phi \text{ and } s' = S, \\ \big[1 - \varphi(s)\big] q(s'|s) & \text{for } s \in \Phi \text{ and } s' \in \Phi, \\ 1 & \text{for } s = s' = S, \\ 0 & \text{for } s = S \text{ and } s' \in \Phi. \end{cases}$$

Recall that our model has two types of rewards: Immediate rewards, $u_i(\mathbf{s}, 0)$, and expected post-transplant rewards, $u_i(\mathbf{s}, 1)$. Although these rewards are defined as a function of the state of the game, because patients' health statuses are independent of each other, we define the rewards of the game mainly in terms of patients' individual health states. We define $r(s, 0)$ to be the immediate reward in days that patient accrues if she waits in state $s \in \Omega$, and $r(s, 1)$ to be the expected post-transplant reward in quality-adjusted life days when she receives a transplant in state $s \in \Omega$. Following recent literature in kidney transplantation [112, 230], to account for the negative side effects of dialysis on the patient's quality of life we assume a quality-adjustment factor 0.8 for being dialysis; e.g. patients are assumed to be indifferent between a year spent on dialysis and 0.8 years not on dialysis. Note that while there may be a loss of quality of life as GFR decreases, we are unaware of any study that quantifies this decrease. Therefore, for the immediate rewards we define:

$$r(s, 0) = \begin{cases} 1 & \text{if } s \in \{1, ..., S-2\}, \\ 0.8 & \text{if } s = S - 1, \\ 0 & \text{if } s = S. \end{cases}$$

We use available post-transplant survival rates, the proportional hazards model and the associated risk adjustment coefficients from Scientific Registry of Transplant Recipients (SRTR) [180, 181] to estimate expected post-transplant survivals. Due to limited data, we assume exponential growth death rates to extrapolate long-term survival rates, as SRTR only models short-term survival. We set biweekly decision epochs and apply a 0.97 annual discount rate for each patient (daily $\widehat{\lambda} = 0.999916$ and biweekly $\lambda = 0.998829$). Because our transition probability estimations are on daily basis and decisions are revisited every two weeks, we

adjust the daily parameters to a biweekly basis. We denote the matrix that governs biweekly GFR transitions by $\mathbf{P} = \widetilde{\mathbf{P}}^{14}$. We also define $\psi^t(s)$ as the total expected discounted immediate reward in quality-adjusted life days that will be accrued in the last $14 - t$ days of the current stage, and recursively calculate it as:

$$\psi^t(s) = \begin{cases} r(s,0) + \widehat{\lambda} \sum_{s' \in \Omega} \widetilde{P}(s'|s)\psi^{t+1}(s') & \text{for } s \in \Omega \text{ and } t = 0, ..., 13, \\ 0 & \text{for } s \in \Omega \text{ and } t = 14. \end{cases}$$

After we discount the expected post-transplant rewards and specify them by a subscript for Patient i, we define the rewards of the game as follows:

$$u_i(\mathbf{s}, m) = \begin{cases} r_i(s_i, 1) & \text{for } \mathbf{s} = (s_1, s_2) \in \mathscr{S} \setminus \mathscr{D} \text{ and } m = 1, \\ 0 & \text{for } \mathbf{s} = (s_1, s_2) \in \mathscr{D} \text{ and } m = 1, \\ \psi_i^0(s_i) & \text{for } \mathbf{s} = (s_1, s_2) \in \mathscr{S} \text{ and } m = 0. \end{cases}$$

For our experiments, we simulate 2500 exchange cases by using the 10-year average frequency of patient-donor characteristics in living-donor kidney transplantations that are available from SRTR for the years 1998-2007. Following the proportional hazards model that we use to estimate the expected post-transplant rewards, our simulations consider donor's age and gender; patient's age, gender and race, and the antigen mismatch status between patient-donor pairs as independent risk factors on patients' expected post-transplant survivals. We assume that patients are of same ethnicity with their incompatible donors, and unrelated to the donor in the exchange who is compatible with her. We simulate the patients' initial GFR ranges uniformly over Φ.

3.3.2 Welfare Loss Due to Patient Autonomy and Equilibrium Selection

We solve our MIP models to characterize socially optimal mixed and pure equilibria. Throughout the rest of this section, we let a socially optimal mixed (pure) equilibrium refer to the equilibrium that maximizes the sum of the patients expected payoffs over the space of mixed (pure) equilibria starting from the initial state of the game. For each case we solve the mathematical programs

$$\max_{(\mathbf{w},\mathbf{x},\mathbf{y})\in\Lambda}\left(\sum_{i\in\mathcal{N}} w_i(\widetilde{\mathbf{s}})\right) \quad \text{and} \quad \max_{(\mathbf{w},\mathbf{x},\mathbf{y})\in\Upsilon}\left(\sum_{i\in\mathcal{N}} w_i(\widetilde{\mathbf{s}})\right),$$

to estimate the cost of restricting our attention to pure strategies in terms of the total number of expected quality-adjusted life days. Note that because $\Upsilon \subseteq \Lambda$, (*i.e.*, the MIP that allows randomized equilibria is a relaxation of the MIP that considers only pure equilibria), these mathematical programs may share the same optimal solution. By Theorems 3.2 and 3.3, $\max_{(\mathbf{w},\mathbf{x},\mathbf{y})\in\Lambda}\left[\sum_{i\in\mathcal{N}} w_i(\widetilde{\mathbf{s}})\right] - \max_{(\mathbf{w},\mathbf{x},\mathbf{y})\in\Upsilon}\left[\sum_{i\in\mathcal{N}} w_i(\widetilde{\mathbf{s}})\right]$ quantifies the aforementioned cost exactly. Our experiments reveal that a socially optimal pure equilibrium is only negligibly worse than a socially randomized optimal equilibrium. In all our instances, it is no more than 0.01%. Therefore, as randomized strategies are less applicable than pure strategies, we narrow our focus to pure equilibria and quantify the social welfare loss borne by patient autonomy. In the rest of this section, we let $\mathbf{A}^*$ refer to a socially optimal pure equilibrium.

We consider a central decision-maker who acts on behalf of both pairs for the society's interest. Provided that transplantation surgeries occur simultaneously and $\widetilde{\lambda} \in (0,1)$ is the social discount factor, the socially optimal policy from this decision-maker's perspective may be modeled as a discrete-time infinite horizon MDP. We assume this decision-maker revisits her decisions periodically at the same frequency that the patients do in the game. We define $W(\mathbf{s})$ as the maximum total expected reward that the whole exchange cycle can gain in this model when the system starts in state $\mathbf{s} \in \mathscr{S}$ which we recursively calculate as:

$$W(\mathbf{s}) = \max\left\{\sum_{i\in\mathcal{N}} u_i(\mathbf{s},1), \sum_{i\in\mathcal{N}} u_i(\mathbf{s},0) + \widetilde{\lambda}\sum_{\mathbf{s}'\in\mathscr{S}} \mathscr{P}(\mathbf{s}'|\mathbf{s})W(\mathbf{s}')\right\} \quad \text{for } \mathbf{s}\in\mathscr{S}. \tag{3.46}$$

We let $\mathscr{X}$ denote the set of states in which exchange is an optimal decision in this model, *i.e.*, $\mathscr{X} = \left\{\mathbf{s}\in\mathscr{S} | W(\mathbf{s}) = \sum_{i\in\mathcal{N}} u_i(\mathbf{s},1)\right\}$, and define $\vartheta_i(\mathbf{s})$ as the expected survival of

Patient $i \in \mathcal{N}$ starting in state $\mathbf{s} \in \mathscr{S}$ under a socially optimal policy, which we recursively calculate as follows:

$$\vartheta_i(\mathbf{s}) = \begin{cases} u_i(\mathbf{s}, 1) & \text{for } s \in \mathscr{X}, \\ F_i(\mathbf{s}, \boldsymbol{\vartheta}_i) & \text{otherwise.} \end{cases} \tag{3.47}$$

Because $\mathbf{A}^*$ is a socially optimal pure equilibrium, $g_i(\widetilde{\mathbf{s}}, \mathbf{a}_i^*, \mathbf{a}_{-i}^*) - \vartheta_i(\widetilde{\mathbf{s}})$ denotes the welfare loss for Patient $i \in \mathcal{N}$, and $\sum_{i \in \mathcal{N}} \left[g_i(\widetilde{\mathbf{s}}, \mathbf{a}_i^*, \mathbf{a}_{-i}^*) - \vartheta_i(\widetilde{\mathbf{s}}) \right]$ denotes the minimum social welfare loss due to patient autonomy. Note that the socially optimal policy may not be an equilibrium of game $\mathcal{G}$. In our experiments, we set $\widetilde{\lambda} = 0.998829$.

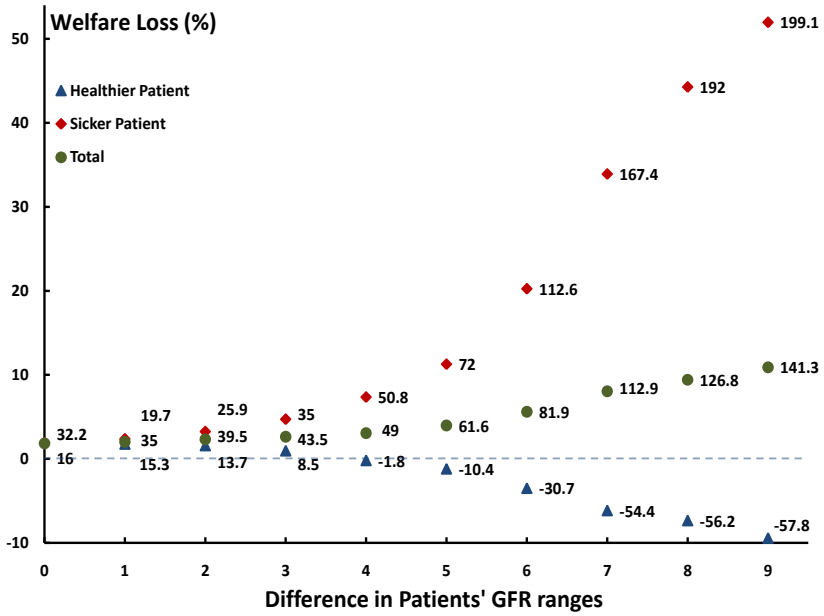

Figure 3.2: Social welfare loss and patients' individual welfare losses due to patient autonomy.

We treat the difference in the patients' GFR ranges in the initial state of the game ($|\widetilde{s}_1 - \widetilde{s}_2|$) as a measure of conflict between their self-interests. We also consider the patients seperately as healthier and sicker. Because lower GFR levels which indicate sicker conditions are represented by higher state indices, Patient i refers to sicker patient if $\widetilde{s}_i \geq \widetilde{s}_{-i}$, and healthier patient otherwise. For each case, we calculate the minimum social welfare loss and

the patients' individual welfare losses in absolute (in quality-adjusted life-weeks) and relative terms as a function of the difference in their GFR ranges. We present the average welfare losses across our numerical experiments in Figure 3.2. In the figure, the number next to each data label indicates the loss in quality-adjusted life weeks.

From the figure, social welfare loss does not decrease as the patients' health statuses diverge, which we interpret as follows: Because the central decision-maker acts solely for the society's interest and the death of one patient leaves the other untransplanted, as one of the patients gets sicker, the central decision-maker becomes more likely to recommend exchange as an optimal decision. On the other hand, when patients are autonomous, the healthier patient can force the sicker patient to wait, although the sicker patient's death would render the exchange infeasible. Also, the sicker patient benefits from the central decision-maker's decisions, and the impact of patient autonomy on her welfare is more dramatic in absolute and relative terms.

As the society's interest may conflict with patients' self-interests, a socially optimal equilibrium strategy may not be an optimal equilibrium strategy that a patient can play. Therefore, for each individual patient we calculate the cost of playing the socially optimal equilibrium strategy rather than any other equilibrium strategy. We let ${}^{i}\mathbf{A}^{*} = ({}^{i}\mathbf{a}_1^{*}, {}^{i}\mathbf{a}_2^{*})$ denote a pure equilibrium that maximizes Patient i's total expected payoff, *i.e.*, ${}^{i}\mathbf{A}^{*} \in \arg\max_{\mathbf{A}\in\Pi} g_i(\widetilde{\mathbf{s}}, \mathbf{a}_1, \mathbf{a}_2)$. Then, $g_i(\widetilde{\mathbf{s}}, {}^{i}\mathbf{a}_1^{*}, {}^{i}\mathbf{a}_2^{*}) - g_i(\widetilde{\mathbf{s}}, \mathbf{a}_1^{*}, \mathbf{a}_2^{*})$ provides an upper bound for Patient i's cost of playing a socially optimal equilibrium strategy rather than any other equilibrium strategy. For each Patient $i \in \mathcal{N}$, by Theorem 3.3 (*iii*), we calculate $g_i(\widetilde{\mathbf{s}}, {}^{i}\mathbf{a}_1^{*}, {}^{i}\mathbf{a}_2^{*})$ by solving the mathematical program $\max_{(\mathbf{w},\mathbf{y},\mathbf{z})\in\Upsilon} w_i(\widetilde{\mathbf{s}})$.

From Table 3.2, as patients' health statuses diverge, a socially optimal equilibrium considers the sicker patient's interests more, that is, playing a socially optimal equilibrium strategy costs less to the sicker patient. Irrespective of the difference in patients' GFR ranges, a socially optimal equilibrium deviates more from the healthier patient's individually optimal equilibrium than it does from the sicker's. In our experiments, the sicker patient under the socially optimal equilibrium is usually very close to her individually optimal equilibrium. Specifically, in 72% of the cases, the sicker patient's individually optimal equilibrium

Table 3.2: Patients' maximum welfare losses from following a socially optimal equilibrium.

		Difference in Patients' GFR Ranges									
Loss	Patient	0	1	2	3	4	5	6	7	8	9
Relative	Healthier	0.76	1.20	1.49	2.11	2.40	3.00	3.54	3.61	3.78	3.82
	Sicker	0.89	0.80	0.71	0.68	0.61	0.58	0.57	0.50	0.26	0.00
Absolute	Healthier	7.43	9.69	12.20	17.08	19.64	24.96	29.73	26.88	28.64	31.13
	Sicker	7.43	6.57	5.75	5.28	6.04	4.15	3.41	2.67	1.26	0.00

Relative losses are in % and absolute losses are in quality-adjusted life weeks.

is within 1% of the socially optimal equilibrium, and in 90% of the cases her individually optimal equilibrium is within 3% of the socially optimal equilibrium.

3.3.3 Valuing Exchanges: An Example

In this section, we elucidate how the patients' quality-adjusted life expectancies from our model can be used to calibrate edge-weights in graphs used to form patient-donor pairs. We create an example graph of patient-donor pairs for which maximizing the total number of transplants may imply adverse welfare outcomes. In Figure 3.3, we have 4 patient-donor pairs with specified characteristics.

For the set of patient-donor pairs in Figure 3.3, we have two possible matching scenarios: In Scenario 1, Patient 1 is matched to Donor 2, Patient 2 is matched to Donor 1, Patient 3 is matched to Donor 4, and Patient 4 is matched to Donor 3. In Scenario 2, Patient 2 is matched to Donor 3, Patient 3 is matched to Donor 2, and Patients 1 and 4 remain untransplanted. Although Scenario 1 maximizes the number of transplants, when we compare the social outcomes under such scenarios, we observe the following: In Scenario 1, an immediate exchange yields a total of 53.27 QALYs. When the patients behave autonomously in each of the matchings, the socially optimal equilibria yields 50.49 QALYs in total. In

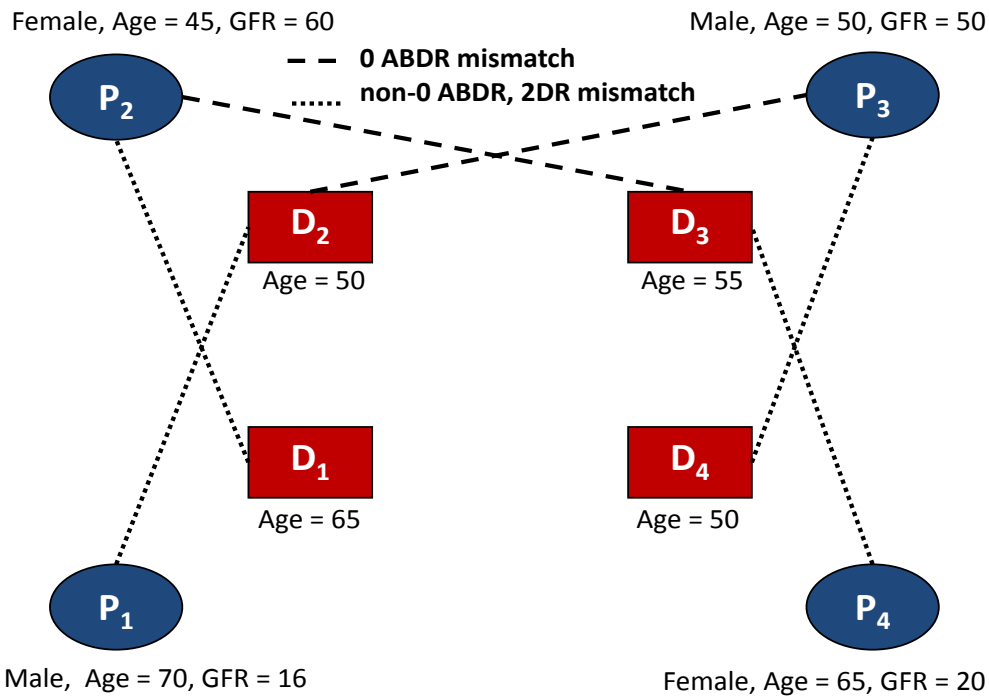

Figure 3.3: Patient-donor characteristics for the matching example

Scenario 2, an immediate exchange yields 52.76 QALYs. Because Patients 1 and 4 are untransplanted, when Patients 2 and 3 behave autonomously, a socially optimal equilibria yield 54.27 QALYs. Note that in this case, because we assume Patients 1 and 4 will never receive a transplant, we calculate their remaining life expectancies by two separate Markov reward chains (see $\mathbf{d}_1$ as an example in the proof of Theorem 3.3 (iv)). Thus, if the patients are autonomous and the edge weight of each possible matching is modeled as the patients' total life expectancies in a socially optimal equilibrium of the game played in that particular matching, then Scenario 2 is optimal although it has fewer transplants than Scenario 1. Note that in Scenario 2, the socially optimal equilibrium provides considerably higher social welfare than that of immediate exchange. Intuitively, when patients behave autonomously, if they are at closer stages of disease, because they conflict less, their matchings yield superior welfare outcomes compared to matchings involving patients at different stages.

3.4 CONCLUSIONS

Kidney exchanges have been formulated as finding matchings in a graph, the timing of exchange has not been addressed yet. In this chapter, we propose a weighting scheme to value kidney exchanges for self-interested and autonomous patients with dynamic health. We model the patients' transplant timing decisions as a non-zero-sum stochastic game and analyze the resulting equilibria of the game. Because a complete characterization of the equilibria is computationally intractable, we develop mathematical programming representations of the resulting equilibrium conditions and analyze the equilibrium selection problem from a societal point of view. The MIP formulation that we develop for pure equilibrium selection can be easily extended to the multi-pair cyclic kidney exchanges such as 3- and 4-way kidney exhanges. Our numerical experiments indicate that matching patients based on 0-1 preferences ignoring the timing of the exchange under patient autonomy may result in socially suboptimal circumstances. We assess the importance of disease progression in timing of an exchange and demonstrate that matching patients at similar stages of CKD provides more preferable outcomes in terms of the social welfare gained by matching patients based on their life expectancies and the social welfare lost by patient autonomy. Because patients may exchange their kidneys prior to initiation of dialysis, our model and results also shed light on the welfare consequences of preemptive PKEs which are recommended but not very common in practice.

4.0 THE OPTIMAL TIMING OF STATIN INITIATION FOR PATIENTS WITH TYPE 2 DIABETES

In this chapter we consider the question of when to initiate statin treatment to maximize a Type 2 diabetes patient's expected QALYs prior to the occurrence of the first CHD or stroke event, or death from all other causes. We refer to these three outcomes collectively as *terminal events*. Prevention of cardiovascular events is one of the primary goals of the ATP III guidelines and the goal of maximizing QALYs prior to a first terminal event is consistent with this goal.

We summarize the contributions of this chapter as follows. First, we develop a model that can guide physicians and patients in the use of statins for the primary prevention of cardiovascular events. Specifically, we formulate the statin initiation problem as a discrete-time infinite-horizon MDP. We derive sufficient conditions for the resulting optimal policy to be of control-limit type, and analyze how these limits change with respect to patient's age. Second, we present numerical results based on a large longitudinal data set from the Mayo Clinic in Rochester, MN. Finally, we compare the performance of the published U.S. guidelines to the optimal policies generated by our model.

The remainder of this chapter is organized as follows: In Section 4.1, we describe our MDP model in detail. In Section 4.2 we analyze the structure of the underlying optimal policies of our model. In Section 4.3 we support our analytical results by a series of numerical experiments and present several policy implications. In Section 4.4 we present conclusions and summarize the limitations of our model and numerical experiments.

4.1 MODEL FORMULATION

In this section, we formulate a discrete-time, infinite-horizon MDP model for the optimal timing of statin initiation for patients with Type 2 diabetes. Once a patient with Type 2 diabetes initiates statin treatment, for the long-term benefit of the treatment, clinical guidelines recommend that she should take statins for the remainder of her life [192, 222]. Assuming there are no severe side effects of the therapy, if we consider the clinical intent for those patients who can tolerate the treatment, we can view statin initiation as a one-time irreversible decision [192]. Therefore, the decision we consider is when to initiate statin treatment over the course of the patient's lifetime based on her CHD and stroke risk profile. The objective of the MDP model is to maximize the patient's QALYs prior to the first terminal event.

Following the UKPDS risk model, we describe the patient's CHD and stroke risk profile by her cholesterol, SBP, HbA1c, age, gender, ethnicity and smoking status at diagnosis. Of these risk factors, patient's age, cholesterol, SBP and HbA1c levels are dynamic. We incorporate the effect of the patient's age on the CHD and stroke risk profile by a time index. Consistent with other studies in the medical literature, we model the evolution of the patient's SBP and HbA1c levels deterministically as a function of time [29, 30, 87, 99, 105].

We model the progression of the patient's on- and off-treatment LR levels stochastically as a finite-state discrete-time Markov chain. We describe the components of our MDP model in detail as follows:

Time Horizon: We assume the treatment decision is revisited periodically (e.g. annual visits to an endocrinologist) over the patient's lifetime prior to the occurrence of the first terminal event. Because the time to first terminal event is random, our model has two separate but back to back decision horizons as non-stationary and stationary (See Figure 4.1 for the division of the decision horizon into two subhorizons). The non-stationary decision horizon is finite and precedes the stationary decision horizon. On the other hand, stationary decision horizon is infinite long. We define $T = \{0, 1, 2, ..., N\}$ as the set of decision epochs, where $T' = T \setminus \{N\}$ represents the set of epochs in the non-stationary horizon. We assume the problem parameters at epoch $N-1$ remain stationary beyond epoch $N-1$. Therefore,

epochs beyond $N-1$ are not differentiated from each other and are represented by N. This division and modeling of the decision horizon reflect the non-stationary nature of risk with respect to age, and provides an approximation framework for the patient's remaining expected QALYs prior to the first terminal event over the time horizon for which there is insufficient medical data due to low sample sizes at high ages. Finally, we let *stage* t refer to time interval between epochs t and $t+1$ and without loss of generality, we assume the length of each stage is $\tau > 0$ years.

States: We discretize the continuous range of LR values by a finite set of states $\mathcal{L}' = \{1, 2, ..., L\}$ where each $\ell \in \mathcal{L}'$ corresponds to a pre-specified *LR-range* and lower indexed ranges indicate lower values of LR. We add an absorbing state $L+1$ to the set of LR-ranges to denote a terminal event, and let $\mathcal{L} = \mathcal{L}' \cup \{L+1\}$. Note that our state description also involves static risk factors, including age, gender, smoking status, and dynamic but non-stochastic risk factors: SBP, HbA1C. Because these factors are not affected by the patient's treatment status in our model, for notational convenience we suppress the dependency on them.

Actions: In each state $\ell \in \mathcal{L}$ there are two possible actions and the action is chosen from the set $\{W, I\}$, where W represents waiting for one more stage and I stands for initiating treatment immediately. We assume that using statins reduces the patient's LR level by a factor ω which we call the patient's *treatment-effect factor*. We define the treatment status of the patient by a binary indicator $m \in \mathcal{M} = \{0, 1\}$, where "0" and "1" refer to *not using* and *using* statins, respectively. Because statin initiation is a one-time irreversible decision, once treatment is initiated m switches from 0 to 1 and remains as such.

Probabilities: We have four types of probabilities in our model: The probabilities of non-CHD or stroke-related death, CHD and stroke probabilities, and the transition probabilities among the LR-ranges. At epoch $t \in T'$, a non-CHD or stroke-related death occurs with probability d_t. Otherwise, if the patient is in state $\ell \in \mathcal{L}'$ under treatment status $m \in \mathcal{M}$, a CHD event occurs with probability $\pi_t^C(\ell, m)$ and a stroke event occurs with probability $\pi_t^S(\ell, m)$ (See Section 4.3.2 for details on how we estimate CHD and stroke probabilities). Assuming that CHD and stroke events are mutually exclusive, *i.e.* they do not occur simultaneously at the same time in any particular stage, we let $\pi_t^{\triangledown}(\ell, m) = \pi_t^C(\ell, m) + \pi_t^S(\ell, m)$

denote the patient's probability of having a CHD or a stroke event in state $\ell \in \mathcal{L}'$ under treatment status $m \in \mathcal{M}$ in stage t.

Given the patient is in state $\ell \in \mathcal{L}$ under treatment status $m \in \mathcal{M}$ at epoch $t \in T'$, the probability of moving into the absorbing state $L+1$ at epoch $t+1$ is denoted by $p_t^m(L+1|\ell)$, where $p_t^m(L+1|\ell) = d_t + [1-d_t]\pi_t^{\triangledown}(\ell, m)$ for $(\ell, m) \in \mathcal{L}' \times \mathcal{M}$ and $p_t^m(L+1|L+1) = 1$ for both $m \in \mathcal{M}$. Given the patient is in state $\ell \in \mathcal{L}'$ at epoch $t \in T'$ and does not incur a terminal event in stage t, the probability of being in state $\ell' \in \mathcal{L}'$ at the next epoch is denoted by $q(\ell'|\ell)$. Note that probabilities $q(\ell'|\ell)$ are conditional on patient's survival from a terminal event. Then, we define $p_t^m(\ell'|\ell)$ to be the patient's probability of being in state $\ell' \in \mathcal{L}$ at epoch $t+1$ given she is in state $\ell \in \mathcal{L}$ under treatment status $m \in \mathcal{M}$ at epoch $t \in T'$, which we write as:

$$p_t^m(\ell'|\ell) = \begin{cases} \big[1 - p_t^m(L+1|\ell)\big] q(\ell'|\ell) & \text{if } \ell, \ell' \in \mathcal{L}', \\ p_t^m(L+1|\ell) & \text{if } \ell \in \mathcal{L}',\ \ell' = L+1, \\ 1 & \text{if } \ell = \ell' = L+1, \\ 0 & \text{otherwise.} \end{cases} \tag{4.1}$$

For convenience we let $\mathbf{Q} = [q(\ell'|\ell)]$ denote the patient's conditional LR-range transition probability matrix and $\mathbf{P}^m(t) = [p_t^m(\ell'|\ell)]$ denote the patient's unconditional transition probability matrix under treatment status $m \in \mathcal{M}$ at epoch $t \in T'$.

Rewards: Studies on statin treatment incorporate the health-related quality of life adjustment due to negative side effects of statins by means of a disutility coefficient [155, 212]. We define $r^m(\ell) = \tau(1 - m\sigma)$ to be the immediate reward in QALYs accrued in state $\ell \in \mathcal{L}'$, under treatment status $m \in \mathcal{M}$, where the parameter $\sigma \in [0, 1]$ is referred to as the *utility decrement* or *disutility* and represents the reduction in quality of life during a year of life due to side effects from medication. Since our objective is to maximize the patient's QALYs prior to the first terminal event, we set all the immediate rewards associated with the absorbing state $L+1$ to zero, *i.e.*, $r^m(L+1) = 0$ for both $m \in \mathcal{M}$. Figure 4.2 illustrates the states, transitions and rewards for a particular stage t. The single node on the left represents the patient's current LR-range at epoch t. The nodes on the right are partitioned into states as LR-ranges and terminal events.

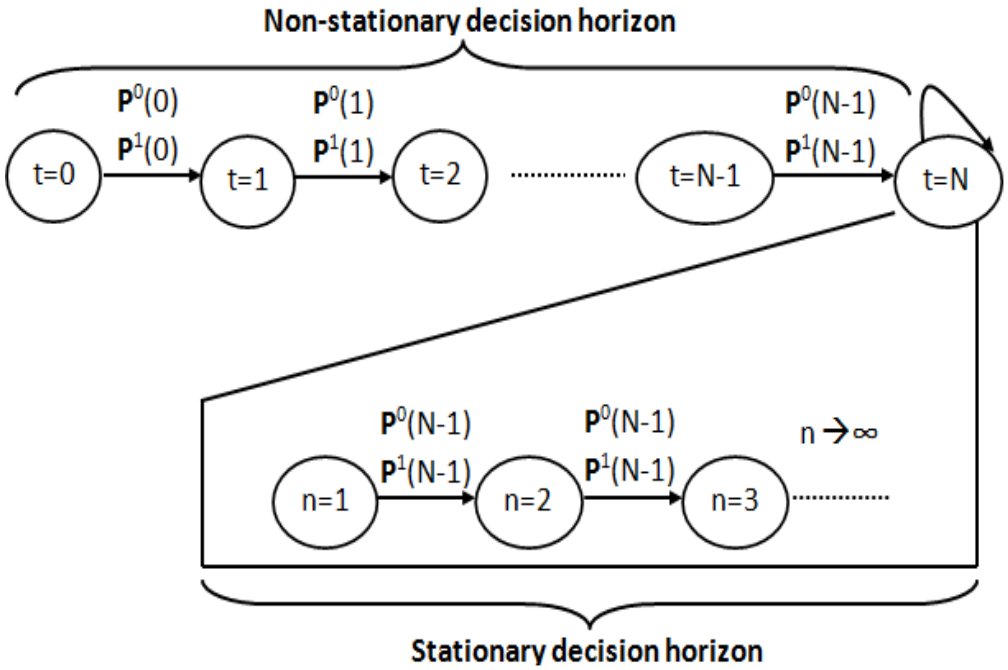

Figure 4.1: Division of the decision horizon into non-stationary and stationary subhorizons. $\mathbf{P}^m(t)$ denotes the probability matrix that governs the transitions in stage $t \in T$ for $m = 0$ (off-treatment) and $m = 1$ (on-treatment).

For notational convenience, in the rest of this chapter, except the transition probability matrices, we let the terms in bold refer to a real-valued $L+1$ dimensional vector, *i.e.*, $\mathbf{v}$ refers to the vector $\big[v(\ell)\big]_{\ell\in\mathcal{L}}$. For convenience, given $\mathbf{v} \in \mathbb{R}^{L+1}$, $\ell \in \mathcal{L}$, $m \in \{0,1\}$ and $t \in T'$, we define $F_t^m(\ell, \mathbf{v}) = \lambda \sum_{\ell'\in\mathcal{L}} p_t^m(\ell'|\ell)v(\ell')$. We also represent componentwise operations and relations between two vectors in vector notation. For instance, given $\mathbf{v}_1 = \big[v_1(\ell)\big]_{\ell\in\mathcal{L}}$ and $\mathbf{v}_2 = \big[v_2(\ell)\big]_{\ell\in\mathcal{L}}$, $\mathbf{v}_1 = \mathbf{v}_2$ refers to $v_1(\ell) = v_2(\ell)$ for all $\ell \in \mathcal{L}$.

In our model, the patient continues to accumulate rewards prior to her first CHD or stroke event. Once she incurs a terminal event she transitions into state $L + 1$, which is absorbing and provides no rewards. Therefore, upon occurrence of a terminal event, the accumulation of rewards stops and the patient terminates the process. We define $\mu_t(\ell)$ as the patient's *expected post-treatment reward* if the treatment is initiated in state $\ell \in \mathcal{L}$ at epoch $t \in T$. Since statin initiation is a one-time decision and the patient uses statins from the time of initiation to the end of her life, the expected post-treatment rewards can be

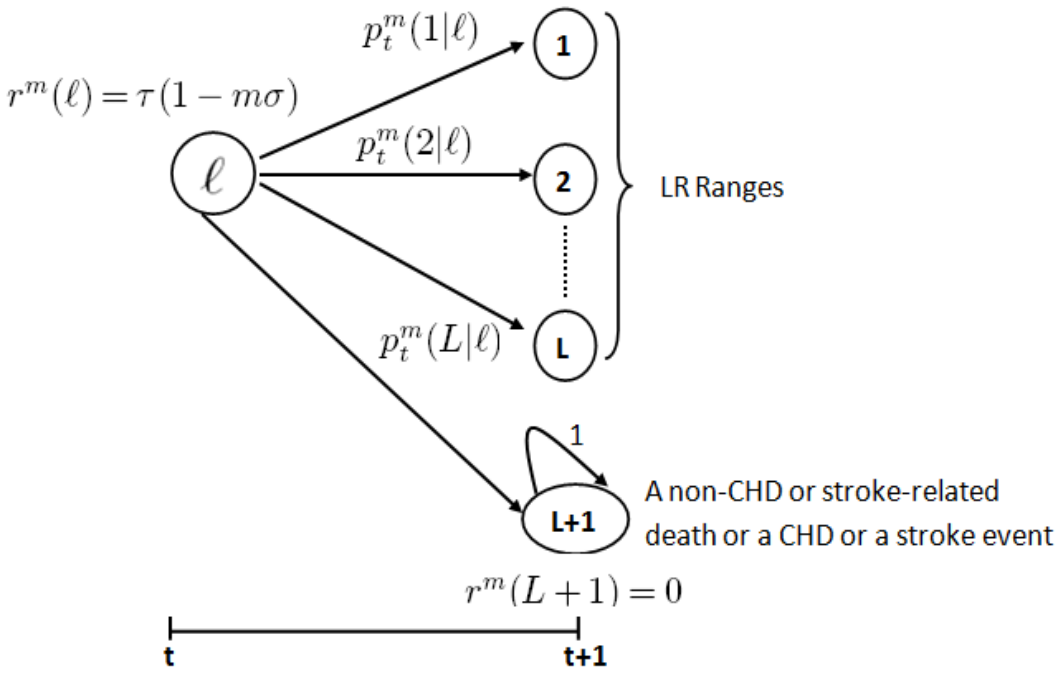

Figure 4.2: State transition diagram at epoch $t \in T'$ under treatment status $m \in \mathcal{M}$.

recursively defined as:

$$\mu_t(\ell) = \begin{cases} r^1(\ell) + F_t^1(\ell, \boldsymbol{\mu}_{t+1}) & \text{for } \ell \in \mathcal{L} \text{ and } t \in T', \\ r^1(\ell) + F_{t-1}^1(\ell, \boldsymbol{\mu}_t) & \text{for } \ell \in \mathcal{L} \text{ and } t = N; \end{cases} \tag{4.2}$$

where $\lambda \in (0, 1)$ is the discount factor per stage [59, 82].

For a patient with no history of CHD or stroke in state $\ell \in \mathcal{L}$ at epoch $t \in T$, we let $u_t(\ell)$ denote the maximum total expected discounted QALYs prior to the first terminal event and we define $a_t(\ell)$ as the corresponding optimal action, which we determine by solving the following optimality equations:

$$u_t(\ell) = \begin{cases} \max\{r^0(\ell) + F_t^0(\ell, \mathbf{u}_{t+1}), \mu_t(\ell)\} & \text{for } \ell \in \mathcal{L} \text{ and } t \in T', \\ \max\{r^0(\ell) + F_{t-1}^0(\ell, \mathbf{u}_t), \mu_t(\ell)\} & \text{for } \ell \in \mathcal{L} \text{ and } t = N. \end{cases} \tag{4.3}$$

Specifically, in state $\ell \in \mathcal{L}$ of epoch $t \in T$, if $u_t(\ell) = \mu_t(\ell)$, then it is optimal to initiate treatment, *i.e.* $a_t(\ell) = I$. Otherwise, it is optimal to wait, *i.e.* $a_t(\ell) = W$. Note that the

expected post-treatment rewards in (4.3) are determined by a separate Markov reward chain in which the patient is on statins. Therefore, they are fixed composite parameters of the model.

4.2 STRUCTURAL PROPERTIES

In this section we derive structural results of the MDP model that we developed in section 4.1. While MDP models have been applied in several other clinical contexts (for an extensive review of discrete-time Markov models in health care see [9, 10, 52, 125, 176]), we provide several extensions. Specifically, within the context of living-donor liver transplantation, Alagöz et al. [10] provides sufficient conditions to prove the existence of an optimal control-limit policy for an infinite-horizon optimal stopping time model. Although reasonable for liver transplant decisions this assumption is not appropriate for long-term chronic diseases, such as diabetes and heart disease, for which the risk of complications and comorbidities changes significantly with age [31]. We provide weaker and more intuitive conditions to establish the optimality of control-limit policies in both stationary and non-stationary contexts. Since most U.S. guidelines do not acknowledge age as an explicit risk factor in treating patients with diabetes we also analyze the time-behavior of the resulting control-limits to investigate the influence of age in treatment design.

We begin our analyses by defining the notion of an "increasing failure rate" (IFR) transition probability matrix, which has been shown to be useful in proving the structural properties of MDPs in maintenance and reliability theory and appears to match clinical data closely in varying contexts [10, 109, 219].

Definition 4.1. *[21] An $n \times n$ stochastic matrix $\mathbf{H} = \big[h(j|i)\big]$ is said to have the IFR property if $\sum_{j=1}^{k} h(j|i)$ is nonincreasing in i for all $k = 1, ..., n$.*

In our model, under treatment status $m \in \mathcal{M}$ at epoch $t \in T'$, if the matrix $\mathbf{P}^m(t)$ is IFR, an intuitive explanation is as follows: The higher the LR the patient has at epoch t under treatment status m, the more likely she is to have a higher LR or to incur a terminal

event at epoch $t+1$. By Proposition 4.1, given the patient's on- and off-treatment transition probabilities have the IFR property at each epoch, the maximum expected QALYs prior to the first terminal event does not increase in LR.

Proposition 4.1. *If $\mathbf{P}^m(t)$ is IFR for all $m \in \mathcal{M}$ and $t \in T'$, then the optimal value function, $u_t(\ell)$, is nonincreasing in $\ell \in \mathcal{L}$ for all $t \in T$.*

Proof. Because $\mathbf{P}^1(N-1)$ is IFR for all $t \in T'$ and $r^1(\ell)$ is nonincreasing in $\ell \in \mathcal{L}$, by the infinite-horizon extension of Theorem 4.7.3 of Puterman [161], $\mu_N(\ell)$ is nonincreasing in $\ell \in \mathcal{L}$. Then, because $\mathbf{P}^1(t)$ is IFR for all $t \in T'$, Theorem 4.7.3 of Puterman [161] itself implies that $\mu_t(\ell)$ is nonincreasing in $\ell \in \mathcal{L}$ for all $t \in T'$. Because $r^0(\ell)$ is nonincreasing in $\ell \in \mathcal{L}$ and $\mu_t(\ell)$ is nonincreasing in $\ell \in \mathcal{L}$ for all $t \in T$, the proof of the monotonicity of $u_t(\ell)$ is similar by applying Theorem 4.7.3 of Puterman [161] and its infinite-horizon extension. □

Next, we define an *expected benefit loss* function which we use to express our main theoretical results. We let $B_t(\ell)$ denote the patient's expected benefit loss in QALYs from delaying the initiation of treatment to the next epoch in LR-range $\ell \in \mathcal{L}$ of epoch $t \in T'$, and define it as $B_t(\ell) = \mu_t(\ell) - F_t^0(\ell, \boldsymbol{\mu}_{t+1})$.

In our problem context, we define a control-limit policy as follows: A patient should initiate treatment if and only if her LR is above some threshold. Note that many published lipid management guidelines, including well known U.S. guidelines, have a control-limit structure depending on the risk factors they use to define the patient's risk profile. Theorem 4.1 provides sufficient conditions for the existence of an optimal control-limit policy. Specifically, it relates the existence of such a policy to the IFR property of the off-treatment transition probability matrices and the monotonicity of the expected benefit loss function. Intuitively a non-decreasing benefit loss with respect to age and LR can be interpreted to mean the benefit of delaying the initiation of treatment does not get smaller as patient gets older, or as her health becomes worse.

Theorem 4.1. *Suppose $\mathbf{P}^0(t)$ is IFR for all $t \in T'$ and $B_t(\ell)$ is nondecreasing in $\ell \in \mathcal{L}'$ for all $t \in T'$. Then, there exists an LR threshold $\ell_t^* \in \mathcal{L}'$ for each $t \in T$ such that the optimal action in state ℓ at epoch t is to initiate treatment if and only if $\ell \geq \ell_t^*$, i.e., $a_t(\ell) = I$ for all $\ell \geq \ell_t^*$, and $a_t(\ell) = W$ otherwise.*

In the rest of this section, for the proofs that we proceed by induction on the iterates of the value iteration algorithm at epoch $t = N$, for $\ell \in \mathcal{L}$ we let $u_N^k(\ell)$ and $\mu_N^k(\ell)$ denote the associated values of $u_N(\ell)$ and $\mu_N(\ell)$ at iteration k, respectively. More explicitly, for $\ell \in \mathcal{L}$ and $k \geq 0$, we define $\mu_N^{k+1}(\ell) = r^1(\ell) + F_{N-1}^1(\ell, \boldsymbol{\mu}_N^k)$ and $u_N^{k+1}(\ell) = \max\left\{r^0(\ell) + F_{N-1}^0(\ell, \mathbf{u}_N^k), \mu_N(\ell)\right\}$. Note that because the state space and rewards are finite and, $\lambda < 1$, if the vectors $\boldsymbol{\mu}_N^0$ and $\mathbf{u}_N^0$ are finite, by Theorem 6.3.1 of Puterman [161], $\lim_{k\to\infty} \boldsymbol{\mu}_N^k = \boldsymbol{\mu}_N$ and $\lim_{k\to\infty} \mathbf{u}_N^k = \mathbf{u}_N$. Because $L+1$ is an absorbing state which does not provide any rewards, $u_N^k(L+1) = \mu_N^k(L+1) = 0$ at each iteration k of the value iteration algorithm. Therefore, $u_N(L+1) = \mu_N(L+1) = 0$. Also, by backwards induction on $t \in T$, it can be easily observed that $u_t(L+1) = \mu_t(L+1) = 0$ for all $t \in T$.

Proof. It is sufficient to show that $u_t(\ell) - \mu_t(\ell)$ is nonincreasing in $\ell \in \mathcal{L}$ for all $t \in T$. For $t = N$, we will prove the result by induction on the iterates of the value iteration algorithm. Initialize $\mathbf{u}_N^0 = \boldsymbol{\mu}_N$, and for some $n \geq 0$, suppose $u_N^n(\ell) - \mu_N(\ell)$ is nonincreasing in $\ell \in \mathcal{L}$. Then, for any arbitrary $\ell \in \mathcal{L}'$, consider the two possible cases for $u_N^{n+1}(\ell) - u_N^{n+1}(\ell+1)$.

1. If $u_N^{n+1}(\ell+1) = \mu_N(\ell+1)$, then since $u_N^{n+1}(\ell) \geq \mu_N(\ell)$,

$$u_N^{n+1}(\ell) - u_N^{n+1}(\ell+1) \geq \mu_N(\ell) - \mu_N(\ell+1).$$

2. If $u_N^{n+1}(\ell+1) > \mu_N(\ell+1)$, then because $u_N^{n+1}(L+1) = \mu_N(L+1) = 0$, we must have $\ell < L$. Therefore, $u_N^{n+1}(\ell+1) = \tau + F_{N-1}^0(\ell+1, \mathbf{u}_N^n)$. Then,

$$\begin{aligned} u_N^{n+1}(\ell) - u_N^{n+1}(\ell+1) &\geq F_{N-1}^0(\ell, \mathbf{u}_N^n) - F_{N-1}^0(\ell+1, \mathbf{u}_N^n) && (4.4)\\ &\geq F_{N-1}^0(\ell, \boldsymbol{\mu}_N) - F_{N-1}^0(\ell+1, \boldsymbol{\mu}_N) && (4.5)\\ &\geq \mu_{N-1}(\ell) - \mu_{N-1}(\ell+1) = \mu_N(\ell) - \mu_N(\ell+1). && (4.6) \end{aligned}$$

In (4.4), because $\ell < L$, the inequality is implied by $u_N^{n+1}(\ell) = \tau + F_{N-1}^0(\ell, \mathbf{u}_N^n)$. Since $\mathbf{P}^0(N-1)$ is IFR, by the induction hypothesis, Lemma 4.7.2 of Puterman [161] implies $F_{N-1}^0(\ell, \mathbf{u}_N^n - \boldsymbol{\mu}_N) \geq F_{N-1}^0(\ell+1, \mathbf{u}_N^n - \boldsymbol{\mu}_N)$ and this yields (4.5). Then, since $\ell < L$, the inequality (4.6) follows from the assumption that $B_{N-1}(\ell)$ is nondecreasing in $\ell \in \mathcal{L}'$. Then, since $\boldsymbol{\mu}_{N-1} = \boldsymbol{\mu}_N$, the equality in (4.6) follows.

Thus, $u_N^{n+1}(\ell) - \mu_N(\ell)$ is nonincreasing in $\ell \in \mathcal{L}$. Then, by induction, the convergence of the algorithm implies that $u_N(\ell) - \mu_N(\ell)$ is nonincreasing in $\ell \in \mathcal{L}$. The proof of the monotonicity of $u_t(\ell) - \mu_t(\ell)$ in $\ell \in \mathcal{L}$ for $t < N$ is similar by backwards induction on t and omitted. □

Next, we focus on how the optimal policy changes with respect to age. It is well established that age is a positive risk factor for CHD and stroke. The mortality data published by the National Center for Health Statistics (NCHS) also state that patient's non-CHD or stroke-related death probability increases by age [134]. Therefore, in the rest of this chapter, for our analyses, we assume that d_t is nondecreasing in $t \in T'$. By the definition of the transition probabilities, this assumption has the following implication:

$$p_{t+1}^m(L+1|\ell) \geq p_t^m(L+1|\ell) \text{ for all } \ell \in \mathcal{L},\, m \in \mathcal{M},\, t \in T' \setminus \{N-1\}. \tag{4.7}$$

Proposition 4.2 expresses the time-monotonicity of the patient's value function.

Proposition 4.2. *The optimal value function vector, $\mathbf{u}_t$, is nonincreasing in $t \in T$.*

Proof. First, by backwards induction on $t \in T$, we will show that $\boldsymbol{\mu}_t$ is nonincreasing in $t \in T$. By definition, we have $\boldsymbol{\mu}_{N-1} = \boldsymbol{\mu}_N$. For some $k+1 < N-1$, assume that $\boldsymbol{\mu}_{k+1} \geq \boldsymbol{\mu}_{k+2}$. Then, for an arbitrary $\ell \in \mathcal{L}'$:

$$\mu_k(\ell) - \mu_{k+1}(\ell) = F_k^1(\ell, \boldsymbol{\mu}_{k+1}) - F_{k+1}^1(\ell, \boldsymbol{\mu}_{k+2}) \geq F_{k+1}^1(\ell, \boldsymbol{\mu}_{k+1} - \boldsymbol{\mu}_{k+2}) \geq 0. \tag{4.8}$$

Since $p_{k+1}^1(L+1|\ell) \geq p_k^1(L+1|\ell)$, by definition, $p_k^1(\ell'|\ell) \geq p_{k+1}^1(\ell'|\ell)$ for all $\ell' \in \mathcal{L}'$ and the first inequality in (4.8) follows. Then, the second inequality in (4.8) follows from the induction hypothesis. Hence, $\boldsymbol{\mu}_k \geq \boldsymbol{\mu}_{k+1}$, and by induction $\boldsymbol{\mu}_t$ is nonincreasing in $t \in T$. Using the time-monotonicity of $\boldsymbol{\mu}_t$, the proof of the monotonicity of $\mathbf{u}_t$ in $t \in T$ is similar to that of $\boldsymbol{\mu}_t$ by backwards induction on t and omitted. □

According to Proposition 4.2, the optimal value function does not increase with age; that is, the patient's expected QALYs prior to the first terminal event do not increase as she ages. Theorem 4.2 defines the structure of the optimal policy with respect to age.

Theorem 4.2. *If* $\mathbf{B}_t$ *is nondecreasing in* $t \in T'$*, then for any* $\ell \in \mathcal{L}$ *and* $t \in T'$*,* $a_t(\ell) = I$ *implies* $a_{t+1}(\ell) = I$*.*

Proof. It is sufficient to show that $u_t(\ell) - \mu_t(\ell)$ is nonincreasing in $t \in T$ for all $\ell \in \mathcal{L}$, which we will prove by backwards induction on t. By definition, $\boldsymbol{\mu}_{N-1} = \boldsymbol{\mu}_N$ and $\mathbf{u}_{N-1} = \mathbf{u}_N$. Therefore, $\mathbf{u}_N - \boldsymbol{\mu}_N = \mathbf{u}_{N-1} - \boldsymbol{\mu}_{N-1}$. As the induction hypothesis, for some $k+1 < N$, suppose $\mathbf{u}_{k+1} - \boldsymbol{\mu}_{k+1} \geq \mathbf{u}_{k+2} - \boldsymbol{\mu}_{k+2}$. Now, for fixed $\ell \in \mathcal{L}$ consider the possible cases for $u_k(\ell) - u_{k+1}(\ell)$.

1. If $u_{k+1}(\ell) = \mu_{k+1}(\ell)$, then because $u_k(\ell) \geq \mu_k(\ell)$,

$$u_k(\ell) - u_{k+1}(\ell) \geq \mu_k(\ell) - \mu_{k+1}(\ell).$$

2. If $u_{k+1}(\ell) > \mu_{k+1}(\ell)$, then

$$\begin{aligned} u_k(\ell) - u_{k+1}(\ell) &\geq F_k^0(\ell, \mathbf{u}_{k+1}) - F_{k+1}^0(\ell, \mathbf{u}_{k+2}) && (4.9) \\ &\geq F_{k+1}^0(\ell, \mathbf{u}_{k+1} - \mathbf{u}_{k+2}) \geq F_{k+1}^0(\ell, \boldsymbol{\mu}_{k+1} - \boldsymbol{\mu}_{k+2}), && (4.10) \end{aligned}$$

   where (4.9) is implied by $u_k(\ell) = r^0(\ell) + F_k^0(\ell, \mathbf{u}_{k+1})$. Since $p_{k+1}^0(L+1|\ell) \geq p_k^0(L+1|\ell)$, by definition, $p_k^0(\ell'|\ell) \geq p_{k+1}^0(\ell'|\ell)$ for all $\ell' \in \mathcal{L}'$, and this yields the first inequality in (4.10). Then, the second inequality in (4.10) is implied by the induction hypothesis. Since $B_{k+1}(\ell) \geq B_k(\ell)$, (4.10) implies $u_k(\ell) - u_{k+1}(\ell) \geq \mu_k(\ell) - \mu_{k+1}(\ell)$.

   Thus, $\mathbf{u}_k - \boldsymbol{\mu}_k \geq \mathbf{u}_{k+1} - \boldsymbol{\mu}_{k+1}$, and the result follows by induction on t. □

Theorem 4.2 states that if the patient's expected benefit loss from delaying the initiation of treatment to the next epoch does not decrease over time then the patient becomes more likely to initiate treatment at the same LR level as she ages. Therefore, if there exists an optimal control-limit policy, the thresholds for treatment do not increase and the patient maintains tighter control of her LR to avoid treatment as she ages.

In the remainder of this section, we will explore the sensitivity of the patient's optimal value function and policy with respect to quality-adjustment and treatment-effect factors. To this end, Proposition 4.3 compares two patients who are identical except for their quality-adjustment and/or treatment-effect factors. The relationship between treatment design and

patient's response to treatment has been widely discussed in the medical literature [240]. Proposition 4.3 formalizes this relationship by stating that if it is optimal to initiate treatment at a given LR level, it must be optimal to do so at the same level as the patient's disutility of using statins decreases, and/or the treatment effect factor increases.

In the rest of the chapter, when we compare two patients, for Patient $i = 1, 2$, we specify the problem parameters, the value functions and the optimal actions by a pre-superscript, $i = 1, 2$.

Proposition 4.3. *Consider two patients who are identical except* ${}^2\sigma \geq {}^1\sigma$ *and/or* ${}^1\omega \geq {}^2\omega$. *Then, for any* $\ell \in \mathcal{L}$ *and* $t \in T$, ${}^2a_t(\ell) = I$ *implies* ${}^1a_t(\ell) = I$.

Proof. Note that if we consider m continuous, $0 \leq m \leq 1$, because $\omega < 1$, it can be easily shown that $\dfrac{\partial \pi_t^C(\ell, m)}{\partial m}$ and $\dfrac{\partial \pi_t^S(\ell, m)}{\partial m}$ are both nonpositive for all $\ell \in \mathcal{L}'$ (See section 4.3.2 for the mathematical definition of the CHD and stroke probabilities, $\pi_t^C(\ell, m)$ and $\pi_t^S(\ell, m)$). Then, by definition (4.1), it is easy to see that $p_t^0(\ell'|\ell) \leq p_t^1(\ell'|\ell)$ for all $\ell, \ell' \in \mathcal{L}'$ and $t \in T'$. Also, given two patients with quality-adjustment factors ${}^1\sigma \leq {}^2\sigma$, if ${}^1p_t^1(\ell'|\ell) \geq {}^2p_t^1(\ell'|\ell)$ for $\ell, \ell' \in \mathcal{L}'$ and $t \in T'$, then it is straightforward to show that ${}^1\boldsymbol{\mu}_t \geq {}^2\boldsymbol{\mu}_t$ for all $t \in T$.

First, we will establish an auxiliary result. Given two patients with ${}^1\sigma \leq {}^2\sigma$, if

$$ {}^1p_t^0(\ell'|\ell) \leq {}^2p_t^0(\ell'|\ell), \text{ and } {}^1p_t^1(\ell'|\ell) \geq {}^2p_t^1(\ell'|\ell) \text{ for all } \ell, \ell' \in \mathcal{L}' \text{ and } t \in T', \tag{4.11} $$

then for any $\ell \in \mathcal{L}$ and $t \in T$, ${}^2a_t(\ell) = I$ implies ${}^1a_t(\ell) = I$. To prove the claim, it is sufficient to show that ${}^1\mathbf{u}_t - {}^1\boldsymbol{\mu}_t \leq {}^2\mathbf{u}_t - {}^2\boldsymbol{\mu}_t$ for all $t \in T$. To establish this result for $t = N$, we will proceed by induction on the iterates of the value iteration algorithm. We will apply the algorithm to ${}^i\mathbf{u}_N$ simultaneously for both $i = 1, 2$. By the convergence of the algorithm it is sufficient to show that ${}^1\mathbf{u}_N^k - {}^1\boldsymbol{\mu}_N \leq {}^2\mathbf{u}_N^k - {}^2\boldsymbol{\mu}_N$ for all $k \geq 0$. Initialize ${}^i\mathbf{u}_N^0 = {}^i\boldsymbol{\mu}_N$ for $i = 1, 2$ and for some $n \geq 0$, suppose ${}^1\mathbf{u}_N^n - {}^1\boldsymbol{\mu}_N \leq {}^2\mathbf{u}_N^n - {}^2\boldsymbol{\mu}_N$. Now, for an arbitrary $\ell \in \mathcal{L}$ consider the possible cases for ${}^2u_N^{n+1}(\ell) - {}^1u_N^{n+1}(\ell)$.

1. If ${}^1u_N^{n+1}(\ell) = {}^1\mu_N(\ell)$, then because ${}^2u_N^{n+1}(\ell) \geq {}^2\mu_N(\ell)$,

$$ {}^2u_N^{n+1}(\ell) - {}^1u_N^{n+1}(\ell) \geq {}^2\mu_N(\ell) - {}^1\mu_N(\ell). $$

2. If ${}^1u_N^{n+1}(\ell) > {}^1\mu_N(\ell)$, then

$$
\begin{aligned}
{}^2u_N^{n+1}(\ell) - {}^1u_N^{n+1}(\ell) &\geq {}^2F_{N-1}^0(\ell, {}^2\mathbf{u}_N^n) - {}^1F_{N-1}^0(\ell, {}^1\mathbf{u}_N^n) && (4.12)\\
&= {}^2F_{N-1}^0(\ell, {}^2\mathbf{u}_N^n - {}^2\boldsymbol{\mu}_N) + {}^2F_{N-1}^0(\ell, {}^2\boldsymbol{\mu}_N) \\
&\qquad - {}^1F_{N-1}^0(\ell, {}^1\mathbf{u}_N^n - {}^1\boldsymbol{\mu}_N) - {}^1F_{N-1}^0(\ell, {}^1\boldsymbol{\mu}_N) && (4.13)\\
&\geq {}^2F_{N-1}^0(\ell, {}^1\mathbf{u}_N^n - {}^1\boldsymbol{\mu}_N) - {}^1F_{N-1}^0(\ell, {}^1\mathbf{u}_N^n - {}^1\boldsymbol{\mu}_N) + {}^2F_{N-1}^0(\ell, {}^2\boldsymbol{\mu}_N) \\
&\qquad - {}^1F_{N-1}^0(\ell, {}^1\boldsymbol{\mu}_N) && (4.14)\\
&\geq {}^2F_{N-1}^0(\ell, {}^2\boldsymbol{\mu}_N) - {}^1F_{N-1}^0(\ell, {}^1\boldsymbol{\mu}_N) && (4.15)\\
&\geq {}^2F_{N-1}^1(\ell, {}^2\boldsymbol{\mu}_N) - {}^1F_{N-1}^1(\ell, {}^1\boldsymbol{\mu}_N) + \tau({}^1\sigma - {}^2\sigma) = {}^2\mu_N(\ell) - {}^1\mu_N(\ell), && (4.16)
\end{aligned}
$$

where (4.12) follows from the fact that ${}^2u_N^{n+1}(\ell) \geq r^0(\ell) + {}^2F_{N-1}^0(\ell, {}^2\mathbf{u}_N^n)$. Then, (4.13) is by adding and subtracting ${}^1F_{N-1}^0(\ell, {}^1\boldsymbol{\mu}_N)$ and ${}^2F_{N-1}^0(\ell, {}^2\boldsymbol{\mu}_N)$ and (4.14) is implied by the induction hypothesis. Since ${}^2p_{N-1}^0(\ell'|\ell) \geq {}^1p_{N-1}^0(\ell'|\ell)$ for all $\ell' \in \mathcal{L}'$, ${}^1\mathbf{u}_N^n \geq {}^1\boldsymbol{\mu}_N$ and ${}^1u_N^n(L+1) = {}^1\mu_N(L+1) = 0$, (4.15) is implied by ${}^2F_{N-1}^0(\ell, {}^1\mathbf{u}_N^n - {}^1\boldsymbol{\mu}_N) \geq {}^1F_{N-1}^0(\ell, {}^1\mathbf{u}_N^n - {}^1\boldsymbol{\mu}_N)$. Finally, we show the inequality in (4.16) as follows: By (4.11), ${}^1p_{N-1}^1(\ell'|\ell) - {}^1p_{N-1}^0(\ell'|\ell) \geq {}^2p_{N-1}^1(\ell'|\ell) - {}^2p_{N-1}^0(\ell'|\ell)$ for all $\ell' \in \mathcal{L}'$. Also, because ${}^1\sigma \leq {}^2\sigma$ and (4.11) holds, ${}^1\boldsymbol{\mu}_N \geq {}^2\boldsymbol{\mu}_N$. Then, since ${}^i\mu_N(L+1) = 0$ for both $i = 1, 2$, ${}^1F_{N-1}^1(\ell, {}^1\boldsymbol{\mu}_N) - {}^1F_{N-1}^0(\ell, {}^1\boldsymbol{\mu}_N) \geq {}^2F_{N-1}^1(\ell, {}^2\boldsymbol{\mu}_N) - {}^2F_{N-1}^0(\ell, {}^2\boldsymbol{\mu}_N)$. By the fact that ${}^1\sigma \leq {}^2\sigma$, this yields the inequality in (4.16).

Thus, ${}^1\mathbf{u}_N^{n+1} - {}^1\boldsymbol{\mu}_N \leq {}^2\mathbf{u}_N^{n+1} - {}^2\boldsymbol{\mu}_N$, and by the convergence of the algorithm the result for $t = N$ follows by induction on n. Then the proof of the fact that ${}^1\mathbf{u}_t - {}^1\boldsymbol{\mu}_t \leq {}^2\mathbf{u}_t - {}^2\boldsymbol{\mu}_t$ for $t \in T$ is similar by backwards induction on t, and omitted.

Now, we will treat each "or" case separately. We will omit the proof of the "and" case since it is similar. If the patients are identical except ${}^1\sigma \leq {}^2\sigma$, then the result directly follows from the auxiliary result that has been shown above. Otherwise, if the patients are identical except ${}^1\omega \geq {}^2\omega$, by (4.43a)-(4.44c), ${}^1\pi_t^{\triangledown}(\ell, 0) = {}^2\pi_t^{\triangledown}(\ell, 0)$ and ${}^1\pi_t^{\triangledown}(\ell, 1) \leq {}^2\pi_t^{\triangledown}(\ell, 1)$ for all $\ell \in \mathcal{L}'$ and $t \in T'$. Then, since ${}^1\mathbf{Q} = {}^2\mathbf{Q}$ and ${}^1d_t = {}^2d_t$ for all $t \in T'$, by definition (4.1), we have ${}^1p_t^1(\ell'|\ell) \geq {}^2p_t^1(\ell'|\ell)$ and ${}^1p_t^0(\ell'|\ell) = {}^2p_t^0(\ell'|\ell)$ for all $\ell, \ell' \in \mathcal{L}'$ and $t \in T'$, and the result follows from the auxiliary result that has been shown above. □

Next, Proposition 4.4 establishes the sensitivity of the patient's optimal value function with respect to simultaneous changes in quality-adjustment and treatment-effect factors. It states that the lower the quality-adjustment factor the patient has, the higher the benefit she gains as the treatment-effect increases. Intuitively, by Proposition 4.3, as the quality-adjustment factor decreases the patient uses statins more often by initiating therapy in a wider set of states. Then, because the treatment reduces the patient's CHD and stroke risks in a more number of states, an increase in treatment-effect factor yields a greater increase in patient's QALYs prior to a terminal event.

Proposition 4.4. *Consider two patients who are identical except* ${}^1\omega \geq {}^2\omega$. *Let* σ_1 *and* σ_2 *be two quality-adjustment factors with* $\sigma_1 \geq \sigma_2$, *and let* ${}^{i,j}u_t(\ell)$ *specify* ${}^iu_t(\ell)$ *when the quality-adjustment factor is* σ_j, *for* $\ell \in \mathcal{L}$, $t \in T$ *and* $i, j = 1, 2$. *Then,* ${}^{1,2}\mathbf{u}_t - {}^{1,1}\mathbf{u}_t \geq {}^{2,2}\mathbf{u}_t - {}^{2,1}\mathbf{u}_t$ *for all* $t \in T$.

Proof. For brevity, we will establish the result only for $t = N$. Let ${}^{i,j}\mu_N(\ell)$ denote the expected post-treatment reward of patient i, $i = 1, 2$, in state $\ell \in \mathcal{L}$ at epoch $t = N$ when her quality-adjustment factor is σ_j, $j = 1, 2$. First, we will show that ${}^{1,2}\boldsymbol{\mu}_N - {}^{1,1}\boldsymbol{\mu}_N \geq {}^{2,2}\boldsymbol{\mu}_N - {}^{2,1}\boldsymbol{\mu}_N$. We will proceed by induction on the iterates of the value iteration algorithm. We will apply the algorithm to ${}^{1,j}\boldsymbol{\mu}_N$ for both $j = 1, 2$. Initialize ${}^{1,j}\boldsymbol{\mu}_N^0 = {}^{2,j}\boldsymbol{\mu}_N$ for $j = 1, 2$. As the induction hypothesis, for some $n \geq 0$, suppose ${}^{1,2}\boldsymbol{\mu}_N^n - {}^{1,1}\boldsymbol{\mu}_N^n \geq {}^{2,2}\boldsymbol{\mu}_N - {}^{2,1}\boldsymbol{\mu}_N$. Note that ${}^{1,2}\mu_N^{n+1}(L+1) = {}^{1,1}\mu_N^{n+1}(L+1) = {}^{2,2}\mu_N(L+1) = {}^{2,1}\mu_N(L+1) = 0$. Then, for an arbitrary $\ell \in \mathcal{L}'$,

$$\begin{aligned} {}^{1,2}\mu_N^{n+1}(\ell) - {}^{1,1}\mu_N^{n+1}(\ell) - \left[{}^{2,2}\mu_N(\ell) - {}^{2,1}\mu_N(\ell)\right] & \\ = {}^1F_{N-1}^1(\ell, {}^{1,2}\boldsymbol{\mu}_N^n - {}^{1,1}\boldsymbol{\mu}_N^n) - {}^2F_{N-1}^1(\ell, {}^{2,2}\boldsymbol{\mu}_N - {}^{2,1}\boldsymbol{\mu}_N) & \\ \geq {}^1F_{N-1}^1(\ell, {}^{1,2}\boldsymbol{\mu}_N^n - {}^{1,1}\boldsymbol{\mu}_N^n - {}^{2,2}\boldsymbol{\mu}_N + {}^{2,1}\boldsymbol{\mu}_N) \geq 0. & \quad (4.17) \end{aligned}$$

Because the patients are identical except ${}^1\omega \geq {}^2\omega$:

$${}^1p_{N-1}^1(\ell'|\ell) \geq {}^2p_{N-1}^1(\ell'|\ell) \text{ and } {}^1p_{N-1}^0(\ell'|\ell) = {}^2p_{N-1}^0(\ell'|\ell) \text{ for all } \ell, \ell' \in \mathcal{L}'. \quad (4.18)$$

Now, because $\sigma_1 \geq \sigma_2$, ${}^{2,2}\boldsymbol{\mu}_N \geq {}^{2,1}\boldsymbol{\mu}_N$. Because ${}^{2,2}\mu_N(L+1) = {}^{2,1}\mu_N(L+1) = 0$, by (4.18) this implies ${}^1F_{N-1}^1(\ell, {}^{2,2}\boldsymbol{\mu}_N - {}^{2,1}\boldsymbol{\mu}_N) \geq {}^2F_{N-1}^1(\ell, {}^{2,2}\boldsymbol{\mu}_N - {}^{2,1}\boldsymbol{\mu}_N)$, yielding the

first inequality in (4.17). The second inequality in (4.17) directly follows from the induction hypothesis. Thus, ${}^{1,2}\boldsymbol{\mu}_N^{n+1} - {}^{1,1}\boldsymbol{\mu}_N^{n+1} \geq {}^{2,2}\boldsymbol{\mu}_N - {}^{2,1}\boldsymbol{\mu}_N$. Then, by induction the convergence of the algorithm yields

$$ {}^{1,2}\boldsymbol{\mu}_N - {}^{1,1}\boldsymbol{\mu}_N \geq {}^{2,2}\boldsymbol{\mu}_N - {}^{2,1}\boldsymbol{\mu}_N. \tag{4.19} $$

Next, for $t = N$, we will apply the value iteration algorithm simultaneously to ${}^{i,j}\mathbf{u}_N$ for $i, j = 1, 2$ to show that ${}^{1,2}\mathbf{u}_N - {}^{1,1}\mathbf{u}_N \geq {}^{2,2}\mathbf{u}_N - {}^{2,1}\mathbf{u}_N$. We will proceed by induction on the iterates of the algorithm. Initialize ${}^{i,j}\mathbf{u}_N^0 = {}^{i,j}\boldsymbol{\mu}_N$ for $i, j = 1, 2$. By (4.19), this implies ${}^{1,2}\mathbf{u}_N^0 - {}^{1,1}\mathbf{u}_N^0 \geq {}^{2,2}\mathbf{u}_N^0 - {}^{2,1}\mathbf{u}_N^0$. As the induction hypothesis, for some $n \geq 0$, suppose ${}^{1,2}\mathbf{u}_N^n - {}^{1,1}\mathbf{u}_N^n \geq {}^{2,2}\mathbf{u}_N^n - {}^{2,1}\mathbf{u}_N^n$. We will make use of the following set of auxiliary results to establish ${}^{1,2}\mathbf{u}_N^{n+1} - {}^{1,1}\mathbf{u}_N^{n+1} \geq {}^{2,2}\mathbf{u}_N^{n+1} - {}^{2,1}\mathbf{u}_N^{n+1}$.

- Since $\sigma_1 \geq \sigma_2$, by treating each patient as two identical patients with different quality-adjustment factors we have,

  $$ {}^{i,1}\mathbf{u}_N^n - {}^{i,1}\boldsymbol{\mu}_N \geq {}^{i,2}\mathbf{u}_N^n - {}^{i,2}\boldsymbol{\mu}_N \text{ for } i = 1, 2. \tag{4.20} $$

  Similarly, since (4.18) is satisfied,

  $$ {}^{2,j}\mathbf{u}_N^n - {}^{2,j}\boldsymbol{\mu}_N \geq {}^{1,j}\mathbf{u}_N^n - {}^{1,j}\boldsymbol{\mu}_N \text{ for } j = 1, 2. \tag{4.21} $$

  (The proofs of (4.20) and (4.21) are given in the proof of Proposition 4.3).

- Define ${}^{i,j}U(\ell) = r^0(\ell) + {}^{i}F_{N-1}^0(\ell, {}^{i,j}\mathbf{u}_N^n)$ for $\ell \in \mathcal{L}$ and $i, j = 1, 2$. For an arbitrary $\ell \in \mathcal{L}$, consider ${}^{1,2}U(\ell) - {}^{1,1}U(\ell) - [{}^{2,2}U(\ell) - {}^{2,1}U(\ell)]$.

  $$ \begin{aligned} {}^{1,2}U(\ell) - {}^{1,1}U(\ell) - \left[{}^{2,2}U(\ell) - {}^{2,1}U(\ell)\right] \\ = {}^{1}F_{N-1}^0(\ell, {}^{1,2}\mathbf{u}_N^n - {}^{1,1}\mathbf{u}_N^n) - {}^{2}F_{N-1}^0(\ell, {}^{2,2}\mathbf{u}_N^n - {}^{2,1}\mathbf{u}_N^n) \geq 0, \end{aligned} $$

  where the inequality is implied by the fact that ${}^{2}p_{N-1}^0(\ell'|\ell) = {}^{1}p_{N-1}^0(\ell'|\ell)$ for all $\ell' \in \mathcal{L}$ and the induction hypothesis. Thus,

  $$ {}^{1,2}\mathbf{U} - {}^{1,1}\mathbf{U} \geq {}^{2,2}\mathbf{U} - {}^{2,1}\mathbf{U}. \tag{4.22} $$

- For fixed $\ell \in \mathcal{L}$, consider ${}^{1,2}\mu_N(\ell) - {}^{2,2}\mu_N(\ell)$.

$$\begin{aligned} {}^{1,2}\mu_N(\ell) - {}^{2,2}\mu_N(\ell) &= {}^{1}F^{1}_{N-1}(\ell, {}^{1,2}\boldsymbol{\mu}_N) - {}^{2}F^{1}_{N-1}(\ell, {}^{2,2}\boldsymbol{\mu}_N) \\ &\geq {}^{1}F^{0}_{N-1}(\ell, {}^{1,2}\boldsymbol{\mu}_N) - {}^{2}F^{0}_{N-1}(\ell, {}^{2,2}\boldsymbol{\mu}_N) \qquad (4.23) \\ &\geq {}^{1}F^{0}_{N-1}(\ell, {}^{1,2}\mathbf{u}^n_N) - {}^{2}F^{0}_{N-1}(\ell, {}^{2,2}\mathbf{u}^n_N) = {}^{1,2}U(\ell) - {}^{2,2}U(\ell). \qquad (4.24) \end{aligned}$$

By the on-treatment transition probabilities in (4.18) it can be easily shown that ${}^{1,2}\boldsymbol{\mu}_N \geq {}^{2,2}\boldsymbol{\mu}_N$. Also, $\big($by (4.18)$\big)$, because ${}^{1}p^{1}_{N-1}(\ell'|\ell) - {}^{1}p^{0}_{N-1}(\ell'|\ell) \geq {}^{2}p^{1}_{N-1}(\ell'|\ell) - {}^{2}p^{0}_{N-1}(\ell'|\ell) \geq 0$ for all $\ell' \in \mathcal{L}'$ and ${}^{1,2}\mu_N(L+1) = {}^{2,2}\mu_N(L+1) = 0$,

$$ {}^{1}F^{1}_{N-1}(\ell, {}^{1,2}\boldsymbol{\mu}_N) - {}^{1}F^{0}_{N-1}(\ell, {}^{1,2}\boldsymbol{\mu}_N) \geq {}^{2}F^{1}_{N-1}(\ell, {}^{2,2}\boldsymbol{\mu}_N) - {}^{2}F^{0}_{N-1}(\ell, {}^{2,2}\boldsymbol{\mu}_N), $$

and this yields (4.23). Then, the inequality in (4.24) is implied by ${}^{1}F^{0}_{N-1}(\ell, {}^{1,2}\boldsymbol{\mu}_N - {}^{1,2}\mathbf{u}^n_N) \geq {}^{2}F^{0}_{N-1}(\ell, {}^{2,2}\boldsymbol{\mu}_N - {}^{2,2}\mathbf{u}^n_N)$ which follows from (4.21) and the fact that ${}^{1}p^{0}_{N-1}(\ell'|\ell) = {}^{2}p^{0}_{N-1}(\ell'|\ell)$ for all $\ell' \in \mathcal{L}$. Thus,

$$ {}^{1,2}\boldsymbol{\mu}_N - {}^{2,2}\boldsymbol{\mu}_N \geq {}^{1,2}\mathbf{U} - {}^{2,2}\mathbf{U}. \qquad (4.25) $$

Next, for an arbitrary $\ell \in \mathcal{L}$ consider the possible cases for ${}^{1,2}u^{n+1}_N(\ell) - {}^{2,2}u^{n+1}_N(\ell)$. Note that ${}^{i,j}u^{n+1}_N(\ell) = \max\left\{{}^{i,j}U(\ell), {}^{i,j}\mu_N(\ell)\right\}$ for $\ell \in \mathcal{L}$ and $i, j = 1, 2$.

1. If ${}^{1,1}u^{n+1}_N(\ell) = {}^{1,1}\mu_N(\ell)$, then by (4.20), ${}^{1,2}u^{n+1}_N(\ell) \leq {}^{1,2}\mu_N(\ell)$. By the definition of ${}^{1,2}u^{n+1}_N(\ell)$, we also have ${}^{1,2}u^{n+1}_N(\ell) \geq {}^{1,2}\mu_N(\ell)$. These imply ${}^{1,2}u^{n+1}_N(\ell) = {}^{1,2}\mu_N(\ell)$. Then,

$$\begin{aligned} {}^{1,2}u^{n+1}_N(\ell) - {}^{1,1}u^{n+1}_N(\ell) - \left[{}^{2,2}u^{n+1}_N(\ell) - {}^{2,1}u^{n+1}_N(\ell)\right] \\ = {}^{1,2}\mu_N(\ell) - {}^{1,1}\mu_N(\ell) - \left[{}^{2,2}u^{n+1}_N(\ell) - {}^{2,1}u^{n+1}_N(\ell)\right] \\ \geq {}^{1,2}\mu_N(\ell) - {}^{1,1}\mu_N(\ell) - {}^{2,2}\mu_N(\ell) + {}^{2,1}\mu_N(\ell) \geq 0, \qquad (4.26) \end{aligned}$$

where the first inequality in (4.26) is implied by (4.20) and the second inequality follows from (4.19).

2. If ${}^{1,1}u^{n+1}_N(\ell) = {}^{1,1}U(\ell)$, then by (4.21), ${}^{2,1}u^{n+1}_N(\ell) = {}^{2,1}U(\ell)$. Now, consider the possible subcases:

a. If ${}^{2,2}u_N^{n+1}(\ell) = {}^{2,2}\mu_N(\ell)$, then by (4.21), ${}^{1,2}u_N^{n+1}(\ell) \leq {}^{1,2}\mu_N(\ell)$. By the definition of ${}^{1,2}u_N^{n+1}(\ell)$, we also have ${}^{1,2}u_N^{n+1}(\ell) \geq {}^{1,2}\mu_N(\ell)$. These imply ${}^{1,2}u_N^{n+1}(\ell) = {}^{1,2}\mu_N(\ell)$. Then,

$$\begin{aligned} {}^{1,2}u_N^{n+1}(\ell) - {}^{1,1}u_N^{n+1}(\ell) - \left[{}^{2,2}u_N^{n+1}(\ell) - {}^{2,1}u_N^{n+1}(\ell)\right] & \\ = {}^{1,2}\mu_N(\ell) - {}^{1,1}U(\ell) - {}^{2,2}\mu_N(\ell) + {}^{2,1}U(\ell) & \\ \geq {}^{1,2}U(\ell) - {}^{1,1}U(\ell) - {}^{2,2}U(\ell) + {}^{2,1}U(\ell) \geq 0, & \quad (4.27) \end{aligned}$$

where the first inequality in (4.27) is implied by (4.25) and the second inequality follows from (4.22).

b. If ${}^{2,2}u_N^{n+1}(\ell) = {}^{2,2}U_N(\ell)$, then because ${}^{1,2}u_N^{n+1}(\ell) \geq {}^{1,2}U(\ell)$, (4.22) implies

$$\begin{aligned} {}^{1,2}u_N^{n+1}(\ell) - {}^{1,1}u_N^{n+1}(\ell) - \left[{}^{2,2}u_N^{n+1}(\ell) - {}^{2,1}u_N^{n+1}(\ell)\right] & \\ \geq {}^{1,2}U(\ell) - {}^{1,1}U(\ell) - \left[{}^{2,2}U(\ell) - {}^{2,1}U(\ell)\right] \geq 0. & \end{aligned}$$

Thus, ${}^{1,2}\mathbf{u}_N^{n+1} - {}^{1,1}\mathbf{u}_N^{n+1} \geq {}^{2,2}\mathbf{u}_N^{n+1} - {}^{2,1}\mathbf{u}_N^{n+1}$. Then, by induction, the convergence of the algorithm yields ${}^{1,2}\mathbf{u}_N - {}^{1,1}\mathbf{u}_N \geq {}^{2,2}\mathbf{u}_N - {}^{2,1}\mathbf{u}_N$. The proof of the fact that ${}^{1,2}\mathbf{u}_t - {}^{1,1}\mathbf{u}_t \geq {}^{2,2}\mathbf{u}_t - {}^{2,1}\mathbf{u}_t$ for $t \in T'$ is similar by backwards induction on $t \in T$ and omitted. □

Note that by Proposition 4.4, the patient's optimal value function does not decrease as σ decreases and/or ω increases.

Finally, we show that our conditions for Theorem 4.1 are less restrictive than those of Alagöz et al. [10] which provides sufficient conditions to discover the existence of a threshold-structured optimal policy for an infinite-horizon optimal stopping time model. In our model, because the optimal policy remains stationary beyond epoch $N-1$, the optimality equations

at epoch N represent a similar infinite-horizon optimal stopping time model. The following conditions are the equivalents of Alagöz et al. [10] in our context at epoch N.

$$\mathbf{P}_{N-1}(0) \text{ is IFR.} \tag{4.28}$$

$$r^0(\ell) \text{ is nonincreasing in } \ell \in \mathcal{L}'. \tag{4.29}$$

$$\mu_N(\ell) \text{ is nonincreasing in } \ell \in \mathcal{L}'. \tag{4.30}$$

$$\sum_{k=j}^{L} p^0_{N-1}(k|\ell) \leq \sum_{k=j}^{L} p^0_{N-1}(k|\ell+1) \text{ for all } j = \ell+1, ..., L \text{ and } \ell = \mathcal{L}' \setminus \{L\}. \tag{4.31}$$

$$\frac{\mu_N(\ell) - \mu_N(\ell+1)}{\mu_N(\ell)} \leq \lambda\big[p^0_{N-1}(L+1|\ell+1) - p^0_{N-1}(L+1|\ell)\big] \text{ for } \ell = \mathcal{L}' \setminus \{L\}. \tag{4.32}$$

By the definition of the immediate rewards, (4.29) holds immediately. By Theorem 4.1, to have an LR-based optimal control-limit policy, in addition to (4.28), instead of (4.30)-(4.32) we require the monotonicity of $B_{N-1}(\ell)$ with respect to $\ell \in \mathcal{L}'$. Next, we will show that it is less restrictive than satisfying (4.30)-(4.32).

Proposition 4.5. *Given $\mathbf{P}_{N-1}(0)$ is IFR, if (4.30)-(4.32) hold then $B_{N-1}(\ell)$ is nondecreasing in $\ell \in \mathcal{L}'$.*

The proof of Proposition 4.5 is preceded by the following result of Alagöz et al. [10].

Lemma 4.1. : *Let $\mathbf{H} = \big[H(j|i)\big]$, $i, j = 1, 2, \ldots, n$, be an $n \times n$ IFR transition probability matrix and $f : \{1, ..., n\} \to \mathbb{R}$ be a nonincreasing function in $i \in \{1, ..., n\}$. Then, for $i = 1, 2, \ldots, n-1$,*

$$(i) \sum_{j=1}^{i} \big[H(j|i) - H(j|i+1)\big] f(j) \geq f(i) \sum_{j=1}^{i} \big[H(j|i) - H(j|i+1)\big],$$

$$(ii) \sum_{j=i+1}^{n} \big[H(j|i) - H(j|i+1)\big] f(j) \geq f(i+1) \sum_{j=i+1}^{n} \big[H(j|i) - H(j|i+1)\big].$$

Proof. Note that by (4.2), $\boldsymbol{\mu}_{N-1} = \boldsymbol{\mu}_N$. Therefore, the expected benefit loss function $B_{N-1}(\cdot)$ can be restated as:

$$B_{N-1}(\ell) = \mu_N(\ell) - F^0_{N-1}(\ell, \boldsymbol{\mu}_N) \text{ for } \ell \in \mathcal{L}'. \tag{4.33}$$

Also note that, since $r^1(L+1) = 0$ and $p^1_{N-1}(L+1|L+1) = 1$, by (4.2), $\mu_N(L+1) = 0$.

Now, suppose (4.30)-(4.32) hold. Fix $\ell \in \mathcal{L}' \setminus \{L\}$ and consider the quantity

$$\sum_{\ell'=1}^{\ell} \big[p^0_{N-1}(\ell'|\ell) - p^0_{N-1}(\ell'|\ell+1)\big]\mu_N(\ell').$$

Since $\mathbf{P}_{N-1}(0)$ is IFR and $\mu_N(\ell')$ is nonincreasing in $\ell' \in \mathcal{L}$, Lemma 4.1 (i) implies

$$\sum_{\ell'=1}^{\ell} \big[p^0_{N-1}(\ell'|\ell) - p^0_{N-1}(\ell'|\ell+1)\big]\mu_N(\ell') \geq \mu_N(\ell) \sum_{\ell'=1}^{\ell} \big[p^0_{N-1}(\ell'|\ell) - p^0_{N-1}(\ell'|\ell+1)\big]. \tag{4.34}$$

Likewise, because (4.31) holds and $\mu_N(\ell')$ is nonincreasing in $\ell' \in \mathcal{L}$, Lemma 4.1 (ii) implies

$$\begin{aligned}\sum_{\ell'=\ell+1}^{L} &\big[p^0_{N-1}(\ell'|\ell) - p^0_{N-1}(\ell'|\ell+1)\big]\mu_N(\ell') \\ &\geq \mu_N(\ell+1) \sum_{\ell'=\ell+1}^{L} \big[p^0_{N-1}(\ell'|\ell) - p^0_{N-1}(\ell'|\ell+1)\big].\end{aligned} \tag{4.35}$$

Note that by the identity,

$$\begin{aligned}\sum_{\ell'=1}^{\ell} \big[p^0_{N-1}(\ell'|\ell) - p^0_{N-1}(\ell'|\ell+1)\big] &= \sum_{\ell'=\ell+1}^{L+1} \big[p^0_{N-1}(\ell'|\ell+1) - p^0_{N-1}(\ell'|\ell)\big] \\ = p^0_{N-1}(L+1|\ell+1) - p^0_{N-1}(L+1|\ell) &+ \sum_{\ell'=\ell+1}^{L} \big[p^0_{N-1}(\ell'|\ell+1) - p^0_{N-1}(\ell'|\ell)\big].\end{aligned}$$

the right-hand side of (4.34) can be restated as:

$$\begin{aligned}\mu_N(\ell) &\sum_{\ell'=1}^{\ell} \big[p^0_{N-1}(\ell'|\ell) - p^0_{N-1}(\ell'|\ell+1)\big] \\ &= \mu_N(\ell)\Big(p^0_{N-1}(L+1|\ell+1) - p^0_{N-1}(L+1|\ell) \\ &\qquad + \sum_{\ell'=\ell+1}^{L} \big[p^0_{N-1}(\ell'|\ell+1) - p^0_{N-1}(\ell'|\ell)\big]\Big).\end{aligned} \tag{4.36}$$

By (4.35) and (4.36), we have

$$\begin{aligned}
&\lambda \sum_{\ell'=1}^{L+1} \left[p^0_{N-1}(\ell'|\ell) - p^0_{N-1}(\ell'|\ell+1)\right] \mu_N(\ell') \\
&\quad \geq \mu_N(\ell) \left[p^0_{N-1}(L+1|\ell+1) - p^0_{N-1}(L+1|\ell)\right] \\
&\qquad + \left[\mu_N(\ell) - \mu_N(\ell+1)\right] \left(\sum_{\ell'=\ell+1}^{L} \left[p^0_{N-1}(\ell'|\ell+1) - p^0_{N-1}(\ell'|\ell)\right] \right). \qquad (4.37)
\end{aligned}$$

Since (4.31) holds and $\mu_N(\ell) \geq \mu_N(\ell+1)$,

$$\left[\mu_N(\ell) - \mu_N(\ell+1)\right] \left(\sum_{\ell'=\ell+1}^{L} \left[p^0_{N-1}(\ell'|\ell+1) - p^0_{N-1}(\ell'|\ell)\right] \right) \geq 0. \qquad (4.38)$$

By (4.37), (4.38) implies

$$\begin{aligned}
&\lambda \sum_{\ell'=1}^{L+1} \left[p^0_{N-1}(\ell'|\ell) - p^0_{N-1}(\ell'|\ell+1)\right] \mu_N(\ell') \\
&\qquad \geq \lambda \mu_N(\ell) \left[p^0_{N-1}(L+1|\ell+1) - p^0_{N-1}(L+1|\ell)\right]. \qquad (4.39)
\end{aligned}$$

Then, since (4.32) holds, (4.39) yields:

$$\lambda \sum_{\ell'=1}^{L+1} \left[p^0_{N-1}(\ell'|\ell) - p^0_{N-1}(\ell'|\ell+1)\right] \mu_N(\ell') \geq \mu_N(\ell) - \mu_N(\ell+1). \qquad (4.40)$$

By (4.33), (4.40) implies $B_{N-1}(\ell+1) \geq B_{N-1}(\ell)$. □

Note that $B_{N-1}(\ell)$ may be nondecreasing in $\ell \in \mathcal{L}'$ without the monotonicity of the expected post-treatment rewards. Also, because the conditions that we provide depend on the IFR property of the off-treatment transition probability matrices but not on the monotonicity of the immediate rewards, the resulting optimal value function may not be monotone to have an optimal control-limit policy.

4.3 NUMERICAL STUDY

In this section, we present numerical results to illustrate our model. We estimate the transition probabilities of our MDP model using the Mayo Clinic Diabetes Electronic Management System (DEMS) data [84], the UKPDS risk models [107, 198], and the NCHS mortality rate tables [134]. DEMS data consist of patients with Type 2 diabetes at the Mayo Clinic in Rochester, MN and maintains longitudinal medical records. The patient data in DEMS are available quarterly with detailed treatment information and laboratory measurements for TC, HDL, SBP, HbA1c and triglycerides levels. The majority of the patients in DEMS are non-smoker Caucasian patients who had no atrial fibrillation at the age of diagnosis, and no prior CHD or stroke. We include patients with data in the years 1993-2005 with at least 10 years of continuous care and this creates a cohort of 663 patients.

For our numerical experiments, we define two patient profiles, one for each gender and present the resulting optimal treatment policies and the maximum expected QALYs prior to the first terminal event for these two profiles. Specifically, we consider a male patient and a female patient who are Caucasian, do not smoke and were diagnosed with Type 2 diabetes at age 40 with no history of CHD, stroke or atrial fibrillation. Our data set provides insufficient observations for patients older than 80. Therefore, we set annual decision epochs for a 40-year non-stationary decision horizon starting at age 40 so that treatment decisions are age-dependent prior to age 79 and remain stationary after age 79, *i.e.*, $\tau = 1$, $k = 0$ and $N = 40$.

4.3.1 Estimating Treatment-Effect and Transition Probabilities

We maximize the utilization of sparsely available data and estimate the incomplete data points to obtain complete sequences of quarterly available TC and HDL levels. We fit cubic splines to each patient's sequence of TC and HDL measurements in an approach similar to Alagöz et al. [8] and Shechter [189].

The effects of using statins on the patient's LR levels have been reported as relative reductions in patients' TC and HDL levels in clinical trials [88, 122]. Therefore, we estimate

the patients' treatment effect factors implicitly through relative reductions in their TC and HDL levels. We assume that using statins changes the patients' current TC and HDL levels by factors c and h, respectively, where $0 < c < 1$ and $h > 1$. To estimate c and h, since the decision of initiating treatment is revisited annually, we observe the treatment's impact on TC and HDL levels by focusing on 6-month intervals before and after the initiation of treatment. Although it is not clinically recommended for the intended long-term benefit of statin therapy [192, 222], in the DEMS data set we observe some patients who initiated treatment more than once after giving up using statins. We consider all initiations and re-initiations during estimating the factors c and h. We let $K(i)$ denote the number of times that patient i initiated treatment for $i = 1, ..., M$, where $M = 663$ denotes the size of the cohort. Then we let the pairs $[v^i_{TC}(j,k,0), v^i_{HDL}(j,k,0)]$ and $[v^i_{TC}(j,k,1), v^i_{HDL}(j,k,1)]$ denote the i^{th} patient's total cholesterol and HDL levels j quarters before and after the k^{th} initiation of treatment, respectively, for $i = 1, ..., M$, $j = 1, 2$, and $k = 1, ..., K(i)$, and estimate c and h by the following formulae:

$$\widehat{c} = \frac{\displaystyle\sum_{i=1}^{M} \frac{1}{K(i)} \sum_{k=1}^{K(i)} \frac{\sum_{j=1}^{2} v^i_{TC}(j,k,1)}{\sum_{j=1}^{2} v^i_{TC}(j,k,0)}}{M} \text{ and } \widehat{h} = \frac{\displaystyle\sum_{i=1}^{M} \frac{1}{K(i)} \sum_{k=1}^{K(i)} \frac{\sum_{j=1}^{2} v^i_{HDL}(j,k,1)}{\sum_{j=1}^{2} v^i_{HDL}(j,k,0)}}{M}. \quad (4.41)$$

In (4.41), each ratio term within the inner sum of the numerator corresponds to the ratio of the average TC or HDL level within 6 months after an initiation of treatment to that within 6 months before that initiation. Using (4.41) over the spline-fitted data we estimate $\widehat{c} = 0.86026$ and $\widehat{h} = 1.07284$, respectively, which imply a 19.815 % reduction in LR levels by treatment, *i.e.*, $\widehat{\omega} = 1 - \widehat{c}/\widehat{h} = 0.19815$.

To estimate the conditional transition probabilities among the LR-ranges for each gender, we use the patients' off-treatment LR levels. We calculate a corresponding off-treatment LR level for each spline-fitted on-treatment LR level. We assume $1/\widehat{c}$ and $1/\widehat{h}$ denote the factors for the inverse effects of treatment on TC and HDL levels; that is, stopping using statins changes the TC level by a factor of $1/\widehat{c}$, and the HDL level by a factor of $1/\widehat{h}$. By using the estimates $1/\widehat{c}$ and $1/\widehat{h}$, we normalize the patients' spline-fitted on-treatment TC and HDL levels so that we obtain sequences of TC and HDL estimates in which all patients are assumed to be off-treatment. We calculate the off-treatment LR levels over these sequences

and discretize the continuous range of LR levels into $L = 13$ ranges. We let state $\ell \in \mathcal{L}'$ refer to interval $\big[LB_{LR}(\ell), UB_{LR}(\ell)\big)$, where $LB_{LR}(\ell)$ and $UB_{LR}(\ell)$ denote the lower and upper bounds of the LR-range ℓ.

Table 4.1: LR-range boundaries.

Boundary	LR-Range (ℓ)												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Lower Bound $\big(LB_{LR}(\ell)\big)$	0	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5
Upper Bound $\big(UB_{LR}(\ell)\big)$	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	∞

Ranges are exclusive of their upper bounds.

Based on this discretization, for each patient, we calculate the total number of off-treatment LR estimates in each LR-range in all quarters and ages. Then, we count the number of transitions from each range to all other ranges between the same quarters of successive ages, and compute the gender-specific conditional LR transition probabilities. We formalize this process for male patients as follows: We let $b^i_{TC}(t,j)$ and $b^i_{HDL}(t,j)$ denote the off-treatment TC and HDL values of male patient i in the j^{th} quarter of age t for $i = 1, ..., N_m$, $j = 1, ..., 4$ and $t = 40, ..., 80$, respectively, where N_m is the number of male patients in the data set. We define two indicator functions: $\psi(z) = \big\{\ell \in \mathcal{L}' : z \in \big[LB_{LR}(\ell), UB_{LR}(\ell)\big)\big\}$, and

$$I^i_{t,j}(\ell) = \begin{cases} 1 & \text{if } \psi\big(b^i_{TC}(t,j)/b^i_{HDL}(t,j)\big) = \ell, \\ 0 & \text{otherwise,} \end{cases} \tag{4.42}$$

for $i = 1, ..., N_m$, $j = 1, ..., 4$, $t = 40, ..., 80$ and $\ell, \ell' \in \mathcal{L}'$. Then the transition probability between ranges $\ell, \ell' \in \mathcal{L}'$ is estimated as follows:

$$q(\ell'|\ell) = \sum_{i=1}^{N_m}\sum_{j=1}^{4}\sum_{t=40}^{79} I^i_{t,j}(\ell) I^i_{t+1,j}(\ell') \Bigg/ \left(\sum_{i=1}^{N_m}\sum_{j=1}^{4}\sum_{t=40}^{79}\sum_{\ell'\in\mathcal{L}'} I^i_{t,j}(\ell) I^i_{t+1,j}(\ell')\right).$$

Finally, we use the NCHS mortality rate tables [134] to estimate the patients' non-CHD or stroke-related death probabilities. We estimate the values of d_t by subtracting the probability of death due to a CHD or a stroke event from the probability of death due to all reasons.

4.3.2 Estimating CHD and Stroke Probabilities

In this section we briefly explain how the UKPDS risk model predicts the CHD and stroke probabilities of a patient who was diagnosed with Type 2 diabetes k years before epoch 0. We use the CHD probability equation of Stevens et al. [198] and stroke probability equation of Kothari et al. [107]. For $(\ell, m) \in \mathcal{L}' \times \mathcal{M}$ and $t \in T'$, we define the probabilities $\pi_t^C(\ell, m)$ and $\pi_t^S(\ell, m)$ by the following equations:

$$\pi_t^C(\ell, m) = 1 - \exp\left\{-\eta_t^C(\ell, m)(\delta_C)^{k+t\tau}\left(\frac{1-(\delta_C)^\tau}{1-\delta_C}\right)\right\}, \tag{4.43a}$$

$$\pi_t^S(\ell, m) = 1 - \exp\left\{-\eta_t^S(\ell, m)(\delta_S)^{k+t\tau}\left(\frac{1-(\delta_S)^\tau}{1-\delta_S}\right)\right\}; \tag{4.43b}$$

where, $\delta_C \geq 0$ and $\delta_S \geq 0$ are constant and identical for all patients, and

$$\zeta_t = \beta_0 \beta_1^{(Age-55)} \beta_2^{Gender} \beta_3^{Ethnicity} \beta_4^{Smoking} \beta_5^{HbA1c(t)-6.72} \beta_6^{[SBP(t)-135.7]/10}, \tag{4.44a}$$

$$\eta_t^C(\ell, m) = \zeta_t \beta_7^{\ln[(1-m\omega)LR_\ell]-1.59}, \tag{4.44b}$$

$$\eta_t^S(\ell, m) = \gamma_0 \gamma_1^{(Age-55)} \gamma_2^{Gender} \gamma_3^{Smoking} \gamma_4^{AF} \gamma_5^{[SBP(t)-135.5]/10} \gamma_6^{(1-m\omega)LR_\ell-5.11}. \tag{4.44c}$$

In (4.44a)-(4.44c), β_0 and γ_0 are called *intercepts*, and each β_i, $i = 1, ..., 7$, and γ_j, $j = 1, ..., 6$, is a nonnegative parameter and called the *risk ratio* for the risk factor appearing as its exponent. Of these risk factors, LR_ℓ denotes the patient's off-treatment LR in state $\ell \in \mathcal{L}'$, and $HbA1c(t)$ (in %) and $SBP(t)$ (in mmHg) denote the patient's HbA1c and SBP levels at epoch t, respectively, and *Age, Gender, Ethnicity, Smoking* and AF are static variables with values determined as follows:

- *Age*: Age of the patient when diagnosed.
- *Gender*: 1 for female; 0 for male.
- *Ethnicity*: Ethnicity of the patient; 1 for Afro-Caribbean; 0 for Caucasian or Asian-Indian.
- *Smoking*: Smoking status at diagnosis; 1 for a smoker at diagnosis of the disease; 0, otherwise.
- AF: Presence of an atrial fibrillation when diagnosed; 1 if the patient had atrial fibrillation at diagnosis of the disease; 0, otherwise.

We assume that LR is a positive risk factor for a CHD or a stroke event, *i.e.*, $\beta_7, \gamma_6 \geq 1$, that is, given all factors other than the patient's cholesterol levels are fixed, an increase in the patient's LR levels do not lead to a decrease in her CHD and stroke probabilities. Note that this assumption is consistent with the results of randomized clinical trials and the parameter estimates of Stevens et al. [198] and Kothari et al. [107].

Because we assume a single value, LR_ℓ, to denote the patient's off-treatment LR in range $\ell \in \mathcal{L}'$, we calculate gender-specific off-treatment LR averages in each range and assign them as the corresponding values of LR_ℓ.

Table 4.2: Gender-specific LR-Range averages (LR_ℓ)

	LR-Range (ℓ)												
Patient	1	2	3	4	5	6	7	8	9	10	11	12	13
Female	2.61	3.26	3.75	4.24	4.74	5.24	5.73	6.22	6.73	7.24	7.73	8.22	9.97
Male	2.63	3.29	3.77	4.25	4.75	5.25	5.73	6.24	6.73	7.24	7.74	8.24	10.87

Finally, because our model assumes deterministic evolution of the patient's SBP and HbA1c levels, we use gender-specific SBP and HbA1c estimates from Denton et al. [53].

4.3.3 Numerical Results

We solve our MDP model to find the optimal treatment policies and illustrate the sensitivity of the patients' optimal value functions and policies with respect to their quality-adjustment and treatment-effect factors. We also evaluate and compare the three most common U.S. guidelines against optimal policies of our model.

We assume $\sigma = 0.02$ as our base case [155, 212]. In all numerical experiments we use an annual discount factor $\lambda = 0.97$ which is commonly the standard in health policy and economics literature [82]. Because the patients' optimal value functions and actions remain stationary beyond age 79, we use 80+ in figures and tables to refer to all ages beyond 79.

In Table 4.3, we present the patients' maximum expected QALYs to their first terminal events from ages 40, 50, 60, 70 and 80, respectively. Table 4.3 confirms that the patients' optimal value functions are monotonically nonincreasing in both LR and age. In Table

4.3, the differences between the optimal value functions range from 2.09 to 2.69 QALYs depending on the age of the patient. Pathophysiological processes affect CHD and stroke risks differently in men and women [156] and the differences in the expected QALYs of the male and the female patient prior to their first terminal events are closely related to such gender-based differences in CHD and stroke risks.

Table 4.3: Patients' maximum expected QALYs prior to their first terminal events.

		LR-Range												
Age	Gender	1	2	3	4	5	6	7	8	9	10	11	12	13
80+	Male	5.93	5.69	5.47	5.29	5.08	4.92	4.74	4.59	4.47	4.35	4.26	4.01	3.65
	Female	8.41	8.13	7.92	7.66	7.45	7.22	7.05	6.89	6.73	6.52	6.40	6.18	5.74
70	Male	7.60	7.41	7.22	7.07	6.89	6.76	6.60	6.47	6.37	6.28	6.21	5.99	5.73
	Female	10.07	9.85	9.69	9.48	9.31	9.12	8.99	8.87	8.74	8.58	8.49	8.31	7.98
60	Male	11.10	10.94	10.78	10.65	10.50	10.38	10.24	10.14	10.05	9.97	9.92	9.73	9.52
	Female	13.65	13.49	13.37	13.22	13.10	12.96	12.86	12.78	12.69	12.57	12.51	12.37	12.14
50	Male	14.87	14.75	14.63	14.54	14.42	14.34	14.23	14.16	14.10	14.04	14.01	13.87	13.73
	Female	17.43	17.32	17.23	17.12	17.04	16.94	16.88	16.82	16.76	16.69	16.65	16.56	16.41
40	Male	18.44	18.36	18.26	18.19	18.11	18.05	17.98	17.93	17.89	17.86	17.84	17.75	17.67
	Female	20.82	20.75	20.69	20.62	20.56	20.50	20.45	20.42	20.38	20.32	20.29	20.23	20.13

From Table 4.3, it is clear that the difference between the patients' optimal value functions in two different LR-ranges increases as they age. The optimal value function of the male patient has a range of 0.77 QALYs at age 40 and 2.58 QALYs at age 80 and beyond. Similarly, the optimal value function of the female patient has a range of 0.69 QALYs at age 40 and increases up to 2.67 QALYs by age 80. Consistent with clinical trials and published risk models, these imply that higher LR levels are more risky in that they affect the patient's QALYs more significantly as she ages.

Figure 4.3 depicts the optimal LR thresholds to initiate treatment for each patient. For instance, the optimal policy at age 40 can be interpreted as follows: Treatment should be initiated for the male patient if his LR level falls into any range that is higher than 6. On the other hand, treatment is not recommended at any LR level for the female patient at age 40. By Theorem 4.2, the optimal LR thresholds are nonincreasing in age for both patients, which implies that the patients are more likely initiate treatment as they get older. Also, note that the male patient's optimal LR thresholds are never higher than those of the female patient, and the deviation between their optimal LR thresholds are more significant at earlier

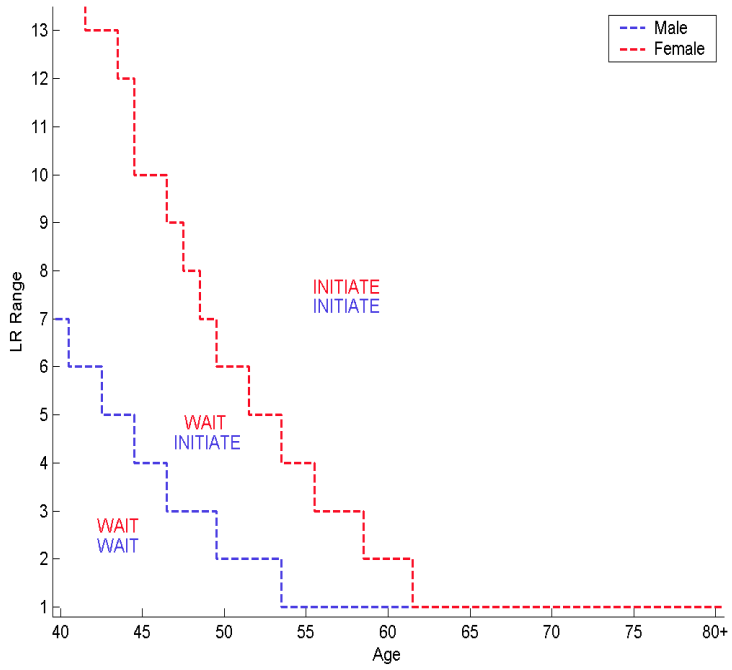

Figure 4.3: Optimal LR-range thresholds (ℓ_t^*) to initiate statin treatment for the base case.

ages. These results are consistent with a recent epidemiological study that has shown that cardiovascular risk reduction by treatment is lower for female patients than it is for male patients [101]. Moreover, they also confirm a meta-analysis of clinical trials for lipid-lowering treatment agents which has demonstrated lesser benefit of treatment for female patients than for male patients [223].

4.3.4 Sensitivity Analysis

To evaluate the effects of disutility and the treatment-effect factor on patients' expected QALYs to first terminal event and optimal policies, we perform one- and two-way sensitivity analyses. Figures 4.4 and 4.5 present the optimal treatment policies under various quality-adjustment factors, and illustrate the fact that the threshold for treatment decreases as the

disutility of statins decreases. It is clear that the optimal time to initiate statin treatment is quite sensitive to disutility of treatment. However, the thresholds of the male patient are never higher than those of the female patient at the same disutility level.

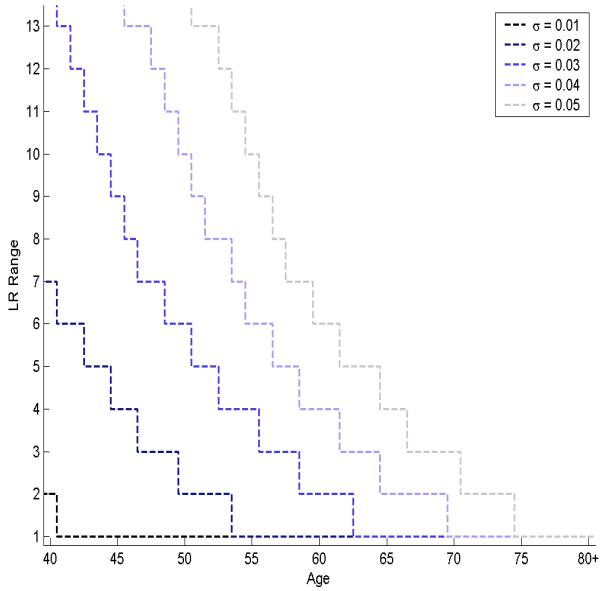

Figure 4.4: Sensitivity of the male patient's optimal policy with respect to σ for the base case value of ω.

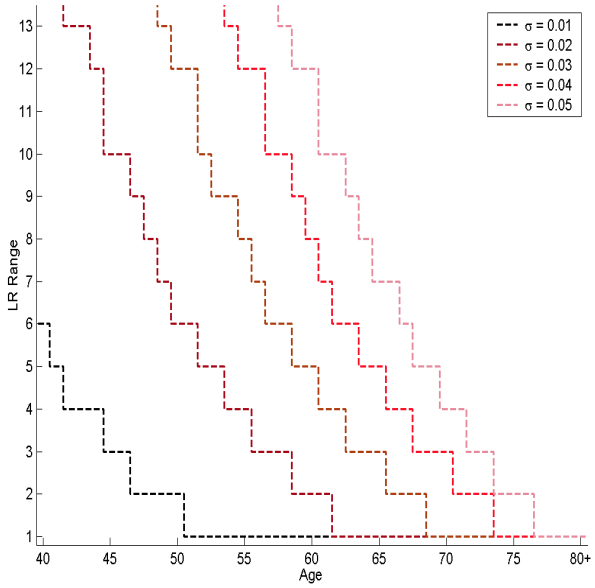

Figure 4.5: Sensitivity of the female patient's optimal policy with respect to σ for the base case value of ω.

In Figure 4.6, we illustrate the sensitivity of the optimal policies with respect to treatment-effect factor, within a $\pm 3\%$ region around the point estimate. We intuitively observe that the thresholds decrease as treatment effect increases. It is notable that the male patient has a lower treatment threshold than the female patient even when his response to treatment is worse than that of the female.

In Tables 4.4 and 4.5, we present the results from our two-way sensitivity analyses. From Table 4.4, an increase in the efficacy of treatment has greater impact on the optimal value function when the disutility of using statins is lower. When both patients have the same quality-adjustment factor, an increase in the treatment efficacy increases the QALYs of the male patient more than the female patient. From Table 4.4, regardless of the efficacy of

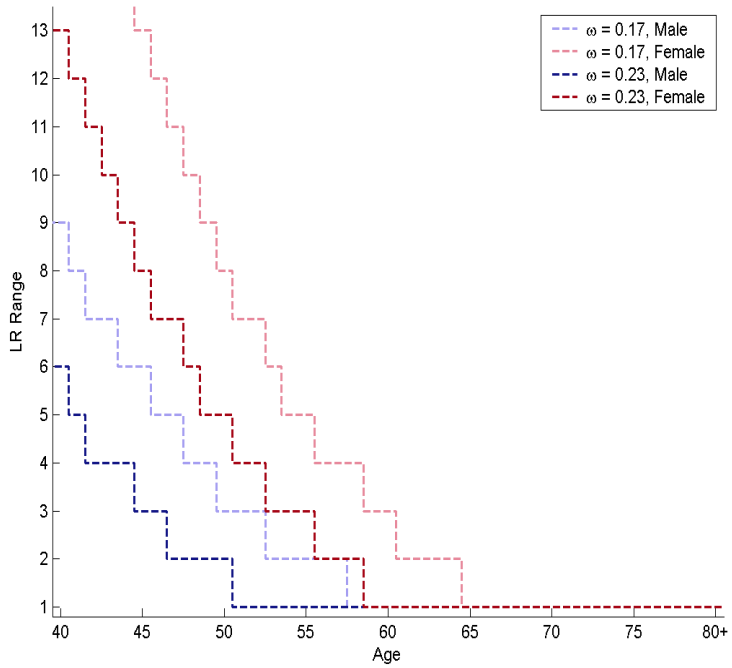

Figure 4.6: Sensitivity of patients' optimal policies with respect to ω for the base case value of σ.

treatment, when the disutility of using statins decreases, the male patient gains more than the female patient. Since increases in expected QALYs with increasing treatment-effect and/or decreasing quality-adjustment factors are greater for higher LR levels, patients that are relatively at higher risks of CHD and stroke benefit more from such changes.

4.3.5 Measuring the Violations of the Assumptions

In this section we evaluate the maximum violations of the assumptions and the conditions presented in Section 4.2. We let $a^+ = \max\{a, 0\}$ for $a \in \mathbb{R}$ and quantify the magnitudes of the maximum violations of the assumptions by the metrics below.

- For $\mathbf{P}^m(t)$ being IFR, $\epsilon_1 = \max_{\ell \in \mathcal{L}\setminus\{L+1\}, k \in \mathcal{L},\, m \in \mathcal{M},\, t \in T'} \left[\sum_{\ell'=1}^{k} \left[p_t^m(\ell'|\ell+1) - p_t^m(\ell'|\ell)\right]^+\right.$.

Table 4.4: Patients' QALY gains at the time of diagnosis when ω increases from 0.17 to 0.23.

		LR-Range												
σ	Gender	1	2	3	4	5	6	7	8	9	10	11	12	13
0.01	Male	0.182	0.190	0.196	0.201	0.205	0.209	0.213	0.217	0.219	0.221	0.223	0.228	0.232
	Female	0.153	0.158	0.163	0.170	0.177	0.184	0.188	0.190	0.192	0.196	0.197	0.201	0.205
0.02	Male	0.154	0.159	0.167	0.174	0.183	0.193	0.204	0.211	0.217	0.219	0.220	0.225	0.228
	Female	0.125	0.128	0.130	0.133	0.136	0.140	0.143	0.145	0.148	0.153	0.155	0.161	0.175
0.03	Male	0.122	0.125	0.130	0.133	0.138	0.142	0.148	0.153	0.157	0.160	0.163	0.180	0.191
	Female	0.099	0.101	0.102	0.103	0.105	0.106	0.107	0.108	0.109	0.110	0.111	0.112	0.115

Table 4.5: Patients' QALY gains at the time of diagnosis when σ decreases from 0.05 to 0.01.

		LR-Range												
ω	Gender	1	2	3	4	5	6	7	8	9	10	11	12	13
0.17	Male	0.284	0.296	0.312	0.325	0.339	0.350	0.363	0.373	0.381	0.387	0.391	0.406	0.414
	Female	0.225	0.231	0.236	0.244	0.250	0.259	0.265	0.272	0.279	0.289	0.294	0.304	0.318
0.19815	Male	0.341	0.358	0.376	0.390	0.407	0.420	0.435	0.446	0.455	0.462	0.467	0.484	0.493
	Female	0.270	0.278	0.285	0.296	0.305	0.318	0.327	0.335	0.343	0.354	0.359	0.371	0.388
0.23	Male	0.399	0.419	0.440	0.455	0.475	0.489	0.506	0.519	0.529	0.537	0.543	0.561	0.573
	Female	0.317	0.328	0.337	0.352	0.366	0.381	0.391	0.400	0.410	0.422	0.428	0.442	0.461

- For $B_t(\ell)$ being nondecreasing in $\ell \in \mathcal{L}'$, $\epsilon_2 = \max_{\ell \in \mathcal{L}' \setminus \{L\},\, t \in T'} [B_t(\ell) - B_t(\ell+1)]^+$.

- For the time-monotonicity of the terminal event probabilities,
  $\epsilon_3 = \max_{\ell \in \mathcal{L}',\, m \in \mathcal{M},\, t \in T' \setminus \{N-1\}} \left[p_t^m(L+1|\ell) - p_{t+1}^m(L+1|\ell)\right]^+$.

- For $B_t(\ell)$ being nondecreasing in $t \in T'$, $\epsilon_4 = \max_{\ell \in \mathcal{L},\, t \in T' \setminus \{N-1\}} [B_t(\ell) - B_{t+1}(\ell)]^+$.

For our data set, the maximum value of the metrics $\epsilon_1 - \epsilon_3$ are observed as follows: $\epsilon_1 = 0.0243$, $\epsilon_2 = 0.0245$ and $\epsilon_3 = 0.0171$. We also observe that $B_t(\ell)$ is nondecreasing in $t \in T'$ for all $\ell \in \mathcal{L}$ in all of our instances; that is, $\epsilon_4 = 0$ across our experiments.

4.3.6 Comparison with Current Treatment Guidelines

In the remainder of this section, we evaluate the performances of three of the U.S. guidelines and compare them with the optimal policy that our model yields. We consider the ADA guidelines, general national ATP III guidelines and its variant specific to diabetes patients. ATP III guidelines specify treatment decisions based on patients' long-term CHD risks and LDL levels. For instance, if the patient's 10-year CHD risk is below 10% and her LDL is above 100 mg/dL, then she should initiate using lipid-lowering agents. Diabetes-specific modification of the ATP III guidelines sets risk independent but tighter LDL thresholds. Below, Table 4.6 summarizes the ATP III guidelines. More conservatively, recent recommendations from the ADA call for immediate initiation of statins after diagnosis [15].

Table 4.6: Description of ATP III guidelines.

Guideline	Treatment Policy
ATP III	Treat based on long-term risk-level-based LDL targets
	10-year CHD Risk $\geq$ 20 % and LDL $>$ 100 mg/dL,
	10-year CHD Risk in between $10-20$ % and LDL $>$ 160 mg/dL,
	10-year CHD Risk $<$ 10 % and LDL $>$ 190 mg/dL
Modified ATP III	Consider diabetes as a cardiovascular risk equivalent for treatment
	Consider everyone as high risk and,
	Treat if LDL exceeds 100 mg/dL

To estimate the patients' expected QALYs prior to their first terminal events under the ATP III guidelines we need to assess their off-treatment 10-year CHD probabilities and LDL levels. We let $\varphi_t(\ell)$ denote the patient's probability of incurring a CHD event in within the next 10 years when she is in state $\ell \in \mathcal{L}'$ of epoch $t \in T'$ and calculate it as:

$$\varphi_t(\ell) = 1 - \exp\left\{-\eta_t^C(\ell, 0)(\delta_C)^{k+t\tau}\left(\frac{1-(\delta_C)^{10}}{1-\delta_C}\right)\right\},$$

where $\eta_t^C(\ell, 0)$ is defined by (4.44a) and (4.44b) [198].

In general, physicians do not measure the patients' LDL levels directly, but rather them it implicitly by the Friedewald's equation using levels of other types of cholesterol such as TC, HDL and triglycerides [227]. Because LR is defined only in terms of the patient's TC and HDL levels, we estimate the patients' triglycerides levels only as a function of age. Specifically, as in the process of estimating the patients' incomplete TC and HDL measurements, we estimate the patients' yearly triglycerides levels by first fitting cubic splines to their incomplete data and taking the average observation of each age over the spline-fitted data of the whole cohort. We let TR_t denote the patient's triglycerides level at epoch $t \in T'$.

Because the patient's HDL can't be predicted only from her LR level, we define an LR-range-specific probability mass function for her HDL. We discretize the continuous range of HDL levels into $H = 14$ ranges and let $h \in \mathcal{H} = \{1, 2, ..., 14\}$ refer to HDL-range $\big[LB_{HDL}(h), UB_{HDL}(h)\big)$. We define $D(h|\ell)$ to be the patient's probability of having an HDL in range $h \in \mathcal{H}$ given her LR is in range $\ell \in \mathcal{L}'$. Because LR is the ratio of the patient's TC to her HDL, we count the total number of HDL estimates in each HDL-range corresponding to each LR-range and estimate the probability $D(h|\ell)$ by dividing the number of HDL estimates in HDL-range $h \in \mathcal{H}$ to the number of total HDL estimates in all HDL-ranges corresponding to LR-range $\ell \in \mathcal{L}'$. The formalization of this process is similar to that of estimating the conditional LR-transition probabilities. To calculate the patients' LR-range-specific LDL levels, we also assign a single off-treatment HDL value, HDL_h, to each HDL-range $h \in \mathcal{H}$. We calculate gender-specific HDL averages in each HDL-range and assign them as the corresponding values of HDL_h. Then, we let $LDL_t(\ell, h)$ denote the LDL of a patient with an LR in range $\ell \in \mathcal{L}'$ and HDL in range $h \in \mathcal{H}$ at epoch $t \in T'$, and calculate it by the Friedewald's equation as $LDL_t(\ell, h) = HDL_h(LR_\ell - 1) - 0.2TR_t$ for $\ell \in \mathcal{L}'$, $h \in \mathcal{H}$ and $t \in T'$. To compute the patients' expected QALYs prior to their first terminal events under ATP III and modified ATP III guidelines, we define $z_t(\ell, h)$ to be the decision recommended by the guideline in LDL-range $\ell \in \mathcal{L}'$ and HDL-range $h \in \mathcal{H}$ at epoch $t \in T'$. Specifically:

$$z_t(\ell, h) = \begin{cases} I & \text{if } \varphi_t(\ell) \geq 0.2 \text{ and } LDL_t(\ell, h) \geq 100 \text{ mg/dL, or} \\ & \quad \varphi_t(\ell) \geq 0.1 \text{ and } LDL_t(\ell, h) \geq 160 \text{ mg/dL, or } LDL_t(\ell, h) \geq 190 \text{ mg/dL,} \\ W & \text{otherwise,} \end{cases}$$

for the ATP III guidelines and,

$$z_t(\ell, h) = \begin{cases} I & \text{if } LDL_t(\ell, h) \geq 100 \text{ mg/dL}, \\ W & \text{otherwise;} \end{cases}$$

for the modified ATP III guidelines.

Since the patient's HDL-range is implicit with respect to her LR-range, in our modeling framework, the decision recommended by the guidelines is probabilistic with respect to her LR-range. We define $\alpha_t(\ell) = \sum_{\{h: z_t(\ell,h)=I\}} D(h|\ell)$ as the probability of initiating treatment in LR-range $\ell \in \mathcal{L}'$ at epoch $t \in T'$ under each of the aforementioned guidelines. Then, for each of the guidelines, we let $\vartheta_t(\ell)$ denote the patient's expected QALYs prior to her first terminal event in LR-range $\ell \in \mathcal{L}'$ of epoch $t \in T'$ and recursively calculate it as:

$$\vartheta_t(\ell) = \begin{cases} \alpha_t(\ell)\mu_t(\ell) + \big[1 - \alpha_t(\ell)\big]\big[r^0(\ell) + F_t^0(\ell, \boldsymbol{\vartheta}_{t+1})\big] & \text{for } \ell \in \mathcal{L}',\ t < N, \\ \alpha_{t-1}(\ell)\mu_t(\ell) + \big[1 - \alpha_{t-1}(\ell)\big]\big[r^0(\ell) + F_{t-1}^0(\ell, \boldsymbol{\vartheta}_t)\big] & \text{for } \ell \in \mathcal{L}',\ t = N. \end{cases}$$

Based on our numerical experiments, from Table 4.7, when $\sigma = 0.01$, there is a loss of less than 0.02 QALYs if statins are immediately initiated rather than following the optimal treatment policy. However, as the disutility of using statins increases, these losses become significant.

Table 4.7: Patients' expected QALY losses due to immediate initiation of treatment rather than following the optimal policy of our model.

		LR-Range												
σ	Gender	1	2	3	4	5	6	7	8	9	10	11	12	13
0.01	Male	*	*	*	*	*	*	*	*	*	*	*	*	*
	Female	0.017	0.011	0.006	0.002	*	*	*	*	*	*	*	*	*
0.02	Male	0.044	0.033	0.023	0.015	0.007	*	*	*	*	*	*	*	*
	Female	0.110	0.098	0.089	0.077	0.068	0.058	0.051	0.045	0.038	0.030	0.026	0.018	0.004
0.03	Male	0.136	0.120	0.104	0.091	0.075	0.064	0.051	0.042	0.034	0.028	0.024	0.013	0.000
	Female	0.249	0.234	0.223	0.208	0.196	0.183	0.174	0.166	0.157	0.145	0.139	0.126	0.104
0.04	Male	0.413	0.397	0.385	0.368	0.355	0.340	0.330	0.321	0.312	0.299	0.292	0.278	0.253
	Female	0.262	0.244	0.224	0.208	0.189	0.176	0.159	0.146	0.136	0.127	0.121	0.098	0.075
0.05	Male	0.411	0.390	0.369	0.352	0.332	0.317	0.298	0.285	0.274	0.264	0.258	0.233	0.209
	Female	0.592	0.576	0.563	0.545	0.531	0.516	0.505	0.496	0.486	0.472	0.465	0.450	0.424

* denotes values < 0.001.

Table 4.8: Patients' expected QALY losses due to following ATP III guidelines rather than the optimal policy of our model.

		LR-Range												
σ	Gender	1	2	3	4	5	6	7	8	9	10	11	12	13
0.01	Male	0.032	0.012	0.006	0.002	*	*	*	*	*	*	*	*	*
	Female	0.019	0.007	0.004	0.002	*	*	*	*	*	*	*	*	*
0.02	Male	0.065	0.088	0.086	0.076	0.068	0.057	0.051	0.045	0.038	0.030	0.026	0.018	0.008
	Female	0.014	0.023	0.018	0.014	0.007	0.003	*	*	*	*	*	*	*
0.03	Male	0.144	0.212	0.217	0.206	0.196	0.183	0.174	0.166	0.158	0.147	0.141	0.129	0.113
	Female	0.058	0.094	0.089	0.087	0.075	0.063	0.051	0.041	0.034	0.028	0.024	0.012	0.005
0.04	Male	0.247	0.363	0.375	0.366	0.355	0.340	0.331	0.322	0.313	0.301	0.295	0.282	0.264
	Female	0.135	0.201	0.200	0.202	0.189	0.175	0.159	0.147	0.138	0.130	0.124	0.106	0.095
0.05	Male	0.367	0.530	0.550	0.542	0.531	0.516	0.506	0.497	0.487	0.474	0.468	0.455	0.435
	Female	0.235	0.332	0.336	0.343	0.332	0.315	0.300	0.286	0.276	0.268	0.262	0.242	0.231

* denotes values < 0.001.

Table 4.9: Patients' expected QALY losses due to following modified ATP III guidelines rather than the optimal policy of our model.

		LR-Range												
σ	Gender	1	2	3	4	5	6	7	8	9	10	11	12	13
0.01	Male	0.005	0.006	0.004	0.002	*	*	*	*	*	*	*	*	*
	Female	0.016	0.009	0.006	0.002	*	*	*	*	*	*	*	*	*
0.02	Male	0.011	0.023	0.018	0.014	0.007	0.003	*	*	*	*	*	*	*
	Female	0.050	0.089	0.086	0.076	0.068	0.057	0.051	0.045	0.038	0.030	0.026	0.018	0.008
0.03	Male	0.056	0.094	0.089	0.087	0.075	0.063	0.051	0.041	0.034	0.028	0.024	0.012	0.005
	Female	0.141	0.218	0.217	0.206	0.196	0.183	0.174	0.166	0.158	0.147	0.141	0.129	0.113
0.04	Male	0.134	0.201	0.200	0.202	0.189	0.175	0.159	0.147	0.138	0.130	0.124	0.106	0.095
	Female	0.257	0.374	0.376	0.366	0.355	0.340	0.331	0.322	0.313	0.301	0.295	0.282	0.264
0.05	Male	0.234	0.332	0.336	0.343	0.332	0.315	0.300	0.286	0.276	0.268	0.262	0.242	0.231
	Female	0.389	0.545	0.551	0.542	0.531	0.516	0.506	0.497	0.487	0.474	0.468	0.455	0.435

* denotes values < 0.001.

Results for the expected QALY losses under ATP III guidelines and its modified version are presented in Tables 4.8 and 4.9, respectively. Clearly the loss is lower under ATP III guidelines than under ADA guidelines, owing to the more aggressive use of statins in the latter. Likewise, because the modified ATP III guidelines consider diabetes as CHD risk equivalent and sets tighter LDL thresholds than the original ATP III guidelines, patients

lose more QALYs under the modified version. From Tables 4.7, 4.8 and 4.9, we observe the QALY loss is more for the male patient; which can be attributed to the earlier onset of cardiovascular risk.

4.4 CONCLUSIONS

Current lipid management guidelines use long-term CHD risk to make treatment recommendations but do not differentiate patients on the basis of disutility of using statins. In this chapter we empirically show the importance of tailoring guidelines to short-term CHD and stroke probabilities, individual patient preferences and patients' responses to statins. We gain insights into the effect of medication side effects on treatment decisions and show that treatment disutility can significantly affect the decision of if and when to initiate statin treatment. Our numerical results empirically confirm the theoretical results which provide scientific evidence to help support the practice of threshold-structured treatment policies. We also illustrate the importance of individualized treatment factors by estimating the patients' QALY gains using our customized policies rather than the current U.S. guidelines. Our experiments indicate that current guidelines may set aggressive thresholds which may lead up to 0.6 QALY loss per patient.

5.0 LIMITATIONS AND FUTURE RESEARCH

This dissertation focuses on two emerging timing problems for diabetes and ESRD patients. It presents the first stochastic game application in healthcare and the first model in the literature that aims to balance the trade-off between the benefits and adverse side effects of statins.

With an ultimate goal of valuing a kidney matching, in Chapter 3 we introduce the timing of an exchange in a prearranged PKE and formulate the problem resulting between the patients as a stochastic game. We analyze the underlying equilibria of the game in detail. In general, showing the existence of a pure equilibrium for stochastic games is challenging. We use the fact that an exchange does not occur unless both patients offer to exchange to show that a pure equilibrium always exists for our model. While our model considers the timing for autonomous and self-interested patients, we recognize the society's objective in equilibrium selection. We develop mathematically tractable MIP models to characterize socially optimal equilibria of the game. We illustrate our analytical results and discuss their policy implications using clinical data. We observe that randomized strategies perform negligibly better than pure strategies. We also quantify the social welfare loss due to patient autonomy and demonstrate that maximizing the number of transplants may be undesirable. Our numerical study shows that patients may exchange their kidneys prior to the initiation of dialysis. Therefore, we also shed light on the welfare consequences of preemptive PKEs which are not common in practice. We believe the model and analyses in this chapter may also lay the groundwork for exchanges of other organs such as liver and bone marrow, for which exchanges are not common but matches are difficult to find [48].

The model and analyses in Chapter 3 have some limitations. First, the model does not consider the arrivals of cadaveric kidneys to any of the patients. In practice because living

donors are preferred to cadaveric donors, when patients are both alive they would prefer the exchange to a cadaveric kidney. In our model, because patient autonomy may delay the timing of an exchange and one of the patients may die before an exchange occurs, the surviving patient is assumed to receive no kidneys from the waiting list in the remainder of her life. However, upon a kidney failure, patients initiate dialysis and register to waiting list for a cadaveric kidney. We can easily incorporate the effects of possibility of receiving a cadaveric kidney from the waiting list into the model by modifying the patients' payoff functions in (3.1) for $\mathbf{s} \in \mathscr{S}$ and $i \in \mathcal{N}$ as follows:

$$g_i(\mathbf{s}, \mathbf{a}_1, \mathbf{a}_2) = \begin{cases} a_1(\mathbf{s})a_2(\mathbf{s})u_i(\mathbf{s}, 1) + \big[1 - a_1(\mathbf{s})a_2(\mathbf{s})\big] F_i\big(\mathbf{s}, \mathbf{g}_i(\mathbf{a}_1, \mathbf{a}_2)\big) & \text{if } \mathbf{s} \in \mathscr{S} \setminus \mathscr{D}, \\ h_i(\mathbf{s}) & \text{otherwise.} \end{cases} \tag{5.1}$$

In (5.1), $h_i(\mathbf{s})$ is a one-time termination payoff and represents Patient i's expected QALYs when the game terminates in state $\mathbf{s}$ due to a death before an exchange occurs and may include the possibility of receiving a cadaveric kidney from the waiting list after initiating dialysis. Note that it is a lump-sum reward and equal to 0 if Patient i is dead in state $\mathbf{s}$. An immediate future research direction would estimate the rewards $\{h_i(\mathbf{s})\}$ by calibrating an explicit or implicit waiting list model for ESRD patients and investigate their effects on patients' strategies in timing the exchange. In such an extension, because the expected payoffs in states $\mathbf{s} \in \mathscr{D}$ do not depend on patients' strategies and rewards $\{h_i(\mathbf{s})\}$ are externally estimated, most of our equilibrium conditions would remain valid in all living states $\mathbf{s} \in \mathscr{S} \setminus \mathscr{D}$ and be translated into MIP formulations similar to those of Chapter 3 for equilibrium selection.

Second, our model treats dialysis initiation as an exogenous probabilistic decision, so that patients initiate dialysis at practical rates. Dialysis initiation is a complex subject [114], and requires a more detailed physiological model which may be mathematically intractable and computationally prohibitive within a game-theoretic framework. Third, as Nash equilibrium eliminates only unilateral deviations, our analyses implicitly assume that patients can't collude. Therefore, it ignores the resistance of an equilibrium against patients' joint deviations. Extension of our analyses to stability-oriented refinements of ordinary Nash equilibria is a promising future research direction. Last, but not least, our model assumes

risk-neutral patients and, our equilibrium analyses and numerical study primarily focus on welfare-maximizing equilibrium selection. However, patients, especially those with failed kidneys and severe health progression, may exhibit highly risk-averse behavior in practice whenever they have a kidney available for transplant. Another promising extension would incorporate risk-sensitivity into the payoffs and/or consider equilibrium selection for risk-averse patients, however such an extension would require more sophisticated mathematical programming representations of the resulting equilibrium conditions.

In Chapter 4 we approach the optimal timing of statin initiation problem by an infinite-horizon MDP. We derive several structural properties of the resulting optimal policies and empirically support them using clinical data. We assess the influence of age- and gender-based risk on the timing of initiation. We also investigate the sensitivity of the resulting policies with respect to disutility of using statins and the reduction in cholesterol levels by treatment. We compare the performance of the resulting policies to that of the ATP III guidelines and show that patients experiencing higher disutility from treatment benefit more from following the policy suggested by our model than the ATP III guidelines.

The model and the numerical study in Chapter 4 have some limitations. First, the source data that we use to estimate the progression of LR levels belong to a single medical center, and the population that the data is drawn from is likely to be healthier than a typical population that may not receive continuous access to healthcare. Second, a limitation for our numerical experiments is that we focus only on Caucasian non-smoker patients due to limited availability of clinical data.

We primarily focus on managing cholesterol levels for Type 2 diabetes and assume that SBP and HbA1c levels change deterministically as a function of time. In practice statin treatment may be supported with blood glucose and blood pressure control medications. An immediate future research would extend the current model in two directions. First, in addition to LR, it may consider stochastically changing SBP and HbA1c levels. Second, it may consider the optimization of multiple treatments for each of the aforementioned risk factors. Note that progressions of LR, SBP and HbA1c are all interrelated as high blood sugar triggers bad cholesterol and increase in bad cholesterol results in an increase in blood pressure. Therefore, such a multi-treatment extension would need the joint transition

functions of LR, SBP and HbA1c, the estimation of which would be computationally more sophisticated and need more data for the reliability of the estimates. Moreover, as state and action spaces will grow exponentially these extensions may suffer from the curse of dimensionality and necessitate the development of approximation algorithms.

Because a Type 2 diabetes patient's CHD and stroke risks can be assessed by various risk models, another future research direction would focus on a robust decision model by considering the risk model-based ambiguities in the transition probabilities. Such a model can be further enhanced by incorporating the ambiguities in transitions among LR, SBP and HbA1c levels that are inherent to estimation under limited data.

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