Using Electronic Health Records to Monitor and Improve Adherence to Medication

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Adherence to medication is a serious problem in the United States, leading to complications and preventable hospitalizations, particularly for patients with chronic diseases. Interventions have been proposed as a means to improve adherence to medication, but the optimal time to perform an intervention has not been well studied. Electronic health records (EHRs) can be used to monitor patient adherence to medication, providing a source of information to help decide when to perform an intervention. We propose a Markov decision process (MDP) model to determine when to perform adherence-improving interventions based on a patient's EHR. We consider the trade-off between the patient's perspective of maximizing (quality-adjusted) time to first adverse health event and the payer's perspective of minimizing the cost of interventions, medication, and adverse events. We use our model to evaluate the costs and benefits of implementing an EHR-based active surveillance system for adherence-improving interventions in the context of cardiovascular disease management. We also provide some theoretical insights into the structure of the optimal intervention policy and the influence of health risks and costs on intervention decisions.

Keywords: Electronic health records, medication adherence, Markov decision process

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1. Introduction

Poor medication adherence has been estimated to cost approximately $100 billion per year in preventable hospitalizations in the United States alone (Osterberg and Blaschke 2005). Recent studies show that while improving adherence results in an increase in medication costs, there are significant overall cost savings, particularly among patients with chronic diseases (Sokol et al. 2005, Ho et al. 2006). Improved adherence can also reduce the risk of adverse events and improve the quality and length of life for many patients. In particular, improving adherence to glucose medications among patients with diabetes in the United States could save $4.68 billion annually in avoided hospitalizations and emergency department visits (Jha et al. 2012). In spite of the benefits of high adherence, poor adherence is recognized as a major challenge in the medical community (Cutler and Everett 2010). In 2007 the National Institutes of Health (NIH) implemented the *Adherence Research Network* to promote research on adherence (National Institutes of Health 2011). The initiative supports 14 institutes and centers across NIH, highlights NIH funding for adherence research, synthesizes current scientific findings on adherence, and provides leadership on future research directions.

While it is difficult to directly measure the medication taken by patients, there are widely accepted proxy measures of adherence, including patient self-reporting, electronic medication monitors on pill canisters, and rates of prescription refills calculated from electronic health records (EHRs). Based on prescription refill estimates of adherence, studies suggest that only 25% of patients remain highly adherent to common treatments such as cholesterol-lowering medication (Benner et al. 2002, Mason et al. 2012). Adherence-improving interventions, such as collaborative decision making and the use of decision aids to choose

medications, have been shown to improve adherence (Weymiller et al. 2007). However, barriers to such interventions include that they are often not reimbursed by third-party payers and the perception that they take time and effort. Furthermore, information about an individual patient's adherence to their prescribed medications is normally unavailable to physicians at the time of encounter with a patient.

Recently, considerable attention has been given to the use of EHRs to improve efficiency and effectiveness of health care delivery. EHRs are systematic collections of patient health information that can aid physicians in making medical decisions. In the United States, the Centers for Medicare and Medicaid Services (CMS) have recently introduced a *Meaningful Use* initiative (US Department of Health & Human Services 2011). The goals of the initiative are to improve safety and efficiency of health care delivery through the use of EHRs, and there is over $20 billion available from the Health Information Technology for Economic and Clinical Health Act (HITECH Act) to promote the adoption of information technology for health care and train skilled workers in this field. Due to incentives created by this program, health care managers are under pressure to meet the objectives of the Meaningful Use initiative and to submit clinical quality measures (CQMs) using certified EHR technology. In addition, in 2012 CMS added new adherence quality measures for oral diabetes medications, some blood pressure medications, and cholesterol medications (statins) based on the percentage of patients who refill at least 80% of their prescriptions over the measurement period (CMS 2012). In light of these new quality measures, there is an increasing need to use measures of adherence to guide the use of interventions at the point of care (Steiner 2012).

EHRs have the potential to enable monitoring of adherence and to identify patients who would benefit most from an adherence-improving intervention. By actively monitoring an individual patient's adherence to medications, which we refer to as *active adherence surveillance* (AAS), health care providers could make such decisions in real time at the point of care. However, implementation of a surveillance system comes at a cost. Therefore in this article we aim to answer the following research question: What are the potential benefits of using EHRs to improve adherence to medication? To answer this question, we use pharmacy claims data for a large population to estimate patient adherence levels to the most commonly used medication for cholesterol control. We present an MDP model to determine the optimal timing of adherence-improving interventions based on AAS of an individual patient's adherence using EHRs. Our model considers both the perspective of the patient, who stands to benefit from the prevention of adverse health events related to poor adherence, and the perspective of the third-party payer (health insurer) that bears the burden of the cost of interventions, medication, hospitalizations, and follow-up care for adverse events related to poor adherence. We present structural properties of our model, including conditions under which a control limit policy exists, and how the control limit policy changes based on a patient's health status and the effectiveness of an intervention.

There are many prescription medications for which poor adherence is recognized as a challenge in preventing the onset or progression of disease (e.g., blood pressure control medications, asthma medications). In this article we provide a specific example based on adherence to *statins*, the most common cholesterol-lowering medication. We evaluate the costs and benefits associated with AAS by using our MDP model to determine the following: (a) the expected quality-adjusted life years (QALYs) before a stroke, a coronary heart disease (CHD) event (such as a heart attack), or death; and (b) medication and intervention costs and

costs associated with the occurrence of strokes and CHD events (the most significant outcomes associated with cholesterol control). To estimate the marginal benefits of implementing the EHR-based system, we compare AAS to a much simpler, and easier to implement, schedule of interventions at regularly spaced intervals (e.g., yearly interventions), which we refer to as *inactive adherence surveillance* (IAS). We also compare our results to outcomes for patients who receive no interventions. In addition, we estimate the potential yearly benefits of applying AAS to the US population.

Our findings have the potential to influence several different stakeholders. First, our findings will help inform CMS about the potential benefits of AAS, and whether such implementations should be added to the list of objectives for their Meaningful Use or other future initiatives. Understanding and improving medication adherence is a natural extension to the current Meaningful Use requirement of *medical reconciliation*, which requires an accurate list of medications the patient is currently taking. Second, our results will help inform third-party health insurers about the potential benefits of reimbursing health care providers for adherence-improving interventions. Third, physicians will benefit from an improved understanding of the relative benefits of addressing adherence to medications for chronic conditions. Finally, patients could directly benefit from improved quality of life and the lower costs that can be achieved by improved adherence.

The remainder of this article is organized as follows. In Section 2 we provide some background on adherence interventions and methods for estimating adherence from EHRs. We also provide a specific example that illustrates measurement of adherence to statins and its relationship to health outcomes. In Section 3 we present an overview of related literature in the areas of machine maintenance and medical decision making. In Section 4 we present our MDP model for determining the optimal time for interventions, and in Section 5 we explore some general insights that can be drawn from our model. In Section 6 we present a case study of cholesterol-lowering treatment to prevent cardiovascular disease in patients with type 2 diabetes. Finally, in Section 7 we provide concluding remarks and discuss future research opportunities.

2. Background on Medication Adherence

Motivation for understanding adherence to medication is summed up in a quote by C. Everett Koop, M.D.: "Drugs don't work in patients who don't take them." Osterberg and Blaschke (2005) cite patient forgetfulness and lack of understanding as possible causes of poor adherence. The authors describe several types of interventions for improving medical adherence, including patient education, increased access to medical care, and improved communication between patients and physicians. For example, interventions such as performing screening tests and reviewing a patient's risk of an adverse health event (e.g., 10-year risk of a stroke or CHD event), or educating a patient about the risk reduction associated with a particular medication, have been shown to improve patient adherence (Weymiller et al. 2007). However, these interventions can be associated with high costs. Lower cost interventions using electronic reminders (e.g., text messages, e-mails) to improve adherence to medication can provide benefits to patient adherence in the short term, but in a review of interventions using electronic reminders, two of the three studies of with a follow-up greater than 6 months showed no effect of the interventions (Vervloet et al. 2012). Thus, in this paper we do not

consider interventions comprised exclusively of electronic reminders.

A common method for measuring patient adherence is to observe the percentage of days covered (PDC) by prescription refills over time. Prescription refills can be observed from pharmacy claims data, a portion of administrative claims data generated as a result of a patient's encounter with the health system. Claims data is an important part of the extended EHR that is collected by third-party payers for payment purposes. If Meaningful Use program objectives are met, then more than 80% of patients will have pharmacy refills recorded as structured data by the end of 2012.

The standard formula for PDC is as follows (Caetano et al. 2006):

$$\text{PDC} = 100 \times \left(\frac{\text{days with an available supply of medication in the time period}}{\text{days in time period}} \right) \%.$$

Figure 1 provides an example of a patient's pharmacy claims for which PDC is estimated over a one-year period. In this example, the patient begins taking the medication with a 30-day supply. The patient makes four refills, each with 90-day supply, during the year. Gaps between the end of the days' supply for one prescription fill and the beginning of the next fill are interpreted as gaps in the patient's adherence to the medication. As shown in Figure 1, refills that have supply exceeding the amount of time to the end of the year (time period) are carried over to the calculation of the PDC for the next time period. Note that this method for computing PDC is not restricted by the days' supply of refills or the refill method (by mail or local pharmacy).

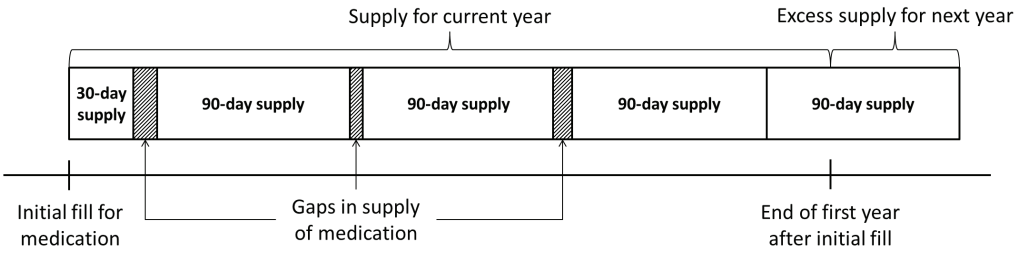

Fig. 1. Diagram of Prescription Refills Used to Calculate the Percentage of Days Covered (PDC).

Combining pharmacy claims data with laboratory data (e.g., cholesterol, blood sugar, blood pressure) and other sources of data in the EHR is often necessary to measure the effects of adherence. For example, the PDC can be linked with the patient's percentage change in metabolic values over the same time period. We illustrate this with a specific example. Consider the case of patients initiating statins to lower their cholesterol and therefore lower their risk of stroke and CHD events. States for the PDC over the course of a year after initiation are defined by the four categories given in Table 1. The adherence states are defined as follows: NON ($0\% \leq \text{PDC} \leq 10\%$); LOW ($10\% < \text{PDC} \leq 40\%$); MED ($40\% < \text{PDC} \leq 80\%$); and HIGH ($80\% < \text{PDC} \leq 100\%$). These specific choices of adherence states are based on those commonly used in the health services research literature (for example, see Rasmussen et al. (2007)). By using laboratory data, we link these adherence states with changes in total cholesterol (TC) from initiation to one year after initiation. Large data sets that combine pharmacy claims data with laboratory data for a large sample of patients can thus be used to estimate the expected change in TC for each PDC level.

The results in Table 1 are based on a study reported by Mason et al. (2012). Table 1 establishes the link between a patient's percentage change in TC and the patient's adherence to medication. Since the patient's risk of cardiovascular events is affected by TC, that risk is also correlated with the patient's adherence to medication (Kothari et al. 2002, Stevens et al. 2001). For this reason, interventions that improve adherence have the potential to reduce cardiovascular risk over time. A method to estimate a stochastic model for changes in PDC and its effect on cardiovascular risk over time is elaborated in Section 6.

Table 1. Adherence States Defined by Percentage of Days Covered (PDC) and the Corresponding Percentage Change in Total Cholesterol (TC) for Patients who Initiate Statins.

Adherence State	PDC	Change in TC
NON	0% – 10%	−5.22%
LOW	10% – 40%	−8.21%
MED	40% – 80%	−18.08%
HIGH	80% – 100%	−25.25%

3. Literature Review

The problem of finding the optimal time to perform an intervention to improve a patient's adherence to a medical treatment is analogous to problems studied in the machine maintenance literature. This has been an active area of research for over 50 years. While we do not attempt to review this literature fully, we highlight related articles. In addition to the literature on machine maintenance, we also review articles on the use of the operations research (OR) models and methods for medical decision making.

3.1. *Machine Maintenance Applications*

Pioneering work on maintenance systems was done by Klein (1962), who considers a stochastically deteriorating system that can be replaced or kept after inspection by a manager. If the system is kept, then the decision is to repair the system or schedule the time of the next inspection. The author assumes that inspection gives the manager enough information to determine the state of the system. The objective of the model is to minimize the long run average cost of the policy. The model uses a Markov chain to represent probabilistic deterioration of the system. The main difference between Klein's model and previous machine maintenance models is that the time between successive transitions (inspections) is under the control of the decision maker (manager). This is similar to the model we present in which a decision maker must choose the optimal time for an adherence-improving intervention. The assumption that the manager gains knowledge of the machine's state through inspection is analogous to a physician gaining knowledge about the patient's adherence behavior through an office visit.

In McCall (1965), Pierskalla and Voelker (1976), Sherif and Smith (1981), Jardine and Buzacott (1985), Valdez-Flores and Feldman (1989), and Pham and Wang (1996), the authors survey maintenance policies

for stochastically failing machines and imperfect repair. The latter topic in particular is consistent with adherence interventions that have an uncertain outcome, which we consider in this article. Butler (1979) considers a *hazardous inspection* model in which, similar to adherence intervention, there is potential harm from inspection (e.g., for adherence intervention this could include a monetary cost of intervention or a loss of utility on behalf of the patient). Nakagawa (1988) extends imperfect repair models to a system degrading over time as it ages, similar to the increasing probability of death from other causes in the model we present. Armstrong (2002) extends deterioration models to the case of preemptive maintenance. This is analogous to the goal of improving a patient's adherence to reduce the likelihood of future adverse events. All these studies have similarities to adherence control (albeit in a much different context), but not a single one combines all the characteristics of our model.

Other notable references include the work of Anderson (1981), which presents three continuous-time MDPs, each with an infinite horizon, continuous state space, and actions for maintenance or replacement of the machine. The models differ in terms of the rate of deterioration. The models are transformed into discrete-time finite-horizon MDPs to prove structural properties that provide insights on their continuous-time counterparts. Anderson provides conditions for each model for which a control limit structure exits and the preventative maintenance level is nonincreasing. Hopp and Wu (1990) extend the work of Anderson on a machine maintenance model with preventative maintenance using an infinite-horizon MDP with a finite state space. They prove a control limit policy and monotonicity. In addition, Hopp and Wu consider the effects of alternate assumptions on the structural properties they prove for their model. For example, they show the structural properties still hold when the system must go down for an entire period when maintenance is performed.

3.2. *Medical Decision Making Applications*

There has been a recent increase in collaboration between the OR community and nonprofit organizations on the treatment and prevention of HIV/AIDS, including studies to improve adherence to treatment. The Population Council, an international nongovernmental organization, published a handbook on designing HIV/AIDS prevention studies using OR methods (Fisher and Foreit 2002). The handbook focuses on descriptive models, applying statistical tests and running cost-effectiveness analysis. The Doris Duke Charitable Foundation (DDCF) has awarded grants recently for the use of OR methods on AIDS Care and Treatment in Africa (ORACTA) (DDCF 2011). These grants include funding for studying effectiveness of interventions (e.g., HIV education, text message medication reminders, and home visits by peer educators). This work helps motivate the potential for prescriptive OR models, such as we discuss in this article, to improve adherence to medication for chronic diseases.

MDPs have been used in a number of medical applications for determining when a particular treatment should start or a specific procedure should take place. For example, Alagoz et al. (2004) consider the optimal timing of liver transplantation using a live donor in order to maximize the patient's total reward. The authors use an infinite-horizon MDP model to determine the optimal timing of this one-time decision. Structural properties are derived, including the existence of a control-limit policy under certain assumptions. Shechter et al. (2008) also present an infinite-horizon MDP model to determine the optimal timing of

HIV therapy. The states in the model represent the patient's CD4 count, and the objective is to maximize life years or QALYs over the patient's lifetime. Results suggest earlier treatment is optimal, contrary to treatment trends at the time of publication.

Maillart et al. (2008) present a partially observable Markov chain model to evaluate various breast cancer screening policies considering implications of patient adherence to screening guidelines and differences in breast cancer incidence and aggression as women age. Evaluation, rather than optimization of policies, is used to selectively compare easy-to-implement policies. Efficient policies are identified based on the trade-off between lifetime breast mortality risk and the expected number of mammograms over a woman's lifetime. Chhatwal et al. (2010) present a finite-horizon discrete-time MDP to determine the optimal timing of breast biopsy given the outcome of a mammogram and the patient's demographic features. The decision epochs are years after age 40, the states represent the patient's risk score, determined after a mammogram, and the actions are to have a biopsy or to have another mammogram the following year. Once the action of biopsy is taken, the patient leaves the decision process. Rewards are defined by QALYs accrued by patients. Chhatwal et al. prove structural properties for their model, including the existence of a control-limit type policy. Results suggest that the decision to biopsy should depend on the patient's age.

Denton et al. (2009) propose an MDP model to find the optimal time to initiate statins in patients with type 2 diabetes for the prevention of cardiovascular events. The states represent the patient's metabolic risk factors. The rewards are monetary rewards for QALYs minus costs of medication and treatment for cardiovascular events, and the action to initiate or defer initiation of treatment is revisited each year. The authors consider the effects of using different cardiovascular risk models to estimate the probability of adverse events, concluding that the risk model chosen can dramatically affect the optimal start times. Their model assumes perfect adherence to treatment. Mason et al. (2012) propose a related MDP model to find the optimal time to initiate statins given the possibility of imperfect adherence. The authors incorporate a Markov model for adherence after the patient begins statins. The authors conclude that timing of initiation does not have as great of an effect on patient outcomes as improving adherence; however, they note that adherence-improving interventions can be costly. This study provides motivation for the study of the optimal time of adherence-improving interventions once treatment has begun.

3.3. *Contributions of this Article to the Literature*

To our knowledge, the problem of finding the optimal time to perform an intervention to improve medication adherence has not been studied before. This problem is analogous to problems studied in the machine maintenance literature; however, there are two main differences:

- We consider a system that is deteriorating in a nonstationary fashion over a finite horizon.
- In our model there is no available action to replace the system; only preventative maintenance may be performed.

Our model also differs in several ways from the literature on MDP models for medical decision making described above:

- The decision to initiate an adherence-improving intervention is a recurring decision and not a one-time decision as considered by Alagoz et al. (2004), Shechter et al. (2008), Denton et al. (2009), and Chhatwal et al. (2010).
- Unlike the majority of the above models, which are infinite-horizon models, our model is finite horizon and nonstationary, to reflect nonstationarity in the risk of adverse events with respect to a patient's age.
- Most notably, our study is unique in its specific application, in the methods and data used to estimate the model parameters, and in the research question we answer.

As a result of the differences between our model and those already in the literature, we make several contributions. We present new structural properties that provide insight into optimal policies of a new type of MDP in the context of recurring interventions, and could be generalized to other medical decision making problems. Our findings include a surprisingly simple but counterintuitive result about how to prioritize interventions among different types of interventions. We use a large data set that combines pharmacy claims data with the laboratory data necessary to construct and solve the MDP model, and we present results based on this model for a specific example in the context of statin treatment for a population of patients at high risk of stroke and CHD events. To our knowledge, these results are the first estimates of the potential benefits that may be derived from active surveillance of patient adherence to medication using EHRs.

4. Model Formulation

In each of a set of discrete decision epochs, a patient on a particular medication is observed to be in a specific health state. The health states are divided into *adherence states*, a *pre-absorbing state*, and an *absorbing state*. The adherence states represent the patient's level of adherence to the medication (e.g., statins), the transient pre-absorbing state represents the first occurrence of adverse health events that the treatment aims to prevent (e.g., a stroke or CHD event) or death from other causes, and the absorbing state indicates that an event or death has occurred previously. At each decision epoch, the decision maker (e.g., the physician) must decide whether or not to implement an intervention with the patient. Thus, one of two possible actions is taken: *implement an intervention* or *defer the decision until the next epoch*. This decision is faced at each decision epoch, provided the patient does not enter the pre-absorbing or absorbing states. The following is a detailed description of the MDP model.

The decision to initiate an adherence-improving intervention is revisited periodically over a finite horizon with T yearly decision epochs. The decision epochs are indexed by $t = 0, 1, 2, \ldots, T-1$, where decision epoch (time) t is associated with the time interval $[t, t+1)$ in the sense that the effect of any decision made at decision epoch t applies only during the time interval $[t, t+1)$; and for simplicity, we refer to this time interval as period t. Time $t = 0$ represents the initial epoch when the patient begins surveillance (the patient begins taking the medication), and T is chosen as a reasonable upper bound on a typical patient's age (e.g., 100 years). For a patient who has not entered the absorbing state at time T, a reward is obtained that estimates the benefits and costs associated with the patient's future survival, based on an estimate of the patient's future remaining life years.

The states of the patient are represented by the set $S \equiv \{0, 0', 1, 2, \ldots, M\}$; for each time $t = 0, \ldots, T$, we let $s_t \in S \setminus \{0, 0'\}$ denote the patient's adherence level over the period $[t, t+1)$, while $s_t = 0'$ indicates that the patient had an adverse health event (fatal or nonfatal) related to adherence, or that the patient died from other causes at time t. State $s_t = 0$ indicates that the patient had an adverse health event or death from other causes before time t. For $s_t \in S \setminus \{0, 0'\}$, a larger value of s_t corresponds to an increased (improved) level of adherence for the patient over the period $[t, t+1)$.

An intervention may be initiated or deferred at any decision epoch, $t \in \{1, \ldots, T-1\}$, and in any state, $s_t \in S \setminus \{0, 0'\}$. The possible set of actions is defined as the following:

$$A_t(s_t) = \begin{cases} \{W, I\} & \text{for } s_t \in S \setminus \{0, 0'\} \text{ and } t = 1, \ldots, T-1, \\ \{W\} & \text{for } s_t \in \{0, 0'\} \text{ or } t = T, \end{cases}$$

so that $a_t(s_t) \in A_t(s_t)$ denotes the action taken at time t when the patient is in state s_t, where the action $a_t = I$ denotes an intervention and the action $a_t = W$ denotes the action of waiting, or deferring the decision until the next decision epoch. The total action space is defined by $A = \{W, I\}$.

There are three types of one-step transitions: (i) transitions between adherence states; (ii) transitions from adherence states to the pre-absorbing state; and (iii) the (certain) transition from the pre-absorbing state to the absorbing state. Given avoidance of state $0'$, the conditional transition probabilities between the adherence states are represented by the matrix $\widetilde{P}_t(a_t) \in \mathbb{R}^{M \times M}$ so that $[\widetilde{P}_t(a_t)]_{i,j}$, the (i, j) element of $\widetilde{P}_t(a_t)$, is equal to the conditional probability $\Pr\{s_{t+1} = j | s_t = i$, action a_t is taken at time t, and $s_{t+1} \neq 0'\}$ for $1 \leq i, j \leq M$. Transitions from adherence states to the pre-absorbing state are represented by the vector $\overline{p}_t \in \mathbb{R}^M$ so that $[\overline{p}_t]_i$, the ith element of the $M \times 1$ (column) vector $\overline{p}_t$, is equal to the conditional probability $\Pr\{s_{t+1} = 0' | s_t = i\}$ for $1 \leq i \leq M$. Note that the probability of entering the pre-absorbing state from each adherence state does not depend on the action taken at time t; rather, if a patient has improved medication adherence from a previous intervention, then the patient's probability of entering the pre-absorbing state is reduced due to that patient being in an improved adherence state at time t. Notice also that by the definition of the transient pre-absorbing state $0'$, it is impossible for a patient to make a one-step transition from an adherence state to the absorbing state 0; therefore all these one-step transition probabilities must be zero. Moreover, after entering the pre-absorbing state, the patient spends one period in that state before making a transition to the absorbing state with probability 1. The complete one-step transition probability matrix is

$$P_t(a_t) = \begin{bmatrix} 1 & 0 & 0_M^\intercal \\ 1 & 0 & 0_M^\intercal \\ 0_M & \overline{p}_t & \operatorname{diag}[1_M - \overline{p}_t]\widetilde{P}_t(a_t) \end{bmatrix}, \tag{1}$$

where 0_M is the $M \times 1$ (column) vector of zeros and 1_M is the $M \times 1$ (column) vector of ones.

There are many possible reward structures for our model, depending on the decision maker's perspective. In this article we define a flexible reward structure that is composed of four parts: (i) a reward for quality-adjusted time gained in the most recent period (e.g., a QALY for an annual decision epoch); (ii) a cost

associated with an adherence intervention; (iii) a state-dependent cost of medication; and (iv) a penalty cost for entering the pre-absorbing state. We define $r_t(s_t, a_t)$ to be the reward accrued at time t in state s_t given action a_t is taken. For $t = 1, \ldots, T-1$, the reward function is defined as

$$r_t(s_t, a_t) = \begin{cases} R \times Q(s_t) - C^{\text{MED}}(s_t) & \text{for } a_t = W \text{ and } s_t = 1, \ldots, M, \\ R \times Q(s_t) - C^{\text{MED}}(s_t) - C^{\text{INT}} & \text{for } a_t = I \text{ and } s_t = 1, \ldots, M, \\ -C_t^{\text{F}} & \text{for } s_t = 0', \\ 0 & \text{for } s_t = 0, \end{cases} \tag{2}$$

where R is the *willingness-to-pay* factor defining a monetary value per QALY and $Q(s_t)$ represents the QALYs accumulated for a patient in state s_t during time epoch t. The quantity $C^{\text{MED}}(s_t)$ denotes the cost of medication for period t; this cost depends on the patient's adherence state since patients do not pay for medication they do not have in their possession. The quantity C^{INT} denotes the cost of an adherence-improving intervention. The quantity C_t^{F} represents a one-time lump sum for the expected future costs of a patient entering the pre-absorbing state $0'$ at time t. This cost penalty reflects a loss associated with failure to avoid an adverse health event. This loss could include costs associated with hospitalization and/or future treatment.

The reward structure presented above represents a combination of the patient objective of maximizing quality-adjusted time to the first adverse health event (which is frequently the clinical intent of preventive treatment (Cleeman et al. 2001)) and the objective of minimizing costs of treatment, considering both costs before the patient enters the absorbing state and expected costs after the patient enters the absorbing state. Additional assumptions about the reward structure are provided in Section 5, and specific values for rewards are provided in Section 6 in the context of cardiovascular disease prevention.

For a patient in state $s_t \in S$ in epoch t, the optimality equations can be written as

$$v_t(s_t) = \max_{a_t \in A_t(s_t)} \left\{ r_t(s_t, a_t) + \lambda \sum_{s_{t+1} \in S} p_t(s_{t+1}|s_t, a_t) v_{t+1}(s_{t+1}) \right\}, \text{ for every } t = 1, \ldots, T-1, \tag{3}$$

where $p_t(s_{t+1}|s_t, a_t)$ is the (s_t, s_{t+1}) element of $P_t(a_t)$, $v_t(s_t)$ is the optimal value function, and $\lambda \in (0, 1]$ is the discount factor used to calculate the value at time t of rewards received at time $t+1$. For every time $t \in \{0, 1, \ldots, T\}$, we define $\mu_t(s_t)$ to be the expected difference between the rewards for quality-adjusted survival benefits and the associated costs, assuming no future interventions, for every $s_t \in S$. We take $\mu_t(0') = -C_t^{\text{F}}$ and $\mu_t(0) = 0$. The end-of-horizon boundary condition is

$$v_T(s_T) = \mu_T(s_T), \text{ for every } s_T \in S. \tag{4}$$

The last decision epoch, T, is selected to represent a reasonable upper bound on the age at which adherence-improving interventions would no longer be advisable due to high competing risks of death from other causes. This end-of-horizon assumption has been made in a number of other medical decision making studies (Denton et al. 2009, Chhatwal et al. 2010, Kurt et al. 2011).

5. Model Properties and Insights

This section provides insights into the structure of our model. First, we discuss some of the assumptions of our model. Next, we present some properties of our model that can reduce the computational effort to solve the MDP, and that provide some insight into the optimal policy for interventions defined by our model. We prove the existence of an optimal control-limit policy. Next, we present a theorem relating the effectiveness of interventions to the optimal control limits for the interventions. Finally, we present a theorem comparing the optimal control limits for two patients where one patient is at a greater risk for adverse health events than the other. Proofs of the properties presented in this section are provided in the Appendix.

5.1. *Model Assumptions*

There are many possible choices for the reward function to use in our MDP model. We chose to blend two criteria for our reward function: (i) the patient's reward for quality-adjusted time to the first adverse health event; and (ii) the payer's cost of treatment, intervention, and care associated with an adverse health event. We make the following assumptions about our model:

$\mathbf{A}_1$: $\widetilde{P}_t(a_t)$ has the increasing failure rate (IFR) property for every $a_t \in A$, and for every $t = 1,\ldots,T-1$;

$\mathbf{A}_2$: $\mu_t(s_t)$ is nondecreasing in s_t for $t = 1,\ldots,T$ and $s_t \in S \setminus \{0\}$;

$\mathbf{A}_3$: $[\bar{p}_t]_i \equiv \Pr\{s_{t+1} = 0' | s_t = i \in S \setminus \{0,0'\}\}$ is nonincreasing in s_t for $t = 1,\ldots,T-1$; and

$\mathbf{A}_4$: $R \times Q(s_t) - C^{\mathrm{MED}}(s_t)$ is a nondecreasing function of s_t for $t = 1,\ldots,T-1$ and $s_t \in S \setminus \{0\}$.

Assumption $\mathbf{A}_1$ states that the Markov chain defining a patient's adherence exhibits the IFR property (see Barlow and Proshan (1965) for a definition of this property). This can be interpreted to mean that the better a patient's adherence level the better it is likely to be in the next period. Our study using observational data (see Section 6) suggests that this is a reasonable assumption. This property has also been observed for a number of other health characteristics (Alagoz et al. 2004, Kurt et al. 2011, Chhatwal et al. 2010). Assumption $\mathbf{A}_2$ states that a patient's expected future rewards for QALYs minus costs, assuming no future interventions, does not decrease as their adherence improves. This assumption is reasonable since improved adherence causes treatment to be more effective at preventing adverse events. Assumption $\mathbf{A}_3$ states that the probability of moving to the pre-absorbing state is nonincreasing in the adherence state. Finally, assumption $\mathbf{A}_4$ states that the difference between $R \times Q(s_t)$, the reward for living through a decision epoch, and $C^{\mathrm{MED}}(s_t)$, the cost of medication, is a nondecreasing function of the adherence state s_t. In addition to the above assumptions, we assume that $R, Q(s_t), C^{\mathrm{INT}}, C_t^{\mathrm{F}}$, and $C^{\mathrm{MED}}(s_t)$ are nonnegative for every value of s_t.

5.2. *Model Properties*

We now discuss some properties associated with the optimal adherence intervention policy and draw comparisons between different types of patients and interventions. We begin by presenting two lemmas that are used to prove our main results.

Lemma 1. *If $\widetilde{P}_t(a_t)$ is IFR and assumption* $\mathbf{A}_3$ *holds, then $P_t(a_t)$ is IFR for $t = 1,\ldots,T-1$.*

This lemma establishes an important connection, in the form of the IFR property, between patient health states and the probability of health outcomes conditioned on those health states. Lemma 1 is useful for other types of medical decision making problems for which the IFR property exists among ordered health states.

Lemma 2. *The value function $v_t(s_t)$ is nondecreasing in s_t, for $t = 1,\ldots,T$ and $s_t \in S \setminus \{0\}$.*

Lemma 2 shows that the patient's expected future rewards do not decrease as adherence to treatment improves. This fact is used to prove Theorem 1, which states that the optimal intervention policy has a simple control-limit structure for the adherence states $s_t = 1,\ldots,M$.

Theorem 1. *If the effect of an intervention at time t is independent of the patient's current adherence state $s_t \in S \setminus \{0,0'\}$ for $t \in \{1,\ldots,T-1\}$, then there exists an optimal control limit $s_t^* \in S \setminus \{0,0'\}$, for every $t \in \{1,\ldots,T-1\}$, such that the optimal action $a_t^*(s_t)$ is given by*

$$a_t^*(s_t) = \left\{ \begin{array}{ll} I, & \text{if } s_t \le s_t^*, \text{ and } s_t \in S \setminus \{0,0'\}, \\ W, & \text{otherwise,} \end{array} \right\} \text{ for } t = 1,\ldots,T-1. \tag{5}$$

Theorem 1 provides sufficient conditions under which the optimal intervention policy has a simple structure, which is important for clinical applications in practice. This structure can also be exploited to achieve computational advantages in computing the optimal policy. This could be particularly relevant for applications involving real-time clinical intervention decisions. This theorem applies when the effect of an intervention is independent of the patient's adherence state; for example, this theorem would apply when all patients transition to high adherence after a perfect intervention. In Section 6 we elaborate this example together with an example using another transition probability matrix that satisfies this condition.

The remainder of this section presents theorems based on the comparison of optimal policies for different types of interventions and different types of patients. We begin with a definition of stochastic dominance relevant to the two theorems.

DEFINITION 1. Given $t \in \{1,\ldots,T-1\}$, $s_t \in S$, and $a_t \in A_t(s_t)$, the one-step transition probability matrix $P_t^{(1)}(a_t)$ is said to stochastically dominate $P_t^{(2)}(a_t)$, denoted by $P_t^{(1)}(a_t) \succcurlyeq P_t^{(2)}(a_t)$, if

$$\sum_{j=k}^{M} P_t^{(1)}(j|i,a_t) \ge \sum_{j=k}^{M} P_t^{(2)}(j|i,a_t) \text{ for every } i,k \in S,$$

where successive values of j and k are always understood to be taken in the order $0,0',1,2,\ldots,M$.

In the context of the following two theorems, stochastic dominance represents that a transition probability matrix for a particular action is superior to a transition probability matrix for another action in terms of the probability of remaining in high adherence states. In order to differentiate the control limits for two interventions, we introduce the following notation: $s_t^*(I_\ell)$ represents the optimal control limit for intervention I_ℓ for $\ell = 1,2$. In addition, we use a superscript to differentiate probabilities, actions, and value functions from the two MDPs in the following lemma and theorem.

Lemma 3. *Given two MDPs, MDP$_1$ with intervention I_1 and MDP$_2$ with intervention I_2, for which $P_t^{(1)}(I_1) \succcurlyeq P_t^{(2)}(I_2)$ and $P_t^{(1)}(W) \equiv P_t^{(2)}(W)$, the following is true:*

$$v_t^{(1)}(s_t) \geq v_t^{(2)}(s_t) \text{ for all } t \text{ and for all } s_t \in S. \tag{6}$$

Thus when one intervention dominates another the expected future rewards can be no worse.

Theorem 2. *Given MDP$_1$ with intervention I_1 and MDP$_2$ with intervention I_2, if $v_t^{(2)}(s_t+1) - v_t^{(2)}(s_t) \leq v_t^{(1)}(s_t+1) - v_t^{(1)}(s_t)$ for all $s_t \in \{1,\ldots,M-1\}$ for $t \in \{1,\ldots,T-1\}$ and if the two MDPs are identical except that $P_t^{(1)}(I_1) \succcurlyeq P_t^{(2)}(I_2)$ and $P_t^{(2)}(I_2) \succcurlyeq P_t^{(2)}(W)$ for $t \in \{1,\ldots,T-1\}$, then $s_t^*(I_1) \geq s_t^*(I_2)$ for $t \in \{1,\ldots,T-1\}$.*

Theorem 2 can be interpreted as follows. If intervention I_1 is more effective than intervention I_2, then the optimal control limit for I_1 in MDP$_1$ should be greater than or equal to the optimal control limit for I_2 in MDP$_2$. In other words, under the optimal policy, intervention I_1 would be implemented for a wider range of adherence states. Intervention I_1 may be used for patients in better adherence states than I_2. The condition that $v_t^{(2)}(s_t+1) - v_t^{(2)}(s_t) \leq v_t^{(1)}(s_t+1) - v_t^{(1)}(s_t)$ for all $s_t \in \{1,\ldots,M-1\}$ for $t \in \{1,\ldots,T-1\}$ intuitively means that under intervention I_1, the improvement in the value function realized by being in adherence state s_t+1 rather than state s_t at time t is at least as large as the corresponding improvement in the value function under intervention I_2. In general the value-function increments $v_t^{(2)}(s_t+1) - v_t^{(2)}(s_t)$ and $v_t^{(1)}(s_t+1) - v_t^{(1)}(s_t)$ will decrease with increasing $s_t \in \{1,\ldots,M-1\}$; and the assumed condition merely requires that the increment $v_t^{(1)}(s_t+1) - v_t^{(1)}(s_t)$ for the more-effective intervention decreases no faster than does the corresponding increment $v_t^{(2)}(s_t+1) - v_t^{(2)}(s_t)$ for the less-effective intervention I_2 as the adherence state s_t improves (increases).

In the next, and final, theorem we use a superscript to index different types of patients in order to compare the optimal intervention thresholds for two types of patients. The superscript for a patient of type 1 is $(1')$ and the superscript for a patient of type 2 is $(2')$.

Theorem 3. *If $\widetilde{P}_t^{(1')}(I) = \widetilde{P}_t^{(2')}(I) \succcurlyeq \widetilde{P}_t^{(2')}(W) = \widetilde{P}_t^{(1')}(W)$ for $t \in \{1,\ldots,T-1\}$ and $v_t^{(1')}(s_t+1) - v_t^{(1')}(s_t) \leq v_t^{(2')}(s_t+1) - v_t^{(2')}(s_t)$ for all $s_t \in \{1,\ldots,M-1\}$ and $t \in \{1,\ldots,T-1\}$, then for two patient types that are identical except that*

$$[\overline{p}_t^{(1')}]_i \geq [\overline{p}_t^{(2')}]_i, \text{ for every } i = 1,\ldots,M \text{ and for } t \in \{1,\ldots,T-1\}, \tag{7}$$

and

$$\mu_T^{(1')}(s_T) \leq \mu_T^{(2')}(s_T), \text{ for every } s_T \in S \tag{8}$$

we have

$$P_t^{(2')}(W) \succcurlyeq P_t^{(1')}(W), \;\; P_t^{(2')}(I) \succcurlyeq P_t^{(1')}(I), \tag{9}$$

and

$$s_t^{*(1')} \leq s_t^{*(2')} \text{ for } t \in \{1,\ldots,T-1\}. \tag{10}$$

Theorem 3 states that if a patient of type 1 has a higher probability of moving to the pre-absorbing state than a patient of type 2, then a patient of type 2 should have interventions in the same or better adherence states when compared with a patient of type 1. Since $P_t^{(2')}(I) \succcurlyeq P_t^{(1')}(I)$, a patient of type 1, the sicker patient, receives less benefit from interventions than a patient of type 2. Interventions that are optimal for a patient of type 2 with better adherence may not be optimal for a patient of type 1. An example of two groups that this theorem could be applied to is males and females since males are generally at higher risk of having stroke and CHD events. Thus, males receive less benefit from interventions than females, and an intervention that is optimal for a female in a given health state may not be optimal for a male in the same health state. This counterintuitive result provides a simple criterion for sorting patients on the basis of importance of an intervention, which could be useful for resource constrained settings.

6. Case Study: Statin Adherence for Patients with Type 2 Diabetes

In this section we present a case study to illustrate the application of our model to evaluate a hypothetical EHR-based AAS system in the context of preventive treatment for cardiovascular disease. Specifically, we investigate adherence interventions for statin treatment among patients with type 2 diabetes. Statins are particularly important for patients with diabetes, since these patients are at two to four times higher risk for stroke and CHD events over patients without diabetes (CDC 2011). Furthermore, long-term adherence to statins is known to be poor (Benner et al. 2002, Mason et al. 2012).

In Section 6.1 we provide our data sources and model parameters. In Section 6.2 we compare active and inactive surveillance policies using the MDP model described in Section 4. We present the optimal policies and expected LYs and costs associated with these policies. We also explore the effects of gender, the patient's health risk, the cost of an intervention, the willingness-to-pay factor, and the type of intervention on the optimal policy. We conclude this section with an estimate of total benefits of AAS to the U.S. diabetes population.

6.1. *Data and Model Parameter Estimation*

The transition probabilities among adherence states were computed from the administrative medical and pharmacy claims data from a large health insurance company that insures patients across the United States. A cohort of 54,036 diabetes patients from this dataset were identified using Healthcare Effectiveness Data and Information Set (HEDIS) criteria for diagnosis of diabetes (National Committee for Quality Assurance 2007). Patients included in the set were required to have five years of continuous enrollment with first encounter dates ranging from January 1995 to June 2004. The PDC by pharmacy fills, described in Section 2, was used as a proxy for patient adherence rates. Once the PDC was computed for each patient, the transition probabilities were computed by counting the number of patients in each adherence state that transitioned to each adherence state in the next year. The associated effect of statins on the patient's TC level for each adherence level was derived from this observational data set as well (see Mason et al. (2012) for a detailed description).

The transition probabilities for stroke and CHD events were derived from the UKPDS risk models (Kothari et al. 2002, Stevens et al. 2001), and the probabilities for death from other causes were calculated from the CDC mortality tables (National Center for Health Statistics 2007). The state of the patient's health (other than their adherence level), which we used to estimate stroke and CHD event probabilities with the UKPDS model, was based on observations from a large cohort of 663 patients receiving treatment for type 2 diabetes at Mayo Clinic, Rochester, MN. Approximately 15,000 measurements of HbA1c (a patient's average blood sugar over two to three months), blood pressure, and cholesterol were collected between 1997 and 2006 through the Mayo Clinic Diabetes Electronic Management System (DEMS) (Gorman et al. 2000).

Table 2. Initial hospitalization costs and follow-up events for adverse events.

Parameter	Cost	Citation
Initial Hospitalization for Stroke	$13,204	AHRQ (2006)
Initial Hospitalization for CHD	$18,590	AHRQ (2006)
Yearly Follow-up for Stroke	$1664	Thom et al. (2006)
Yearly Follow-up for CHD	$2576	Thom et al. (2006)

For all of our experiments we assumed a maximum age of $T = 100$ as the age at which interventions would be discontinued and a discount factor of $\lambda = 0.97$ which corresponds to a 3% yearly discount rate (Gold et al. 1996). For the base case, we assumed a willingness to pay of $R =$ $100,000 (Evans et al. 2004) and a cost of statins of $C^{\text{MED}}(s_t) = \$212 \times \delta(s_t)$, where $\delta(s_t)$ represents the mean PDC of a patient in adherence state s_t (Red Book 2009). The cost of an intervention for the base case was estimated to be $C^{\text{INT}} = \$90$ (Chapman et al. 2010). This intervention cost includes telephone counseling to improve medication adherence and reinforcement of the message by a pharmacist. The initial and follow-up costs of stroke and CHD events were drawn from sources in the health services research literature provided in Table 2. The one-time penalty of entering the absorbing state, C_t^{F}, is computed with a Markov chain using these costs and probabilities governing patient survival.

The adherence states used in the numerical experiments are NON ($0\% \leq \text{PDC} \leq 10\%$), LOW ($10\% < \text{PDC} \leq 40\%$), MED ($40\% < \text{PDC} \leq 80\%$), and HIGH ($80\% < \text{PDC} \leq 100\%$) (Mason et al. 2012). The transition probability matrices, $\widetilde{P}_t(a_t)$, were estimated to be

$$\widetilde{P}_t(W) = \begin{array}{c} \\ \text{NON} \\ \text{LOW} \\ \text{MED} \\ \text{HIGH} \end{array} \begin{array}{c} \begin{array}{cccc} \text{NON} & \text{LOW} & \text{MED} & \text{HIGH} \end{array} \\ \begin{pmatrix} 0.787 & 0.106 & 0.082 & 0.025 \\ 0.498 & 0.205 & 0.213 & 0.084 \\ 0.199 & 0.154 & 0.390 & 0.257 \\ 0.028 & 0.046 & 0.189 & 0.737 \end{pmatrix} \end{array},$$

and

$$\widetilde{P}_t(I) = \begin{array}{c} \\ \text{NON} \\ \text{LOW} \\ \text{MED} \\ \text{HIGH} \end{array} \begin{array}{c} \begin{array}{cccc} \text{NON} & \text{LOW} & \text{MED} & \text{HIGH} \end{array} \\ \begin{pmatrix} 0.091 & 0.165 & 0.257 & 0.487 \\ 0.091 & 0.165 & 0.257 & 0.487 \\ 0.091 & 0.165 & 0.257 & 0.487 \\ 0.091 & 0.165 & 0.257 & 0.487 \end{pmatrix} \end{array}.$$

The matrix $\widetilde{P}_t(I)$ was estimated based on the proportion of patients occupying each of the adherence states in their first year of treatment. This assumption was made since an intervention may act to "reset" a patient's adherence level to the level it was when the patient initially began treatment. In addition, we considered the more optimistic case that a patient moves to state HIGH with probability 1. Use of this intervention provides a conservative estimate of the improvement achievable through interventions. The use of actual data to estimate the probabilities among the adherence states inherently includes the effects of diet, exercise, and other behavioral changes.

6.2. *Numerical Results*

Numerical experiments were conducted to find the optimal policy for adherence-improving interventions based on the above model parameters. The model was solved using backwards recursion, implemented in C/C++. Each experiment took less than ten seconds to run using a 2.83GHz PC with 8GB of RAM. Experiments were run for males and females, starting at age 40, assuming a variety of different risk states and different intervention cost estimates. The perfect and imperfect interventions described in Section 6.1 were both evaluated. We represent different risk states by the patient's TC and high-density lipoprotein (HDL), also known as "good" cholesterol, each given as one of low (L), medium (M), high (H), and very high (V). These are the most significant metabolic factors influencing a patient's risk of stroke or CHD events according to the UKPDS model. While there are a total of 16 patient risk states defined by clinically-relevant thresholds (Cleeman et al. 2001), for brevity we provide policies and numerical results for representative patients with low risk (low TC and very high HDL), medium risk (medium TC and medium HDL), and high risk (very high TC and low HDL).

6.2.1. *Active vs. Inactive Surveillance*

To estimate the potential benefits of using EHRs to improve adherence to medication at the population level, we compared the expected LYs from age 40 prior to an event or death and the expected discounted total costs comprising the costs of intervention, statin treatment, and hospitalizations and follow-up care for CHD events and stroke found using the optimal AAS policy and the IAS policy. IAS involves periodic interventions that do not rely on a patient's adherence level. We considered interventions that occur every k years ($k = 1, 2, 3, 4$, or 5) after a patient begins taking medication, regardless of the patient's adherence state. The IAS policy is useful for comparison since it requires no pharmacy or laboratory data and is therefore much easier to implement in practice. We also considered the use of no interventions.

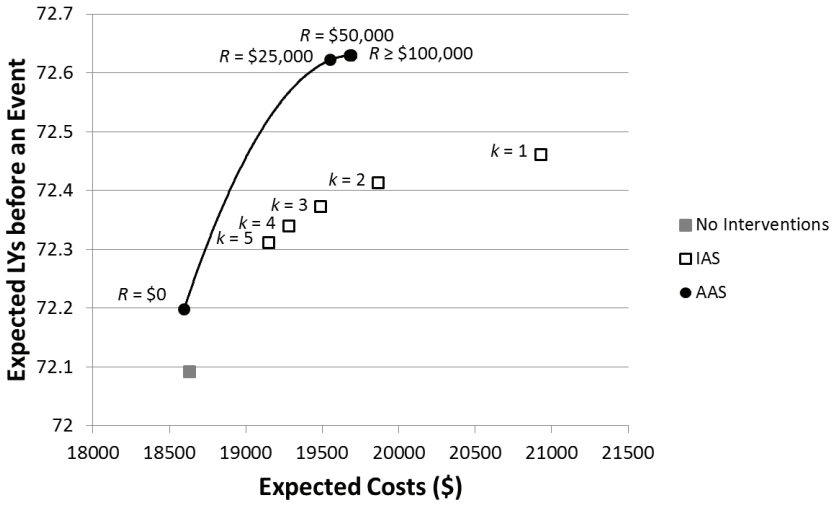

Fig. 2. Comparison of expected LYs verses costs for medication, interventions, and treatment of events for active adherence surveillance (AAS) policies (with varying R values) and inactive adherence surveillance (IAS) policies (when interventions occur every k years) for female patients using imperfect interventions. Results are a weighted average of LYs and costs for the 16 possible risk states.

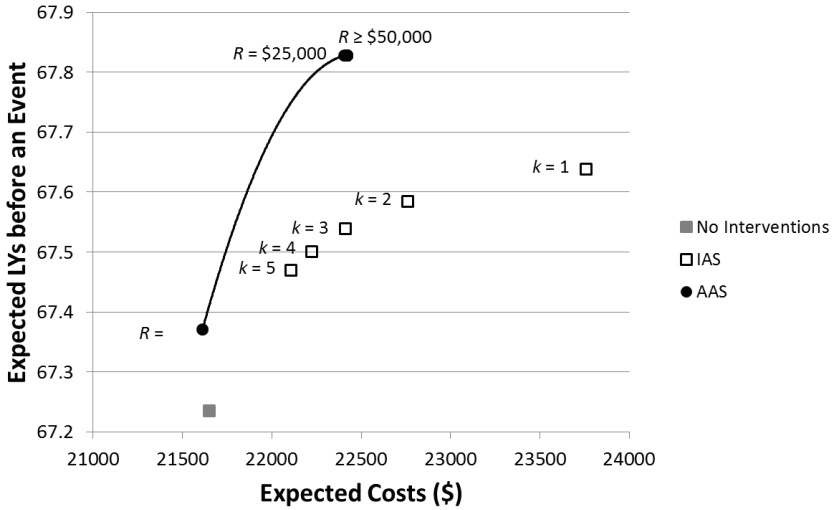

Fig. 3. Comparison of expected LYs verses costs, as shown in Figure 2, for male patients.

Figures 2 and 3 show the expected LYs vs. costs for AAS, IAS, and no treatment, for females and males. Imperfect interventions were used for these results. We evaluated different AAS policies by varying the willingness-to-pay factor from $R = \$0$ to $R = \$1{,}000{,}000$. When the willingness-to-pay factor is varied, different weights are placed on LYs and costs. As this factor increases, a larger weight is placed on maximizing the patient's LYs rather than minimizing costs. We observe that AAS outperforms IAS, for females and males, yielding greater expected LYs before an event or death and lower expected costs when $R \geq \$25{,}000$. When $R = \$100{,}000$, the base case value for our experiments, the average female patient using AAS receives an expected 0.17 additional LYs with a \$1237 reduction in costs over IAS ($k = 1$), and the average male patient using AAS receives an expected 0.19 additional LYs with a \$1335 reduction in costs over IAS ($k = 1$). AAS resulted in no interventions for patients with HIGH adherence. The higher expected costs incurred by IAS are presumably due in part to unnecessary interventions for patients with HIGH adherence to treatment, highlighting the benefit of AAS. It is particularly interesting that there are major gender differences in the expected LYs before an event or death. Based on our results, we observe that males are expected to have an adverse event or death approximately 5 years earlier than females.

While AAS dominates IAS for all 16 risk states, there are significant differences in the magnitude of the differences in expected cost and LYs for patients with different risk of CHD events and stroke. Figure 4 presents results for females with low, medium, and high risk in a format similar to Figure 2. Patients with low risk can expect to have their first event or death later in life than patients with medium or high risk. Also, as a patient's risk increases, her benefit over no treatment and her benefit over IAS increases. Thus, it appears the benefit of AAS is increasing in patient risk. We also note that the expected costs and LYs are less sensitive to changes in the willingness-to-pay factor as risk increases. The observations for males are consistent with the results for females.

We performed sensitivity analysis on the type of intervention. When a perfect intervention is considered, AAS ($R = \$100{,}000$) and IAS ($k = 1$) achieve nearly the same expected LYs before an adverse health event or death, with AAS providing 0.00037 fewer LYs for females and the same expected LYs for males. AAS results in an average reduction in costs of \$350 for females and \$519 for males. Thus, if perfect interventions were achievable, the benefit of AAS would be diminished.

6.2.2. *Sensitivity to Cost of Intervention*

We performed sensitivity analysis on the cost of interventions using cost estimates for interventions from the literature (Chapman et al. 2010). When interventions are free, we observe that patients should have yearly interventions starting at age 41 ($t = 1$), the earliest possible age for interventions to occur in our model, since there is no downside for free interventions. For $C^{\text{INT}} = \$10$, \$90, or \$142, we observe female patients should have yearly interventions starting at the ages listed in Tables 3 and 4. The optimal policy for male patients follows a similar pattern to the optimal policy for female patients, but male patients should start having interventions up to 13 years earlier than female patients, depending on the type and cost of intervention. The differences between the policies for male and female patients are likely due to the fact that males generally have an earlier onset of risk for cardiovascular events than females.

The optimal policy, presented in Tables 3 and 4, exhibits a control limit structure, as expected from

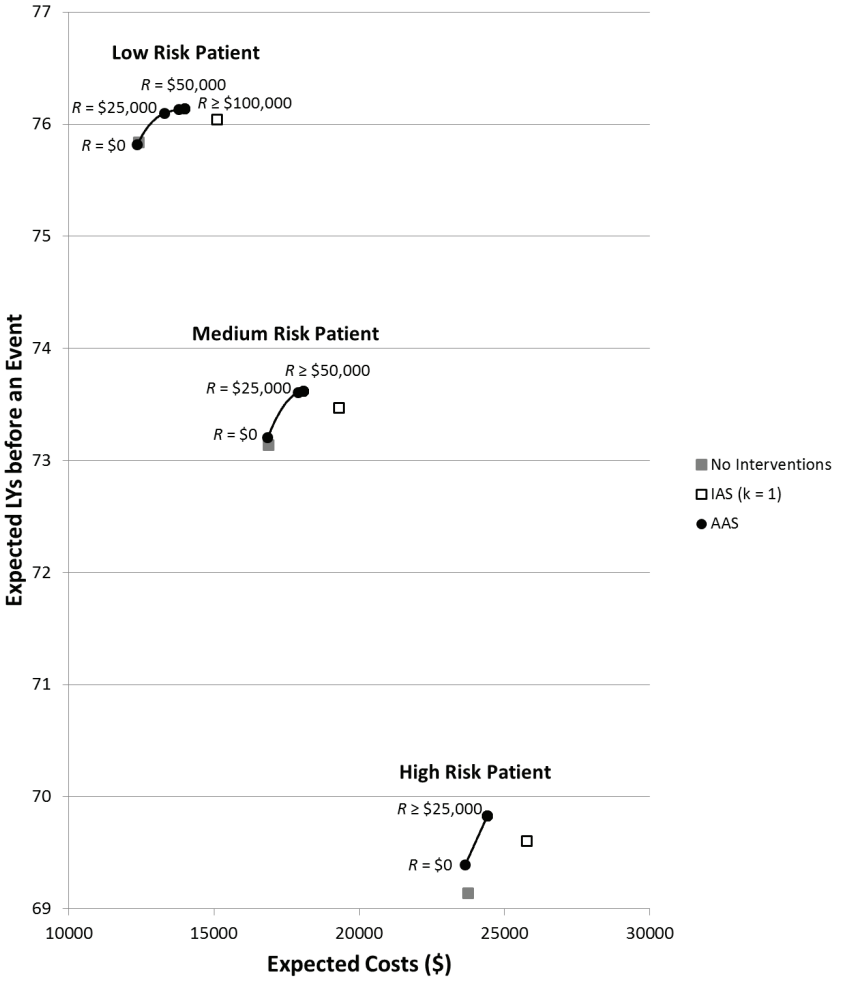

Fig. 4. Comparison of expected LYs verses costs for medication, interventions, and treatment of events for active adherence surveillance (AAS) policies (with varying R values) and yearly inactive adherence surveillance (IAS) for female patients using imperfect interventions. Results are compared for low, medium, and high risk patients.

Theorem 1. We also observe that the control limit tends to increase with respect to age with the exception that at very old ages interventions are no longer optimal. The latest age of intervention ranges from 95 to 98, depending on the patient's risk level and the cost of the intervention. We expect this is due to the end of horizon approximation in which we truncate the decision horizon at $T = 100$.

6.2.3. *Sensitivity to Individual Patient Risk Factors*

In general, female patients and patients with lower risk stop having interventions earlier due to lower risk of stroke and CHD events. The policies are very insensitive to changes in the cost of interventions, particularly for males and patients in higher risk states. We observe that the higher cost interventions have a shorter range for which it is optimal to perform the interventions; that is, the interventions start later and do not continue as late in life. The female patients have fewer interventions overall, with interventions starting later and ending earlier. This is likely due to the fact that being male is a risk factor for stroke and CHD events, the events statins help prevent.

When perfect interventions are considered, it is always optimal for male and female patients to have interventions when their adherence is less than HIGH. The use of perfect interventions for patients with HIGH adherence depends on the intervention cost and risk state. For imperfect interventions, however, patients with HIGH adherence should never have an intervention since the probability of remaining in the HIGH adherence state under an intervention is lower than the probability of remaining in the HIGH adherence state without an intervention.

6.2.4. *Potential Yearly Benefits of AAS to the U.S. Diabetes Population*

In order to estimate the benefits of AAS applied to all diabetes patients in the United States, we first estimated the prevalence of diabetes in the United States using population estimates, by age and gender, based on the 2010 U.S. Census (U.S. Census Bureau 2011), and the estimated diabetes prevalence by state and age range reported by Danaei et al. (2009). Next, we estimated the number of newly diagnosed diabetes patients for each gender, for every state and the District of Columbia, and for each age, starting at age 40. Patients

Table 3. Optimal ages to begin having yearly interventions for female patients using active surveillance. Imperfect (probabilistic) interventions are assumed. Note: '–' denotes it is never optimal for the patient to have interventions.

Low Risk			
	\$10	\$90	\$142
NON	41	41	41
LOW	41	41	41
MED	41	41	45
HIGH	–	–	–

Medium Risk			
	\$10	\$90	\$142
NON	41	41	41
LOW	41	41	41
MED	41	41	41
HIGH	–	–	–

High Risk			
	\$10	\$90	\$142
NON	41	41	41
LOW	41	41	41
MED	41	41	41
HIGH	–	–	–

were defined as *newly diagnosed* in 2010 if they were a diabetes patient at age 40 or an older patient diagnosed later in life. Patients were identified as newly diagnosed past age 40 if the population of total patients diagnosed at earlier ages was less than the diagnosed population at the given age. This accounts for increases in population and diabetes prevalence with respect to age.

Table 5 provides a yearly estimate of the differences in expected LYs and costs over the remaining years of life for newly diagnosed diabetes patients aged 40 or older with IAS ($k = 1$) and AAS relative to no interventions. According to our model, the implementation of IAS ($k = 1$), compared to no interventions, would increase LYs for the U.S. population at a cost of $5212/LY. In comparison, AAS would increase LYs over no interventions for the U.S. population at a cost of $1099/LY. Using AAS in place of IAS ($k = 1$) would result in over 131,000 additional LYs among adults newly diagnosed with diabetes while saving over $1.05 billion per year.

7. Conclusions

The CMS Meaningful Use initiative has the potential to encourage improved efficiency and effectiveness of healthcare delivery through the use of EHRs. Based on our results we found that the use of EHRs to improve adherence has the potential to significantly delay the onset of adverse events or death, and reduce expected costs of treatment, hospitalization, and follow-up care associated with adverse events such as stroke and CHD. From the population perspective, we found that AAS is cost effective compared with no interventions at a cost of $1099 spent per LY added prior to CHD, stroke, or death. This cost per LY added is very low with respect to commonly used thresholds (Evans et al. 2004). In addition, AAS results in significant cost savings over IAS ($k = 1$) while providing more than 131,000 additional event-free LYs to newly diagnosed diabetes patients each year at a savings of $1.05 billion per year. These estimated annual benefits highlight the potential benefits of AAS. Our study considers the use of AAS for a subpopulation in the United States that is at a high risk of stroke and CHD events; however, AAS could be used for the broader U.S. population and for patients on other medications, yielding additional savings.

From the individual patient perspective, males receive an average of 0.19 additional LYs before an event or death over IAS ($k = 1$) at a reduction in costs of $1335, and females receive 0.17 additional LYs at a cost

Table 4. Optimal ages to begin having yearly interventions for female patients using active surveillance. Perfect interventions are assumed.

Low Risk			
	$10	$90	$142
NON	41	41	41
LOW	41	41	41
MED	41	41	41
HIGH	41	49	58

Medium Risk			
	$10	$90	$142
NON	41	41	41
LOW	41	41	41
MED	41	41	41
HIGH	41	41	45

High Risk			
	$10	$90	$142
NON	41	41	41
LOW	41	41	41
MED	41	41	41
HIGH	41	41	41

Table 5. Yearly differences in costs (billions) and future LYs for newly-diagnosed diabetes patients using yearly inactive adherence surveillance (IAS, $k = 1$) and active adherence surveillance (AAS) relative to no adherence interventions.

	Males		Females		Total Population	
	LYs	Cost (billions)	LYs	Cost (billions)	LYs	Cost (billions)
IAS ($k = 1$)	144,742	\$0.70	145,337	\$0.82	290,077	\$1.51
AAS	210,939	\$0.17	210,144	\$0.29	421,082	\$0.46

savings of \$1237 over IAS ($k = 1$). These increases in LYs over IAS ($k = 1$) are an order of magnitude greater than the benefits seen through some prevention programs that are part of standard practice in the United States. For example, childhood vaccination against measles, mumps, and rubella results in an increase of 0.017 LYs (Wright and Weinstein 1998). In addition, the increase in LYs from AAS over no interventions is even greater. The benefits of AAS over IAS and no interventions increase with increasing patient risk. In other words, patients at higher risk of adverse events stand to have greater benefit from AAS.

We found the optimal policy for adherence-improving interventions to exhibit a control-limit type policy. This is consistent with the theoretical results we presented. This simple structure is intuitively appealing and could be exploited to achieve computational advantages in the context of large MDPs requiring fast solutions. From our numerical experiments, it appears that the control limit is increasing with respect to age. Once a patient begins having interventions, it is generally optimal to continue having yearly interventions until very late in life. Such a simple policy is encouraging for the application of AAS system in the already complex clinical environment.

We proved several new structural properties, for finite horizon nonstationary MDPs, related to the optimal control limit when interventions of different effectiveness are considered, and when patients of different levels of risk are considered. Theorem 3 in particular provides insight through a simple yet counterintuitive rule for prioritizing patient interventions. While we presented Theorems 2 and 3 in the context of the problem we are applying our model to (the optimal timing of adherence-improving interventions for patients with type 2 diabetes), these theoretical properties and our model are generalizable to many other contexts. For example, in the context of machine maintenance, Theorem 3 could be useful in scheduling maintenance for different types of machines that have different levels of reliability.

Although the outcomes of the AAS policy dominated the easier-to-implement IAS outcomes, our model did not account for the possibility of initial set-up costs and ongoing maintenance costs for such a system. While the data our model is based on is generally available in administrative claims systems and laboratory information systems, the development of a decision support system that collects and utilizes the data would have some cost associated with instantiation of the system in a clinical environment. Since these costs are likely to vary significantly among implementations we did not consider this in our analysis; however, it is worth noting that our model can easily be modified to incorporate any maintenance costs that would be necessary to use AAS. In addition, our model could be used to estimate the payback time for the initial costs

of the system by calculating expected return on investment of using AAS over IAS. Furthermore, CMS incentives for participation in the Meaningful Use program may offset some of the costs of implementation.

There are some practical challenges associated with the use of EHR data for applications such as we discuss. First, patients do not always stay with the same insurance provider. There may be a limited amount of time for which there is continuous information for each patient. This challenge may eventually be overcome by the development of a universal EHR. Second, our model assumes population level data can be used to estimate parameters for individual patients. In the case of adherence to medical treatments, such as statin therapy, this is reasonable because researchers have not been able to identify ways to predict adherence on the basis of available health data. Nevertheless, the use of population level data represents a barrier to more accurate prediction of adherence that might be possible with additional data. Third, in order for AAS to be implemented at the point of care, EHRs will need to collect and compute patient information such as PDC for prescribed medications (to estimate the patients adherence level) and patient health information (such as blood pressure and cholesterol) to estimate the risk of adverse events. While we have demonstrated in this article it is possible to overcome these challenges, the ability to rapidly collect and combine such data presents a challenge for some health systems.

Future research could build on our model in several ways. For example, we considered interventions for a single medical treatment; future studies could extend the current model to include the optimal timing of interventions for patients on multiple medications. This extension generates a number of interesting questions. Would there be correlations between interventions? In other words, could an intervention for one medication influence adherence to another medication? Could an intervention be designed that would simultaneously improve adherence to multiple medications? Furthermore, interesting questions arise about the relative importance of interventions. Our model could be extended to include more than one type of intervention in the action space for the one medication problem to help prioritize among different types of interventions with varying costs and levels of effectiveness. In addition, our model could be amended to help prioritize interventions for different medications. Additional variations on our model could include different assumptions about the effectiveness of interventions. Although there is no evidence at present, it is possible that interventions may provide diminishing improvement to adherence over time. As we pointed out in the introduction, the recent substantial commitment of resources and efforts by the medical community to improve the current state of knowledge about medication adherence presents a number research opportunities for the OR community. Our model lays the foundation for some of these future studies.

Appendix: Proofs of Lemmas and Theorems from Section 5

Proof of Lemma 1: Since $\widetilde{P}_t(a_t)$ is IFR by assumption $\mathbf{A}_1$, with (i,j) element $\widetilde{p}_t(j|i,a_t) \equiv [\widetilde{P}_t(a_t)]_{i,j}$, it follows that for each $k \in \{1,\ldots,M\}$, the quantity $\widetilde{q}_t(k|i,a_t) = \sum_{j=k}^{M} \widetilde{p}_t(j|i,a_t)$ is nondecreasing in i for $i = 1,\ldots,M$. The matrix multiplication $\mathrm{diag}[1_M - \overline{p}_t]\widetilde{P}_t(a_t)$ involves multiplying the ith row of $\widetilde{P}_t(a_t)$ through by $1 - [\overline{p}_t]_i$ for $i \in \{1,\ldots,M\}$. Therefore, since $1 - [\overline{p}_t]_i$ is nondecreasing in i by assumption $\mathbf{A}_3$, it follows that the

$(M+2)\times M$ matrix

$$Y \equiv \begin{bmatrix} 0_M^\intercal \\ 0_M^\intercal \\ \mathrm{diag}[1_M - \bar{p}_t]\widetilde{P}_t(a_t) \end{bmatrix} \tag{11}$$

with (u,v) element $Y_{u,v}$ for $u \in \{0,0',1,\ldots,M\}$ and $v \in \{1,\ldots,M\}$ satisfies the following IFR-like property: for each fixed $k \in \{1,\ldots,M\}$, the function $y(u) \equiv \sum_{v=k}^{M} Y_{u,v}$ is nondecreasing in u for $u \in \{0,0',1,\ldots,M\}$. Similarly, it follows that the $(M+2)\times(M+1)$ matrix

$$Z \equiv \begin{bmatrix} 0 & 0_M^\intercal \\ 0 & 0_M^\intercal \\ \bar{p}_t & \mathrm{diag}[1_M - \bar{p}_t]\widetilde{P}_t(a_t) \end{bmatrix} \tag{12}$$

with (u,v) element $Z_{u,v}$ for $u \in \{0,0',1,\ldots,M\}$ and $v \in \{0',1,\ldots,M\}$ satisfies the following IFR-like property: for each fixed $k \in \{0',1,\ldots,M\}$, the function $z(u) \equiv \sum_{v=k}^{M} Z_{u,v}$ is nondecreasing in u for $u \in \{0,0',1,\ldots,M\}$ because of the following observations: (i) the matrix Z is obtained by concatenating the $(M+1)$-dimensional column vector $\left[0,0,\bar{p}_t^\intercal\right]^\intercal$ and the $(M+2)\times M$ matrix Y, which has just been shown to satisfy the required IFR-like property; and (ii) for each of the last M rows of Z, the row sums to 1 because a one-step transition from the associated adherence state to the absorbing state is impossible. Finally, we observe that $P_t(a_t)$ is obtained by concatenating the $(M+2)$-dimensional column vector $\left[1,1,0_M^\intercal\right]^\intercal$ and the $(M+2)\times(M+1)$ matrix Z, which has just been shown to satisfy the IFR-like property; therefore $P_t(a_t)$ satisfies the required IFR property because each row of the latter matrix sums to 1. □

Proof of Lemma 2: The proof of Lemma 2 parallels the argument justifying Proposition 4.7.3 of Puterman (1994) after properly accounting for the exclusion of the absorbing state from assumptions $\mathbf{A}_2$ and $\mathbf{A}_4$. Now $r_t(0,a_t) = 0$ for $t \in \{1,\ldots,T\}$ and for $a_t \in A_t(0)$ by (2), and we have $v_T(0) = \mu_T(0) = 0$ by (4); therefore from the optimality equation (3) for state 0, we see that

$$v_t(0) = 0 \text{ for } t \in \{1,\ldots,T-1\}. \tag{13}$$

The rest of the proof that $v_t(s_t)$ is nondecreasing in s_t for $s_t \in S\setminus\{0\}$ and $t \in \{1,\ldots,T\}$ requires us to exploit the optimality equation (3) for state s_t and any other state $s_t^\dagger \geq s_t$ together with the IFR property of $P_t(a_t)$, Equation (13), and Lemma 4.7.2 of Puterman (1994) in a backward induction argument that proceeds as follows. First we observe that at time T, assumption $\mathbf{A}_2$ and Equation (4) ensure that $v_T(s_T)$ is nondecreasing for $s_T \in S\setminus\{0\}$. Now we assume that $v_u(s_u)$ is nondecreasing in s_u for $s_u \in S\setminus\{0\}$ and $u \in \{t+1,\ldots,T\}$. From the optimality equation for state $s_t \in S\setminus\{0\}$ with optimal action $a_t^*(s_t)$, we have by (13) that

$$v_t(s_t) = r_t(s_t,a_t^*(s_t)) + \sum_{j\in S\setminus\{0\}} p_t(j|s_t,a_t^*(s_t))v_{t+1}(j). \tag{14}$$

We choose another adherence state $s_t^\dagger \geq s_t$ arbitrarily. To show that $v_t(s_t^\dagger) \geq v_t(s_t)$, we exploit the IFR property of $P_t(a_t)$ to conclude that for $s_u^\ddagger \in S\setminus\{0\}$, the function

$$q_u(k|s_u^\ddagger,a_u) \equiv \sum_{j=k}^{M} p_u(j|s_u^\ddagger,a_u) \tag{15}$$

is nondecreasing in $s_u^\ddagger$ for all $k \in S$, $a_u \in A_u(s_u^\ddagger)$, and $u \in \{1,\ldots,T\}$. We apply Puterman's Lemma 4.7.2 in which we make the associations $x'_j \leftrightarrow p_t(j|s_t,a_t^*(s_t))$, $x_j \leftrightarrow p_t(j|s_t^\dagger,a_t^*(s_t))$, and $v_j \leftrightarrow v_{t+1}(j)$ for $j \in S\setminus\{0\}$. With the latter assignments, we can combine Equation (2), assumption $\mathbf{A}_4$, Equation (14), and the definition (15) of $q_u(k|s_u^\ddagger,a_u)$ to conclude from Puterman's Lemma 4.7.2 that

$$\begin{aligned} v_t(s_t) &\le r_t(s_t^\dagger,a_t^*(s_t)) + \sum_{j\in S\setminus\{0\}} p_t(j|s_t^\dagger,a_t^*(s_t))v_{t+1}(j) \\ &\le \max_{a_t\in A_t(s_t^\dagger)} \left\{ r_t(s_t^\dagger,a_t) + \sum_{j\in S} p_t(j|s_t^\dagger,a_t)v_{t+1}(j) \right\} = v_t(s_t^\dagger) \end{aligned}$$

by (13) and the optimality equation (3) for state $s_t^\dagger$. Thus we see that $v_t(s_t)$ is nondecreasing in s_t for $s_t \in S\setminus\{0\}$ so the induction hypothesis is satisfied. □

Proof of Theorem 1: The proof parallels the analysis establishing Theorem 4.7.4 of Puterman (1994) after making suitable adjustments to handle states 0 and $0'$ separately. For convenience we make the assignment $a_t(s_t) = 0$ when taking the action W at time t given than the patient is in health state $s_t \in S$; similarly we assign $a_t(s_t) = 1$ when taking action I at time t given the patient's health state $s_t \in S$ for $t \in \{1,\ldots,T-1\}$. Because $A_t(s_t) = \{W\}$ for $s_t \in \{0,0'\}$, we have $a_t^*(s_t) = 0$ for $s_t \in \{0,0'\}$ and $t \in \{1,\ldots,T-1\}$.

Paralleling the proof of Theorem 4.7.4 of Puterman (1994), the following properties are essential to the argument for each $t \in \{1,\ldots,T-1\}$:

- $\mathbf{B}_1$: $r_t(s_t,a_t)$ is nondecreasing in s_t for $s_t \in S\setminus\{0,0'\}$ and $a_t \in \{0,1\}$;
- $\mathbf{B}_2$: $q_t(k|s_t,a_t)$ as defined by Equation (15) is nondecreasing in s_t for $s_t \in S\setminus\{0,0'\}$ and for all $k \in S$, $a_t \in \{0,1\}$;
- $\mathbf{B}_3$: $r_t(s_t,a_t)$ is a subadditive function on $[S\setminus\{0,0'\}]\times\{0,1\}$;
- $\mathbf{B}_4$: $q_t(k|s_t,a_t)$ is a subadditive function on $[S\setminus\{0,0'\}]\times\{0,1\}$ for all $k \in S$; and
- $\mathbf{B}_5$: the terminal value function $v_T(s_T)$ is nondecreasing in s_t for $s_t \in S\setminus\{0,0'\}$.

Property $\mathbf{B}_1$ follows immediately from Equation (2) and assumption $\mathbf{A}_4$. Properties $\mathbf{B}_2$ and $\mathbf{B}_5$ follow from Lemmas 1 and 2, respectively. Verifying property $\mathbf{B}_3$ is equivalent to showing that for every $\eta \in \{1,\ldots,M-1\}$ and $s_t \in \{1,\ldots,M-\eta\}$ and for $a_t = 0$, the second partial difference

$$\underset{s_t}{\Delta}\underset{a_t}{\Delta}\ r_t(s_t,0) \equiv r_t(s_t+\eta,1) - r_t(s_t+\eta,0) - r_t(s_t,1) + r_t(s_t,0)$$

is nonpositive. By (2) we have

$$\begin{aligned} \underset{s_t}{\Delta}\underset{a_t}{\Delta}\ r_t(s_t,0) &= [R\times Q(s_t+\eta) - C^{\mathrm{MED}}(s_t+\eta) - C^{\mathrm{INT}}] - [R\times Q(s_t+\eta) - C^{\mathrm{MED}}(s_t+\eta)] \\ &\quad - [R\times Q(s_t) - C^{\mathrm{MED}}(s_t) - C^{\mathrm{INT}}] + [R\times Q(s_t) - C^{\mathrm{MED}}(s_t)] \\ &= 0 \ \text{ for } \ \eta \in \{1,\ldots,M-1\},\ s_t \in \{1,\ldots,M-\eta\},\ \text{ and } \ t \in \{1,\ldots,T-1\}. \end{aligned}$$

The verification of condition $\mathbf{B}_4$ is similar to the verification of condition $\mathbf{B}_3$. For $\eta \in \{1,\ldots,M-1\}$, $s_t \in \{1,\ldots,M-\eta\}$, $k \in S$, and $t \in \{1,\ldots,T-1\}$, the second partial difference

$$\underset{s_t}{\Delta}\underset{a_t}{\Delta}\ q_t(k|s_t,0) = [q_t(k|s_t+\eta,1) - q_t(k|s_t,1)] - [q_t(k|s_t+\eta,0) - q_t(k|s_t,0)] \tag{16}$$

must be nonpositive for the following reasons: (i) by assumption, the effect of an intervention at time t is independent of the patient's health state at that time so that the first term in square brackets on the right-hand side of Equation (16) must vanish; and (ii) Lemma 1 ensures that the second term in square brackets is nonnegative. Thus we see that $\underset{s_t}{\Delta}\underset{a_t}{\Delta}\ q_t(k|s_t,0) \le 0$ for $\eta \in \{1,\ldots,M-1\}$, $s_t \in \{1,\ldots,M-\eta\}$, $k \in S$, and $t \in \{1,\ldots,T-1\}$ so that property $\mathbf{B}_4$ follows.

To complete the proof of Theorem 1, we need to establish that the function

$$w_t(s_t,a_t) \equiv r_t(s_t,a_t) + \sum_{j=1}^{M} p_t(j|s_t,a_t)v_{t+1}(j)$$

is subadditive on $[S\setminus\{0,0'\}]\times\{0,1\}$. By the subadditivity of $q_t(k|s_t,a_t)$ on $[S\setminus\{0,0'\}]\times\{0,1\}$ for all $k \in S$, we have for $1 \le s_t^- \le s_t^+ \le M$, $0 \le a_t^- \le a_t^+ \le 1$, and $k \in S$,

$$\sum_{j=k}^{M}[p_t(j|s_t^-,a_t^-) + p_t(j|s_t^+,a_t^+)] \le \sum_{j=k}^{M}[p_t(j|s_t^-,a_t^+) + p_t(j|s_t^+,a_t^-)]. \tag{17}$$

By Lemma 2, the value function $v_{t+1}(j)$ is nondecreasing for $j \in S\setminus\{0,0'\}$; therefore we can apply Lemma 4.7.2 of Puterman (1994) to obtain

$$\sum_{j=1}^{M}[p_t(j|s_t^-,a_t^-) + p_t(j|s_t^+,a_t^+)]v_{t+1}(j) \le \sum_{j=1}^{M}[p_t(j|s_t^-,a_t^+) + p_t(j|s_t^+,a_t^-)]v_{t+1}(j). \tag{18}$$

For $\eta \in \{1,\ldots,M-1\}$ and $s_t \in \{1,\ldots,M-\eta\}$, we can express (18) as

$$0 \ge \sum_{j=1}^{M}[\ \underset{s_t}{\Delta}\underset{a_t}{\Delta}\ p_t(j|s_t,0)]v_{t+1}(j) = \ \underset{s_t}{\Delta}\underset{a_t}{\Delta}\ \left[\sum_{j=1}^{M} p_t(j|s_t,0)v_{t+1}(j)\right]; \tag{19}$$

and from property $\mathbf{B}_3$ we obtain the analogous result

$$\underset{s_t}{\Delta}\underset{a_t}{\Delta}\ r_t(s_t,0) \le 0 \text{ for } \eta \in \{1,\ldots,M-1\}, s_t \in \{1,\ldots,M-\eta\}, \text{ and } t \in \{1,\ldots,T-1\}. \tag{20}$$

Combining (19) and (20) we see that $\underset{s_t}{\Delta}\underset{a_t}{\Delta}\ w_t(s_t,0) \le 0$ for $\eta \in \{1,\ldots,M-1\}$, $s_t \in \{1,\ldots,M-\eta\}$, and $t \in \{1,\ldots,T-1\}$, so that $w_t(s_t,a_t)$ is subadditive on $[S\setminus\{0,0'\}]\times\{0,1\}$. Applying Lemma 4.7.1 of Puterman (1994), we see that there exists a control limit s_t^* for $t \in \{1,\ldots,T-1\}$ such that Equation (5) holds. □

Proof of Lemma 3: First we establish Equation (6) for the absorbing and pre-absorbing states $\{0,0'\}$ separately, and then we use backward induction to establish (6) for the adherence states. From Equations (2) and (4), we see that

$$v_T^{(1)}(s_T) = v_T^{(2)}(s_T) = \begin{cases} -C_T^{\mathrm{F}}, & \text{if } s_T = 0', \\ 0, & \text{if } s_T = 0. \end{cases} \tag{21}$$

From Equation (13), we have

$$v_t^{(1)}(0) = v_t^{(2)}(0) = 0 \text{ for } t \in \{1,\ldots,T-1\}. \tag{22}$$

Moreover from Equation (2) and the optimality equation (3) for the pre-absorbing state $0'$, we see that

$$v_t^{(1)}(0') = v_t^{(2)}(0') = -C_t^{\mathrm{F}} \text{ for } t \in \{1,\ldots,T-1\}. \tag{23}$$

Combining (21), (22), and (23), we see that Equation (6) holds for $s_t \in \{0,0'\}$ and $t \in \{1,\ldots,T\}$.

To handle the adherence states, we start with the observation that Equation (4) yields $v_T^{(1)}(s_T) = \mu_T(s_T) = v_T^{(2)}(s_T)$, for $s_T \in S \setminus \{0,0'\}$. Thus, $v_T^{(1)}(s_T) \geq v_T^{(2)}(s_T)$ for $s_T \in S \setminus \{0,0'\}$. For the inductive step we assume $v_\tau^{(1)}(s_\tau) \geq v_\tau^{(2)}(s_\tau)$ for $s_\tau \in S \setminus \{0,0'\}$ and $\tau \in \{t+1,\ldots,T\}$. Now we must show $v_t^{(1)}(s_t) \geq v_t^{(2)}(s_t)$ for $s_t \in S \setminus \{0,0'\}$. Let $a_t^{(2)*}(s_t)$ be the optimal action for MDP_2 at time t for a patient in state $s_t \in S \setminus \{0,0'\}$. It follows that

$$\begin{aligned}
v_t^{(1)}(s_t) &\geq r_t(s_t, a_t^{(2)*}(s_t)) + \lambda \sum_{s_{t+1}=0}^{M} p_t^{(1)}(s_{t+1}|s_t, a_t^{(2)*}(s_t)) v_{t+1}^{(1)}(s_{t+1}) && (24)\\
&\geq r_t(s_t, a_t^{(2)*}(s_t)) + \lambda \sum_{s_{t+1}=0}^{M} p_t^{(2)}(s_{t+1}|s_t, a_t^{(2)*}(s_t)) v_{t+1}^{(1)}(s_{t+1}) && (25)\\
&\geq r_t(s_t, a_t^{(2)*}(s_t)) + \lambda \sum_{s_{t+1}=0}^{M} p_t^{(2)}(s_{t+1}|s_t, a_t^{(2)*}(s_t)) v_{t+1}^{(2)}(s_{t+1}) && (26)\\
&= v_t^{(2)}(s_t) \text{ for } s_t \in S.
\end{aligned}$$

Inequality (24) follows from the fact that $v_t^{(1)}(s_t)$, the optimal value function for MDP_1, is bounded below by the value function for any other policy (in this case the optimal policy for MDP_2). To establish (25), we observe that $P_t^{(1)}(I_1) \succcurlyeq P_t^{(2)}(I_2)$ and $P_t^{(1)}(W) \equiv P_t^{(2)}(W)$ together imply that

$$\sum_{s_{t+1}=k}^{M} p_t^{(1)}(s_{t+1}|s_t, a_t^{(2)*}(s_t)) \geq \sum_{s_{t+1}=k}^{M} p_t^{(2)}(s_{t+1}|s_t, a_t^{(2)*}(s_t)) \text{ for } s_t \in S \setminus \{0,0'\} \text{ and } k \in S; \tag{27}$$

and (27) is a strict equality for $k = 0'$. Because $v_t^{(1)}(s_t)$ is nondecreasing in s_t for $s_t \in S \setminus \{0\}$ by Lemma 2 above, we can apply Puterman's Lemma 4.7.2 to Equation (27), thereby showing that

$$\sum_{s_{t+1}=0'}^{M} p_t^{(1)}(s_{t+1}|s_t, a_t^{(2)*}(s_t)) v_{t+1}^{(1)}(s_{t+1}) \geq \sum_{s_{t+1}=0'}^{M} p_t^{(2)}(s_{t+1}|s_t, a_t^{(2)*}(s_t)) v_{t+1}^{(1)}(s_{t+1}); \tag{28}$$

and in view of Equation (22), we see that the summations on both sides of (28) can be extended to start at the absorbing state 0, so that for $s_t \in S \setminus \{0,0'\}$, we have

$$\sum_{s_{t+1}=0}^{M} p_t^{(1)}(s_{t+1}|s_t, a_t^{(2)*}(s_t)) v_{t+1}^{(1)}(s_{t+1}) \geq \sum_{s_{t+1}=0}^{M} p_t^{(2)}(s_{t+1}|s_t, a_t^{(2)*}(s_t)) v_{t+1}^{(1)}(s_{t+1}); \tag{29}$$

and Inequality (25) follows immediately from (29). Inequality (26) holds by the inductive hypothesis. Thus, $v_t^{(1)}(s_t) \geq v_t^{(2)}(s_t)$ for all t and for all $s_t \in S$. □

To prove Theorem 2, we must first establish the following variant of Lemma 4.7.2 of Puterman (1994) in which the summations $\sum x_j$ and $\sum x'_j$ are finite rather than infinite, and the summands $\{x_j\}$ and $\{x'_j\}$ are unconstrained in sign.

Lemma 4. *Let $\mathbb{J} \equiv \{0,1,\ldots,L\}$ denote a finite index-set; and let $\{x_j : j \in \mathbb{J}\}$ and $\{x'_j : j \in \mathbb{J}\}$ be finite real-valued sequences satisfying $\sum_{j=k}^{L} x_j \geq \sum_{j=k}^{L} x'_j$ for $k \in \mathbb{J}$ and $\sum_{j=0}^{L} x_j = \sum_{j=0}^{L} x'_j$. If $v_{j+1} \geq v_j$ for $j = 0,1,\ldots,L-1$, then $\sum_{j=0}^{L} x_j v_j \geq \sum_{j=0}^{L} x'_j v_j$.*

Proof of Lemma 4: If in the proof of Puterman's Lemma 4.7.2 we replace the infinite upper limit on each summation with the upper limit L, then all summations are finite and hence well defined even if some of the $\{x_j : j \in \mathbb{J}\}$ or $\{x'_j : j \in \mathbb{J}\}$ are negative; and the same analysis used for Puterman's Lemma 4.7.2 yields the desired conclusion. □

Proof of Theorem 2: The proof is by contradiction. If the desired conclusion of the theorem is false, then there is a time $u \in \{1,\ldots,T-1\}$ for which $s^*_u(I_1) < s^*_u(I_2)$; therefore we can find an adherence state $s_u \in S \setminus \{0,0'\}$ such that $s^*_u(I_1) < s_u \leq s^*_u(I_2)$ and

$$\begin{aligned} & R \times Q(s_u) - C^{\mathrm{MED}}(s_u) - C^{\mathrm{INT}} + \lambda \sum_{s_{u+1}=0}^{M} p_u^{(1)}(s_{u+1}|s_u, I_1) v_{u+1}^{(1)}(s_{u+1}) \\ & < R \times Q(s_u) - C^{\mathrm{MED}}(s_u) + \lambda \sum_{s_{u+1}=0}^{M} p_u^{(1)}(s_{u+1}|s_u, W) v_{u+1}^{(1)}(s_{u+1}), \end{aligned}$$

because by the construction of the control limit $s^*_u(I_1)$ as specified in Lemma 4.7.1 of Puterman (1994), the right- and left-hand sides of the above display cannot be equal; and from the above inequality, it follows immediately that

$$\lambda \sum_{s_{u+1}=0}^{M} \left(p_u^{(1)}(s_{u+1}|s_u, I_1) - p_u^{(1)}(s_{u+1}|s_u, W) \right) v_{u+1}^{(1)}(s_{u+1}) < C^{\mathrm{INT}}. \tag{30}$$

Moreover, because $s_u \leq s^*_u(I_2)$, we have

$$\lambda \sum_{s_{u+1}=0}^{M} \left(p_u^{(2)}(s_{u+1}|s_u, I_2) - p_u^{(2)}(s_{u+1}|s_u, W) \right) v_{u+1}^{(2)}(s_{u+1}) \geq C^{\mathrm{INT}}. \tag{31}$$

From (30), (31), and the condition $\lambda \in (0,1]$, it follows that

$$\sum_{s_{u+1}=0}^{M} \left(p_u^{(1)}(s_{u+1}|s_u, I_1) - p_u^{(1)}(s_{u+1}|s_u, W) \right) v_{u+1}^{(1)}(s_{u+1}) < \sum_{s_{u+1}=0}^{M} \left(p_u^{(2)}(s_{u+1}|s_u, I_2) - p_u^{(2)}(s_{u+1}|s_u, W) \right) v_{u+1}^{(2)}(s_{u+1}). \tag{32}$$

To contradict (32), first we must show that the following two conditions always hold: (i) for all $t \in \{1,\ldots,T-1\}$ and for every $s_t \in S \setminus \{0,0'\}$ and $k \in S$, we have

$$\sum_{s_{t+1}=k}^{M} \left(p_t^{(1)}(s_{t+1}|s_t, I_1) - p_t^{(1)}(s_{t+1}|s_t, W) \right) \geq \sum_{s_{t+1}=k}^{M} \left(p_t^{(2)}(s_{t+1}|s_t, I_2) - p_t^{(2)}(s_{t+1}|s_t, W) \right); \tag{33}$$

and (ii) we have

$$v_t^{(1)}(s_t) \geq v_t^{(2)}(s_t) \text{ for all } s_t \in S \text{ and } t \in \{0,1,\ldots,T\}. \tag{34}$$

Condition (33) follows from the assumptions that $P_t^{(1)}(I_1) \succcurlyeq P_t^{(2)}(I_2)$ and $P_t^{(1)}(W) \equiv P_t^{(2)}(W)$ for $t \in \{1,\ldots,T-1\}$, and condition (34) follows from Lemma 3. Now we use conditions (33) and (34) to show that (32) cannot be true. By Lemma 4 the following inequality holds for $t \in \{1,\ldots,T-1\}$:

$$\sum_{s_{t+1}=0'}^{M} \left[p_t^{(1)}(s_{t+1}|s_t,I_1) - p_t^{(1)}(s_{t+1}|s_t,W)\right] v_{t+1}^{(1)}(s_{t+1}) \geq \sum_{s_{t+1}=0'}^{M} \left[p_t^{(2)}(s_{t+1}|s_t,I_2) - p_t^{(2)}(s_{t+1}|s_t,W)\right] v_{t+1}^{(1)}(s_{t+1}). \tag{35}$$

(Note that Lemma 4.7.2 of Puterman (1994) is not sufficient to establish (35) because the terms in square brackets in (35) are not all guaranteed to be nonnegative; and in this situation Lemma 4 is required instead.) In view of Equation (22), we see that the summation on both sides of (35) can be extended to start at the absorbing state 0, yielding

$$\sum_{s_{t+1}=0}^{M} \left[p_t^{(1)}(s_{t+1}|s_t,I_1) - p_t^{(1)}(s_{t+1}|s_t,W)\right] v_{t+1}^{(1)}(s_{t+1}) \geq \sum_{s_{t+1}=0}^{M} \left[p_t^{(2)}(s_{t+1}|s_t,I_2) - p_t^{(2)}(s_{t+1}|s_t,W)\right] v_{t+1}^{(1)}(s_{t+1}) \tag{36}$$

for $s_t \in S \setminus \{0,0'\}$ and $t \in \{1,\ldots,T-1\}$. Finally, the following inequality holds by applying Lemma 4, the assumptions that $v_t^{(2)}(s_t+1) - v_t^{(2)}(s_t) \leq v_t^{(1)}(s_t+1) - v_t^{(1)}(s_t)$ for all $s_t \in \{1,\ldots,M-1\}$ and $t \in \{1,\ldots,T-1\}$, and $P_t^{(2)}(I_2) \succcurlyeq P_t^{(2)}(W)$ for $t \in \{1,\ldots,T-1\}$ together with condition (34):

$$\sum_{s_{t+1}=0}^{M} \left[p_t^{(2)}(s_{t+1}|s_t,I_2) - p_t^{(2)}(s_{t+1}|s_t,W)\right] v_{t+1}^{(1)}(s_{t+1}) \geq \sum_{s_{t+1}=0}^{M} \left[p_t^{(2)}(s_{t+1}|s_t,I_2) - p_t^{(2)}(s_{t+1}|s_t,W)\right] v_{t+1}^{(2)}(s_{t+1}) \tag{37}$$

for every $s_t \in S \setminus \{0,0'\}$ and $t \in \{1,\ldots,T-1\}$. We establish Equation (37) as follows. If in Lemma 4 we make the following associations: (i) $x_j \leftrightarrow p_t^{(2)}(s_{t+1}=j|s_t,I_2) - p_t^{(2)}(s_{t+1}=j|s_t,W)$ for $j=0',1,\ldots,M$; (ii) $x'_j \leftrightarrow 0$ for $j=0',1,\ldots,M$; and (iii) $v_j \leftrightarrow v_{t+1}^{(1)}(s_{t+1}=j) - v_{t+1}^{(2)}(s_{t+1}=j)$ for $j=0',1,\ldots,M$, then we see from (23) that

$$v_j = 0 \text{ for } j = 0', \tag{38}$$

from Lemma 3 we have

$$v_j \geq 0 \text{ for } j = 1,\ldots,M. \tag{39}$$

From (38), (39), and the assumption that $v_t^{(2)}(s_t+1) - v_t^{(2)}(s_t) \leq v_t^{(1)}(s_t+1) - v_t^{(1)}(s_t)$ for all $s_t \in \{1,\ldots,M-1\}$ and $t \in \{1,\ldots,T-1\}$, we see that $v_j \leq v_{j+1}$ for $j=0',1,\ldots,M-1$. Therefore all the hypotheses of Lemma 4 are satisfied so that we have $\sum_{j\in S\setminus\{0\}} v_j x_j \geq \sum_{j\in S\setminus\{0\}} v_j x'_j$, from which we immediately have

$$\sum_{j=0'}^{M} [p_t^{(2)}(s_{t+1}=j|s_t,I_2) - p_t^{(2)}(s_{t+1}=j|s_t,W)] \times [v_{t+1}^{(1)}(s_{t+1}=j) - v_{t+1}^{(2)}(s_{t+1}=j)] \geq 0. \tag{40}$$

Rearranging (40), we have

$$\sum_{s_{t+1}=0'}^{M} [p_t^{(2)}(s_{t+1}|s_t,I_2) - p_t^{(2)}(s_{t+1}|s_t,W)] v_{t+1}^{(1)}(s_{t+1}) \geq \sum_{s_{t+1}=0'}^{M} [p_t^{(2)}(s_{t+1}|s_t,I_2) - p_t^{(2)}(s_{t+1}|s_t,W)] v_{t+1}^{(2)}(s_{t+1}); \tag{41}$$

and in view of (22), we can extend the summation on both sides of (41) so that they start at the absorbing state 0, yielding Equation (37). Therefore from (36) and (37) we have

$$\sum_{s_{t+1}=0}^{M}\big(p_t^{(1)}(s_{t+1}|s_t,I_1)-p_t^{(1)}(s_{t+1}|s_t,W)\big)v_{t+1}^{(1)}(s_{t+1})\geq\sum_{s_{t+1}=0}^{M}\big(p_t^{(2)}(s_{t+1}|s_t,I_2)-p_t^{(2)}(s_{t+1}|s_t,W)\big)v_{t+1}^{(2)}(s_{t+1}) \tag{42}$$

for every $s_t\in S\setminus\{0,0'\}$ and $t\in\{1,\ldots,T-1\}$. In view of Inequality (42), we see that (32) is false; and thus the desired conclusion follows immediately. □

Proof of Theorem 3: To conserve space, we summarize the main points, with references to the relevant methods used in previous proofs. Equation (9) is shown by an argument similar to that involving (11) and (12) in the proof of Lemma 1. We show Equation (10) using a proof by contradiction similar to the proof of Theorem 2. If the desired conclusion (10) is false, then there is a time $u\in\{1,\ldots,T-1\}$ for which $s_u^{*(1')}>s_u^{*(2')}$; and by an argument similar to that involving Equations (30) through (32), we deduce from the latter inequality that

$$\sum_{s_{u+1}=0}^{M}\big(p_u^{(2')}(s_{u+1}|s_u,I)-p_u^{(2')}(s_{u+1}|s_u,W)\big)v_{u+1}^{(2')}(s_{u+1})<\sum_{s_{u+1}=0}^{M}\big(p_u^{(1')}(s_{u+1}|s_u,I)-p_u^{(1')}(s_{u+1}|s_u,W)\big)v_{u+1}^{(1')}(s_{u+1}). \tag{43}$$

Then by an argument paralleling Equations (33) through (42), we show that the following relation is always true for every time $t\in\{1,\ldots,T-1\}$:

$$\sum_{s_{t+1}=0}^{M}\big(p_t^{(2')}(s_{t+1}|s_t,I)-p_t^{(2')}(s_{t+1}|s_t,W)\big)v_{t+1}^{(2')}(s_{t+1})\geq\sum_{s_{t+1}=0}^{M}\big(p_t^{(1')}(s_{t+1}|s_t,I)-p_t^{(1')}(s_{t+1}|s_t,W)\big)v_{t+1}^{(1')}(s_{t+1}). \tag{44}$$

Because (44) contradicts (43), the desired conclusion follows. □

References

AHRQ. 2006. Nationwide Inpatient Sample. Tech. rep., Healthcare Cost and Utilization Project.

Alagoz, O., L.M. Maillart, A.J. Schaefer, M.S. Roberts. 2004. The Optimal Timing of Living-Donor Liver Transplantation. *Manage Sci* **50**(10) 1420–1430.

Anderson, M.Q. 1981. Monotone Optimal Preventive Maintenance Policies for Stochastically Failing Equipment. *Naval Research Logistics Quarterly* **28**(3) 347–358.

Armstrong, M.J. 2002. Age Repair Policies for the Machine Repair Problem. *Eur J Oper Res* **138** 127–141.

Barlow, R.E., F. Proshan. 1965. *Mathematical Theory of Reliability*. Wiley.

Benner, J.S., R.J. Glynn, H. Mogun, P.J. Neumann, M.C. Weinstein, J. Avorn. 2002. Long-term persistence in use of statin therapy in elderly patients. *JAMA* **288**(4) 455–461.

Butler, D.A. 1979. A Hazardous-Inspection Model. *Manage Sci* **25**(1) 79–89.

Caetano, P.A., J.M.C. Lam, S.G. Morgan. 2006. Toward a Standard Definition and Measurement of Persistence with Drug Therapy: Examples from Research on Statin and Antihypertensive Utilization. *Clinical Therapeutics* **28** 1411–1424.

CDC. 2011. *National Diabetes Fact Sheet*. http://www.cdc.gov/diabetes/pubs/factsheet11.htm.

Chapman, R.H., C.P. Ferrufino, S.L. Kowal, P. Classi, C.S. Roberts. 2010. The Cost and Effectiveness of Adherence-Improving Interventions for Antihypertensive and Lipid-Lowering Drugs. *Int J Clin Pract* **64**(2) 169–181.

Chhatwal, J., O. Alagoz, E.S. Burnside. 2010. Optimal Breast Biopsy Decision-Making Based on Mammographic Features and Demographic Factors. *Operations Research* **58**(6) 1577–1591.

Cleeman, J.I., S.M. Grundy, D. Becker, L.T. Clark, R.S. Cooper, M. A. Denke, W.J. Howard, D.B. Hunninghake, D.R. Illingworth, R.V. Luepker, P. McBride, J.M. McKenney, R.C. Pasternak, N.J. Stone, L. Van Horn, H.B. Brewer, N.D. Ernst, D. Gordon, D. Levy, B. Rifkind, J.E. Rossouw, P. Savage, S.M. Haffner, D.G. Orloff, M.A. Proschan, J.S. Schwartz, C.T. Sempos, S.T. Shero, E.Z. Murray. 2001. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* **285**(19) 2486–2497.

CMS. 2012. Medicare Health & Drug Plan Quality and Performance Ratings: 2013 Part C & Part D Technical Notes: First Plan Preview. Tech. rep., Baltimore, MD: Centers for Medicare & Medicaid Services.

Cutler, D.M., W. Everett. 2010. Thinking Outside the Pillbox - Medication Adherence as a Priority for Health Care Reform. *The New England Journal of Medicine* **362** 1553–1555.

Danaei, G., A.B. Friedman, S. Oza, C.J.L. Murray, M. Ezzati. 2009. Diabetes Prevalence and Diagnosis in U.S. States: Analysis of Health Surveys. *Population Health Metrics* **7** 16.

DDCF. 2011. *African Health Research: Operations Research*. http://www.ddcf.org/Medical-Research/Program-Strategies/African-Health-Research/Operations-Research/.

Denton, B.T., M. Kurt, N.D. Shah, S.C. Bryant, S.A. Smith. 2009. Optimizing the Start Time of Statin Therapy for Patients with Diabetes. *Med Decis Making* **29** 351–367.

Evans, C., M. Tavakoli, B. Crawford. 2004. Use of Quality Adjusted Life Years and Life Years Gained as Benchmarks in Economic Evaluations: A Critical Appraisal. *Health Care Management Science* **7**(1) 43–49.

Fisher, A.A., J.R. Foreit. 2002. Designing HIV/AIDS Intervention Studies: An Operations Research Handbook. Tech. rep., Population Council.

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

Gorman, C. A., B. R. Zimmerman, S. A. Smith, S. F. Dinneen, J. B. Knudsen, D. Holm, B. Jorgensen, S. Bjornsen, K. Planet, P. Hanson, R. A. Rizza. 2000. DEMS - a second generation diabetes electronic management system. *Computer Methods and Programs in Biomedicine* **62**(2) 127–140.

Ho, P.M., D.J. Magid, F.A. Masoudi, D.L. McClure, J.S. Rumsfeld. 2006. Adherence to Cardioprotective Medications and Mortality among Patients with Diabetes and Ischemic Heart Disease. *BMC Cardiovascular Disorders* **6**(48).

Hopp, W.J., S.-C. Wu. 1990. Machine Maintenance with Multiple Maintenance Actions. *IIE Trans* **22**(3) 226–233.

Jardine, A.K.S., J.A. Buzacott. 1985. Equipment Reliability and Maintenance. *Euro J Oper Res* **19** 285–296.

Jha, A.K., R.E. Aubert, J. Yao, J.R. Teagarden, R.S. Epstein. 2012. Greater Adherence to Diabetes Drugs is Linked to Less Hospital Use and Could Save Nearly $5 Billion Annually. *Health Affairs* **31**(8) 1836–1846.

Klein, M. 1962. Inspection-Maintenance-Replacement Schedules under Markovian Deterioration. *Manage Sci* **9**(1) 25–32.

Kothari, V., R.J. Stevens, A.I. Adler, I.M. Stratton, S.E. Manley, H.A. Neil, R.R. Holman. 2002. UKPDS 60 - Risk of Stroke in Type 2 Diabetes Estimated by the United Kingdom Prospective Diabetes Study Risk Engine. *Stroke* **33**(7) 1776–1781.

Kurt, M., B.T. Denton, A. Schaefer, N. Shah, S. Smith. 2011. The Structure of Optimal Statin Initiation Policies for Patients with Type 2 Diabetes. *IIE Transactions on Healthcare* **1**(1) 49–65.

Maillart, L.M., J.S. Ivy, S. Ransom, K. Diehl. 2008. Assessing Dynamic Breast Cancer Screening Policies. *Operations Research* **56**(6) 1411–1427.

Mason, J.E., D.A. England, B.T. Denton, S.A. Smith, M. Kurt, N.D. Shah. 2012. Optimizing Statin Treatment Decisions for Diabetes Patients in the Presence of Uncertain Future Adherence. *Med Decis Making* **32**(1) 154 – 166.

McCall, J.T. 1965. Maintenance Policies for Stochastically Failing Equipment: A Survey. *Manage Sci* **11**(5) 493–524.

Nakagawa, T. 1988. Sequential Imperfect Preventive Maintenance Policies. *IEEE T Reliab* **37**(3) 295–298.

National Center for Health Statistics. 2007. National Vital Statistics Reports. Tech. Rep. 5.

National Committee for Quality Assurance. 2007. *HEDIS 2007 Volume 2 Techinical Specifications*.

National Institutes of Health. 2011. *Adherence Research Network*. http://obssr.od.nih.gov/scientific_areas/health_behaviour/adherence/adherenceresearchnetwork.aspx.

Osterberg, L., T. Blaschke. 2005. Adherence to Medication. *New England Journal of Medicine* **353** 487–497.

Pham, H., H. Wang. 1996. Imperfect Maintenance. *Euro J Oper Res* **94** 425–438.

Pierskalla, W.P., J.A. Voelker. 1976. A Survey of Maintenance Models: The Control and Surveillance of Deteriorating Systems. *Naval Research Logistics Quarterly* **23** 353–388.

Puterman, M.L. 1994. *Markov Decision Processes: Discrete Stochastic Dynamic Programming*. John Wiley & Sons, Inc, Hoboken, New Jersey.

Rasmussen, J.N., A. Chong, D.A. Alter. 2007. Relationship Between Adherence to Evidence-based Pharmacotherapy and Long-term Mortality after Acute Myocardial Infarction. *JAMA* **297**(2) 177–186.

Red Book. 2009. Red Book: 2009 Edition. Tech. rep., Thomson Healthcare, Inc.

Shechter, S.M., M.D. Bailey, A.J. Schaefer, M.S. Roberts. 2008. The Optimal Time to Initiate HIV Therapy Under Ordered Health States. *Operations Research* **56**(1) 20–33.

Sherif, Y.S., M.L. Smith. 1981. Optimal Maintenance Models for Systems Subject to Failure – A Review. *Naval Research Logistics Quarterly* **28**(1) 47–74.

Sokol, M.C., K.A. McGuigan, R.R. Verbrugge, R.S. Epstein. 2005. Impact of Medication Adherence on Hospitalization Risk and Healthcare Cost. *Medical Care* **43**(6) 521–530.

Steiner, J.F. 2012. Rethinking Adherence. *Annals of Internal Medicine* **157** 580–585.

Stevens, R.J., V. Kothari, A.I. Adler, I.M. Stratton, R.R. Holman. 2001. The UKPDS Risk Engine: a Model for the Risk of Coronary Heart Disease in Type 2 Diabetes (UKPDS 56). *Clinical Science* **101**(6) 671–679.

Thom, T., N. Haase, W. Rosamond, V.J. Howard, J. Rumsfeld, T. Manolio, Z.J. Zheng, K. Flegal, C. O'Donnell, S. Kittner, D. Lloyd-Jones, D.C. Goff, Y.L. Hong, R. Adams, G. Friday, K. Furie, P. Gorelick, B. Kissela, J. Marler, J. Meigs, V. Roger, S. Sidney, P. Sorlie, J. Steinberger, S. Wasserthiel-Smoller, M. Wilson, P. Wolf. 2006. Heart Disease and Stroke Statistics – 2006 Update – A Report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* **113**(6) E85–E151.

U.S. Census Bureau. 2011. 2010 Census Summary File 1 - United States. Tech. rep.

US Department of Health & Human Services. 2011. *Electronic Health Records and Meaningful Use*. http://healthit.hhs.gov/portal/server.pt/community/healthit_hhs_gov__meaningful_use_announcement/2996.

Valdez-Flores, C., R.M. Feldman. 1989. A Survey of Preventative Maintenance Models for Stochastically Deteriorating Single-Unit Systems. *Naval Research Logistics* **36** 419–446.

Vervloet, M., A.J. Linn, J.C.M. van Weert, D.H. de Bakker, M.L. Bouvy, L. van Dijk. 2012. The Effectiveness of Interventions using Electronic Reminders to Improve Adherence to Chronic Medication: a Systematic Review of the Literature. *J Am Med Inform Assoc* **19** 696–704.

Weymiller, A.J., V.M. Montori, L.A. Jones, A. Gafni, G.H. Guyatt, S.C. Bryant, T.J.H. Christianson, R.J. Mullan, S.A. Smith. 2007. Helping Patients With Type 2 Diabetes Mellitus Make Treatment Decisions. *Archives of Internal Medicine* **167** 1076–1082.

Wright, J.C., M. C. Weinstein. 1998. Gains in Life Expectancy from Medical Interventions – Standardizing Data on Outcomes. *New England Journal of Medicine* **339** 380–386.