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An Analytics-Driven Approach for Optimal Individualized Diabetes Screening

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Type 2 diabetes is a chronic disease that affects millions of Americans and puts a significant burden on the healthcare system. The medical community sees screening patients to identify and treat prediabetes and diabetes early as an important goal; however, universal population screening is operationally not feasible, and screening policies need to take characteristics of the patient population into account. For instance, the screening policy for a population in an affluent neighborhood may differ from that of a safety-net hospital. The problem of optimal diabetes screening—whom to screen and when to screen—is clearly important, and small improvements could have an enormous impact. However, the problem is typically only discussed from a practical viewpoint in the medical literature; a thorough theoretical framework from an operational viewpoint is largely missing. In this study, we propose an approach that builds on multiple methods—partially observable Markov decision process (POMDP), hidden Markov model (HMM), and predictive risk modeling (PRM). It uses available clinical information, in the form of electronic health records (EHRs), on specific patient populations to derive an optimal policy, which is used to generate screening decisions, individualized for each patient. The POMDP model, used for determining optimal decisions, lies at the core of our approach. We use HMM to estimate the cohort-specific progression of diabetes (i.e., transition probability matrix) and the emission matrix. We use PRM to generate observations—in the form of individualized risk scores—for the POMDP. Both HMM and PRM are learned from EHR data. Our approach is unique because (i) it introduces a novel way of incorporating predictive modeling into a formal decision framework to derive an optimal screening policy; and (ii) it is based on real clinical data. We fit our model using data on a cohort of more than 60,000 patients over 5 years from a large safety-net health system and then demonstrate the model's utility by conducting a simulation study. The results indicate that our proposed screening policy outperforms existing guidelines widely used in clinical practice. Our estimates suggest that implementing our policy for the studied cohort would add one quality-adjusted life year for every patient, and at a cost that is 35% lower, compared with existing guidelines. Our proposed framework is generalizable to other chronic diseases, such as cancer and HIV.

Key words: healthcare operations; partially observable MDP; machine learning; type 2 diabetes
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> An ounce of prevention is worth a pound of cure. - Benjamin Franklin[1]

1. Introduction

Type 2 diabetes (hereinafter *diabetes*) is a highly prevalent chronic disease and a major cause of morbidity and mortality worldwide. This disease is associated with major macrovascular complications (e.g., heart attacks, stroke, and peripheral vascular disease) and microvascular complications (e.g., diabetes-related nephropathy, neuropathy, and retinopathy). It is the seventh leading cause of death in the United States (Petersen 2016). Approximately 9.4% of the US population (30.3 million people) suffer from diabetes, with

an additional 34% (84.1 million people) having prediabetes, an asymptomatic stage in which blood glucose is higher than normal but below the diagnostic threshold for diabetes (Centers for Disease Control and Prevention, 2020). The disease imposes substantial financial burdens, with direct costs (e.g., hospital care and prescriptions) estimated at $237 billion per year and indirect costs (e.g., work-related absenteeism) estimated at $90 billion per year (American Diabetes Association, 2018).

Like many chronic diseases, diabetes has a prolonged asymptomatic period—on average, 9–12 years before clinical diagnosis (Lu et al., 2010)—during which screening and early detection are possible (see Figure 1). Hemoglobin A1c (A1c) and fasting blood glucose are the most common diabetes screening and diagnostic tests utilized in clinical practice (American Diabetes Association, 2019). The A1c test is the most widely used test to screen for diabetes (because it does not require patients to fast before their blood work) and is considered the gold standard for monitoring the diagnosed disease during treatment.[2] The test measures the patient's A1c levels, representing average glucose over the preceding 90 days, and is different from the patient's blood glucose level.[3] A1c levels run across a continuum.

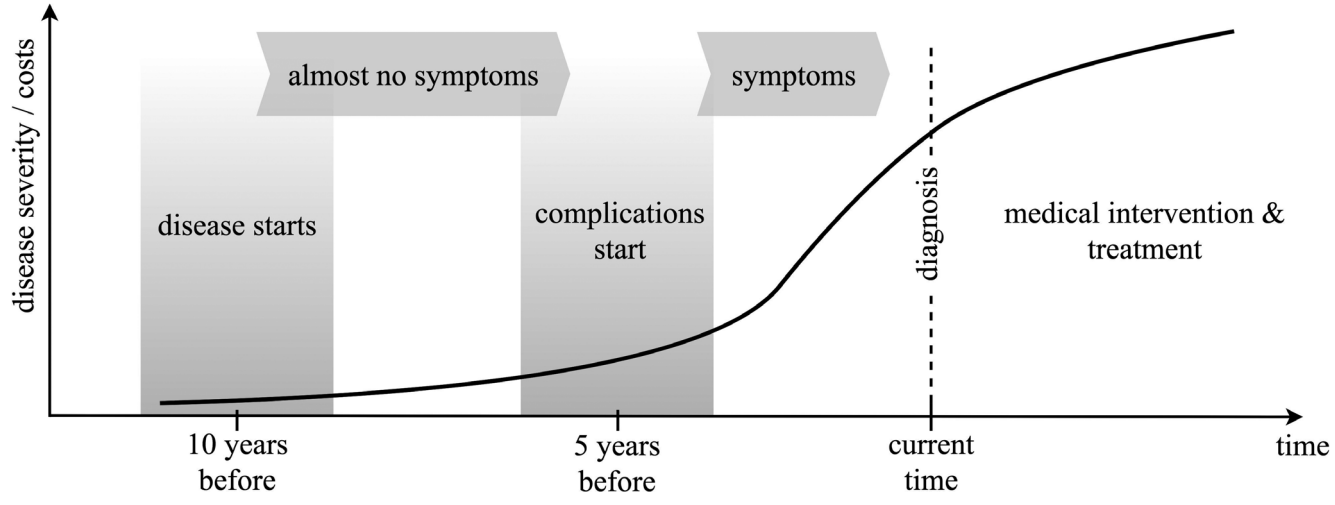
For diagnostic and treatment purposes, clinical practice typically recognizes two glycemic categories —*prediabetes*, if the A1c value lies between 5.7% and 6.5%, and *diabetes*, if the A1c value exceeds 6.5%. Dysglycemia, which refers to abnormal glucose levels, thus, occurs when A1c levels exceed 5.7%. Although progression to diabetes can be reversed by lifestyle modifications and other interventions such as bariatric surgery, many patients with prediabetes develop diabetes (Zhang et al., 2003a,b) . Individuals with prediabetes typically require less expensive treatments, primarily focusing on lifestyle changes (e.g., diet and exercise) to manage the disease and prevent its progression to diabetes. Given the high costs associated with managing and treating diabetes, it is critical to identify patients before they develop the disease. In particular, identifying individuals with prediabetes allows early treatment with evidence-based interventions to delay or prevent the development of diabetes (NIDDKD 2016).

Screening individuals who have diabetes or are at risk for developing diabetes and timely surveillance of patients with prediabetes are, therefore, critical for improving population-level health outcomes and reducing healthcare costs. Systematic diabetes screening can help identify patients at high risk of developing the disease and target preventive interventions. The importance of timely screening has been widely highlighted in academic literature (Gilmer and O'-nor 2010, Lin et al., 2018), by government organizations such as U.S. Department on Health and Human Services (2004), and by the mainstream media (Brody 2014).

The two largest nonprofit organizations focused on diabetes in the United States are the American Diabetes Association (ADA) and the U.S. Preventive Services Task Force (USPSTF), both of which provide screening guidelines. However, these guidelines are broad and generic. For example, according to USPSTF, anyone between the ages of 40 and 70 who is overweight or obese should be screened. If initial screening results for type 2 diabetes are normal, screening should be repeated every 3 years (Pippitt et al., 2016).

These guidelines imply that over 70% of the US population meet the screening criteria (Sheehy et al., 2010), and screening all the eligible patients is not operationally and financially feasible. Indeed, existing literature finds the cost of discovering a true positive

Figure 1 The Disease Develops for a Long Time Asymptomatic, and the Costs Increase Very Quickly Once Symptoms Start

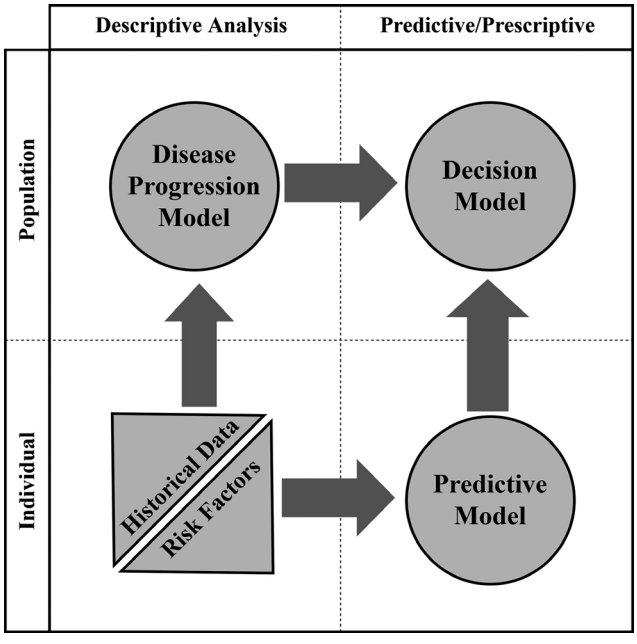


to be high—~ $8500 in 2020 US dollars, according to (O'Connor et al., 2001); similar figures are reported in other studies (e.g., Chatterjee et al., 2013, Johnson et al., 2005, Kahn et al., 2010).

The high costs, low effectiveness, and the large universe of screening candidates render these guidelines operationally and financially impractical. Thus, it is critical that screening be aimed at patients who either have diabetes or are likely to develop diabetes. Furthermore, timing is important because delays in catching the disease can result in a decreased quality of life and a significant increase in healthcare costs. The clinical world lacks an optimal screening strategy that can identify in a precise and timely manner which individuals to screen (and when) using available clinical information (e.g., EHR data). Considering that nearly one in four adults with diabetes (~ 7.3 million) remain undiagnosed, the need for an improved screening policy, that will allow the identification of such patients, cannot be overstated.

This study proposes a multi-method, data-driven decision-making framework, depicted in Figure 2, in which a sequential decision model is used to generate individualized screening recommendations. The framework incorporates real clinical information at the population level to estimate transition and emission rates using a disease progression model. Furthermore, clinical information at the individual level is used to train a predictive model that identifies individuals' risk of having or developing diabetes, which enables the decision model to identify which individuals to screen and when. The strategy optimally trades off the uncertain cost associated with not screening against the potential benefits of screening to maximize expected health outcomes, expressed as quality-adjusted life years (QALYs).

Figure 2 Multi-Method Decision-Making Framework



Our proposed screening strategy builds on multiple methods. At its core lies a partially observable Markov decision process (POMDP) model (upper right square in Figure 2) used to derive the optimal policy. However, specifying the POMDP model requires knowledge of various parameter values (e.g., transition and observation probabilities). While previous work in this area has made certain assumptions about the parameter values or obtained them via simulation models (e.g., Sandikçi et al., 2008), we estimate the parameter values from clinical data. More specifically, we estimate transition and emission probabilities from historical patient data using a Hidden Markov Model (HMM) (Figure 2, upper left). Furthermore, we generate risk scores—that serve as observations to update the belief state about the patient and to generate observation matrix for the unscreened states—using a predictive risk model (PRM) (Figure 2, lower right). The risk scores are individualized because PRM uses statistical models/machine learning to incorporate available patient-level risk factors. The reward structure for the POMDP cannot be estimated from clinical health information and is, thus, obtained from clinical literature.

We develop our approach using a detailed dataset of more than 62,000 patients from the Parkland Health & Hospital System (PHHS), a large safety-net health system in Texas. Using a detailed simulation study, we show that our proposed screening strategy can improve patient outcomes by 2.06 QALYs per patient, compared with opportunistic screening—an ad-hoc approach often used in practice in which the individual is screened whenever she visits the provider, and the doctor determines that the individual needs to undergo an A1c screening test. Furthermore, this improvement in QALYs is double—and at a cost that is a third less—compared with the widely used ADA guidelines.[4] We also show the extent of potential savings that implementing our framework could bring—~ $2.6 million annually for PHHS and, if implemented for 10% of the US population, $7.1 billion annually nationwide—compared with the ADA guidelines. Finally, we investigate the robustness of our strategy to changes in parameters by conducting a detailed sensitivity analysis. The analysis shows no significant or unjustifiable changes in the outcomes due to changes in parameters.

The rest of the paper is organized as follows: Section 2 provides literature review. Section 3 describes

the framework. Section 4 describes the data and provides parameter estimates. We derive and discuss the optimal screening policy in Section 5. In Section 6, we conduct a simulation study to compare the performance of policy derived from our proposed framework with the existing guidelines; we also perform sensitivity analyses. We discuss managerial implications in Section 7. Section 8 concludes the paper.

2. Literature Review

We review relevant literature about diabetes screening and the three main methodological approaches that we employ—POMDP, HMM, and PRM. We focus on the healthcare operations literature, especially around contributions that involve decision-making.

2.1. Diabetes Screening

The use of cost-effectiveness analysis to compare the effectiveness of screening policies is well established in the literature (Chatterjee et al., 2013, Chen et al., 2001, Hoerger et al., 2004, Howard et al., 2010, Kahn et al., 2010, O'Connor et al., 2001). However, the bulk of these studies simulate a cohort of patients to evaluate universal or opportunistic diabetes screening. Yang et al. (2013) formulate the problem of finding the optimal biennial obesity screening threshold from a societal viewpoint and present a numerically derived solution using dynamic programming. A state is defined as an age-specific population-wide probability density function of the body mass index. Their results suggest that the focus should be on childhood obesity screening, but they avoid making a clear recommendation regarding screening policies. Lee et al. (2018) and Meyer et al. (2014) focus on diabetes treatment strategies but do not specifically focus on screening.

2.2. Markov Decision Processes for Medical Decision-Making

Markov decision processes (MDPs) and POMDPs are the methodological tools of choice for sequential decision-making problems in healthcare, especially for chronic diseases such as diabetes (e.g., Hoerger et al., 2004, Santoso and Mareels 2001, Shih et al., 2007), HIV/AIDS (e.g., Garg et al., 2012, Lee et al., 2014, Shechter et al., 2008), and cancer (e.g., Ahsen and Burnside 2018, Ayer et al., 2012, Chhatwal et al., 2010, Maillart et al., 2008, Nohdurft et al., 2017, Petousis et al., 2019, Zhang et al., 2012a). MDPs and POMDPs have also been employed to obtain optimal policies in other settings, such as to design therapeutic regimens for hypertension (Zargoush et al., 2018), develop personalized treatments (Ibrahim et al., 2016), and address emergency room congestion (Patrick 2011).

2.3. Hidden Markov Models for Modeling Disease Progression

Disease progression modeling is essential in many areas, including drug development and clinical trial design. Challenges associated with modeling disease progression include, but are not limited to: (i) progression heterogeneity—patients vary in their progression trajectories; (ii) incomplete patient records—information is sometimes censored or missing; (iii) discrete observations—patients' records of the progression are observed and recorded at discrete times with varied intervals, even though disease progression is continuous; and (iv) irregularity of observations due to irregular visits to the healthcare provider (Wang et al., 2014). Consequently, the bulk of the literature on disease progression modeling focuses on evidence-based modeling using machine learning and statistical techniques based on observational data.

A popular method is to model disease progression with a Markov model, where the states represent the patient's true health, which are typically hidden (i.e., not directly observable). In this model—referred to as HMM—the states are revealed using noisy observations (in the form of test results). For example, Jackson et al. (2003) use HMMs to estimate transition rates between disease states of abdominal aortic aneurysm. Liu et al. (2015) propose an effective learning method for continuous-time HMMs by dealing with the challenges of estimating the posterior-state probabilities and the computation of end-state conditional statistics. Sukkar et al. (2011) develop a six-state HMM for Alzheimer's disease by calculating transitions between states and conditional observation probabilities. In another study, Sukkar et al. (2012) use HMM to identify more granular disease stages than the three currently accepted clinical stages of Alzheimer's disease. In addition, simulation has been used to model disease progression and obtain state transitions (Lee et al., 2008). Denton (2018) and Siebert et al. (2012) provide best practices on estimating the transition rates between states, including the use of HMMs. Popov et al. (2017) study the effect of missing observations on the estimation accuracy of HMM parameters and compare several methods using simulation. Their study finds that missing observations reduce estimation accuracy and that a method called "marginalization of missing observations" produces the smallest estimation error.

2.4. Predictive Modeling in Healthcare

Predictive modeling, a part of healthcare analytics, employs statistical models or machine learning to predict an outcome or a risk using a collection of variables (predictors). Such models are increasingly being used to improve healthcare decision-making, such as

personalized diabetes management (Bertsimas et al., 2017) and development of chemotherapy regimens for cancer treatment (Bertsimas et al., 2016). Analytics has also been used in developing screening policies for breast cancer (Maillart et al., 2008), colorectal cancer (Bjarnadottir et al., 2018), HIV (Deo et al., 2015), and prostate cancer (Bertsimas et al., 2018).

The use of predictive models in diabetes screening is not new. Collins et al. (2011) systematically review 43 risk-prediction models that include 4–64 predictors, including age, family history, body mass index (BMI), hypertension, and fasting glucose levels. The most commonly used method among these 43 models is logistic regression. Notably, the bulk of the studies either remove incomplete cases or do not mention how missing data are treated; this is a significant limitation when dealing with data extracted from electronic health records (EHRs), which typically have a substantial amount of missing information.

2.5. Contributions

This study makes a two-pronged contribution to the literature. First, we demonstrate how to use three well-established methodological approaches together: (i) POMDP model for determining optimal decisions; (ii) HMM for generating transition and emission probabilities for the POMDP model (using EHR data); and (iii) PRM for predicting the risk of a patient developing diabetes, and for generating observation matrix for the unscreened states (also using EHR data). While each of these three methods has been employed independently to answer specific research questions in the healthcare decision-making literature, our study is the first, to the best of our knowledge, which uses all three methods together to address an important practical decision-making problem. We note that most papers using POMDP models assume that transition rates are known and observations are available. In contrast, we use available clinical information on patients to estimate transition and emission rates (via HMM) and generate risk scores (using PRM) to inform decision-making.

In doing so, we add to the line of work that proposes integrated frameworks for screening individuals. For example, Lin et al. (2018) proposes a unified decision support framework to efficiently and economically monitor a large number of patients by exploiting the similarity between them. Their framework integrates a collaborative modeling approach (for prognosis) and a selective sensing approach (formulated as an optimization problem) that enables them to identify high-risk individuals more accurately and faster than existing benchmark methods.

Second, from a practical standpoint, we provide a framework that produces a detailed, population-specific screening policy that identifies *whom* to screen, *when* to screen, and *how often* to rescreen after initial screening. It incorporates long-term patient outcomes, cost, and detailed individual patient information to generate a practical and implementable individualized screening strategy. We demonstrate the workings of our framework in the clinical setting of PHHS, serving a (mostly) medically indigent population.

The research questions and solutions presented here were generated in multiple conversations with the physicians at PHHS, who were primarily interested in developing a screening policy for a set of patients who have not been screened before. We note that while our framework is intended for diabetes screenings, it can also be used to develop screening policies for other chronic diseases, including cancer and HIV/AIDS, where medical information is available in the form of EHRs.

3. Model

The sequential screening decision-making problem is formulated as a POMDP model, in which the states represent a patient's health status. Disease progression (transition) and emission probabilities are estimated from clinical data on patients using HMMs. Costs and the effectiveness of interventions are derived from the medical literature, and their applicability to our cohort is verified with clinical experts. We use PRM to generate individualized risk scores that are used in two ways: (i) as observations to inform the screening recommendations when implementing the policy; and (ii) to derive the observation matrix for the unscreened states for the POMDP model. Next, we describe details of all components of the framework.

3.1. The Decision-Making Model (POMDP)

We formulate our decision-making problem as a POMDP because the current state of the system—the patient's true health status—is not directly observable. The method uses a probabilistic belief distribution over the unobservable health states, which is informed by observations obtained from routine healthcare visits. The model assumes that the Markov property (approximately) holds, that is, the transition to future health states can be approximated using only the current state and current actions. This assumption is quite popular in the healthcare operations literature that model disease progression (Ahsen and Burnside 2018, Garg et al., 2012, Hoerger et al., 2004, Lee et al., 2014, Santoso and Mareels 2001, Shechter et al., 2008, Shih et al., 2007).

A discrete-time POMDP model is defined as a 7-tuple $(\mathscr{S}, \mathscr{A}, \mathscr{P}, \Omega, \mathscr{O}, \mathscr{R}, \lambda)$, where $\mathscr{S}$ is the set of states, $\mathscr{A}$ is the set of actions, $\mathscr{P}$ is the set of transition

probabilities between the states, Ω is the set of all observations, $\mathcal{O}$ is the set of observation probabilities, $\mathcal{R}$ is the reward function, and λ is a discount factor (Cassandra et al., 1994). Below, we provide a detailed description of each of these components. Following existing literature, we assume the following: (i) the decision-maker is the clinician who acts on behalf of the patient; (ii) screening decisions are made at discrete times when the patient sees the clinician; and (iii) the screening decision for a given patient is independent of other patients.

3.1.1. Decision Epochs and Time Horizon. We use 1 year as a decision epoch corresponding to annual visits to a clinician (Chhatwal et al., 2010). Decisions are made at the beginning of each epoch, starting from the first time the patient meets the clinician. We denote the epochs by $t = \{0, \ldots, T\}$, where T is the time horizon.

3.1.2. State Space. Clinical practice classifies patients into three stages based on their glycated hemoglobin level (i.e., A1c level): healthy (A1c below 5.7%), prediabetes (A1c between 5.7% and 6.5%), and diabetes (A1c above 6.5%). The state space ($\mathcal{S}$) in our model consists of seven distinct states, with the three stages extended to six, by including the screening status information for the patient. More specifically, the three unscreened states are: *healthy* (s_H), *prediabetes* (s_P), *diabetes* (s_D), while the three screened states are: *screened healthy* (s_{SH}), *screened prediabetes* (s_{SP}), and *screened diabetes* (s_{SD}). The three screened states represent the outcomes of the screening process, that is, a patient cannot be in one of these states unless she is screened in that period. We separate the states to account for different costs and outcomes associated with the screening process (i.e., screened patients will receive interventions). Our seventh and final state is *death*, an absorbing state (s_Δ). Thus, $S = \{s_H, s_P, s_D, s_{SH}, s_{SP}, s_{SD}, s_\Delta\}$ and is depicted in Figure 3. The state space is partially observable, with death being the only fully observable state. Note that the screening test is not entirely without error; for example, a healthy patient with the incorrect screening result of prediabetes would internally still be in the state s_{SH}.

3.1.3. Action Space. The action space, $\mathcal{A} = \{a_S, a_N\}$, represents the decision to screen (a_S) or not to screen (a_N) a patient. We use $a_t \in \mathcal{A}$ to denote the action taken at decision epoch t.

3.1.4. Transition Probabilities. Transition probability, denoted by $p\{s_{t+1}|s_t, a_t\}$, represents the probability of a patient moving from the current state ($s_t \in \mathcal{S}$) to the state ($s_{t+1} \in \mathcal{S}$). Transition probabilities are associated with the arcs of the Markov model underlying the POMDP (depicted in Figure 3). We use $\mathcal{P}_{a_t}$ to represent the set of all transition probabilities organized as a state transition matrix for action $a_t \in \mathcal{A}$.

For convenience, we drop the index t and denote this probability as $p\{s'|s, a\}$, equivalently the probability of transitioning to state s' given state s and action a. Thus, the two transition matrices are: $\mathcal{P}_{a_s}$, representing the action: *to screen*, and $\mathcal{P}_{a_N}$, representing the action: *not to screen*. Note that (i) transition probabilities may change for a given patient over time and (ii) we use age-specific transition probabilities, which account for the fact that incidence rates of diabetes and mortality change as a patient ages. Appendix A provides step-by-step details on the construction of these two matrices.

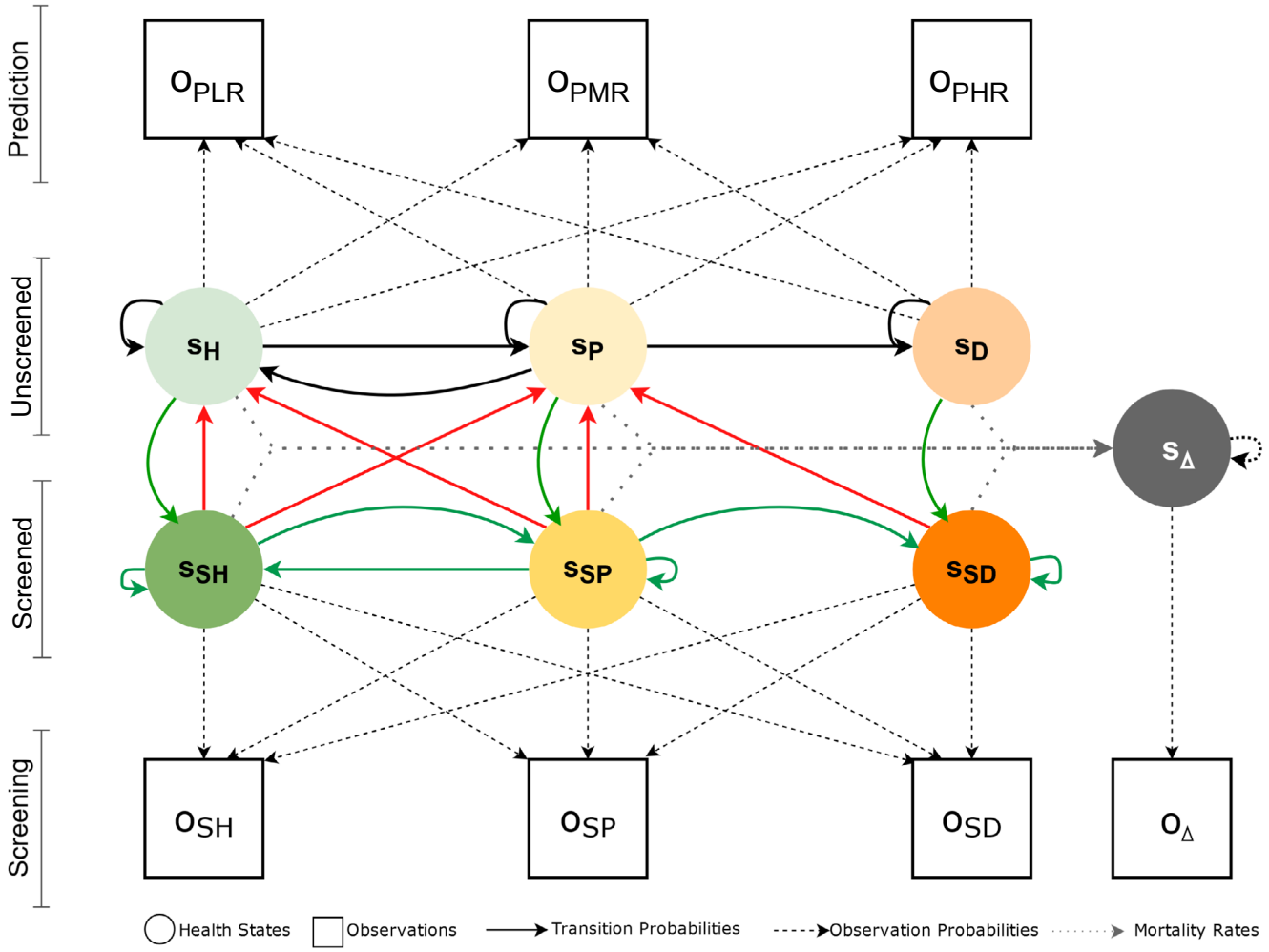
Given the irreversible nature of chronic diabetes, patients who enter the diabetes state are likely to stay there permanently. We, therefore, do not include an arc from s_D to s_P or s_D to s_H. A patient who was screened with prediabetes (diabetes) enters into the state s_{SP} (s_{SD}). We assume that a positive screening result will influence the progression trajectory of the patient due to intervention(s)/treatment(s) she receives (e.g., pharmaceutical drugs, lifestyle changes). We use the parameters $\eta_{regression}$ and $\eta_{progression}$ to capture the effects of such interventions in our model with the following relationship:

$$p_{s_P,s_H} = \frac{p_{s_{SP},s_{SH}}}{\eta_{regression}}; p_{s_P,s_D} = \frac{p_{s_{SP},s_{SD}}}{\eta_{progression}}.$$

Based on conversations with our clinical collaborators, lifestyle intervention programs can increase the chance of reverting from prediabetes to healthy by close to 10% (i.e., $\eta_{regression} = 1.1$) while reducing the chance of progressing to diabetes by 50% ($\eta_{progression} = 0.5$). Appendix A provide details on how the complete transition matrices are constructed from clinical information stored in EHRs.

3.1.5. Observations and Observation Probabilities. At each decision epoch, an observation (signal), $o \in \Omega$, provides information about the true underlying unobservable health state of the patient. In our model, these observations come from two sources: (i) PRM, and (ii) screening results (assuming the patient has undergone a screening). The PRM-generated observations indicate the risk of a patient developing diabetes, classified as low (o_{PLR}), medium (o_{PMR}), or high (o_{PHR}) (Section 3.3 provides details). Screening a patient yields three possible observations: screened as healthy (o_{SH}), screened as prediabetic (o_{SP}), and screened as diabetic (o_{SD}). The observation o_Δ indicates that the patient is observed dead. Altogether, this yields the following set of observations:

Figure 3 **POMDP Model with Health States (Screened and Unscreened), Observations (Screening and Predicted Risk), and Transitions. Black Arcs Correspond to the Natural Progression of Diabetes. Green Arcs Correspond to Transitions after a Screening is Performed. Red Arcs Correspond to Transitions from Screened States to Unscreened States. Observation Probabilities are Shown in Different Shades Where Darker Arrows Indicate a Larger probability. Note That Screenings Reveal much more Information about the true Underlying State Compared to Risk Predictions [Color figure can be viewed at wileyonlinelibrary.com]**



$\Omega = \{o_{PLR}, o_{PMR}, o_{PHR}, o_{SH}, o_{SP}, o_{SD}, o_\Delta\}$. Note that the initial screening decision will have observations only from PRM because no known prior screening (A1c) results are available.

The predictive models and screening tests are not perfect. Observations are only probabilistically connected to the unobservable states via the observation matrix $\mathcal{O}$, which consists of observation probabilities $\mathcal{O}(o|s)$ representing the probability of observing o, given that the true state of the patient is s and action a was chosen. The observation matrix for the screened states and unscreened states is estimated separately from data (see Sections 3.2.1 and 3.3.2 for details).

3.1.6. Belief States. Let $\Pi(S)$ denote the probability simplex over the state space $\mathcal{S}$, also called the belief space. In our case, with seven states, the simplex is defined as $\Pi(S) = \left\{\pi \in \mathbb{R}^7 : \sum_{s=1}^{7} \pi(s) = 1, \pi(s) \geq 0 \forall s\right\}$. The vector $\boldsymbol{\pi}$ is called a belief state representing the decision-maker's knowledge about the health state of a patient. The belief state is expressed as a set of probabilities, one for each possible state. To denote the belief state for a patient at decision epoch t we add a subscript, that is,

$$\pi_t = (\pi_t(s_H), \pi_t(s_P), \pi_t(s_D), \pi_t(s_{SH}), \pi_t(s_{SP}), \pi_t(s_{SD}), \pi_t(s_\Delta)).$$

An example of a belief state for an unscreened patient would be $\boldsymbol{\pi} = (0.1, 0.6, 0.3, 0, 0, 0, 0)$, indicating that the patient has a 10% chance to be healthy, a 60% chance to be prediabetic, and a 30% chance of diabetes. Given that the patient was not screened and is

alive, the probability of a patient being in a screened state or the death state is zero.

3.1.7. Reward Functions. The optimal policy in a POMDP maximizes the expected sum of the discounted rewards over the decision horizon T, defined as follows:

$$E\left[\sum_{t=0}^{T}\lambda^t r_t\right],$$

where λ is the discount rate and r_t is the immediate reward at time t.

Rewards depend on the states and actions taken and the complete set of possible rewards is captured in the reward function $r(s,a,s')$, where a is the action taken in state s followed by a transition to state s'. In our formulation, the reward structure does not change with time and the rewards are determined by whether the patient was screened or not (captured in s'). Consequently, the reward function can be simplified to $r(s',a)$, and formulated as follows:

$$r(s,a)=\begin{cases} Q, & S'=S_H, a=a_N \\ (1-\alpha_P)Q, & S'=S_P, a=a_N \\ (1-\alpha_{UD})Q, & S'=S_D, a=a_N \\ Q, & S'=S_H, a=a_S \\ (1-\alpha_P)Q, & S'=S_P, a=a_S \\ (1-\alpha_{UD})Q, & S'=S_D, a=a_S \\ Q-C_S, & S'=S_{SH}, a=a_S \\ (1-\alpha_P)Q-C_P-C_S, & S'=S_{SP}, a=a_S \\ (1-\alpha_{DD})Q-C_D-C_S, & S'=S_{SD}, a=a_S \end{cases}, \quad (1)$$

where Q is the value of a QALY (Neumann et al., 2014). α_P, α_{UD}, and α_{DD} represent the yearly reduction in QALYs due to prediabetes, undiagnosed diabetes, and diagnosed diabetes, respectively. C_s represents the complete cost of diabetes screening, C_D represents the annual direct medical costs for new-onset diabetes, and C_P represents the annual incremental direct medical costs for a patient with prediabetes. Table 3 provides a detailed description of all parameters, together with their estimates.

We note three things. First, the rewards are identical when s' is the same, independent of the action. This is because the action only represents the clinician's recommendation; the cost is realized when the patient follows the recommendation (i.e., participates in the screening process), as represented by a transition to a screened state. Second, there are no rewards for transitioning to screened states under the no-screening action ($a=a_N$)—a patient can only transition to a screened state via the action: "to screen" (that is, when $a=a_S$). Finally, the total reward for a patient is impacted primarily by the sequence of states during the decision horizon. For example, a patient who stays healthy longer will receive a higher total reward compared to a patient who develops diabetes earlier. Being in a screened state changes the transition probabilities—a patient with prediabetes who is screened is more likely to receive an intervention and get better (i.e., p_{s_P,s_H} increases) and less likely to develop diabetes (i.e., p_{s_P,s_D} decreases). Thus, screening has a significant impact on the reward.

3.1.8. Bayesian Belief State Update and Optimality Equation. Given a new observation $o\in\Omega$-representing a predicted risk level or a screening result, the belief state $\boldsymbol{\pi}$ is updated to $\boldsymbol{\pi}'$ using Bayes' rule. For each state $s'\in\mathcal{S}$ we calculate an updated belief state value:

$$\pi'(s')=\frac{\mathcal{O}(o|s')\sum_{s\in\mathcal{S}}p\{s'|s,a\}\pi(s)}{\sum_{s'\in\mathcal{S}}\mathcal{O}(o|s')\sum_{s\in\mathcal{S}}p\{s'|s,a\}\pi(s)}. \quad (2)$$

The POMDP can be reformulated as a continuous state MDP, and the optimal solution is obtained by solving the Bellman optimality equations (Puterman 2005).

$$v(s,\boldsymbol{\pi})=\max_{a\in\mathcal{A}}\left\{r(s,a)+\lambda\sum_j\sum_{s'}\sum_o p\{s'|s,a\}\mathcal{O}(o|s')v(s',\boldsymbol{\pi}')\pi_j\right\},$$
$$\forall s\in\mathcal{S}, \pi\in\Pi(\mathcal{S}), \quad (3)$$

where $\lambda\in[0,1)$ is the discount rate.

3.1.9. Incorporating a Capacity Constraint. Many practical problems require a policy that satisfies a capacity constraint such as one that restricts the number of patients for whom a hospital can administer the complete screening process every period. This enables a hospital like PHHS to direct its resources in the most effective manner.

Mathematically, this constraint can be expressed as follows: $\Pr^{\pi}(a=a_s)=\zeta$. That is, the probability with which any patient is screened under policy $\boldsymbol{\pi}$ is restricted to be equal to ξ, the proportion of total patients that can be screened every period, on average. An optimization problem with such an equality constraint can be reformulated as an unconstrained optimization using a Lagrange multiplier (Bertsekas 1976, Tessler et al., 2018), as follows:

$$\min_{\delta\geq 0}\max_{\pi\in\Pi}\mathrm{L}(\delta,\pi)=\min_{\delta\geq 0}\max_{\pi\in\Pi}\{v(s,\pi)-\delta(\Pr^{\pi}(a=a_s)-\xi)\}, \quad (4)$$

where δ is a Lagrange multiplier.

Note that the second term in Equation (4) can be separated into two parts. The first part ($-\delta Pr^{\pi}(a=a_s)$)

is the discounted sum of screening penalties. If we let $\delta' = \delta \sum_{t=0}^{T} \lambda^{-t}$, equivalent to an implied penalty for each performed screening,[5] δ' can be incorporated into the reward structure (and thereby, in Equation (3)) by modifying the cost of screening from C_S to $C'_S = C_S + \delta'$, yielding a modified value function $v'(s, \boldsymbol{\pi})$. Furthermore, the second part ($\delta\xi$) is independent of the policy and can be moved out of the maximization, as follows:

$$\min_{\delta \geq 0} \left\{ \max_{\boldsymbol{\pi} \in \Pi} \{v'(s, \boldsymbol{\pi})\} + \delta\xi \right\}, \tag{5}$$

The maximization step in the new formulation can be solved for different values of δ' using standard POMDP solvers, and the minimization is done by choosing the solution with the lowest implied penalty.

3.2. Disease Progression Model (HMM)

A practical implementation of POMDP requires reliable estimates of transition probabilities between the unobservable states from noisy and incomplete data extracted from EHR systems. HMMs are popular when dealing with Markov models, where the states are unobservable and only revealed through noisy observations. We model the screened states: s_{SH}, s_{SP}, s_{SD}, as *hidden* states such that the HMM represents the trajectory of a patient as a sequence of random variables X_t for time $t = \{1, 2, \ldots T\}$. The corresponding observations are the test results extracted from the EHR, represented by the sequence of random variables Y_t whose realization is one of the three possible values: o_{SH}, o_{SP}, o_{SD}. Similar to a conventional Markov model, the transition matrix is defined as follows:

$$M = \{m_{ij}\} = P(X_t = j | X_{t-1} = i). \tag{6}$$

However, the probabilities cannot be directly estimated because the realizations of X_t are not observable. HMMs solve this problem by using observations (realizations of Y_t) that provide information about the unobservable state. The observations in our case are screening results whenever they are available and missing observation otherwise. The *emission probability matrix* defines the probabilistic connection between states and observations,

$$N = \{n_j(y_t)\} = P(Y_t = y_t | X_t = j). \tag{7}$$

The initial state distribution (at $t = 1$) is defined by the vector q, with elements $q_i = P(X_1 = i)$ for each state i. The aim is to estimate the parameters of the HMM, $\sigma = (\mathscr{M}, \mathscr{N}, q)$ from observational data. The emission probabilities $\mathscr{N}$ and the transition matrix $\mathscr{M}$ provide data-driven estimates for the observation probabilities and the transition probabilities between the unobservable states in the POMDP specific to the cohort under consideration.

The standard estimation procedure is the Baum–Welch algorithm, which utilizes the expectation–maximization iterative algorithm to find the estimates of the model's parameters using a set of historical observations (Huang et al., 2001). Our choice of the Baum–Welch algorithm stems from multiple studies in the literature that have highlighted the significance and appropriateness of this algorithm, including when using EHR data.[6] More specifically, we use the EM algorithm implemented in the *R* package *seqHMM* (Helske and Helske 2019). Here, missing observations, that do not provide additional information regarding the hidden states, are handled by setting their emission probabilities for all hidden states to one.

Even though our data contain a significant number of missing observations (as is typical with EHR data), our approach is valid. For example, Popov et al. (2017) study the effect of missing observations on the estimation accuracy of HMM parameters. They compare several methods using simulation and conclude that the "marginalization of missing observations" method, that we use, performs best.

3.2.1. Observation Matrix for Screened States ($\mathscr{O}_S$).

Observation probabilities reflect the reliability of the screening (A1c) test—that is, the probability of observing a screening (A1c test) result that truly reveals the patient's health state. For example, what is the likelihood that a patient with diabetes is correctly tested to have diabetes or that a healthy patient is inaccurately tested as having prediabetes. From Equation (7), we can see that the POMDP's observation matrix for the screened states s_{SH}, s_{SP}, s_{SD} is equivalent to the HMM emission probability matrix $\mathscr{N}$ resulting in $\mathscr{O}_S(o|s) = n_s(o)$ for $o \in \{o_{SH}, o_{SP}, o_{SD}\}$ and $s \in \{s_{SH}, s_{SP}, s_{SD}\}$.

3.3. Predictive Risk Model (PRM)

PRMs are statistical models used in clinical applications that use several patient characteristics to predict a patient's risk of developing or having a disease. Many PRMs have been developed for diabetes. They offer many attractive features, including a wide selection of available prediction methods, a simple and efficient learning process, and the possibility of data-driven feature selection (Collins et al., 2011). A particularly attractive feature of PRMs is the availability of methods that deal with missing data. This is especially useful when working with EHR data, where the information available for patients can vary widely.

Any PRM that produces a risk score for each patient can be used for our framework as long as it has the

property that patients with higher scores are more likely to have abnormal blood glucose levels. While almost half the surveyed risk models do not mention how missing information is treated, multiple imputation is generally recommended for clinical data (De Goeij et al., 2013).

We base our PRM on logistic regression with prior multiple imputation to deal with missing values. To implement the PRM, we extract the frequently used risk predictors from the EHR and include additional relevant information, such as the patient's medications. To make the PRM more robust, we apply the popular L1 regularization (LASSO) to the logistic regression.[7]

3.3.1. Generating Risk Scores. A logistic regression models the log odds of an event—in our case, whether the patient is in an abnormal glycemic state (prediabetes or diabetes)—as follows: $l = \log\frac{P(Y=1)}{1-P(Y=1)} = \beta_0 + \beta^T x$. Here Y represents the event, the feature vector $\boldsymbol{x}$ captures patient characteristics (extracted from the EHR system), and $\boldsymbol{\beta}$ is the coefficient vector obtained by optimizing the log-likelihood function that is penalized by a regularization term, as follows:

$$\min_{\beta_0,\boldsymbol{\beta}} \frac{1}{N}\sum_{i=1}^{N} \log P\left(y_i|\boldsymbol{x}_i;\beta_0,\boldsymbol{\beta}\right) + \lambda\|\boldsymbol{\beta}_1\|.$$

The regularization term penalizes the optimization using the L1 norm of the parameter vector $\boldsymbol{\beta}$ with a weight of λ. This penalty enforces sparsity by pushing parameters to zero. We use the standard procedure to find λ. In particular, we use a 10-fold cross-validation on the training data and select the largest value of λ such that the error is within one standard error of the minimum (Friedman et al., 2010). Training a model with multiple imputation (De Goeij et al., 2013) consists of the following key steps:

- **Impute Missing Data**: To treat missing values, we use multiple imputation (multivariate imputation by chained equations; MICE) implemented in the *R* package (van Buuren and Groothuis-Oudshoorn 2011). We follow the standard recommendation to (i) impute numeric data with predictive mean matching; (ii) impute categorical data with polytomous regression imputation; and (iii) create five imputed datasets.
- **Train and pool the model**: We train a model on each imputed dataset and then use mean pooling to obtain a single final model. During this process, 10-fold cross-validation on the imputed datasets is used to select λ.

Finally, we convert the predicted risk score produced by the logistic regression into discrete observations for the POMDP. We use two thresholds: t_1 and t_2, such that the predicted score is divided into three ranges representing low, medium, and high risk of diabetes ($o_{PLR}, o_{PMR}, o_{PHR}$).

3.3.2. Observation Matrix for Unscreened States ($\mathcal{O}_U$). The standard way to evaluate a classification model's predictive power, such as the logistic regression with decision thresholds, is to apply it to a *test set* to produce a confusion matrix, also known as an error matrix (Fawcett 2006). Each row of the confusion matrix represents a true class label, while each column represents a predicted class label. The confusion matrix contains the count of how often the predictive model predicts each class label for the test instances with a given true class label.

In our case, this is a 3×3 matrix $\mathscr{C}$ with the true class labels representing the health states (healthy, prediabetes, and diabetes), and the predicted class labels representing the predicted observations derived from the risk score (low risk, medium risk, and high risk). Each cell, $\mathscr{C}_{o,s}$, contains the count of how many test instances with the true class label $s \in \{s_H, s_P, s_D\}$ were predicted as $o \in \{o_{PLR}, o_{PMR}, o_{PHR}\}$. The maximum likelihood estimate of the POMDP's observation matrix entries for the unscreened states, $\mathcal{O}_U(o|s)$, can be directly derived from the confusion matrix as follows:

$$\mathcal{O}_U(o|s) = \frac{P(o,s)}{P(s)} = \frac{\mathscr{C}_{o,s}}{\sum_{o' \in \{o_{PLR},o_{PMR},o_{PHR}\}} \mathscr{C}_{o',s}}.$$

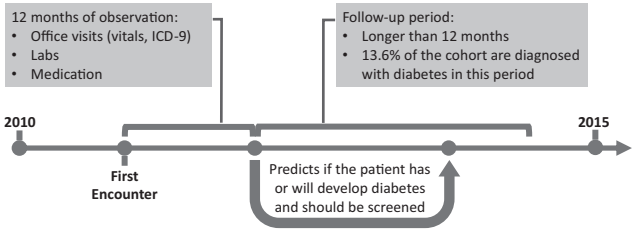
Each possible combination of risk score thresholds (t_1 and t_2) allows us to obtain a different observation matrix from the same predictive model. Finding the optimal observation matrix is not a straightforward problem, because it depends not only on the model's predictive power but also on the importance of the information provided to the POMDP, in the form of transition probabilities and the reward structure. To find close to optimal thresholds, we solve the POMDP for a grid of values, t_1 and t_2 in the range $0 < t_1 < t_2 < 1$ and choose the values with the largest total expected reward. It is important to note that the method of creating an observation matrix is general and can be applied to any kind of predictive model.

3.3.3. Complete Observation Matrix ($\mathcal{O}$). The complete observation matrix ($\mathcal{O}$) for the POMDP is a convolution of the observation matrices for the screened ($\mathcal{O}_S$) and unscreened states ($\mathcal{O}_U$), given as follows:

$$\mathcal{O} = \begin{pmatrix} \mathcal{O}_S & 0^{3\times 3} & 0^{3\times 1} \\ 0^{3\times 3} & \mathcal{O}_U & 0^{3\times 1} \\ 0^{1\times 3} & 0^{1\times 3} & 1 \end{pmatrix}$$

Here $0^{a\times b}$ is a $a \times b$ null matrix and "1" represents the fact that the probability of transitioning from a death state to a death state is one.

Figure 4 A Visual Illustration of the Setup of the PRM Model



4. Data and Parameter Estimation

4.1. Data Description

The EHR data used in this study come from PHHS, one of the largest safety-net health systems in the United States that provides comprehensive primary care, specialty care, and hospital services. PHHS experiences over 1 million outpatient visits and 250,000 emergency room visits annually. A common EHR system is used across all clinical settings in the health system.

4.1.1. Overall Cohort. Our overall cohort consists of 62,721 patients between the ages of 18 and 64 who receive their primary care services at PHHS. The data span the years from 2010 to 2014 and no individual was diagnosed with diabetes when they entered the cohort. We have extracted detailed information on these patients from the EHRs, including demographics (e.g., age, race), comorbidities (e.g., whether the patient experienced a heart attack), use of medications (including for treating diabetes), and laboratory tests (e.g., random blood glucose). All data were extracted by month and then aggregated to quarters or years depending on the model. Appendix B provides additional details on our cohort construction along with summaries of key variables.

We use this overall cohort for estimating transition matrix for the POMDP (Section 4.2 provides details). In order to estimate transition probabilities, we need a minimum of two observations (A1c tests) per patient; however, only 28,103 patients (45% of our overall cohort) meet this criterion.[8] We first estimate transition probabilities on a quarterly basis and then convert them to annual transition probabilities.

4.1.2. PRM Cohort. The PRM cohort is a subset of the overall cohort, that we use to learn the PRM and estimate the observation matrix for the POMDP (Section 4.3 provides details). The PRM cohort consists of patients who meet both of the following criteria: (i) they have not undergone a gold standard A1c (screening) test during the 12 months after the first encounter, implying that they have not been diagnosed with diabetes or prediabetes; and (ii) they have an A1c test result available in the follow-up period, ranging from 12 to 48 months, depending on a patient's first encounter with the provider (Figure 4 provides a visual illustration). This results in a PRM cohort of 12,071 patients.

Table 1 provides summary statistics of the PRM cohort. The average patient is 48 years old, with an average BMI of 31.4. The cohort is ~ 70% female and 40% non-Hispanic black. Furthermore, 60% of patients either use charity pay or self-pay, reflecting the population's indigent nature.

The dependent variable in the regularized logistic regression model is a binary variable indicating whether the patient has Dysglycemia in the follow-up period, based on the A1c level (recorded in the EHR).

Our choice of PRM cohort construction allows us to maintain the model's fidelity. Specifically, including only those patients for which we have no prior A1c result ensures that the model is not affected by the interventions given to patients who have known prediabetes or diabetes. More importantly, this ensures the model's validity in terms of its capability to detect risk in undiagnosed patients. It is worth emphasizing that the PRM does not make the decision to screen, and it does not use the true health state; instead, it learns to predict the risk of a patient's having Dysglycemia, given the available clinical information for each patient.

4.2. Estimating the Disease Progression Model

The disease progression model estimates the transition probabilities for the POMDP model using the HMM method (described in Section 3.2). The results from the gold standard tests for patients in the overall cohort serve as the observations (denoted by o_{SH}, o_{SP}, o_{SD}). The trajectory of a given patient is a set of discrete observations at various times. Given that patients may not visit their care providers frequently or regularly, not every period contains a recorded observation corresponding to a patient visit. For example, a hypothetical trajectory is (o_{SP},*,*,*,*,o_{SP},*,*,o_{SD},*,o_{SD}), denoting a sequence of observations for a single patient during 11 periods. Here, "*" represents a missing value for a period in which no test result is available, reflecting one of the following scenarios: (i)

Table 1 Key Characteristics of the PRM cohort

Characteristic *N*	Availability	Entire Cohort 12,071	Normal glycemia 6136	Dysglycemia 4328	Diabetes 1607
Continuous Data (Mean (SE))					
Age	100.00%	47.5 (0.1)	45.2 (0.14)	49.7 (0.14)	50.2 (0.22)
Year of education	4.72%	8.7 (0.01)	9 (0.01)	8.4 (0.01)	8.4 (0.02)
BMI	87.24%	31.4 (0.06)	29.8 (0.08)	32.2 (0.1)	35.2 (0.19)
Random blood glucose	62.65%	97.5 (0.12)	93.1 (0.13)	97.5 (0.16)	113 (0.53)
High-density cholesterol	51.62%	51.7 (0.1)	53.6 (0.14)	51.1 (0.17)	47.3 (0.25)
Triglycerides	51.62%	146.4 (0.65)	136.3 (0.85)	148.2 (1.01)	174.9 (2.33)
White blood cells count	60.94%	7.4 (0.02)	7.3 (0.03)	7.4 (0.03)	7.7 (0.04)
Ferritin	7.76%	140.1 (0.82)	145.8 (1.28)	124.6 (0.94)	159.8 (2.67)
Pulse	99.33%	76.2 (0.09)	75.8 (0.13)	76 (0.15)	77.8 (0.25)
Systolic blood pressure	99.34%	129.1 (0.14)	126.2 (0.2)	131 (0.23)	135.3 (0.38)
Cholesterol	51.62%	193.5 (0.25)	191.4 (0.35)	195.1 (0.42)	196.3 (0.7)
Nominal Data (Proportion (SE))					
Sex					
Male	100.00%	30.1 (0.04)	30.2 (0.06)	30.1 (0.07)	31.3 (0.12)
Race					
White	99.40%	13.3 (0.03)	14.2 (0.04)	11.7 (0.05)	10.1 (0.08)
Other	99.40%	4.9 (0.02)	4.9 (0.03)	4.8 (0.03)	4.8 (0.05)
Black (non-Hispanic)	99.40%	39.8 (0.04)	37.2 (0.06)	44.4 (0.08)	44.5 (0.12)
Hispanic	99.40%	42 (0.05)	43.7 (0.06)	39.1 (0.07)	40.6 (0.12)
Insurance/Financial					
Commercial	100.00%	13.2 (0.03)	12.6 (0.04)	14.1 (0.05)	10.6 (0.08)
Charity	100.00%	40 (0.04)	40 (0.06)	39.8 (0.07)	42.1 (0.12)
Medicaid–Medicare	100.00%	26.7 (0.04)	25.9 (0.06)	27.9 (0.07)	30.8 (0.12)
Pending	100.00%	0.2 (0)	0.2 (0.01)	0.2 (0.01)	0.1 (0.01)
Self-pay	100.00%	20 (0.04)	21.2 (0.05)	18 (0.06)	16.4 (0.09)
VA	100.00%	0 (0)	0 (0)	0 (0)	0 (0)
Tobacco user					
Never	99.60%	69.5 (0.04)	70 (0.06)	68.7 (0.07)	66.3 (0.12)
Passive	99.60%	1.9 (0.01)	1.9 (0.02)	1.8 (0.02)	1.9 (0.03)
Quit	99.60%	16.4 (0.03)	15.5 (0.05)	18 (0.06)	19.7 (0.1)
Yes	99.60%	12.2 (0.03)	12.6 (0.04)	11.5 (0.05)	12.1 (0.08)
Alcohol use					
User	97.60%	16.3 (0.03)	16.3 (0.05)	16.3 (0.06)	13.7 (0.09)
Comorbidities					
Hypertension	100.00%	46.9 (0.05)	43.7 (0.06)	52.8 (0.08)	62.7 (0.12)
Family History	100.00%	28.8 (0.04)	27.7 (0.06)	30.8 (0.07)	38 (0.12)
Congestive Heart Failure	100.00%	2.3 (0.01)	2.3 (0.02)	2.4 (0.02)	3.9 (0.05)
Hyperlipidemia	100.00%	22.8 (0.04)	20.7 (0.05)	26.5 (0.07)	29.8 (0.11)
Medications					
Steroid	100.00%	18.1 (0.04)	18.2 (0.05)	17.8 (0.06)	17.4 (0.09)
Blood Pressure	100.00%	45.5 (0.05)	42.8 (0.06)	50.4 (0.08)	61.4 (0.12)

Note: Each row in has at least one pair of cohorts where the difference in means is statistically significant.

patient did not visit the provider; or (ii) patient visited the provider, but no screening test was ordered; or (iii) patient visited the provider, who ordered the screening test, but the patient decided not to undergo the test. These trajectories serve as an input to estimate the HMM model.

Missing observation is handled by setting the emission probability for the missing observation for all hidden states to one (Helske and Helske 2019). Quarterly rates are then converted to annual transition probabilities (see Appendix A for details).

The estimated transition probabilities for the overall cohort are listed below.

$$\mathscr{P} = \begin{pmatrix} p_{s_{SH},s_{SH}} & p_{s_{SH},s_{SP}} & p_{s_{SH},s_{SD}} \\ p_{s_{SP},s_{SH}} & p_{s_{SP},s_{SP}} & p_{s_{SP},s_{SD}} \\ p_{s_{SD},s_{SH}} & p_{s_{SD},s_{SP}} & p_{s_{SD},s_{SD}} \end{pmatrix} = \begin{pmatrix} 0.94 & 0.059 & 0 \\ 0.033 & 0.931 & 0.035 \\ 0 & 0 & 1 \end{pmatrix}.$$

Note that the following transition probabilities are zero: from healthy to diabetes ($p_{s_{SH},s_{SD}}$); from diabetes to prediabetes ($p_{s_{SD},s_{SP}}$), and from diabetes to healthy ($p_{s_{SD},s_{SH}}$), captured as missing arrows in Figure 3. The (zero) transitions reflect the clinical nature of the disease—diabetes is irreversible and preceded by prediabetes—and implemented as restrictions in the Markov model. Estimating the transition probabilities

without these structural zeros results in negligibly small probabilities supporting our choice of this model.

It is important to highlight that disease progression can differ significantly depending on characteristics of a patient such as age, sex, race, and BMI. Some of these differences can be addressed by estimating transition probability matrices for sub-cohorts stratified by these factors. Appendix A.3 shows results for different sub-cohorts and provides details on how transition probability matrix is expanded to the entire state space (all seven states) of the POMDP.

4.2.1. Observation Matrix for Screened States ($\mathcal{O}_S$). The observation matrix for the screened states, represented by the emission probabilities, is generated using HMM. The following matrix shows estimates for the overall cohort.

$$\mathcal{O}_S = \begin{array}{c} \\ s_{SH} \\ s_{SP} \\ s_{SD} \end{array} \begin{array}{c} \begin{array}{ccc} o_{SH} & o_{SP} & o_{SD} \end{array} \\ \begin{pmatrix} 0.942 & 0.055 & 0.004 \\ 0.066 & 0.867 & 0.066 \\ 0.008 & 0.094 & 0.898 \end{pmatrix} \end{array}.$$

This matrix provides observation probabilities to POMDP and represents screening test accuracy; for example, given that the patient is healthy, there is a 94.2% chance that a screening test will be in the A1c range representing the observation "screened as healthy." The off-diagonal values are error probabilities; we find that screening tests are relatively accurate.

4.3. Learning the Predictive Risk Model

We first extract over 40 features from the EHR data for the PRM cohort and then use multiple imputation to address missing data (De Goeij et al., 2013). All features are scaled to z-scores, and logistic regression with L1 regularization is performed. To identify important features and their contribution to the predictive model, we perform manual feature selection and therefore do not use regularization. We start with a regression model with just the strongest feature. We then add one feature at a time to the regression model and re-run it.

Table 2 Top 10 Features that Feed into the PRM

Feature	Odds Ratio*	AUC†
Mean Random Blood Glucose (RBG) level	1.67	65.53%
BMI	1.40	68.50%
Systolic BP	1.14	71.17%
Hypertension	1.04	72.10%
Family history	1.19	72.10%
High density cholesterol	0.85	72.60%
Age	1.19	72.87%
Blood pressure medication	1.06	72.87%
Cholesterol medication	1.09	73.15%
Cholesterol HDL ratio	1.02	73.42%

*Notes**Odds ratio is estimated from a univariate logistic regression model for each variable separately.
†AUC is estimated from a multivariate logistic regression model; the estimation process is repeated by adding one variable at a time, starting with the most important feature, namely "Mean RBGLevel."

Table 2 provides the odds ratio for the 10 strongest features (estimated from a univariate logistic regression model for each variable separately), representing the odds of having or developing prediabetes or diabetes (i.e., Dysglycemia) compared with being healthy in the follow-up period. The table also shows area under the receiver operating characteristic curve (AUC) (Hajian-Tilaki 2013), representing the predictive accuracy of the binary classifier, obtained using 10-fold cross-validation. The first classifier only uses the mean RBG level, and each row adds a predictor. For example, the AUC in Row 3 (of Table 2) represents a model using mean RBG level, BMI, and systolic BP. The strongest indicator is the mean random blood glucose level, known to be a strong predictor of diabetes (Bowen et al., 2017). As can be observed, adding features can significantly improve the predictive power of the model.

4.3.1. Observation Matrix for Unscreened States ($\mathcal{O}_U$). The observation matrix for the unscreened states is estimated from confusion matrix (described in Section 3.3.2), obtained via (10-fold) cross-validation, is listed below.

$$\mathcal{O}_U = \begin{array}{c} \\ s_H \\ s_P \\ s_D \end{array} \begin{array}{c} \begin{array}{ccc} o_{PLR} & o_{PMR} & o_{PHR} \end{array} \\ \begin{pmatrix} 0.651 & 0.285 & 0.064 \\ 0.422 & 0.407 & 0.171 \\ 0.216 & 0.463 & 0.320 \end{pmatrix} \end{array}.$$

In the matrix, the columns represent predicted observations of low, medium, and high risk. For example, a patient in the true state healthy (s_H) has a 65.1% chance of being classified as low risk by the model. An observation matrix with ones along the matrix's diagonal and zero otherwise represents perfect observations (no classification error). Thus, the closer the real observation matrix is to this perfect matrix, the more information the observations provide to the POMDP for updating the belief state in Equation (2).

We highlight two things. First, $\mathcal{O}_U$ is only applicable when the patient does not undergo any screening, that is, only for true states (s_H, s_P, s_D); as such it is *essential* for initial screening decisions. Furthermore, in comparison to $\mathcal{O}_U$, $\mathcal{O}_S$ (the observation matrix for screened states) is much closer to the perfect matrix.

Table 3 Parameters Derived from Clinical Literature

Parameter	Description	Source	Value
C_s	Cost of diabetes screening process	(Johnson et al., 2005, O'Connor et al., 2001, Zhang et al., 2003)	\$346
Q	Quality-Adjusted Life Year in US dollars	(Neumann et al., 2014b)	\$50,000
C_D	Direct medical costs per year for new-onset diabetes	(Chatterjee et al., 2013)	\$4174
C_P	Incremental direct medical costs per year for a patient with prediabetes	(Chatterjee et al., 2013)	\$1316
α_P	Annual utility decrease in living with prediabetes	(Ackermann et al., 2009, Kontodimopoulos et al., 2009, Neumann et al., 2014a)	0.16
α_{UD}	Annual utility decrease in living with undiagnosed diabetes	(Ackermann et al., 2009, Bahia et al., 2017, Kontodimopoulos et al., 2009, Zhang et al., 2012b)	0.2
α_{DD}	Annual utility decrease in living with diagnosed diabetes	(Ackermann et al., 2009, Bahia et al., 2017, Kontodimopoulos et al., 2009, Zhang et al., 2012b)	0.18
m	Age-Adjusted mortality rate in United States in 2016	(Kochanek et al., 2017, Murphy et al., 2017)	0.0084
m_D	Age-adjusted mortality rate for diabetes in 2016	(Kochanek et al., 2017, Murphy et al., 2017)	0.00021
$\zeta_{screening}$	Uptake rate of diabetes screening*	(Davies 1999, Eborall et al., 2012, Khunti et al., 2015, Orton et al., 2013, Park et al., 2008)	0.644
$\eta_{regression}$	Coefficient for the effectiveness of intervention represented as an increase in regression to health	(Neumann et al., 2014a)	1.1
$\eta_{progression}$	Coefficient for the effectiveness of intervention represented as a decrease in progression to diabetes	(Neumann et al., 2014a)	0.5

*Notes**Uptake rate is the percentage of people who have been recommended screening and have undergone screening.

This means that screening results provide much more information to the POMDP compared to observations from PRM and, therefore, affect the belief state much more. In practice, this means that observations from the PRM are typically most important until the first screening result is obtained.

4.4. Parameter Estimation

The available dataset allow us to estimate some parameter values; for others, we rely on the existing clinical literature. For example, the reward structure and the effectiveness of interventions cannot be estimated from EHR data. Table 3 lists the various parameters obtained from clinical literature; column "Source" lists the references used.

For PHHS, we estimate $\xi = 0.05$, a number consistent with the literature (Edelman et al., 2002, 2004). Furthermore, the estimated cost of screening process for PHHS (C_S = \$346) is also consistent with the literature (Johnson et al., 2005, O'Connor et al., 2001, Zhang et al., 2003). The solution to reformulated optimization model that includes this capacity constraint results in an implied penalty of δ' = \$8000, yielding the total cost of screening as \$8,346 (i.e., $C'_S = C_S + \delta'$ = \$346+ \$8,000 = \$8,346).

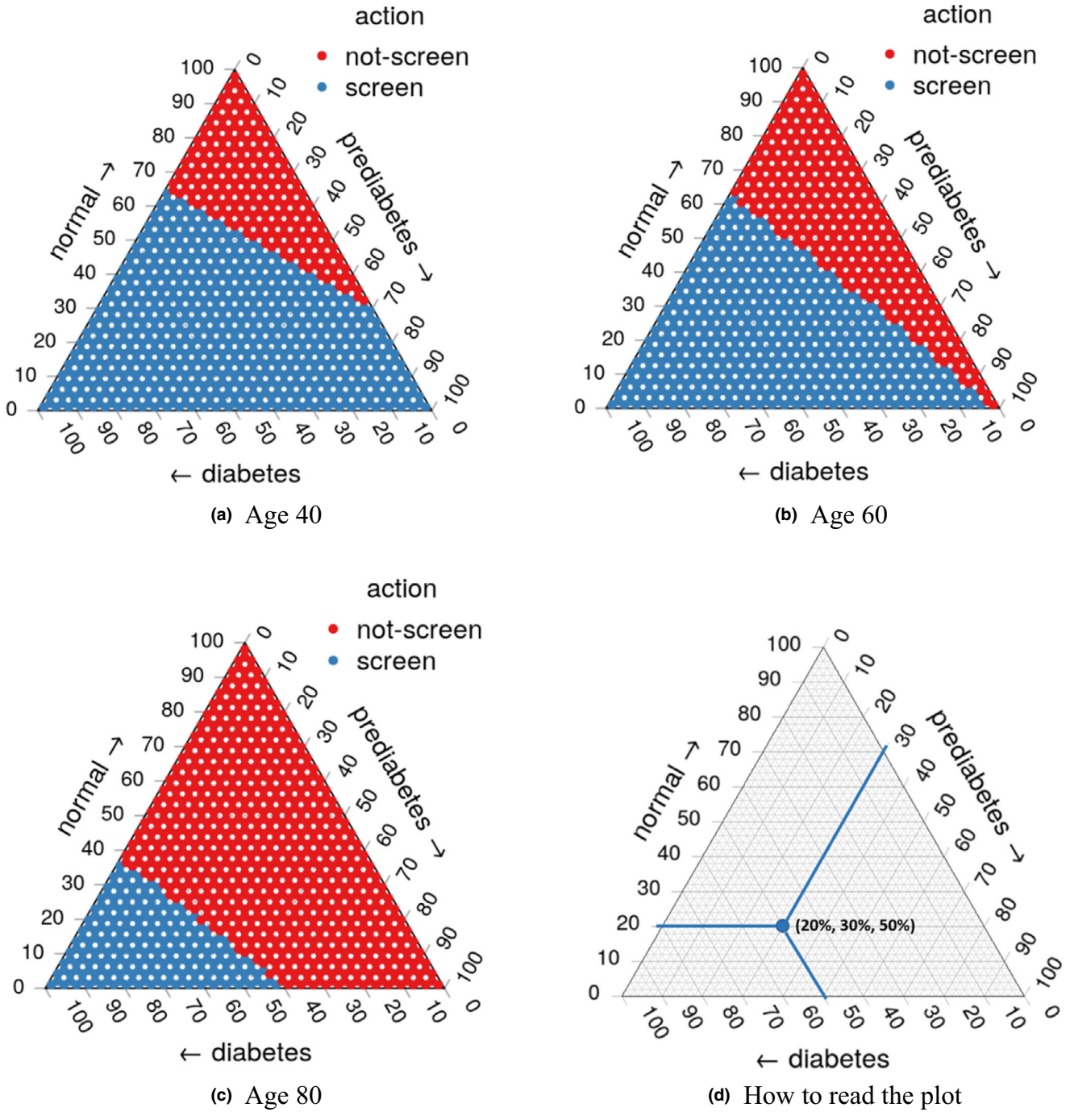
5. Determining the Optimal Screening Policy

POMDPs are known to be hard to solve, and the size of the proposed model cannot be solved exactly using dynamic programming in a reasonable amount of time given available computing resources. Several approaches have been proposed in the literature to solve larger POMDPs. Examples are the two-pass algorithm Smallwood and Sondik (1973), incremental pruning (Cassandra et al., 2013, Zhang and Liu 1996), and grid-based approximation approaches (see Ahuja and Birge (2020) for a review). Some of these approaches are still computationally expensive for larger problems. We use a version of a popular approximation method called point-based value iteration (PBVI) introduced by Pineau et al. (2003). To implement PBVI, we first identify belief points that are reachable from the initial belief by following all combinations of actions and observations until a sufficient number of points is created (typically tens of thousands of points that span all important regions of the belief space). Then, backward induction using the Bellman equation is performed using only the previously identified belief points.[9]

The exact number of belief points needed is not clear. We experimented with a wide range of belief points—from 100 to 10,000—and find that the total discounted expected reward did not change significantly after we reached 1000, which is the number we used. We obtained the optimal policy for the complete cohort as well as for each sub-cohort, using the sub-cohort specific parameters (specified in Appendix A.3). For simulation and numerical comparison of various approaches, we use the overall cohort-specific parameters.

The belief space has seven dimensions (one for each state), but we can visualize a projection on the three unscreened states as a ternary plot showing the simplex. We evaluate the policy on a uniform grid over

Figure 5 **Ternary Plots Representing the Decision Boundary and Actions Associated with Each Belief Point for a Hispanic Female Patient at (a) Age 40, (b) Age 60, and (c) Age 80. Similar Policies can be Generated for Patients in Other Sub-Cohorts. (d) Shows How the Axes of the Plot should be Read [Color figure can be viewed at wileyonlinelibrary.com]**



(a) Age 40 (b) Age 60

(c) Age 80 (d) How to read the plot

the simplex and show the optimal action. Figure 5 shows ternary plots for an illustrative patient—overweight Hispanic female patient—at ages 40, 60, and 80. Blue dots represent belief points where the optimal action is "screen." A straight line can approximate the decision boundary between screening and not screening states through the belief space representing a threshold policy. A patient should be screened whenever the belief about the patient's health falls below the threshold line.

We note that as a patient ages, the decision boundaries move toward the bottom-left vertex of the ternary plot, implying that the model requires more and stronger evidence to screen older patients. For example, it is not optimal to screen an 80-year-old patient with a belief state of $(s_H, s_P, s_D) = (30\%, 40\%, 30\%)$, but

a patient with the same belief state at age 60 should be screened as soon as possible under the optimal policy. This conclusion is consistent with clinical practice (Gilmer and O'Connor 2010).

5.1. Applying Screening Policy to an Individual

To produce individualized screening recommendations, we need the optimal age-dependent policy for the patient. If the patient is a member of a sub-cohort for which a specific policy is available, then that policy is used; otherwise, the cohort-wide policy is applied.

To begin, we need an initial belief state for the patient specifying the probability of the patient being in healthy, prediabetes, and diabetes state. This belief state can be obtained in a number of ways: (i) It can be determined by the clinician during the first visit; (ii) A predictive model (similar to PRM) can be used to predict the belief state if prior clinical information is available for the patient; or (iii) If no information if available, the prevalence of healthy, prediabetes, and diabetes in the cohort or the best-matching sub-cohort can be used. The initial belief state is updated every period using the PRM. At each decision period, if the optimal policy indicates the action "to screen," the patient could be flagged in the EHR system, informing the clinician that the patient should be recommended for screening during the next visit.

6. Comparison Using Simulation

6.1. Simulation Model

There exists extensive literature related to the comparison of screening policies using cost-effectiveness analysis (Chatterjee et al., 2013, Chen et al., 2001, Hoerger et al., 2004, Howard et al., 2010, Kahn et al., 2010, O'Connor et al., 2001). Most of the studies simulate a cohort of patients to evaluate the cost-effectiveness of either mass screening or opportunistic screening. We use simulation to evaluate the effectiveness of the proposed screening policy and compare it with prototypical guidelines. To simulate the natural progression of diabetes and its complications such as retinopathy, nephropathy, and neuropathy, we use Markov models developed by Chen et al. (2001). The costs associated with each stage of the complications are obtained from existing literature (Chen et al., 2001, Howard et al., 2010).

The simulation consists of a hypothetical cohort of 50,000 patients. Each patient enters the simulation at age 30, and we use a 50-year horizon. Our choice of the patient's initial belief state is the set of prevalence values for each stage of diabetes, which is 0.508, 0.358, and 0.133, representing the prevalence of healthy, prediabetes, and diabetes, respectively (also listed in Appendix C.1). At each subsequent visit, we update the belief state using either the observation from screening (if the patient is screened) or from the PRM (if unscreened). If it is from PRM, the observations are simulated by drawing from the observation matrix for the unscreened states ($\mathcal{O}_U$).

To obtain the optimal policy, we implement our model; the values of parameters such as costs, incidence, prevalence, and mortality rates are obtained from existing literature (Chen et al., 2001, Howard et al., 2010, Kahn et al., 2010). We simulate seven scenarios representing different screening policies, including those generated from our proposed framework. Appendix C provides details on each step of the simulation.

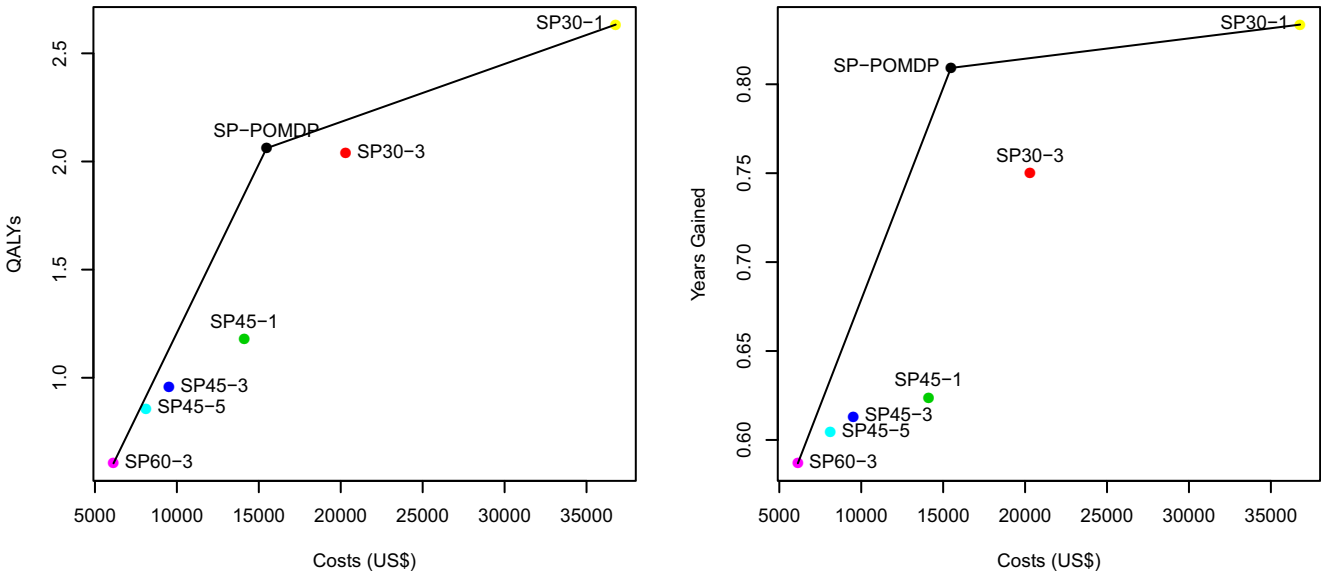
Table 4 provides a comparison of various screening policies that differ in (i) the age at which patients are

Table 4 Comparison Between Various Screening Policies in Terms of Cost-Effectiveness, Years and QALYs Gained, TTD Improvement and Events Prevented (from 50 Replications)

Screening Policy[†]	ICER (cost per QALY, $US)[§] (SD)	Years Gained[¶] (SD)	QALYs gained[§,¶] (SD)	Improvement in TTD[‡,¶] (SD)	Macrovascular events prevented[‖] (SD)	Microvascular events prevented[‖] (SD)	Deaths prevented[‖] (SD)	% of Population screened each year
SP30-3	$27,042 (1268)	0.75 (0.04)	2.04 (0.05)	19 (0.2)	22 (1.6)	207 (4)	48 (2)	14.6%
SP45-1	$37,366 (1755)	0.62 (0.04)	1.18 (0.03)	14 (0.1)	21 (1.5)	178 (4)	45 (2)	14.7%
SP45-3	$31,155 (1791)	0.61 (0.04)	0.96 (0.03)	11 (0.1)	20 (1.4)	165 (4)	44 (2)	14.4%
SP45-5	$29,644 (2175)	0.60 (0.04)	0.86 (0.03)	9 (0.1)	20 (1.5)	157 (4)	44 (2)	13.2%
SP60-3	$32,201 (2966)	0.59 (0.04)	0.60 (0.03)	6 (0.1)	19 (1.4)	142 (4)	42 (2)	7.8%
SP30-1 (MS)	$36,801 (1233)	0.83 (0.05)	2.63 (0.05)	25 (0.2)	23 (1.5)*	229 (4)*	50 (2)	35.6%
SP-POMDP	$20,426 (1339)	0.81 (0.04)	2.06 (0.05)	18 (0.2)	23 (1.5)*	219 (5)*	49 (2)	6.5%

Notes.[†]Screening policies are abbreviated as SPXX-Y where XX is the age at the first screening and then the screening is repeated every Y years. For example, SP45-1 means that the earliest age at which the patient should be screened is 45 and, subsequently, the screening should be repeated every year; MS, Maximum screening.
[‡]Mean improvement in time to diagnosis (TTD) gained by each screening policy compared with opportunistic screening.
[§]All costs and QALYs are discounted at 3% per year.
[¶]Per patient.
[‖]Per 1000 patients.
*Indicates no statistically significant differences between policies.

Figure 6 Costs Per QALY (Left) and Cost Per Years Gained (Right) of Seven Screening Guidelines, Compared with Opportunistic Screening in Terms of QALYs and Years of Life Gained, Respectively. The Efficient Frontier is Shown as a Line [Color figure can be viewed at wileyonlinelibrary.com]



first screened, and (ii) the frequency of rescreening. We provide comparisons on multiple metrics: incremental cost-effectiveness ratio (ICER) (Meltzer 1997), the absolute number of years gained, QALYs gained, improvement in time-to-diagnosis (TTD), macrovascular events prevented, microvascular events prevented, and deaths prevented. We obtain ICER by comparing each policy with opportunistic screening —an ad-hoc approach in which the individual is screened whenever she visits the provider, and the doctor determines that the individual needs to undergo an A1c screening test.

The screening policy closest to the ADA guidelines is SP45-3, meaning that screening should be initiated for everyone 45 or older and repeated every 3 years. The ADA screening guidelines begin screening earlier in the presence of other risk factors, but we do not incorporate this aspect into our simulation for simplicity. Our proposed policy selectively targets patients who are at a high risk of developing diabetes and will benefit the most in the long run from being screened at each visit.

Based on Table 4, we observe that our proposed policy, SP-POMDP, performs better on every single metric compared to all other policies except the maximum screening policy (SP30-1). Compared to SP45-3 (the policy closest to the ADA guidelines), SP-POMDP is 34% more cost-effective, detects prediabetes or diabetes patients 7 years earlier, and prevents more macro- and microvascular events, by 15% and 33%, respectively. Figure 6 presents the results in the form of an efficient frontier, which consists of three policies: SP30-1, SP-POMDP, and SP60-3, implying that all other policies are inefficient. The SP-POMDP is slightly inferior to SP30-1, but consumes significantly fewer resources.

6.1.1. Reasons for Superior Performance. There are three main reasons why our proposed approach yields better performance compared to existing approaches. First, our proposed policy is targeted, in contrast to existing guidelines (e.g., from the ADA) that are generic and operationally infeasible to implement. By formulating the screening question as an optimization problem where the belief about the patient's health status is updated at each period, we are able to generate a screening policy that is (i) dynamic—screening decisions can be adjusted based on the predicted disease evolution for each individual patient at each period; and (ii) focuses on "high-risk" patients—those who are likely to have or develop diabetes. Second, the PRM incorporates over 40 individual-level risk factors and, consequently, has a relatively high accuracy of detecting diabetes in undiagnosed patients. Existing guidelines do not rely on predicted risk but only on the presence or absence of a small number of risk factors (e.g., age and BMI). Finally, the forward-looking nature of the POMDP framework allows us to optimize and dynamically adjust the screening frequency. The screening decision incorporates not only what we currently know about the patient, but it takes disease evolution and future costs into account. In contrast, the screening frequency in existing guidelines is static.

6.2. Sensitivity Analysis

We perform two sets of sensitivity analyses. In the first set, we evaluate the sensitivity to various cost

parameters, including C_s' (total cost of diabetes screening), α_P (annual utility decrement of living with prediabetes), α_{UD} (annual utility decrement of living with undiagnosed diabetes), and α_{DD} (annual utility decrement of living with diagnosed diabetes. In the second set, we evaluate the sensitivity to the transition and observation probabilities (see Table 5 for results).

Not surprisingly, the model is sensitive to the total cost of screening, which directly impacts cost-effectiveness, QALYs gained, and improvement in TTD. As expected, the higher the total cost of screening, the less cost-effective the policy is. The policy recommends postponing the screening, resulting in lower QALYs gained. Second, higher values of QALY and higher screening uptake rates ($\zeta_{screening}$) translate into higher reward and more cost-effective policies, gains in QALYs, and an improvement in TTD. This is because higher uptake rates allow the policies to screen people sooner. Third, slower progression rates mean patients take more time to develop diabetes, which implies that screenings can be postponed without increasing costs. Finally, a more accurate PRM yields more informative observation probabilities resulting in more cost-effective policies that lead to QALY gains and an improvement in TTD.

7. Managerial and Policy Implications

The development of screening policies for diabetes that incorporate individualized risk factors has significant local and national policy implications. As shown in Table 4, our proposed policy (SP-POMDP) screens fewer people from the population than other guidelines. Furthermore, it can improve outcomes by 2.06 QALYs per patient – 110% more than the current ADA guidelines—and does so in a more cost-effective manner, with an ICER that is 35% less than the existing ADA guidelines (SP45-3).

Given the cost-effectiveness of our proposed policy, implementing our proposed approach could yield significant financial savings. For example, within PHHS, implementing SP-POMDP for a cohort of 12,000 patients could save almost $129 million over five decades ($2.6 million annually, on average), compared to the established ADA guidelines. These savings, driven by ICER difference between the two policies,[10] are significant, especially for a publicly funded hospital.

Furthermore, assuming that 10% of the US population—~ 33 million patients—is similar to our cohort (i.e., indigent with limited economic resources and served by similar safety-net hospitals),[11] implementing our approach for this population could result in savings of roughly $354 billion over five decades ($7.1 billion annually, on average), compared with the ADA guidelines. Additional (indirect) savings for this population stem from: (i) a reduction in macrovascular events, which translates into an annual savings of ~ $5.5 million; (ii) a reduction in microvascular events, which translates into an annual savings of ~ $926 million; (iii) early diagnosis of diabetes, which helps lower expenses associated with treating diabetes and its complications, ~ $46.2 billion per year (saving in the utility of patients' lives); and (iv) a reduction in preventable deaths, which translates into an annual savings of ~ $1.4 billion (the equivalent of the QALYs saved).[12]

These costs do not consider the general improvement in patient well-being and the reduced psychological burdens of patients and their families who help care for the patients. The savings could be

Table 5 Sensitivity Analysis Based on Varying Each Parameter by ±20%

Parameters	Change	ICER ($US)	Years gained	QALYs gained	TTD improved	Macrovascular events prevented	Microvascular events prevented	Deaths prevented
Reference		$20,426	0.81	2.06	18	23	219	49
Total costs of screening (C_s')	–20%	$17,751	0.82	2.57	22	23	228	49
	+20%	$28,669	0.8	0.92	5	22	202	48
QALY	–20%	$30,412	0.8	0.91	5	21	199	48
	+20%	$17,895	0.81	2.53	22	23	224	50
Treatment costs (C_P, C_D)	–20%	$20,878	0.8	2.06	18	23	219	49
	+20%	$20,336	0.82	2.06	18	23	216	50
Disutilities ($\alpha_P, \alpha_{UD}, \alpha_{DD}$)	–20%	$20,500	0.83	2.07	18	23	216	50
	+20%	$20,416	0.79	2.05	18	23	219	48
Uptake rate of screening ($\zeta_{screening}$)	–20%	$20,782	0.83	2.07	18	23	216	50
	+20%	$18,136	0.81	2.54	22	23	226	50
Transition Probabilities*	–20%	$28,449	0.8	0.91	5	23	199	49
	+20%	$18,355	0.82	2.56	23	23	226	49
Observation Probabilities	–20%	$20,254	0.8	2	17	22	215	49
for unscreened states†	+20%	$17,826	0.81	2.59	23	23	230	49

Notes: *Change of progression rates toward diabetes, regression rates are adjusted in the opposite way.
†20% more accurate predictive model and 20% less accurate predictive model. The predictive model's accuracy is calculated from the confusion matrix by dividing the sum of diagonals by the whole matrix.

redirected to preventive services, health promotion, and disease management for patients with diabetes and other chronic health conditions. The key message to convey with this analysis is that while exact numbers may be arguable, the potential for cost savings due to an improved screening process is substantial. Importantly, given that diabetes is the most expensive chronic disease in the United States, the potential of our approach to improve the efficiency and effectiveness of the US healthcare system is immense.

8. Discussion

Diabetes is a preventable chronic disease that affects millions of American adults and costs hundreds of billions of dollars (American Diabetes Association, 2018). It progresses with a long asymptomatic period —9–12 years, on average (Lu et al., 2010). Thus, it is critical to screen patients with undiagnosed diabetes or those at an elevated risk of developing diabetes. Early intervention can prevent the progression of the disease and development of associated complications, which can result in substantial savings. Existing guidelines such as those from the ADA (American Diabetes Association, 2019) and USPSTF are generic and would present a costly operational challenge if implemented on the entire population (Chatterjee et al., 2013). To the best of our knowledge, there does not exist an individualized screening strategy for detecting patients with diabetes or prediabetes that takes costs and disease progression into account. This is the void we attempt to fill.

In this study, we propose a *targeted* screening policy that uses available information on individual patients to identify *whom* to screen (i.e., which patients should receive the gold-standard A1c test) and *when* to screen (i.e., in which period). It relies on multiple methods and incorporates clinical data on patients obtained from an EHR system, making it practically implementable in many settings. In particular, POMDP is used to determine optimal decisions at each period (a year). HMM is used to estimate transition and emission probabilities for the POMDP. PRM is used to generate risk scores, individualized for each patient, that are used as observations in the POMDP to inform screening recommendations as well as to derive the observation matrix for the unscreened states for the POMDP. Thus, a key contribution is to build a framework using these three methods to address a practical healthcare decision-making problem.

We develop and validate our model on a proprietary dataset of more than 62,000 patients over 5 years from a large safety-net hospital and demonstrate, using a detailed simulation analysis, that our proposed framework produces a screening policy that can improve patient outcomes by 106%, at only 65% of the screening cost, compared with existing guidelines. Sensitivity analyses show no significant or unjustifiable change in the simulation results due to changes in the model parameters.

Integrating predictive models with optimization methods is critical to solving challenging and important problems in healthcare and beyond. In this study, we have demonstrated how existing methods that rely on real data (HMM and PRM) can be combined with a model for sequential decision-making (POMDP) to produce an optimal screening policy that incorporates cohort- and sub-cohort-specific characteristics and individualized risk levels derived from clinical data.

8.1. Limitations

Our study has several limitations. From a methodological standpoint, the POMDP approach relies on the strong assumption that the Markov property holds, at least approximately. However, our assumption is consistent with previous work, which shows that Markov models are useful approximations for disease progression models (see Section 2 for a literature review). Second, our state space is primarily based on a single measure (A1c), resulting in a simplistic single-dimensional state space. Our review of the literature and conversations with the practitioners reveal that A1c is the most commonly used clinical test to screen for diabetes. Age-specific transition probabilities represent the effect of age. While the inclusion of additional covariates (e.g., body mass index) may enrich the model, it also increases the state space and model complexity, substantially increasing the computational effort required to solve such a model. Note that these additional covariates are used in the PRM and thus incorporated in the model. Third, we only consider two actions—*screen* and *do not screen*. Expanding the state and action space will require the estimation of all associated transition parameters. Therefore, smaller state and action spaces are preferable from a practical standpoint. Fourth, the estimation of the disease progression rates relies on the available screening results from EHR data. Thus, it applies only to screened patients with visits to the health system under consideration. We estimate the transition rates of unscreened patients by using a factor representing treatment effectiveness. This is a simplistic approach that requires more research. Fifth, we estimate disease progression rates from a cohort of patients, ages 18–64, and then apply this model to patients potentially outside this age range. This is a result of a limitation in the available data. Finally, our analysis is limited to patients from one safety-net hospital system. The estimated parameters may not be directly applicable to other patient populations (e.g., privately

insured patients). Nonetheless, we believe our methodological approach is generalizable and can be applied, with modifications, in other contexts where similar data are available.

8.2. Directions for Future Research

There are several ways that future research could, and should, follow-up on our work. From a methodological standpoint, an expanded state space based on additional patient-level measures (e.g., BMI) that impact disease progression would enrich the model. An expanded action space that provides additional options—for example, patient monitoring—would also enhance the model. From an implementation standpoint, future research should look at applying our data-driven approach to other settings (e.g., hospitals that are not classified as safety net) and other chronic diseases, such as cancer and HIV, where early detection offers substantial clinical benefits and improves patient outcomes.

Furthermore, our approach may be used to develop screening strategies in non-healthcare settings, for example, in K-12 education, where identifying children at risk of failing allows educators to develop targeted programs to help them. There is also an opportunity to expand to analytical models of service systems where every customer may not have the same need. Future research should also explore new data-driven approaches that develop individualized treatment regimens soon after a patient is diagnosed with diabetes. This screening approach is highly relevant for managers and policymakers to make the most efficient use of their limited resources for diabetes screening, prevention, and treatment.

8.3. Conclusion

Our paper has important implications for practitioners, managers, policymakers, and scholars. We propose an individualized screening policy—one that is data-driven, is based on a large set of available information (through EHRs) and utilizes multiple methods to identify which patients to screen, and when, based on the risk of having or developing diabetes and prediabetes. We demonstrate, using simulation models, that our proposed policy is highly cost-effective compared with existing guidelines. Our work offers practitioners and policymakers a way to optimally utilize resources, especially in a resource-constrained setting, to maximize patient health.

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Appendix A. Estimation of Transition Probabilities

Obtaining a practically implementable optimal policy from the POMDP model requires an accurate estimate of transition probabilities from the EHR data. However, the EHR data do not record all the information that is needed. The base transition probabilities from the EHR must be adjusted to account for (i) patient mortality, because we do not observe death in our data; (ii) effects of the intervention, both progression (to diabetes) and regression (to healthy states); and (iii) screening uptake rates by the patients. We rely on published literature and official statistics to perform these adjustments. The adjustment steps are discussed in detail below.

A.1. Base Transition Probabilities

We use screening result data for the overall cohort of 62,721 patients (hereafter referred to as sequences) to obtain "base" transition probabilities. For each patient, we have information covering roughly 5 years. We use annual decision periods; however, to use the available data more efficiently, we split them into 20 quarters with information related to whether and when the gold standard tests (that yield A1c values) were performed.[13] We first estimate the quarterly transition rates and later converted to annual rates.

Table A1 shows the sequence of observations (from screening) for 10 randomly sampled patients. The notations o_{SH} (screened as healthy), o_{SP} (screened as prediabetic), and o_{SD} (screened as diabetic) represent the patient's observations/test results based on the A1c level, and cells marked with "*" represent a quarter in which no A1c test was performed. For example, Patient #3 had two screenings (in quarters 7 and 8), which resulted in A1c values in the healthy range. Patient #60 had six A1c values and was classified as prediabetic in quarters 4 and 6 and diabetic in others.

It is important to emphasize that A1c tests are not perfect, and some screening observations may not match the patient's actual health state. For example, patients may be screened as diabetic in one quarter and prediabetic in a later quarter. In such cases, it is

Table A1 Statistics of the A1c Test Results in the Dataset

Qtr	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
#3	*	*	*	*	*	*	o_{SH}	o_{SH}	*	*	*	*	*	*	*	*	*	*	*	*
#38	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	o_{SH}
#49	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	o_{SH}	*	*
#53	*	*	*	*	*	*	*	*	*	*	*	*	*	*	o_{SH}	*	*	*	*	*
#60	*	o_{SD}	*	o_{SP}	*	o_{SP}	o_{SP}	o_{SD}	*	o_{SD}	*	*	*	*	*	*	*	*	*	*
#67	*	o_{SP}	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
#69	*	o_{SP}	o_{SH}	o_{SP}	o_{SP}	o_{SP}	o_{SP}	o_{SP}	o_{SP}	o_{SP}	o_{SP}	o_{SP}	o_{SP}	o_{SP}	o_{SP}	o_{SP}	o_{SP}	o_{SP}	o_{SP}	o_{SP}
#70	*	*	*	*	*	*	*	*	o_{SD}	*	o_{SD}	*	o_{SD}	o_{SD}	*	o_{SD}	*	o_{SD}	*	o_{SD}
#83	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	o_{SH}	*	*	*
#86	*	o_{SP}	o_{SP}	o_{SP}	o_{SP}	o_{SP}	o_{SP}	o_{SP}	o_{SP}	o_{SP}	o_{SH}	o_{SP}	o_{SP}	o_{SP}	o_{SP}	o_{SH}	o_{SP}	o_{SP}	o_{SP}	o_{SP}

possible that even though the patient's health state did not change, the screening results were different.[14] HMMs are robust against these measurement errors as they allow us to estimate emission probabilities (analogous to observation probabilities in POMDPs). The percentage of incorrectly screened observations is typically small. We find that an A1c test correctly identifies the true health state as diabetes nine times out of 10 in our data.

Figure A1 displays the frequency of each type of observation (o_{SH}, o_{SP}, and o_{SD}). Figure A2 shows the histogram of the number of A1c results per patient in our dataset; the greater the availability of results per patient, the greater the information to estimate transition probabilities. Table A2 provides summary statistics of the A1c test results.

Of the 62,721 sequences, we observe 3886 sequences with transitions from healthy to prediabetes, 3819 sequences with transitions from prediabetes to diabetes and 3282 sequences with transitions from prediabetes to healthy. This information is sufficient to estimate transition probabilities. Quarterly transition rates are translated into equivalent annual base transition probabilities using the following formula: $\mathscr{P} = (\mathscr{P}_{\text{quarterly}})^4$, where we note that raising the matrix to the power of four uses matrix multiplication (Chhatwal et al., 2016).

A.2. Cohort-Wide Transition Probabilities

We estimate the base transition matrix ($\mathscr{P}$) between screened states from the observed screening results for our overall cohort, listed below.

$$\mathscr{P} = \begin{pmatrix} p_{s_{SH},s_{SH}} & p_{s_{SH},s_{SP}} & p_{s_{SH},s_{SD}} \\ p_{s_{SP},s_{SH}} & p_{s_{SP},s_{SP}} & p_{s_{SP},s_{SD}} \\ p_{s_{SD},s_{SH}} & p_{s_{SD},s_{SP}} & p_{s_{SD},s_{SD}} \end{pmatrix} = \begin{pmatrix} 0.94 & 0.059 & 0 \\ 0.033 & 0.931 & 0.035 \\ 0 & 0 & 1 \end{pmatrix}.$$

These numbers are similar to what is reported in existing (albeit limited) literature. For example, the transition rate from s_{SP} to s_{SD} is 0.035 – Tuomilehto et al. (2001) reports a similar rate of 0.03.

A.3. Transition Probabilities Specific to Sub-cohorts

While one can create sub-cohorts based on many patient characteristics chosen by experts familiar with the cohort, we focus on four key characteristics often used by providers: age, gender, race, and BMI. We estimate transition probabilities for the sub-cohort defined by each characteristic (see tables below), then use these probabilities in the POMDP decision model to create sub-cohort-specific optimal policies. Below, we list the three important probabilities, healthy to prediabetes (p_{s_H,s_P}), prediabetes to healthy (p_{s_P,s_H}), and prediabetes to diabetes (p_{s_P,s_D}) for each category of these sub-cohorts.

Figure A1 Distribution of A1c Values in the Dataset [Color figure can be viewed at wileyonlinelibrary.com]

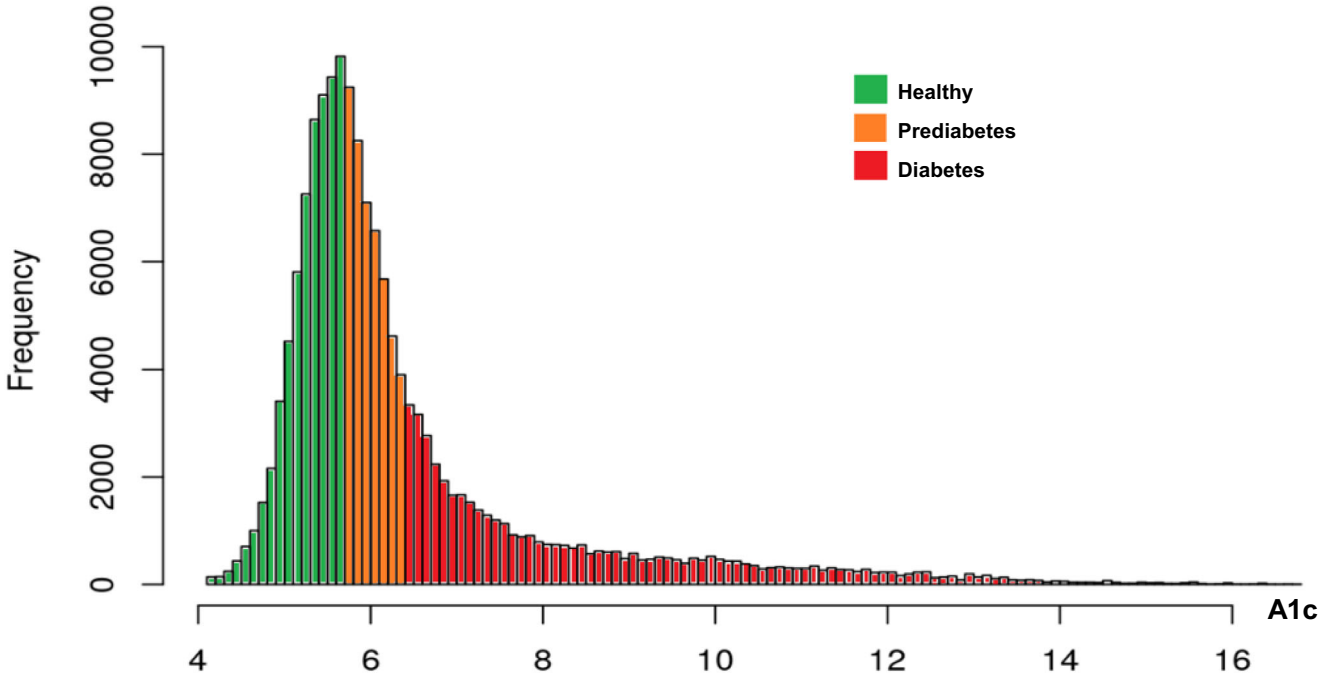

Figure A2 Distribution of the Number of A1c Tests in the Dataset [Color figure can be viewed at wileyonlinelibrary.com]

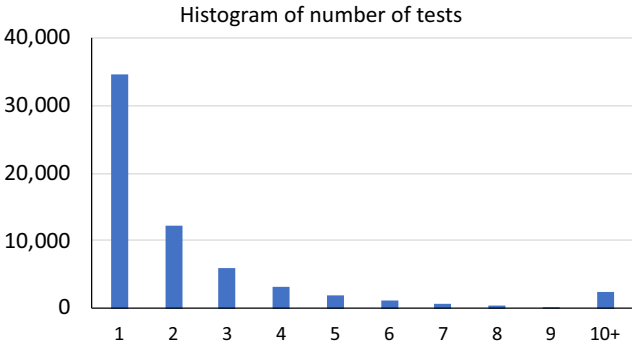

Table A2 Summary Statistics of A1c Values in the Dataset

Min	1st Q	Median	Mean	3rd Q	Max
4.1	5.5	5.9	6.5	6.7	16.8

A.3.1. Age-Specific Transition Probabilities.

Age	p_{s_H,s_P}	p_{s_P,s_H}	p_{s_P,s_D}
[30, 40)	0.057	0.048	0.039
[40, 50)	0.072	0.023	0.043
[50, 60]	0.078	0.030	0.033
≥ 60	0.076	0.037	0.031

A.3.2. Gender-Specific Transition Probabilities.

Gender	p_{s_H,s_P}	p_{s_P,s_H}	p_{s_P,s_D}
Male	0.057	0.036	0.041
Female	0.060	0.032	0.033

A.3.3. Race-Specific Transition Probabilities.

Race	p_{s_H,s_P}	p_{s_P,s_H}	p_{s_P,s_D}
White	0.054	0.056	0.041
Hispanic	0.060	0.038	0.037
Non-Hispanic Black	0.064	0.027	0.030
Asian	0.037	0.000	0.039

A.3.4. BMI-Specific Transition Probabilities.

BMI	p_{s_H,s_P}	p_{s_P,s_H}	p_{s_P,s_D}
< 18.5 (underweight)	0.024	0.073	0.015
18.5–24.9 (normal)	0.033	0.047	0.019
25–29.9 (overweight)	0.045	0.023	0.029
≥ 30 (obese)	0.081	0.035	0.041

Key observations are as follows: First, the probability of developing prediabetes increases with age and BMI. Second, the probability is higher for females. Third, compared with patients who are white, the probability of developing prediabetes is higher for patients who are Hispanic and non-Hispanic Black. However, the probability of transitioning from prediabetes to diabetes is similar across all categories for each patient characteristics except in the case of BMI.

A.4. Effectiveness of Intervention

We obtained the intervention effectiveness ($\eta_{regression}$) and disease progression rate ($\eta_{progression}$) from Neumann et al. (2014), who found that lifestyle intervention programs can increase the chance of reverting from prediabetes to healthy by ~ 10% (i.e., $\eta_{regression} = 1.1$) and reduces the chance of progressing to diabetes by 50% (i.e., $\eta_{progression} = 0.5$). The base transition matrix was obtained from screening results. We assume that screened patients will receive the appropriate interventions. The corresponding transition matrix for the action "not screen"—appropriate for transitions between unobservable states (s_H, s_P, s_D)—is obtained by correcting for the intervention effect as follows:

$$p_{s_P,s_H} = \frac{p_{s_{SP},s_{SH}}}{\eta_{regression}} \text{ and } p_{s_P,s_D} = \frac{p_{s_{SP},s_{SD}}}{\eta_{progression}}.$$

A.5 Uptake Rate of Screening

Not every patient who is sent by the physician for screening gets screened. Using average of the available values from the existing literature (Davies 1999, Eborall et al., 2012, Khunti et al., 2015, Orton et al., 2013, Park et al., 2008), we determined the uptake rate for out cohort as follows: $\xi_{screening} = 0.644$.

A.6. Adjusting for Mortality Rates

The observation period in our cohort ends at age 65, and we do not have information on deaths in our data. Thus, we cannot directly estimate the event of death from the data. Instead, we use age-specific mortality rates reported by the CDC (Kochanek et al., 2019, p. 24), listed below.

Age	Total (%)	Total male (%)	Total female (%)
< 20	0.103	0.131	0.073
[20, 30)	0.217	0.309	0.120
[30, 40)	0.319	0.423	0.214
[40, 50)	0.532	0.661	0.405
[50, 60)	1.225	1.524	0.939
[60, 70)	2.524	3.160	1.950
[70, 80)	5.725	6.862	4.783
≥ 80	19.445	21.591	18.090

The report states that 3% of deaths are attributable to diabetes, and we adjust the mortality rates accordingly. This, together with the age-dependent transition matrices, is used to construct complete age-dependent transition matrices, including transitions to death, through the following two steps:

Step 1: Calculate age-specific mortality rate m for each of the three disease states: healthy (m_H), prediabetic (m_P), and diabetic (m_D), where we use the prevalence rates of healthy ($prev_H$), prediabetic ($prev_P$), and diabetic ($prev_D$) in the general population. Assuming that $m_H = m_P$, we obtain m_D as follows:

$$m_D = \frac{(m - (prev_H m_H + prev_P m_P))}{prev_D}.$$

Step 2: Adjust base transition matrix (P) without death for the action "no screening" as follows:

$$\mathscr{P}^{3\times3}_{a_N} = \begin{pmatrix} p_{S_H,S_H}(1-m_H) & p_{S_H,S_P}(1-m_H) & p_{S_H,S_D}(1-m_H) \\ p_{S_P,S_H}(1-m_P) & p_{S_P,S_P}(1-m_P) & p_{S_P,S_D}(1-m_P) \\ p_{S_D,S_H}(1-m_D) & p_{S_D,S_P}(1-m_D) & p_{S_D,S_D}(1-m_D) \end{pmatrix}.$$

Similarly, adjust the base transition matrix for the action "screen" as follows:

$$\mathscr{P}^{3\times3}_{a_S} = \begin{pmatrix} p_{S_{SH},S_{SH}}(1-m_H) & p_{S_{SH},S_{SP}}(1-m_H) & p_{S_{SH},S_{SD}}(1-m_H) \\ p_{S_{SP},S_{SH}}(1-m_P) & p_{S_{SP},S_{SP}}(1-m_P) & p_{S_{SP},S_{SD}}(1-m_P) \\ p_{S_{SD},S_{SH}}(1-m_D) & p_{S_{SD},S_{SP}}(1-m_D) & p_{S_{SD},S_{SD}}(1-m_D) \end{pmatrix}.$$

For ease of notation, we will use $\Delta = \begin{pmatrix} m_H \\ m_P \\ m_D \end{pmatrix}$.

Furthermore, let $\mathscr{P}^{3\times3}_{a_{N\Delta}}$ and $\mathscr{P}^{3\times3}_{a_{S\Delta}}$ represent the first three rows and columns of $\mathscr{P}_{a_{N\Delta}}$ and $\mathscr{P}_{a_{S\Delta}}$, respectively. Note that these matrices are not complete; we need to add the transition rate between death states, as explained next.

A.7. Constructing the Final (Adjusted) Matrix for POMDP

Given that the POMDP consists of seven states: three unscreened health states, three screened health states, and the state representing death (s_Δ), we require two 7×7 transition probability matrices (TPMs), one for each action. The TPMs for the action "do not screen" ($\mathscr{P}_{a_N}$) is constructed as follows:

$$\mathscr{P}_{a_N} = \begin{pmatrix} \mathscr{P}^{3\times3}_{a_N} & 0^{3\times3} & \Delta \\ \mathscr{P}^{3\times3}_{a_N} & 0^{3\times3} & \Delta \\ 0 & 0^{1\times3} & 1 \end{pmatrix},$$

where we add two 3×3 transition matrices of all zeroes, indicating that transition to a screened state is not possible under the action "do not screen." We construct a TPM for the action "to screen" ($\mathscr{P}_{a_S}$) in a similar way and adjust the probabilities for the screening uptake rate, as follows:

$$\mathscr{P}_{a_S} = \begin{pmatrix} \left(1-\zeta_{screening}\right)\mathscr{P}^{3\times3}_{a_N} & \zeta_{screening}\mathscr{P}^{3\times3}_{a_S} & \Delta \\ \left(1-\zeta_{screening}\right)\mathscr{P}^{3\times3}_{a_N} & \zeta_{screening}\mathscr{P}^{3\times3}_{a_S} & \Delta \\ 0 & 0^{1\times3} & 1 \end{pmatrix}$$

We constructed these final matrices for each subcohort and age group. For example, the transition matrices for an overweight 40-year-old Hispanic female are listed below.

$\mathcal{P}_{a_N}$	s_H	s_P	s_D	s_{SH}	s_{SP}	s_{SD}	s_Δ
s_H	0.946	0.050	0.000	0.000	0.000	0.000	0.004
s_P	0.027	0.910	0.059	0.000	0.000	0.000	0.004
s_D	0.000	0.000	0.984	0.000	0.000	0.000	0.016
s_{SH}	0.946	0.050	0.000	0.000	0.000	0.000	0.004
s_{SP}	0.027	0.910	0.059	0.000	0.000	0.000	0.004
s_{SD}	0.000	0.000	0.984	0.000	0.000	0.000	0.016
s_Δ	0.000	0.000	0.000	0.000	0.000	0.000	1.000

$\mathcal{P}_{a_S}$	s_H	s_P	s_D	s_{SH}	s_{SP}	s_{SD}	s_Δ
s_H	0.337	0.018	0.000	0.609	0.032	0.000	0.004
s_P	0.010	0.324	0.021	0.019	0.603	0.019	0.004
s_D	0.000	0.000	0.350	0.000	0.000	0.634	0.016
s_{SH}	0.337	0.018	0.000	0.609	0.032	0.000	0.004
s_{SP}	0.010	0.324	0.021	0.019	0.603	0.019	0.004
s_{SD}	0.000	0.000	0.350	0.000	0.000	0.634	0.016
s_Δ	0.000	0.000	0.000	0.000	0.000	0.000	1.000

It is worth emphasizing that, by construction, rows 1–3 are identical to rows 4–6 in both the matrices, $\mathcal{P}_{a_N}$ and $\mathcal{P}_{a_S}$. The intervention's effect following screening is not encoded in different rows, representing the "state from" which the patient transitions. Instead it is encoded in the "states to" which the patient transitions, and differs between going to unscreened states and going to screened states. To illustrate, consider the action "screen" (a_S). If a prediabetic patient decides to undergo screening, there is a 60.3% likelihood that the patient will be prediabetic (s_{SP}) at the end of this period and this rate is independent on whether the patient was screened (s_{SP}) or not screened (s_P) in the last period. After a screening is performed, the probability of transitioning to a healthier state increases.

Appendix B. Cohort Description

The overall cohort consists of established patients between the ages of 18 and 64 from 2010 to 2014 who had not been diagnosed with diabetes when they entered the cohort. A patient is considered to be *established* if she seeks all primary care from PHHS, as quantified by an index visit between January 1, 2012, and June 30, 2013; and two or more outpatient visits between the index visit and December 31, 2014, where the index visit is defined as the first interaction of the patient with the hospital system (see Figure 4 in the main manuscript). The overall cohort consists of 62,721 patients. Table B1 shows the summary statistics for some key variables.

Table B1 Summary Statistics of the Complete Cohort

Characteristic	Mean	Standard Error
Age	46.51	0.026
BMI	30.82	0.020
BP Systolic	128.12	0.042
Male	0.34	0.001
White	0.14	0.001
Non-Hispanic Black	0.29	0.00
Hispanic	0.52	0.000
Alcohol	0.20	0.001
Tobacco	0.15	0.001

Appendix C. Details of the Simulation Study

The simulation consists of a hypothetical cohort of 50,000 patients, with characteristics described in Table 1 in the main manuscript. We simulate seven scenarios that differ only in the screening policy implemented. All scenarios are compared to a base scenario, in which we implement opportunistic screening—an ad-hoc approach in which the individual is screened whenever she visits the provider (the "opportunity"), and the doctor determines that the individual needs to undergo a screening test. In other words, the decision to screen a patient under opportunistic screening is at the discretion of the healthcare provider. For the simulation, we represent this decision by a random variable with a screening probability depending on the patient's unobservable health state. A provider is more likely to recommend screening for sicker patients or those who display symptoms.

The simulation is an aging loop in which patients enter at age 30 and leave either when they die or reach a simulation horizon of 50 years (see Figure C1). Below, we provide a detailed explanation of each part of the simulation loop.

C.1. Patients

We initialize each patient using the diabetes prevalence rate at each stage of the disease in the cohort, as described in Table C1. We also assign diabetic complications to the patients that already have diabetes using the prevalence rates from Chen et al. (2001), Howard et al. (2010), and Kahn et al. (2010). The development of these complications and the diabetes progression Markov models are shown in Figure C2 with prevalence rates for each of the states listed in Table C1.

C.2. Updating Health Status

At the beginning of each iteration, each patient's health status is updated according to the Markov models in Figure C2 using the progression rates listed in Table C2.

Figure C1 Simulation Loop for the Base Scenario

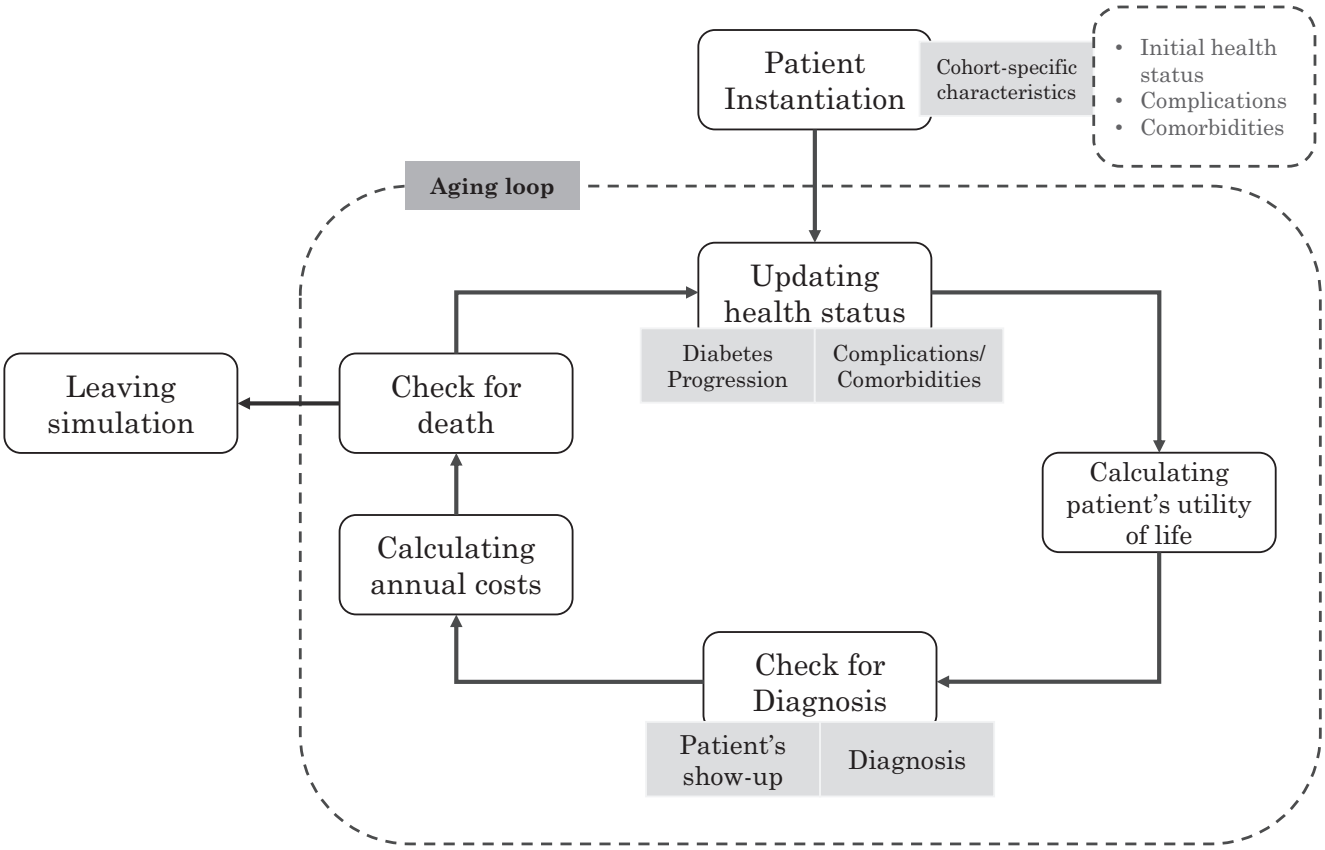

Table C1 Prevalence Rates of Diabetes and Its Complication Stages

Disease	Stages				
Diabetes	Healthy	Pre-diabetes	Diabetes		
	0.508	0.358	0.133		
Retinopathy	NDR	NPDR	PDR	ME	B
	0.5	0.2	0.05	0.25	0
Nephropathy	NNP	MA	PR	ESRD	CVD
	0.579	0.2	0.05	0.025	0.146
Neuropathy	NNR	SNR	LEA		
	0.7	0.3	0		

NDR: No Diabetic Retinopathy, NPDR: Non-proliferative Diabetic Retinopathy, PDR: Proliferative Diabetic Retinopathy, ME: Macular Edema, B: Blindness.
NNP: No Nephropathy, MA: Microalbuminuria, PR: Proteinuria, ESRD: End-Stage Renal Disease, CVD: Cardo Vascular Disease, DE: Death.
NNR: No Neuropathy, SNR: Symptomatic Neuropathy, LEA: Lower Extremity Amputation.

C.3. Calculating the Patient's Utility

At each iteration, the patient's utility of life is calculated using results from studies based on the EQ-5D index (Ackermann et al., 2009, Bahia et al., 2017, Zhang et al., 2012). The utilities used for different health conditions are provided in Table C3.

C.4. Diagnosis and Screening

To simulate a realistic screening process, we include two probabilities in each simulation iteration: (i) the probability of a patient visiting the healthcare provider, given their condition, and (ii) the probability of the provider detecting a complication in the patient during the visit. Both probabilities are affected by observable symptoms. That is, patients who experience symptoms are more likely to visit a healthcare provider, and the provider is more likely to recommend screening. Symptoms are related to the true health state of the patient and tend to intensify over time. For diabetes, the average time to diagnosis (TTD) from onset of the disease is approximately 10 years; for diabetes-related complications, TTD is usually 3 years (Lu et al., 2010). This implies that complications typically manifest—in a probabilistic manner —around TTD after disease onset.

We classify symptom severity into three categories: no symptoms, mild symptoms, and moderate to strong symptoms (typically associated with advanced stages of diabetes). We associate the annual visit and detection probabilities of 10%, 25%, and 55%, respectively, with these three symptom categories for the simulation. Although these probabilities are chosen based on discussions with the practitioners, they can be adjusted, depending on the characteristics of the patient (e.g., race). Because the cohort considered in our case is relatively homogeneous, we use a single set of probabilities.

Table C2 Progression Rates for Transitions in Diabetes and Its Complications

Disease	Transitions				
Diabetes	s_H to s_P	s_P to s_H	s_P to s_D		
	0.048	0.0328	0.0348		
Retinopathy	NDR to NPDR	NPDR to PDR	NPDR to ME	PDR to B	ME to B
	0.073	0.0103	0.1928	0.0148	0.033
Nephropathy	NNP to MA	MA to PR	PR to ESRD	ESRD to CVD	CVD to DE
	0.0267	0.1572	0.0042	0.5	0.2
Neuropathy	NNR to SNR	SNR to LEA	LEA to DE		
	0.0144	0.028	0.02		

Figure C2 Markov Progression Models of Diabetes and its Complications. NDR: No Diabetic Retinopathy, NPDR: Non-proliferative Diabetic Retinopathy, PDR: Proliferative Diabetic Retinopathy, ME: Macular Edema, B: Blindness. NNP: No Nephropathy, MA: Microalbuminuria, PR: Proteinuria, ESRD: End-Stage Renal Disease, CVD: Cardo Vascular Disease, DE: Death NNR: No Neuropathy, SNR: Symptomatic Neuropathy, LEA: Lower Extremity Amputation

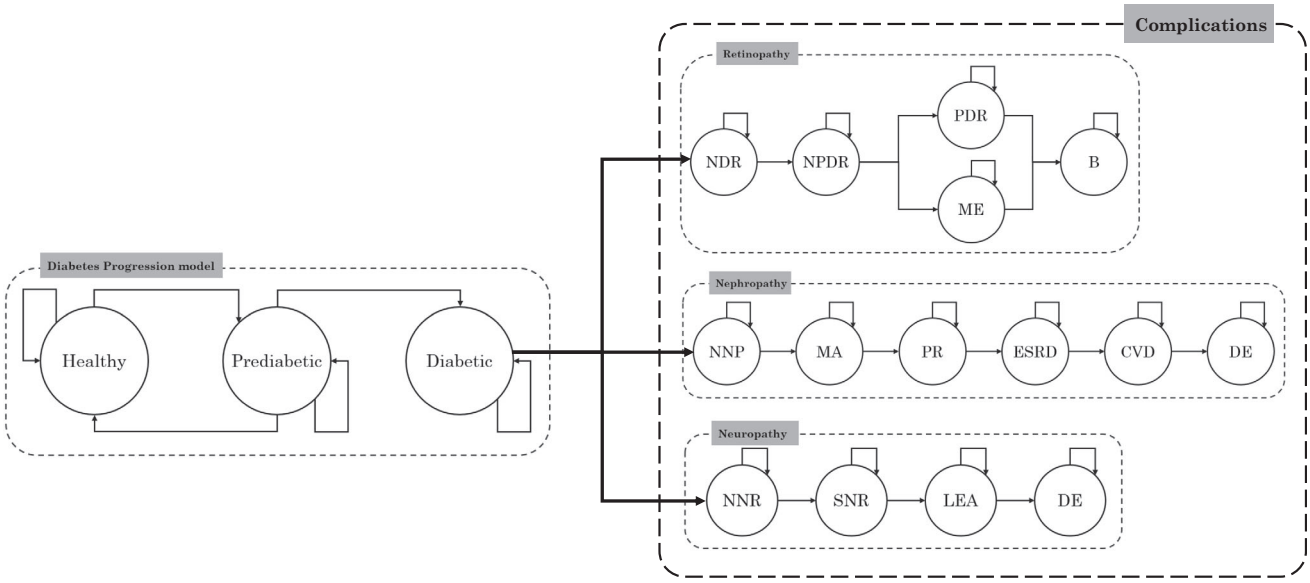

Table C3 Life Utilities for Different Health Conditions

Condition	Utility of life for living with the condition
Healthy	1
Pre-Diabetes	0.84
Diagnosed Diabetes	0.82
Undiagnosed Diabetes	0.8
Blindness	0.69
ESRD	0.61
CVD	0.63
LEA	0.59

For opportunistic screening, we also use symptom severity to determine the chance that the healthcare provider deems the symptoms severe enough to order screening. Generally, screening will be recommended for patients who display symptoms of the disease. For the guideline-based screening policies (e.g., SP45-3), the provider follows the policy every time the patient visits, although opportunistic screening is an option that the provider can always exercise.

For our proposed approach (SP-POMDP), the patient's initial belief state is set as prevalence values for each stage of diabetes (listed in Table C1). We simulate the observations by drawing from the observation matrix for the unscreened states, $\mathcal{O}_U$, based on patient's health state. The optimal policy is then used to determine the screening action and update the patient's current belief state for the next period.

C.5. Patient's Annual Costs

The total annual costs incurred per patient include screening and treating various diabetes-related complications (Chen et al., 2001, Howard et al., 2010, Kahn et al., 2010) (see Table C4 below). All costs are discounted at a rate of 3% per year.

Table C4 Costs Associated with Diabetes and its Complications

Type of cost	Detail	Costs
Visit and Screening	Visit	\$134
	Screening	\$192
Intensive Glycemic control	Drugs	\$862
	Outpatient	\$910
Conventional Glycemic control	Total	\$765
Microvascular complications	Blindness	\$1997
	Photocoagulation	\$2682
	ESRD	\$68,131
	LEA (per operation)	\$31,139
Macrovascular complications	CVD	\$2757
Intensive Hypertension Control	Drugs	\$686
	Outpatient	\$217
Conventional Hypertension control	Drugs	\$394
	Outpatient	\$149

C.6. Leaving the Simulation

At the end of each year, a patient will leave the simulation if she dies (including due to complications caused by diabetes); or if she reaches the simulation horizon of 50 years.

C.7. Simulation Summary

Below is a brief overall summary of the simulation implemented in this study.

Patient instantiation—this is done using the cohort-specific characteristics, shown in Table B1:

(i) **Initial health status**: This is randomly generated for each patient using a probability distribution over the three health states $(s_H, s_P, s_D) =$ (50.8%, 35.8%, 13.3%), listed in Table C1 (in Appendix C.1)., as the prevalence rates of each state of the disease. At this stage, no screenings have been performed.

(ii) **Complications and Comorbidities:** Patients who are diabetic can have complications or comorbidity based on the prevalence rates of diabetes complications (also listed in Table C1). For example, a diabetic patient at instantiation has a 20% chance of having nonproliferative diabetic retinopathy and a 25% chance of having macular edema.

Simulation

(I) Initiation
  (a) A patient enters the simulation at age 30.
  (b) The patient's current status (stage of the disease) is assigned with a probability distribution based on the cohort characteristics.
  (c) Each diabetic patient is assigned a diabetic complication using the probabilities provided in Table C2.

(II) Iteration for each patient (if the simulation horizon has not been reached and the patient is alive):
  (a) The patient will either stay in the same disease state or transition to another disease state based on the probabilities specified in Table C3 (in Appendix C.2).
  (b) The patient presents at a healthcare facility with a probability based on her current health status (i.e., sicker patients are more likely to visit the provider).
  (c) Given that the patient visits the provider, she gets screened according to the specific policy. The policies considered in the simulation are:
    (i) *Opportunistic screening:* The patients get screened based on a probability that depends on symptom severity. Sicker patients (and those who display symptoms) have a higher chance of being selected for screening by the provider.
    (ii) *SPXX-Y:* The patient receives the first screening at age XX, and the screening is repeated every Y years. For example, SP45-1 means that the earliest age at which the patient is screened is 45 and, subsequently, the screening is repeated every year.
    (iii) *SP-POMDP:* The patient gets screened following the framework developed in this study.
  (d) All costs and QALYs are calculated

(III) **End:** The simulation ends when the simulation horizon of 50 years is reached.

Additional notes

1. We assume that the patient is not aware of the used screening policy, and therefore it does not affect patients' probability of visiting the healthcare provider.
2. The simulated healthcare provider strictly follows the policy for screening recommendations, but the actual screening also depends on the patient's decision to have the screening performed (i.e., the uptake rate).

Appendix D. Table of Notation

T	Number of decision epochs/simulation horizon	s_t	State of POMDP model at decision epoch t
$\mathscr{S}$	Set of all possible states of the POMDP model	s_H	State: healthy
s_P	State: prediabetic	s_D	State: diabetic
s_{SH}	State: screened healthy	s_{SP}	State: screened prediabetic
s_{SD}	State: screened diabetic	s_Δ	State: death
a_t	Action taken at decision epoch t	$\mathscr{A}$	Set of all available actions
a_S	Action: recommend screening	a_N	Action: do not recommend screening
$\mathscr{P}$	Transition probability matrix of the POMDP model	$\eta_{progression}$	Coefficient for the effectiveness of intervention represented as a decrease in progression to diabetes
$\eta_{regression}$	Coefficient for the effectiveness of intervention represented as an increase in regression to health	Ω	Set of all possible observations
o_{SH}	Observation: screened healthy	o_{SP}	Observation: screened prediabetic
o_{SD}	Observation: screened diabetic	o_{PLR}	Observation: predicted as low risk
o_{PMR}	Observation: predicted as medium risk	o_{PHR}	Observation: predicted as high risk
$\mathscr{O}$	Observation probability matrix of the POMDP model	π	Belief state
Π	Belief space	λ	Discount rate
X_t	Hidden state at time t of the HMM	Y_t	Observation at time t for the HMM
$\mathscr{M}$	Time-dependent stochastic transition matrix of the HMM	$\mathscr{N}$	Emission transition matrix of the HMM
$n_j(y_t)$	Probability of observing observation y_t at time t for state j	q	Initial state distribution of the HMM
σ	Set of parameters of the HMM	Q	Quality-adjusted life year
C_s	Cost of diabetes screening process	C_D	Direct medical costs per year for a new-onset diabetes
C_P	Incremental direct medical costs per year for a patient with prediabetes	α_P	Annual utility decrease of living with prediabetes
α_{UD}	Annual utility decrease of living with undiagnosed diabetes	α_{DD}	Annual utility decrease of living with diagnosed diabetes
m	Age-adjusted mortality rate	m_D	Age-adjusted mortality rate for diabetes
$\zeta_{screening}$	Uptake rate of diabetes screening	l_d	Lifespan decrement due to diabetes
$\eta_{regression}$	Coefficient for the effectiveness of intervention represented as an increase in transition probabilities to healthy	$\eta_{progression}$	Coefficient for the effectiveness of intervention represented as a decrease in transition probability to diabetes
C'_S	Total cost of diabetes screening	ξ	Fraction of total patients that can be screened every period
δ	Lagrange Multiplier	δ'	Implied penalty

Notes

[1]http://www.ushistory.org/franklin/philadelphia/fire.htm
[2]https://www.niddk.nih.gov/health-information/diabetes/overview/tests-diagnosis/a1c-test
[3]Glucose level, also known as blood sugar, is different from A1c, although the two are connected. The blood sugar, measured in mg/dL, represents the concentration of glucose in the bloodstream at the time of the measurement. Glucose levels vary during the day, depending on food intake and activity level. Therefore, single glucose level measurements are not sufficient indicators to determine if a patient has Dysglycemia. A1c measures the percentage (%) of red blood cells with a sugar coating and reflects an individual's average blood sugar over the past 2–3 months. For screening, diagnosis, and management purposes, clinicians typically utilize the A1c percent result. While one can check blood glucose levels at home (e.g., using a blood sugar meter), such devices cannot check for A1c, which requires a laboratory test.
[4]The ADA guidelines recommend screening all asymptomatic adults who are overweight and who have one or more diabetes risk factors. For all others, screening should begin at age 45 and repeated at (a minimum of) 3-year intervals. ADA also recommends screening for prediabetes beginning at age 45 for all people (American Diabetes Association, 2019).
[5]δ' can be interpreted as the cost by which the screening process cost would need to be inflated in the optimization, so the policy focuses only on the most important patients using the available number of screenings.
[6]For example, Zraiaa (2010) notes that "…given a sequence of observations, or set of such sequences, …(the problem of finding) the most likely set of model parameters…is solved by the Baum-Welch algorithm, using standard techniques of statistical inference."
[7]Predictive modeling in clinical research is a fast-evolving field, and better risk predictors or more powerful prediction models may become available. Our framework is able to take full advantage of these enhanced models.
[8]The mean (St. Dev) of the number of observations (A1c tests) per patient is 2.5 (3.34).
[9]We implement PBVI using the popular *pomdp-solve* via the R (R Core Team 2018) package called "pomdp." (Kamalzadeh and Hahsler 2019)
[10]The figure of $2.6 million is derived as follows. Difference in ICER per patient between SP-POMDP and SP45-3 is $31,155–$20,426 = $10,729 (from Table 4). Thus, total savings for 12,000 patients over 50 years is 12,000 × 10,279 = $128,748,000, translating into an annual savings of $128,748,000/50 = $2,574,960.

[11]Our assumption stems from the fact that (i) safety net hospitals provided 17.4% of uncompensated care and 23% of charity care, even though they make up about 5% of US hospitals (Masterson 2019); (ii) safety-net hospitals accounted for 33% of inpatient stays (Sutton et al., 2006); and (iii) according to the US Census Bureau, 8.5% of the population is uninsured (https://www.census.gov/library/publications/2019/demo/p60-267.html).

[12]To illustrate, consider the case of macrovascular events. Implementing SP-POMDP saves three more macrovascular events for every 1000 patients compared to SP45-3 (= 23-20 from Table 4). Given that each macrovascular event is associated with $2757 (see Appendix C.5), savings for 33 million patients over 50 years can be calculated as follows: $(3/1000 \times 33{,}000{,}000 \times 2{,}757) = \$272{,}943{,}000$. This translates into annual savings of $\$272{,}943{,}000/50 = \$5{,}458{,}860$. Note that (i) savings from early diagnosis of diabetes incorporate the fact that utility of living with undiagnosed diabetes is 0.8 (= 1 - α_{UD}; see Table 3) and (ii) savings from reduction in preventable deaths incorporate the fact that diabetes reduces life expectancy by an average of 8.5 years for a 50 years old, which is the average age of a diabetic patient in our cohort (see Table 1); source: https://www.webmd.com/diabetes/news/20101201/diabetes-cuts-years-off-life-span-of-americans.

[13]The dataset consists of over 150,000 A1c values.

[14]This is particularly true for patients who are at the threshold; patients who have an A1c value of, say, 6.4% may be classified as diabetic when according to the ADA guidelines they should be considered prediabetic.

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