Data-Driven Decision-Making for Medications Management Modalities

by

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ABSTRACT

One of the critical issues in the U.S. healthcare sector is attributed to medications management. Mismanagement of medications can not only bring more unfavorable medical outcomes for patients, but also imposes avoidable medical expenditures, which can be partially accounted for the enormous $750 billion that the American healthcare system wastes annually. The lack of efficiency in medical outcomes can be due to several reasons. One of them is the problem of drug intensification: a problem associated with more aggressive management of medications and its negative consequences for patients.

To address this and many other challenges in regard to medications mismanagement, I take advantage of data-driven methodologies where a decision-making framework for identifying optimal medications management strategies will be established based on real-world data. This data-driven approach has the advantage of supporting decision-making processes by data analytics, and hence, the decision made can be validated by verifiable data. Thus, compared to merely theoretical methods, my methodology will be more applicable to patients as the ultimate beneficiaries of the healthcare system.

Based on this premise, in this dissertation I attempt to analyze and advance three streams of research that are influenced by issues involving the management of medications/treatments for different medical contexts. In particular, I will discuss (1) management of medications/treatment modalities for new-onset of diabetes after solid organ transplantations and (2) epidemic of opioid prescription and abuse.

DEDICATION

To my parents for their unwavering belief in education.

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I would like to express my deepest gratitude to my advisor, Dr. Soroush Saghafian, for giving me a once-in-a-lifetime opportunity of studying my Ph.D., believing in me through hard times, showing me what it takes to be a professional and unbiased scholar, and helping me to achieve something that I could have never imagined to accomplish.

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Chapter 1

INTRODUCTION

One of the critical issues in the U.S. healthcare sector is attributed to medications management. Mismanagement of medications can not only bring more unfavorable medical outcomes for patients, but also imposes avoidable medical expenditures, which can be partially accounted for the enormous $750 billion that the American healthcare system wastes annually. The lack of efficiency in medical outcomes can be due to several reasons. One of them is the problem of drug intensification: a problem associated with more aggressive management of medications and its negative consequences for patients.

To address this and many other challenges in regard to medications mismanagement, we take advantage of data-driven methodologies where a decision-making framework for identifying optimal medications management strategies will be established based on real-world data. This data-driven approach has the advantage of supporting decision-making processes by data analytics, and hence, the decision made can be validated by verifiable data. Thus, compared to merely theoretical methods, our methodology will be more applicable to patients as the ultimate beneficiaries of the healthcare system.

Based on this premise, in this dissertation we attempt to analyze and advance three streams of research that are influenced by issues involving the management of medications/treatments for different medical contexts. In particular, we will discuss (1) management of medications/treatment modalities for new-onset of diabetes after solid organ transplantations and (2) epidemic of opioid prescription and abuse.

1.1 Medications Management for New-Onset Diabetes after Transplant

As reported by the United Network of Organ Sharing, nearly 20,000 kidney transplantations were conducted in the U.S. in 2017 (140,992 cases since 2010) (UNOS, 2018). According to the Organ Procurement and Transplantation Network (OPTN), the average cumulative probability of 1 to 10-year organ rejection after kidney transplantation is estimated to be 6.35% to 48.7% (OPTN, 2011). To reduce the risk of organ rejection post-transplant, physicians typically use an intensive amount of an immunosuppressive (a.k.a. anti-rejection) drug (e.g., tacrolimus). However, due to the well-known *diabetogenic effect*, excessive exposure to an immunosuppressive drug may induce New Onset Diabetes After Transplantation (NODAT) which refers to incidence of diabetes in a patient with no history of diabetes prior to transplantation (Chakkera et al., 2009).

Our clinical data shows that more than 80% (20%) of patients who undergo transplantation are in danger of becoming pre-diabetic (diabetic), mainly because of intensive amount of immunosuppressive drugs used in practice. Considering the total number of transplantations carried out worldwide, this can account for more than 90,000 new patients per year who are in danger of elevated blood glucose levels. Elevated blood glucose levels, in turn, increase the risk of organ rejection and may result in re-transplantation, which is a costly medical operation. Although physicians attempt to control the risk of elevated blood glucose levels by putting the patient on insulin, using insulin should be coordinated with the intensity of the immunosuppressive drug(s) used, because unnecessary use of insulin is harmful (Kromann et al., 1981). Despite this conundrum faced by physicians, there is currently no clear guideline on how these medications should be simultaneously managed. Our goal in this research is to address this deficit. To this end, we will discuss my two studies

in chapters 2-3, where the first study is a fundamental theoretical/numerical analysis that deals with actual management of medications after transplant, and the second study is an empirical research about incidence of hyperglycemia (i.e., elevated blood glucose levels) as a result of using immunosuppressive drugs.

1.2 Opioid Prescription and Abuse Epidemic

According to the Centers for Disease Control and Prevention (CDC), a total of 47,055 drug-related deaths ocurred in 2014, among which opioid analgesics were the main contributing factor accounting for 18,893 deaths (40% of total deaths). These opioid painkillers may ultimately result in heroin addiction/overdose, which caused additional 10,574 deaths in the same year (CDC, 2015). In addition, the societal costs of opioid prescription abuse in the U.S. can get up to $78.5 billion (including healthcare cost, workplace cost, and criminal justice cost) (MedlinePlus.gov, 2016), and almost 2 million people are estimated to be dependent on prescription opioids or abusing them (USA Today, 2016). All these factors have prompted CDC to call this problem an epidemic.

To address this issue, CDC proposed a set of guidelines for prescribing opioids for chronic pain (Dowell et al., 2016), which mainly focus on reducing the strength or duration of supply for these medications. However, as mentioned by the American Medical Association (AMA), some of these guidelines may not reflect the existing evidence (AMA, 2016a): *"[. . .] while the AMA supports many of the recommendations, we continue to have serious concerns that some either contain a degree of specificity not supported by the existing evidence or conflict with official Food and Drug Administration (FDA)-approved product labeling for opioid analgesic products."* More importantly, these guidelines make very general recommendations for prescribing opioid painkillers, leaving the ultimate prescription decision up to a provider/physician

(Dowell et al., 2016): *"Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient."* Despite the clear intuition behind this strategy, the extent where potential benefits of these medications would be comparable to their side effects/risks is not completely known.

We attempt to address the foregoing question in chapter 4. In particular, we will explore evidence for a potential trade-off between benefits and risks of using opioid painkillers. To this end, we utilize *Commercial Insurance and Medical Claims* data, which contains the history of medical encounters and prescribed medications for millions of patients over a three-year period. Employing some machine learning algorithms, we make statistical inference about whether or not there exist associations between benefits/risks and (1) using opioid painkillers, (2) using non-opioid painkillers, and (3) duration of supply. Furthermore, we make this inference in the presence of different patient's characteristics, which include (1) demographics (e.g., age and gender), (2) behavioral risk factors (e.g., history of alcohol consumption, smoking, mental disorder, and substance abuse), and (3) route of encounter (e.g., inpatient vs. outpatient).

Chapter 2

ROBUST STOCHASTIC DECISION-MAKING FOR MEDICATIONS MANAGEMENT: A DATA-DRIVEN APPROACH

2.1 Introduction

As reported by the United Network of Organ Sharing, nearly 20,000 kidney transplantations were conducted in the U.S. in 2017 (140,992 cases since 2010) (UNOS, 2018). According to the Organ Procurement and Transplantation Network (OPTN), the average cumulative probability of 1 to 10-year organ rejection after kidney transplantation is estimated to be 6.35% to 48.7% (OPTN, 2011). To reduce the risk of organ rejection post-transplant, physicians typically use an intensive amount of an immunosuppressive (a.k.a. anti-rejection) drug (e.g., tacrolimus). However, due to the well-known *diabetogenic effect*, excessive exposure to an immunosuppressive drug may induce New Onset Diabetes After Transplantation (NODAT) which refers to incidence of diabetes in a patient with no history of diabetes prior to transplantation (Chakkera et al., 2009).

To illustrate this point, we use a data set of 407 patients who had kidney transplant surgery at our partner hospital between 1999 and 2006. Based on this data set, Figure 2.1 depicts the empirical cumulative distribution functions (C.D.F.s) of blood glucose level (measured by the HbA1c test) right before and one month after transplantation for patients who had no prior history of diabetes. As can be seen, more than 80% (20%) of patients who undergo transplantation are in danger of becoming pre-diabetic (diabetic), mainly because of intensive amounts of an immunosuppressive drug used in practice. Considering the total number of transplantations carried out worldwide,

this can account for more than 90,000 new patients per year who are in danger of elevated blood glucose levels.

Elevated blood glucose levels, in turn, increase the risk of organ rejection and may result in re-transplantation, which is a costly operation (Bentley and Hanson, 2011). To control the risk of elevated blood glucose levels, a patient may need diabetes medications (e.g., insulin). However, in the current practice, immunosuppressive drugs and diabetes medications are typically prescribed by different departments (transplantation/nephrology and endocrinology, respectively) of a hospital. This, in turn, results in a sequential management of these medications, which may reduce the efficacy of treatments. In addition, diabetes medications cannot be prescribed arbitrarily, because unnecessary use of such medications is harmful (Kromann et al., 1981). Therefore, the use of a diabetes medication should be coordinated with the intensity of the immunosuppressive drug used. Despite guidelines on how to manage these medications separately, there is currently no clear guideline on how to coordinate these regimens (i.e., how to simultaneously manage these medications). Our goal in this study is to address this deficit while taking into account the following issues:

Measurement Errors. Blood glucose levels are measured by test procedures such as *Fasting Plasma Glucose* (FPG) and *Hemoglobin A1c* (HbA1c), which have a wide range of false-positive and false-negative errors (Bennett et al., 2007). In addition, the concentration of immunosuppressive drugs is measured in practice through test procedures such as *Abbott Architect* and *Magnetic Immunoassay*, which are similarly error-prone (Bazin et al., 2010).

Estimation Errors. Estimating various parameters (e.g., the probabilistic consequences of various medications on a patient's future health) from data sets is typically subject to errors for a variety of reasons including lack of comprehensive data and data entry errors among others. Furthermore, medication strategies are typically op-

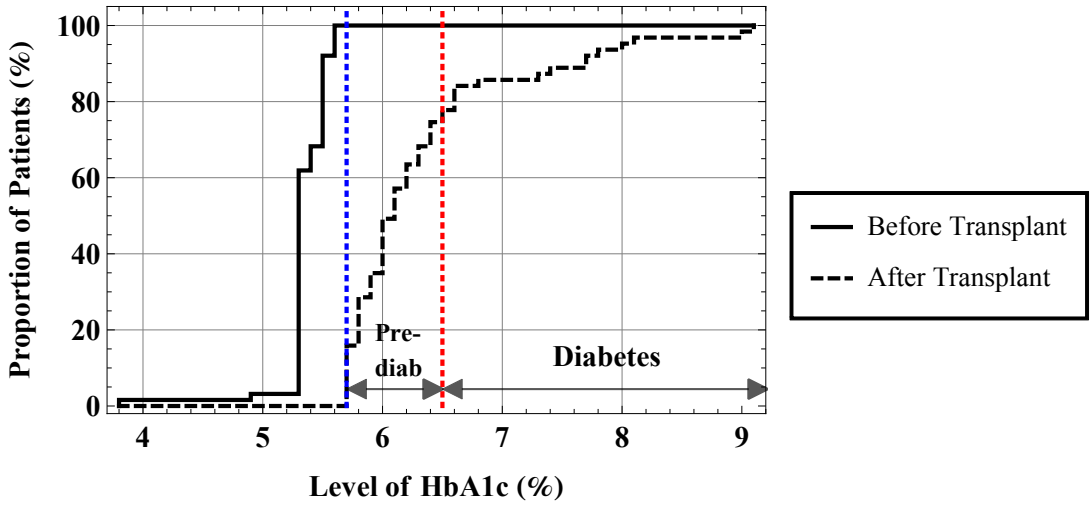


Figure 2.1: Empirical C.D.F.s of Patients' Hemoglobin A1c (HbA1c) Level in Our Data Set: An Illustration of the Diabetogenic Effect of Immunosuppressive Drugs. The Left (Right) Vertical Dotted Line Shows the Threshold for Pre-diabetes (Diabetes) as Defined by American Diabetes Association (ADA, 2012).

timized with respect to such estimated parameters. Thus, unless carefully adjusted, they may not represent patients' best medical interest.

Ambiguity Attitudes. Incomplete/imprecise information (which results in the foregoing estimation errors) typically makes physicians face ambiguity with respect to unknown consequences of treatment choices and their impact on a patient's health outcomes. Furthermore, physicians have a range of ambiguity attitudes in prescribing treatments: while some show high conservatism (high ambiguity aversion), others may exhibit low conservatism (low ambiguity aversion) (see, e.g., Han et al. (2009), Arad and Gayer (2012), and Berger et al. (2013)).

Static and Dynamic Risk Factors. Both static/time-invariant (e.g., race and gender) and dynamic/time-variant (e.g., blood pressure and body mass index) risk factors play an important role in effective coordination of post-transplant medication regimens, because they both affect organ rejection and/or diabetes complications.

Ignoring any of the above-mentioned issues can yield suboptimal medication strategies that may harm patients. Thus, in finding a solution for the conundrum discussed earlier, one also needs an approach that allows addressing such issues in an integrated way. To this end, we use a dynamic decision-making approach termed Ambiguous Partially Observable Markov Decision Process (APOMDP)—an extension of the traditional POMDP approach recently proposed by Saghafian (2018). Utilizing the APOMDP approach allows us to find a dynamically optimal way of coordinating immunosuppressive and diabetes medications during each patient visit while accounting for (1) imperfect state information about the patient's health (caused by measurement errors), (2) model misspecifications (caused by estimation errors), (3) a range of attitudes towards model misspecifications (caused by physicians' ambiguity attitudes), and (4) several dynamic and/or static risk factors (age, gender, race, diabetes history, body mass index (BMI), blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride, and uric acid). This approach enables us to provide the first study (to the best of our knowledge) that (a) simultaneously analyzes two medical conditions with conflicting risks (i.e., post-transplant organ rejection versus NODAT), and (b) integrates such risks with both static and dynamic patient-dependent characteristics.

Our study contributes to both theory and application. From the application perspective, we contribute to the medical literature by presenting new clinically relevant findings:

(1) We calibrate our APOMDP model based on a clinical data set. Utilizing this data set, we first estimate unobservable disease progression rates, inaccuracies of medical test procedures, and reward-related parameters (e.g., quality of life and life expectancy). Using these estimations along with the APOMDP approach, we then generate risk-specific medication strategies for use in practice.

(2) For non-White patients with age≥50, no diabetes history, and low-risk levels of cholesterol, HDL, LDL, triglyceride, and uric acid, we find that, under the optimal medication policy, a more conservative physician prescribes more intensive regimens of immunosuppressive drugs as well as diabetes medications than a less conservative one. This implies that, for patients with these risk factors, a more conservative physician should be more concerned about both risks of organ rejection and NODAT compared to a less conservative physician. However, this does not hold for male patients with age<50, diabetes history, hypertension, and high-risk levels of cholesterol, HDL, and LDL.

(3) Variations in physicians' attitude toward ambiguity will not have a homogeneous impact on the intensity of drugs prescribed under the optimal policy. Thus, drug intensification (i.e., use of intensified levels of medication regimens) observed in the current practice should not be attributed merely to physicians' behavior toward ambiguity. Our result suggests that lack of adherence to (or knowledge of) the optimal medications is the main contributor to using intensive regimens.

(4) Our study sheds light on the predictors of tacrolimus dose variability. Specifically, we find that risk factors such as age, gender, race, BMI, blood pressure, HDL, and LDL make patients more vulnerable to the risk of organ rejection. Furthermore, the diabetogenic effect of tacrolimus is more likely to influence male patients with age≥50, diabetes history, hypertension, high cholesterol, and low HDL. This implies that, when using high-dose tacrolimus, such patients become more dependent on diabetes medications than others.

(5) We compare the performance of the optimal medication policies that we obtain from the APOMDP approach with (a) benchmarks from the current medical practice, and (b) medication policies that arise when one uses a traditional POMDP approach. We consider performance measures such as quality-adjusted life expectancy (QALE),

medical expenditure, and the intensity of prescribed medications. Some of the main insights generated from our comparison are as follows:

- Compared to the current medical practice, and depending on different risk factors, our optimal medication policies can improve (per patient per year) the average (a) QALE up to 4.58%, and (b) medical expenditures up to 11.57%. In particular, for cohorts of patients formed by age, diabetes history, blood pressure, cholesterol, HDL, and triglyceride, our proposed medication strategies yield the highest improvements in QALE while incuring the least amount of medical expenditure, providing more *cost-effective* ways of managing medications.

- We find that deriving optimal strategies via a traditional POMDP instead of using the APOMDP approach (i.e., ignoring inevitable parameter ambiguities) may cause a patient to lose between 1.04 and 4.68 weeks of QALE over the course of first year post-transplant, while imposing between \$31 and \$214 more medical expenditures per patient to the system during the same time.

From the theory perspective, our contributions are two-fold: (1) we demonstrate the use of the APOMDP approach to make *robust* dynamic decisions under both imperfect state information and model misspecifications. Since both imperfect state information and model misspecifications are inevitable in many applications including those in the general field of medical decision-making, our work sheds light on the advantages of an applicable new tool. Specifically, our approach empowers a decision maker who is facing hidden states to dynamically optimize actions under a variety of possible models (a "cloud" of models as opposed to a single model), and thereby gain robustness to potential model misspecifications. Importantly, this removes the need to perform sensitivity analyses on such potential misspecifications. (2) We develop a closed-form expression for the optimal value function (based on the

piecewise-linearity and convexity property) which enables us to solve our APOMDP formulation optimally. We also establish (a) an analytical link between the decision maker's ambiguity attitude and the intensity of optimal medication regimens, (b) monotonicity results for the optimal medication policy, and (c) a lower bound for the optimal value function.

In closing this section, we provide a roadmap for the implementation of our APOMDP approach in the management of post-transplant medications. Figure 2.2 shows a data-driven decision support system (DSS) that not only can assist physicians in their post-transplant medications management decisions, but can also influence medical guidelines. This DSS can achieve these goals by using our proposed approach to better balance risks of organ rejection and diabetes complications (based on each patient's characteristics), while incorporating physicians' attitudes toward ambiguous outcomes along with various other factors such as false-positive and false-negative error rates of medical tests and lack of data for valid estimation.

The rest of this chapter is organized as follows. In §2.2, we provide a brief literature review. In §2.3, we present our APOMDP approach, and in §2.4, we demonstrate some of its theoretical/structural properties. Our numerical study including our clinical data set and parameter estimations as well as the resulted findings are described in §2.5. Finally, I concelude the chapter in §2.6, and discuss some avenues for future research.

2.2 Related Studies

We divide the related studies into six categories, and describe each separately below.

Studies on Medical Decision-Making for Diabetes. The main body of literature analyzing diabetes from a decision-making perspective uses Markov Decision Process

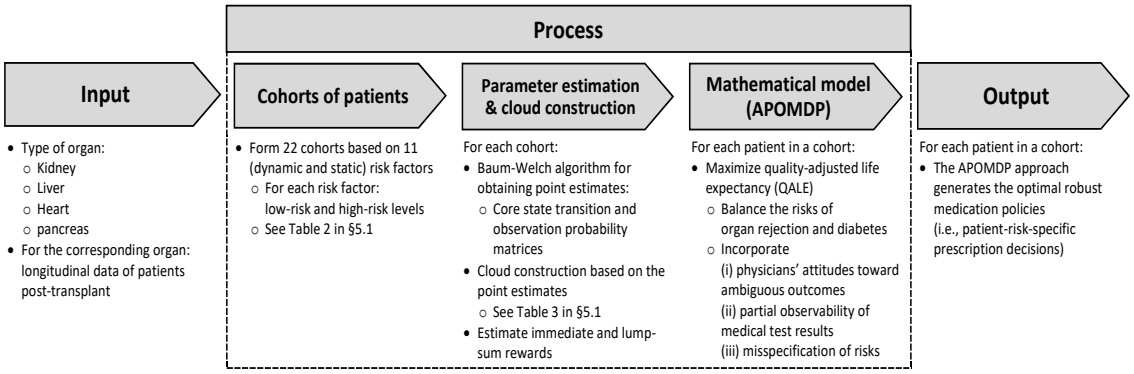


Figure 2.2: Data-driven DSS for Post-Transplant Medications Management: An Implementation Roadmap

(MDP) models to focus on optimal initiation time of statin (see, e.g., Denton et al. (2009)), and optimal interval for other diabetes medications (see, e.g., Mason et al. (2014)). Unlike this stream of research, we (1) address the management of diabetes medications in the presence of an opposing medication (i.e., an immunosuppressive drug), and (2) consider partial observability of health states that arises due to the inevitable measurement errors in medical tests (e.g., FPG and HbA1c). Furthermore, the above studies require incorporating dynamic risk factors as part of the state space definition, which may aggravate the so-called "curse of dimensionality." Instead, our proposed approach directly incorporates such factors into optimal medication strategies.

Operations Research/Management Science Studies on Pre-Transplant Period. The majority of Operations Research/Management Science studies on transplantation focus on the *pre-transplant* period, and typically study mechanisms to facilitate a better match between supply and demand of organs (see, e.g., Su and Zenios (2005); Bertsimas et al. (2013), and Ata et al. (2016)). To the best of our knowledge, our study is among the first in the OR/MS literature to consider *post-transplantation* decisions.

Studies on POMDP Applications in Healthcare. In the medical decision-making field, POMDP models have been applied mainly for cancer screening research. Examples include mammography screening in breast cancer (see, e.g., Ayer et al. (2012)), screening in prostate cancer (see, e.g., Zhang (2011)), and colonoscopy screening in colorectal cancer (see, e.g., Erenay et al. (2014)). Compared to this stream, our proposed APOMDP approach (1) provides optimal policies that are robust to model misspecifications, (2) incorporates physicians' behavorial attitudes toward model misspecifications, and (3) is customized with eleven static/dynamic risk factors. From the medical perspective, the latter is an improvement, since age and history of screening/treatment are the typical risk factors that have been considered thus far in the extant literature.

Studies on Robust Dynamic Decision-Making. Among theoretical studies addressing robustness in dynamic decision-making, we refer to those solving MDPs with respect to a worst-case scenario (i.e., utilizing a *max-min* approach) within the set of possible transition probabilities (see, e.g., Iyengar (2005); Nilim and El Ghaoui (2005), and Xu and Mannor (2012)). However, as noted by Delage and Mannor (2010), generated policies under a max-min approach are often too conservative. To address this, Saghafian (2018) proposes an APOMDP approach, where a controller makes decisions based on a weighted average of both the worst and the best possible outcomes. Moreover, unlike the above-mentioned literature on robust MDPs, the APOMDP approach allows for making robust decisions under partial observability of system states. This is an important advantage for various applications, including our focus in this study where measurement errors are inevitable (e.g., due to false positive/negative errors of medical tests). Considering the worst and the best possible outcomes (as opposed to all possible outcomes) is also important for partially observable systems, because it does not add much to the computational complexity.

Applications of robust dynamic decision-making in medical problems have been centered around robust MDP formulations. Goh et al. (2018) develops a robust Markov chain framework for analyzing cost-effectiveness of colorectal cancer screening policies. Steimle et al. (2018) proposes a multi-model MDP for managing blood pressure and cholesterol, where model ambiguity is considered by averaging the performance of a given policy across different MDP models. Kaufman et al. (2011) and Zhang et al. (2017) model max-min MDPs for optimizing decisions on liver transplantation and glycemic control in diabetes management, respectively, where transition probabilities can vary within an uncertainty set. Compared to this stream, our work is the first study of a medical decision-making problem that considers both (1) model ambiguity and (2) behavioral attitudes of physicians towards ambiguity.

Studies on Measuring Ambiguity Attitudes. The ambiguity attitude of a decision maker can be characterized by either parametric or nonparametric methods. In the former, the ambiguity attitude is represented by utility-based models from the economics literature (see, e.g., Arad and Gayer (2012) Peysakhovich and Karmarkar (2015)), whereas, in the latter, it is measured by using behavioral scales based on sociodemographic characteristics of decision makers (see, e.g., Han et al. (2009)). Our APOMDP framework is a parametric approach based on the so-called α-maxmin expected utility (α-MEU) preferences (Ghirardato et al., 2004), which measure a convex combination of the lowest (i.e., maxmin) and the highest (i.e., maxmax) possible outcomes based on the parameter $\alpha \in [0, 1]$. The parameter α captures a range of individuals' attitudes towards ambiguity, such that its high (low) values represent high (low) levels of ambiguity aversion (for empirical investigations of the α-MEU function, see Ahn et al. (2014) and the references therein).

The so-called range of ambiguity attitude has been estimated or set by the extant literature endogenously or exogenously. In the former, this parameter is inferred

by conducting hypothesis testing with survey-/questionnaire-based experiments (see, e.g., Chen et al. (2007)). However, in the latter, this parameter is set without resorting to empirical experiments (see, e.g., Ahn et al. (2014)). Compared to this stream, we can employ the DSS (shown in Figure 2) to implement our APOMDP approach and optimize decisions (about medication regimens) for any level of ambiguity attitude in [0,1]. Therefore, our methodology can also be used to determine the best level of ambiguity attitude (i.e., the one that yields the highest QALE among all possible levels). Based on this premise, our findings in this study are not predictive of physicians' behavior. Instead, they are prescriptive: they generate insights into what physicians should be targeting in their practice (both given their own level of ambiguity attitude and across all such possible levels).

Other Studies from the Medical Literature. We note that our work is also related to three streams in the medical literature: (1) incorporating the measurement errors of medical tests in decision-making for medication regimens (see, e.g., Bennett et al. (2007)), (2) analyzing the diabetogenic effect of immunosuppressive drugs (see, e.g., Chakkera et al. (2009) and Boloori et al. (2015)), and (3) customizing tacrolimus dose variability based on different risk factors (see, e.g., Yasuda et al. (2008)). Utilizing the APOMDP approach along with our clinical data set, we contribute to all of these three streams.

2.3 The Ambiguous POMDP Approach

We use a discrete-time, finite-horizon ambiguous POMDP (APOMDP) approach (see Saghafian (2018)) to determine optimal decisions that maximize QALE of a patient with respect to risks of organ rejetion and NODAT complications. At each patient's visit, a decision maker (DM hereafter)—typically a physician—measures the patient's (1) lowest concentration of tacrolimus (in the body) known as *trough level*

or C_0, and (2) blood glucose level. Then, after evaluating whether the patient has a low, medium or high C_0, and whether s/he is diabetic, pre-diabetic, or healthy, the DM needs to make two decisions: (a) whether to use a low, medium or high dosage of tacrolimus, and (b) whether or not to put the patient on insulin. As noted earlier, these decisions need to be made jointly and in an orchestrated way. This is mainly due to the interactions between tacrolimus and insulin as well as their joint effect on the patient's health state. If prescribed, any medication will be used over the course of one month until the patient's next visit. As a result, the patient's health state with respect to both his/her C_0 level and diabetes condition may move to a new state in the next visit, and this routine continues throughout the planning horizon.

In addition to identifying optimal decisions and investigating their cost-effectiveness, we use this setting to study unnecessary intensification of prescribed medications. We do so by comparing the effect of using (a) lower dosages of tacrolimus, and (b) insulin versus not using it. Furthermore, our notion of simultaneous prescriptions facilitates the care coordination between "Transplantation/Nephrology" and "Endocrinology" departments of a hospital that are typically in charge of administering tacrolimus and insulin, respectively.

2.3.1 The Elements of the APOMDP Approach

The elements of our APOMDP approach are as follows. All vectors are considered to be in a column format, and " $'$ " represents the matrix transpose operator.

Decision epochs: Decision epochs correspond to a patient's visits and are denoted by $n = 1, 2, ..., N$, where n represents the number of months post-transplant. We consider one year post-transplant as our planning horizon ($N = 12$), because it represents the time period during which medication management strategies are (a) most important, and (b) most variable among physicians particularly for tacrolimus regimens

(see, e.g., Staatz and Tett (2004) and Schiff et al. (2007)).

Core state space: $S = \{\Delta, \nabla\} \cup \mathcal{S}$, where $\mathcal{S} = \big\{s_i, i = 1, 2, \ldots, 9\big\}$, and s_i's are described in Table 2.1. In addition, Δ and ∇ represents "death" and "organ rejection," respectively. We note that ∇ and Δ are fully observable and absorbing states: the decision process ends if either of these two states is reached prior to the end of planning horizon.

Observation state space: $O = \{\Delta, \nabla\} \cup \mathcal{O}$, where $\mathcal{O} = \big\{o_i, i = 1, 2, \ldots, 9\big\}$, and o_i is the observation made by the DM leading him to think that the patient is in the ith core state. For instance, o_1 is the observation that the patient is in s_1: medical tests suggest a low C_0 level while having organ survival and diabetic conditions.

Action space: $A = \big\{a_i, i = 1, 2, \ldots, 6\big\}$, where a_i's are described in Table 2.1. Letting $a \preceq \widehat{a}$ represent the fact that a is more intensive than $\widehat{a}$ (or $\widehat{a}$ is less intensive than a), it can be seen from Table 2.1 that $a_1 \preceq a_2 \preceq a_3$, $a_4 \preceq a_5 \preceq a_6$, $a_1 \preceq a_4$, $a_2 \preceq a_5$, $a_3 \preceq a_6$, and $a_1 \preceq a_6$. Thus, a_1 (a_6) corresponds to administrating the most (least) intensive medication regimen. Similarly, we use the notation $a \npreceq \widehat{a}$ to represent situations where $a \preceq \widehat{a}$ does not hold (i.e., when either $\widehat{a} \preceq a$ or when there is no ordering between the two).

Ambiguity set ("cloud" of models): $M = \{m_1, m_2, ..., m_K\}$, where K is the number of models in the "cloud." As mentioned in §**??**, estimating transition and observation probability matrices from a data set is subject to errors. This, in turn, results in model misspecifications which warrants the cloud of models (as opposed to a single model). Each model in M represents a different estimation for the core state transition and observation probability matrices (defined below). In §2.5.1, we describe how we have used a clinical data set, obtained from our partner hospital, to construct this cloud of models.

Core state transition probability: $\mathbf{P}_m = \{\mathbf{P}_m^a : a \in A\}$, where for each $a \in A$,

Table 2.1: Description of Parts of Core Health States and Actions

State	**Transplant Condition*** **(Tacrolimus C_0)**	**Diabetes Condition**
s_1	Low	
s_2	Medium	Diabetes (type II)
s_3	High	
s_4	Low	
s_5	Medium	Pre-diabetes
s_6	High	
s_7	Low	
s_8	Medium	Healthy
s_9	High	

$*$ With the patient experiencing an organ survival

Action	**Prescription (Tacrolimus dose)**	**Prescription (Insulin use)**
a_1	High	
a_2	Medium	Yes
a_3	Low	
a_4	High	
a_5	Medium	No
a_6	Low	

$\mathbf{P}_m^a = [p_m^a(j|i)]_{i,j\in S}$, and $p_m^a(j|i) = Pr\{j|i,a,m\}$ is the probability of moving from state i to state j when taking action a under model $m \in M$.

Observation probability: $\mathbf{Q}_m = \{\mathbf{Q}_m^a : a \in A\}$, where for each $a \in A$, $\mathbf{Q}_m^a = [q_m^a(o|j)]_{j\in S, o\in O}$, and $q_m^a(o|j) = Pr\{o|j,a,m\}$ is the probability of observing o under model m and action a when being at core state j.

Information space: $\Pi = \Big\{\boldsymbol{\pi} = [\pi_i]_{i\in S} \in \mathbb{R}^{|S|} : \sum_{i=1}^{|S|} \pi_i = 1, \pi_1, \pi_2 \in \{0,1\}, \pi_3, \ldots, \pi_{11} \in [0,1]\Big\}$, where $\boldsymbol{\pi}$ is an information vector over the state space S. Since Δ (death) and ∇ (organ rejection) are fully observable states, $\boldsymbol{\pi} = [1,\ldots,0]'$ and $\boldsymbol{\pi} = [0,1,\ldots,0]'$ represent death and alive with organ rejection, respectively.

Belief space: In order to distinguish between fully and partially observable states, we define a belief vector $\mathbf{b}$ such that, for any $\boldsymbol{\pi} \neq [1, 0, \ldots, 0]'$ or $\boldsymbol{\pi} \neq [0, 1, \ldots, 0]'$, $\mathbf{b} = [0, 0, b_3, \ldots, b_{11}] = \boldsymbol{\pi}$ (i.e., DM's belief about C_0 and blood glucose levels in an alive patient without an organ rejection). We also let Π_{PO} be the set of all such belief vectors (PO: partially observable).

We use the *Bayes' Rule* in a matrix format to update the elements of the belief vector $\mathbf{b}$ under a model m when action a is taken and observation o is made:

$$B(\mathbf{b}, a, o, m) = \frac{(\mathbf{b}'\mathbf{P}_m^a \mathbf{Q}_m^{a,o})'}{Pr\{o|\mathbf{b}, a, m\}}, \tag{2.1}$$

where $B(\mathbf{b}, a, o, m) : \Pi_{PO} \times A \times O \times M \rightarrow \Pi_{PO}$ is the belief updating operator, $\mathbf{Q}_m^{a,o}$ is the diagonal matrix formed by the column o of $\mathbf{Q}_m^a$, and

$$Pr\{o|\mathbf{b}, a, m\} = \sum\nolimits_{i \in S} b_i \sum\nolimits_{j \in S} p_m^a(j|i)\; q_m^a(o|j) \tag{2.2}$$

is the conditional probability that the DM will make observation o given the belief vector $\mathbf{b}$, action a, and model m.

Immediate reward: $\mathbf{r}_n(a) = [r_n(s, a) \geq 0]_{s \in S}$ for $a \in A$, where $r_n(s, a)$ is the quality of life that a patient accrues when in state $s \in \mathcal{S}$ and taking action a in period $n < N$ (based on experiencing death, an organ rejection, or an organ survival while having different blood glucose levels). Note that a patient experiencing death does not gain any immediate reward (i.e., $r_n(\Delta, a) = 0$) and $0 \leq r_n(\nabla, a) \leq r_n(s, a)$ for all $a \in A$ and $s \in \mathcal{S}$.

Lump-sum reward: $\mathbf{R}_n = [R_n(s) \geq 0]_{s \in S}$, where $R_n(s)$ is a lump-sum reward (in QALE) gained by a patient whenever s/he leaves the decision process at state s. This can happen either (1) at the end of the planning horizon ($n = N$), when this value serves as a terminal reward that the patient accrues for his/her remaining lifetime,

or (2) during the planning horizon ($n < N$), if s/he experiences a death or an organ rejection, where $R_n(\Delta) = 0$ and $0 \leq R_n(\nabla) \leq R_n(s)$ for all $s \in \mathcal{S}$.

Ambiguity attitude set: $\Lambda = \{\lambda : 0 \leq \lambda \leq 1\}$, where λ represents the DM's *conservatism level*, and captures his/her range of attitude towards ambiguity. We note that this is the same as parameter α in the α-MEU function described in §**??**.

Discount factor: $\beta \in [0, 1]$, which allows us to obtain the present value of QALE gained in future.

Using the elements of the APOMDP approach described above, we now present its optimality equation. For the information vector $\boldsymbol{\pi}$, DM's conservatism level λ, and any period $n \leq N$, we have:

$$V_n(\boldsymbol{\pi}, \lambda) = \begin{cases} R_n(\Delta), & \text{if } \boldsymbol{\pi} = [1, \ldots, 0]', \\ R_n(\nabla), & \text{if } \boldsymbol{\pi} = [0, 1, \ldots, 0]', \\ V_n(\mathbf{b}, \lambda), & \text{otherwise,} \end{cases} \tag{2.3}$$

where

$$V_n(\mathbf{b}, \lambda) = \begin{cases} \mathbf{b}'\mathbf{R}_N, & \text{if } n = N, \\ \max\limits_{a \in A} \{U_n(\mathbf{b}, a, \lambda)\}, & \text{if } n < N. \end{cases} \tag{2.4}$$

In (2.4), the utility function $U_n(\mathbf{b}, a, \lambda)$ is defined as:

$$U_n(\mathbf{b}, a, \lambda) = \mathbf{b}'\mathbf{r}_n(a) + \lambda \min_{m \in M} \Big\{ H_n(\mathbf{b}, a, m, \lambda) \Big\} + (1 - \lambda) \max_{m \in M} \Big\{ H_n(\mathbf{b}, a, m, \lambda) \Big\}, \tag{2.5}$$

where

$$H_n(\mathbf{b},a,m,\lambda) = \beta \sum_{o\in O} Pr\{o|\mathbf{b},a,m\}V_{n+1}\Big(B\left(\mathbf{b},a,o,m\right),\lambda\Big). \tag{2.6}$$

The first term in the RHS of (2.5) represents the expected current "reward" (in QALE) in period n when the belief vector is $\mathbf{b}$, and the action is a. The other terms in the RHS of (2.5) denote the expected "reward-to-go" for period n, which is calculated as the weighted average of the worst and the best possible expected rewards that can be obtained in future. In (2.5), as λ increases (decreases), the utility function becomes more (less) dependent on the worst total "reward" that can be achieved in the "cloud" of models. Thus, a higher (lower) λ represents the ambiguity attitude of a more (less) conservative DM (see, e.g., Chen et al. (2007) and Ahn et al. (2014)). By varying λ, our framework allows us to capture the behavioral attitudes of physicians, and evaluate their effects on the intensity of medications administered. We note that $\lambda = 1$ represents an extension of existing robust dynamic programming approaches (see, e.g., Iyengar (2005); Nilim and El Ghaoui (2005)) to settings with partially observable states.

Finally, we define the worst model and the best model in period n as the minimizer and maximizer of $H_n\left(\mathbf{b},a,m,\lambda\right)$ defined in (2.6), respectively:

$$\underline{m}_n\left(\mathbf{b},a,\lambda\right) = \arg\min_{m\in M}\Big\{H_n\left(\mathbf{b},a,m,\lambda\right)\Big\}, \overline{m}_n\left(\mathbf{b},a,\lambda\right) = \arg\max_{m\in M}\Big\{H_n\left(\mathbf{b},a,m,\lambda\right)\Big\}. \tag{2.7}$$

For the ease of notation, we may refer to these worst and best models as $\underline{m}$ and $\overline{m}$, respectively.

2.4 Structural Results

We now establish some structural properties, which allow us to analyze our APOMDP model, and thereby gain insights into the simultaneous management of post-transplant medications. Compared to the earlier work of Saghafian (2018) that establishes structural results for general APOMDPs, we make use of the specific properties of the medical problem under consideration, and provide (1) a closed-form expression for the piecewise-linear and convex (PLC) value function, (2) an analytical link between the DM's conservatism level and his actions (i.e., the intensity of prescribed medications), (3) a lower bound for the optimal value function, and (4) specific monotonicity results for the optimal policy.

Piecewise-Linearity and Convexity of Value Function. Unlike traditional POMDPs, it is known that the value function in an APOMDP is not necessarily piecewise-linear and convex (PLC) in the belief vector (Saghafian, 2018). This may prevent us from using solution algorithms (similar to those used for POMDPs), since many of them rely on the PLC property of the value function. Thus, to guarantee the PLC property for the value function in our problem, we make use of the definition of a *belief-independent worst-case* (BIWC) member in the cloud of models M:

Definition 2.4.1 (Saghafian 2018) *$\underline{m}_n(\mathbf{b}, a, \lambda) \in M$ defined in (2.7) is said to be a BIWC member of M, if it is constant in the belief vector $\mathbf{b}$.*

This implies that, irrespective of the DM's belief about a patient's health state, there exists a set of transition and observation matrices (given the action and conservatism level) that yields the least total reward (in QALE). If such a model exists in M, then the optimal value function is PLC in the belief vector $\mathbf{b}$ (see Proposition 2

in Saghafian (2018)), and hence, can be written as:

$$V_n(\mathbf{b}, \lambda) = \max_{\boldsymbol{\psi} \in \Psi_{n,\lambda}} \{\mathbf{b}' \boldsymbol{\psi}\} \quad \forall\, \mathbf{b} \in \Pi_{PO},\ \forall\, \lambda \in \Lambda,\ \forall\, n \leq N, \tag{2.8}$$

where $\Psi_{n,\lambda}$ is some finite set. Equation (2.8) is analogous to the use of POMDPs proposed by Smallwood and Sondik (1973). Based on (2.8), to characterize the value function, one only needs to characterize the set $\Psi_{n,\lambda}$.

Although the existence of a BIWC member in the cloud of models M can be a relatively restrictive assumption, we are able to provide a sufficient condition. We do so by benefiting from the notion of *model informativeness* (as a generalization of Blackwell ordering): if, under an action $a \in A$, $\mathbf{P}^a_m \mathbf{Q}^a_m = \mathbf{P}^a_{\widehat{m}} \mathbf{Q}^a_{\widehat{m}} \mathbf{W}$ for some stochastic matrix $\mathbf{W}$, then model m is said to be *less informative* than model $\widehat{m}$ (for notational simplicity, we suppress the dependency on a). It follows that if one model is less informative than the others, then it is a BIWC member in M (see Proposition 3 in Saghafian (2018)). Utilizing our clinical data set in Appendix A.2.3, we discuss scenarios where the model informativeness condition (and thus the existence of a BIWC member) is satisfied in our setting. In other settings where this property does not hold, one can extend the ambiguity set so that it includes a BIWC member. This will substantially reduce the underlying computational complexity by ensuring that (2.8) holds, and can provide a close approximation.

Assuming that M is such that it has a BIWC member, we now establish a closed-form analytical representation for the set of $\boldsymbol{\psi}$-vectors, $\Psi_{n,\lambda}$. This, together with (2.8), enables us to characterize and solve the optimal value function in our problem. All the proofs are provided in Appendix A.1.

Proposition 2.4.1 (Representation of $\boldsymbol{\psi}$-Vectors) *Suppose M is such that it has a BIWC member. Let $\underline{m}$ and $\overline{m}$ be the BIWC member and the best-case model of M*

defined by (2.7). Then, the set of $\boldsymbol{\psi}$-vectors ($\Psi_{n,\lambda}$) in (2.8) can recursively be obtained as:

$$\Psi_{N,\lambda} = \{\mathbf{R}_N\} \quad \forall\, \lambda \in \Lambda, \tag{2.9}$$

$$\begin{aligned}\Psi_{n,\lambda} = \Big\{\boldsymbol{\psi} \in \mathbb{R}^{|S|} : \boldsymbol{\psi} = \mathbf{r}_n(a) + \lambda\Big(\beta \sum_{o\in O} \mathbf{P}^a_{\underline{m}} \mathbf{Q}^{a,o}_{\underline{m}}\, \boldsymbol{\psi}^{(\mathbf{b},a,o)}_{\underline{m}}\Big) \\ +(1-\lambda)\Big(\beta \sum_{o\in O} \mathbf{P}^a_{\overline{m}} \mathbf{Q}^{a,o}_{\overline{m}}\, \boldsymbol{\psi}^{(\mathbf{b},a,o)}_{\overline{m}}\Big), \\ a \in A,\ \boldsymbol{\psi}^{(\mathbf{b},a,o)}_{\underline{m}}, \boldsymbol{\psi}^{(\mathbf{b},a,o)}_{\overline{m}} \in \Psi_{n+1,\lambda}\Big\} \quad \forall\, \lambda \in \Lambda, \forall\, n < N,\end{aligned} \tag{2.10}$$

where

$$\boldsymbol{\psi}^{(\mathbf{b},a,o)}_m = \arg \max_{\boldsymbol{\psi}\in\Psi_{n+1,\lambda}} \{\mathbf{b}' \mathbf{P}^a_{\ m} \mathbf{Q}^{a,o}_m \boldsymbol{\psi}\} \quad \forall\, \mathbf{b} \in \Pi_{PO},\ \forall\, a \in A,\ \forall\, m \in M,\ \forall\, o \in O. \tag{2.11}$$

The characterization of the set of $\boldsymbol{\psi}$-vectors in Proposition 2.4.1 depends on identifying both models $\underline{m}$ and $\overline{m}$. Although $\underline{m}$ can be obtained in the ambiguity set M without the need for solving the APOMDP model (see our discussion above), $\overline{m}$ cannot be identified a priori. To address this, we present the following alternative approach for characterizing the $\boldsymbol{\psi}$-vectors:

$$\begin{aligned}\widetilde{\Psi}_{n,\lambda} = \Big\{\widetilde{\boldsymbol{\psi}} \in \mathbb{R}^{|S|} : \widetilde{\boldsymbol{\psi}} = \mathbf{r}_n(a) + \lambda\Big(\beta \sum_{o\in O} \mathbf{P}^a_{\underline{m}} \mathbf{Q}^{a,o}_{\underline{m}}\, \widetilde{\boldsymbol{\psi}}^{(\mathbf{b},a,o)}_{\underline{m}}\Big) \\ +(1-\lambda)\Big(\beta \sum_{o\in O} \mathbf{P}^a_{\ m} \mathbf{Q}^{a,o}_m\, \widetilde{\boldsymbol{\psi}}^{(\mathbf{b},a,o)}_m\Big), \\ a \in A, m \in M \setminus \{\underline{m}\}, \widetilde{\boldsymbol{\psi}}^{(\mathbf{b},a,o)}_{\underline{m}}, \widetilde{\boldsymbol{\psi}}^{(\mathbf{b},a,o)}_m \in \widetilde{\Psi}_{n+1,\lambda}\Big\} \quad \forall\, \lambda \in \Lambda, \forall\, n < N.\end{aligned} \tag{2.12}$$

Then, $\Psi_{n,\lambda}$ in (2.10) can be obtained from $\widetilde{\Psi}_{n,\lambda}$ in (2.12) by applying the Monahan's algorithm (Monahan, 1982). The equation in (2.12) implies that, even if we consider all models in $M \setminus \{\underline{m}\}$, using the Monahan's algorithm, we can shrink the set of the $\boldsymbol{\psi}$-vectors to those attributed only to $\underline{m}$ and $\overline{m}$.

Effect of DM's Conservatism Level on Drug Intensification. As noted earlier, the DM's conservatism (i.e., ambiguity attitude) may affect the intensification of medication regimens. To study this phenomenon, we start by defining the following conditions. In Appendix A.2.5, we also numerically test the validity of conditions in this section using our clinical data set, and discuss whether and when such conditions hold.

Condition 2.4.1 (Monotonicity of Reward) *(i) Under any action $a \in A$, the immediate reward vector $\mathbf{r}_n(a)$ is nondecreasing in state $s \in S$, and (ii) the lump-sum reward vector $\mathbf{R}_n$ is nondecreasing in state $s \in S$.*

Condition 2.4.1 implies that better health states have higher immediate and lump-sum rewards (in QALE). For example, compared to a patient with an organ rejection, a patient with an organ survival is expected to have a higher quality of life (all else equal).

Condition 2.4.2 (TP_2 Transitions) *For all $m \in M$ and $a \in A$, the kernels $\mathbf{P}_m^a$ and $\mathbf{Q}_m^a$ are TP_2 (i.e., all their second-order minors are non-negative).*

Condition 2.4.2 imposes a specific ordering between each two consecutive rows of $\mathbf{P}$ and $\mathbf{Q}$ matrices. For example, this condition implies that, upon taking the same medication regimen, a patient with a better health state is more likely to move to a more favorable state than another patient who is in a worse health state (all else equal).

For later use, here we also define the well-known TP_2 stochastic ordering between two belief vectors. Since each belief vector $\mathbf{b}$ yields a probability mass function, TP_2-ordering (shown as "$\preceq_{TP_2}$") is equivalent to the weak monotone likelihood ratio (MLR) ordering:

Definition 2.4.2 (Whitt 1982) *A belief vector* $\mathbf{b}$ *is said to be dominated by another belief vector* $\widehat{\mathbf{b}}$ *in the MLR-ordering sense (shown as* $\mathbf{b} \preceq_r \widehat{\mathbf{b}}$*) if the ratio* $\widehat{\mathbf{b}}/\mathbf{b}$ *is nondecreasing in its elements.*

From the medical standpoint, Definition 2.4.2 implies that a patient with associated belief vector $\widehat{\boldsymbol{b}}$ is more likely to be in a better health state than another patient with associated belief vector $\boldsymbol{b}$. We also need to define the following condition, where for notational simplicity, we let $\underline{m}(a,\lambda) = \underline{m}_n(\mathbf{b},a,\lambda)$ and $\overline{m}(a,\lambda) = \overline{m}_n(\mathbf{b},a,\lambda)$ for any action a and conservatism level λ. In addition, $B(\mathbf{b},a,o,m)$ is the belief-updating operator defined in Equation (2.1). Similarly, we denote by $\big[Pr\{o|\mathbf{b},a,m\}\big]_{o\in O}$ the vector of observation probabilities, where $Pr\{o|\mathbf{b},a,m\}$ is the conditional probability that a DM will make observation o given the belief vector $\mathbf{b}$, action a, and model m (see Equation (2.2) in §2.3.1).

Condition 2.4.3 *Fix belief vector* $\mathbf{b} \in \Pi_{PO}$ *and time period* $n < N$*. Then, for all* $a, \widehat{a} \in A$ *with* $a \not\preceq \widehat{a}$*, there exists a conservatism level* $\lambda^* \in \Lambda$ *such that, for all* $\lambda \geq \lambda^*$*, we have:*

(i) $\big[Pr\{o|\mathbf{b},\widehat{a},\underline{m}(\widehat{a},\lambda^*)\}\big]_{o\in O} \preceq_{TP_2} \big[Pr\{o|\mathbf{b},a,\underline{m}(a,\lambda^*)\}\big]_{o\in O}$,

$\big[Pr\{o|\mathbf{b},a,\underline{m}(a,\lambda)\}\big]_{o\in O} \preceq_{TP_2} \big[Pr\{o|\mathbf{b},\widehat{a},\underline{m}(\widehat{a},\lambda)\}\big]_{o\in O}$,

(ii) $B\big(\mathbf{b},\widehat{a},o,\underline{m}(\widehat{a},\lambda^*)\big) \preceq_{TP_2} B\big(\mathbf{b},a,o,\underline{m}(a,\lambda^*)\big)$,

$B\big(\mathbf{b},a,o,\underline{m}(a,\lambda)\big) \preceq_{TP_2} B\big(\mathbf{b},\widehat{a},o,\underline{m}(\widehat{a},\lambda)\big)$,

(iii) Parts (i)-(ii) also hold for the best model $\overline{m}$*.*

To better understand Condition 2.4.3, let DM_{base} represent a *baseline* DM with the conservatism level λ^* introduced in Condition 2.4.3. Also, we denote by DM_{gen} a general DM with a conservatism level λ such that $\lambda \geq \lambda^*$ (i.e., DM_{gen} is more conservative than DM_{base}). Then, part (i) of Condition 2.4.3 has the following implication for the medical practice: DM_{base} (DM_{gen}) is more (less) likely to have a better medical observation if prescribing a less intensive medication regimen (compared to a more intensive one). Furthermore, part (ii) of Condition 2.4.3 implies that DM_{base} (DM_{gen}) has a better (worse) updated belief about a patient's health state (in the TP_2 sense) when taking less intensive (than more intensive) medications. Parts (i)-(ii) of Condition 2.4.3 also require different utilizations of models (from the ambiguity set) under different conservatism levels: for any $a \in A$ and any $\lambda, \widehat{\lambda} \in \Lambda$ such that $\lambda \neq \widehat{\lambda}$, $\underline{m}(a, \lambda) \neq \underline{m}(a, \widehat{\lambda})$ and $\overline{m}(a, \lambda) \neq \overline{m}(a, \widehat{\lambda})$. Otherwise, unlike our results in Theorem 2.4.1 or Corollary 2.4.1 (discussed below), the level of conservatism would have no impact on the intensity of medication regimens.

Theorem 2.4.1 (Effect of λ on Drug Intensification) *Let $a_n^*(\mathbf{b}, \lambda)$ be the optimal medication action for any belief vector $\mathbf{b} \in \Pi_{PO}$, conservatism level $\lambda \in \Lambda$, and time period $n < N$. Also, let λ^* represent the baseline conservatism level introduced in Condition 2.4.3. Then, under Conditions 2.4.1–2.4.3, for any $\lambda \geq \lambda^*$, we have $a_n^*(\mathbf{b}, \lambda) \preceq a_n^*(\mathbf{b}, \lambda^*)$.*

Theorem 2.4.1 provides insights into conditions under which the optimal medication regimen becomes more intensive as the DM's conservatism level increases compared to a baseline level. This result, however, may not hold for all patients, because the sufficient conditions in Theorem 1 may not hold for them. In particular, in Corollary 1 we show that if for some patients Condition 3 is reserved (i.e., the reverse of orderings and inequalities in parts (i)-(ii) of Condition 2.4.3 hold), then

the optimal medication regimen for them becomes less intensive as the DM's conservatism level increases. Thus, while under the optimal policy for some patients a more conservative physician prescribes more intensive medications than a less conservative one, for some patients this result might be reversed. In §2.5.2, we make use of our clinical data set and shed more light on patient characteristics for which either of these two cases holds.

Corollary 2.4.1 *Under Conditions 2.4.1, 2.4.2, and reverse of 2.4.3, for any $\lambda \geq \lambda^*$, we have $a_n^*(\mathbf{b}, \lambda^*) \preceq a_n^*(\mathbf{b}, \lambda)$.*

Monotonicity of the Optimal Medication Policy. When the optimal policy is monotone, a simple *control-limit* policy becomes optimal, making the complex search for an optimal medication policy a much simpler task. Furthermore, as we will discuss, the control-limit policy provides an easy-to-implement guideline for the medical practice. To establish the monotonicity of the optimal policy, we need the following condition.

Condition 2.4.4 *Suppose the value function is PLC and define vectors $\boldsymbol{\phi}_m^{(\boldsymbol{b},a)} = \sum_{o \in O} \mathbf{P}_m^a \mathbf{Q}_m^{a,o} \boldsymbol{\psi}_m^{(\boldsymbol{b},a,o)}$ (for all $\boldsymbol{b} \in \Pi_{PO}$, $a \in A$, and $m \in M$), where $\boldsymbol{\psi}_m^{(\mathbf{b},a,o)}$ is defined in (2.11). Then, for any $a, \widehat{a} \in A$ such that $a \preceq \widehat{a}$ and $\lambda \in \Lambda$, vectors $\boldsymbol{\phi}_{\underline{m}(\boldsymbol{b},\widehat{a},\lambda)}^{(\boldsymbol{b},\widehat{a})} - \boldsymbol{\phi}_{\underline{m}(\boldsymbol{b},a,\lambda)}^{(\boldsymbol{b},a)}$ and $\boldsymbol{\phi}_{\overline{m}(\boldsymbol{b},\widehat{a},\lambda)}^{(\boldsymbol{b},\widehat{a})} - \boldsymbol{\phi}_{\overline{m}(\boldsymbol{b},a,\lambda)}^{(\boldsymbol{b},a)}$ are nondecreasing in their elements.*

Conditions 2.4.4 implies that, when taking a less intensive medication regimen compared to a more intensive one, the resulted difference between the reward to-go (in QALE) is nondecreasing along core health states.

Theorem 2.4.2 (Monotone Optimal Medication Policy) *Let $a_n^*(\mathbf{b}, \lambda)$ be the optimal medication action for period n. Then, under Condition 2.4.4, $\boldsymbol{b} \preceq_{TP_2} \widehat{\boldsymbol{b}}$ yields $a_n^*(\boldsymbol{b}, \lambda) \preceq a_n^*(\widehat{\boldsymbol{b}}, \lambda)$.*

Theorem 2.4.2 simplifies the search for an optimal medication policy. For instance, consider two patients, patients 1 and 2, where patient 2 is believed to be in a better health condition than patient 1 (in the TP_2 sense). Then, if the optimal medication policy for patient 1 is "tacrolimus: low dosage" and "no insulin," then patient 2 should be prescribed with the same regimen. On the other hand, if patient 2 is optimally prescribed by "tacrolimus: high dosage" and "insulin," then patient 1 must follow the same prescription. In general, Theorem 2.4.2 transfers the typically complex search for an optimal medication policy to a much simpler monotonic search. In particular, under the condition of Theorem 2.4.2, the optimal policy will be of control-limit (or switching-curve to be more precise) type, where we only need to impose limits on the belief state, and change the action as we pass the limits. This provides an easy-to-implement guideline for use in practice.

Bounds for the Value Function. For our numerical experiments, we solve our APOMDP model optimally based on Proposition 2.4.1. However, the time complexity of finding an optimal policy (at any period n and for any conservatism level λ) is $O\left(|M||A||S||\Psi_{n+1,\lambda}|^{|O|}\right)$ (see Papadimitriou and Tsitsiklis (1987) and Hauskrecht (2000) for discussions about the time and space complexities of (PO)MDPs). Although we alleviate this effect by implementing the Monahan's algorithm (Monahan, 1982) to eliminate dominated $\boldsymbol{\psi}$-vectors, to further streamline computational burdens, we now develop a bound for the value function in (2.4). We let $J_n(\mathbf{b}, \lambda)$ be the approximate value function, and $a^{*,J}(\mathbf{b}, \lambda)$ be its corresponding action (denoted by a^J for the ease of notation). In the optimal value function $V_n(\mathbf{b}, \lambda)$, the DM computes the expected future reward based on his/her updated belief about the patient's health state (i.e., expected reward-to-go). However, in the approximate value function $J_n(\mathbf{b}, \lambda)$, the DM first obtains his/her expected belief (over all updated belief

vectors), and then the reward based on the expected belief:

$$\begin{aligned} J_n(\mathbf{b},\lambda) = \mathbf{b}'\mathbf{r}_n(a^J) + \lambda \min_{m\in M}\left\{\beta J_{n+1}\left(\mathbf{b}'\mathbf{P}_m^{a^J},\lambda\right)\right\} \\ +(1-\lambda)\max_{m\in M}\left\{\beta J_{n+1}\left(\mathbf{b}'\mathbf{P}_m^{a^J},\lambda\right)\right\}, \end{aligned} \tag{2.13}$$

where we obtain $\mathbf{b}'\mathbf{P}_m^{a^J}$ from $\sum_{o\in O} Pr\{o|\mathbf{b},a^J,m\}\ B\left(\mathbf{b},a^J,o,m\right)$ by following the Bayesian update in Equation (2.1) and the fact that $\sum_{o\in O}\mathbf{Q}_m^{a,o} = \mathbb{I}$, where $\mathbb{I}$ is an identity matrix. Proposition 2.4.2 shows that the optimal value function $V_n(\mathbf{b},\lambda)$ is tightly bounded from below by the approximate value function $J_n(\mathbf{b},\lambda)$.

Proposition 2.4.2 (Performance Bound) *Suppose (i) the ambiguity set M has a BIWC member, (ii) $|p_m^a(j|i) - p_{\widehat{m}}^a(j|i)| \le \eta$ for some $\eta \ge 0$ ($\forall\ a \in A$, $\forall\ m,\widehat{m} \in M$, $\forall\ i,j \in S$), and (iii) $\overline{r}$ is the maximum possible reward in each period. Also, let $\epsilon_{n+1} = \epsilon_q \sum_{l=0}^{N-n-1}\beta^l + \epsilon_r\beta^{N-n}$, where ϵ_q and ϵ_r are upper bounds for the quality of life and lump-sum reward, respectively. Then, we have:*

$$V_n(\mathbf{b},\lambda) - J_n(\mathbf{b},\lambda) \le \min\left\{\frac{\beta\ \eta\ \epsilon_{n+1}\ |S|}{1-\beta}, \frac{\overline{r}\left(1-\beta^N\right)}{1-\beta}\right\}\ \forall \mathbf{b}\in\Pi_{PO}, \forall\lambda\in\Lambda, \forall n < N. \tag{2.14}$$

In Proposition 2.4.2, ϵ_q is a bound for the quality of life (QOL) score, which is a score between 0 and 1. Similarly, ϵ_r is a bound on the lump-sum reward, which is a function of residual life expectancy and a discount rate, such that as the discount rate approaches 1, the lump-sum reward approaches QOL (see §2.5.1 for more details regarding these reward parameters). We note that the bound provided by ϵ_{n+1} is relatively tight. For example, it goes to 0 as $\beta \to 0$, and to $((N-n-1)\epsilon_q + \epsilon_r)$ as $\beta \to 1$. Also, for $\beta \in [0,1)$, this bound asymptotically approaches $\frac{\epsilon_q}{1-\beta}$ as $N \to \infty$. Furthermore, Proposition 2.4.2 implies that, when the DM follows a^J

instead of the optimal policy a^*, the reward loss (in QALE) will be less than or equal to the RHS of (2.14). We note that, under the following conditions, $J_n(\mathbf{b}, \lambda)$ converges to $V_n(\mathbf{b}, \lambda)$, making the performance bound in (2.14) completely tight: (1) when transition probabilities under different models get closer to each other (i.e., different models in the cloud of models M become more similar), η approaches 0, (2) when $\beta \in [0, 1)$ and the time horizon increases, ϵ_{n+1} asymptotically approaches $\frac{\epsilon_q}{1-\beta}$, which, in turn, approaches 0 as a patient's health status gets aggravated, and (3) when β approaches 0 (i.e., the DM decides upon medications regimens in a myopic approach). Furthermore, when β approaches 1, the performance bound in (2.14) approaches $N\overline{r}$ which is small when N or $\overline{r}$ is small. In general, the bound in (2.14) is advantageous for the DM, because it enables him/her to obtain a near-optimal performance.

2.5 Numerical Experiments

In this section, we first explain the following elements from our clinical data set: the main risk factors affecting NODAT patients, the estimation of the set of transition and observation probability matrices using our data set, the estimation of the reward functions (in QALE), and the mechanism used to validate our estimated parameters. We then describe the results we have obtained from our numerical experiments, and shed light on their implications for researchers, practitioners, and those influencing medical guidelines.

2.5.1 Data and Parameter Estimation

The Clinical Data Set. The clinical data set we use in this study contains information of 407 patients who had a kidney transplant operation over a period of seven years (1999–2006) at our partner hospital. The information pertains to each patient's

visit at months 1, 4, and 12 post-transplant and includes the following attributes: (1) demographic (e.g., age, race, gender, etc.), (2) clinical (e.g., blood pressure, body mass index (BMI), cholesterol level, etc.), (3) immunosuppressive drugs (e.g., tacrolimus) and diabetes medications (e.g., insulin) prescribed by physicians, and (4) results of medical tests (FPG, HbA1c, and Architect). Further details about our data set can be found in our earlier study (Boloori et al., 2015).

Interpolation and Imputation. Since our data set only includes information at months 1, 4, and 12 post-transplant, we employ the *cubic spline interpolation* method (see, e.g., Alagoz et al. (2005)) to simulate the natural clinical history of patients for months 1 to 12 post-transplant. Prior to that, to replace missing values in the data entries, we employ *multiple imputations by chained equations* (MICE) by the R computing package (see, e.g., Buuren and Groothuis-Oudshoorn (2011) for more details).

Risk Factors. As noted earlier, our goal is to derive robust optimal medication policies based on different risk factors. Table 2.2 summarizes the main risk factors affecting NODAT patients, where each risk factor is considered to be *low* or *high*. In this table: (1) age is classified based on a 50-year-old threshold, making an almost equal percentage of patients in each age category (the median age of patients in our data set is 53 years, and 40% of patients are below 50). (2) Non-White race includes Hispanic, Black, and Native Americans. (3) Diabetes history refers to the existence of diabetes prior to the time of transplant (Among 407 patients, there were 115 patients (28%) with the history of diabetes before or at the time of transplant). (4) The thresholds for classifying risk factors (except for age, gender, race, and blood pressure) as low/high is based on MedPlus (2018). (5) Blood pressure is defined as "low" for patients with systolic and diastolic blood pressure of "<120" and "<80" mm Hg, respectively, whereas it is defined as "high" when at least one of these conditions

Table 2.2: Description of Main Risk Factors and Their Levels (See Also Boloori et al. (2015))

Risk Factor (Abbreviation)	**Unit**	**Low Level**	**High Level**	**Static (S)/ Dynamic (D)**
Age	Years	<50	$\geq$ 50	S
Gender	—	Female	Male	S
Race	—	White	non-White	S
Diabetes history (Diab Hist)	—	No	Yes	S
Body mass index (BMI)	kg/m^2	<30	$\geq$30	D
Blood pressure (BP)	—	Normal	Hypertension	D
Total cholesterol (Chol)	mg/dL	<200	$\geq$200	D
High-density lipoportein (HDL)	mg/dL	$\geq$40	<40	D
Low-density lipoportein (LDL)	mg/dL	<130	$\geq$130	D
Triglyceride (TG)	mg/dL	<150	$\geq$150	D
Uric acid (UA)	mg/dL	<7.3	$\geq$7.3	D

is violated (AHA, 2018).

Choice of Medication Regimens and Health States. To gain insights into effective post-transplant medication management strategies, we consider tacrolimus as the primary immunosuppressive drug. We do so because (1) it has been shown that tacrolimus is superior to other immunosuppressive drugs (e.g., cyclosporine) in preventing organ rejection for kidney transplantations (see, e.g., Bowman and Brennan (2008)), and (2) tacrolimus is the main immunosuppressive drug used in our partner hospital: based on our data set, 95% of patients are put on tacrolimus. We also observe from our data set that 94% of patients who are put on diabetes medications post-transplant (a) are prescribed insulin, and (b) are put on a fixed dosage of it. Therefore, we (a) consider insulin as the main diabetes medication, and (b) assume it is prescribed in a fixed dosage (see also Denton et al. (2009) and Mason et al. (2014) for a similar assumption).

Unlike insulin, which is prescribed in a fixed dosage, physicians prescribe tacrolimus based on C_0 (trough level). A lower (higher) C_0 is known to be associated with a higher (lower) risk of organ rejection (see, e.g., Staatz et al. (2001)). The target therapeutic range of C_0 at our partner hospital is 10-12 mg/dL (month 1 post-transplant), 8-10 mg/dL (month 4 post-transplant), and 6-8 mg/dL (month 12 post-transplant). Thus, we lable any $C_0 \in [4, 8)$, $[8, 10)$, $[10, 14]$ mg/dL as "low," "medium," and "high," respectively. Similarly, we use lables "low," "medium," and "high" to refer to tacrolimus prescription dosages [0.05,0.10], (0.10,0.20], and (0.20,0.25] mg/kg/day, respectively. These discrete settings are consistent with the literature on therapeutic monitoring of immunosuppressive drugs (see, e.g., Schiff et al. (2007)). Also, from the diabetes perspective, blood glucose levels are measured by FPG and HbA1c tests, where a patient with FPG$\geq$126 (100 $\leq$FPG$<$ 126) mg/dL or HbA1c$\geq$6.5% (5.7 $\leq$HbA1c$<$6.5%) is labled as diabetic (pre-diabetic), whereas FPG$<$100 mg/dL or HbA1c$<$5.7% is labled as healthy (ADA, 2012).

Estimation of Probability Matrices and Cloud Construction. For each cohort of patients in Table 2.2, we construct a cloud of probabilistic models in two phases:

Phase 1: Point Estimates. We employ the *Baum-Welch* (BW) algorithm (Welch, 2003) to obtain point estimations for core state transition and observation probability matrices (lines 6–9 in Table 2.3). As inputs to this algorithm, we use (1) the sequence of medical observations (tacrolimus C_0 and blood glucose levels) and actions (prescribed medications) from our clinical data set and (2) initial transition and observation probability matrices. We note that the BW algorithm is iterated 1,000 times to account for the inevitable variability caused by considering random initial probability matrices. Thus, we treat the average outputs of the BW algorithm over all iterations as our point estimates. Despite 1,000 iterations, the resulted point estimates may not be reliable. Thus, we address this issue by constructing the cloud of

models.

Phase 2: Cloud Construction. We construct an ambiguity set as a cloud of probabilistic models surrounding the point estimates resulted from phase 1. We first identify the set of all probability matrices that are within an ϵ-distance from the points estimates. To this end, we characterize the distance by the *Kullback-Leibler* (KL) divergence criterion (a.k.a. *relative entropy*), which is applied on each row of probability matrices (see Table 2.3 for the notation used):

$$d_{KL}\big(\mathbf{v}, \mathbf{P}^a_{BW}(i)\big) = \sum_{j \in S} \mathbf{v}(j) \log_2 \Big(\frac{\mathbf{v}(j)}{p^a_{BW}(j|i)}\Big) \qquad \forall\, \mathbf{v} \in \mathbb{V}, \forall\, a \in A, \forall\, i \in S \setminus \{\Delta, \nabla\}, \tag{2.15}$$

where $\mathbf{P}^a_{BW} = [p^a_{BW}(j|i)]_{i,j \in S}$ is the point estimate returned by the BW algorithm, and $\mathbf{P}^a_{BW}(i)$ is the i^{th} row in matrix $\mathbf{P}^a_{BW}$ (the same procedure is used for matrix $\mathbf{Q}^a_{BW} = [q^a_{BW}(o|j)]_{j \in S, o \in O}$). We note that we do not apply the KL distance in (2.15) for the absorbing states (i.e., death Δ and organ rejection ∇) in probability matrices. Instead, we simply consider a unit row vector for the first two rows in these matrices.

Because of the KL divergence in (2.15), the cloud of models is an infinite set (line 12 in Table 2.3). However, since we require the existence of a BIWC member in the cloud (see §2.4), we randomly select a finite number (i.e., $|M|$) of samples from this set, such that the BIWC member condition is satisfied (lines 13–15 in Table 2.3). This, in turn, makes the cloud of models a finite set. In Appendix A.2.3, we provide further details on the existence of a BIWC member in our clinical data set, and in Appendix A.2.4, we validate our estimations of the set of transition and observation probability matrices.

Estimation of the Initial Observation Probability Matrix. Our partner hos-

Table 2.3: A Pseudocode for Constructing the Cloud of Models (Transition and Observation Probability Matrices)

Inputs	**1**	Initial transition (randomly generated)/observation (see below) probability matrices
	2	Sequence of medical observations and actions (for each cohort) from our data set
	3	Kullback-Leibler (KL) distance bound = $\epsilon \geq 0$ (e.g., $\epsilon = 0.05$)
	4	$\mathbb{V} = \left\{ \mathbf{v} = [v_i]_{1 \leq i \leq \lvert S \rvert} \in \mathbb{R}_+^{\lvert S \rvert} : \sum_{i=1}^{\lvert S \rvert} v_i = 1 \right\}$
	5	Number of distinct models in the cloud (the ambiguity set) = $\lvert M \rvert$
Phase 1	**6**	**for** i = 1 to 1,000 // number of iterations
	7	**do** *Baum-Welch* algorithm // using inputs 1–2
	8	**return** core state transition and observation probability matrices
	9	**return** point estimates $\mathbf{P}_{BW}^a$ and $\mathbf{Q}_{BW}^a$ for each action $a \in A$
		// average of outputs over 1,000 iterations
Phase 2	**10**	**while** the model informativeness condition is not met for $\mathbf{P}_m$ and $\mathbf{Q}_m$ $(\forall m \in M)$
	11	**for each** $a \in A$ and $i = 3$ to $\lvert S \rvert$
		// i: any core health state except death and organ rejection
	12	$\mathbb{V}_P(i) = \{\mathbf{v} : \mathbf{v} \in \mathbb{V}, d_{KL}\big(\mathbf{v}, \mathbf{P}_{BW}^a(i)\big) \leq \epsilon\}$,
		$\mathbb{V}_Q(i) = \{\mathbf{v} : \mathbf{v} \in \mathbb{V}, d_{KL}\big(\mathbf{v}, \mathbf{Q}_{BW}^a(i)\big) \leq \epsilon\}$
		// using inputs 3–4
	13	**for** $m = 1$ to $\lvert M \rvert$ // using input 5
	14	**do** randomly select vectors $\mathbf{p} \in \mathbb{V}_P(i)$ and $\mathbf{q} \in \mathbb{V}_Q(i)$
	15	$\mathbf{P}_m^a(i) = \mathbf{p}$ and $\mathbf{Q}_m^a(i) = \mathbf{q}$
	16	**return** probability sets $\mathbf{P}_m$, $\mathbf{Q}_m$ (for all $m \in M$)

pital conducts two tests to measure blood glucose levels: if HbA1c $\geq 6.5\%$ ($5.7 \leq$ HbA1c $< 6.5\%$) or FPG ≥ 126 ($100 \leq$ FPG < 126) mg/dL, then the patient is said to have diabetes type II (pre-diabetes). Each of these tests have their own specificity and sensitivity values (see, e.g., Bennett et al. (2007)). Using the notations in Table 2.4, we then have:

$$sp^H = 1 - \Big(sp_{5.7}^{A1C}(1 - sp_{100}^{FPG}) + sp_{100}^{FPG}(1 - sp_{5.7}^{A1C}) + (1 - sp_{100}^{FPG})(1 - sp_{5.7}^{A1C}) \Big), \tag{2.16a}$$

$$sn^{PD} = sn_{100}^{FPG}(1 - sn_{5.7}^{A1C}) + sn_{5.7}^{A1C}(1 - sn_{100}^{FPG}) + sn_{100}^{FPG} sn_{5.7}^{A1C}. \tag{2.16b}$$

Note that sp^{PD} is obtained by (2.16a), and sn^D is obtained by (2.16b), where, the cut-off values of "5.7" and "100" are replaced by "6.5" and "126," respectively. Letting $\mathbf{Q}^D = [q_{ij}^D]_{i,j\in\{1,2,3\}}$ and $\mathbf{Q}^T = [q_{ij}^T]_{i,j\in\{1,2,3\}}$ be the diabetes, transplant, and overall initial observation probability matrices, respectively, we have:

$$\mathbf{Q}^D = \begin{bmatrix} sn^D sn^{PD}\left(1 - sn^D\right) & 1 + sn^{PD} sn^D - \left(sn^{PD} + sn^D\right) & \\ sp^H\left(1 - sp^{PD}\right) & sp^{PD} sn^{PD} & sp^{PD}\left(sp^H - sn^{PD}\right) - sp^H + 1 \\ \left(1 - sp^H\right)\left(1 - sp^{PD}\right) & \left(1 - sp^H\right) sp^{PD} & sp^H \end{bmatrix},$$

$$\mathbf{Q}^T = \begin{bmatrix} sp_8^T\left(1 - sp_8^T\right) sp_{10}^T & \left(1 - sp_8^T\right)\left(1 - sp_{10}^T\right) & \\ sp_{10}^T\left(sp_8^T - sn_8^T\right) - sp_8^T + 1 & sp_{10}^T sn_8^T & sp_8^T\left(1 - sp_{10}^T\right) \\ 1 + sn_8^T sn_{10}^T - \left(sn_8^T + sn_{10}^T\right) & sn_8^T\left(1 - sn_{10}^T\right) & sn_{10}^T \end{bmatrix},$$

$$\mathbf{Q} = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & \dots & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & \dots & 0 & 0 & 0 \\ 0 & 0 & q_{11}^T q_{11}^D & q_{11}^T q_{12}^D & q_{11}^T q_{13}^D & \dots & q_{13}^T q_{11}^D & q_{13}^T q_{12}^D & q_{13}^T q_{13}^D \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\ 0 & 0 & q_{31}^T q_{31}^D & q_{31}^T q_{32}^D & q_{31}^T q_{33}^D & \dots & q_{33}^T q_{31}^D & q_{33}^T q_{32}^D & q_{33}^T q_{33}^D \end{bmatrix}.$$

There is no consensus in the medical literature about the specificity/sensitivity of the foregoing medical tests. However, the specificity (sensitivity) usually increases (decreases) with increasing cut-off points. This is reflected in the values in Table 2.4. We note that, using our APOMDP approach, we can account for other reasonable

Table 2.4: Parameters for Calculating Specificity and Sensitivity of Observing Medical Test Results

Notation	Description	Value
sp_{100}^{FPG}	Specificity: healthy (FPG< 100 mg/dL)	85%
sp_{126}^{FPG}	Specificity: healthy/pre-diabetes (FPG< 126 mg/dL)	90%
sn_{100}^{FPG}	Sensitivity: pre-diabetes/diabetes (FPG≥ 100 mg/dL)	90%
sn_{126}^{FPG}	Sensitivity: diabetes (FPG≥ 126 mg/dL)	85%
$sp_{5.7}^{A1C}$	Specificity: healthy (HbA1c< 5.7%)	85%
$sp_{6.5}^{A1C}$	Specificity: healthy/pre-diabetes (HbA1c< 6.5%)	90%
$sn_{5.7}^{A1C}$	Sensitivity: pre-diabetes/diabetes (HbA1c≥ 5.7%)	90%
$sn_{6.5}^{A1C}$	Sensitivity: diabetes (HbA1c≥ 6.5%)	85%
sp^{H}	Specificity: healthy (based on FPG & HbA1c)	see (2.16a)
sp^{PD}	Specificity: healthy/pre-diabetes (based on FPG & HbA1c)	see (2.16a)
sn^{PD}	Sensitivity: pre-diabetes/diabetes (based on FPG & HbA1c)	see (2.16b)
sn^{D}	Sensitivity: diabetes (based on FPG & HbA1c)	see (2.16b)
sp_{8}^{T}	Specificity: low C_0 (Architect–threshold< 8 mg/dL)	85%
sp_{10}^{T}	Specificity: low/medium C_0 (Architect–threshold< 10 mg/dL)	90%
sn_{8}^{T}	Sensitivity: medium/high C_0 (Architect–threshold≥ 8 mg/dL)	90%
sn_{10}^{T}	Sensitivity: high C_0 (Architect–threshold≥ 10 mg/dL)	85%

values.

Estimation of Immediate and Lump-Sum Rewards. As introduced in §2.3, the immediate reward, $r_n(s, a)$, represents the quality of life that a patient receives in period n based on core health state $s \in S$, and the action taken $a \in A$. We obtain these rewards based on the *quality-of-life* (*qol*), which is a score in $[0, 1]$, where 0 (1) represents death (full health). Let a core health state be dichotomized into transplant and diabetes-related states: s^T and s^D, and $r_n(s^T, a)$ and $r_n(s^D, a)$ be the corresponding immediate rewards for these health states, respectively. Also, let $\langle x, y \rangle$

denote the average of two real numbers x and y. Then, we have for all $a \in A$ and $n \leq N-1$: $r_n(s,a) = \big\langle r_n(s^T,a), r_n(s^D,a) \big\rangle$, where

$$r_n(s^T,a) = \begin{cases} qol(\text{organ rejection})/12, & \text{if } s^T = \text{Organ rejection}, \\ qol(\text{organ survival})/12, & \text{if } s^T = \text{Organ survival (different } C_0\text{'s)}, \end{cases} \tag{2.17a}$$

$$r_n(s^D,a) = \begin{cases} qol(\text{diabetes})/12, & \text{if } s^D = \text{Diabetic}, \\ qol(\text{pre-diabetes})/12, & \text{if } s^D = \text{Pre-diabetic}, \\ qol(\text{healthy})/12, & \text{if } s^D = \text{Healthy}. \end{cases} \tag{2.17b}$$

In (2.17a)-(2.17b), we note that the length of each period in our problem is one month, and thus, the corresponding *qol* scores are converted to a monthly basis (i.e., divided by 12).

Furthermore, the lump-sum reward denoted by $R_n(s)$ is the QALE that a patient receives based on the core state s whenever s/he leaves the decision process (e.g., organ rejection or at the end of time horizon). Let $RLE(s,n) \geq 0$ be the *residual life expectancy* score (i.e., the expected remaining life years at any point of time) attributed to core state s in period n. Following Sassi (2006), we assume:

$$R_n(s) = \frac{qol(s)\big(1 - e^{-r\ RLE(s,n)}\big)}{r} \qquad \forall\ s \in S, \forall\ n \leq N, \tag{2.18}$$

where r is a discount rate which accounts for degradation of the core health state over the remaining lifetime of a patient. In (2.18), $qol(s) = \big\langle qol(s^T), qol(s^D) \big\rangle$, and $RLE(s,n) = \big\langle RLE(s^T,n), RLE(s^D,n) \big\rangle$, where $RLE(s^T,n)$ and $RLE(s^D,n)$ are defined similar to (2.17a)-(2.17b). Further details about estimating the required parameters (e.g., *qol* and *RLE* scores) can be found in Appendix A.2.1. When comparing

our optimal policies with other benchmarks in §2.5.2, we perform sensitivity analyses on the estimated reward parameters by changing the values of *qol* and *RLE* (see Appendix A.5). Moreover, although in our base estimates we assign an equal weight to diabetes and organ rejection outcomes (by taking the average of their related rewards), in our sensitivity analyses (Appendix A.5), we consider different values for *qol* and *RLE* such that organ rejection outcomes can have a higher impact compared to diabetes outcomes.

2.5.2 Numerical Results, Guidelines, and Policy Implications

In this section, we present our numerical results including the robust optimal medication policies for different cohorts of patients (§2.5.2) and comparison of our optimal policies with other policies including the current medical practice (§2.5.2). As we will discuss, these results have important implications for guideline makers as well as individual physicians and patients.

Robust Optimal Medication Policies.

We obtain optimal medication policies from our APOMDP approach separately for 22 cohorts of patients based on the risk factors in Table 2.2. To illustrate our results for each of these cohorts and for computational tractability, we consider 3 different values for the DM's conservatism level (i.e., $\lambda \in \{0.0, 0.5, 1.0\}$) and 3 models for the ambiguity set (i.e., $|M| = 3$). We also set the KL divergence bound ϵ in Table 2.3 as 0.05. We consider 0.05 instead of lower values such as 0.01 or 0.02 simply to increase the likelihood of satisfying the model informativeness condition. Furthermore, we use a 2-simplex to represent a cut of the belief space under a specific concentration of tacrolimus. For example, a 2-simplex under "Low C_0" indicates $b_3, b_6, b_9 \neq 0$ and $b_4, b_5, b_7, b_8, b_{10}, b_{11} = 0$ (i.e., the patient is alive and is believed to have organ survival

with low C_0, while the exact diabetes status is not perfectly known). Although we calculate optimal medications over the entire belief space Π_{PO}, which is an 8-simplex, we choose these cuts to understand the interaction of two medications under different risks of organ rejection and diabetes complications. We aim to provide insights for the medical practice into the following questions:

- *Question 1.* What is the impact of risks of organ rejection and diabetes complications on the optimal medication regimens?
- *Question 2.* What is the impact of various patient risk factors on the optimal medication regimens?
- *Question 3.* What is the impact of DM's conservatism levels on the optimal medication regimens?

To address these three questions, we summarize our main findings in Observations 2.5.1–2.5.3, and discuss their implications for the medical practice.

Remark 2.5.1 *Based on the discussion in §??, our observations and implications here are not predictive of what a physician will do under a specific conservatism level. They are rather prescriptive in that they shed light on what a physician should be doing (given his/her conservatism level) based on the optimal policies we find from our APOMDP approach. Since we are able to characterize the optimal policy for any given level of conservatism, we are also able to shed light on the optimal policy that is based on the best conservatism level.*

Observation 2.5.1 (Optimal Medication Policies) *(i) Under low or medium C_0, the optimal tacrolimus regimen is to use the high dose as long as the risk of diabetes is not very high. However, as this risk increases, using less intensive tacrolimus regimens (e.g., medium or low dose) becomes optimal. (ii) Under high C_0, it is optimal*

to use low-dose tacrolimus regardless of the underlying risk of diabetes. (iii) When tacrolimus is prescribed in medium or high dose, insulin should be used to avoid the potential onset of diabetes, even when the patient has a considerable chance of being diabetes-free.

To better understand Observation 2.5.1, let us consider (a) different levels of C_0 (to reflect on different risks of organ rejection), and (b) four patients each corresponding to a specific belief vector (to represent different risks of diabetes complications). These patients are identified in Figure A.3 in Appendix A.3 via vectors $\tilde{b}$. For example, patient 1 has $\tilde{b} = [0.80, 0.15, 0.05]$ (i.e., 80%, 15%, and 5% risks (*perceived* by the DM) of being diabetic, pre-diabetic, and healthy, respectively). Patients 1, 2, and 3 have a high risk of being diabetic, pre-diabetic, and healthy, respectively, while patient 4 has an equal risk among these three conditions. We present the following results from Figure A.3:

Low C_0: when the risk of diabetes is not very high (e.g., for patients 2–4), the optimal tacrolimus regimen is the high dose, which is consistent with the current practice. However, unlike the current practice, we observe that for patients with a high risk of diabetes (e.g., patient 1) the optimal tacrolimus regimen is the medium dose (for all patient cohorts). In addition, the optimal insulin regimen for patient 1 (3) is to use (not use) insulin. However, unlike the current practice, insulin is the optimal regimen even when the risk of diabetes is lowered compared to patient 1: patient 2 under all cohorts and patient 4 under all cohorts except being non-White female with no diabetes history and normal levels of Chol, HDL, and LDL.

Medium C_0: when C_0 is medium, using med-dose tacrolimus is the first choice in the current practice. However, we find that when the risk of diabetes is low (e.g., patients 2 and 3), the optimal tacrolimus regimen is the high dose (for all patient cohorts). As the diabetes risk increases (e.g., patients 1 and 4), we find that the optimal tacrolimus

regimen becomes the low/medium dose for non-obese, female patients with age<50, hypertension, normal HDL, and high levels of LDL and TG. In addition, similar to patients with low C_0, we observe that, for patients with medium C_0, it is optimal to use insulin even when the diabetes risk is relatively low (unlike the current practice). For example, in addition to patient 1, we find that patients 2 and 4 (i.e., those with lower risk of diabetes compared to patient 1) should also be prescribed by insulin (for patient cohorts formed by high levels of all risk factors except Chol).

High C_0: when C_0 is high, organ rejection is unlikely, and hence, using low (or medium) dose of tacrolimus is recommended over high dose in the medical practice. Our results confirm the optimality of this recommendation for all patient cohorts. However, as the diabetes risk is lowered (e.g., patients 3 and 4), using low/med-dose tacrolimus is optimal only for specific patient cohorts (e.g., non-White patients with age<50 and normal levels of BP and Chol). Also, unlike the current practice, we find that even for patients whose risk of diabetes is not very high (e.g., patients 2 and 4) it is optimal to use insulin (for obese, female patients with age≥50, diabetes history, and high LDL).

In Observation 2.5.1, we addressed Question 1 (i.e., how the optimal medication regimens are affected by different risks of organ rejection and diabetes complications). In the next two observations, we explore the impact of variations in risk factors (Question 2) and the DM's conservatism level λ (Question 3) on medication regimens. Therefore, instead of specific belief vectors (e.g., patients 1–4 in Observation 2.5.1), we consider all belief vectors (i.e., all patients). In particular, we utilize the optimal policy regions depicted in Figure A.3 in Appendix A.3, and make the following:

Observation 2.5.2 (Tacrolimus Requirement and the Diabetogenic Effect) *Under any conservatism level λ, (i) the optimal policy region for using high-dose tacrolimus is larger for non-White, male, obese patients with age≥50, hypertension,*

low HDL, and high LDL (compared to cohorts formed by the opposing risk levels along each of these risk factors), and (ii) the optimal policy region for using insulin (along with high/med-dose tacrolimus) is larger for male patients with age≥50, diabetes history, hypertension, high Chol, and low HDL (compared to cohorts formed by the opposing risk levels along each of these risk factors).

It is known in the medical literature that age and race can be predictors of tacrolimus dose variability (see, e.g., Yasuda et al. (2008)). However, Observation 2.5.2(i) suggests that the dosage of tacrolimus should be adjusted based on other risk factors such as age, gender, race, BMI, blood pressure, HDL, and LDL. This implies that such risk factors could make patients more vulnerable to the risk of organ rejection, and hence, to offset this effect, the optimal tacrolimus regimens put more emphasis on higher dosages of tacrolimus for such patients. In addition, regarding Observation 2.5.2(ii), Figure A.3 shows (as an example) that the policy regions for actions a_1 and a_2 (i.e., using insulin along with medium/high dosage of tacrolimus) are larger for patients with age≥50 compared to those with age<50. Observation 2.5.2(ii) reveals risk factors under which the diabetogenic effect of tacrolimus is stronger. These findings address Question 2 and are useful for the medical practice, especially because they highlight that the blood glucose level of patients with specific risk factors should be monitored more closely than other patients in the post-transplant period.

Finally, we address Question 3 by making the following:

Observation 2.5.3 (The Effect of Conservatism Levels) *Increasing the conservatism level, λ, results in using (i) more intensive medication regimens (for both tacrolimus and insulin) for non-White patients with age≥50, no diabetes history, and low-risk levels of Chol, HDL, LDL, TG, and UA, and BMI (both non-obese and obese), and (ii) less intensive tacrolimus regimens for male patients with age<50, di-*

abetes history, hypertension, and high-risk levels of Chol, HDL, and LDL. However, increasing λ does not change the intensity of medication regimens for patients with White race, female gender, normal blood pressure, and high-risk levels of TG and UA.

For example, as can be observed from Figure 2.3(b), for a non-White patient, a higher conservatism level results in larger optimal policy regions for using high-dose tacrolimus (as opposed to medium-dose) and insulin (as opposed to not using it). On the other hand, based on Figure 2.3 (parts (a), (c), and (d)), we find that for a patient with age$<$50, diabetes history, or hypertension, increasing the conservatism level results in smaller optimal policy regions in which higher dose of tacrolimus is prescribed. Regarding this observation, in §2.4 we explored relevant analytical results via Theorem 2.4.1 and Corollary 2.4.1. In particular, we presented sufficient conditions under which an increase in the conservatism level λ (compared to a baseline level) results in more (or less) intensive medications regimens (equivalently, a larger (or smaller) optimal policy region for such regimens).

Observation 2.5.3 has other implications for the medical practice. For non-White patients with age$\geq$50, no diabetes history, and normal levels of Chol, HDL, LDL, TG, and UA, Observation 3 implies that a more conservative DM should be more concerned about both risks of organ rejection and NODAT compared to a less conservative DM (which, in turn, results in elevating the intensity of both regimens). However, for male patients with age$<$50, diabetes history, hypertension, and high-risk levels of Chol, HDL, and LDL, a more conservative DM should be more concerned about the potential risk of NODAT than that of organ rejection compared to a less conservative DM. This may be due to the diabetogenic effect of tacrolimus, which could make the more conservative DM prescribe less intensive tacrolimus regimens. Also, for White, female patients with normal blood pressure, and high-risk levels of TG and UA, increasing the conservatism level does not drastically affect the intensity

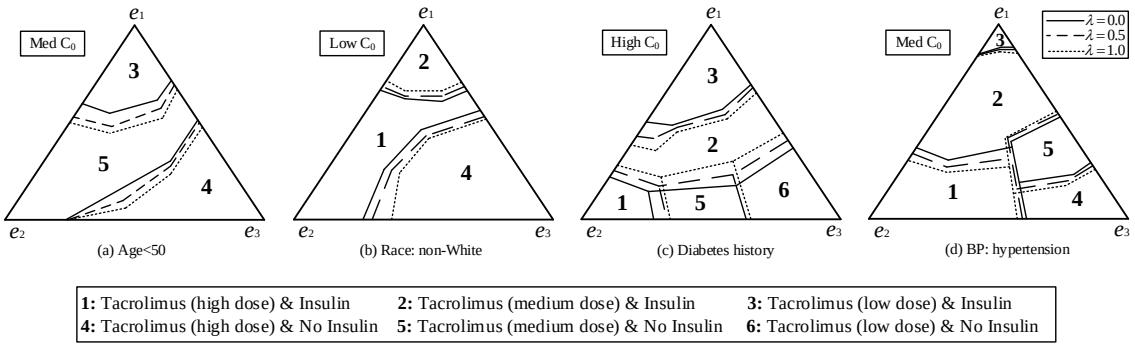


Figure 2.3: Variations in Optimal Medication Policies (in the Same Period) Based on Different Conservatism Levels (e_1, e_2, e_3 Represent Diabetic, Pre-Diabetic, and Healthy Conditions, Respectively; e_j Denotes a Unit Vector with j^{th} Element Equal to 1 and Other Elements Equal To 0)

of prescribed medications under the optimal policy. This, in turn, implies that, for these cohorts, there is no significant difference between a more conservative DM and a less conservative one in utilizing medications optimally to balance risks of organ rejection and diabetes complications.

Finally, Observation 2.5.3 reveals that variations in physicians' attitude toward ambiguity will not show a homogeneous pattern with respect to the intensity of the drugs used, if physicians follow the optimal policy. Thus, drug intensification (i.e., use of intensified levels of medication regimens) observed in the current practice should not be attributed merely to physicians' behavior toward ambiguity. Instead, our findings suggest that lack of adherence to (or knowledge of) the optimal medications might be the main cause of using intensive regimens in the current practice.

Comparison of Optimal Policies with the Current Practice.

We aim to show the potential impact of considering the ambiguity caused by model misspecifications and the partial observability of medical tests. To this end, we have developed a micro-simulation model (see Appendix A.4) to simulate costs and patients' life expectancies during the planning horizon under (1) the optimal policies

obtained from our APOMDP approach, (2) four benchmark policies that resemble the current medical practice under different scenarios, and (3) a policy that is obtained by a traditional POMDP (i.e., by ignoring the underlying ambiguity) (see Appendix A.4 for more details).

Benchmark Policies. In the current medical practice, the outcomes of medical tests (observations) are treated as the actual health state of the patient (see, e.g., Bennett et al. (2007)), based on which physicians prescribe medication regimens. Furthermore, tacrolimus is typically administered based on a combination of an observation (i.e., C_0 level) and time elapsed post-transplant. However, there is currently no consensus among physicians on how C_0 level and elapsed time should be incorporated in prescribing tacrolimus (see, e.g., Staatz and Tett (2004) and Schiff et al. (2007)). To address this variation among physicians, we consider four different benchmark policies that are typically used in the current practice (see Table 2.5). As Table 2.5 shows, for the first three months post-transplant, tacrolimus is prescribed in high dosage in all of these four benchmark policies. This is consistent with the fact that in the current practice patients are consistently kept on high levels of tacrolimus during the first months post-transplant (see, e.g., Ghisdal et al. (2012)) so as to avoid organ rejection. However, after the first three months, the four policies differ: benchmark 1 (4) represents the most (least) intensive policy for prescribing tacrolimus. For example, when the patient is observed to have medium C_0 (i.e., observations o_2, o_5, or o_8) during months 4-6 post-transplant, the regimen under benchmark 1 is to use high dosage of tacrolimus (i.e., actions a_1 or a_4), whereas the regimen under benchmark 4 is to use medium dosage of tacrolimus (i.e., actions a_2 or a_5). Moreover, consistent with the current practice, in all four benchmark policies, insulin is not prescribed for a patient who is observed to be diabetic free (i.e., a patient with FPG$<$ 126 mg/dL or HbA1C$<$ 6.5%).

We compare the APOMDP, POMDP, and benchmark approaches based on three performance measures: (1) average QALE achieved, (2) average medical expenditures (see Appendix A.2.2 for related cost estimations), and (3) average number of times that insulin and different dosage of tacrolimus are prescribed (Tables 2.6, 2.7, 2.8, and 2.9 show the results). The latter allows us to examine whether or not our methodology yields less intensive medication regimens compared to the current practice. Furthermore, since dynamic risk factors are subject to change throughout the time horizon, in our simulation we allow each dynamic risk factor to take either a low or a high level in each period (i.e., unlike static risk factors, we do not run the simulation for each of low-risk and high-risk levels of dynamic risk factors, separately). Considering seven dynamic and four static risk factors in our study, we therefore have $7 + 4 \times 2 = 15$ (and not 22) cohorts of patients in Tables 2.6-2.9. We make the following observations from the results presented in Tables 2.6-2.9:

Observation 2.5.4 (Impact) *During one year post-transplant, compared to other polices (i.e., benchmarks 1-4 and POMDP), our optimal policy on average (i) improves the QALE per patient up to 4.58%, (ii) reduces the medical expenditures per patient up to 11.57%, and (iii) prescribes high-dose tacrolimus up to 3.69 fewer times per patient, med-dose tacrolimus up to 1.48 more times per patient, low-dose tacrolimus up to 2.09 fewer times per patient, and insulin up to 2.12 more times per patient.*

Based on Observation 2.5.4 and the results provided in Tables 2.6-2.9, we shed light on the following implications for medical practitioners, as well as those influencing medical guidelines and recommendations: (1) The improvements in QALE and cost made by our optimal policy are not uniform across all cohorts of patients. From Tables 2.6-2.8, we observe that for some cohorts of patients our approach yields the most improvement in QALE while incuring the least amount of medical expenditure.

These cohorts include patients with (a) age<50, (b) diabetes history, (c) normal or hypertensive blood pressure, (d) normal or high levels of cholsterol and triglyceride, and (e) normal or low HDL. (2) Gains obtained by following our proposed policies compared to the current practice are higher versus benchmark policies 1 and 2 than the other benchmark policies. The intensity of medications prescribed under these policies could be a contributing factor. For example, by following benchmark policies 1 and 2 in one year (compared to our optimal policy), a patient takes high-dose tacrolimus up to 3.69 more times, while taking insulin up to 2.09 fewer times. As a result, the patient becomes more vulnerable against the diabetogenic effect of tacrolimus and NODAT complications. (3) The comparison between our APOMDP approach and the POMDP approach reveals that, had we ignored the underlying model misspecifications, each patient would have lost between 0.02 and 0.09 QALE on average (i.e., between 1.04 and 4.68 weeks), while incuring between $31 and $214 more medical costs during one year post-transplant. This shows the importance of considering model misspecifications that are inevitable when data is used to estimate parameters: one should not rely on a single model to derive effective medication strategies. (4) The above-mentioned improvements in performance measures are obtained over our planning horizon (i.e., one-year post-transplant). Since, compared to other approaches, the APOMDP approach could (a) result in better outcomes in each time period and (b) move the patient to a better health state over time, the potential improvements could be more significant had these measures been calculated over a longer horizon (e.g., two-year post-transplant).

Finally, in Appendix A.5, we conduct sensitivity analyses on the estimated reward values (where both transplant and diabetes-related parameters are varied simultaneously), and find that the results discussed above are robust to the estimated values.

2.6 Conclusion

Immunosuppressive medications are currently intensively prescribed in the post-transplant period to ensure a low risk of organ rejection. However, this practice has been shown to increase the risk of new-onset diabetes after transplantation (NODAT), which, in turn, necessitates the use of medications such as insulin. To provide guidelines for the simultaneous management of post-transplant medications such as tacrolimus and insulin, we develop an ambiguous POMDP (APOMDP) model that maximizes the quality-adjusted life expectancy (QALE) of patients, while controlling the risk of organ rejection and NODAT. Utilizing our APOMDP approach along with a data set of patients who underwent kidney transplantation at our partner hospital, we establish a data-driven approach in which (1) the physician's ambiguity attitude toward model misspecifications is defined based on a combination of the worst and the best possible outcomes in the "cloud" of models, (2) core state and observation transition probability matrices are patient risk-factor specific but subject to potential estimation errors, and (3) optimal policies are customized for different cohorts of patients.

Analyzing the APOMDP model, we first present some structural properties. These include piecewise-linearity and convexity of the value function, a theoretical link between a decision maker's conservatism level and the intensity of prescribed medications, monotonicity of the optimal medication policy, and a feasible bound on the value function as an approximation. We then perform various numerical experiments using our clinical data set, and discuss their implications. For example, we observe that under the optimal policy for some patient cohorts (e.g., non-White patients with age$\geq$50, no diabetes history, and low cholesterol) a more conservative physician is more concerned about both risks of organ rejection and NODAT than a less con-

servative physician. Also, for other patient cohorts (e.g., male patients with age<50, diabetes history, and hypertension), a more conservative DM is more concerned (under the optimal policy) about the risk of NODAT than that of organ rejection compared to a less conservative physician.

We also compare our proposed optimal policies with four benchmark policies that represent the current medical practice (under different scenarios), and a POMDP approach that ignores the underlying model misspecifications. Our results show that, depending on different risk factors considered for each patient, in one year post-transplant our optimal policy (compared to other policies) (a) improves the average QALE up to 4.58%, (b) reduces the medical expenditures per patient up to 11.57%, and (c) prescribes high-dose tacrolimus up to 3.69 fewer times per patient. The other important implications of the above-mentioned results for practitioners and guideline makers are: (1) Cohorts of patients formed by age, diabetes history, blood pressure, cholesterol, HDL, and triglyceride will benefit most from our methodology, because for such patients our approach yields the most improvement in QALE while incuring the least medical expenditure. (2) Practitioners or guideline makers should not rely on a single model to derive effective medication strategies: had we ignored the underlying model misspecifications, each patient on average would have lost between 1.04 and 4.68 weeks of QALE during one year, while incuring between \$31 and \$214 more medical costs durign the same period.

Our study has some limitations: (1) We consider 11 different risk factors each having two levels (i.e., low vs. high). This creates as many as $2^{11} = 2,048$ risk profiles for patients. However, we consider $2 \times 11 = 22$ cohorts of patients by changing one risk factor at a time. This allows us to focus on the effect of each individual risk factor separately. However, this disallows us to study the potential interactions between the risk factors. To perform such a study, we note that one needs to estimate transition

and observation probabilities for each of the 2^{11} risk profiles, which, in turn, requires data of about $10,000$ patients (i.e., more than half of all kidney transplantations in the U.S. in 2015 (UNOS, 2018)). This is much larger than the number of patients seen at our partner hospital. Furthermore, one needs enough data to estimate the reward functions (e.g., QALE values) for all of these 2^{11} cohorts of patients. Nevertheless, as noted earlier, we believe that our approach of considering 22 cohorts of patients is strong enough to detect the impact of each risk factor on optimal prescription of medications. (2) We consider tacrolimus as the main immunosuppressive drug in this study, based on the practice at our partner hospital. Some of our results might be specific to tacrolimus, and should not be extended to other immunosuppressive drugs without additional analysis. Furthermore, unlike the case at our partner hospital, multiple immunosuppressive drugs may be used in parallel in some medical practices. Including all such drugs in our APOMDP approach will increase state and action spaces, aggravating the so-called "curse of dimensionality." This will necessitate using some approximation schemes (e.g., utilizing a lower bound approach similar to the one we discussed in §2.4, or obtaining policies via approximate dynamic programming).

Future research can extend our work in two other directions. First, our approach can be applied to other solid organs (e.g., liver and pancreas) with the goal of creating a multi-organ data-driven decision-support system. Compared to kidney transplantation, where one can use dialysis when facing organ rejection, dialysis is not feasible for other organs. As a result, risk of organ rejection is expected to be higher for other organs compared to kidney, and this, in turn, can affect optimal medication policies. Second, future research may consider a resource allocation problem for hospitals, where the challenge is to effectively allocate limited resources (e.g., insulin and tacrolimus along with nurses and beds) to Endocrinology and Nephrology departments of hospitals for managing NODAT patients. This will create coordinated

efforts between different parts of a hospital, and hence, may further reduce expenditures while improving the care delivery process.

Table 2.5: Description of Benchmark Policies Based on Medical Observations and Time Elapsed Post-transplant

Month	Observation	Benchmark			
		1	**2**	**3**	**4**
1–3	$\boldsymbol{o_1}$	a_1	a_1	a_1	a_1
	$\boldsymbol{o_2}$	a_1	a_1	a_1	a_1
	$\boldsymbol{o_3}$	a_1	a_1	a_1	a_1
	$\boldsymbol{o_4}$,$\boldsymbol{o_7}$	a_4	a_4	a_4	a_4
	$\boldsymbol{o_5}$,$\boldsymbol{o_8}$	a_4	a_4	a_4	a_4
	$\boldsymbol{o_6}$,$\boldsymbol{o_9}$	a_4	a_4	a_4	a_4
Month	**Observation**	**Benchmark**			
		1	**2**	**3**	**4**
4–6	$\boldsymbol{o_1}$	a_1	a_1	a_1	a_1
	$\boldsymbol{o_2}$	a_1	a_1	a_2	a_2
	$\boldsymbol{o_3}$	a_1	a_2	a_3	a_3
	$\boldsymbol{o_4}$,$\boldsymbol{o_7}$	a_4	a_4	a_4	a_4
	$\boldsymbol{o_5}$,$\boldsymbol{o_8}$	a_4	a_4	a_5	a_5
	$\boldsymbol{o_6}$,$\boldsymbol{o_9}$	a_4	a_5	a_6	a_6
Month	**Observation**	**Benchmark**			
		1	**2**	**3**	**4**
7–12	$\boldsymbol{o_1}$	a_1	a_1	a_2	a_2
	$\boldsymbol{o_2}$	a_2	a_2	a_2	a_3
	$\boldsymbol{o_3}$	a_2	a_3	a_3	a_3
	$\boldsymbol{o_4}$,$\boldsymbol{o_7}$	a_4	a_4	a_5	a_5
	$\boldsymbol{o_5}$,$\boldsymbol{o_8}$	a_5	a_5	a_5	a_6
	$\boldsymbol{o_6}$,$\boldsymbol{o_9}$	a_5	a_6	a_6	a_6

Table 2.6: Comparison of Medication Policies Based on Average QALE (Years) (Numbers in Parenthesis Represent Standard Deviation)*

Cohort	Benchmark 1**	Benchmark 2	Benchmark 3***	Benchmark 4***	Average of benchmarks	POMDP	APOMDP
Age<50	16.36 (0.16)	16.56 (0.05)	16.98 (0.25)	16.94 (0.12)	16.71 (0.08)	17.08 (0.15)	17.14 (0.17)
Age≥50	9.15 (0.16)	9.33 (0.17)	9.80 (0.19)	9.75 (0.16)	9.5075 (0.09)	9.82 (0.17)	9.85 (0.18)
Gender:Female	17.74 (0.11)	17.88 (0.16)	18.07 (0.19)	18.10 (0.25)	17.95 (0.17)	18.12 (0.11)	18.17 (0.21)
Gender:Male	15.35 (0.14)	15.51 (0.18)	15.88 (0.21)	15.91 (0.22)	15.66 (0.28)	15.90 (0.10)	15.93 (0.24)
Race:White	16.16 (0.10)	16.25 (0.18)	16.58 (0.14)	16.60 (0.17)	16.40 (0.23)	16.62 (0.08)	16.68 (0.06)
Race:non-White	13.25 (0.08)	13.41 (0.18)	14.04 (0.16)	14.02 (0.10)	13.68 (0.41)	13.97 (0.24)	14.02 (0.22)
DiabHist:No	14.66 (0.18)	14.76 (0.09)	15.01 (0.15)	15.14 (0.15)	14.89 (0.22)	15.15 (0.16)	15.19 (0.13)
DiabHist:Yes	8.32 (0.25)	8.52 (0.19)	8.73 (0.04)	8.75 (0.02)	8.58 (0.20)	8.94 (0.11)	8.96 (0.10)
BMI	13.65 (0.10)	13.79 (0.23)	14.10 (0.06)	14.08 (0.16)	13.91 (0.22)	14.12 (0.09)	14.15 (0.01)
BP	13.34 (0.08)	13.52 (0.16)	13.82 (0.19)	13.77 (0.20)	13.61 (0.22)	13.80 (0.09)	13.89 (0.02)
Chol	13.06 (0.04)	13.18 (0.19)	13.56 (0.18)	13.50 (0.18)	13.33 (0.24)	13.60 (0.13)	13.68 (0.05)
HDL	13.08 (0.10)	13.22 (0.08)	13.49 (0.13)	13.55 (0.17)	13.34 (0.22)	13.71 (0.14)	13.78 (0.10)
LDL	13.20 (0.15)	13.37 (0.04)	13.86 (0.10)	13.90 (0.16)	13.58 (0.35)	13.82 (0.24)	13.90 (0.23)
TG	13.05 (0.27)	13.09 (0.24)	13.46 (0.24)	13.40 (0.20)	13.25 (0.21)	13.47 (0.18)	13.51 (0.17)
UA	12.86 (0.14)	12.90 (0.20)	13.08 (0.18)	13.15 (0.19)	13.00 (0.14)	13.23 (0.22)	13.25 (0.17)

* Due to the large number of instances in our simulation ($\approx 1.3 \times 10^8$), we report standard deviation instead of standard error.

** Among all benchmarks, benchmark 1 yields the lowest average QALE across all cohorts.

*** Among all benchmarks, benchmark 3 yields the highest average QALE for age (both cohorts), non-White race/BMI/BP/Chol/TG, and benchmark 4 yields the highest average QALE for gender/diab hist (both cohorts), White race/HDL/LDL/UA.

Table 2.7: Comparison of Medication Policies Based on Average Cost ($) (Numbers in Parenthesis Represent Standard Deviation)*

Cohort	Benchmark 1**	Benchmark 2	Benchmark 3***	Benchmark 4***	Average of benchmarks	POMDP	APOMDP
Age<50	5,733 (67.2)	5,507 (65.4)	5,371 (99.2)	5,405 (97.8)	5,504 (41.98)	5,163 (50.7)	5,098 (78.5)
Age≥50	5,811 (95.5)	5,674 (66.5)	5,478 (77.8)	5,495 (51.8)	5,611 (37.32)	5,352 (89.7)	5,245 (97.5)
Gender:Female	5,950 (83.9)	5,879 (76.2)	5,650 (50.2)	5,536 (94.6)	5,754 (38.98)	5,521 (94.6)	5,415 (67.6)
Gender:Male	5,963 (98.5)	5,884 (77.4)	5,611 (59.5)	5,588 (75.3)	5,762 (39.45)	5,640 (67.9)	5,584 (70.3)
Race:White	5,715 (67.4)	5,630 (84.7)	5,253 (59.5)	5,204 (69.4)	5,451 (35.42)	5,144 (93.2)	5,113 (91.8)
Race:non-White	6,377 (82.0)	6,205 (96.0)	5,417 (87.9)	5,461 (57.3)	5,865 (41.04)	5,504 (58.2)	5,452 (90.6)
DiabHist:No	5,770 (88.0)	5,691 (76.7)	5,347 (80.9)	5,223 (54.7)	5,508 (38.05)	5,218 (93.7)	5,180 (85.3)
DiabHist:Yes	6,863 (63.5)	6,814 (88.5)	6,630 (69.5)	6,597 (79.6)	6,726 (37.94)	6,212 (51.3)	6,147 (80.8)
BMI	5,895 (92.8)	5,798 (74.8)	5,520 (54.4)	5,584 (77.5)	5,699 (38.06)	5,506 (88.3)	5,443 (98.8)
BP	5,881 (59.3)	5,815 (88.4)	5,451 (59.3)	5,566 (85.4)	5,678 (37.20)	5,488 (69.4)	5,274 (75.8)
Chol	6,111 (55.2)	6,005 (53.1)	5,603 (99.5)	5,688 (91.9)	5,852 (38.90)	5,566 (53.5)	5,494 (55.5)
HDL	5,835 (90.6)	5,805 (70.5)	5,619 (58.6)	5,545 (50.4)	5,701 (34.60)	5,329 (68.6)	5,144 (72.9)
LDL	5,925 (85.4)	5,836 (54.7)	5,497 (66.7)	5,383 (97.0)	5,660 (38.85)	5,578 (82.9)	5,391 (77.7)
TG	6,252 (79.3)	6,118 (62.6)	5,780 (50.2)	5,916 (86.6)	6,017 (35.56)	5,774 (65.3)	5,616 (90.6)
UA	5,944 (68.9)	5,831 (70.5)	5,674 (83.4)	5,513 (85.7)	5,741 (38.74)	5,423 (50.4)	5,280 (65.9)

* Due to the large number of instances in our simulation ($\approx 1.3 \times 10^8$), we report standard deviation instead of standard error.

** Among all benchmarks, benchmark 1 yields the highest Chol/TG, cost across all cohorts.

*** Among all benchmarks, benchmark 3 yields the lowest average cost for age (both cohorts), non-White race/BMI/BP/ Chol/TG, and benchmark 4 yields the lowest average cost for gender/diab hist (both cohorts), White race/HDL/LDL/UA.

Table 2.8: QALE and Cost Improvement of APOMDP Policy over Other Policies (Comparisons Are Made Based on Average QALE/Cost Values Reported in Tables 2.6-2.7)

	Cohort	Benchmark Worst*	Benchmark Best**	Benchmarks Average***	POMDP
% increase in QALE	Age<50	4.77%	0.94%	2.57%	0.35%
	Age≥50	7.65%	0.51%	3.60%	0.31%
	Gender:Female	2.42%	0.39%	1.23%	0.28%
	Gender:Male	3.78%	0.13%	1.72%	0.19%
	Race:White	3.22%	0.48%	1.71%	0.36%
	Race:non-White	5.81%	-0.14%	2.49%	0.36%
	DiabHist:No	3.62%	0.33%	2.01%	0.26%
	DiabHist:Yes	7.69%	2.40%	4.43%	0.22%
	BMI	3.66%	0.35%	1.73%	0.21%
	BP	4.12%	0.51%	2.06%	0.65%
	Chol	4.75%	0.88%	2.63%	0.59%
	HDL	5.35%	1.70%	3.30%	0.51%
	LDL	5.30%	0.00%	2.36%	0.58%
	TG	3.52%	0.37%	1.96%	0.30%
	UA	3.03%	0.76%	1.92%	0.15%
	Average**	4.58%	0.79%	2.38%	0.35%
% decrease in cost	Age<50	12.46%	5.36%	7.38%	1.28%
	Age≥50	10.79%	4.44%	6.52%	2.04%
	Gender:Female	9.88%	2.23%	5.89%	1.96%
	Gender:Male	6.79%	0.07%	3.09%	1.00%
	Race:White	11.77%	1.78%	6.20%	0.61%
	Race:non-White	16.97%	-0.64%	7.04%	0.95%
	DiabHist:No	11.39%	0.83%	5.95%	0.73%
	DiabHist:Yes	11.65%	7.32%	8.61%	1.06%
	BMI	8.30%	1.41%	4.49%	1.16%
	BP	11.51%	3.36%	7.12%	4.06%
	Chol	11.23%	1.98%	6.12%	1.31%
	HDL	13.43%	7.80%	9.77%	3.60%
	LDL	9.91%	-0.15%	4.75%	3.47%
	TG	11.32%	2.92%	6.666%	2.81%
	UA	12.58%	4.41%	8.03%	2.71%
	Average**	11.57%	4.01%	6.51%	1.93%

* Highest improvement made by the APOMDP policy against benchmarks.

** Lowest improvement made by the APOMDP policy against benchmarks.

*** Improvement made by the APOMDP policy against average of benchmarks.

**** Average of improvement under each column (across all cohorts).

Table 2.9: Comparison of Medication Policies (Based on Average Number of Medications Prescribed under Each Policy)

Cohort	**Benchmark 1**				**Benchmark 2**				**Benchmark 3**			
	1*	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Age:L**	7.76	3.91	0.33	3.97	7.05	2.96	1.99	4.00	3.99	5.12	2.89	4.07
Age:H	8.13	3.87	0.00	4.21	6.73	3.08	2.19	4.10	4.13	5.39	2.48	4.17
Gender:L	8.10	3.65	0.25	3.72	7.15	3.25	1.60	4.37	4.24	5.32	2.44	4.45
Gender:H	8.46	3.54	0.00	4.48	7.08	3.35	1.57	4.28	4.41	4.99	2.6	3.96
Race:L	7.29	4.17	0.54	3.85	6.64	3.10	2.26	4.30	4.16	4.90	2.94	3.60
Race:H	7.56	4.35	0.09	4.34	6.54	3.47	1.99	4.30	3.62	5.24	3.14	3.84
DiabHist:L	8.38	3.46	0.16	3.89	6.97	2.80	2.23	4.34	4.36	5.24	2.40	3.79
DiabHist:H	7.54	4.14	0.32	4.07	6.64	2.90	2.46	4.55	3.98	5.53	2.49	4.24
BMI	7.82	3.55	0.63	4.30	7.42	2.90	1.68	3.69	4.08	5.50	2.42	4.34
BP	8.30	3.70	0.00	4.40	7.36	2.54	2.10	4.26	3.94	5.13	2.93	3.96
Chol	7.86	3.94	0.20	4.11	6.79	2.96	2.25	4.15	4.14	4.93	2.93	4.11
HDL	8.35	3.53	0.12	3.92	7.41	3.09	1.50	3.96	4.12	5.77	2.11	3.98
LDL	7.94	4.06	0.00	4.46	7.32	3.01	1.67	4.38	3.69	4.99	3.32	4.03
TG	7.61	3.62	0.77	3.96	6.83	3.39	1.78	4.34	3.72	5.19	3.09	4.46
UA	7.74	4.26	0.00	4.26	6.53	3.23	2.24	4.11	4.24	5.77	1.99	4.40
Difference***	3.69	-0.63	-2.06	-2.09	2.73	-1.41	-0.32	-2.01	-0.18	0.79	0.39	-2.12
Cohort	**Benchmark 4**				**POMDP**				**APOMDP**			
	1	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Age:L	4.05	3.15	3.80	3.98	4.07	4.35	2.58	5.24	3.66	4.87	2.47	5.12
Age:H	4.13	3.29	3.58	4.15	4.88	4.33	1.79	7.48	4.68	4.81	1.51	7.62
Gender:L	3.55	2.68	4.77	3.95	4.77	4.05	2.18	5.18	4.13	4.44	2.43	4.94
Gender:H	4.37	2.73	3.90	4.15	5.18	3.89	1.93	5.47	5.05	4.03	1.92	5.70
Race:L	3.77	2.80	4.43	3.81	4.71	3.83	2.46	4.84	4.65	3.97	2.38	4.89
Race:H	3.72	2.79	4.49	4.37	5.05	3.87	2.08	5.77	4.83	4.06	2.11	5.85
DiabHist:L	4.12	2.58	4.3	3.88	4.65	3.81	2.54	5.31	4.12	4.27	2.61	4.85
DiabHist:H	3.74	2.65	4.61	4.41	3.95	4.41	2.64	7.50	3.25	5.03	2.72	8.14
BMI	3.83	2.53	4.64	4.39	4.83	4.17	2.00	6.17	4.15	4.79	2.06	6.88
BP	4.21	2.64	4.15	4.20	5.07	3.85	2.08	5.96	4.25	4.70	2.05	6.38
Chol	3.73	3.46	3.81	4.11	5.02	3.94	2.04	6.13	4.34	4.79	1.87	6.78
HDL	3.96	3.64	3.40	4.28	4.56	3.76	2.68	6.07	3.78	4.69	2.53	6.67
LDL	3.82	3.29	3.89	4.34	5.14	3.66	2.20	6.13	4.55	4.52	1.93	6.98
TG	3.56	3.28	4.16	4.08	4.66	3.38	2.96	6.13	4.15	4.03	2.82	6.56
UA	3.87	3.48	3.62	4.11	4.22	4.03	2.75	5.68	3.97	4.17	2.86	5.88
Difference***	-0.34	-1.48	1.82	-2.07	0.48	-0.52	0.04	-0.28	—	—	—	—

* 1,2,3,4: number of times (on avg.) that high/med/low-dose tacrolimus and insulin are prescribed in 1 year, respectively.

** L: low level; H: high level

*** Average of differences with the optimal policy (average is taken over all cohorts).

Chapter 3

CHARACTERIZATION OF REMITTING AND RELAPSING HYPERGLYCEMIA IN POST-RENAL-TRANSPLANT RECIPIENTS

3.1 Introduction

Hyperglycemia is a well-described complication following solid organ transplantation Bloom and Crutchlow (2008); Kesiraju et al. (2014); Räkel and Karelis (2011). Among patients without a prior history of diabetes mellitus (DM), hyperglycemia that either persists after transplant, or which resolves but later recurs and persists, is termed new onset diabetes after transplant (NODAT). Hyperglycemia and NODAT are strong predictors of graft failure and cardiovascular mortality occurring commonly after solid organ transplant Bloom and Crutchlow (2008); Kesiraju et al. (2014); Räkel and Karelis (2011). The occurrence of hyperglycemia or development of NODAT have been attributed to many factors, including (1) immunosuppressive drugs and their diabetogenic effects, (2) other demographic and medical-related risk factors, and (3) inpatient hyperglycemic conditions.

Regarding the first factor, Table 3.1 summarizes studies on the diabetogenic effect of anti-rejection agents (e.g., tacrolimus, sirolimus, cyclosporine, glucocorticoids, and steroid) with respect to different solid organ transplantations (e.g., kidney, liver, and pancreas). The main insights from this literature are related to: (1) the efficacy of a drug in preventing organ rejection while imposing less risk for hyperglycemia or NODAT, (2) the relative benefits/side effects of two or more drugs when compared with each other, and (3) the potentials of drugs when switching from one therapy to another.

In addition to immunosuppressive drugs, the literature has analyzed other demographic or medical-related risk factors to establish possible statistically significant associations with hyperglycemia and NODAT (Table 3.2). The majority of the literature in this stream attempts to (1) derive associations between risk factor(s) and a continuous variable (linear regression models) that represents hyperglycemia/NODAT status (e.g., blood glucose level measured by hemoglobin A1c and fasting plasma glucose tests), (2) demonstrate the same effect for a categorical variable (i.e., whether a patient suffers from hyperglycemia or not, at a specific point of time) by applying logistic regression models, or (3) discuss the probability of survival from hyperglycemia/NODAT at a single point of time (Cox regression models).

Furthermore, recent evidence indicates that hyperglycemia occurring in the immediate post-transplant period (i.e., during the post-operative hospital stay) is also associated with NODAT (see, e.g., Chakkera et al. (2009) and Chakkera et al. (2010)).

In spite of all these efforts, none of these factors (immunosuppressive drugs and their diabetogenic effects, demographic and medical-related risk factors, and inpatient hyperglycemic conditions) have been analyzed with respect to the time course of post-transplant complications. Specifically, one critical aspect that is overlooked by the literature is an understanding and analysis of *remitting and relapsing* hyperglycemia in post-solid organ transplant recipients. Such an understanding can be critical because (1) the insights gained can be quite different from those previously known for the incidence of hyperglycemia and (2) these insights can be extended to other chronic diseases with the possibility of remitting and relapsing, such as cancer and multiple sclerosis. To the best of our knowledge, this is the first study analyzing the first and recurrent incidence of hyperglycemia. In particular, utilizing a population of renal transplant recipients who had no history of DM before transplantation, we undertake a set of analyses to determine which contributing factors are significantly associated

with the first incidence, and which ones are significantly associated with the recurrent incidence.

3.2 Materials and Methods

3.2.1 Study Cohort.

After obtaining Mayo Clinic Institutional Review Board (Mayo Clinic IRB) approval (Continuing Review #: PR13-004295-01) and written informed consent from all participating patients, this study conducts an analysis of 292 patients who underwent a renal transplant between 1999 and 2006 in Mayo Clinic Arizona, and who had no history of DM prior to surgery. Briefly, all patients were monitored at the time of transplant as well as month 1, 4, and 12 post-transplant. The available data included (1) demographic data such as age, race, and gender, (2) baseline patient characteristics including body mass index (BMI), blood pressure (BP), total cholesterol (Chol), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), uric acid (UA), and triglyceride (TG), (3) type of immunosuppressive drugs and diabetes medications that were used by the patients, (4) trough level of tacrolimus (as the main immunosuppressive drug used in this study), and (5) results of fasting plasma glucose (FPG) and Hemoglobin A1c (HbA1c) tests as measures of glycemic control. All major abbreviations used in this study are explained in Table 3.3.

3.2.2 Definitions.

NODAT was defined as HbA1c $\geq$ 6.5%, or FPG $\geq$ 126 mg/dL, or the requirement of diabetes medications (e.g., insulin or oral agent) after patient discharge from hospital Chakkera et al. (2010, 2009). We apply this criteria to determine the incidence of post-transplant hyperglycemia, which may happen just once or for multiple

times (recurrent). We refer to either of these conditions as instances of *remitting and relapsing* hyperglycemia.

3.2.3 Statistical Methods.

We now explain the statistical inference methods we employed to analyze the effects of immunosuppressive drugs, the corresponding risk factors, and the inpatient period conditions on the first and recurrent incidence of post-transplant hyperglycemia. The statistical models used were: (i) The Cox regression model with time-dependent covariates, which measures the *proportional hazard* imposed on the response variable (hyperglycemia incidence) by covariates that change over time. For example, the BMI of a patient may change as his/her weight changes (Chol, HDL, and LDL are some other examples of such covariates). As another example, whether the patient uses an immunosuppressive drug at a specific time or not can be considered as a time-dependent covariate. Therefore, we sought to fully comprehend the effect of these changing behaviors on the recurrent incidence of hyperglycemia. (ii) Cox regression model with time-independent covariates, which measures the proportional hazard imposed on the response variable (the first incidence of hyperglycemia) by covariates at the time of the first incidence of hyperglycemia. (iii) Kaplan-Meier survival analysis to characterize the cumulative probability of experiencing hyperglycemia over time.

The statistical analyses also include *multiple imputations by chained equations* (MICE) Buuren and Groothuis-Oudshoorn (2011), which we used to replace some missing data (with the prevalence of less than 10% in our data set) with validated values. We conducted all statistical analyses by using the R computing package.

3.3 Results

3.3.1 Demographic and Baseline Characteristics of Patients.

Among 407 patients in the study cohort, there were 115 patients with the history of diabetes. The remaining 292 patients had no indication of diabetes prior to or at the time of their transplants. The average age of patients who had no diabetes before transplant was 49.7 years, while those who had diabetes before had the average age of 56. Table 3.4 summarizes the demographic data along with some other baseline characteristics of patients.

3.3.2 Incidence of Hyperglycemia.

Regarding the definition of remitting and relapsing hyperglycemia, Table 3.5 summarizes different hyperglycemic states that can occur after renal transplantation. Therefore, 79 (27.06%) patients experienced *remitting and relapsing* post-transplant hyperglycemia (and hence the hyperglycemia for the first time). Among these patients, 19+3+1+24=47 patients experienced hyperglycemia multiple times, while 20+11+1=32 had it just once. As an example of the potential remitting and relapsing nature of post-transplant hyperglycemia, there are 11 patients who developed hyperglycemia at 4 months, which resolved at 12 months.

3.3.3 Summary of Immunosuppressive Treatment Regimens.

This section sheds light on information about main immunosuppressive medications that have been considered for this study (tacrolimus, steroid, and sirolimus). As mentioned before, we focus on 292 patients with no prior history of diabetes.

Tacrolimus

Tacrolimus (Prograf) is the main immunosuppressive drug utilized in this study. Fig 3.1 (the first three columns) demonstrates the number of patients at month 1, 4, and 12 using tacrolimus, which include 283, 275, and 270 patients (out of 292 patients), respectively. As our primary interest in this study is to analyze the incidence of hyperglycemia, we further classified patients in terms of whether they experienced hyperglycemia at a specific time or not, and Fig 3.1 reveals this information as well.

Another important point regarding tacrolimus is the dosage goals and achieved levels at different points of time. Tacrolimus goals are adjusted to avoid toxicity and to the lowest dose possible to avoid rejection per clinical standards of care. This is a standard clinical practice and is based on individual response and pharmacokinetics. Table 3.6 summarizes this information. It should be noted that the achieved levels of tacrolimus are represented in terms of the average trough level of tacrolimus.

Steroid

Steroid is the second main immunosuppressive drug incorporated in this study. Fig 3.1 (the second three columns) illustrates the number of patients at month 1, 4, and 12 using steroid, which include 138, 147, and 140 patients (out of 292 patients), respectively. This shows that in comparison with tacrolimus which was used by the majority of patients, fewer patients used steroid. (According to what explained for tacrolimus, the percentages of patients using tacrolimus at months 1, 4, and 12 were $283/292 = 97\%$, $275/292 = 94\%$, and $270/292 = 92\%$, respectively.) Fig 3.1 also shows the number of patients who used steroid and experienced hyperglycemia.

Steroid is usually prescribed by the following mechanism. If after using induction steroids (which last for up to 5 days post-transplant) a patient has an organ rejection,

she will receive a taper dose of steroid (i.e., slow withdrawal). Then, by 1 month post-transplant, the patient will be put on the maintenance regimen of 5 mg daily (which is a low dosage), unless the patient has another rejection(s) later and needs possibly extra dosage of steroid therapy. To this end, we observed the following from the data set: (1) Among the 292 patients, only 20 patients had organ rejection at month 1, and hence, had to use a taper dose of steroid at this month. Therefore, there remained 272 patients who had no rejection during month 1. (2) Among 20 patients at month 1, 4 patients at month 4 and 1 patient at month 12 experienced organ rejection (these were mutually exclusive patients). (3) Among 272 patients at month 1, 5 patients at month 4 and 6 patients at month 12 experienced organ rejection (these were mutually exclusive patients). Therefore, according to the mechanism explained before, it can be concluded that 4+5+1+6=16 patients (out of 292) had increased dose of steroid (i.e., more than 5 mg daily) after 1 month post-transplant. Furthermore, as explained before, according to Fig 3.1, 138, 147, and 140 patients used steroid at months 1, 4, and 12, respectively. Therefore, 138-(4+1)=133, 147-(4+5)=138, and 140-(1+6)=133 patients remained on the regimen of 5 mg daily at months 1, 4, and 12, respectively.

Sirolimus

Sirolimus (Rapamune) is the third main immunosuppressive drug incorporated in this study. Fig 3.1 shows that sirolimus was utilized by a very small proportion of patients.

3.3.4 Time-Dependent Cox Regression Model: Recurrent Incidence of Hyperglycemia.

To address events that may occur repeatedly, such as the repeated occurrence of hyperglycemia, we need to incorporate covariates that change over time (e.g., BMI, BP, etc.). To this end, we employed a Cox regression model with time-dependent

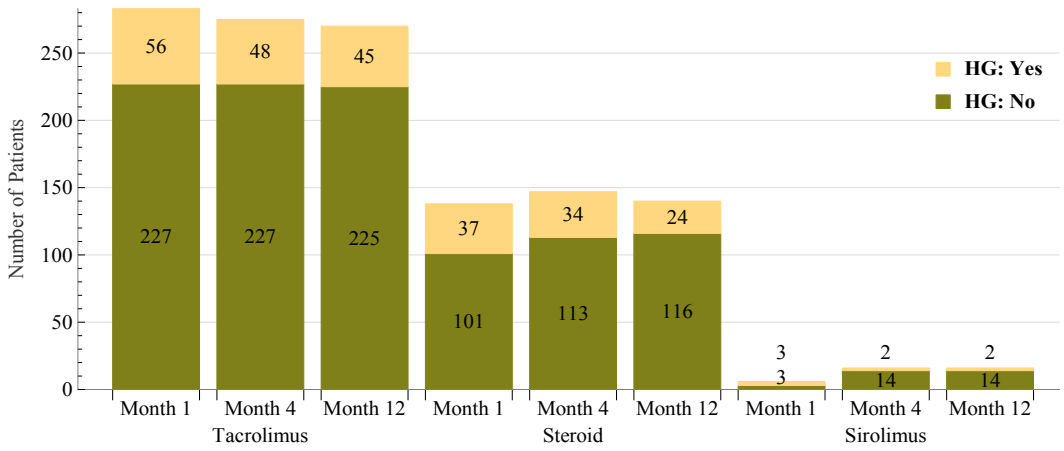


Figure 3.1: Number of Patients Who Used Immunosuppressive Drugs at Months 1, 4, and 12. Such Patients Are Further Classified as Having Hyperglycemia (HG) or Not at That Specific Time Points.

covariates and recurrent events, where each event is assumed to occur once a patient meets the criteria defined in Table 3.5. The performance measure in this model is the *hazard ratio* (HR), such that if mean HR ≥ 1, the corresponding covariate will have a positive effect on the response variable (and vice versa).

According to Table 3.8 (Part I), induction immunosuppressive agents (thymoglobulin and simulect) and steroids were significantly associated with lower and higher chance of recurrent hyperglycemia, respectively. However, neither using tacrolimus nor its average trough level was significantly associated with the repeated occurrence of hyperglycemia. Therefore, one cannot establish the diabetogenic effect of tacrolimus when hyperglycemia occurs repeatedly. As we will see in the next section, this finding is in a sharp contrast with the case where only the first incident of hyperglycemia is considered.

3.3.5 Time-Independent Cox Regression Model: First Incidence of Hyperglycemia.

The reason that the diabetogenic effect of tacrolimus cannot be established when hyperglycemia is occurring repeatedly may be due to the fact that tacrolimus dosage is usually reduced with the passage of time after transplant (see Table 3.6). To test this hypothesis, we analyzed the immunosuppressive effect when hyperglycemia happens for the first time. We used a time-independent Cox regression model, in which only covariates at the time of first occurrence are considered. According to Table 3.8 (Part II), the average trough level of tacrolimus is significantly associated with a higher chance of first hyperglycemia incident, which implies that the diabetogenic effect of tacrolimus can be established in this case. This observation highlights the importance of differentiating between the first and recurrent incidents of hyperglycemia.

As other observations made in this regard, induction immunosuppressive agents (thymoglobulin and simulect) are significantly associated with lower chance of first hyperglycemia. However, we cannot establish any significant association between using steroid and the first incidence of hyperglycemia. This can be due to the fact that high dosages of steroid were only considered for a small proportion of patients in month 1 post-transplant (see section "Summary of Immunosuppressive Treatment Regimens" for more information).

3.3.6 Kaplan-Meier Analysis: Hyperglycemia Incidence.

The results of time-independent analysis established by the Cox regression model shows the significant association between the average trough level of tacrolimus and the first incidence of hyperglycemia. Here, we aim to use *Kaplan-Meier survival analysis* to calculate the probability of having hyperglycemia obtained from Kaplan-Meier survival curves.

To this end, we consider the main *stratum* based on average trough level of tacrolimus classified as "$\leq$ 10" and "$>$ 10" mg/dL. In order to fully comprehend the effect of these levels on the incidence of hyperglycemia, we conduct unadjusted (univariate) analysis as well as ten adjusted analyses for those risk factors mentioned before. However, to incorporate these risk factors into the Kaplan-Meier survival analysis, they should be discretized in classes, which are shown in Table 3.7. It should be noted that the classification thresholds for each of these risk factors have been set so as to distinguish the groups in terms of health-related risks (e.g., BMI of 30 kg/m^2 for obesity). Furthermore, except age, gender, race, and blood pressure, other thresholds have been obtained from MedPlus (2018). Regarding the blood pressure, if the systolic and diastolic blood pressure are "$<$120" and "$<$80" mm Hg, respectively, the patient is normal. Otherwise, the patient has hypertension. These thresholds have been obtained from AHA (2018).

Fig 3.2 presents the above-mentioned survival curves. For simplicity, patients with an average tacrolimus trough level of less than or equal to (more than) 10 mg/dL are said to have *Trough-level 0 (1)*. Fig 3.2A shows that Trough-level 1 patients have significantly higher chance of experiencing hyperglycemia (HG) than Trough-level 0 patients (i.e., Logrank P $<$0.0001). Specifically, almost all of the former group experience HG by month 4 (i.e., probability of experiencing HG $\approx$ 100%), while the latter group still have about 80% chance of not experiencing HG by year 1. Although we made these observations for the unadjusted (univariate) analysis, the same behavior can be seen for adjusted analyses: the chance of experiencing HG is significantly different (i.e., Logrank P $<$0.0001) across groups formed by different risk factors (see Figs 3.2B-3.2K). Furthermore, Trough-level 1 patients with any of the following conditions almost certainly experience HG by month 1: non-White ethnicity, obese (BMI $>$30 kg/m^2), and LDL $\geq$130 mg/dL. Moreover, Trough-level

1 patients with any of the following conditions experience HG by month 1 with a chance not less than 90%: age>50, male, hypertension, Chol ≥200 mg/dL, HDL <40 mg/dL, UA ≥7.3 mg/dL, or TG ≥150 mg/dL.

3.3.7 Other Risk Factors for the Incidence of Hyperglycemia.

We also analyzed the associations of other well-known risk factors for both the first and recurrent incidence of hyperglycemia. To this end, we again applied two types of Cox regression model. The results of these analyses are provided in Table 3.9. We found that age and HDL were significantly associated with the first incident of hyperglycemia, whereas age, race (non-White), BMI, HDL, and UA were significant risk factors for the recurrent incidence of hyperglycemia.

Combining these results with those in Table 3.8, it can be stated that the first incidence of hyperglycemia is more attributed to the diabetogenic effect of tacrolimus. However, in the absence of such an effect, the recurrent incidence of hyperglycemia is mainly imputed to other risk factors (e.g., age, race (non-White), BMI, HDL, and UA). A review of Tables 3.8 and 3.9 also shows potential consequences of choosing the right statistical tool in determining the diabetogenic effect of immunosuppressive drugs or corresponding risk factors for hyperglycemia incidence. In addition, observing that the first and recurrent types of hyperglycemia are subject to different risk factors might have broader implications for other similar chronic diseases. The current literature largely overlooks time-dependent analyses, and our results shed light on the importance of closing this gap.

3.3.8 Impact of the Inpatient Period.

Prior studies have addressed the importance of the inpatient period: what happens to patients during post-transplant hospitalization may have an impact on pa-

tient's conditions after hospital discharge Chakkera et al. (2010, 2009). To evaluate the impact of inpatient period, we analyzed the effect of (1) average bed glucose result (bed.avg), which is obtained by a poke test, (2) average blood glucose result (blood.avg), and (3) inpatient hyperglycemia (in.hyp) on the incidence of hyperglycemia. Table 3.10 summarizes the results obtained from our statistical methods. Based on Table 3.10, the average bed and blood glucose results are significantly associated with both the first and the recurrent incidence of hyperglycemia. However, the occurrence of inpatient hyperglycemia is only associated with recurrent incidence of hyperglycemia.

3.4 Discussion

Our analyses highlight the complex nature of post-renal transplant hyperglycemia. Some patients never exhibit hyperglycemia, some develop permanent hyperglycemia (NODAT), while for others hyperglycemia may be transient or even recurrent. Hyperglycemia and NODAT have been mostly analyzed for a short period after transplantation Chien et al. (2008); Ghisdal et al. (2012). However, their incidence may be underestimated by such short-term studies (see Bee et al. (2011); Cosio et al. (2001); Davidson and Wilkinson (2004); Honda et al. (2013); Kaposztas et al. (2011); Mozaffarian et al. (2007) for some studies analyzing long-term analyses). Our results show that if the diabetogenic effect of immunosuppressive drugs is of interest, short-term analyses might be preferred, while long-term analyses are more suitable when studying other risk factors.

The idea of analyzing hyperglycemia from this perspective (i.e., time course of complications) can also be extended to other chronic diseases in which both the first incident and the recurrent ones need to be monitored. For example, prostate cancer and breast cancer are among diseases that may show signs only once or may do so

from time to time with periods of remission in between Cardoso et al. (2012); Mohler et al. (2004). For this category of diseases, considering both time-dependent and time-independent analyses (as we did in this study) may provide new and important insights.

There are some limitations in our study. First, due to the nature of our study, having patients' information on a more regular basis (e.g., monthly) would improve the accuracy of our results. Second, if the data set included patients' information after the first year post-transplant, we would be able to conduct a more robust Cox regression and Kaplan-Meier survival analysis. Third, although, according to Table 3.5, 79 patients (who experienced post-transplant hyperglycemia for the first time) are sufficient for the purpose of our analyses, it might be a relatively small sample. Finally, even though sirolimus and steroid were used for the minority of patients (in comparison with tacrolimus), we had no information about the exact dosages and trough levels of these two drugs. Otherwise, we could also evaluate the possible association between their trough levels and incidence of hyperglycemia.

Finally, some of our findings may not be generalizable to other types of solid organ transplants (e.g., heart, liver, and pancreas). Therefore, testing our findings can be a fruitful path for future research. By extending the idea of this study and incorporating the time course of complications for other organs, one can establish a holistic framework to analyze (a) the diabetogenic effect of immunosuppressive drugs, and (b) the effect of other risk factors.

3.5 Conclusion

We analyzed the effects of (1) immunosuppressive drugs, (2) risk factors, and (3) inpatient hyperglycemia on the first and recurrent incidence of post-transplant hyperglycemia in patients who had no history of diabetes mellitus prior to their

transplants. We employed two statistical inference methods: (1) Cox regression model with time-dependent covariates to analyze hyperglycemia with recurrence and (2) Cox regression model with time-independent covariates to evaluate the first incidence of hyperglycemia. We also employed Kaplan-Meier survival analysis to characterize the cumulative probability of experiencing post-transplant hyperglycemia over time.

Based on the results obtained from these methods, we can state that the diabetogenic effect of tacrolimus (based on its trough level) can be established when hyperglycemia is experienced for the first time. However, in a sharp contrast, this effect cannot be established for the recurrent incidents of hyperglycemia. This difference might be due to the fact that tacrolimus dosage is reduced by physicians over time. As the diabetogenic effect is ruled out, our results show that age, race (non-White), BMI, HDL, steroid use, and uric acid are the only significant risk factors for the recurrent incidence.

Table 3.1: Classification of Literature Based on the Diabetogenic Effect of Immunosuppressive Drugs

Drug Type	**Organ Type**	**Selected References**
Tacrolimus	Kidney/ Liver	Bułanowski et al. (2012); Duvoux et al. (2013) Furth et al. (1996); Herrero et al. (2003) Kurzawski et al. (2012); Levy et al. (2004) Levy et al. (2006); Marchetti (2004) Mecule et al. (2010); O'grady et al. (2002) Ramachandran et al. (2014); Saliba et al. (2007) Sharif et al. (2010); Stevens et al. (2012) Taylor et al. (2005)
Sirolimus	Kidney/ Liver	Cohen et al. (2012); Johnston et al. (2008) Matias et al. (2008); Montero and Pascual (2015) Romagnoli et al. (2006); Stevens et al. (2012) Teutonico et al. (2005); Van Laecke et al. (2009) Vodenik et al. (2009)
Cyclosporine	Kidney	Bending et al. (1987); Borda et al. (2011) Dresner et al. (1989); Hjelmesæth et al. (2001) Hricik et al. (1991); Meerwein et al. (2011) Mora (2010); Ramos-Cebrian et al. (2007) Taylor et al. (1999, 2005) Van Den Hoogen et al. (2013); Wyzgal et al. (2003)
Glucocorticoids	Kidney/ Pancreas	Kappe et al. (2015); Liu et al. (2014) Rafacho et al. (2014); Taylor et al. (2005) Van Genugten et al. (2014) Van Raalte and Diamant (2014) Wajngot et al. (1992) Wise et al. (1973)
Steroid	Kidney/ Pancreas	Farris et al. (2010); Gelens et al. (2008) Rajab et al. (2007); Wissing and Pipeleers (2014)

Table 3.2: Classification of Literature Based on the Impact of Risk Factors on Hyperglycemia and NODAT

Risk Factor	**Organ Type**	**Selected References**
Age	Kidney/Liver	Carter et al. (2014); Gaynor et al. (2015)
		Kuo et al. (2010); Luan et al. (2010)
		Lv et al. (2014); Palepu and Prasad (2015)
		Park et al. (2015); Pirsch et al. (2015)
		Rodrigo et al. (2006)
Gender	Kidney/Liver	Lv et al. (2014); Palepu and Prasad (2015)
		Parvizi et al. (2014); Rodrigo et al. (2006)
		Soule et al. (2005); Tokodai et al. (2014)
		Wauters et al. (2012); Yadav et al. (2013)
Race/Ethnicity	Kidney	Bayer et al. (2010); Carter et al. (2014)
		Lane and Dagogo-Jack (2011); Luan et al. (2010)
		Palepu and Prasad (2015); Rodrigo et al. (2006)
BMI	Kidney/Liver	Carter et al. (2014); Gaynor et al. (2015)
		Kuo et al. (2010); Lane and Dagogo-Jack (2011)
		Palepu and Prasad (2015); Park et al. (2015)
		Pirsch et al. (2015); Rodrigo et al. (2006)
Cadaveric organ	Kidney/Liver	Gaynor et al. (2015); Kuo et al. (2010)
		Lv et al. (2014); Palepu and Prasad (2015)
		Park et al. (2015); Rodrigo et al. (2006)
Hepatitis C Virus	Kidney/Liver	Carter et al. (2014); Kuo et al. (2010)
		Lane and Dagogo-Jack (2011); Lv et al. (2014)
		Park et al. (2015); Rodrigo et al. (2006)
Hypertension	Kidney	Ghanta et al. (2014); Lane and Dagogo-Jack (2011)
		Luan et al. (2010); Park et al. (2015)
		Salifu et al. (2005)
Diabetes History	Kidney	Carter et al. (2014); Lane and Dagogo-Jack (2011)
		Lv et al. (2014); Rodrigo et al. (2006)
		Salifu et al. (2005)

Table 3.3: Description of Abbreviations Used in This Study

Abbreviation	**Description**
HG	Hyperglycemia
FPG	Fasting plasma glucose
HbA1c	Hemoglobin A1c
C_0	Trough level of tacrolimus
BMI	Body mass index
BP	Blood pressure
Chol	Total cholesterol
HDL	High-density lipoprotein cholesterol
LDL	Low-density lipoprotein cholesterol
TG	Triglyceride
UA	Uric acid

Table 3.4: Demographic and Baseline Characteristics of Patients at the Time of Transplant

Characteristics	**Diabetes History** (**n = 115**)	**No Diabetes History** (**n = 292**)
Age (year)	$56.0 \pm 10.4^{*}$	49.7 ± 14.6
Gender: Male (%)	61.74	56.16
Race: White** (%)	59.13	75.34
BMI (kg/m^2)	28.7 ± 5.4	27.0 ± 5.6
Donor: Live*** (%)	52.17	67.47
Pre-transplant FPG (mg/dL)	143.8 ± 52.3	92.8 ± 11.3
Pre-transplant HbA1c (%)	6.9 ± 1.5	5.5 ± 0.3
Pre-transplant UA (mg/dL)	6.3 ± 2.3	6.6 ± 2.1
Pre-transplant Chol(mg/dL)	183.0 ± 47.4	181.9 ± 46.0
Pre-transplant HDL (mg/dL)	50.6 ± 16.0	50.6 ± 16.0
Pre-transplant LDL (mg/dL)	94.2 ± 33.0	93.9 ± 34.8
Pre-transplant TG (mg/dL)	191.2 ± 94.7	179.0 ± 87.7

* mean ± standard deviation,

** versus non-white (including Native American, Hispanic, and Black races),

*** versus cadaveric.

Table 3.5: Percentage of Patients Satisfying the Criteria

Time	**Having the criteria?**							
Month 1	No	Yes	No	No	Yes	Yes	No	Yes
Month 4	No	No	Yes	No	Yes	No	Yes	Yes
Month 12	No	No	No	Yes	No	Yes	Yes	Yes
# of patients	213	20	11	1	19	3	1	24
% of patients	72.95	6.85	3.77	0.34	6.51	1.03	0.34	8.22

Table 3.6: Tacrolimus Goals and Achieved Levels (Average Trough Level) at Months 1, 4, and 12

Time point	**Tacrolimus goal**	**Tacrolimus achieved average trough level**
1 month	10-12 mg/dL	11.88 mg/dL
4 months	8-10 mg/dL	9.59 mg/dL
12 months	6-8 mg/dL	7.83 mg/dL

Table 3.7: Description of Groups Formed by Risk Factors

Risk Factors	**Unit**	**Group 0**	**Group 1**
Age	Years	<50	$\geq$ 50
Gender	—	Female	Male
Race	—	White	non-White
BMI	kg/m^2	<30 (non-obese)	$\geq$30 (obese)
BP	—	Normal	Hypertension
Chol	mg/dL	<200	$\geq$200
HDL	mg/dL	$\geq$40	<40
LDL	mg/dL	<130	$\geq$130
TG	mg/dL	<150	$\geq$150
UA	mg/dL	<7.3	$\geq$7.3

Table 3.8: Effect of Immunosuppressive Drugs on Hyperglycemia: The Results of Two Statistical Inference Methods (Numbers in Bold Represent Statistically Significant Covariates at 95% Confidence Level).

Covariates	**Part I: Time-dependent**				**Part II: Time-independent**			
	Mean HR	**Lower CI**[a]	**Upper CI**	**P-value**[b]	**Mean HR**	**Lower CI**	**Upper CI**	**P-value**
Simulect[c] (unadj[e])	0.51	0.274	0.953	**0.035**	0.655	0.299	1.437	0.291
Simulect (adj[f])	0.267	0.131	0.543	**0.000**	0.444	0.190	1.036	0.060
Thymoglobulin[c] (unadj)	0.68	0.480	0.950	**0.025**	0.645	0.401	1.038	0.071
Thymoglobulin (adj)	0.658	0.458	0.947	**0.024**	0.640	0.388	1.055	0.080
Avg. C_0 (unadj)	0.993	0.859	1.147	0.924	1.949	1.793	2.120	**0.000**
Avg. C_0 (adj)	0.992	0.859	1.146	0.912	1.982	1.788	2.197	**0.000**
Tacrolimus[d] (unadj)	0.922	0.434	1.963	0.834	1.285	0.470	3.512	0.625
Tacrolimus (adj)	0.689	0.297	1.601	0.387	1.156	0.397	3.370	0.790
Sirolimus[d] (unadj)	1.329	0.655	2.694	0.431	0.834	0.305	2.279	0.723
Sirolimus (adj)	1.786	0.852	3.745	0.124	0.810	0.280	2.344	0.697
Steroid[d] (unadj)	1.230	0.894	1.691	0.204	1.248	0.803	1.939	0.325
Steroid (adj)	1.562	1.131	2.158	**0.007**	1.441	0.900	2.305	0.128

[a] 95% confidence interval,

[b] P-values are obtained based on standard Normal distribution,

[c] An immunosuppressive agent: Induction therapy,

[d] An immunosuppressive agent: Maintenance therapy,

[e] Unadjusted (univariate) analysis,

[f] All adjusted analyses were done based on age, race, gender, BMI, BP, Chol, HDL, LDL, UA, and TG.

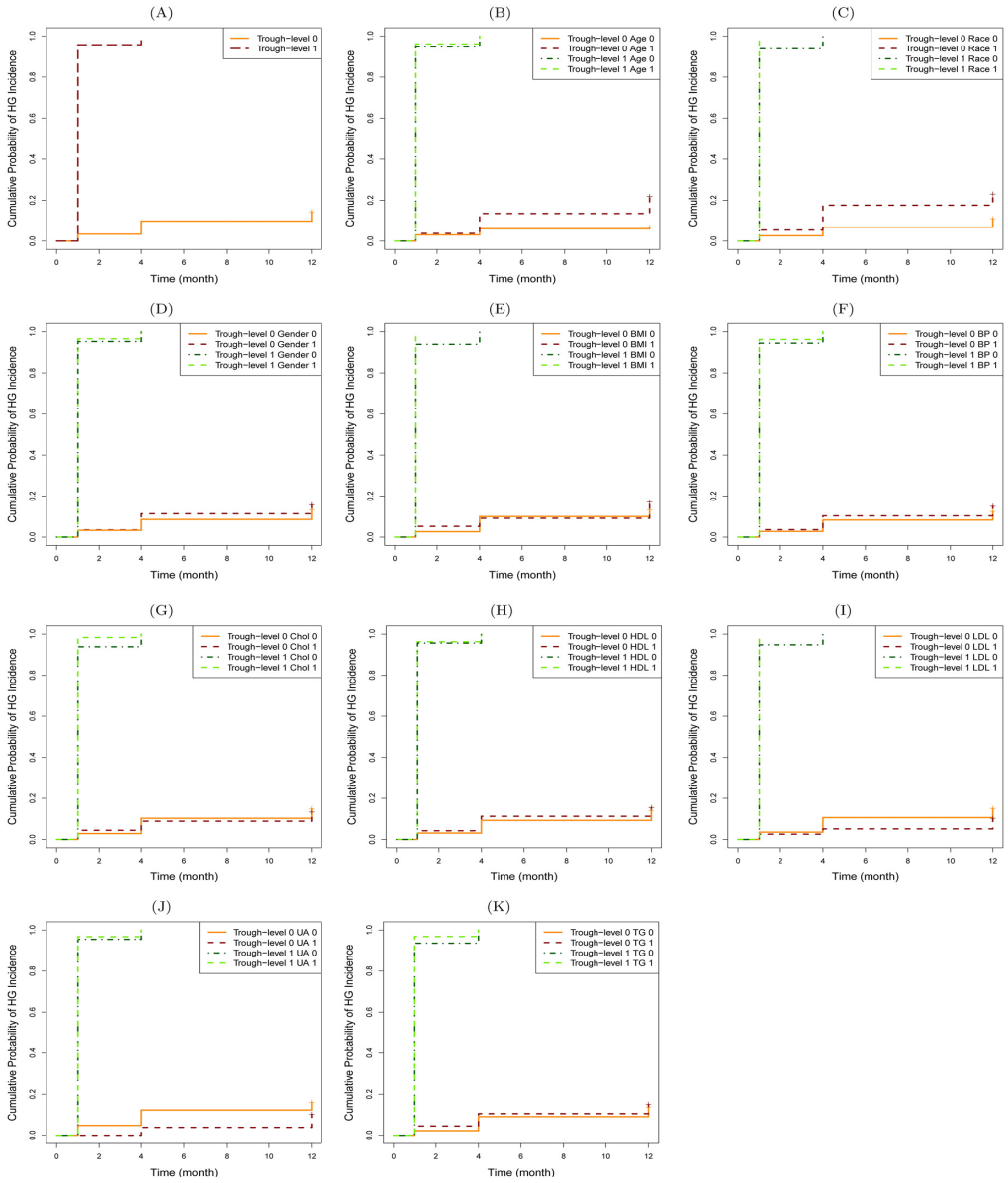


Figure 3.2: Kaplan-Meier Survival Curves: Cumulative Probability of Experiencing Hyperglycemia (%) as a Result of Having Different Average Trough Levels of Tacrolimus: ≤10 mg/dL vs. >10 mg/dL. In All Parts (A)-(K), P-Value <0.0001 by the Logrank Test. (+ Represents Censored Events.) (A) Unadjusted (Univariate) Analysis; (B)–(K) Are Adjusted Analysis with Age, Race, Gender, BMI, BP, Chol, HDL, LDL, UA, and TG, Respectively.

Table 3.9: Risk Factors That Affect the Incidence of Hyperglycemia

Risk Factors	**Part I: Time-dependent**				**Part II: Time-independent**			
	Mean HR	**Lower CI***	**Upper CI**	**P-value****	**Mean HR**	**Lower CI**	**Upper CI**	**P-value**
Age	1.044	1.031	1.056	**0.000**	1.022	1.004	1.040	**0.018**
Race: Non-White***	1.769	1.234	2.536	**0.002**	1.195	0.707	2.019	0.506
Gender: Male	1.108	0.738	1.661	0.621	1.105	0.658	1.854	0.706
BMI	1.048	1.017	1.079	**0.002**	0.976	0.932	1.023	0.314
BP	1.001	0.987	1.015	0.903	0.996	0.979	1.014	0.672
Chol	1.001	0.995	1.008	0.699	1.007	0.998	1.015	0.133
HDL	0.976	0.960	0.992	**0.003**	0.972	0.950	0.993	**0.010**
LDL	0.995	0.987	1.003	0.204	0.997	0.986	1.007	0.509
UA	0.833	0.722	0.961	**0.012**	0.829	0.680	1.010	0.063
TG	1.002	1.000	1.004	0.145	1.002	0.999	1.004	0.206

* 95% confidence interval,

** P-values are obtained based on standard Normal distribution,

*** Including Native American, Hispanic, and Black.

Table 3.10: Effect of Inpatient Period on Hyperglycemia Incidence

Inpatient	**Part I: Time-dependent**				**Part II: Time-independent**			
Parameters	**Mean HR**	**Lower CI**[a]	**Upper CI**	**P-value**[b]	**Mean HR**	**Lower CI**	**Upper CI**	**P-value**
bed.avg[e] (unadj[c])	1.029	1.024	1.035	**0.000**	1.023	1.013	1.032	**0.000**
bed.avg (adj[d])	1.024	1.018	1.030	**0.000**	1.018	1.008	1.029	**0.000**
blood.avg[f] (unadj)	1.031	1.023	1.038	**0.000**	1.022	1.011	1.033	**0.000**
blood.avg (adj)	1.024	1.016	1.032	**0.000**	1.018	1.007	1.030	**0.002**
in.hyp[g] (unadj)	3.509	1.557	7.908	**0.002**	2.162	0.874	5.347	0.095
in.hyp (adj)	2.496	1.080	5.768	**0.032**	1.543	0.613	3.885	0.358

[a] 95% confidence interval,

[b] P-values are obtained based on standard Normal distribution,

[c] Unadjusted (univariate) analysis,

[d] All adjusted analyses were done based on age, race, gender, BMI, BP, Chol, HDL, LDL, UA, and TG,

[e] Average bed glucose result,

[f] Average blood glucose result,

[g] Inpatient hyperglycemia.

Chapter 4

MACHINE LEARNING FOR THE OPIOID PRESCRIPTION AND ABUSE EPIDEMIC

4.1 Introduction

According to the Centers for Disease Control and Prevention (CDC), a total of 47,055 drug-related deaths ocurred in 2014, among which opioid analgesics were the main contributing factor accounting for 18,893 deaths (40% of total deaths). These opioid painkillers may ultimately result in heroin addiction/overdose,[1] which caused additional 10,574 deaths in the same year (CDC, 2015). In addition, the societal costs of opioid prescription abuse in the U.S. can get up to $78.5 billion (including healthcare cost, workplace cost, and criminal justice cost) (MedlinePlus.gov, 2016), and almost 2 million people are estimated to be dependent on prescription opioids or abusing them (USA Today, 2016). All these factors have prompted CDC to call this problem an epidemic.[2]

During the same period that opioid/heroin-related deaths soared up from 5,990 (in 1999) to 29,467 (in 2014) (i.e., a 492% increase), the sales of prescription opioids have been quadrupled (CDC, 2016). A part of this increased sale befitted the ever-growing urge for more opioid prescription in 1990s, and the fact that opioid therapies for chronic pain was perceived to be efficient while imposing a low risk of addiction (CNN, 2016b). However, this trend headed in a wrong direction by overprescription of opioid painkillers: "*As of 2011, 75% of the world's opioid prescription drugs are*

[1] 80% of heroin users are originally prescription drug users (DEA, 2015).

[2] The Obama administration proposed a $1.1 billion bill in 2016 to fight this epidemic (whitehouse.gov, 2016).

prescribed and swallowed up in a country that makes up less than 5% of the world's population, leading to the most common cause of unintentional death in America today – drug overdoses." (CNN, 2016a)

To address this issue, CDC proposed a set of guidelines for prescribing opioids for chronic pain (Dowell et al., 2016), which mainly focus on reducing the strength or duration of supply for these medications. However, as mentioned by the American Medical Association (AMA), some of these guidelines may not reflect the existing evidence (AMA, 2016a): *"[. . .] while the AMA supports many of the recommendations, we continue to have serious concerns that some either contain a degree of specificity not supported by the existing evidence or conflict with official Food and Drug Administration (FDA)-approved product labeling for opioid analgesic products."* More importantly, these guidelines make very general recommendations for prescribing opioid painkillers, leaving the ultimate prescription decision up to a provider/physician (Dowell et al., 2016): *"Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient."* Despite the clear intuition behind this strategy, the extent where potential benefits of these medications would be comparable to their side effects/risks is not completely known.

We aim to explore evidence for the trade-off between benefits and risks of using opioid painkillers. To this end, we utilize *Commercial Insurance and Medical Claims* data, which contains the history of medical encounters and prescribed medications for millions of patients over a three-year period. Employing some machine learning algorithms, we make statistical inference about whether or not there exist associations between benefits/risks and (1) using opioid painkillers, (2) using non-opioid painkillers, and (3) duration of supply. Furthermore, we make this inference in the presence of different patient's characteristics, which include (1) demographics (e.g.,

age and gender), (2) behavioral risk factors (e.g., history of alcohol consumption, smoking, mental disorder, and substance abuse), and (3) route of encounter (e.g., inpatient vs. outpatient).

The contributes of our study to the medical literature are two-fold: (1) we characterize the efficiency of pain medications (in managing pain) through three different notions,[3] and show how these characterizations would impact the trade-off between risks and benefits of prescribing opioids. (2) We employ novel machine learning algorithms that are very capable in predicting risks of using (or not using) opioids based on several demographic/clinical/behavioral characteristics of patients.

The rest of the chapter is organized as follows. In §4.2, we provide a literature review. In §4.3, we discuss the data and the design of our problem. In §2.5.2, we present numerical results obtained from our machine learning algorithms, and in §4.5 I conclude the chapter and discuss the next steps for this research.

4.2 Related Literature

Prescription of Opioid Painkillers and Prediction of Side Effects. Cochran et al. (2014) analyze different risk factors that are associated with the incidence of opioid abuse or diagnosis of opioid dependence (by comparing these patients with those who do not experience such events). They find that age, gender, duration of supply, filling prescriptions at multiple pharmacies, and history of mental health disorders would contribute to these events. Liang and Turner (2015) use a Cox proportional hazard model (i.e., survival analysis) to establish statistical associations between time from the first opioid prescription until the first overdose and strength of prescribed opioid. They also adjust their model based on confounding factors, including age,

[3]If (1) at least one encounter, (2) the majority of encounters, or (3) all encounters is/are due to an unresolved pre-existing medical condition.

gender, pain-related symptoms, history of mental illness, and drug abuse. Ciesielski et al. (2016) use a multivariate logistic regression to measure the likelihood of developing opioid dependence or abuse with respect to demographic, physiological or behavioral risk factors: high dose of opioid, age, history of mental illness, alcohol abuse, and smoking are among factors that are stochastically associated with opioid abuse or dependence. Dasgupta et al. (2016) conduct a prospective (observational) study to analyze the impact of prescribed opioids (in different daily dose thresholds) on overdose death. Worley et al. (2015) take a different approach in addressing the opioid epidemic. They utilize the concept of drug reinforcement values from the behavioral economics literature (e.g., time and money spent on obtaining these drugs), and establish an association with whether or not patients acquire these drugs from standard sources (e.g., physicians) (for broader discussions in this regard, see references therein). Finally, for reviews of studies that have analyzed the prescription of opioid painkillers and their impact on developing addiction, drug dependence, or incidence of overdose/death, one can refer to Fishbain et al. (2007) and Nuckols et al. (2014).

Machine Learning for Opioid Risk Assessment. While the above-mentioned studies mainly utilize conventional methods of statistical analyses, there also exist a new body of literature applying machine learning algorithms to address the opioid epidemic from different angles. Haller et al. (2016) employ Natural Language Processing (NLP) techniques to develop a risk assessment tool for predicting risks of drug abuse/addiction before a prescription is written. They also adjust this tool with respect to confounding factors such as age, history of drug abuse, and psychological disorders (see Lingeman et al. (2017) for another application of NLP in the opioid epidemic). Che et al. (2017) adopt two types of neural network models (i.e., Deep Feed-Forward Neural Network (DNN) and Recurrent Neural Network (RNN))

to make predictions (i.e., classification) about the possibility of becoming a long-term opioid user, and how these users are clinically diagnosed to be dependent on these medications. They also compare these methods with other algorithms (including logistic regression, support vector machine, and random forest) to show the classification/prediction power that can be attained by employing deep learning algorithms. Crosier et al. (2017) use random forests to predict the possibility of having an opioid overdose. They find that any record of criminal history and number of overdose incidents in a patient's insurance network are strong predictors for an opioid overdose. Vunikili et al. (2018) utilize an Extreme Gradient Boosting (XGBoost) algorithm along with a logistic regression to not only predict the risk of opioid abuse, overdose, and death, but also account for interactions of different opioid-related painkillers. For an illustration of different machine learning algorithms and their applications in healthcare problems, one can refer to Deo (2015).

Impact of Emergency Department and Hospital Admission. Although the epidemic of opioid prescription is mainly attributed to primary care providers, two other factors also play critical roles in this problem: emergency department visits and post-operation pains. Regarding the former, Barnett et al. (2017) address the high variability of opioid prescription rates by physicians when patients have a visit to the emergency department (ED) within a hospital. By measuring the relative quartiles of the prescription rates, they categorize low-density and high-density opioid prescribers, and show how these two categories would result in different rates of long-term opioid use for patients (even after an ED discharge). Addressing a broader perspective, Poon and Greenwood-Ericksen (2014) shed light on the role of emergency medicine physicians in this epidemic, how they can take advantage of prescription drug monitoring programs (PDMP) database in managing their prescriptions, and how residency education should provider training for these physicians in utilizing

PDMPs. Axeen et al. (2018) compare the opioid prescription rates in EDs with those in office visits (i.e., non-ED). They surprisingly find that, over a period of seventeen years, office-based prescriptions have had an increasing trend, while ED-based prescriptions have been on a decline. For some other works that study the impact of ED visits on opioid prescription, dependence, and abuse, one can refer to Braden et al. (2010), Mazer-Amirshahi et al. (2014), Chacko et al. (2017), Lynch and Yealy (2018)

In addition, treatment of post-surgical pains with opioid is reported to be another cause for the onset of opioid addiction: as many as seven million patients in the U.S. are in danger of post-operation opioid dependence/addiction (ASER, 2016). For studies showing that opioid prescription during hospital stay is associated with long-term opioids usage after hospital discharge, one can refer to Pletcher et al. (2008), Calcaterra et al. (2016), and Jena et al. (2016).

Measuring Pain and Efficacy of Pain Management. As noted earlier, the main objective of our study is to address the trade-off between risks/side effects and potential benefits of opioid painkillers. In §4.3, we demonstrate how we characterize the efficacy of using these medications based on type and frequency of diagnoses made by providers. Nevertheless, we provide a brief review of extant literature on methods developed to measure efficacy of pain management strategies. Ong et al. (2005) conduct a meta-analysis of studies that have explored the impact of five different medication interventions on pain management for patients after surgical operations. Nalamachu (2013) review studies that have evaluated the efficacy and side effects of three medication modes for pain management. They further break down these studies based on underlying types of pain (e.g., post-operative, back, migraine, etc.) (see also Martell et al. (2006) for a review of studies on chronic back pain). For reviews of clinical, physiological, and laboratory-based methods for measuring pain,

one can refer to Huskisson (1974) and Chapman (1985).

4.3 Data and Problem Design

The data we use in this study comes from the IBM MarketScan Research Database of commercial claims and encounters (CCAE) for 2008-2010. The CCAE database contains several data tables, including (1) inpatient admissions (Table I), (2) inpatient services (Table S), (3) outpatient services (Table O), (4) outpatient pharmaceutical claims (Table D), (5) drugs information (Table R), and (6) annual insurance enrollment of patients (Table A). In Appendix B.1, we describe some of the most important variables in these data tables (see Table B.1).

4.3.1 Information of Utilized Drugs

In this study, we not only analyze opioid painkillers, but also take non-opioid analgesics into consideration so as to properly address the efficacy of pain medications. To this end, we retrieve 20 different opioids and 33 different non-opioids from our data (see Table B.2 in §B.1). It should be noted that some of these opioids/nonopioids could be used in a same drug. For example, "Acetaminophen/propoxyphene" with strength 325MG-50MG is a drug, where "propoxyphene" ("Acetaminophen") is an opioid (nonopioid) with the strength of 50 (325) milligram.

Furthermore, we break down the strength of opioid analgesics by using the *Morphine Milligram Equivalent* (MME) that transforms the strength of any opioid painkiller to a common measure (see Palliative Drugs (2009) and CMS (2018) for more details about the MME conversion rates).

4.3.2 Patients Inclusion Criteria

As noted earlier, the information of (1) patients' prescription history and (2) their inpatient/outpatient encounters is provided in different data tables. Thus, we need to merge these tables to link such encounters to corresponding prescriptions. To this end, we apply the following inclusion criteria for selecting patients (i.e., a patient whose case does not apply to this criteria is excluded from our analysis):

(1) Full enrollment in 2008-2010 (i.e., 36 months).

(2) No history of cancer.[4]

(3) At least one episode of an opioid analgesic supply (with number of refills ≥ 1), where an opioid analgesic is selected from Table B.1 (see §B.1).

(4) No history of opioid side effects (i.e., abuse, overdose, death, etc.) within the first 90 days of 2008 (as the beginning of data time frame).

(5) No analgesic supply (opioid or non-opioid) within the first 90 days of 2008.

(6) No analgesic supply (opioid or non-opioid) before the first registered encounter.

Regarding criterion (4), if, for example, an overdose occurs, we must know which medications the patient has used prior to that incidence. We consider the 90-day time span to account for medications that would have significant impacts on this incidence. Furthermore, regarding criterion (5), we aim to link an analgesic prescription to a potential medical condition (because of which that prescription was made in the first place). Similar to criterion (4), we consider the 90-day time span for this purpose.[5]

[4]We use the following terms for tracking cancer-related cases: cancer, neoplasm, malignant, malignancy, benign, carcinoma, and palliative.

[5]After applying all these inclusion criteria, there exist a total of 1,203,439 patients in our data.

Now, we explain the independent variables that we use in this study along with our outcome (dependent) variables. Prior to that, we need the following definition.

Definition 4.3.1 (Time Window) *A time window is a T-day period starting from the beginning of the first opioid supply. In this study, we consider three different thresholds (i.e., $T \in \{30, 90, 180\}$ days). Note that T is different from the 90-day threshold we use in the inclusion criteria.*

We note that a patient may be prescribed with medications multiple times, such that the time range of his/her drug supplies is spanned over several months/years. Therefore, to account for multiple drug supplies, we increase the time window (introduced in Definition 4.3.1) by 1 after every T days (this is the case for only those patients with multiple drug supplies).

4.3.3 Independent Variables

In this study, we consider the following independent variables:

(1) Prescription-related variables in a time window: adjusted strength of opioids (in MME), adjusted strength of non-opioids (in milligram or MG), and total duration of supply. We shows how to measure these three variables by Example 4.3.1. Also, Table 4.1 shows the average and standard deviation of these variables obtained from our data under different time windows.

Example 4.3.1 *Suppose in a 90-day time window, a patient has two episodes of supply: the first supply with 10 days, opioids MME = 50, and non-opioids MG = 100, and the second supply with 25 days, opioids MME = 20, and non-opioids MG = 60. Then, we have:*

Table 4.1: Average of Adjusted Strengths and Duration of Supply under Different Time Windows (Numbers in Parenthesis Represent Standard Deviation)

Variable	**Window (days)**		
	30	**90**	**180**
Adjusted strength opioids (MME)	8.598 (23.05)	11.387 (27.106)	12.142 (28.489)
Adjusted strength non-opioids (gram)	0.567 (1.368)	0.758 (1.682)	0.812 (1.793)
Total duration of supply (days)	9.933 (9.947)	16.813 (20.723)	19.862 (30.299)

Adjusted strength of opioids $= (10 * 50 + 25 * 20)/(10 + 25) = 28.57$ MME,

Adjusted strength of non-opioids $= (10 * 100 + 25 * 60)/(10 + 25) = 71.43$ MG,

Total duration of supply $= 10 + 25 = 35$ days.

(2) Demographic factors: age and gender.[6]

(3) Behavioral issues with a history along with each of the following factors: alcohol consumption, smoking, substance drug abuse, non-substance drug abuse, and mental disorders. We identify these factors via two routes: (1) a diagnosis made (by using *The International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM codes)) and (2) types of drugs prescribed for addressing these issues (by using the therapeutic class in the CCAE data). In Tables B.3-B.4 in §B.1, we provide a list of corresponding ICD-9-CM codes and related drugs utilized for this purpose.

(4) Type of the first encounter: inpatient versus outpatient.

(5) History of using non-opioid analgesics before the first opioid supply.

[6]The CCAE data does not include information on race.

Based on this premise, we have three main independent (prescription-related) variables and nine other variables (i.e., confounding factors used for adjusting the foregoing three variables). In Table 4.2, we show the summary of these confounding factors.

Furthermore, since the duration of each supply is used to calculate the strengths of opioids/non-opioids, we obtain the coefficient of correlation $\rho \in [-1, 1]$ between the total duration of supply and adjusted strengths of opioids and non-opioids, such that $\rho \to 1$ (-1) represents a positive (negative) linear relationship, whereas $\rho \to 0$ would imply no relationship. Figure 4.1 shows the plots of adjusted strengths of opioids and non-opioids against total duration of supply based on time window of 90 days. As can be observed, for the relationship between duration of supply and adjusted strength of opioid (non-opioid), $\rho = -0.062$ (-0.068). Since both of these coefficients are very close to 0, it would be reasonable to assume no correlation between these variables.

4.3.4 Dependent Variables

In order to address the trade-off between side effects and potential benefits of opioid analgesics, we analyze two event types.

Definition 4.3.2 (Event Type 1: Opioid Side Effects) *We say event type 1 has occurred if, in a time window, there is at least one incidence of (1) poisoning, (2) abuse, (3) dependence, or (4) any adverse effect caused by an opioid or heroin. We use the ICD-9-CM codes in the primary diagnosis to identify such incidence (see Table B.5 in §B.1 for the list of these codes).*[7]

Regarding Definition 4.3.4, we note that these are high-risk events. Thus, even if

[7]In the CCAE data, there are up to 15 diagnoses in Table I and up to 2 diagnoses in Table O. However, we only consider information related to the primary diagnosis to avoid any under-/over-fitting.

they happen only once, they could be very detrimental to a patient. Therefore, we differentiate between no incidence and at least one incidence of such events.

Next, we present the following definition, which lays the foundation for characterizing the second event type, which is related to the potential benefits of opioids. To this end, we identify the medical condition due to which an opioid was prescribed in the first place, consider a time period of X days prior to the first opioid supply, and monitor all encounters in this X-day period. To estimate X, we use the 95th percentile of number of days between all encounters prior to the first supply and that supply (based on the CCAE data, we estimate that $X = 35$ days).

Definition 4.3.3 (Baseline Medical Condition) *A patient is said to have a baseline medical condition if, among all encounters in an X-day period prior to the first opioid supply, the majority (i.e., at least 50%) of primary diagnoses pertains to that medical condition.*

Definition 4.3.4 (Event Type 2: Benefits of Pain Medications) *Let C_B be the baseline medical condition introduced in Definition 4.3.3, and C_n represent the medical condition in time window $n \geq 1$. Then, we say that event type 2 has occurred (in time window n) if $C_n = C_B$. Thus, we set*

$$\text{Event Type 2 (in window } n) = \begin{cases} 1, \text{ if } C_n = C_B, \\ 0, \text{ if } C_n \neq C_B. \end{cases} \tag{4.1}$$

A value of 1 for Event 2 in a time window means that the baseline medical condition still exists (i.e., not resolved) in that window. Hence, Event 2 = 0 implies the benefits of using pain medications, whereas Event 2 = 1 implies the opposite. The

Table 4.2: Characteristics of Patients Based on Confounding Factors (1,203,439: Total Number of Patients after Applying Inclusion Criteria; Numbers in Parenthesis Represent Standard Deviation)

Characteristic	**Value**
Age	40.84 (15.46)
Gender (female)	695,264/1,203,439 = 57.77%
History: mental disorder	405,714/1,203,439 = 33.71%
History: smoke	26,123/1,203,439 = 2.17%
History: alcohol	6,528/1,203,439 = 0.54%
History: substance abuse	1,744/1,203,439 = 0.14%
History: non-substance abuse	1,282/1,203,439 = 0.11%
History: non-opioid use	99,186/1,203,439 = 8.24%
First encounter: inpatient	2,744/1,203,439 = 0.23%

way C_n is defined (i.e., the medical condition in window n) would play a critical role in Equation (4.1). We consider three scenarios for defining C_n.

Definition 4.3.5 (Scenarios for C_n) *There are three scenarios for defining C_n:*
Scenario I: C_n refers to the primary diagnosis for any encounter (i.e., at least once).
Scenario II: C_n refers to the primary diagnosis for the majority of encounters.
Scenario III: C_n refers to the primary diagnosis for all encounters.

Incorporating these three scenarios in Equation (4.1) would have different clinical implications about the benefits of using pain medications. Under scenario I, a patient must have at least one encounter (with the primary diagnosis being the same as the baseline medical condition), so that the medications used in that time window are not deemed as effective. However, under scenario II (III), the majority (all) of encounters in a window must be related to the baseline condition to yield the same outcome.

Therefore, scenario I (III) characterizes the most (least) restrictive notion of benefits of pain medications. In this study, we obtain our results based on scenario II, and leave scenarios I/III as future steps of this research.

4.4 Numerical Results

4.4.1 Statistical Analysis

We use three machine learning methods to predict the incidence of type 1 and 2 events (see Definitions 4.3.2-4.3.4 for these two events). These methods include: (1) logistic regression, (2) random forest, and (3) recurrent neural networks. In this study, we show the results for the first two methods, and leave the latter as a future step of this research. These methods are typically established for *cross-sectional* studies (i.e., where patients' records are registered at only one point in time). However, in our study, we aim to monitor the prescription of painkillers (and their influence on patients' outcomes) over time (i.e., *longitudinal* study). Therefore, we employ some variants of these methods: *Generalized Estimating Equations Logistic Regression* (GEE Logit) (Wilson and Lorenz, 2015) and *Mixed-Effects Random Forest* (MERF) (Hajjem et al., 2014).

4.4.2 Results and Comparison of Methods

In this section, we present the results that we obtain from the above-mentioned methods. In particular, we show associations between incidence of type 1 and 2 events and our independent variables in Tables 4.3-4.4 in Appendix B.1. We note that the random forest method is not suitable for statistical inference. Instead, it is a very powerful approach for prediction/classification. Therefore, here, we only present the results for the logistic regression method. Later, we will compare the classification

performance of these methods. Based on results in Tables 4.3-4.4, we present the following observations.

Observation 4.4.1 (Event 1) *(i) Higher incidence of type 1 event (i.e., observing opioid side effects such as abuse, overdose, etc.) is associated with the following factors: younger age, male patients, history of mental disorder, history of alcohol consumption, history of smoking, and history of substance abuse. (ii) Patients with the following characteristics have higher risk of experiencing event 1: no history of using non-opioid painkillers before their first opioid supply, the first encounter being in an outpatient (rather than inpatient) setting, longer supply of pain medications, and prescribed by higher (lower) strength of opioids (non-opioids). (iii) Among all risk factors, history of mental disorder, history of alcohol consumption, and history of any non-substance abuse would have the highest impact on the incidence of event 1. (iv) Increasing the length of time window (from 30 to 180 days) would not change the type of associations between risk factors and the incidence of event 1.*

Observation 4.4.2 (Event 2) *Inefficiency of pain medications is associated with female patients, having history of mental disorder and smoking, history of using non-opioid painkillers before the first opioid supply, and the first encounter being in an inpatient setting.*

Regarding Observation 4.4.2, we also note that inefficiency of pain medications is not associated with the history of alcohol consumption and or substance abuse. Furthermore, longer supplies of pain medications and stronger opioids do not result in more efficiency in managing pain. Of note, these results are obtained based on scenario II (see Definition 4.3.5). As mentioned before, as future steps of this research, we intend to run our results based on scenarios I/III as well. Similar to the case for

event 1, our results show that increasing the time window (from 30 to 180 days) would not typically alter the type associations between risk factors and the outcome.

Finally, we compare the classification power of the two methods we use in this study. We do this by performing a 10-fold cross-validation, where for each fold, we train our method by using almost 90% of our data, and then test the trained method on the remaining part (10%) of the same data. Figure 4.2 shows the *Receiving Operating Characteristic* (ROC) curves for these two methods when we implement them for time windows of 90 and 180 days. The area under the curve (AUC) in these ROC curves is indicative of the classification power, where a higher AUC represent a better method. We note that random forests are among machine learning algorithms that typically result in a better classifications compared to more traditional methods such as logistic regression. However, as illustrated in Figure 4.2, the performance of logistic regression is comparable to that of random forest. One reason for this observation is the size of trees in the random forest which is set as 50.[8]

4.4.3 Correlation Between Observations

In longitudinal data, there may exist correlation between consecutive observations (e.g., strengths of opioid in two consecutive time windows). Therefore, we aim to explore these correlations by means of autocorrelation functions. Figure 4.3 shows these functions plotted for the duration of supply (days), strength of opioids (MME), and strength of non-opioids (gram), where the time window is 30 days. Based on Figure 4.3, for all of these three variables, one can observe that:

- The autocorrelation function (ACF) has exponential decays,
- The partial autocorrelation function (PACF) cuts off after lag 1, and

[8]Due to the size of our data, we could not run the algorithm for higher number of trees (e.g., 100 or 500).

- The inverse autocorrelation function (IACF) cuts off after lag 2.

Therefore, it would be reasonable to assume an autoregressive of order 2 (i.e., AR(2)) for the correlations between consecutive observations for the above-mentioned three variables (see, e.g., Montgomery et al. (2015) for a detailed discussion about autocorrelation functions).

4.5 Conclusion

To address the epidemic of opioid prescription and abuse, the CDC proposed some guidelines with the main focus being on reducing the strength or duration of supply for these medications. However, some of these guidelines may not reflect the existing clinical evidence, or may be very general for prescribing opioid painkillers. We attempt to contribute to this stream by addressing potential benefits of opioid medications compared to their side effects/risks. In particular, we explore evidence for a potential trade-off between benefits and risks of using opioid painkillers. To this end, we utilize data from commercial insurance and medical claims, which contains the history of medical encounters and prescribed medications for millions of patients over a three-year period. Employing machine learning algorithms (Generalized Estimating Equations Logistic Regression and Mixed-Effects Random Forests), we make statistical inference about whether or not there exist associations between benefits/risks and (1) using opioid painkillers, (2) using non-opioid painkillers, and (3) duration of supply. Furthermore, we make this inference in the presence of different patient's characteristics, including demographical and behavioral risk factors.

Our results show that younger age, being male, history of mental disorder, history of alcohol consumption, history of smoking, and history of substance abuse are associated with higher risk of opioid's side effects (e.g., abuse, overdose, etc.). Also, patients with the following characteristics have higher risk of experiencing side ef-

fects: no history of using non-opioid painkillers before their first opioid supply, the first encounter being in an outpatient (rather than inpatient) setting, longer supply of pain medications, and prescribed by higher (lower) strength of opioids (non-opioids). Furthermore, regarding the efficiency of pain medications, our results show that lack of efficiency is associated with female patients, having history of mental disorder and smoking, history of using non-opioid painkillers before the first opioid supply, and the first medical encounter being in an inpatient setting. We also note that longer supplies of pain medications and stronger opioids do not result in higher efficiency in managing pain.

Finally, as future steps of this research, we aim to implement another machine learning algorithm (*Recurrent Neural Network*) as a more powerful classification method, and compare its results with the current two methods (logistic regression and random forest). We will also explore other characterizations of pain medications efficiency in addressing the trade-off between risks and benefits of pain medications (see scenarios I/II/III in Definition 4.3.5).

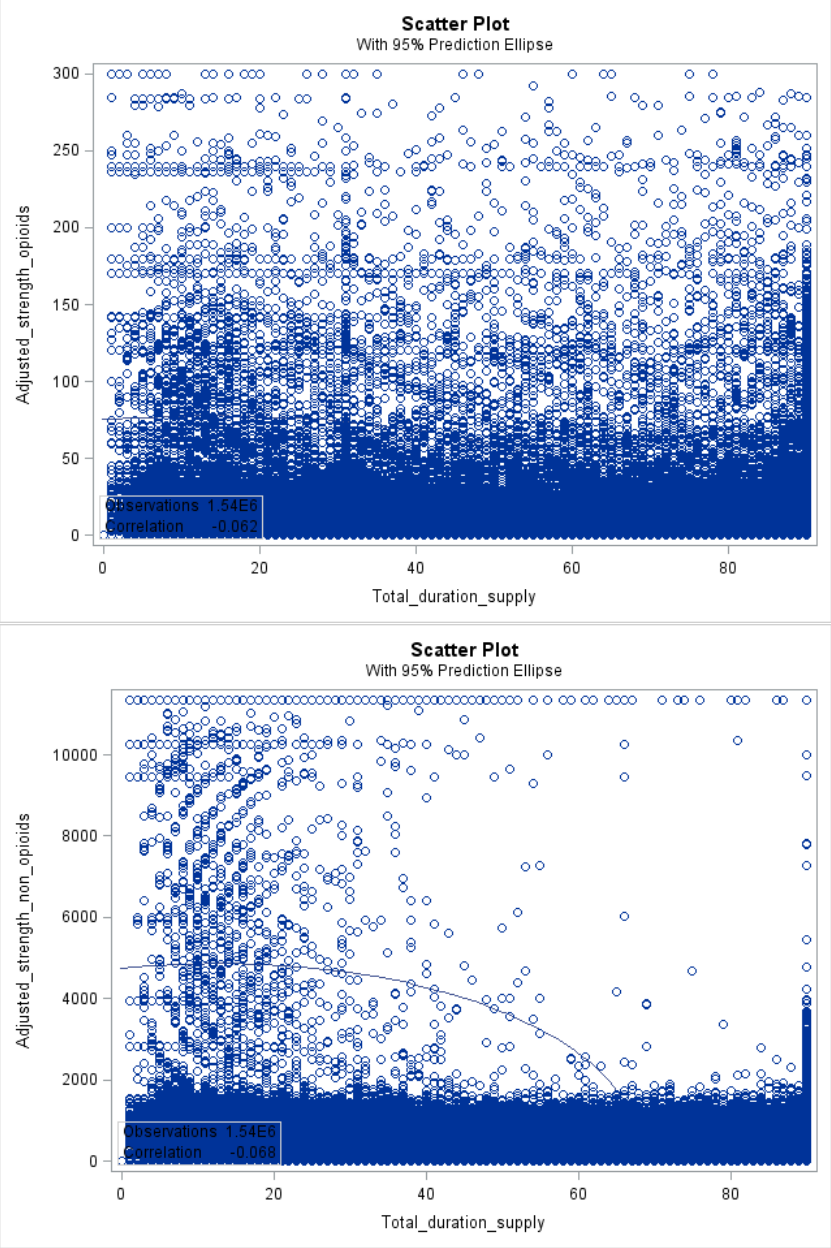
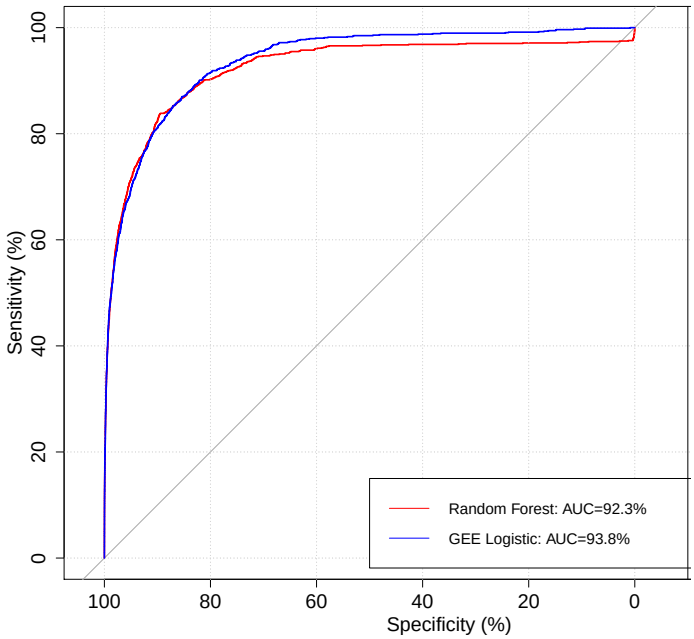
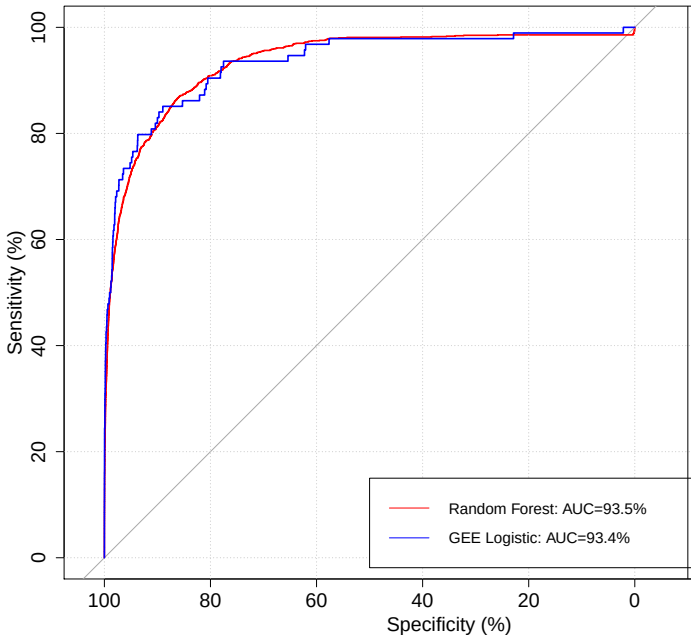


Figure 4.1: Plots of Adjusted Strengths of Opioids and Non-Opioids Against Total Duration of Supply Based on a Time Window of 90 Days (Pearson Correlation Coefficients Are Statistically Significant with P-Value <.0001; Opioid (Non-Opioid) Strengths Are in MME (MG)).



(a) Event 1: window 90



(b) Event 1: window 180

Figure 4.2: ROC Curves for Different Methods for Time Window of 90 Days (AUC: Area under the Curve).

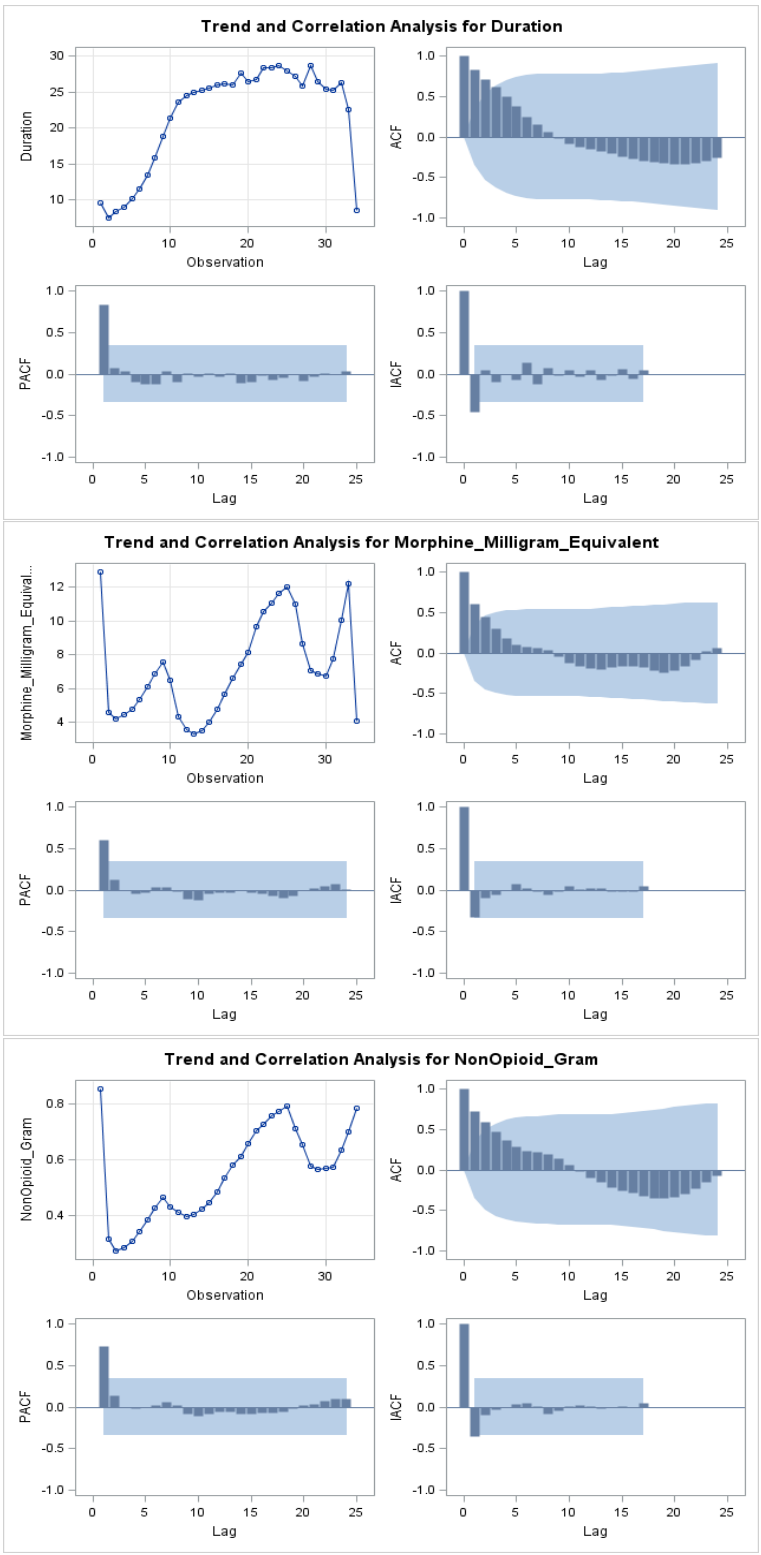


Figure 4.3: Autocorrelation Function Plots (ACF: Autocorrelation Function; PACF: Partial Autocorrelation Function; IACF: Inverse Autocorrelation Function)

Table 4.3: Results from GEE Logit Method: Incidence of Type 1 Event
(OR CI: Odds Ratio 95% Confidence Interval; P-value $\leq .05$ Represents a Significant Statistical Association)

Variable	**Window (days)**					
	30		**90**		**180**	
	OR CI	P-value	OR CI	P-value	OR CI	P-value
Age	(0.946,0.958)	<.0001	(0.949,0.958)	<.0001	(0.953,0.961)	<.0001
Gender (female)	(0.371,0.548)	<.0001	(0.464,0.626)	<.0001	(0.478,0.617)	<.0001
History: mental disorder	(28.902,59.045)	<.0001	(24.839,48.439)	<.0001	(29.669,56.906)	<.0001
History: smoke	(1.423,3.642)	0.0006	(1.338,2.760)	0.0004	(1.238,2.322)	0.001
History: alcohol	(4.455,8.471)	<.0001	(4.710,7.815)	<.0001	(4.644,7.077)	<.0001
History: substance abuse	(1.324,3.375)	0.0017	(2.213,4.616)	<.0001	(2.506,4.642)	<.0001
History: non-substance abuse	(13.158,26.991)	<.0001	(13.514,23.507)	<.0001	(15.186,24.254)	<.0001
History: non-opioid use	(0.397,0.765)	0.0004	(0.481,0.809)	0.0004	(0.528,0.847)	0.0008
First encounter: inpatient	(0.230,1.615)	0.3193	(0.288,2.168)	0.6469	(0.385,2.237)	0.867
Total duration of supply	(1.078,1.093)	<.0001	(1.026,1.031)	<.0001	(1.015,1.017)	<.0001
Adjusted strength opioids	(1.006,1.0105)	<.0001	(1.008,1.012)	<.0001	(1.010,1.013)	<.0001
Adjusted strength non-opioids	(0.198,0.506)	<.0001	(0.220,0.617)	0.0001	(0.229,0.626)	0.0002

Table 4.4: Results from GEE Logit Method: Incidence of Type 2 Event
(OR CI: Odds Ratio 95% Confidence Interval; P-value $\leq$ .05 Represents a Significant Statistical Association)

Variable	**Window (days)**					
	30		**90**		**180**	
	OR CI	P-value	OR CI	P-value	OR CI	P-value
Age	(0.994,1.003)	0.4874	(0.998,1.003)	0.6202	(1.002,1.002)	<.0001
Gender (female)	(0.773,0.9015)	<.0001	(0.809,0.860)	<.0001	(0.805,0.818)	<.0001
History: mental disorder	(1.028,1.133)	0.0021	(1.054,1.081)	<.0001	(1.053,1.070)	<.0001
History: smoke	(1.017,1.112)	0.0072	(1.047,1.1041)	<.0001	(1.056,1.111)	<.0001
History: alcohol	(0.860,0.956)	0.0003	(0.842,0.930)	<.0001	(0.826,0.910)	<.0001
History: substance abuse	(0.786,0.970)	0.0114	(0.815,0.987)	0.0264	(0.802,0.969)	0.0089
History: non-substance abuse	(0.725,0.925)	0.0014	(0.775,0.980)	0.022	(0.748,0.925)	0.0007
History: non-opioid use	(1.088,1.173)	<.0001	(1.116,1.218)	<.0001	(1.167,1.200)	<.0001
First encounter: inpatient	(1.087,1.291)	0.0001	(1.034,1.207)	0.0052	(0.989,1.157)	0.0921
Total duration of supply	(1.026,1.039)	<.0001	(1.002,1.011)	0.0033	(1.004,1.004)	<.0001
Adjusted strength opioids	(1.003,1.008)	<.0001	(1.002,1.006)	<.0001	(1.003,1.004)	<.0001
Adjusted strength non-opioids	(0.945,1.050)	0.8915	(0.950,1.006)	0.121	(0.980,0.991)	<.0001

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APPENDIX A

APPENDIX OF CHAPTER 2

Proof of Proposition 2.4.1. First, we show the result for the final period ($n = N$). We have from (2.4): $V_N(\mathbf{b}, \lambda) = \mathbf{b}'\mathbf{R}_N$. Also, due to the existence of a BIWC member in M, the value function is piecewise-linear and convex in $\mathbf{b}$ (see our discussion in §2.4). Thus, from (2.8), we have: $V_N(\mathbf{b}, \lambda) = \max_{\boldsymbol{\psi} \in \Psi_{N,\lambda}} \{\mathbf{b}'\boldsymbol{\psi}\}$. Combining these results, it is trivial to show that $\Psi_{N,\lambda} = \{\mathbf{R}_N\}$, and thus, the result holds for $n = N$. Next, we show the result for other periods ($n < N$). From (2.4)-(2.7), we have for any $\mathbf{b} \in \Pi_{PO}$ and $\lambda \in \Lambda$:

$$V_n(\mathbf{b}, \lambda) = \max_{a \in A} \Big\{ \mathbf{b}'\mathbf{r}_n(a) + \lambda \Big(\beta \, \Sigma_{o \in O} Pr\{o|\mathbf{b}, a, \underline{m}\} \; V_{n+1}\big(B\left(\mathbf{b}, a, o, \underline{m}\right), \lambda\big) \Big) + (1-\lambda) \Big(\beta \, \Sigma_{o \in O} Pr\{o|\mathbf{b}, a, \overline{m}\} \; V_{n+1}\big(B\left(\mathbf{b}, a, o, \overline{m}\right), \lambda\big) \Big) \Big\} \tag{A.1a}$$

$$= \max_{a \in A} \left\{ \mathbf{b}'\mathbf{r}_n(a) + \lambda \Big(\beta \, \Sigma_{o \in O} Pr\{o|\mathbf{b}, a, \underline{m}\} \; \max_{\boldsymbol{\psi}} \left\{ \frac{\mathbf{b}'\mathbf{P}^a_{\underline{m}}\mathbf{Q}^{a,o}_{\underline{m}}}{Pr\{o|\mathbf{b}, a, \underline{m}\}} \, \boldsymbol{\psi} \right\} \Big) + (1-\lambda) \Big(\beta \, \Sigma_{o \in O} Pr\{o|\mathbf{b}, a, \overline{m}\} \; \max_{\boldsymbol{\psi}} \left\{ \frac{\mathbf{b}'\mathbf{P}^a_{\overline{m}}\mathbf{Q}^{a,o}_{\overline{m}}}{Pr\{o|\mathbf{b}, a, \overline{m}\}} \, \boldsymbol{\psi} \right\} \Big) \right\} \tag{A.1b}$$

$$= \max_{a \in A} \Big\{ \mathbf{b}'\mathbf{r}_n(a) + \lambda \big(\beta \, \Sigma_{o \in O} \max_{\boldsymbol{\psi}} \left\{ \mathbf{b}'\mathbf{P}^a_{\underline{m}}\mathbf{Q}^{a,o}_{\underline{m}}\boldsymbol{\psi} \right\} \big) + (1-\lambda) \big(\beta \, \Sigma_{o \in O} \max_{\boldsymbol{\psi}} \left\{ \mathbf{b}'\mathbf{P}^a_{\overline{m}}\mathbf{Q}^{a,o}_{\overline{m}}\boldsymbol{\psi} \right\} \big) \Big\}, \tag{A.1c}$$

where (A.1b) is obtained by following (2.1) and the fact that the value function is piecewise-linear and convex in $\mathbf{b}$, and hence, it can have the form of (2.8). Now, similar to what we have for (2.11) (in the main body), letting $\boldsymbol{\psi}^{(\mathbf{b},a,o)}_m = \arg \max_{\boldsymbol{\psi} \in \Psi_{n+1,\lambda}} \{\mathbf{b}'\mathbf{P}^a_m\mathbf{Q}^{a,o}_m\boldsymbol{\psi}\}$, (A.1c) results in (for any $\mathbf{b} \in \Pi_{PO}$, $\lambda \in \Lambda$, and $n < N$):

$$V_n(\mathbf{b},\lambda) = \max_{a\in A}\Big\{\mathbf{b}'\mathbf{r}_n(a) + \mathbf{b}'\Big(\lambda\big(\beta\ \Sigma_{o\in O}\mathbf{P}^a_{\underline{m}}\mathbf{Q}^{a,o}_{\underline{m}}\boldsymbol{\psi}^{(\mathbf{b},a,o)}_{\underline{m}}\big) + (1-\lambda)\big(\beta\ \Sigma_{o\in O}\mathbf{P}^a_{\overline{m}}\mathbf{Q}^{a,o}_{\overline{m}}\boldsymbol{\psi}^{(\mathbf{b},a,o)}_{\overline{m}}\big)\Big)\Big\}. \tag{A.2}$$

Now, since any $\boldsymbol{\psi}$-vector in (2.10) is a function of action $a \in A$, (A.2) and (2.8) (see §2.4 in the main body) become equivalent (see pages 1076–1077 in Smallwood and Sondik (1973)). Hence, we can conclude that $\boldsymbol{\psi} = \mathbf{r}_n(a) + \lambda\big(\beta\ \Sigma_{o\in O}\mathbf{P}^a_{\underline{m}}\mathbf{Q}^{a,o}_{\underline{m}}\ \boldsymbol{\psi}^{(\mathbf{b},a,o)}_{\underline{m}}\big) + (1-\lambda)\big(\beta\ \Sigma_{o\in O}\mathbf{P}^a_{\overline{m}}\mathbf{Q}^{a,o}_{\overline{m}}\ \boldsymbol{\psi}^{(\mathbf{b},a,o)}_{\overline{m}}\big)$. ■

Proof of Theorem 2.4.1. Let $\widehat{a} = a^*_n(\mathbf{b},\lambda^*)$ be the optimal medication action under the baseline conservatism level λ^*. Using the definition of optimal value function (see Equation (2.4) in the main body), we then have:

$$U_n(\mathbf{b},\widehat{a},\lambda^*) \geq U_n(\mathbf{b},a,\lambda^*) \qquad \text{for all } a\in A \quad \text{s.t.} \quad a \not\preceq \widehat{a}. \tag{A.3}$$

Now, if we show that the following result holds for all $\lambda \in \Lambda$ such that $\lambda \geq \lambda^*$:

$$U_n(\mathbf{b},\widehat{a},\lambda^*) - U_n(\mathbf{b},\widehat{a},\lambda) \leq U_n(\mathbf{b},a,\lambda^*) - U_n(\mathbf{b},a,\lambda), \tag{A.4}$$

then, we have:

$$\begin{aligned} U_n(\mathbf{b},\widehat{a},\lambda) &= U_n(\mathbf{b},\widehat{a},\lambda^*) - [U_n(\mathbf{b},\widehat{a},\lambda^*) - U_n(\mathbf{b},\widehat{a},\lambda)] && \text{(A.5a)}\\ &\geq U_n(\mathbf{b},a,\lambda^*) - [U_n(\mathbf{b},\widehat{a},\lambda^*) - U_n(\mathbf{b},\widehat{a},\lambda)] && \text{(A.5b)}\\ &\geq U_n(\mathbf{b},a,\lambda^*) - [U_n(\mathbf{b},a,\lambda^*) - U_n(\mathbf{b},a,\lambda)] && \text{(A.5c)}\\ &= U_n(\mathbf{b},a,\lambda), && \text{(A.5d)} \end{aligned}$$

where (A.5b) is obtained by following the results in (A.3), and (A.5c) is obtained by following the result in (A.4) (after multiplying both sides of (A.4) by a negative sign).

By our result in (A.5), we know that the optimal medication action under conservatism level λ cannot be any action $a \in A$ such that $a \not\preceq \widehat{a}$, and hence, the result of Theorem 2.4.1 is obtained. We now show that the result in (A.4) holds under Conditions 2.4.1–2.4.3. By following Conditions 2.4.1–2.4.2 and utilizing the result of Theorem 1 in Saghafian (2018), part (ii) of Condition 2.4.3 yields:

$$\begin{aligned}
V_{n+1}\Big(B(\mathbf{b},\widehat{a},o,\underline{m}(\widehat{a},\lambda^*)),\lambda^*\Big) &\leq V_{n+1}\Big(B(\mathbf{b},a,o,\underline{m}(a,\lambda^*)),\lambda^*\Big),\\
V_{n+1}\Big(B(\mathbf{b},\widehat{a},o,\overline{m}(\widehat{a},\lambda^*)),\lambda^*\Big) &\leq V_{n+1}\Big(B(\mathbf{b},a,o,\overline{m}(a,\lambda^*)),\lambda^*\Big),\\
V_{n+1}\Big(B(\mathbf{b},a,o,\underline{m}(a,\lambda)),\lambda\Big) &\leq V_{n+1}\Big(B(\mathbf{b},\widehat{a},o,\underline{m}(\widehat{a},\lambda)),\lambda\Big),\\
V_{n+1}\Big(B(\mathbf{b},a,o,\overline{m}(a,\lambda)),\lambda\Big) &\leq V_{n+1}\Big(B(\mathbf{b},\widehat{a},o,\overline{m}(\widehat{a},\lambda)),\lambda\Big).
\end{aligned} \tag{A.6}$$

Next, we have:

$$\begin{aligned}
&\sum_{o\in O} Pr\{o|\mathbf{b},\widehat{a},\underline{m}(\widehat{a},\lambda^*)\}V_{n+1}\Big(B(\mathbf{b},\widehat{a},o,\underline{m}(\widehat{a},\lambda^*)),\lambda^*\Big)\\
&\qquad\leq \sum_{o\in O} Pr\{o|\mathbf{b},\widehat{a},\underline{m}(\widehat{a},\lambda^*)\}V_{n+1}\Big(B(\mathbf{b},a,o,\underline{m}(a,\lambda^*)),\lambda^*\Big) \qquad \text{(A.7a)}\\
&\qquad\leq \sum_{o\in O} Pr\{o|\mathbf{b},a,\underline{m}(a,\lambda^*)\}V_{n+1}\Big(B(\mathbf{b},a,o,\underline{m}(a,\lambda^*)),\lambda^*\Big), \qquad \text{(A.7b)}
\end{aligned}$$

where (A.7a) is obtained by the result of (A.6). Also, by Condition 2.4.2, $\mathbf{P}^a_m$ and $\mathbf{Q}^a_m$ are TP_2. Thus, by following the result of Lemma 4.1 (part a) of Rieder (1991),

we have, for any $a \in A$ and $m \in M$, $B(\mathbf{b}, a, o, m) \preceq_{TP_2} B(\mathbf{b}, a, \widehat{o}, m)$ for any $o, \widehat{o} \in O$ such that $o \leq \widehat{o}$. Using this result together with part (i) of Condition 2.4.3, we utilize the result of Lemma 1.1 in Lovejoy (1987) to obtain (A.7b). We also note that in (A.7), we only obtain the inequality for one of four scenarios in (A.6). The other three scenarios are obtained in a similar fashion. Next, utilizing our results in (A.7), and following the definition of the immediate reward vector (see Equation (2.17) in §2.5 in the main body), we have for $\widehat{a} = a_n^*(\mathbf{b}, \lambda^*)$, $a \not\preceq \widehat{a}$, and $\lambda^* \geq \widehat{\lambda}$:

$$\begin{aligned}
&\mathbf{b}'\mathbf{r}_n(\widehat{a}) + \lambda^* H_n\Big(\mathbf{b}, \widehat{a}, \underline{m}(\widehat{a}, \lambda^*), \lambda^*\Big) + (1-\lambda^*) H_n\Big(\mathbf{b}, \widehat{a}, \overline{m}(\widehat{a}, \lambda^*), \lambda^*\Big) \\
&\leq \mathbf{b}'\mathbf{r}_n(a) + \lambda^* H_n\Big(\mathbf{b}, a, \underline{m}(a, \lambda^*), \lambda^*\Big) + (1-\lambda^*) H_n\Big(\mathbf{b}, a, \overline{m}(a, \lambda^*), \lambda^*\Big), \\
&\mathbf{b}'\mathbf{r}_n(\widehat{a}) + \lambda H_n\Big(\mathbf{b}, \widehat{a}, \underline{m}(\widehat{a}, \lambda), \lambda\Big) + (1-\lambda) H_n\Big(\mathbf{b}, \widehat{a}, \overline{m}(\widehat{a}, \lambda), \lambda\Big) \\
&\geq \mathbf{b}'\mathbf{r}_n(a) + \lambda H_n\Big(\mathbf{b}, a, \underline{m}(a, \lambda), \lambda\Big) + (1-\lambda) H_n\Big(\mathbf{b}, a, \overline{m}(a, \lambda), \lambda\Big).
\end{aligned} \tag{A.8}$$

Finally, multiplying both sides of the second inequality in (A.8) by a negative sign, and then adding the two inequalities in (A.8), we will get $U_n(\mathbf{b}, \widehat{a}, \lambda^*) - U_n(\mathbf{b}, \widehat{a}, \lambda) \leq U_n(\mathbf{b}, a, \lambda^*) - U_n(\mathbf{b}, a, \lambda)$, which is the result in (A.4). This completes the proof. ■

In Lemma A.1.1, we provide a more detailed sufficient condition for part (ii) of Condition 2.4.3.

Lemma A.1.1 *Let $K_m^a(o|i,j) = p_m^a(j|i) q_m^a(o|j)$ for all $i, j \in S$ and $o \in O$. Then, if $\frac{K^a_{\underline{m}(a,\lambda^*)}(o|i,j)}{K^{\widehat{a}}_{\underline{m}(\widehat{a},\lambda^*)}(o|i,j)}$ and $\frac{K^{\widehat{a}}_{\underline{m}(\widehat{a},\lambda)}(o|i,j)}{K^a_{\underline{m}(a,\lambda)}(o|i,j)}$ are nondecreasing in $j \in S$, for all $i \in S, o \in O$, we have $B\big(\mathbf{b}, \widehat{a}, o, \underline{m}(\widehat{a}, \lambda^*)\big) \preceq_{TP_2} B\big(\mathbf{b}, a, o, \underline{m}(a, \lambda^*)\big)$ and $B\big(\mathbf{b}, a, o, \underline{m}(a, \lambda)\big) \preceq_{TP_2} B\big(\mathbf{b}, \widehat{a}, o, \underline{m}(\widehat{a}, \lambda)\big)$.*

Proof of Lemma A.1.1. We have for all $j_1, j_2 \in S$ s.t. $j_1 \leq j_2$, for all $o \in O$, and

for conservatism level λ:

$$\frac{K^a_{\underline{m}(a,\lambda^*)}(o|i,j_1)}{K^{\widehat{a}}_{\underline{m}(\widehat{a},\lambda^*)}(o|i,j_1)} \leq \frac{K^a_{\underline{m}(a,\lambda^*)}(o|i,j_2)}{K^{\widehat{a}}_{\underline{m}(\widehat{a},\lambda^*)}(o|i,j_2)} \tag{A.9a}$$

$$\Rightarrow \frac{b_i\ K^a_{\underline{m}(a,\lambda^*)}(o|i,j_1)}{b_i\ K^{\widehat{a}}_{\underline{m}(\widehat{a},\lambda^*)}(o|i,j_1)} \leq \frac{b_i\ K^a_{\underline{m}(a,\lambda^*)}(o|i,j_2)}{b_i\ K^{\widehat{a}}_{\underline{m}(\widehat{a},\lambda^*)}(o|i,j_2)} \tag{A.9b}$$

$$\Rightarrow \frac{\sum_{i\in S} b_i\ K^a_{\underline{m}(a,\lambda^*)}(o|i,j_1)}{\sum_{i\in S} b_i\ K^{\widehat{a}}_{\underline{m}(\widehat{a},\lambda^*)}(o|i,j_1)} \leq \frac{\sum_{i\in S} b_i\ K^a_{\underline{m}(a,\lambda^*)}(o|i,j_2)}{\sum_{i\in S} b_i\ K^{\widehat{a}}_{\underline{m}(\widehat{a},\lambda^*)}(o|i,j_2)} \tag{A.9c}$$

$$\Rightarrow \frac{\frac{\sum_{i\in S} b_i\ K^a_{\underline{m}(a,\lambda^*)}(o|i,j_1)}{Pr\{o|\mathbf{b},a,\underline{m}(a,\lambda^*)\}}}{\frac{\sum_{i\in S} b_i\ K^{\widehat{a}}_{\underline{m}(\widehat{a},\lambda^*)}(o|i,j_1)}{Pr\{o|\mathbf{b},\widehat{a},\underline{m}(\widehat{a},\lambda^*)\}}} \leq \frac{\frac{\sum_{i\in S} b_i\ K^a_{\underline{m}(a,\lambda^*)}(o|i,j_2)}{Pr\{o|\mathbf{b},a,\underline{m}(a,\lambda^*)\}}}{\frac{\sum_{i\in S} b_i\ K^{\widehat{a}}_{\underline{m}(\widehat{a},\lambda^*)}(o|i,j_2)}{Pr\{o|\mathbf{b},\widehat{a},\underline{m}(\widehat{a},\lambda^*)\}}}, \tag{A.9d}$$

where, in (A.9c), the part after ($\Rightarrow$) is obtained from the part before ($\Rightarrow$) by multiplying both sides in $\frac{Pr\{o|\mathbf{b},\widehat{a},\underline{m}(\widehat{a},\lambda^*)\}}{Pr\{o|\mathbf{b},a,\underline{m}(a,\lambda^*)\}}$. By the definitions of the belief updating operator (see Equation (2.1) in §2.3 in the main body), and the TP_2-ordering for belief vectors (see §2.4 in the main body), the last part of (A.9c) implies that: $B(\mathbf{b},\widehat{a},o,\underline{m}(\widehat{a},\lambda^*)) \preceq_{TP_2} B(\mathbf{b},a,o,\underline{m}(a,\lambda^*))$ and $B(\mathbf{b},\widehat{a},o,\overline{m}(\widehat{a},\lambda^*)) \preceq_{TP_2} B(\mathbf{b},a,o,\overline{m}(a,\lambda^*))$, where, the second TP_2-ordering is also obtained by part (iii) of Condition 2.4.3. Furthermore, by the same lines of proof, we have: $B(\mathbf{b},a,o,\underline{m}(a,\lambda)) \preceq_{TP_2} B(\mathbf{b},\widehat{a},o,\underline{m}(a,\lambda))$ and $B(\mathbf{b},a,o,\overline{m}(a,\lambda)) \preceq_{TP_2} B(\mathbf{b},\widehat{a},o,\overline{m}(\widehat{a},\lambda))$. ■

Proof of Corollary 2.4.1. The result is obtained by the same lines of proof in Theorem 2.4.1. ■

Proof of Theorem 2.4.2. For any $a,\widehat{a} \in A$ and $\mathbf{b},\widehat{\mathbf{b}} \in \Pi_{PO}$ such that $a \preceq \widehat{a}$ and $\mathbf{b} \preceq_{TP_2} \widehat{\mathbf{b}}$, if we show that $U_n(\mathbf{b},\widehat{a},\lambda) - U_n(\mathbf{b},a,\lambda) \leq U_n(\widehat{\boldsymbol{b}},\widehat{a},\lambda) - U_n(\widehat{\boldsymbol{b}},a,\lambda)$, then the result follows from Lemma 2.1 in Lovejoy (1987). To this end, we have:

$$U_n(\mathbf{b},\widehat{a},\lambda) - U_n(\mathbf{b},a,\lambda) = \mathbf{b}'\mathbf{r}_n(\widehat{a}) + \lambda\Big(\beta\sum_{o\in O} Pr\{o|\mathbf{b},\widehat{a},\underline{m}\}\; V_{n+1}\big(B(\mathbf{b},\widehat{a},o,\underline{m}),\lambda\big)\Big)$$
$$+(1-\lambda)\Big(\beta\sum_{o\in O} Pr\{o|\mathbf{b},\widehat{a},\overline{m}\}\; V_{n+1}\big(B(\mathbf{b},\widehat{a},o,\overline{m}),\lambda\big)\Big)$$
$$-\mathbf{b}'\mathbf{r}_n(a) - \lambda\Big(\beta\sum_{o\in O} Pr\{o|\mathbf{b},a,\underline{m}\}\; V_{n+1}\big(B(\mathbf{b},a,o,\underline{m}),\lambda\big)\Big)$$
$$-(1-\lambda)\Big(\beta\sum_{o\in O} Pr\{o|\mathbf{b},a,\overline{m}\}\; V_{n+1}\big(B(\mathbf{b},a,o,\overline{m}),\lambda\big)\Big) \tag{A.10a}$$

$$= \lambda\beta\Big(\mathbf{b}'\Big(\sum_{o\in O}\mathbf{P}^{\widehat{a}}_{\underline{m}(\boldsymbol{b},\widehat{a},\lambda)}\mathbf{Q}^{\widehat{a},o}_{\underline{m}(\boldsymbol{b},\widehat{a},\lambda)}\boldsymbol{\psi}^{(\mathbf{b},\widehat{a},o)}_{\underline{m}(\boldsymbol{b},\widehat{a},\lambda)} - \sum_{o\in O}\mathbf{P}^{a}_{\underline{m}(\boldsymbol{b},a,\lambda)}\mathbf{Q}^{a,o}_{\underline{m}(\boldsymbol{b},a,\lambda)}\boldsymbol{\psi}^{(\mathbf{b},a,o)}_{\underline{m}(\boldsymbol{b},a,\lambda)}\Big)\Big)$$
$$+(1-\lambda)\beta\Big(\mathbf{b}'\Big(\sum_{o\in O}\mathbf{P}^{\widehat{a}}_{\overline{m}(\boldsymbol{b},\widehat{a},\lambda)}\mathbf{Q}^{\widehat{a},o}_{\overline{m}(\boldsymbol{b},\widehat{a},\lambda)}\boldsymbol{\psi}^{(\mathbf{b},\widehat{a},o)}_{\overline{m}(\boldsymbol{b},\widehat{a},\lambda)} - \sum_{o\in O}\mathbf{P}^{a}_{\overline{m}(\boldsymbol{b},a,\lambda)}\mathbf{Q}^{a,o}_{\overline{m}(\boldsymbol{b},a,\lambda)}\boldsymbol{\psi}^{(\mathbf{b},a,o)}_{\overline{m}(\boldsymbol{b},a,\lambda)}\Big)\Big) \tag{A.10b}$$

$$= \beta\;\mathbf{b}'\Big(\lambda\Big(\boldsymbol{\phi}^{(\boldsymbol{b},\widehat{a})}_{\underline{m}(\boldsymbol{b},\widehat{a},\lambda)} - \boldsymbol{\phi}^{(\boldsymbol{b},a)}_{\underline{m}(\boldsymbol{b},a,\lambda)}\Big)+(1-\lambda)\Big(\boldsymbol{\phi}^{(\boldsymbol{b},\widehat{a})}_{\overline{m}(\boldsymbol{b},\widehat{a},\lambda)} - \boldsymbol{\phi}^{(\boldsymbol{b},a)}_{\overline{m}(\boldsymbol{b},a,\lambda)}\Big)\Big), \tag{A.10c}$$

where (A.10a) is obtained by following equations (2.5)-(2.7) and the definition of the immediate reward vector $\mathbf{r}_n(a)$ (see Equation (2.17) in the main body), (A.10b) is obtained because of the PLC property of the value function, and (A.10c) is obtained by our notion in Condition 2.4.4.

Now, since TP_2 ordering is stronger than the first order stochastic ordering ($\preceq_{st}$), $\mathbf{b} \preceq_{TP_2} \widehat{\mathbf{b}}$ implies $\mathbf{b} \preceq_{st} \widehat{\mathbf{b}}$. Therefore, by Lemma 1.1 in Lovejoy (1987), it is sufficient to show that the vector inside the outer parenthesis in (A.10c) is nondecreasing in its elements. Since both λ and $1-\lambda$ are non-negative, this is obtained by Condition 2.4.4. ■

Proof of Proposition 2.4.2. Let $\underline{\underline{m}}_n(\mathbf{b},a,\lambda) = \arg\min_{m\in M}\big\{J_{n+1}(\mathbf{b}'\mathbf{P}^a_m,\lambda)\big\}$, $\overline{\overline{m}}_n(\mathbf{b},a,\lambda) = \arg\max_{m\in M}\big\{J_{n+1}(\mathbf{b}'\mathbf{P}^a_m,\lambda)\big\}$, where, for notational simplicity, we refer

to $\underline{\underline{m}}_n(\mathbf{b},a,\lambda)$ and $\overline{\overline{m}}_n(\mathbf{b},a,\lambda)$ as $\underline{\underline{m}}$ and $\overline{\overline{m}}$, respectively (we use different notations for $\underline{\underline{m}}$ and $\overline{\overline{m}}$ to distinguish them with $\underline{m}$ and $\overline{m}$ defined in (2.7); see §2.3.1 in the main body). Also, let $\widehat{\boldsymbol{\psi}}_m^{(\mathbf{b},a)} = \arg\max_{\widehat{\boldsymbol{\psi}}\in\widehat{\Psi}_{n+1,\lambda}}\{\mathbf{b}'\mathbf{P}_m^a\widehat{\boldsymbol{\psi}}\}$. Then, based on the definition of the approximate value function in (2.13), it is trivial to show (by induction) that $J_n(\mathbf{b},\lambda)$ has the PLC property; i.e., $J_n(\mathbf{b},\lambda) = \max_{\widehat{\boldsymbol{\psi}}\in\widehat{\Psi}_{n,\lambda}}\{\mathbf{b}'\widehat{\boldsymbol{\psi}}\}, \forall\ \mathbf{b}\in\Pi_{PO}, \forall\ \lambda\in\Lambda, \forall\ n\le N$, where $\widehat{\Psi}_{N,\lambda} = \{\mathbf{R}_N\}, \forall\ \lambda\in\Lambda$ and

$$\widehat{\Psi}_{n,\lambda} = \Bigg\{\widehat{\boldsymbol{\psi}} = \mathbf{r}_n(a) + \lambda\Big(\beta\ \mathbf{P}_{\underline{\underline{m}}}^a\ \widehat{\boldsymbol{\psi}}_{\underline{\underline{m}}}^{(\mathbf{b},a)}\Big) + (1-\lambda)\Big(\beta\ \mathbf{P}_{\overline{\overline{m}}}^a\ \widehat{\boldsymbol{\psi}}_{\overline{\overline{m}}}^{(\mathbf{b},a)}\Big), \\ a\in A,\ \widehat{\boldsymbol{\psi}}_{\underline{\underline{m}}}^{(\mathbf{b},a)}, \widehat{\boldsymbol{\psi}}_{\overline{\overline{m}}}^{(\mathbf{b},a)} \in \widehat{\Psi}_{n+1,\lambda}\Bigg\}\ \ \forall\ n<N, \forall\ \lambda\in\Lambda. \tag{A.11}$$

For any action $a\in A$, we let $\boldsymbol{\psi}(a)\in\Psi_{n,\lambda}$ and $\widehat{\boldsymbol{\psi}}(a)\in\widehat{\Psi}_{n,\lambda}$ be the vectors attributed to action a (without loss of generality, we assume that every action yields one vector). Letting $\|\dots\|_1$ be the $\mathcal{L}_1$-norm, we have from Equation (2.10) (in the main body) and (A.11):

$$\begin{aligned}\Big\|\boldsymbol{\psi}(a) - \widehat{\boldsymbol{\psi}}(a)\Big\|_1 &= \beta\,\|\,\lambda\Big(\Sigma_{o\in O}P_{\underline{\underline{m}}}^a Q_{\underline{\underline{m}}}^{a,o}\boldsymbol{\psi}_{\underline{\underline{m}}}^{(\mathbf{b},a,o)} - P_{\underline{\underline{m}}}^a\widehat{\boldsymbol{\psi}}_{\underline{\underline{m}}}^{(\mathbf{b},a)}\Big) \\ &\quad +(1-\lambda)\Big(\Sigma_{o\in O}P_{\overline{\overline{m}}}^a Q_{\overline{\overline{m}}}^{a,o}\boldsymbol{\psi}_{\overline{\overline{m}}}^{(\mathbf{b},a,o)} - P_{\overline{\overline{m}}}^a\widehat{\boldsymbol{\psi}}_{\overline{\overline{m}}}^{(\mathbf{b},a)}\Big)\Big\|_1 \qquad \text{(A.12a)} \\ &\le \beta\ \lambda\left\|\Sigma_{o\in O}P_{\underline{\underline{m}}}^a Q_{\underline{\underline{m}}}^{a,o}\boldsymbol{\psi}_{\underline{\underline{m}}}^{(\mathbf{b},a,o)} - P_{\underline{\underline{m}}}^a\widehat{\boldsymbol{\psi}}_{\underline{\underline{m}}}^{(\mathbf{b},a)}\right\|_1 \\ &\quad +\beta\ (1-\lambda)\left\|\Sigma_{o\in O}P_{\overline{\overline{m}}}^a Q_{\overline{\overline{m}}}^{a,o}\boldsymbol{\psi}_{\overline{\overline{m}}}^{(\mathbf{b},a,o)} - P_{\overline{\overline{m}}}^a\widehat{\boldsymbol{\psi}}_{\overline{\overline{m}}}^{(\mathbf{b},a)}\right\|_1, \qquad \text{(A.12b)}\end{aligned}$$

where (A.12b) is obtained by the triangular inequality, and

$$\left\| \sum_{o \in O} P^a_{\underline{m}} Q^{a,o}_{\underline{m}} \boldsymbol{\psi}^{(\mathbf{b},a,o)}_{\underline{m}} - P^a_{\underline{\underline{m}}} \widehat{\boldsymbol{\psi}}^{(\mathbf{b},a)}_{\underline{\underline{m}}} \right\|_1 \tag{A.13a}$$

$$= \left\| \Sigma_{o \in O} P^a_{\underline{m}} Q^{a,o}_{\underline{m}} \boldsymbol{\psi}^{(\mathbf{b},a,o)}_{\underline{m}} - P^a_{\underline{\underline{m}}} \widehat{\boldsymbol{\psi}}^{(\mathbf{b},a)}_{\underline{\underline{m}}} + P^a_{\underline{m}} \widehat{\boldsymbol{\psi}}^{(\mathbf{b},a)}_{\underline{m}} - P^a_{\underline{m}} \widehat{\boldsymbol{\psi}}^{(\mathbf{b},a)}_{\underline{\underline{m}}} \right\|_1$$

$$\leq \left\| P^a_{\underline{m}} \Big(\Sigma_{o \in O} Q^{a,o}_{\underline{m}} \boldsymbol{\psi}^{(\mathbf{b},a,o)}_{\underline{m}} - \widehat{\boldsymbol{\psi}}^{(\mathbf{b},a)}_{\underline{\underline{m}}} \Big) \right\|_1 + \left\| \Big(P^a_{\underline{m}} - P^a_{\underline{\underline{m}}} \Big) \widehat{\boldsymbol{\psi}}^{(\mathbf{b},a)}_{\underline{\underline{m}}} \right\|_1 \tag{A.13b}$$

$$= \left\| P^a_{\underline{m}} \Sigma_{o \in O} Q^{a,o}_{\underline{m}} \Big(\boldsymbol{\psi}^{(\mathbf{b},a,o)}_{\underline{m}} - \widehat{\boldsymbol{\psi}}^{(\mathbf{b},a)}_{\underline{\underline{m}}} \Big) \right\|_1 + \left\| \Big(P^a_{\underline{m}} - P^a_{\underline{\underline{m}}} \Big) \widehat{\boldsymbol{\psi}}^{(\mathbf{b},a)}_{\underline{\underline{m}}} \right\|_1 \tag{A.13c}$$

$$\leq \left\| \boldsymbol{\psi}^{(\mathbf{b},a,o)}_{\underline{m}} - \widehat{\boldsymbol{\psi}}^{(\mathbf{b},a)}_{\underline{\underline{m}}} \right\|_1 + |S| \, \eta \, \epsilon_{n+1}, \tag{A.13d}$$

where, in (A.13c), the first term is obtained by the triangular inequality, and the second term is obtained by condition (ii) in Proposition 2.4.2 and our result after this proof (proof of Proposition 2.4.2, supplement). We note that the same inequality as (A.13c) can be obtained for $\overline{m}$ and $\overline{\overline{m}}$. From (A.12b) and (A.13c), we have:

$$\| \boldsymbol{\psi}(a) - \widehat{\boldsymbol{\psi}}(a)_1$$

$$\leq \beta \Bigg(\lambda \, \left\| \boldsymbol{\psi}^{(\mathbf{b},a,o)}_{\underline{m}} - \widehat{\boldsymbol{\psi}}^{(\mathbf{b},a)}_{\underline{\underline{m}}} \right\|_1 + (1 - \lambda) \, \left\| \boldsymbol{\psi}^{(\mathbf{b},a,o)}_{\overline{m}} - \widehat{\boldsymbol{\psi}}^{(\mathbf{b},a)}_{\overline{\overline{m}}} \right\|_1 + |S| \, \eta \, \epsilon_{n+1} \Bigg). \tag{A.14}$$

Letting

$$\boldsymbol{\Delta}_n(\boldsymbol{\psi}, \widehat{\boldsymbol{\psi}}) = \left\| \boldsymbol{\psi} - \widehat{\boldsymbol{\psi}} \right\|_1 \; \forall \, \boldsymbol{\psi} \in \Psi_{n,\lambda}, \forall \, \widehat{\boldsymbol{\psi}} \in \widehat{\Psi}_{n,\lambda}, \forall \, \lambda \in \Lambda, \forall \, n \leq N, \tag{A.15}$$

$$\boldsymbol{\Delta} = \max_{\boldsymbol{\psi}\in\Psi_{n,\lambda},\widehat{\boldsymbol{\psi}}\in\widehat{\Psi}_{n,\lambda},n\leq N,\lambda\in\Lambda}\Big\{\boldsymbol{\Delta}_n(\boldsymbol{\psi},\widehat{\boldsymbol{\psi}})\Big\}, \tag{A.16}$$

we then have from (A.14)-(A.16):

$$\boldsymbol{\Delta} \leq \beta\big(\boldsymbol{\Delta} + |S|\ \eta\ \epsilon_{n+1}\big) \Rightarrow \Big\|\boldsymbol{\psi}(a) - \widehat{\boldsymbol{\psi}}(a)\Big\|_1 \leq \boldsymbol{\Delta} \leq \frac{\beta}{1-\beta}|S|\ \eta\ \epsilon_{n+1}. \tag{A.17}$$

Now, without loss of generality, we assume that the optimal and approximate policies result in two different medications regimens; i.e., for any $a_i, a_j \in A$ such that $a_i \neq a_j$, we have:

$$\boldsymbol{\psi}(a_i) = \arg\max_{\boldsymbol{\psi}\in\Psi_{n,\lambda}}\Big\{\mathbf{b}'\boldsymbol{\psi}\Big\} \quad \text{and} \quad \widehat{\boldsymbol{\psi}}(a_j) = \arg\max_{\widehat{\boldsymbol{\psi}}\in\widehat{\Psi}_{n,\lambda}}\Big\{\mathbf{b}'\widehat{\boldsymbol{\psi}}\Big\}. \tag{A.18}$$

Then, we have:

$$\begin{aligned}
V_n(\mathbf{b},\lambda) - J_n(\mathbf{b},\lambda) =& \big|V_n(\mathbf{b},\lambda) - J_n(\mathbf{b},\lambda)\big| \\
=& \Big|\mathbf{b}'\boldsymbol{\psi}(a_i) - \mathbf{b}'\widehat{\boldsymbol{\psi}}(a_j)\Big| \\
\leq& \Big|\mathbf{b}'\boldsymbol{\psi}(a_i) - \mathbf{b}'\widehat{\boldsymbol{\psi}}(a_i)\Big| \\
\leq& \Big\|\boldsymbol{\psi}(a_i) - \widehat{\boldsymbol{\psi}}(a_i)\Big\|_1 \\
\leq& \frac{\beta}{1-\beta}|S|\ \eta\ \epsilon_{n+1},
\end{aligned} \tag{A.19}$$

where, in (A.19), the first term is obtained by the fact that $V_n(\mathbf{b},\lambda) \geq J_n(\mathbf{b},\lambda)$, the first inequality is obtained based on (A.18) (which indicates that $\mathbf{b}'\widehat{\boldsymbol{\psi}}(a_j) \geq$

$\mathbf{b}'\widehat{\boldsymbol{\psi}}(a_i)$), the second inequality is obtained due to the fact that $b_i \leq 1,\ \forall i \in S$, and the last inequality is obtained based on our result in (A.17). Moreover, we have $V_n(\mathbf{b},\lambda) - J_n(\mathbf{b},\lambda) \leq V_n(\mathbf{b},\lambda) \leq \overline{r} + \beta\,\overline{r} + \cdots + \beta^{N-1}\,\overline{r} = \overline{r}\sum_{l=0}^{N-1}\beta^l$, where the second inequality is obtained by the fact that $\overline{r}$ is the maximum possible reward collected in each period. Together with our results in (A.19), this completes the proof. ■

Proof of Proposition 2.4.2 (supplement). Here, we show that for each $\widehat{\boldsymbol{\psi}}$-vector defined in (A.11), when there are k periods remaining until the end of the horizon ($\widehat{\boldsymbol{\psi}} = [\widehat{\psi}_i]_{i\in S} \in \widehat{\Psi}_{N-k}, k < N$), we have $\widehat{\psi}_i \leq \epsilon_{N-k}$ for all $i \in S$. We prove this lemma by using induction. First, note that for $k = 0$ and $\lambda \in \Lambda$, we have $\widehat{\boldsymbol{\psi}} = \mathbf{R}_N$ for all $\widehat{\boldsymbol{\psi}} \in \widehat{\Psi}_{N,\lambda}$. Also, by the assumption in Proposition 2.4.2, $R_N(i) \leq \epsilon_r = \epsilon_r\beta^0$ for all $i \in S$. Next, we assume (by induction) that the result holds when there are $1 \leq k < N$ periods remained until the end of time horizon (i.e., k periods to go). For all $\widehat{\boldsymbol{\psi}} = [\widehat{\psi}_i]_{i\in S} \in \widehat{\Psi}_{N-k,\lambda}$:

$$\widehat{\psi}_i \leq \epsilon_q\left(1 + \cdots + \beta^{k-1}\right) + \epsilon_r\beta^k \qquad \forall\, i \in S. \tag{A.20}$$

Now, we show that the result holds for $k+1$ periods to go. Combining the results in (A.11) and (A.20), and letting

$$\mathbf{r}_n(a) + \beta\,\mathbf{P}_m^a\,\widehat{\boldsymbol{\psi}}_m^{(\mathbf{b},a)} = \left[r_n(a,i) + \beta\,\Sigma_{j\in S}p_m^a(j|i)\widehat{\psi}_j\right]_{i\in S}, \tag{A.21}$$

we have for every row of the vector in (A.21):

$$\begin{aligned} r_n(a,i) + \beta\,\Sigma_{j\in S}p_m^a(j|i)\widehat{\psi}_j &\leq \epsilon_q + \beta\big(\epsilon_q\left(1 + \cdots + \beta^{k-1}\right)\big) + \epsilon_r\beta^{k+1} \\ &= \epsilon_q\left(1 + \cdots + \beta^k\right) + \epsilon_r\beta^{k+1}. \end{aligned} \tag{A.22}$$

As the same procedure in (A.22) can be applied to other rows in (A.21), the

result holds for the vector in (A.21). Now, because (1) this component-wise ordering is preserved under any model m, and (2) each $\widehat{\boldsymbol{\psi}}$-vector is a convex combination of vectors in the left-hand side of (A.21), the result follows: $\widehat{\psi}_i \leq \epsilon_{N-k}$ (in Proposition 2.4.2 we use $k = N - n - 1$). ■

A.2 Parameter Estimation and Validation

A.2.1 Estimation of Parameters for Reward Vectors

Immediate Reward: Diabetes. We obtain *qol*(diabetes) and *qol*(healthy) for different risk factors from the extant literature (e.g., Zhang et al. (2012)) . We then interpolate these values to measure *qol*(pre-diabetes). We assume that: (1) *qol*(healthy) always equals 1 across low-level risk factors, and (2) for some risk factors whose *qol*(diabetes) cannot be obtained directly from literature (e.g., cholesterol), *qol*(healthy) − *qol*(diabetes) = 0.2 (in one year) which is consistent with the medical literature (Zhang et al., 2012).

Immediate Reward: Transplantation. The majority of patients with kidney failure/rejection after transplant undergo dialysis (see, e.g., Messa et al. (2008)). Thus, experiencing an organ rejection would be equivalent to undergoing dialysis. We estimate *qol*(organ survival) and *qol*(organ rejection) for "Age" and "Gender" from the extant literature (Laupacis et al., 1996). For other risk factors, we assume these scores are equal to 0.65 and 0.80 (0.55 and 0.70) for a low-level (high-level) risk factor (see, e.g., Laupacis et al. (1996)).

Lump-Sum Reward: Diabetes. We estimate *RLE* scores for "diabetes" and "healthy" conditions from the extant literature (see, e.g., Narayan et al. (2003)). Note that (1) for some risk factors for which these scores cannot be directly estimated from literature (e.g., blood pressure and HDL), we assume that *RLE*(healthy) −

RLE(diabetes) = 12 years which is consistent with the medical literature (Narayan et al., 2003), and (2) similar to the case for the immediate reward, we interpolate these values to obtain RLE(pre-diabetes).

Lump-Sum Reward: Transplantation. We obtain RLE scores for RLE(organ rejection) and RLE(organ survival) for "Age," "Gender," and "Race" from USRDS (2014). For other risk factors, we assume that RLE(organ rejection) and RLE(organ survival) are equal to 15.00 and 19.50 (12.00 and 16.50) for low-level (high-level) risk factors (USRDS, 2014).

Tables A.2–A.4 show the actual values of the above-mentioned reward parameters. We also note that, in Online Appendix E, we address sensitivity analyses for these reward parameters. These analyses enable us to also demonstrate the robustness of our solutions to estimation errors for reward parameters.

- Information in Table A.2 is obtained from the following sources: Bardage and Isacson (2001); Redekop et al. (2002); Picavet et al. (2004); Huang et al. (2007); Vetter et al. (2011); Zhang et al. (2012).

- Information in Table A.3 is obtained from the following sources: Wilson et al. (1988); Criqui et al. (1993); Grover et al. (2000); Narayan et al. (2003); Franco et al. (2005); Clarke et al. (2009); Leal et al. (2009); Cunningham et al. (2011); Chen et al. (2014)

- Information in Table A.4 is obtained from the following sources: Laupacis et al. (1996); Liu et al. (2008); USRDS (2014).

A.2.2 Estimation of Medical Expenditures for Comparing Policies

One of the performance measures to compare different policies is the average cost incurred due to transplant-related and diabetes-related complications. We use a back-

Table A.1: Notations for Estimating Medical Cost Expenditures

c^D: Indirect cost of diabetes during a month; $c^D = \$210$ (Dall et al., 2014)
c^{PD}: Indirect cost of pre-diabetes during a month; $c^{PD} = \$40$ (Dall et al., 2014)
C_n^D: Total indirect cost attributed to diabetes/pre-diabetes in period n
c^{rej}: Cost of having an organ rejection at any time; $c^{rej} = \$29,392$ (Lee et al., 2009)
C_n^T: Total indirect cost attributed to transplant-related complications in period n

of-the-envelope calculation to estimate cost measures. Since our ultimate result is to decide upon medication regimens, we do not consider the direct cost of medications used. This cost can be interpreted as the *monetary* values of disutilities caused by risks of organ rejection and diabetes complications. Table A.1 shows the notation used. Let $b_{i,n}$ be the probability of being in core state i in period n. Then, under the medication action $a \in A$ and model $m \in M$, the transplant-related cost is obtained as $C_n^T = c^{rej} \sum_{i \in S} b_{i,n}\ p_m^a\left(\nabla | i\right),\ \ n = 1, ..., N$. Also, the diabetess-related cost is obtained as $C_n^D = (b_{6,n} + b_{7,n} + b_{8,n}) * c^{PD} + (b_{3,n} + b_{4,n} + b_{5,n}) * c^D, n = 1, ..., N$, where the first and second term inside $(\dots)$ represents $Pr\{$having pre-diabetes in period $n\}$ and $Pr\{$having diabetes in period $n\}$, respectively.

A.2.3 Model Informativeness in the Medical Context

We show examples of $\mathbf{P}/\mathbf{Q}$ matrices (estimated from our clinical data set), where the model informativeness condition (discussed in §2.4) is met. Note that, due to the large sizes of matrices and number of actions, we only present the results for actions a_1 and a_4. As can be observed from these matrices (see Table A.5-A.6), model $m = 1$ is the least informative model in the cloud of models M, and hence, it can be considered as a fixed BIWC member.

A.2.4 Validation

We validate our estimated probability matrices via the following steps.

Expert opinion: after obtaining the point estimates for **P/Q** matrices, we consulted them with our co-authors who are physician experts in the endocrinology as well as transplantation/nephrology areas. Then, they guided us to further adjust the Baum-Welch algorithm, and bring these matrices more to clinical realism.

Clinical data: first, we let s_n, o_n, and a_n be the health state, the observaion, and the action in period $n < N$, respectively (unless otherwise stated). We use *cross-validation* by splitting our data into *training* and *testing* sets (with equal size of patients in each set): (1) calibrating point estimates for **P/Q** matrices from the training set and (2) validating these estimated parameters on the testing set. For the validation process, we target the progression of blood glucose levels and tacrolimus trough levels, where (a) transition rates are captured by our estimated **P/Q** matrices, and (b) information regarding the actual prescribing decisions by physicians in any period $n < N$ (e.g., observation o_n from medical test results and medical regimen a_n prescribed by physicians) is retrieved from the testing set (see Figure A.1a). Also, to account for the variability of training and testing sets, we iterate the foregoing procedure 10 times, where we randomly select different sets each time. To characterize our validation criteria, we first define the following measure:

$$Pr\{\hat{o}_{n+1} = o | o_n, a_n, a_{n+1}\} = \sum_{s_{n+1} \in S} \sum_{s_n \in S} q^{a_n}(o_n|s_n) * p^{a_n}(s_{n+1}|s_n) * q^{a_{n+1}}(o|s_{n+1}), \tag{A.23}$$

where the three terms on the RHS are described by our illustration in Figure A.1b. Box 1: since observation o_n and action a_n are known from the testing data, the

probability of being in core state s_n is captured by $q^{a_n}(o_n|s_n)$. Box 2: knowing a_n as the medical action in period n, the probability of having a transition to a new core state is captured by $p^{a_n}(s_{n+1}|s_n)$. Box 3: knowing a_{n+1} as the medical action in period $n+1$, the probability of making a new observation is measured by $q^{a_{n+1}}(o|s_{n+1})$. Using the measure introduced in Equation (A.23), we now define four validation criteria:

$$\text{Criterion 1: violation in matching observations } = 1 - Pr\{\hat{o}_{n+1} = o_{n+1}|o_n, a_n, a_{n+1}\}, \tag{A.24a}$$

$$\text{Criterion 2: likelihood of death } = Pr\{\hat{o}_{n+1} = \Delta|o_n, a_n, a_{n+1}\}, \tag{A.24b}$$

$$\text{Criterion 3: likelihood of organ rejection } = Pr\{\hat{o}_{n+1} = \nabla|o_n, a_n, a_{n+1}\}, \tag{A.24c}$$

$$\text{Criterion 4: likelihood of developing diabetes } = \sum_{o\in\{o_1,o_2,o_3\}} Pr\{\hat{o}_{n+1} = o|o_n, a_n, a_{n+1}\}, \tag{A.24d}$$

where criterion 1 measures the percentage of times that our estimation does not match the actual observation o_{n+1} in the testing data. Criteria 2–4 represent measuring the likelihoods of deaths, organ rejection, and onset of diabetes when following our estimated parameters. Since these estimations are used in conjunction with the the actual prescribing decisions by physicians (i.e., the data from the testing set), this helps us to calibrate our derived parameters against existing decision processes in the medical practice.

Note that these validation criteria are obtained for each patient in the testing data set (i.e., 203 patients) and pair of periods $(n, n+1)$ for $n \leq 11$. Together with 10 iterations for our cross-validation, there will be a total of $\approx 20,000$ cases under each cohort of patients. The results for the four criteria are reported in Figure A.2.

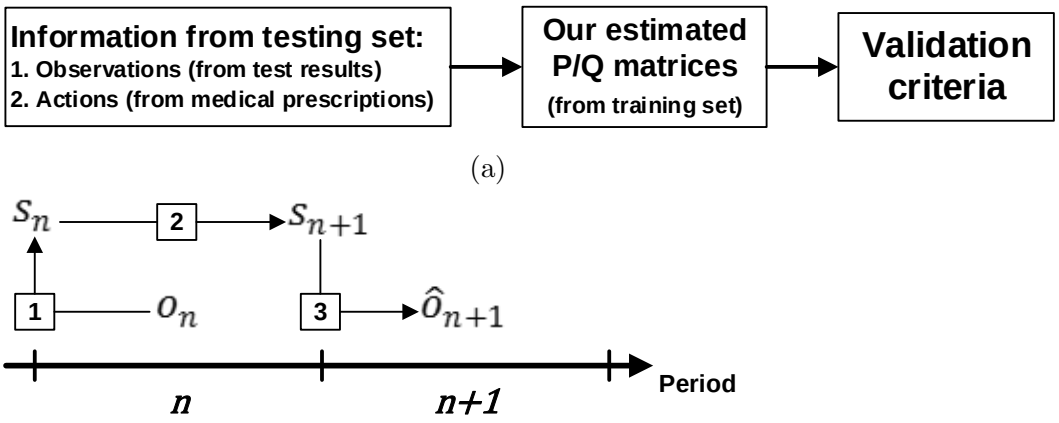

Figure A.1: An Illustration for Our Validation Mechanism

We note that, for death and organ rejection, we use two benchmark thresholds: one from our clinical data and the other from the national data (OPTN, 2011). We also observe that there exist differences between these two thresholds for each of death and organ rejection (e.g., average rates of organ rejection in our data and the national data are 8.108% and 6.35%, respectively). This, may be, in part, due to the fact that the corresponding data sets were collected throughout different years: 1999–2006 for our data, and 2008–2015 for the national data. We also note that, for the case of developing diabetes, the average rate obtained from our data (i.e., 22%) is very close to that reported by the medical literature (i.e., 22.9%) (see, e.g., Woodward et al. (2003)). The results in Figure A.2 shows that our estimated parameters can yield reasonable outcomes compared to the existing decision processes (either the practice from our partner hospital or other national healthcare settings). Finally, for the validation of reward parameters, although we obtain the values of qol and RLE from the extant literature (see Appendix B.1), we conduct various sensitivity analyses to check the robustness of our numerical results (see Appendix E for more details).

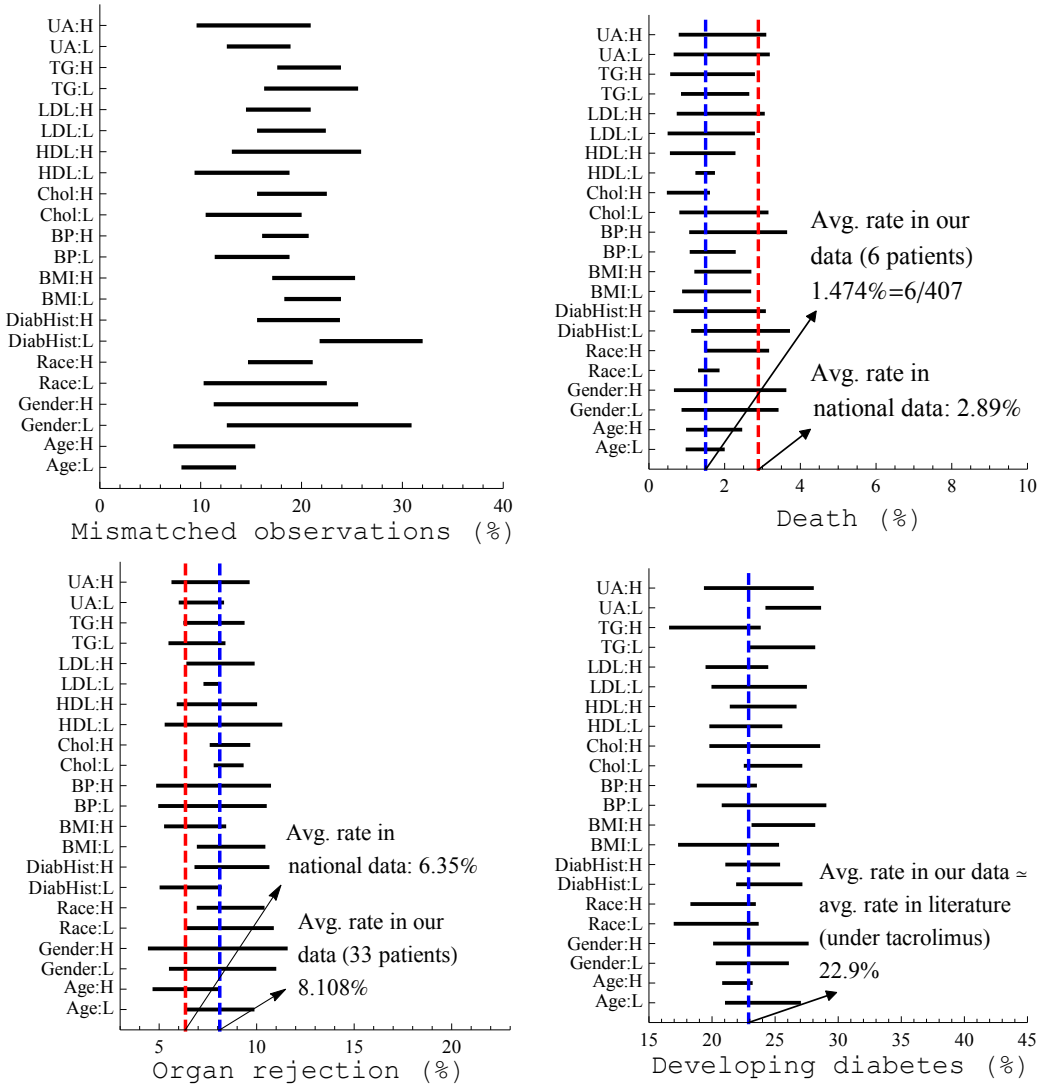

Figure A.2: 95% Confidence Intervals for the Validation Criteria in Equations (A.24a)–(A.24d) (Numbers on X-axis Represent Likelihoods)

A.2.5 Numerical Evaluation of Sufficient Conditions

Regarding the four sufficient conditions that we employed to establish our structural properties (§2.4 in the main body), here, we numerically evaluate the validity of these conditions using our data set.

Condition 2.4.1 (Monotonicity of Reward). As can be observed from Equations

(2.17a), (2.17b), and (2.18) (§2.5.1 in the main body), Condition 2.4.1 is met in our medical problem.

Condition 2.4.2 (TP_2 Transitions). Since $\mathbf{P}_m^a$ and $\mathbf{Q}_m^a$ are both 11×11 matrices, there will be a total of $2 \times \binom{11}{2} \times \binom{11}{2} = 6,050$ different 2×2 minors. Considering all actions and models, there will be a total of $6,050 \times 6 \times 3 = 108,900$ such minors. We obtain the average % of violations (i.e., a negative 2×2 minor) over all of these 108,900 cases. Based on the results in Table A.10, Condition 2.4.2 holds in the majority of cases.

Condition 2.4.3. We utilize both Condition 2.4.3 and its reverse in our analytical results on the impact of conservatism level λ on the intensity of medication regimens (see our discussion before Corollary 2.4.1 in §2.4). Hence, we do not numerically evaluate Condition 2.4.3 in our numerical results.

Condition 2.4.4. There are 8 different comparisons among ordered actions. Also, considering a uniform grid with a 0.2 resolution, we will have $\binom{|\mathcal{S}|+5-1}{5} = \binom{13}{5}$ =1,287 different belief vectors for $\mathbf{b} \in \Pi_{PO}$. For the time horizon length, we consider a 3-month horizon. Together with a 3-month planning horizon, 3 comparisons among different models, and 10 comparisons along each row $i \in |S|$, there will be a total of $8 \times 1,287 \times 3 \times 3 \times 10 = 926,640$ different comparisons. We provide the average % of violations over all of these 926,640 cases in Table A.10. Despite minor violations in Condition 2.4.4, our numerical results in §2.5.2 (the optimal policy regions) imply that there can exist control-limit policies across different risk factors.

A.3 Robust Optimal Medication Policies (Other Cohorts)

Regarding our results from Observation 2.5.1, here in Figure A.3 we present our results for all cohorts of patients.

A.4 Micro-Simulation Model for Comparing Policies

See Table A.7 for the micro-simulation model.

Line 5: 43,758 $= \left(\begin{smallmatrix} |\mathcal{S}|+10-1 \\ 10 \end{smallmatrix} \right) = \left(\begin{smallmatrix} 18 \\ 10 \end{smallmatrix} \right)$ different initial belief vectors (10=1/0.1, where 0.1 is the resolution).

Lines 6–10: $\Psi^A_{n,\lambda}$ is the set of $\boldsymbol{\psi}$-vectors for our APOMDP approach (obtained from Proposition 2.4.1; §2.4 in the main body). Since the POMDP approach ignores the ambiguity, it utilizes each model instead of the whole cloud of models. Thus, we can obtain the corresponding set of $\boldsymbol{\psi}$-vectors for the POMDP from $\Psi^A_{n,\lambda}$ by ignoring λ and considering m instead of M. We show this set by $\Psi^P_{n,m}$ for each model $m \in M$.

Lines 11–16: for each initial belief vector **(representing an individual patient)**, we simulate his/her life during the planning horizon under each policy. For each patient, we consider 1,000 replications in our simulation to account for (a) the simulation bias, (b) possible medical observations, and (c) different levels of a risk factor (for dynamic risk factors). These replications are set such that each policy can be simulated under the same medical observations or risk levels. Therefore, any variations in the end results would be attributed only to the performance of each policy (and not the underlying stochasticity of our simulation).

Lines 17–26: we return the performance measure (e.g., avg. QALE) for POMDP and benchmark approaches. We note that we do not consider ambiguity (and hence the APOMDP objective function) for these approaches. Thus, they are evaluated based on each individual model m (and not the conservatism level λ). Therefore, when comparing our APOMDP approach with the POMDP and benchmark policies, we report the performance measures by taking average results over all models in the cloud. For each approach, we (1) obtain the medication regimen based on the current belief vector in each time period, (2) measure the outcome (e.g., QALE) in that period

based on the regimen and the belief vector, and (3) update the belief vector for the next period. We then repeat this procedure for all time periods, and finally return the cumulative measure over the planning horizon (for each individual patient).

Lines 27–35: we return the outcomes for our APOMDP approach based on the same procedure above, with the difference that we follow this procedure for each conservatism level λ. We note that the APOMDP approach determines the optimal medication regimen based on the worst and the best models in the cloud ($\underline{m}$ and $\overline{m}$). However, when we update a belief vector, this has to be done under each individual model. Therefore, in lines 32–34, we take the average of the updated belief vectors over all models.

Lines 37–38: considering number of iterations (1,000) and initial belief vectors (43,758), we return the average outcomes over a total of $43,758 \times 1,000 \times |\Lambda| \approx 1.3 \times 10^8$ instances for the APOMDP approach and $43,758 \times 1,000 \times |M| \approx 1.3 \times 10^8$ instances for the POMDP and benchmark approaches.

A.5 Sensitivity Analyses for Reward Parameters

In Table A.11, we consider eight parameter sets for conducting sensitivity analyses for *qol* and *RLE* values, where both transplanted-related (e.g., organ rejection/survival) and diabetes-related (e.g., healthy/diabetic) reward parameters are changed simultaneously. Also, the values in Table A.11 are set such that the occurrence of diabetes (compared to an organ rejection) has a higher (e.g., sets 1–4) or lower (e.g., sets 7–8) impact on a patient's QALE. This, in turn, can address different preferences of patients/providers with respect to organ rejection and diabetes outcomes. Then, for each parameter set in Table A.11, we run our simulation model to compare the optimal policies obtained from our APOMDP approach against the benchmarks (similar to the results presented in Tables 2.6-2.7 in the main body).

We then report the average improvement in QALE (per patient) in Table A.12. As can be observed from this table, the results in §2.5.2 of the main body are robust to estimation errors in reward parameters.

Table A.2: Input Parameters for the Immediate Reward (Column "Values" Includes the Estimated Values for QOL(Diabetes) and QOL(Healthy), Respectively)

Factor	Level	Values
Age	Low	0.79,1.00
	High	0.75,0.96
Gender	Low	0.78,1.00
	High	0.82,1.00
Race	Low	0.79,1.00
	High	0.76,0.97
Diab Hist	Low	0.80,1.00
	High	0.60,0.80
BMI	Low	0.83,1.00
	High	0.78,0.96
BP	Low	0.80,1.00
	High	0.65,0.85

Factor	Level	Values
Chol	Low	0.80,1.00
	High	0.58,0.78
HDL	Low	0.80,1.00
	High	0.62,0.82
LDL	Low	0.80,1.00
	High	0.58,0.78
TG	Low	0.80,1.00
	High	0.62,0.82
UA	Low	0.80,1.00
	High	0.51,0.71

Table A.3: Input Parameters for the Lump-sum Reward (Column "Values" Includes the Estimated Values for RLE(Diabetes) and RLE(Healthy), Respectively)

Factor	Level	Values
Age	Low	33.01,47.18
	High	13.86,21.09
Gender	Low	28.03,40.83
	High	24.87,35.72
Race	Low	26.39,37.57
	High	28.48,40.88
Diab Hist	Low	23.44,34.13
	High	6.29,16.98
BMI	Low	24.23,36.23
	High	14.68,26.68
BP	Low	20.00,32.00
	High	16.83,28.83

Factor	Level	Values
Chol	Low	17.62,29.62
	High	16.10,28.10
HDL	Low	22.13,34.13
	High	14.75,22.75
LDL	Low	22.13,34.13
	High	17.79,29.79
TG	Low	22.13,34.13
	High	14.75,22.75
UA	Low	22.13,34.13
	High	18.13,30.13

Table A.4: Input Parameters for the Immediate and Lump-sum Reward Vectors (Column "Values" Includes the Estimated Values for Organ Rejection and Organ Survival, Respectively; The Left (Right) Table Includes QOL (RLE) Scores)

Factor	Level	Values
Age	Low	0.65,0.80
	High	0.59,0.74
Gender	Low	0.62,0.77
	High	0.62,0.77

Factor	Level	Values
Age	Low	18.80,25.28
	High	7.75,10.46
Gender	Low	15.10,20.55
	High	14.77,19.74
Race	Low	14.80,19.88
	High	13.69,18.38

Table A.5: Set of **P** and **Q** Matrices Estimated from Our Data Set (Action a_1)

$$
\mathbf{P}^{a_1}_{m=1} = \begin{pmatrix}
1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0. & 1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0.00681372 & 0.0124505 & 0.0511819 & 0.537164 & 0.266778 & 0.00981724 & 0.062657 & 0.0278762 & 0.00458408 & 0.0118908 & 0.00878662 \\
0.00751639 & 0.00883785 & 0.0602023 & 0.245941 & 0.545602 & 0.00948253 & 0.0276829 & 0.0660651 & 0.00657957 & 0.00924982 & 0.0128405 \\
0.0102003 & 0.00567662 & 0.0202381 & 0.154302 & 0.678176 & 0.00468744 & 0.0212342 & 0.0770074 & 0.00576591 & 0.00577582 & 0.0169366 \\
0.0057853 & 0.0158703 & 0.00878238 & 0.0497038 & 0.0282457 & 0.0458427 & 0.438479 & 0.216776 & 0.012159 & 0.116785 & 0.06157 \\
0.00687891 & 0.0131233 & 0.0121686 & 0.0224588 & 0.04922 & 0.0385303 & 0.194102 & 0.441404 & 0.019733 & 0.0608755 & 0.141505 \\
0.00835953 & 0.0101422 & 0.0103174 & 0.0133608 & 0.0588088 & 0.0157693 & 0.125166 & 0.564431 & 0.00687547 & 0.0358615 & 0.150908 \\
0.00480529 & 0.0140364 & 0.007546 & 0.0265074 & 0.0137826 & 0.0132096 & 0.0938992 & 0.0534071 & 0.0417127 & 0.484337 & 0.246756 \\
0.00608287 & 0.0124811 & 0.00807462 & 0.0179491 & 0.0156387 & 0.0156464 & 0.0490228 & 0.0965136 & 0.0505721 & 0.212273 & 0.515745 \\
0.00628541 & 0.0092122 & 0.00789687 & 0.0132755 & 0.0249036 & 0.00845813 & 0.0297009 & 0.122416 & 0.0170334 & 0.11903 & 0.641788 \\
1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0. & 1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0.00294406 & 0.00883219 & 0.0431796 & 0.542689 & 0.270854 & 0.00686948 & 0.0824338 & 0.033366 & 0. & 0.00490677 & 0.00392542 \\
0.00202224 & 0.00505561 & 0.0525784 & 0.239636 & 0.565217 & 0.00808898 & 0.033367 & 0.0839232 & 0.00101112 & 0.00404449 & 0.00505561 \\
0.00403633 & 0.00201816 & 0.0110999 & 0.14329 & 0.703345 & 0.00201816 & 0.0232089 & 0.0998991 & 0. & 0.00100908 & 0.00807265 \\
0.00104712 & 0.00942408 & 0.00314136 & 0.0387435 & 0.0219895 & 0.0418848 & 0.470157 & 0.225131 & 0.00732984 & 0.0122513 & 0.0586387 \\
0.00098142 & 0.006917 & 0.00395257 & 0.0148221 & 0.041502 & 0.034585 & 0.200593 & 0.474308 & 0.0158103 & 0.0062253 & 0.144269 \\
0.00197824 & 0.00396648 & 0.00098912 & 0.00692384 & 0.0504451 & 0.0098912 & 0.12364 & 0.610287 & 0.00197824 & 0.0356083 & 0.154303 \\
0. & 0.00920245 & 0.00204499 & 0.0153374 & 0.00715746 & 0.00715746 & 0.095092 & 0.0480573 & 0.0378323 & 0.525562 & 0.252556 \\
0.000996016 & 0.00796813 & 0.000996016 & 0.00697211 & 0.00996016 & 0.00896414 & 0.0498008 & 0.0936255 & 0.0498008 & 0.224104 & 0.546813 \\
0.00100503 & 0.00502513 & 0. & 0.00201005 & 0.0201005 & 0.00100503 & 0.0301508 & 0.121608 & 0.0140704 & 0.120603 & 0.684422 \\
1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0. & 1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0.00134879 & 0.00754194 & 0.0489525 & 0.560721 & 0.272643 & 0.00864321 & 0.0448135 & 0.025228 & 0.00392757 & 0.0180025 & 0.00817826 \\
0.00325161 & 0.00520184 & 0.0523417 & 0.25482 & 0.570687 & 0.00758449 & 0.0132199 & 0.0612715 & 0.00580602 & 0.011298 & 0.0145174 \\
0.00649306 & 0.00265873 & 0.00748836 & 0.158369 & 0.712275 & 0.00364796 & 0.00754597 & 0.0707157 & 0.00426058 & 0.00664943 & 0.0198967 \\
0.0000736682 & 0.0105928 & 0.00358942 & 0.0449759 & 0.0201531 & 0.0447736 & 0.446868 & 0.226388 & 0.0117438 & 0.128932 & 0.0619096 \\
0.00206698 & 0.00835772 & 0.00867745 & 0.0190741 & 0.0393351 & 0.0325497 & 0.190003 & 0.467368 & 0.018215 & 0.0645927 & 0.14976 \\
0.00372449 & 0.00546 & 0.00767673 & 0.0107396 & 0.0480244 & 0.00671191 & 0.116505 & 0.599494 & 0.00407877 & 0.0364498 & 0.161135 \\
0.00101611 & 0.0107824 & 0.00173462 & 0.0187317 & 0.00536828 & 0.0109092 & 0.0898649 & 0.0481006 & 0.0439419 & 0.513174 & 0.256377 \\
0.00342503 & 0.00834015 & 0.00366496 & 0.0126339 & 0.00637246 & 0.0134667 & 0.0422562 & 0.093354 & 0.0487412 & 0.222041 & 0.545704 \\
0.00411813 & 0.00463481 & 0.00413036 & 0.00911029 & 0.0155729 & 0.00638048 & 0.0212353 & 0.120216 & 0.0114876 & 0.121758 & 0.681356 \\
1. & 0. & 0. & 0. & 0. & 0. & & & & & \\
0. & 1. & 0. & 0. & 0. & 0. & & & & & \\
0. & 0. & 0.615 & 0.098 & 0.011 & 0.19 & 0.03 & 0.003 & 0.045 & 0.007 & 0.001 & & & & \\
0. & 0. & 0.076 & 0.585 & 0.061 & 0.024 & 0.181 & 0.019 & 0.006 & 0.043 & 0.005 & & & & \\
0. & 0. & 0.011 & 0.098 & 0.615 & 0.003 & 0.03 & 0.19 & 0.001 & 0.007 & 0.045 & & & & \\
0. & 0. & 0.052 & 0.008 & 0.001 & 0.683 & 0.108 & 0.012 & 0.116 & 0.018 & 0.002 & & & & \\
0. & 0. & 0.006 & 0.049 & 0.005 & 0.084 & 0.651 & 0.068 & 0.014 & 0.111 & 0.012 & & & & \\
0. & 0. & 0.001 & 0.008 & 0.052 & 0.012 & 0.108 & 0.683 & 0.002 & 0.018 & 0.116 & & & & \\
0. & 0. & 0.002 & 0. & 0. & 0.019 & 0.003 & 0. & 0.829 & 0.132 & 0.015 & & & & \\
0. & 0. & 0. & 0.002 & 0. & 0.002 & 0.018 & 0.002 & 0.102 & 0.791 & 0.083 & & & & \\
0. & 0. & 0. & 0. & 0.002 & 0. & 0.003 & 0.019 & 0.015 & 0.132 & 0.829 & & & & \\
1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & & & & \\
0. & 1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & & & & \\
0. & 0. & 0.626 & 0.097 & 0.016 & 0.174 & 0.027 & 0.005 & 0.047 & 0.007 & 0.001 & & & & \\
0. & 0. & 0.08 & 0.59 & 0.069 & 0.022 & 0.164 & 0.019 & 0.006 & 0.045 & 0.005 & & & & \\
0. & 0. & 0.015 & 0.108 & 0.615 & 0.004 & 0.03 & 0.172 & 0.001 & 0.008 & 0.047 & & & & \\
0. & 0. & 0.054 & 0.008 & 0.001 & 0.673 & 0.105 & 0.017 & 0.12 & 0.019 & 0.003 & & & & \\
0. & 0. & 0.007 & 0.051 & 0.006 & 0.086 & 0.634 & 0.075 & 0.015 & 0.113 & 0.013 & & & & \\
0. & 0. & 0.001 & 0.009 & 0.053 & 0.016 & 0.116 & 0.663 & 0.003 & 0.021 & 0.118 & & & & \\
0. & 0. & 0.003 & 0.001 & 0. & 0.025 & 0.004 & 0.001 & 0.817 & 0.128 & 0.021 & & & & \\
0. & 0. & 0. & 0.003 & 0.003 & 0.003 & 0.024 & 0.003 & 0.104 & 0.772 & 0.091 & & & & \\
0. & 0. & 0. & 0.001 & 0.003 & 0.001 & 0.004 & 0.025 & 0.019 & 0.141 & 0.806 & & & & \\
1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & & & & \\
0. & 1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & & & & \\
0. & 0. & 0.616 & 0.092 & 0.01 & 0.204 & 0.03 & 0.003 & 0.038 & 0.006 & 0.001 & & & & \\
0. & 0. & 0.07 & 0.587 & 0.062 & 0.023 & 0.194 & 0.02 & 0.004 & 0.036 & 0.004 & & & & \\
0. & 0. & 0.016 & 0.099 & 0.603 & 0.005 & 0.033 & 0.2 & 0.001 & 0.006 & 0.037 & & & & \\
0. & 0. & 0.057 & 0.008 & 0.001 & 0.694 & 0.103 & 0.011 & 0.108 & 0.016 & 0.002 & & & & \\
0. & 0. & 0.006 & 0.054 & 0.006 & 0.079 & 0.66 & 0.069 & 0.012 & 0.103 & 0.011 & & & & \\
0. & 0. & 0.001 & 0.009 & 0.055 & 0.018 & 0.112 & 0.679 & 0.003 & 0.017 & 0.106 & & & & \\
0. & 0. & 0.002 & 0. & 0. & 0.024 & 0.004 & 0. & 0.832 & 0.124 & 0.014 & & & & \\
0. & 0. & 0. & 0.002 & 0. & 0.003 & 0.023 & 0.002 & 0.095 & 0.792 & 0.083 & & & & \\
0. & 0. & 0. & 0. & 0.002 & 0.001 & 0.004 & 0.024 & 0.021 & 0.134 & 0.814 & & & &
\end{pmatrix}
$$

$$
\mathbf{Q}^{a_1}_{m=1} = \begin{pmatrix}
1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0. & 1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0. & 0. & 0.626 & 0.097 & 0.016 & 0.174 & 0.027 & 0.005 & 0.047 & 0.007 & 0.001 \\
0. & 0. & 0.08 & 0.59 & 0.069 & 0.022 & 0.164 & 0.019 & 0.006 & 0.045 & 0.005 \\
0. & 0. & 0.015 & 0.108 & 0.615 & 0.004 & 0.03 & 0.172 & 0.001 & 0.008 & 0.047 \\
0. & 0. & 0.054 & 0.008 & 0.001 & 0.673 & 0.105 & 0.017 & 0.12 & 0.019 & 0.003 \\
0. & 0. & 0.007 & 0.051 & 0.006 & 0.086 & 0.634 & 0.075 & 0.015 & 0.113 & 0.013 \\
0. & 0. & 0.001 & 0.009 & 0.053 & 0.016 & 0.116 & 0.663 & 0.003 & 0.021 & 0.118 \\
0. & 0. & 0.003 & 0.001 & 0. & 0.025 & 0.004 & 0.001 & 0.817 & 0.128 & 0.021 \\
0. & 0. & 0. & 0.003 & 0.003 & 0.003 & 0.024 & 0.003 & 0.104 & 0.772 & 0.091 \\
0. & 0. & 0. & 0.001 & 0.003 & 0.001 & 0.004 & 0.025 & 0.019 & 0.141 & 0.806 \\
1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0. & 1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0. & 0. & 0.616 & 0.092 & 0.01 & 0.204 & 0.03 & 0.003 & 0.038 & 0.006 & 0.001 \\
0. & 0. & 0.07 & 0.587 & 0.062 & 0.023 & 0.194 & 0.02 & 0.004 & 0.036 & 0.004 \\
0. & 0. & 0.016 & 0.099 & 0.603 & 0.005 & 0.033 & 0.2 & 0.001 & 0.006 & 0.037 \\
0. & 0. & 0.057 & 0.008 & 0.001 & 0.694 & 0.103 & 0.011 & 0.108 & 0.016 & 0.002 \\
0. & 0. & 0.006 & 0.054 & 0.006 & 0.079 & 0.66 & 0.069 & 0.012 & 0.103 & 0.011 \\
0. & 0. & 0.001 & 0.009 & 0.055 & 0.018 & 0.112 & 0.679 & 0.003 & 0.017 & 0.106 \\
0. & 0. & 0.002 & 0. & 0. & 0.024 & 0.004 & 0. & 0.832 & 0.124 & 0.014 \\
0. & 0. & 0. & 0.002 & 0. & 0.003 & 0.023 & 0.002 & 0.095 & 0.792 & 0.083 \\
0. & 0. & 0. & 0. & 0.002 & 0.001 & 0.004 & 0.024 & 0.021 & 0.134 & 0.814
\end{pmatrix}
$$

$$
\mathbf{Q}^{a_1}_{m=2} = \begin{pmatrix}
1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0. & 1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0. & 0. & 0.615 & 0.098 & 0.011 & 0.19 & 0.03 & 0.003 & 0.045 & 0.007 & 0.001 \\
0. & 0. & 0.076 & 0.585 & 0.061 & 0.024 & 0.181 & 0.019 & 0.006 & 0.043 & 0.005 \\
0. & 0. & 0.011 & 0.098 & 0.615 & 0.003 & 0.03 & 0.19 & 0.001 & 0.007 & 0.045 \\
0. & 0. & 0.052 & 0.008 & 0.001 & 0.683 & 0.108 & 0.012 & 0.116 & 0.018 & 0.002 \\
0. & 0. & 0.006 & 0.049 & 0.005 & 0.084 & 0.651 & 0.068 & 0.014 & 0.111 & 0.012 \\
0. & 0. & 0.001 & 0.008 & 0.052 & 0.012 & 0.108 & 0.683 & 0.002 & 0.018 & 0.116 \\
0. & 0. & 0.002 & 0. & 0. & 0.019 & 0.003 & 0. & 0.829 & 0.132 & 0.015 \\
0. & 0. & 0. & 0.002 & 0. & 0.002 & 0.018 & 0.002 & 0.102 & 0.791 & 0.083 \\
0. & 0. & 0. & 0. & 0.002 & 0. & 0.003 & 0.019 & 0.015 & 0.132 & 0.829 \\
1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0. & 1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0. & 0. & 0.626 & 0.097 & 0.016 & 0.174 & 0.027 & 0.005 & 0.047 & 0.007 & 0.001 \\
0. & 0. & 0.08 & 0.59 & 0.069 & 0.022 & 0.164 & 0.019 & 0.006 & 0.045 & 0.005 \\
0. & 0. & 0.015 & 0.108 & 0.615 & 0.004 & 0.03 & 0.172 & 0.001 & 0.008 & 0.047 \\
0. & 0. & 0.054 & 0.008 & 0.001 & 0.673 & 0.105 & 0.017 & 0.12 & 0.019 & 0.003 \\
0. & 0. & 0.007 & 0.051 & 0.006 & 0.086 & 0.634 & 0.075 & 0.015 & 0.113 & 0.013 \\
0. & 0. & 0.001 & 0.009 & 0.053 & 0.016 & 0.116 & 0.663 & 0.003 & 0.021 & 0.118 \\
0. & 0. & 0.003 & 0.001 & 0. & 0.025 & 0.004 & 0.001 & 0.817 & 0.128 & 0.021 \\
0. & 0. & 0. & 0.003 & 0.003 & 0.003 & 0.024 & 0.003 & 0.104 & 0.772 & 0.091 \\
0. & 0. & 0. & 0.001 & 0.003 & 0.001 & 0.004 & 0.025 & 0.019 & 0.141 & 0.806 \\
1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0. & 1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0. & 0. & 0.616 & 0.092 & 0.01 & 0.204 & 0.03 & 0.003 & 0.038 & 0.006 & 0.001 \\
0. & 0. & 0.07 & 0.587 & 0.062 & 0.023 & 0.194 & 0.02 & 0.004 & 0.036 & 0.004 \\
0. & 0. & 0.016 & 0.099 & 0.603 & 0.005 & 0.033 & 0.2 & 0.001 & 0.006 & 0.037 \\
0. & 0. & 0.057 & 0.008 & 0.001 & 0.694 & 0.103 & 0.011 & 0.108 & 0.016 & 0.002 \\
0. & 0. & 0.006 & 0.054 & 0.006 & 0.079 & 0.66 & 0.069 & 0.012 & 0.103 & 0.011 \\
0. & 0. & 0.001 & 0.009 & 0.055 & 0.018 & 0.112 & 0.679 & 0.003 & 0.017 & 0.106 \\
0. & 0. & 0.002 & 0. & 0. & 0.024 & 0.004 & 0. & 0.832 & 0.124 & 0.014 \\
0. & 0. & 0. & 0.002 & 0. & 0.003 & 0.023 & 0.002 & 0.095 & 0.792 & 0.083 \\
0. & 0. & 0. & 0. & 0.002 & 0.001 & 0.004 & 0.024 & 0.021 & 0.134 & 0.814
\end{pmatrix}
$$

$$
\mathbf{Q}^{a_1}_{m=3} = \begin{pmatrix}
1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0. & 1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0. & 0. & 0.615 & 0.098 & 0.011 & 0.19 & 0.03 & 0.003 & 0.045 & 0.007 & 0.001 \\
0. & 0. & 0.076 & 0.585 & 0.061 & 0.024 & 0.181 & 0.019 & 0.006 & 0.043 & 0.005 \\
0. & 0. & 0.011 & 0.098 & 0.615 & 0.003 & 0.03 & 0.19 & 0.001 & 0.007 & 0.045 \\
0. & 0. & 0.052 & 0.008 & 0.001 & 0.683 & 0.108 & 0.012 & 0.116 & 0.018 & 0.002 \\
0. & 0. & 0.006 & 0.049 & 0.005 & 0.084 & 0.651 & 0.068 & 0.014 & 0.111 & 0.012 \\
0. & 0. & 0.001 & 0.008 & 0.052 & 0.012 & 0.108 & 0.683 & 0.002 & 0.018 & 0.116 \\
0. & 0. & 0.002 & 0. & 0. & 0.019 & 0.003 & 0. & 0.829 & 0.132 & 0.015 \\
0. & 0. & 0. & 0.002 & 0. & 0.002 & 0.018 & 0.002 & 0.102 & 0.791 & 0.083 \\
0. & 0. & 0. & 0. & 0.002 & 0. & 0.003 & 0.019 & 0.015 & 0.132 & 0.829 \\
1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0. & 1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0. & 0. & 0.626 & 0.097 & 0.016 & 0.174 & 0.027 & 0.005 & 0.047 & 0.007 & 0.001 \\
0. & 0. & 0.08 & 0.59 & 0.069 & 0.022 & 0.164 & 0.019 & 0.006 & 0.045 & 0.005 \\
0. & 0. & 0.015 & 0.108 & 0.615 & 0.004 & 0.03 & 0.172 & 0.001 & 0.008 & 0.047 \\
0. & 0. & 0.054 & 0.008 & 0.001 & 0.673 & 0.105 & 0.017 & 0.12 & 0.019 & 0.003 \\
0. & 0. & 0.007 & 0.051 & 0.006 & 0.086 & 0.634 & 0.075 & 0.015 & 0.113 & 0.013 \\
0. & 0. & 0.001 & 0.009 & 0.053 & 0.016 & 0.116 & 0.663 & 0.003 & 0.021 & 0.118 \\
0. & 0. & 0.003 & 0.001 & 0. & 0.025 & 0.004 & 0.001 & 0.817 & 0.128 & 0.021 \\
0. & 0. & 0. & 0.003 & 0.003 & 0.003 & 0.024 & 0.003 & 0.104 & 0.772 & 0.091 \\
0. & 0. & 0. & 0.001 & 0.003 & 0.001 & 0.004 & 0.025 & 0.019 & 0.141 & 0.806 \\
1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0. & 1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0. & 0. & 0.616 & 0.092 & 0.01 & 0.204 & 0.03 & 0.003 & 0.038 & 0.006 & 0.001 \\
0. & 0. & 0.07 & 0.587 & 0.062 & 0.023 & 0.194 & 0.02 & 0.004 & 0.036 & 0.004 \\
0. & 0. & 0.016 & 0.099 & 0.603 & 0.005 & 0.033 & 0.2 & 0.001 & 0.006 & 0.037 \\
0. & 0. & 0.057 & 0.008 & 0.001 & 0.694 & 0.103 & 0.011 & 0.108 & 0.016 & 0.002 \\
0. & 0. & 0.006 & 0.054 & 0.006 & 0.079 & 0.66 & 0.069 & 0.012 & 0.103 & 0.011 \\
0. & 0. & 0.001 & 0.009 & 0.055 & 0.018 & 0.112 & 0.679 & 0.003 & 0.017 & 0.106 \\
0. & 0. & 0.002 & 0. & 0. & 0.024 & 0.004 & 0. & 0.832 & 0.124 & 0.014 \\
0. & 0. & 0. & 0.002 & 0. & 0.003 & 0.023 & 0.002 & 0.095 & 0.792 & 0.083 \\
0. & 0. & 0. & 0. & 0.002 & 0.001 & 0.004 & 0.024 & 0.021 & 0.134 & 0.814
\end{pmatrix}
$$

Table A.6: Set of **P** and **Q** Matrices Estimated From Our Data Set (Action a_4)

$$
\mathbf{P}^{a_4}_{m=1} = \begin{pmatrix}
1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0. & 1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0.00693287 & 0.0202604 & 0.318274 & 0.423754 & 0.0786672 & 0.0561535 & 0.0646978 & 0.0150251 & 0.00728763 & 0.00625794 & 0.00268894 \\
0.00758777 & 0.0120293 & 0.0929377 & 0.628211 & 0.0889157 & 0.0189517 & 0.111595 & 0.0215623 & 0.00501643 & 0.01021114 & 0.00298179 \\
0.00621426 & 0.0129155 & 0.068431 & 0.490837 & 0.263369 & 0.0164166 & 0.0814037 & 0.046068 & 0.00537204 & 0.00350803 & 0.00546512 \\
0.00802008 & 0.0256709 & 0.0182616 & 0.0234351 & 0.0124323 & 0.275033 & 0.352296 & 0.0659679 & 0.0934737 & 0.0999839 & 0.0254259 \\
0.00825767 & 0.0199626 & 0.00722561 & 0.0261505 & 0.0123397 & 0.0856678 & 0.51147 & 0.0854594 & 0.0321867 & 0.178535 & 0.0327452 \\
0.00719233 & 0.0143644 & 0.00922481 & 0.0194035 & 0.017997 & 0.0631054 & 0.397044 & 0.226725 & 0.0215598 & 0.139221 & 0.0841622 \\
0.00702691 & 0.0260703 & 0.0174529 & 0.0172521 & 0.0111719 & 0.0494646 & 0.0628704 & 0.0170942 & 0.306848 & 0.391857 & 0.0928916 \\
0.00578912 & 0.0152919 & 0.0108229 & 0.0254042 & 0.011396 & 0.0254327 & 0.0904856 & 0.0156401 & 0.104007 & 0.607076 & 0.0886551 \\
0.00546508 & 0.0141237 & 0.0113879 & 0.0246632 & 0.017678 & 0.019788 & 0.0659401 & 0.0433119 & 0.078201 & 0.448996 & 0.270445 \\
1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0. & 1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0.00291545 & 0.0165209 & 0.328474 & 0.432459 & 0.0758017 & 0.0515063 & 0.0631681 & 0.01069 & 0.00680272 & 0.00971817 & 0.00194363 \\
0.00303337 & 0.00808898 & 0.0899899 & 0.643074 & 0.0920121 & 0.0131446 & 0.110212 & 0.0192113 & 0.00202224 & 0.0171891 & 0.00202224 \\
0.00099001 & 0.00899101 & 0.0639361 & 0.497502 & 0.281718 & 0.0110989 & 0.0779221 & 0.041958 & 0.001998 & 0.006699301 & 0.00699301 \\
0.001998 & 0.0189981 & 0.00799201 & 0.0119883 & 0.0029997 & 0.288711 & 0.373626 & 0.0659341 & 0.0939061 & 0.111888 & 0.021978 \\
0.00119861 & 0.0129096 & 0.000993049 & 0.0109235 & 0.0029715 & 0.08143 & 0.543198 & 0.0913605 & 0.0248262 & 0.19861 & 0.0307845 \\
0.001 & 0.008 & 0.002 & 0.007 & 0.007 & 0.06 & 0.416 & 0.245 & 0.014 & 0.153 & 0.087 \\
0.00192864 & 0.02025007 & 0.00867888 & 0.0096432 & 0.00192864 & 0.0433944 & 0.0675024 & 0.0125362 & 0.317261 & 0.429122 & 0.0877531 \\
0.00103734 & 0.00829876 & 0.00311203 & 0.0155602 & 0.00103734 & 0.0165975 & 0.096473 & 0.0124481 & 0.0954357 & 0.662863 & 0.0871369 \\
0.00095328 9 & 0.00762631 & 0.00285987 & 0.0152526 & 0.00762631 & 0.013346 & 0.0695901 & 0.042898 & 0.0705434 & 0.486177 & 0.283127 \\
1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0. & 1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0.00135902 & 0.0165893 & 0.320636 & 0.444987 & 0.0720303 & 0.0591123 & 0.0679763 & 0.00902922 & 0.00250056 & 0.00398384 & 0.00179677 \\
0.00222741 & 0.00854968 & 0.0837141 & 0.663621 & 0.0782115 & 0.0155087 & 0.12038 & 0.0170339 & 0.0001196813 & 0.00846189 & 0.00209568 \\
0.00115807 & 0.00965799 & 0.0564959 & 0.513491 & 0.269379 & 0.0118311 & 0.0851925 & 0.0453934 & 0.00108491 & 0.00131735 & 0.00499863 \\
0.0040257 & 0.0204169 & 0.0179388 & 0.0246904 & 0.00827067 & 0.286601 & 0.370897 & 0.0546441 & 0.089028 & 0.0976146 & 0.0258729 \\
0.00449361 & 0.0149301 & 0.00128562 & 0.0329591 & 0.00615935 & 0.0856641 & 0.538785 & 0.0754861 & 0.0290864 & 0.178079 & 0.0330718 \\
0.00341852 & 0.00911162 & 0.00288865 & 0.0230407 & 0.0158821 & 0.061026 & 0.412009 & 0.2306651 & 0.0182461 & 0.136786 & 0.0869404 \\
0.00351356 & 0.0216158 & 0.0161842 & 0.0161001 & 0.0071754 & 0.0506583 & 0.0672991 & 0.0092741 & 0.309434 & 0.405424 & 0.0933215 \\
0.00196924 & 0.011805 & 0.00846512 & 0.0260754 & 0.0064788 & 0.0232741 & 0.0972076 & 0.00790907 & 0.1011053 & 0.629007 & 0.0867559 \\
0.00144506 & 0.0101576 & 0.00862888 & 0.022759 & 0.0146461 & 0.016763 & 0.0686791 & 0.0413019 & 0.0736234 & 0.458484 & 0.283512 \\
1. & 0. & 0. & 0. & 0. & 0. & 0. & & & & \\
0. & 1. & 0. & 0. & 0. & 0. & 0. & & & & \\
0 & 0 & 0.615 & 0.098 & 0.011 & 0.19 & 0.03 & 0.003 & 0.045 & 0.007 & 0.001 \\
0 & 0 & 0.076 & 0.585 & 0.061 & 0.024 & 0.181 & 0.019 & 0.006 & 0.043 & 0.005 \\
0 & 0 & 0.011 & 0.098 & 0.615 & 0.003 & 0.03 & 0.19 & 0.001 & 0.007 & 0.045 \\
0 & 0 & 0.052 & 0.008 & 0.001 & 0.683 & 0.108 & 0.012 & 0.116 & 0.018 & 0.002 \\
0 & 0 & 0.006 & 0.049 & 0.005 & 0.084 & 0.651 & 0.068 & 0.014 & 0.111 & 0.012 \\
0 & 0 & 0.001 & 0.008 & 0.052 & 0.012 & 0.108 & 0.683 & 0.002 & 0.018 & 0.116 \\
0 & 0 & 0.002 & 0. & 0. & 0.019 & 0.003 & 0. & 0.829 & 0.132 & 0.015 \\
0 & 0 & 0. & 0. & 0.002 & 0.002 & 0.018 & 0.002 & 0.102 & 0.791 & 0.083 \\
0 & 0 & 0. & 0. & 0. & 0. & 0.003 & 0.019 & 0.015 & 0.132 & 0.829 \\
0. & 1. & 0. & 0. & 0. & 0. & 0. & & & & \\
0. & 0. & 0. & 0. & 0. & 0. & 0. & & & & \\
0 & 0 & 0.608 & 0.094 & 0.02 & 0.197 & 0.03 & 0.007 & 0.037 & 0.006 & 0.001 \\
0 & 0 & 0.081 & 0.582 & 0.058 & 0.026 & 0.189 & 0.019 & 0.005 & 0.036 & 0.004 \\
0 & 0 & 0.01 & 0.108 & 0.603 & 0.003 & 0.035 & 0.196 & 0.001 & 0.007 & 0.037 \\
0 & 0 & 0.062 & 0.01 & 0.002 & 0.669 & 0.103 & 0.022 & 0.111 & 0.017 & 0.004 \\
0 & 0 & 0.008 & 0.06 & 0.006 & 0.089 & 0.64 & 0.064 & 0.015 & 0.107 & 0.011 \\
0 & 0 & 0.001 & 0.011 & 0.001 & 0.011 & 0.119 & 0.664 & 0.002 & 0.02 & 0.111 \\
0 & 0 & 0.003 & 0.001 & 0. & 0.02 & 0.003 & 0.001 & 0.819 & 0.126 & 0.027 \\
0 & 0 & 0. & 0.003 & 0.003 & 0.003 & 0.003 & 0.002 & 0.109 & 0.786 & 0.078 \\
0 & 0 & 0. & 0.001 & 0. & 0.003 & 0.004 & 0.02 & 0.014 & 0.146 & 0.812 \\
0. & 1. & 0. & 0. & 0. & 0. & 0. & & & & \\
0. & 0. & 0. & 0. & 0. & 0. & 0. & & & & \\
0 & 0 & 0.625 & 0.097 & 0.013 & 0.184 & 0.029 & 0.004 & 0.041 & 0.006 & 0.001 \\
0 & 0 & 0.078 & 0.589 & 0.069 & 0.023 & 0.173 & 0.02 & 0.005 & 0.038 & 0.005 \\
0 & 0 & 0.019 & 0.112 & 0.605 & 0.006 & 0.033 & 0.178 & 0.001 & 0.007 & 0.039 \\
0 & 0 & 0.042 & 0.007 & 0.001 & 0.685 & 0.107 & 0.015 & 0.121 & 0.019 & 0.003 \\
0 & 0 & 0.005 & 0.04 & 0.005 & 0.086 & 0.646 & 0.076 & 0.015 & 0.114 & 0.013 \\
0 & 0 & 0.001 & 0.008 & 0.041 & 0.021 & 0.123 & 0.663 & 0.004 & 0.022 & 0.117 \\
0 & 0 & 0.002 & 0. & 0. & 0.014 & 0.002 & 0. & 0.834 & 0.13 & 0.018 \\
0 & 0 & 0. & 0. & 0.002 & 0. & 0.013 & 0.002 & 0.104 & 0.785 & 0.092 \\
0 & 0 & 0. & 0. & 0.002 & 0. & 0.002 & 0.013 & 0.026 & 0.149 & 0.808
\end{pmatrix}
$$

$$
\mathbf{Q}^{a_4}_{m=1} = \begin{pmatrix}
1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0. & 1. & 0. & 0. & 0. & 0. & 0. & 0. & 0. & 0. \\
0 & 0 & 0.615 & 0.098 & 0.011 & 0.19 & 0.03 & 0.003 & 0.045 & 0.007 & 0.001 \\
0 & 0 & 0.076 & 0.585 & 0.061 & 0.024 & 0.181 & 0.019 & 0.006 & 0.043 & 0.005 \\
0 & 0 & 0.011 & 0.098 & 0.615 & 0.003 & 0.03 & 0.19 & 0.001 & 0.007 & 0.045 \\
0 & 0 & 0.052 & 0.008 & 0.001 & 0.683 & 0.108 & 0.012 & 0.116 & 0.018 & 0.002 \\
0 & 0 & 0.006 & 0.049 & 0.005 & 0.084 & 0.651 & 0.068 & 0.014 & 0.111 & 0.012 \\
0 & 0 & 0.001 & 0.008 & 0.052 & 0.012 & 0.108 & 0.683 & 0.002 & 0.018 & 0.116 \\
0 & 0 & 0.002 & 0. & 0. & 0.019 & 0.003 & 0. & 0.829 & 0.132 & 0.015 \\
0 & 0 & 0. & 0. & 0.002 & 0. & 0.003 & 0.019 & 0.015 & 0.132 & 0.829 \\
0. & 1. & 0. & 0. & 0. & 0. & 0. & & & & \\
0. & 0. & 0. & 0. & 0. & 0. & 0. & & & & \\
0 & 0 & 0.608 & 0.094 & 0.02 & 0.197 & 0.03 & 0.007 & 0.037 & 0.006 & 0.001 \\
0 & 0 & 0.081 & 0.582 & 0.058 & 0.026 & 0.189 & 0.019 & 0.005 & 0.036 & 0.004 \\
0 & 0 & 0.01 & 0.108 & 0.603 & 0.003 & 0.035 & 0.196 & 0.001 & 0.007 & 0.037 \\
0 & 0 & 0.062 & 0.01 & 0.002 & 0.669 & 0.103 & 0.022 & 0.111 & 0.017 & 0.004 \\
0 & 0 & 0.008 & 0.06 & 0.006 & 0.089 & 0.64 & 0.064 & 0.015 & 0.107 & 0.011 \\
0 & 0 & 0.001 & 0.011 & 0.001 & 0.011 & 0.119 & 0.664 & 0.002 & 0.02 & 0.111 \\
0 & 0 & 0.003 & 0.001 & 0. & 0.02 & 0.003 & 0.001 & 0.819 & 0.126 & 0.027 \\
0 & 0 & 0. & 0.003 & 0.003 & 0.003 & 0.003 & 0.002 & 0.109 & 0.786 & 0.078 \\
0 & 0 & 0. & 0.001 & 0. & 0.003 & 0.004 & 0.02 & 0.014 & 0.146 & 0.812 \\
0. & 1. & 0. & 0. & 0. & 0. & 0. & & & & \\
0. & 0. & 0. & 0. & 0. & 0. & 0. & & & & \\
0 & 0 & 0.625 & 0.097 & 0.013 & 0.184 & 0.029 & 0.004 & 0.041 & 0.006 & 0.001 \\
0 & 0 & 0.078 & 0.589 & 0.069 & 0.023 & 0.173 & 0.02 & 0.005 & 0.038 & 0.005 \\
0 & 0 & 0.019 & 0.112 & 0.605 & 0.006 & 0.033 & 0.178 & 0.001 & 0.007 & 0.039 \\
0 & 0 & 0.042 & 0.007 & 0.001 & 0.685 & 0.107 & 0.015 & 0.121 & 0.019 & 0.003 \\
0 & 0 & 0.005 & 0.04 & 0.005 & 0.086 & 0.646 & 0.076 & 0.015 & 0.114 & 0.013 \\
0 & 0 & 0.001 & 0.008 & 0.041 & 0.021 & 0.123 & 0.663 & 0.004 & 0.022 & 0.117 \\
0 & 0 & 0.002 & 0. & 0. & 0.014 & 0.002 & 0. & 0.834 & 0.13 & 0.018 \\
0 & 0 & 0. & 0. & 0.002 & 0. & 0.013 & 0.002 & 0.104 & 0.785 & 0.092 \\
0 & 0 & 0. & 0. & 0.002 & 0. & 0.002 & 0.013 & 0.026 & 0.149 & 0.808
\end{pmatrix}
$$

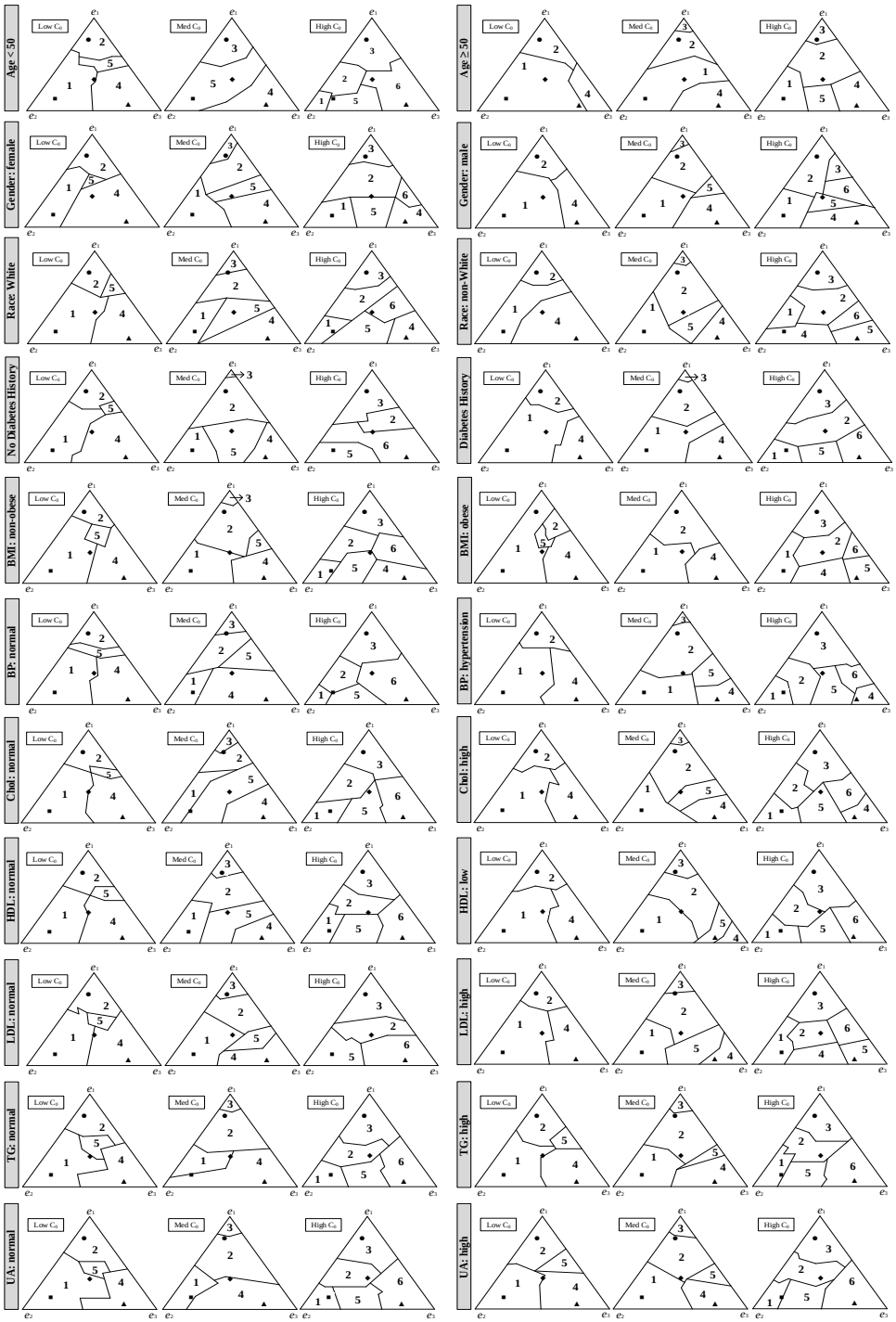

Figure A.3: Optimal Medication Policies for the First Visit Based on Different C_0 Levels and Diabetes Complications (e_1, e_2, e_3 Represent Diabetic, Pre-Diabetic, and Healthy Conditions, Respectively; e_j Denotes a Unit Vector with j^{th} Element Equal to 1 and Other Elements Equal To 0); Results Are Presented for the Case $\lambda = 0.5$

Table A.7: A Pseudocode for the Simulation Model (Superscripts A, P, and B Represent APOMDP, POMDP, and Benchmark Approaches, Respectively)

Inputs	1	planning time horizon: $N = 12$
	2	size of cloud: $\|M\| = 3$, size of ambiguity attitude set: $\|\Lambda\| = 3$
	3	cohort of patients: based on each risk factor in Table 2.2 (§2.5.1 in the main body)
	4	for the corresponding cohort: probability matrices $\mathbf{P}_m$,$\mathbf{Q}_m$ $(\forall m \in M)$ and reward parameters $\mathbf{r}_n(a)$, $\mathbf{R}_n$ $(\forall n \leq N, \forall a \in A)$ (see §2.5.1)
	5	$\mathbf{b}_i$, $i = 1, \ldots, 43758$ (43,758 initial belief vectors based on uniform grids with a 0.1 resolution)
Sets of ψ-vectors	6	**for** time period $n = 1$ to N
	7	**for each** conservatism level $\lambda \in \Lambda$
	8	**return** $\Psi^A_{n,\lambda}$ for the corresponding cohort ($\Psi^A_{n,\lambda}$: set of $\boldsymbol{\psi}$-vectors for the APOMDP approach)
	9	**for each** model $m \in M$
	10	**return** $\Psi^P_{n,m}$ for the corresponding cohort ($\Psi^P_{n,m}$: set of $\boldsymbol{\psi}$-vectors for the POMDP approach)
Initialization for all policies	11	**for** $i = 1, \ldots, 43758$ (number of initial belief vectors each representing an individual patient)
	12	**for** $j = 1$ to 1,000 (number of replications)
	13	**initialize** time period $n = 1$ and belief vector in this period: $\mathbf{b}^A_n = \mathbf{b}^P_n = \mathbf{b}^B_n = \mathbf{b}_i$
	14	**do** randomly generate sequences of observations $\mathbb{O} = \left(o_1, \ldots, o_{N-1}\right)$, $o_k \in O$, $k = 1, \ldots, N-1$
	15	**if** the corresponding cohort belongs to a dynamic risk factor
	16	**do** randomly generate a sequence of risk levels $\mathbb{L} = \left(l_1, l_2, \ldots, l_N\right)$, $l_k \in \{\text{low}, \text{high}\}$, $k = 1, \ldots, N$

Table A.8: Continuation of Table A.7 (Part 1)

Only follow for POMDP or benchmark	17	**for each** model $m \in M$
	18	**if** $n = N$ then **return** performance measure $\text{QALE}_N^P = (\mathbf{b}_N^P)'\mathbf{R}_N$ or $\text{QALE}_n^B = (\mathbf{b}_N^B)'\mathbf{R}_N$, and **go to** line 26 *
	19	**else if** $n < N$ then **go to** line 20
	20	**use** $\mathbf{b}_n^P$, m, and $\Psi_{n,m}^P$ to **identify** the medication regimen a^P
	21	**use** observation o_n and Table 2.5 (see §2.5.2) to **identify** the medication regimen a^B
	22	**return** performance measure: $\text{QALE}_n^P = (\mathbf{b}_n^P)'\mathbf{r}_n(a^P)$ or $\text{QALE}_n^B = (\mathbf{b}_n^B)'\mathbf{r}_n(a^B)$ if $o_n \in O \setminus \{\Delta, \nabla\}$
		$\text{QALE}_n^P = (\mathbf{b}_n^P)'\mathbf{R}_n$ or $\text{QALE}_n^B = (\mathbf{b}_n^B)'\mathbf{R}_n$ if $o_n \in \{\Delta, \nabla\}$
	23	**use** $\mathbf{b}_n^P$, a^P, o_n, and m to **update** the belief vector for the next time period $\mathbf{b}_{n+1}^P$ **
	24	**use** $\mathbf{b}_n^B$, a^B, o_n, and m to **update** the belief vector for the next time period $\mathbf{b}_{n+1}^B$
	25	**set** $n = n + 1$ and **go to** line 18
	26	**add** the performance measures over all periods and **return** the outcome $\mathbf{\Omega}_{ijm} = \{\text{QALE}, \text{COST}, \text{Number of medications}\}$

* As other measures, cost is measured by the procedure in Online Appendix B.2, and number of medications is determined from the regimens obtained in lines 20–21.

** For updating a belief vector, we use the Bayesian update in Equation (2.1) in §2.3.1.

Table A.9: Continuation of Table A.7 (Part 2)

Only follow for APOMDP	27	**for each** conservatism level $\lambda \in \Lambda$
	28	**if** $n = N$ then **return** performance measure $\text{QALE}_N^A = (\mathbf{b}_N^A)'\mathbf{R}_N$ and **go to** line 36
	29	**else if** $n < N$ then **go to** line 30
	30	**use** $\mathbf{b}_n^A$, λ, and $\Psi_{n,\lambda}^A$ to **identify** the medication regimen a^A
	31	**return** performance measure: $\text{QALE}_n^A = (\mathbf{b}_n^A)'\mathbf{r}_n(a^A)$ if $o_n \in O \setminus \{\Delta, \nabla\}$; $\text{QALE}_n^A = (\mathbf{b}_n^A)'\mathbf{R}_n$ if $o_n \in \{\Delta, \nabla\}$
	32	**for each** model $m \in M$
	33	**use** $\mathbf{b}_n^A$, a^A, o_n, and m to **update** the belief vector for the next time period $\mathbf{b}_{n+1}^A(m)$
	34	**return** the average of updated belief vectors from all models $\mathbf{b}_{n+1}^A = (\sum_{m \in M} \mathbf{b}_{n+1}^A(m))/\lvert M \rvert$
	35	**set** $n = n + 1$ and **go to** line 28
	36	**add** the performance measures over all periods and **return** the outcome $\boldsymbol{\Omega}_{ij\lambda} = \{\text{QALE}, \text{COST}, \text{Number of medications}\}$
	37	**return** the average outcome for POMDP or benchmark (average over $43,758 \times 1,000 \times \lvert M \rvert \approx 1.3 \times 10^8$ instances)
	38	**return** the average outcome for APOMDP (average over $43,758 \times 1,000 \times \lvert \Lambda \rvert \approx 1.3 \times 10^8$ instances)

Table A.10: Average Percentage of Violations for Sufficient Conditions under Different Risk Factors

Condition	**Age**	**Gender**	**Race**	**Diab Hist**
Condition 2.4.2	(10.19,10.73)	(12.95,17.60)	(11.16,15.61)	(13.39,19.27)
Condition 2.4.4	(19.21,14.61)*	(6.57,19.09)	(10.29,2.02)	(9.13,7.25)
Condition	**BMI**	**BP**	**Chol**	**HDL**
Condition 2.4.2	(14.75,13.83)	(12.62,5.02)	(19.07,11.14)	(15.79,11.40)
Condition 2.4.4	(16.11,13.98)	(11.43,8.50)	(9.12,10.07)	(16.11,13.79)
Condition	**LDL**	**TG**	**UA**	
Condition 2.4.2	(14.91,13.79)	(12.42,6.33)	(10.40,13.56)	
Condition 2.4.4	(18.31,15.60)	(18.21,4.13)	(11.73,9.84)	

* $(x, y)\%$ represent the avg. % of violations for low/high risk levels, respectively.

Table A.11: Reward Parameters for the Sensitivity Analyses (D: diabetes; H: Healthy; R: Rejection; S: Survival)

Set	**Risk Level**	**qol**				**RLE**			
		D	**H**	**R**	**S**	**D**	**H**	**R**	**S**
1	Low	0.90	1.00	0.80	0.95	33	40	18	28
	High	0.75	0.85	0.65	0.80	25	32	13	22
2	Low	0.80	0.95	0.70	0.90	27	35	15	25
	High	0.65	0.80	0.55	0.75	19	27	9	20
3	Low	0.70	0.90	0.60	0.85	21	30	12	22
	High	0.55	0.75	0.45	0.70	11	19	6	16
4	Low	0.60	0.85	0.50	0.80	15	23	8	18
	High	0.45	0.70	0.35	0.65	5	12	3	13
5	Low	0.80	0.95	0.90	1.00	27	35	20	30
	High	0.70	0.80	0.75	0.85	20	27	18	26
6	Low	0.70	0.90	0.80	0.95	21	30	17	27
	High	0.60	0.85	0.65	0.80	14	22	13	22
7	Low	0.60	0.85	0.70	0.90	15	23	15	25
	High	0.50	0.70	0.55	0.75	10	18	8	18
8	Low	0.50	0.80	0.60	0.85	12	20	12	22
	High	0.40	0.65	0.45	0.70	5	10	5	15

Table A.12: Sensitivity Analyses under Categories Shown in Table A.11

Cohort	Set							
	1	2	3	4	5	6	7	8
Age:L*	5.8, 2.8, 0.8, 0.8**	4.2, 2.7, 0.2, 0.4	5.4, 3.6, 0.5, 0.2	5.2, 3.7, 0.6, 0.5	5.2, 3.2, 1.4, 1.5	5.6, 3.9, 0.8, 0.9	5.1, 3.1, 1.0, 0.9	4.2, 3.9, 0.9, 1.2
Age:H	3.4, 1.8, 0.7, 1.1	6.2, 4.3, 0.0, 0.0	5.0, 3.7, 1.1, 1.1	5.0, 4.3, 0.2, 0.7	5.1, 2.6, 0.4, 0.8	3.4, 3.7, -0.1, 0.1	5.0, 4.0, 0.3, 1.0	4.2, 2.2, 1.2, 0.9
Gender:L	3.6, 2.5, 0.2, 0.2	4.7, 3.5, 0.7, 1.2	4.8, 4.0, 0.0, 0.1	5.8, 2.9, 0.2, 0.3	5.9, 3.5, 1.0, 1.5	5.8, 2.1, 0.8, 0.8	4.5, 3.6, 0.2, 0.2	5.8, 4.2, 0.9, 0.2
Gender:H	5.4, 3.6, 0.6, 0.2	3.9, 3.4, 0.2, 0.6	4.4, 3.1, 0.1, 0.8	3.6, 2.8, 0.2, 0.7	4.8, 3.2, 0.4, 0.3	5.2, 4.4, 1.1, 1.0	4.2, 2.9, 0.8, 1.2	5.8, 2.5, 0.5, 0.6
Race:L	4.2, 3.7, 0.6, 0.8	3.4, 1.6, 0.6, 0.4	5.2, 3.4, 1.1, 1.2	5.7, 2.3, 0.4, 0.8	5.8, 4.4, 0.4, 0.7	4.6, 2.4, 1.1, 1.3	4.0, 3.6, 1.4, 1.3	5.2, 3.7, 1.6, 1.5
Race:H	5.1, 3.8, 0.9, 0.9	5.2, 4.4, 1.6, 1.5	5.8, 4.0, 0.5, 0.6	4.6, 3.7, 0.5, 0.2	5.6, 3.3, 0.7, 0.9	4.7, 3.1, 0.5, 0.5	4.8, 3.1, 0.1, -0.1	4.8, 3.6, 0.9, 0.9
DiabHist:L	5.2, 3.4, 1.1, 1.5	4.3, 2.9, 0.3, 0.6	5.2, 3.5, 1.5, 1.4	5.4, 3.9, 0.5, 0.3	4.7, 2.8, 1.1, 1.3	5.4, 3.5, 0.4, 0.7	4.5, 2.9, 0.3, 0.5	4.3, 3.7, 1.1, 1.1
DiabHist:H	5.7, 4.5, 1.3, 0.7	5.7, 4.0, 0.1, 0.1	5.0, 3.4, 0.1, 0.1	5.6, 4.1, 0.5, 0.1	5.1, 2.1, 0.9, 1.0	4.2, 2.8, 0.3, 0.7	5.3, 3.4, 1.4, 1.0	5.5, 3.1, 0.8, 0.3
BMI	5.2, 3.2, 1.1, 0.9	4.2, 4.7, 1.0, 0.9	6.2, 4.6, 0.7, 0.9	5.5, 4.6, 0.0, -0.1	4.8, 3.0, 0.4, 0.2	5.1, 4.4, 1.3, 1.5	6.8, 4.6, 0.5, 0.9	4.1, 2.6, 0.5, 0.6
BP	6.9, 4.2, 1.2, 1.1	6.9, 4.1, 0.9, 0.6	5.0, 4.0, 1.3, 1.2	6.9, 4.3, 1.1, 1.1	4.2, 3.9, 1.0, 0.7	4.7, 3.2, 0.6, 0.7	6.9, 3.8, 0.9, 0.8	4.2, 2.7, 0.6, 0.4
Chol	5.3, 2.3, 0.0, -0.1	5.4, 3.6, 0.4, 0.2	6.0, 3.1, 0.5, 0.4	5.6, 3.9, 0.2, 0.4	6.3, 4.7, 0.0, 0.1	4.9, 3.6, 1.0, 1.2	4.7, 3.5, 1.0, 1.0	6.2, 4.7, 1.4, 1.5
HDL	5.3, 4.6, 0.5, 1.0	7.0, 3.5, 1.1, 1.2	6.4, 4.5, 0.3, 0.3	6.9, 4.5, 0.3, 0.3	5.8, 3.7, 0.2, 0.3	4.8, 3.4, 0.4, 0.7	5.4, 4.5, 0.9, 0.9	4.3, 3.8, 1.2, 1.0
LDL	6.4, 4.7, 0.7, 0.8	5.9, 3.7, 0.9, 0.9	5.1, 3.3, 0.8, 0.5	5.7, 3.2, 0.8, 0.5	6.6, 4.0, 0.1, 0.3	5.4, 3.6, 0.8, 0.9	5.9, 4.0, 0.6, 0.9	6.1, 4.0, 0.6, 0.4
TG	5.8, 3.8, 1.2, 1.5	5.3, 4.4, 1.1, 1.3	4.2, 2.3, 0.0, 0.1	4.9, 3.4, 1.0, 1.1	6.3, 4.8, 1.1, 1.0	4.3, 3.0, 0.5, 0.4	5.9, 3.8, 0.3, 0.3	4.3, 3.8, 1.0, 0.9
UA	6.4, 4.4, 1.2, 1.0	6.1, 4.3, 1.3, 1.2	6.6, 5.0, 0.7, 0.8	5.9, 3.7, 0.3, 1.0	5.4, 3.6, 0.6, 0.6	6.0, 3.5, 0.1, 0.5	4.1, 2.8, 0.3, 0.3	4.1, 3.7, 0.1s, 0.3

* L: low level; H: high level

** These numbers identify the improvements in QALE (in percentage) made by our optimal (APOMDP) policy against benchmark policies 1, 2, 3, and 4, respectively.

APPENDIX B

APPENDIX OF CHAPTER 4

Table B.1: List of Some of Variables in Data Tables (See §4.3 For More Details; Same Variable May Exist in Different Tables)

Table A	**Table I**	**Table S**	**Table O**	**Table D**	**Table R**
Patient ID	Patient ID	Patient ID	Patient ID	Patient ID	Drug ID
Age	Service year	Service year	Service year	Service year	Metric size
Gender	Age	Service place	Service place	Age	Package size
Monthly	Gender	Provider type	Provider type	Gender	Strength
Enrollment	Admission date	Age	Age	Drug ID	Road administration
	Discharge date	Gender	Gender	Days supply	DEA schedule type
	Discharge status	Admission date	Service date start	# units dispensed	Therapeutic class
	Diagnostic category	Discharge date	Service date finish	# refills	Drug name
	Diagnosis codes	Diagnostic category	Diagnostic category	Therapeutic class	
	Procedure codes	Diagnosis codes	Diagnosis codes	All payments	
	All payments	Procedure codes	Procedure codes	Region	
	Region	All payments	All payments		
		Region	Region		

Table B.2: List of Opioid and Non-Opioid Analgesics

Opioids		**Non-opioids**		
Buprenorphine	Morphine	Acetaminophen	Etodolac	Nabumetone
Butorphanol	Opium	Antipyrine	Fenoprofen Calcium	Naproxen
Codeine	Oxycodone	Aspirin	Flurbiprofen	Oxaprozin
Dihydrocodeine	Oxymorphone	Benzocaine	Ibuprofen	Piroxicam
Fentanyl	Pentazocine	Bromfenac Sodium	Indomethacin	Rofecoxib
Hydrocodone	Propoxyphene	Celecoxib	Ketoprofen	salicylamide
Hydromorphone	Sufentanil	Choline Magnesium Trisalicylate	Ketorolac Tromethamine	Salsalate
Levorphanol	Tapentadol	Choline Salicylate	magnesium Salicylate	Sodium Salicylate
Meperidine	Tramadol	Diclofenac	Meclofenamate Sodium	Sulindac
Methadone	Nalbuphine	Diclofenac Potassium	Mefenamic Acid	Tolmetin Sodium
		Diflunisal	Meloxicam	Ziconotide

Table B.3: List of Drugs Used for Characterizing Behavioral Risk Factors (Based on Their Therapeutic Class)

Factor	**Drugs**
Alcohol	Acamprosate, Disulfiram
Smoking	Bupropion, Clonidine, Nortriptyline, Varenicline
Substance abuse	Buprenorphine, Nalmefene, Naloxone, Naloxegol, Naltrexone
Mental disorders	Any drug in the CCAE data whose "Therapeutic Class" is in $\{29-31, 63-77, 214-216\}$

Table B.4: List of ICD-9-CM Codes Used for Characterizing Behavioral Risk Factors

Factor	**ICD-9-CM Codes**
Alcohol	303.92, 303.93, 305, 305.01, 305.02, 305.03, 357.50, 425.50, 535.30, 535.31, 571.00 571.10, 571.20, 571.30 , 760.71, 790.30, 977.30, 980.00, E860.0, E860.1, E947.3 V11.30, V79.10
Smoking	305.10, 649.00, 649.01, 649.02, 649.03, 649.04, 989.84, E869.4, V15.82
Substance abuse	304.10, 304.11, 304.12, 304.13, 304.60, 304.61, 304.62, 304.63, 304.80, 304.81, 304.82 304.83, 304.90, 304.91, 304.92, 304.93, 648.30, 648.31, 648.32, 648.33, 648.34, 965.10 965.40, 965.61, 965.69, 965.70, 965.80, 965.90, 966.00, 966.10, 966.20, 966.30, 966.40 967.00, 967.10, 967.20, 967.30, 967.40, 967.50, 967.60, 967.80, 967.90, 968.00, 968.10 968.20, 968.30, 968.40, 968.60, 968.70, 968.90, 969.00, 969.10, 969.20, 969.30, 969.40 969.50, 969.80, 969.90, 970.00, 970.89, 970.90, 975.00, 975.10, 975.20, 975.30 E850.4, E850.6, E850.7, E850.8, E850.9, E851.0, E852.0, E852.10, E852.20, E852.30 E852.40, E852.50, E852.80, E852.90, E853.0, E853.10, E853.20, E853.80, E853.90 E854.0, E854.20, E854.30, E854.80, E855.0, E855.10, E855.20, E855.30, E855.40 E855.50, E855.60, E855.80, E855.90, E935.4, E935.7, E935.8, E935.9, E937.00 E937.10, E937.20, E937.30, E937.40 , E937.50, E937.60, E937.80, E937.90, E938.00 E938.10, E938.20, E938.30, E938.40, E938.60, E938.70, E938.90, E939.0, E939.1 E939.2, E939.3, E939.4, E939.5, E939.6, E939.7, E939.8, E939.9, E940.0, E940.8 E940.9, E945.1, E945.2, E945.3, E950.0, E950.1, E950.2 , E950.3, E980.0, E980.1 E980.2, E980.3, V14.50, V14.60
Non-substance abuse	304.20, 304.21, 304.22, 304.23, 304.30, 304.31, 304.32, 304.33, 304.40, 304.41, 304.42 304.43, 304.50, 304.51, 304.52, 304.53, 305.20, 305.21, 305.22, 305.23, 305.30, 305.31 305.32, 305.33, 305.60, 305.61, 305.62, 305.63, 305.70, 305.71, 305.72, 305.73, 760.73 760.75, 969.60, 969.72, 970.81, E854.1, E939.6
Mental disorders	V110, V111, V112, V114, V118, V119, V1240, V1249, V7900

Table B.5: List of ICD-9-CM Codes to Identify Any Adverse Effect Caused by an Opioid or Heroin

Code	**Description**
304.00	Opioid type dependence, unspecified
304.01	Opioid type dependence, continuous
304.02	Opioid type dependence, episodic
304.03	Opioid type dependence, in remission
304.70	Combinations of opioid type drug with any other drug dependence, unspecified
304.71	Combinations of opioid type drug with any other drug dependence, continuous
304.72	Combinations of opioid type drug with any other drug dependence, episodic
304.73	Combinations of opioid type drug with any other drug dependence, in remission
305.50	Opioid abuse, unspecified
305.51	Opioid abuse, continuous
305.52	Opioid abuse, episodic
305.53	Opioid abuse, in remission
965.00	Poisoning by opium (alkaloids), unspecified
965.01	Poisoning by heroin
965.02	Poisoning by methadone
965.09	Poisoning by other opiates and related narcotics
E850.0	Accidental poisoning by heroin
E850.1	Accidental poisoning by methadone
E850.2	Accidental poisoning by other opiates and related narcotics
E935.0	Heroin causing adverse effects in therapeutic use
E935.1	Methadone causing averse effects in therapeutic use
E935.2	Other opiates and related narcotics causing adverse effects in therapeutic use