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Screening for preclinical Alzheimer's disease: Deriving optimal policies using a partially observable Markov model

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Abstract Alzheimer's Disease (AD) is believed to be the most common type of dementia. Even though screening for AD has been discussed widely, there is no screening program implemented as part of a policy in any country. Current medical research motivates focusing on the preclinical stages of the disease in a modeling initiative. We develop a partially observable Markov decision process model to determine optimal screening programs. The model contains disease free and preclinical AD partially observable states and the screening decision is taken while an individual is in one of those states. An observable diagnosed preclinical AD state is integrated along with observable mild cognitive impairment, AD and death states. Transition probabilities among states are estimated using data from Knight Alzheimer's Disease Research Center (KADRC) and relevant literature. With an objective of maximizing expected total quality-adjusted life years (QALYs), the output of the model is an optimal screening program that specifies at what points in time an individual over 50 years of age with a given risk of AD will be directed to undergo screening. The screening test used to diagnose preclinical AD has a positive disutility, is imperfect and its sensitivity and specificity are estimated using the KADRC data set. We study the impact of a potential intervention with a parameterized effectiveness and disutility on model outcomes for three different risk profiles (low, medium and high). When intervention effectiveness and disutility are at their best, the optimal screening policy is to screen every year between ages 50 and 95, with an overall QALY gain of 0.94, 1.9 and 2.9 for low, medium and high risk profiles, respectively. As intervention effectiveness diminishes and/or its disutility increases, the optimal policy changes to sporadic screening and then to never screening. Under several scenarios, some screening within the time horizon is optimal from a QALY perspective. Moreover, an in-depth analysis of costs reveals that implementing these policies are either cost-saving or cost-effective.

Keywords Alzheimer's disease, Screening, Partially observable Markov decision process, Optimal policy, Operations research

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Highlights

- We develop a partially observable Markov decision process (POMDP) model to compute optimal screening policies for Alzheimer's disease maximizing expected total quality-adjusted-life-years.
- Our POMDP model incorporates preclinical stages of the disease and is built upon a biomarker-based test.

– We study the impact of the quality of a potential intervention on model outcomes when applied to individuals with different risk profiles who are diagnosed with preclinical AD.
– We find that an intervention with positive characteristics leads to optimal policies that include multiple episodes of screening and is either cost-saving or cost-effective.

1 Introduction

According to the World Alzheimer Report 2018 delivered by Alzheimer's Disease International, there are over 50 million people suffering from dementia in the world, and the number is projected to increase to more than 152 million by 2050 [1]. The total annual cost of dementia is estimated to be a trillion US dollars per year and is expected to double by 2030. Alzheimer's Disease (AD) is believed to be the most common type of dementia, accounting for two-thirds of the total with a greater proportion in the higher age ranges.

AD is a disease with an insidious onset. Difficulties in retrieving information on recent experiences (impaired episodic memory), problems with finding locations and orientation (declining visuospatial skills), and word-finding difficulties are among the early symptoms of the disease. As AD progresses, there is a general decline in multiple cognitive functions related to daily activities. The Mini Mental State Examination (MMSE) [2], a test that consists of thirty questions each worth one point, is used widely in clinical practice to assess cognitive abilities. Individuals scoring below a certain cutoff point are likely to be demented. A questionable MMSE score typically leads to further testing and staging. Clinical Dementia Rating (CDR) is a commonly used instrument for the staging of AD and related dementias. Assessments are made in six domains of cognitive and functional performance: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care, using information obtained through a semi-structured interview of the patient and a reliable informant [3]. The clinical assessment of the patient may be accompanied by a diagnostic workup that involves neuroimaging techniques such as Positron Emission Tomography (PET) scans and Magnetic Resonance Imaging (MRI) as well as assessment of biomarker levels observed in cerebrospinal fluid (CSF) inspection.

At the time being, AD is not curable. As the disease progresses through the CDR stages of mild, moderate to severe, the patients become increasingly more dependent on caregivers. There are two classes of medications approved for the treatment of symptoms. The first class is acetylcholinesterase inhibitors (AChEIs) with three members: donepezil, galantamine, and rivastigmine. The second class is the glutamate modulator with a single member: memantine. The approved drugs have positive effects on cognition, behaviour and activities of daily living. Some studies indicate that medication use may slow down disease progression. The reader may refer to the reviews of Kaduszkiewicz et al. and Kirby et al. for further details about the effectiveness of AChEIs and memantine respectively [4, 5].

Despite its prevalence, there are currently no population screening policies in any country for AD, unlike, for instance, certain types of cancer. Screening has the goal of distinguishing individuals that may have a condition so that early intervention can lead to benefits. As there is no cure or established preventive measures for AD, benefits of screening have been difficult to justify. The idea of screening for AD and its potential benefits are discussed in various platforms such as in Leon Thal Symposium series [6] and the National Alzheimer's Project Act (NAPA) in the U.S. [7]. However these are only drafts of possible national plans. The screening question has been investigated by researchers using various modeling approaches. Two simulation based studies found screening beneficial [8, 9]. Weimer and Sager's Monte Carlo simulation analyzes the costs and benefits of screening using MMSE as the indicator of cognitive decline [8]. Getsios et al. employ a discrete event simulation framework using data from a donepezil treatment research conducted in the U.K. [9]. They build an indicator that combines MMSE score for cognition, Neuropsychiatric Inventory (NPI) score for behavior and Activities of Daily Living and Instrumental Activities of Daily Living (ADL and IADL) scores for function domains. Both studies find that screening results in cost-savings and health benefits for the individual and the society. A cohort model with two different treatment scenarios depending on the MMSE course over time developed by Barnett et al. also proposes early screening so that interventions can be cost effective [10]. Dixon et al. compared the results of a hypothetical one-time screening program with a no screening program on people aged 75 or older in England and Wales and found that a screening program could be cost effective if treatments and social care interventions were to be more effective [11]. Yu et al. modeled AD progression using a Markov model and investigated cost-effectiveness of a screening program in Korea [12]. Based on a two-stage screening process where treatment starts immediately once the individual is screened positive, the authors analyzed the sensitivity of the cost-effectiveness of a nationwide screening program. Their results suggest that the parameter having the most im-

pact on cost-effectiveness is treatment effectiveness. In a recent study, Michaud et al. develop a state-transition model to project lifetime Quality Adjusted Life Years (QALYs) and costs for a cohort of 65-year-old MCI patients in the U.S. [13]. They design and compare four different test-and-treat policies based on the patient's risk level with two treatment policies (treat everyone vs. no one). They find that testing and treating low-risk MCI patients is the most cost-effective strategy and the level of treatment effectiveness is the most critical parameter that affects the results. Finally, Önen et al. build a Markov Decision Process (MDP) model with the objective of optimizing a combination of costs and QALYs where the screening decision is based on the MMSE score [14]. Their model finds never screening as the optimal outcome under current and similar treatment effectiveness levels. Through extensive sensitivity analyses, they indicate the levels of treatment effectiveness needed for a change in the optimal policy in favor of screening.

The limitations associated with interventions conducted after cognitive deficiencies associated with AD become clinically observable have led researchers to focus on preclinical aspects of the disease. It is now known that years long amyloid deposition lead to amyloid plaques which, most of the time, precede neurofibrillary tangles that seem to lead to neurodegeneration. In 2011, the joint workgroups of National Institute on Aging (NIA) and the Alzheimer's Association (AA) revised and updated the diagnostic criteria and guidelines for diagnosis proposed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) in 1984 [15–19]. The most crucial difference was the elimination of equating this decades-long disease with its terminal dementia stage. New definition of AD is a continuum that can be diagnosed with the help of biomarkers even before the subtlest clinical symptoms appear. The introduction of biomarker testing enabled this inevitable, though very belated development.

The new criteria sets define three stages, starting from the pre-clinical AD, progressing first to the initial clinical stage that is MCI due to AD, and then to the late clinical stage that is AD dementia. The preclinical AD stage is further subdivided into three as Asymptomatic amyloidosis, which corresponds to amyloid positivity either on PET or in CSF; Stage 1 plus neurodegeneration referring to either tau positivity or hippocampal atrophy on MRI or hypometabolism on PET; Stage 2 plus subtle cognitive decline referring to subtle decline from the previous level of cognitive functioning, not yet fulfilling MCI criteria [18]. Thus, in addition to conventional neuroimaging biomarkers, the three CSF biomarkers were also introduced: the first is the amyloid-β fragment ($A\beta_{1-42}$) of the membrane-spanning amyloid precursor protein and the second and third are two measures of the microtubule-associated protein tau (MAP-τ): total tau (t-τ) and phospho-tau (p-τ). The fibrillary form of the amyloid-β fragment is the main constituent of parenchymal deposits known as amyloid plaques (APs), while the paired helical filaments composed of pathologically hyperphosphorylated tau is the main constituent in the intraneuronal deposits known as the neurofibrillary tangles (NFTs). APs are the result of years-long amyloid deposition, which is a pre-clinical phenomenon and culminates in the NFT formation still in the pre-clinical phase [16]. On the other hand, NFTs seem to be the primary driver of neurodegeneration, which in turn leads to earliest subjectively reported cognitive symptoms in the third preclinical stage and, finally, objectively documented ones in the first clinical stage that is MCI. Figure 1 illustrates the relationship between biomarkers and clinical stages by depicting progression from normal to abnormal levels of biomarkers, cognition and clinical function as a cascade.

The NIA-AA workgroup recently updated and unified their 2011 criteria sets and named the new proposal as the "Research Framework" [19]. The major perspective change in this new set seems to be the almost complete revocation of the syndromal approach to AD and defining it as a pure biological construct instead. Grouping the biomarkers into one of amyloid deposition (CSF $A\beta_{1-42}$ or amyloid PET), τ deposition (CSF p-τ or tau PET) or neurodegeneration (CSF t-τ, fluorodeoxyglucose PET or anatomic MRI) they introduced their biological construct of AD as the AT(N) system. In this new system, amyloid positivity by itself automatically includes the individual in the "Alzheimer's continuum," regardless of the state of other biomarkers and also regardless of the clinical stage, which are defined as cognitively unimpaired (CU), MCI and dementia. In this framework, only a CU individual with A-T-(N)- state is called a "normal" individual. A+ qualifies an individual for the "Alzheimer's pathological change" (APC) state even when T and (N) are both negative. The A+T+ case is associated with AD state, regardless of the state of (N). The Alzheimer's continuum includes an "APC with Non-Alzheimer's Pathology" (NAP) state when the individual is A+T-(N)+. A- along with a positive T and/or N marker is classified as NAP. All these classifications are made regardless of the clinical stage. This classification scheme is not intended for clinical practice yet, hence the name "research framework". In [20], Frisoni et al. emphasize the necessity of

using biomarkers in the diagnosis of AD. They describe the barriers that hamper their widespread use in clinical practice, such as difficulties in reimbursement and describe a roadmap for adaptation of biomarkers-based tests to improve their utilization in clinical practice.

Driving drug trials to a new type of research based on biomarkers became a hope for discovering possible treatment plans for AD before symptoms appear [21]. In other words, primary or secondary prevention strategies for the emergence of the APC and AD in CU individuals and tertiary prevention and treatment for AD-MCI and AD dementia are saught [18]. A large proportion of these trials are based on the amyloid hypothesis of AD which was introduced in [22] for the first time. According to this hypothesis, if amyloid beta accumulation is identified early and eliminated, the progression to AD may be stopped. Furiak et al. put the hypothesis to test by building a simulation model that is based on screening asymptomatic individuals in the population who are 55 years or older. Inevitably, they had to make an assumption regarding treatment of positively screened individuals and they assumed that the treatment slowed down disease progression by 50% [23]. They reported a decrease of 20 AD cases per 1000 screened. In another simulation study, Furiak et al. consider rescreening options every five or ten years until age 80 or death [24]. In terms of number of cases avoided in the population, screening every ten years forever delivers the best outcome.

In this paper, we take the Alzheimer's continuum as a basis and build a partially observable Markov decision process (POMDP) model to determine optimal screening programs for AD. The focus is on the preclinical phase of the disease and biomarker-based screening is considered. We use the Adult Children Study longitudinal database from the Knight Alzheimer's Disease Research Center of the Washington University School of Medicine in St. Louis to estimate transition probabilities that involve preclinical states. The sensitivity and specificity of the screening test is also estimated using the same data set. Our model incorporates a possible intervention plan (medical and/or lifestyle modifications) if an individual is preclinically diagnosed with APC. The effect of this therapeutic or lifestyle intervention on disease progression and model outcomes is investigated parametrically because there are several studies that report potential positive impacts of different intervention plans on the progression of AD [10, 25].

The importance of formulating medical and health care decision problems using the POMDP framework was first discussed in Smallwood et al. [26] where the unobservable states were used to indicate the patient's disease status. Since then, screening models for several types of cancer, diabetes and infectious diseases have been built using POMDPs [27–29]. The POMDP setting is crucial in our modeling approach in order to address the preclinical stages of the disease and our study is the first one that optimizes expected QALYs and determines screening policies for Alzheimer's disease by taking the preclinical phase of the disease into account. We also provide evidence that implementing these policies may be cost-effective and even cost-saving while expected QALYs are optimized. Hence the results of our work may be used to implement screening policies for AD and ultimately improve societal health and healthcare costs. The organization of the paper is as follows. We present our model and go over data requirements for building an instance of the model in Section 2. Computational results and related analyses are given in Section 3. Finally we conclude and give further research directions in Section 4.

2 Methods

2.1 The Model

The objective of screening programs is to detect individuals with a specific disease at the earliest stage possible. Hence we focus on establishing screening programs for individuals who have not encountered symptoms of MCI or clinical AD, i.e CU individuals. We build a discrete-time, finite-horizon POMDP model in which the preclinical stage of the disease is captured by the unobservable states (or core states). By definition, the current (true) state of the process cannot be known as far as the core states are concerned and there can only be a belief associated with it based on observations. Given the observation, the probability of being in a certain core state is assumed to be known. Thus there is an information matrix representing the conditional probabilities relating the observations to the possible true states of the process. When POMDPs are applied to medical decision making settings that involve diagnostic tests, the test result becomes the observation that leads to belief updates. Therefore the sensitivity and specificity of the test are utilized in constructing the information matrix.

Figure 2 illustrates our model framework where partially observable states associated with CU clinical stage are within the dashed box. Transitions from any state to death state (absorbing state) are possible, we do not illustrate transitions to this state in Figure 2 for readability purposes.

We assume that a decision is made regarding whether or not to give a screening test to an individual who is in one of the core states at the beginning of each year.

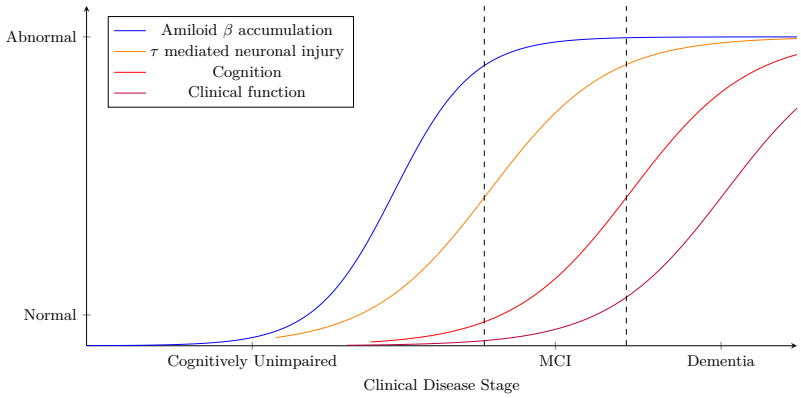

Fig. 1: Simplified hypothetical model of dynamic biomarkers of AD as presented by Jack et al. [16]

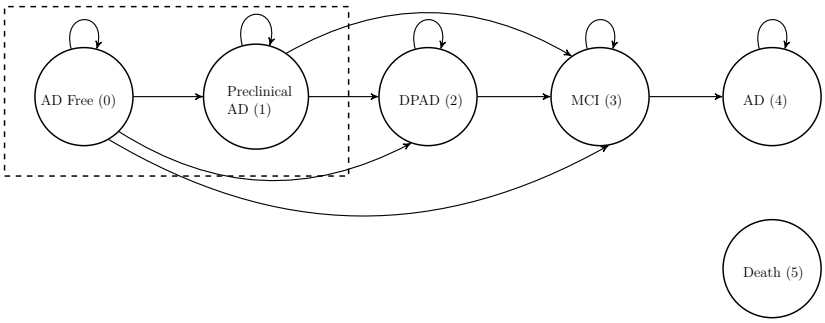

Fig. 2: The POMDP Model Framework

The screening test is based on CSF inspection and depending on the Amyloid beta biomarker $A\beta_{1-42}$ level observed, it is classified as either positive or negative. The screening test is not perfect and its accuracy is reflected by its sensitivity and specificity levels. If the screening test result is positive, the individual moves to a completely observable "diagnosed preclinical AD" state, referred to as the "DPAD" state. If the test result is negative, the beliefs associated with the partially observable states are updated. If a screening test is not conducted, we assume no observation can be made and the beliefs are updated accordingly. The individual continues within normal course of aging and possible disease progression. Throughout the whole process, an individual can develop MCI, progress to clinical AD or may die from all possible causes with non-negative probability.

The notation used in the model is as follows:

- t: Decision epochs, $t = 0, 1, ..., T < \infty$. Our cycle time is one year and t is the number of years above a predetermined age.
- s_t: State of the individual at the beginning of decision epoch t. $s_t \in S = \{0, 1, 2, 3, 4, 5\}$ where 0 stands for the AD free normal state (corresponding to A-T-N- in the research framework), 1 stands for the preclinical stage of the disease, 2 refers to DPAD, 3 refers to MCI, 4 is clinical AD and 5 is the death state. The first two states are partially observable whereas the rest of the states are fully observable. The subset containing the partially observable states is denoted as $S^{PO} = \{0, 1\}$.
- a_t: Action chosen at decision epoch t, $a_t \in A = \{N, Y\}$, where N stands for not to screen and Y to screen. These actions apply to an individual who may be in either one of the partially observable states.
- O_N: Observation space when action is not to screen. We assume that no observation is made when the screening test is not performed, i.e. $O_N = \{\emptyset\}$.
- O_Y: Observation space when action is to screen. It represents the space of screening test results. When the individual undergoes screening, the possible outcomes of the screening test are recorded as either $A\beta^-_{1-42}$ or $A\beta^+_{1-42}$. Therefore we set $O_Y = \{-, +\}$.
- o_t: Observation of the screening test at time t, $o_t \in O_Y$.
- Π_t: Belief vector where each entry $\pi_t(s)$ defines the belief that the individual is in state s at the begin-

ning of decision epoch t.

$$\Pi_t = [\pi_t(0), \pi_t(1), \pi_t(2), \pi_t(3), \pi_t(4), \pi_t(5)]$$

with $\sum_{s \in S} \pi_t(s) = 1$.

- b_t: Belief vector over partially observable states where

$$b_t = [b_t(0), b_t(1)]$$

This vector represents the belief that the individual is in one of the partially observable states. It is equal to the first two entries of π_t. If $b_t \neq [0, 0]$, then $\sum_{s \in S^{PO}} b_t(s) = 1$. Astrom et al. proved that $b_t(s)$ is a sufficient statistic of the entire history of the individual [30].

- P_t^N: State transition probability matrix at the beginning of time t when action is not to screen. Each entry of this matrix $p_t^N(s'|s)$ represents the probability that the individual will be in state $s' \in S$ at the beginning of decision epoch $t+1$ given that he/she was in state $s \in S$ at the beginning of decision epoch t and a no screening action was taken.
- $P_t^{(Y,o)}$: State transition probability matrix at the beginning of time t when action is to screen. Each entry $p_t^{(Y,o)}(s'|s)$ represents the probability that the individual will be in state $s' \in S$ at the beginning of decision epoch $t+1$ given that he/she was in state $s \in S$ at the beginning of decision epoch t and a screening action was taken which resulted in observation o. For example $p_t^{(Y,-)}(3|1)$ represents the probability that an individual in state 1 at the beginning of period t will be in state 3 at the beginning of period $t+1$ when the screening action is conducted and $A\beta_{1-42}^-$ is observed. Note that for $s \in S \setminus S^{PO}$, transition probabilities do not depend on observations and will be the same for different versions of transition probability matrices.
- Q_t: Information matrix representing the probability of observing a screening test result given the individual is in state $s \in S^{PO}$ when the action chosen is to screen. For example the entry $q_t(+|1) \in Q_t$ represents the probability that the observation of the test is $o = +$ at decision epoch t and the individual's true health state is $s = 1$. As such, this matrix is derived from the sensitivity and the specificity of the screening test.
- $r_t^N(s)$: Immediate reward gained between beginnings of epochs t and $t+1$, when the individual is in state $s \in S$ and action $a = N$ is chosen at the beginning of decision epoch t. The reward is a function of an individual's QALY at that state.
- $r_t^Y(s)$: Immediate reward gained between epochs t and $t+1$ when the individual is in state $s \in S$ and action $a = Y$ is chosen at the beginning of decision epoch t. For $s_t \in S \setminus S^{PO}$, $r_t^Y(s) = r_t^N(s) = r_t(s)$. For $s \in S^{PO}$, the reward is a function of an individual's QALY at that state and also QALY degradation due to possible complications of the screening test. It is computed via: $r_t^Y(s) = \sum_{o \in O_Y} q_t^Y(o|s) r_t^{Y,o}(s)$, where $r_t^{(Y,o)}(s)$ reflects the immediate reward received at state s with an observation o at time t.
- h: Disutility of the screening test.
- l: Disutility of the intervention conducted while in DPAD state.
- $V_t(\Pi_t)$: Value function that gives the expected remaining reward when the belief vector is Π_t.
- $V_t(s)$: Value function that gives the expected remaining reward when the individual is in state s at the beginning of decision epoch t.
- γ: Discount factor, $0 \leq \gamma \leq 1$.

The belief vector for all $s' \in S^{PO}$ at the beginning of epoch $t+1$ is updated via Bayes rule:

$$\tilde{b}_{t+1}(s'|Y,o) = \tilde{b}^Y_{b_t,o}(s') = \frac{\sum_{s \in S^{PO}} b_t(s) p_t^{(Y,o)}(s'|s) q_t(o|s)}{\sum_{s \in S^{PO}} b_t(s) q_t(o|s)}$$

$$\tilde{b}_{t+1}(s'|N) = \tilde{b}^N_{b_t}(s') = \frac{\sum_{s \in S^{PO}} b_t(s) p_t^N(s'|s)}{\sum_{s \in S^{PO}} b_t(s)}$$

$$= \sum_{s \in S^{PO}} b_t(s) p_t^N(s'|s) \ as \sum_{s \in S^{PO}} b_t(s) = 1$$

We need to normalize $\tilde{b}_{t+1}(s'|Y,o)$ and $\tilde{b}_{t+1}(s'|N)$ because belief states are only defined over $s \in S^{PO}$, hence:

$$b_{t+1}(s|Y,o) = b^Y_{b_t,o}(s) = \frac{\tilde{b}^Y_{b_t,o}(s)}{\sum_{s' \in S^{PO}} \tilde{b}^Y_{b_t,o}(s')}$$

$$b_{t+1}(s|N) = b^N_{b_t}(s) = \frac{\tilde{b}^N_{b_t}(s)}{\sum_{s' \in S^{PO}} \tilde{b}^N_{b_t}(s')}$$

The sequence of events of our model are summarized in Figure 3.

Let $V_t^*(\pi_t)$ represent the expected QALYs the individual can attain when the current belief vector is π_t. Because there is no action to be taken for $s \in S \setminus S^{PO}$ and no transitions exist from completely observable states to partially observable ones in our setting, we can write the value functions of the completely observable states as follows:

$$V_t^*(s) = r_t(s) + \gamma \sum_{s' \in S \setminus S^{PO}} p_t(s'|s) V_{t+1}^*(s')$$

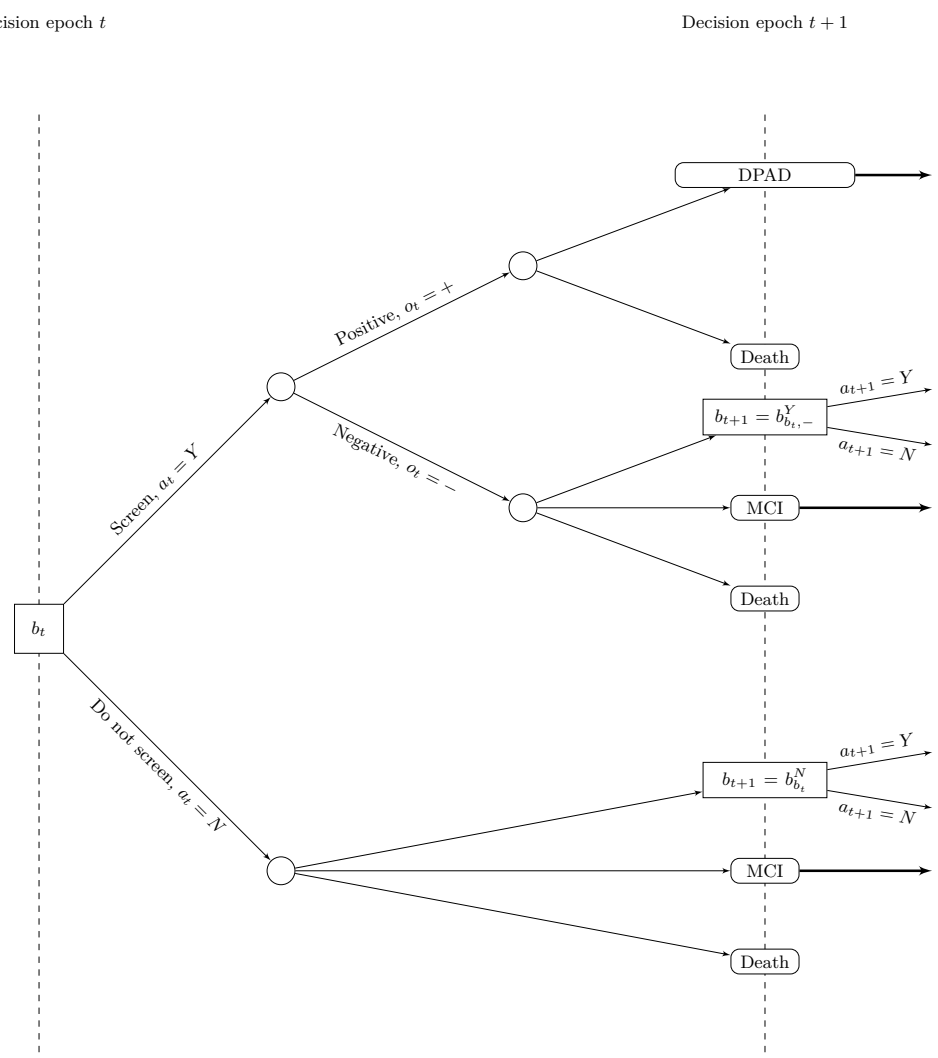

Fig. 3: Sequence of Events

For a given vector π_t we have:

$$V_t^*(\pi_t) = \begin{cases} \max\{V_t^*(b_t, N), V_t^*(b_t, Y)\}, \ \textit{for } b_t \neq [0,0] \\ V_t^*(2), \ \textit{for } \Pi_t = [0,0,1,0,0,0] \\ V_t^*(3), \ \textit{for } \Pi_t = [0,0,0,1,0,0] \\ V_t^*(4), \ \textit{for } \Pi_t = [0,0,0,0,1,0] \\ 0, \qquad \textit{for } \Pi_t = [0,0,0,0,0,1] \end{cases}$$

where

$$\begin{aligned} V_t^*(b_t, N) = \sum_{s \in S^{PO}} b_t(s) \Big(& r_t^N(s) \\ & + \gamma \Big(\sum_{s' \in S^{PO}} p_t^N(s'|s) V_{t+1}^*(b_{b_t}^N) \\ & + \sum_{s' \in S \setminus S^{PO}} p_t^N(s'|s) V_{t+1}^*(s') \Big) \Big) \end{aligned}$$

$$\begin{aligned} V_t^*(b_t, Y) = \sum_{s \in S^{PO}} b_t(s) \Big(& q_t(-|s) \Big(r_t^{(Y,-)}(s) \\ & + \gamma \Big(\sum_{s' \in S^{PO}} p_t^{(Y,-)}(s'|s) V_{t+1}^*(b_{b_t,-}^Y) \\ & + \sum_{s' \in S \setminus S^{PO}} p_t^{(Y,-)}(s'|s) V_{t+1}^*(s') \Big) \Big) \\ & + \sum_{s \in S^{PO}} b_t(s) \Big(q_t(+|s) \Big(r_t^{(Y,+)}(s) \\ & + \gamma \Big(\sum_{s' \in S^{PO}} p_t^{(Y,+)}(s'|s) V_{t+1}^*(b_{b_t,+}^Y) \\ & + \sum_{s' \in S \setminus S^{PO}} p_t^{(Y,+)}(s'|s) V_{t+1}^*(s') \Big) \Big) \Big) \end{aligned}$$

Since we assume that a person who is screened and has a positive test result makes a transition to the completely observable DPAD state (2), $p_t^{(Y,+)}(s'|s) = 0, \forall s' \in S^{PO}$.

Then, $V_t^*(b_t, Y)$ becomes:

$$
\begin{aligned}
V_t^*(b_t, Y) = \sum_{s \in S^{PO}} b_t(s)\Big(q_t(-|s)\Big(r_t^{(Y,-)}(s) \\
+\gamma\Big(\sum_{s' \in S^{PO}} p_t^{(Y,-)}(s'|s) V_{t+1}^*(b^Y_{b_t,-}) \\
+ \sum_{s' \in S \setminus S^{PO}} p_t^{(Y,-)}(s'|s) V_{t+1}^*(s')\Big)\Big)\Big) \\
+ \sum_{s \in S^{PO}} b_t(s)\Big(q_t(+|s)\Big(r_t^{(Y,+)}(s) \\
+\gamma\Big(\sum_{s' \in S \setminus S^{PO}} p_t^{(Y,+)}(s'|s) V_{t+1}^*(s')\Big)\Big)\Big)
\end{aligned}
$$

Theoretically, these value functions can be computed using dynamic programming techniques like backward induction of value iteration. However, the number of action-observation histories grows exponentially which makes this problem difficult to solve. This phenomenon is known as "the curse of history" [31]. Smallwood and Sondik showed that the optimal value function is piecewise linear and convex for all $t \leq T$ and the value function $V_t^*(b_t)$ can be represented using a finite set of vectors called alpha vectors in a finite horizon model [26]. The result below states that this is valid for our model as well.

Theorem 1 *The optimal value function $V_t^*(b_t)$ is piecewise linear and convex for all $t \leq T$, and hence can be expressed as the maximum of a finite number of linear functions. That is, $V_t^*(b_t) = \max_{0 \leq i \leq |\alpha_t|} \sum_{s \in S^{PO}} b_t(s)\alpha_t^i(s)$ for some $\alpha_t = \{\alpha_t^0, \alpha_t^1, ...\}$ where $\alpha_t^i = [\alpha_t^i(s)]_{s \in S^{PO}}$ are called the α-vectors.*

The proof of this theorem can be found in Appendix A. Based on this result, then, finitely many α-vectors help define the value function. Indeed, generating all α-vectors and finding the one(s) that maximizes the value function will be sufficient to solve the system of equations and find the optimal policy. The drawback of this approach is the exponential growth in the number of α-vectors as the problem size grows, leading to computational intractability. In such cases, heuristic approaches may be necessary. In our case, our model is small and simple enough to be solved optimally with this approach with reasonable effort when reinforced with a reduction technique developed by Eagle [32] and as stated in Appendix D.

2.2 Building a Model Instance

In this section we describe how we build an instance to implement our model. We choose our time horizon to be 50 years, so $T = 49$, and discount factor is $\gamma = 0.98$. When $t = 0$, the starting age of an individual is 50 years as in the work of Jack et al. [33].

2.2.1 Transition probability matrices

There are different versions of transition probability matrices based on the screening decision and resulting observation. The general structure of the matrices is as follows:

$$
P_t^{\cdot,\cdot} = \begin{pmatrix}
\cdot & \cdot & \cdot & \cdot & 0 & \cdot \\
0 & \cdot & \cdot & \cdot & 0 & \cdot \\
0 & 0 & \cdot & \cdot & \cdot & \cdot \\
0 & 0 & 0 & \cdot & \cdot & \cdot \\
0 & 0 & 0 & 0 & \cdot & \cdot \\
0 & 0 & 0 & 0 & 0 & 1
\end{pmatrix}
$$

The square on the lower right represents the transitions among completely observable states, including the death state. The double-lined rectangle in the upper right represents transitions from partially observable states to death. These transition probabilities do not depend on actions and observations and they are taken from the literature. The dashed lined rectangles represent the transitions from and to the DPAD state. This state is also observable. We assume that some lifestyle or therapeutic intervention takes place at this state. However, there are no established interventions or associated transition probabilities that we can borrow from the literature. Therefore these probabilities will be parameterized to reflect varying effectiveness levels of possible interventions.

Transition probabilities from partially observable states to state 4 are equal to 0. This means individuals may not proceed from a CU state directly to clinical AD within one year. Our data set supports this assumption. The transition probability matrices have 0 values on their lower triangles since AD is a disease that has always a forward progression.

The rectangles with thick borders represent the transitions involving the core states. The transition probabilities between the two core states and from these states to the MCI state are estimated by applying a multi-state Markov (MSM) model on a data set that comes from the Adult Children Study of the Knight Alzheimer's Disease Research Center of the Washington University School of Medicine in St. Louis. [1] We

[1] In the Adult Children Study, the Knight Alzheimer's Disease Research Center of the Washington University School of Medicine in St. Louis aimed to gather a cohort of cognitively normal middle age individuals to observe the progression of biomarkers before symptoms of AD appear. The project is still recruiting volunteers to become a complete longitudinal database for future promising research. The participants are

denote the estimated matrix as MSM_t. MSM models are widely used in modeling disease progression [36–40]. An MSM model requires observing the state of individuals at particular points on a continuous time basis from which a maximum likelihood transition intensity matrix is estimated. MSM models may include covariates. The intensity rates can then be translated into transition probabilities. More detailed information on MSM methodology can be found in [37]. Our data set contains 169 participants, (112 women, 57 men) aged between 43 and 82 years at their baseline. All baseline CDR assessments of these participants are 0. For each participant, there are up to 4 CSF test results with a total of 412 observed $A\beta_{1-42}$ values. Lumbar puncture dates are usually 3 or 4 years apart for the same participant. The MMSE score of participants is between 24 and 30 while the CDR is either 0 or 0.5 with 0.5 occurring 4 times. The most recent CSF record belongs to 2013 while the first records are from 2003. We use R's MSM package [41] to estimate the transition intensities. Each participant's characteristics (APOE genotype, date of birth, gender) are recorded along with $A\beta_{1-42}$, $t-\tau$ and $p-\tau$ results. These were introduced as potential covariates in the MSM model and only age turned out to be significant. To simplify, we pool the age in three ranges: the first range covering ages 50 to 64, the second range covering ages 65 to 79 and the third range covering ages 80 to 99 by using the estimates that correspond to the beginning of each range. Table 1 summarizes the key parameters and their sources that lead to the estimation of the transition probability matrices.

Among the three transition probability matrices P_t^N, $P_t^{Y,+}$, $P_t^{Y,-}$, we start by describing the non-zero entries of P_t^N. These are:

$$
\begin{aligned}
&p_t^N(0|0) = MSM_t(0|0)(1-d_t)\\
&p_t^N(1|0) = MSM_t(1|0)(1-d_t)\\
&p_t^N(3|0) = MSM_t(3|0)(1-d_t)\\
&p_t^N(5|0) = p_t^N(5|1) = p_t^N(5|2) = d_t\\
&p_t^N(1|1) = MSM_t(1|1)(1-d_t)\\
&p_t^N(3|1) = MSM_t(3|1)(1-d_t)\\
&p_t^N(2|2) = (1-g_t)(1-d_t)\\
&p_t^N(3|2) = g_t(1-d_t)\\
&p_t^N(3|3) = (1-y_t)(1-(d_t+(1-d_t)w_t))\\
&p_t^N(4|3) = y_t(1-(d_t+(1-d_t)w_t))\\
&p_t^N(5|3) = p_t^N(5|4) = d_t+(1-d_t)w_t\\
&p_t^N(4|4) = 1-(d_t+(1-d_t)w_t)\\
&p_t^N(5|5) = 1
\end{aligned}
$$

When action is to screen and the observation is negative, the transition probability matrix is the same as the one described for the no screening action. In other words, $p_t^{(Y,-)}(s'|s) = p_t^N(s'|s)$ for all $(s,s') \in S \times S$. When action is to screen and the observation is positive, individuals immediately move to the DPAD state. Thus the transition probabilities associated with core states are zero. The non-zero elements of the probability transition matrix $p_t^{(Y,+)}(s'|s)$ that are different than $p_t^{(Y,-)}(s'|s)$ are:

$$
\begin{aligned}
&p_t^{(Y,+)}(2|0) = (1-g_t)(1-d_t)\\
&p_t^{(Y,+)}(3|0) = g_t(1-d_t)\\
&p_t^{(Y,+)}(2|1) = (1-g_t)(1-d_t)\\
&p_t^{(Y,+)}(3|1) = g_t(1-d_t)
\end{aligned}
$$

The numerical values of the parameters are as follows.

$$
MSM_t = \begin{pmatrix} 0.9932 & 0.0067 & 0.0001 \\ 0.000 & 0.9568 & 0.0432 \\ 0.000 & 0.000 & 1.000 \end{pmatrix}, \forall t \in [0,14]
$$

$$
MSM_t = \begin{pmatrix} 0.9699 & 0.0290 & 0.0011 \\ 0.000 & 0.93 & 0.07 \\ 0.000 & 0.000 & 1.000 \end{pmatrix}, \forall t \in [15,29]
$$

$$
MSM_t = \begin{pmatrix} 0.8728 & 0.1197 & 0.0075 \\ 0.000 & 0.8878 & 0.1122 \\ 0.000 & 0.000 & 1.000 \end{pmatrix}, \forall t \in [30,49]
$$

$$
\begin{aligned}
&d_t = 0.0041, \forall t \in [0,4]\\
&d_t = 0.0086, \forall t \in [5,14]\\
&d_t = 0.0180, \forall t \in [15,24]\\
&d_t = 0.0448, \forall t \in [25,34]\\
&d_t = 0.1273, \forall t \in [35,49]
\end{aligned}
$$

cognitively normal, community-dwelling research volunteers. The inclusion criteria for the study are listed as positive or negative family history of AD, normal cognition at study entry (CDR=0), absence of a neurological, psychiatric, or systemic illness that might affect cognition or interfere with longitudinal follow-up among other criteria. Participants are asked to undergo a personal interview, blood draw, brain scan, PET scan and spinal fluid collection. A compensation of up to $425 for time and effort is announced [34]. Details about recruitment and assessment methods of CSF and imaging tests for the participants have been published [35] and can be found in KADRC website.

Table 1: Description of parameters

d_t	Age dependent annual death rate from all causes except AD	National Vital Statistics 2016 report [42]
w_t	Age dependent annual death rate from AD	National Vital Statistics 2016 report [42]
y_t	Annual transition rate from MCI to AD	Neumann et al. [43]
g_t	Annual transition rate from DPAD to MCI	Assumed and parameterized
MSM_t	Age dependent transition probability matrix between states 0, 1 and 3	Estimated from Knight ADRC data using multistate model

$$w_t = 0, \qquad \forall t \in [0, 24]$$
$$w_t = 0.0172, \forall t \in [25, 34]$$
$$w_t = 0.0930, \forall t \in [35, 49]$$
$$y_t = 0.15, \quad \forall t \in [0, 49]$$
$$g_t \in [0, 0.10], \forall t \in [0, 49]$$

For MSM_t matrices, the states represented in the rows and columns are 0, 1 and 3. The corresponding transition probability matrices are given in Appendix B. A matrix with a specific subscript remains the same until the subscript value changes. For example, all $p_t^N(.|.)$ matrices for t between 0-4 are equal to $p_0^N(.|.)$.

2.2.2 Information matrix

The information matrix is estimated from Knight ADRC data once the instances are classified as positive or negative based on their $A\beta_{1-42}$ levels. The elements $q_t(-|0)$ and $q_t(+|1)$ of the information matrix represent the specificity and the sensitivity of the test respectively. This results in the information matrix given below.

$$Q_t = \begin{pmatrix} q_t(-|0) & q_t(+|0) \\ q_t(-|1) & q_t(+|1) \end{pmatrix} = \begin{pmatrix} 0.75 & 0.25 \\ 0.133 & 0.867 \end{pmatrix}$$

Because there is no observation when action is not to screen, there is no information matrix associated with this action. If some sort of self detection becomes possible, the sensitivity and the specificity of that particular mechanism can be used to build the associated information matrix.

2.2.3 Initial belief

In POMDP-based screening models, the initial belief vector is usually built via risk estimating models. Different demographic and genetic factors are known to have an impact on the probability that an individual may become an AD patient. Although there are studies that estimate the risk of developing dementia based on individual characteristics such as age, gender, level of education or existence of APOE4 gene [44–46], estimating an individual's risk of developing AD is not within the scope of this research. Instead, we use three different $b_0(1)$ values to reflect three different risk profiles. The higher the value of $b_0(1)$, the higher the belief of the decision maker about an individual to be in the preclinical state of the disease. The baseline value for $b_0(1)$ value is anchored at the prevalence of AD in a population. In [47], the prevalence of the disease is estimated at 11 %. We use $b_0(1) = 0.11$ as the baseline value and refer to this case as the low risk profile. We analyze two other profiles for the initial belief vector that we refer to as medium and high risk profiles. We associate the values $b_0(1) = 0.4$ and $b_0(1) = 0.7$ with these profiles so as to sample the interval at almost equal increments.

2.2.4 Rewards-QALYs

Our rewards consist of QALYs associated with being in a particular state and if applicable, the disutility associated with screening or a possible intervention. QALY values for the clinical states of the disease come mainly from Neumann et al. [48], where QALY values associated with CU, mild AD, moderate AD, severe AD are given as 0.88, 0.68, 0.54 and 0.37 respectively. For MCI, Neumann et al. report a QALY value of 0.73 [43]. Another reference for the QALY of MCI is the study of Ready et al., where a Quality of Life rating of 3.6/5 can be translated to 0.72 QALYs [49]. The disutility of the screening test is taken from Ward et al. [50]. The disutility of the possible intervention plan (e.g. side effects of therapeutic intervention) is taken into account as a parameter that decreases the QALY of the associated state. All QALY values used in this paper are summarized in Table 2.

2.3 Costs

When evaluating a screening policy, it is important to establish the expected total cost associated with it along with the expected total benefits. Our objective

Table 2: QALY values and their sources

Partially observable states, i.e. $s \in S^{PO}$	0.88	Neumann et al. [43]
MCI	0.73	Neumann et al. [43] Ready et al. [49]
AD	0.4	Robust estimation from Neumann et al. [48]
Death	0	Convention
Intervention disutility, l	[0, 0.15]	Assumed
CSF test disutility, h	0.01	Ward et al. [50]

Table 3: Costs in 2018 US dollars and their sources

Partially observable states, i.e. $s \in S^{PO}$	14,999	Alemayehu and Warner [51]
DPAD	17,143	Arbitrarily chosen
MCI	23,143	Leon and Neumann [52]
AD	40,156	Leon and Neumann [52]
Death	0	Convention
Screening test	2,269	Wimo et al. [53]

function is QALY-based and does not include monetary costs. We will now describe how we compute the costs associated with a screening policy, starting with a description of parameters.

The cost of being in a partially observable state is taken from the work of Alemayehu and Warner [51]. They estimated health care costs for an elderly at age 65, which we took as the baseline average, to be \$10,245 in year 2000 dollars. We use Leon and Neumann's cost estimates for MCI and AD states where total cost of MCI, moderate and severe AD stages are \$18,507, \$23,931 and \$32,112 respectively, in year 2006 dollars [52]. These figures include treatment costs. Since we have a single state that combines moderate and severe AD stages, we associate a cost of \$32,112 with our state in order not to be underestimating total costs. The screening test cost is taken from the work of Wimo et al. [53]. For our model framework, the cost of screening is taken as the cost of the combination of primary care (including clinical examination, laboratory tests, computerized tomography scan and the MMSE), specialist clinical examination and CSF test. The amount is determined to be $2,130$ in 2014 US dollars [53]. As a baseline value, we assume the cost of intervention to be the same as that of treatment for mild AD (5 dollars/day in 2009) [52]. Table 3 summarizes the cost values in 2018 US dollars and their sources. To compute the expected cost of a never screening policy, we first compute the expected cost of an individual starting at state $i \in S^{PO}$. The expected total cost of an individual in state i at time $t = 0$ is computed via:

$$TotalCost(i) = cost(i, N) + \sum_{t=1}^{T} \gamma^t \Big(\sum_{j \in S} (p_{t-1}^N(j|i))^t * cost(j, N) \Big)$$

where $cost(i, N)$ represents the cost of being at state i and no screening action is chosen. As $b_0(s) \neq [0, 0]$, we have

$$E[TotalCost] = b_0(0)TotalCost(0) + b_0(1)TotalCost(1)$$

To compute the expected cost of implementing a given (optimal) screening policy, we need to record the number of screening occurances until time t. Let $M \neq 0$ be the total number of screening periods provided by a policy up to time t. Remember that an individual with a positive test result will not be tested again because he/she will enter one of the completely observable states. For an individual who is in either of the partially observable states, there are $M + 1$ possible cases that might be realized up to time t. These cases are as follows: the first test result is positive, the first test result is negative and the second test result is positive, ..., first $M - 1$ test results are negative and the M^{th} test result positive, all M test results are negative. Details of the computations associated with the probabilities of these cases can be found in Appendix C. Once the probabilities for the possible cases are computed, these are incorporated into the expected total cost computation of the screening policy similar to computation of the expected total cost of a never screening policy.

3 Results

We solve our POMDP model using Monahan's algorithm with Eagle's reduction based on eliminating strictly dominated α-vectors [32]. The pseudo-code of the algorithm is given in Appendix D. The expected costs associated with resulting optimal policies are computed as described in the previous section. All computations were done using MATLAB software [54] on a 2.6 GHz 8GB computer.

3.1 Model Results

The three factors that are analyzed in the computational study are as follows.

- The initial belief of being in state 1 is provided as an input to the model. We experiment with three distinct values of $b_0(1)$: 0.11, 0.4, 0.7 corresponding to low, medium and high risk profiles respectively.
- A possible intervention may stop disease progression ($g_t = 0$) or it may only slow it down ($g_t > 0$). We experiment with g_t values between 0 and 0.05 at 0.01 increments. As discussed below, our findings indicate that when $g_t = 0.05$, never screening becomes the optimal policy.
- The reward for the DPAD state may diminish due to the disutility associated with the intervention. We experiment with $l \in [0, 0.15]$ and $r_t(2) \in [0.73, 0.88]$ at 0.03 increments.

We compute the optimal policy for each combination of the levels, leading to $3 \times 6 \times 6$ instances. The resulting optimal policies and related outcomes can be found in Tables 4-6. All tables have nine columns: ID

of the instance, reward of DPAD state ($r_t(2)$), intervention effectiveness (g_t), optimal screening policy, expected total discounted QALY ($E[TQALY]$), difference in terms of reward between the optimal policy and the never screening policy ($\Delta QALY$), difference in terms of cost between the optimal policy and the never screening policy ($\Delta Cost$). We also compute the cost per QALY value of the optimal screening policy by dividing $\Delta Cost$ by $\Delta QALY$. Finally, we report the expected total cost ($E[TotalCost]$) of the optimal outcome.

When we study the results associated with the low risk profile given in Table 4, we observe several instances where never screening is the optimal policy. Instance 1, which is the most optimistic setting with highest reward for the DPAD state and highest intervention effectiveness suggests that the optimal policy is to screen every year between ages 50 and 95, i.e. a total of 46 times, leading to a QALY gain of 0.94. Keeping the intervention effectiveness at its best, the occurrences of screening tests diminish quickly as the the reward for the DPAD state decreases. When $r_t(2) = 0.82$, the optimal policy is to screen 8 times, most of them after age 80, leading to an expected QALY gain of 0.12. The optimal screening policy switches to never screening when the reward of the DPAD state is 0.79.

Similarly, as the reward of the DPAD state remains at its best but the effectiveness of the intervention decreases, the optimal policy contains less screening occurrences. For $g_t = 0.01$, the optimal screening policy is to screen 21 times, all taking place after the age of 60, leading to a 0.29 QALY gain. When $g_t = 0.04$, the optimal screening policy is never to screen.

Figures 4 (a), (b) and (c) depict most of the data presented in Tables 4-6. The horizontal axis represents the effectiveness of the intervention and the vertical axis represents the reward associated with the DPAD state. The legend is given in Figure 4 (d). The pattern scale highlights QALY gains and geometric shapes correspond to different levels of cost per QALY values. When Figure 4 is studied at a high level, one observes that optimality of a never screening policy is most common in Figure 4 (a). In addition, QALY gains beyond 1 are not present in this figure, whereas Figure 4 (c) has the most combinations that lead to QALY gains of 1 or more. For instance 1 in Table 6 that corresponds to the most optimistic setting of intervention effectiveness and DPAD state reward for the high risk profile, a QALY gain of 2.9 is possible by screening every year until the age of 95. As intervention effectiveness or the DPAD state reward declines, there are less screening occurrences in optimal policies and QALY gains decline. Likewise, as the reward of the DPAD state decreases, the optimal policy contains less screening occurrences and QALY gains decline. It is possible to observe that the medium risk profile is in between the two cases. For example, when $g_t = 0$ and $r_t(2) = 0.85$, the optimal policy includes 19 screening occurrences for the low risk profile and 20 for the medium and high risk profiles, leading to 0.4, 1.3 and 2.3 QALY gains respectively. When $g_t = 0.01$ and $r_t(2) = 0.88$, the optimal screening policy is to screen 21, 22 and 22 times with QALY gains of 0.3, 0.9 and 1.8 for the three profiles respectively.

3.2 Cost Implications of Screening Policies

In Tables 4-6, we report cost figures associated with the computed optimal policies. Specifically, we report the expected total cost of the policy, a comparison with a no screening policy and a change in costs to change in QALYs ratio. We call a policy cost-saving if its expected total cost is less than that of a no screening policy. We call a policy cost effective if the change in costs to change in QALYs ratio is positive, indicating a cost increase, but the ratio is less than or equal to $50,000$. For the low risk profile, when g_t and $r_t(2)$ are at their best, applying the optimal screening policy is costly but highly cost effective since the spendings per QALY is estimated to be \$729 in Table 4. It is also important to note that all optimal policies that are computed are either cost-saving or cost-effective. While cost savings are modest for the low risk profile, savings up to $\$52,292$ and $\$103,126$ may be possible for medium and high risk profiles. An interesting observation is that when the intervention effectiveness is at its best, implementing the optimal screening policy results in a decrease of expected total costs for all profiles.

All of these observations confirm the importance of the factors that are subject to experimentation in this Section. It is not only the optimal policy that depends on the effectiveness and potential disutility of a possible intervention that takes place in the DPAD state, but it is also QALY gains and costs associated with it. This effect becomes more significant as the initial belief of an individual being in the preclinical AD state becomes stronger.

4 Discussion

In this paper, we introduced a model to find optimal screening policies for AD. Our model uses a POMDP framework that includes the preclinical stage of the disease and is inline with the 2011 NIA-AA criteria. The partially observable disease free and preclinical states we introduce into our model help us capture the essence

Table 4: Optimal policy and associated cost results for a low risk individual with $b_0(1) = 0.11$, $\gamma = 0.98$, $h = 0.01$

ID	$r_t(2)$	g_t	Optimal Policy	E[TQALY]	Δ QALY	Δ Cost	$\frac{\Delta Cost}{\Delta QALY}$	E[TotalCost] in U.S. $
1	0.88	0	Every year until 95 (included)	20.2	0.94	685	729	396,922
2	0.88	0.01	[60 67 70 73 76 78 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94]	19.6	0.29	6,514	22,462	402,751
3	0.88	0.02	[68 75 80 81 82 83 84 85 86 87 88 89 90 91 92 93 95]	19.4	0.13	4,806	36,969	401,043
4	0.88	0.03	[77 81 82 83 85 86 88 89 91 93 95]	19.3	0.05	2,176	43,520	398,413
5	0.88	0.04	Never Screen	19.3	0	0	–	396,237
6	0.85	0	[50 55 65 68 70 73 76 78 80 81 82 83 84 85 86 87 88 90 92]	19.7	0.39	-5,122	-13,133	391,115
7	0.85	0.01	[68 75 80 81 82 83 85 87 89 91]	19.4	0.11	902	8,200	397,139
8	0.85	0.02	Never Screen	19.3	0	0	–	396,237
9	0.82	0	[52 67 75 80 82 84 86 89]	19.4	0.12	-9,287	-77,392	386,950
10	0.82	0.01	Never Screen	19.3	0	0	–	396,237
11	0.79	0	Never Screen	19.3	0	0	–	396,237
12	0.76	0	Never Screen	19.3	0	0	–	396,237
13	0.73	0	Never Screen	19.3	0	0	–	396,237

Table 5: Optimal policy and associated cost results for a medium risk individual with $b_0(1) = 0.4$, $\gamma = 0.98$, $h = 0.01$

ID	$r_t(2)$	g_t	Optimal Policy	E[TQALY]	Δ QALY	Δ Cost	$\frac{\Delta Cost}{\Delta QALY}$	E[TotalCost] in U.S. $
1	0.88	0	Every year until 95 (included)	20.2	1.9	-50,667	-26,667	397,388
2	0.88	0.01	[50 60 67 70 73 76 78 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94]	19.2	0.9	-6,781	-7,534	441,274
3	0.88	0.02	[50 68 75 80 81 82 83 84 85 86 87 88 89 90 91 92 93 95]	18.6	0.3	1,493	4,977	449,548
4	0.88	0.03	[65 75 81 82 83 85 86 88 89 91 93 95]	18.4	0.1	3,339	33,390	451,394
5	0.88	0.04	Never Screen	18.3	0	0	–	448,055
6	0.85	0	[50 51 60 66 68 70 73 76 78 80 81 82 83 84 85 86 87 88 90 92]	19.6	1.3	-52,292	-40,225	395,763
7	0.85	0.01	[50 68 75 80 81 82 83 85 87 89 91]	18.8	0.5	-2,528	-5,056	445,527
8	0.85	0.02	[50 75 81 83 85 87 90]	18.4	0.1	2,072	20,720	450,127
9	0.85	0.03	Never Screen	18.3	0	0	–	448,055
10	0.82	0	[50 55 73 80 82 84 86 89]	19.1	0.8	-32,779	-40,974	415,276
11	0.82	0.01	[50 74 81 84 87]	18.4	0.1	-22,313	-223,130	425,742
12	0.82	0.02	Never Screen	18.3	0	0	–	448,055
13	0.79	0	[50 71 84]	18.5	0.2	-2,863	-14,315	445,192
14	0.79	0.01	Never Screen	18.3	0	0	–	448,055
15	0.76	0	Never Screen	18.3	0	0	–	448,055
16	0.73	0	Never Screen	18.3	0	0	–	448,055

Table 6: Optimal policy and associated cost results for a high risk individual with $b_0(1) = 0.7$, $\gamma = 0.98$, $h = 0.01$

ID	$r_t(2)$	g_t	Optimal Policy	E[TQALY]	ΔQALY	ΔCost	$\frac{\Delta Cost}{\Delta QALY}$	E[TotalCost] in U.S. $
1	0.88	0	Every year until 95 (included)	20.2	2.9	-102,021	-35,180	397,852
2	0.88	0.01	[50 51 65 69 72 75 78 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94]	19.1	1.8	-56,760	-31,533	443,113
3	0.88	0.02	[50 51 71 78 80 81 82 83 84 85 86 87 88 89 90 91 92 93 95]	18.3	1	-25,819	-25,819	474,054
4	0.88	0.03	[50 69 79 81 82 84 85 87 88 90 92 94]	17.6	0.3	-140	-467	499,733
5	0.88	0.04	[65 80 82 84 86 88 90 92 94]	17.4	0.1	156	1,560	500,029
6	0.88	0.05	Never Screen	17.3	0	0	–	499,873
7	0.85	0	[50 51 52 61 66 69 72 75 78 80 81 82 83 84 85 86 87 88 90 92]	19.6	2.3	-103,126	-44,837	396,747
8	0.85	0.01	[50 51 67 73 79 81 82 83 85 87 89 91]	18.6	1.3	-56,850	-43,731	443,023
9	0.85	0.02	[50 65 76 81 83 85 87 90]	17.8	0.5	-7,342	-14,684	492,531
10	0.85	0.03	[50 80 82 85 88]	17.4	0.1	1,798	17,980	501,671
11	0.85	0.04	Never Screen	17.3	0	0	–	499,873
12	0.82	0	[50 51 67 73 80 82 84 86 89]	19	1.7	-94,682	-55,695	405,191
13	0.82	0.01	[50 52 80 82 85]	18.1	0.8	-50,499	-63,124	449,374
14	0.82	0.02	[50 80 83 87]	17.4	0.1	1,370	13,700	501,243
15	0.82	0.03	Never Screen	17.3	0	0	–	499,873
16	0.79	0	[50 51 80 83]	18.4	1.1	-92,414	-84,013	407,459
17	0.79	0.01	[50 82]	17.6	0.3	1,467	4,890	501,340
18	0.79	0.02	Never Screen	17.3	0	0	–	499,873
19	0.76	0	50	17.8	0.5	2,268	4,536	502,141
20	0.76	0.01	Never Screen	17.3	0	0	–	499,873
21	0.73	0	Never Screen	17.3	0	0	–	499,873

of the Alzheimer's disease continuum. To our knowledge, this is the first study that seeks optimal screening policies at the preclinical stage. We used data from Knight ADRC and estimated the transition probabilities between partially observable states and from these to MCI using hidden Markov models with a misclassification error matrix estimated as the sensitivity and specificity values of the CSF test. Other parameter values were taken from different relevant sources in the literature. Our model is designed to maximize the expected total QALYs for an individual. In addition, we computed the costs associated with the optimal screening policies for generated optimal policies. We solved different instances of this model depending on the risk profiles of individuals and values of two different parameters: the effectiveness and the disutility of a potential intervention that may take place in the DPAD state. We find that developing screening policies may be beneficial for individuals with different risk profiles depending on the characteristics of the planned intervention. A

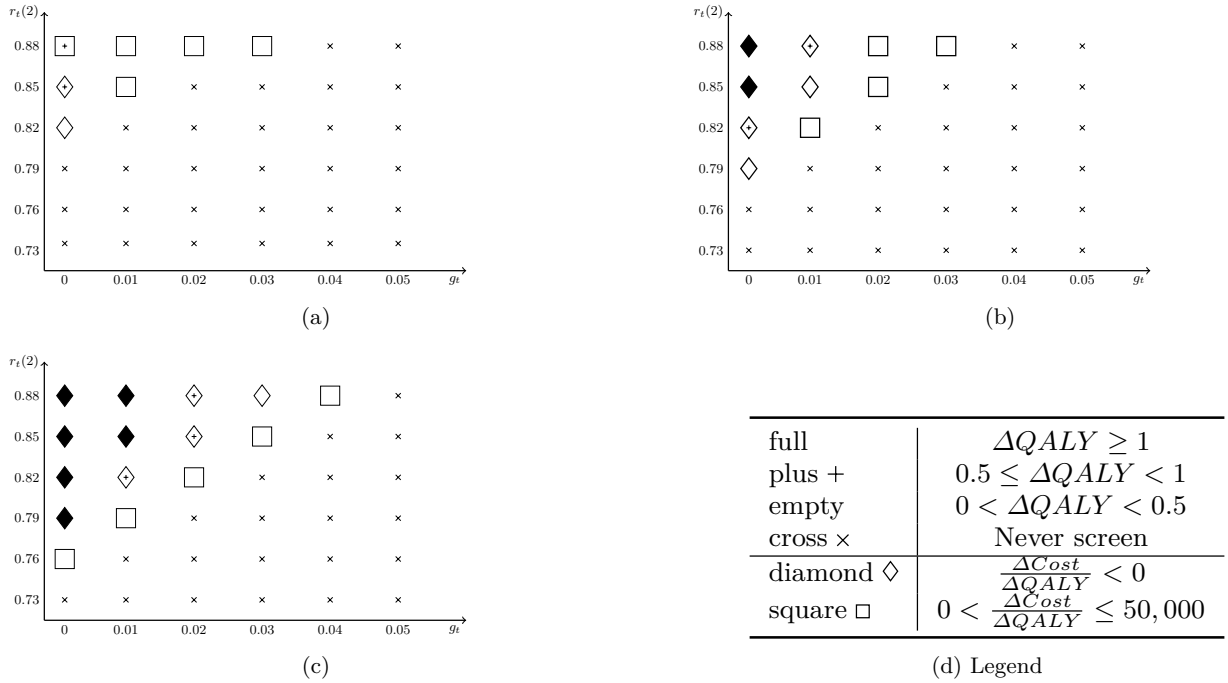

Fig. 4: QALY gains and cost-effectiveness with respect to $r_t(2)$ and g_t for a) a low risk individual, b) a medium risk individual and c) a high risk individual

high quality potential intervention motivates screening for all risk profiles. As the quality of the intervention deteriorates, the screening occurrences in the optimal policy decrease. Whenever screening is optimal, policies are either cost-effective or cost-saving, with more significant gains in QALYs and costs for the high risk profile.

Our model has limitations. The data used for estimation of transition probabilities is not very large and censored. Costs and QALY values are mostly taken from U.S. based studies. We did not consider a second test (like biopsy for cancer) to make sure that there are no false positive individuals who will transition into the DPAD state and may possibly be placed under an intervention. These limitations can be overcome with further research. As more data accumulates from different countries, the issues concerning censoring and validation can be addressed better. An extensive longitudinal database would eliminate the necessity to use data from different sources, which would improve the overall consistency of the study. As more research is reported on the onset and progression of AD and the related biomarkers, our model can be modified accordingly and can be tuned to the findings. An immediate modeling extension would be to incorporate a secondary test with the goal of decreasing the risk of "over treatment" if and when a more reliable test that distinguishes false positives from true positives at the preclinical stage becomes available.

A variation of this study could analyze the results of the POMDP model by using a different test, for instance a test that is based on imaging rather than CSF inspection. Such a test may have different accuracy levels and cost implications. Our model could help compare different test alternatives from a screening policy perspective. Another direction for future research is to focus on building the initial belief required as input for the POMDP model based on an individual's characteristics. Existing risk scoring studies may constitute a starting point and a mechanism that converts risk scores to beliefs can be built. Finally, it is possible to envision our model as a means of assessing different possible intervention plans. Policy makers may perform a risk stratification of their population and estimate the costs and benefits associated with implementing a particular intervention plan. Since developing an intervention plan has its own costs, our model may help establish the value of an intervention by depicting its benefits.

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A Proof of Theorem 1

Proof. (By induction) Step T: By definition, at $t = T$ we have $V_T^*(b_T) = \sum_{s\in S^{PO}} b_T(s) r_T(s)$. Since $r_T(s)$ is constant for all $s \in S$, $V_T^*(b_T)$ can be expressed as one linear function of b_T. Step t: Assume that $V_{t+1}^*(b_{t+1})$ is piecewise linear and convex $\forall b_{t+1}$. Then there exists a set of vectors $\alpha_{t+1} = \{\alpha_{t+1}^0, \alpha_{t+1}^1, ...\}$ where $V_{t+1}^*(b_t) = \max_{0\le i\le|\alpha_{t+1}|} \sum_{s\in S^{PO}} b_{t+1}(s)\alpha_{t+1}^i(s)$. We define $\alpha_{b_t,t+1}^{a,o}$ for $a = Y$and $\alpha_{b_t,t+1}^{a}$ for $a = N$ as follows:

$\alpha_{b_t,t+1}^{Y,o}(s) = \alpha_{t+1}^{\iota(Y,o,b_t)}(s)$ *for* $s \in S^{PO}$ *and* $o \in O_Y$
$\alpha_{b_t,t+1}^{N}(s) = \alpha_{t+1}^{\iota(N,b_t)}(s)$ *for* $s \in S^{PO}$

where

$$\iota(Y,o,b_t) = \arg\max_i \sum_{s\in S^{PO}} b_{b_t,o}^Y(s)\alpha_{t+1}^i(s), \quad \iota(N,b_t) = \arg\max_i \sum_{s\in S^{PO}} b_{b_t}^N(s)\alpha_{t+1}^i(s)$$

For $a = Y$, we replace $V_{t+1}^*(b_{b_t,o}^Y(s))$ with $\sum_{s\in S^{PO}} (b_{b_t,o}^Y(s))\alpha_{b_t,t+1}^{Y,o}(s)$ and $b_{b_t,o}^Y$ with the normalized Bayesian update formula:

$$\begin{aligned}
V_t(b_t,Y) &= \sum_{s\in S^{PO}} b_t(s) r_t^Y(s) + \gamma \sum_{o\in O}\sum_{s\in S^{PO}} b_t(s) q_t^Y(o|s)\Big(\sum_{s'\in S^{PO}} p_t^{(Y,o)}(s'|s) V^*(b_{b_t,o}^Y) + \sum_{s'\in S\setminus S^{PO}} p_t^{(Y,o)}(s'|s) V_{t+1}^*(s')\Big) \\
&= \sum_{s\in S^{PO}} b_t(s) r_t^Y(s) + \gamma \sum_{o\in O}\sum_{s\in S^{PO}} b_t(s) q_t^Y(o|s)\Big(\sum_{s'\in S^{PO}} p_t^{(Y,o)}(s'|s) \sum_{s\in S^{PO}} b_{b_t,o}^Y \alpha_{b_t,t+1}^{Y,o} + \sum_{s'\in S\setminus S^{PO}} p_t^{(Y,o)}(s'|s) V_{t+1}^*(s')\Big) \\
&= \sum_{s\in S^{PO}} b_t(s) r_t^Y(s) + \gamma \sum_{o\in O}\sum_{s\in S^{PO}} b_t(s) q_t^Y(o|s)\Big(\sum_{s'\in S^{PO}} p_t^{(Y,o)}(s'|s)\Big(\sum_{s\in S^{PO}} \frac{\tilde b_{b_t,o}^Y(s)}{\sum_{s'\in S^{PO}} \tilde b_{b_t,o}^Y(s')}\Big)\alpha_{b_t,t+1}^{Y,o} \\
&\quad + \sum_{s'\in S\setminus S^{PO}} p_t^{(Y,o)}(s'|s) V_{t+1}^*(s')\Big)
\end{aligned}$$

Since $\sum_{s\in S^{PO}} b_t(s) = 1$ we get:

$$\begin{aligned}
V_t(b_t,Y) &= \sum_{s\in S^{PO}} b_t(s) r_t^Y(s) + \gamma \sum_{o\in O}\sum_{s\in S^{PO}} b_t(s) q_t^Y(o|s)\Big(\sum_{s'\in S^{PO}} p_t^{(Y,o)}(s'|s)\alpha_{b_t,t+1}^{Y,o} + \sum_{s'\in S\setminus S^{PO}} p_t^{(Y,o)}(s'|s) V_{t+1}^*(s')\Big) \\
&= \sum_{s\in S^{PO}} b_t(s) r_t^Y(s) + \sum_{s\in S^{PO}} b_t(s)\gamma \sum_{o\in O} q_t^Y(o|s)\Big(\sum_{s'\in S^{PO}} p_t^{(Y,o)}(s'|s)\alpha_{b_t,t+1}^{Y,o} + \sum_{s'\in S\setminus S^{PO}} p_t^{(Y,o)}(s'|s) V_{t+1}^*(s')\Big)
\end{aligned}$$

Similarly, for $a = N$ we have:

$$\begin{aligned}
V_t(b_t,N) &= \sum_{s\in S^{PO}} b_t(s) r_t^N(s) + \gamma \sum_{s\in S^{PO}} b_t(s)\Big(\sum_{s'\in S^{PO}} p_t^N(s'|s) V^*(b_{b_t}^N) + \sum_{s'\in S\ S^{PO}} p_t^N(s'|s) V_{t+1}^*(s')\Big) \\
&= \sum_{s\in S^{PO}} b_t(s) r_t^N(s) + \gamma \sum_{s\in S^{PO}} b_t(s)\Big(\sum_{s'\in S^{PO}} p_t^N(s'|s) \sum_{s\in S^{PO}} b_{b_t}^N \alpha_{b_t,t+1}^N + \sum_{s'\in S\setminus S^{PO}} p_t^N(s'|s) V_{t+1}^*(s')\Big) \\
&= \sum_{s\in S^{PO}} b_t(s) r_t^N(s) + \gamma \sum_{s\in S^{PO}} b_t(s)\Big(\sum_{s'\in S^{PO}} p_t^N(s'|s)\Big(\sum_{s\in S^{PO}} \frac{\tilde b_{b_t}^N(s)}{\sum_{s'\in S^{PO}} \tilde b_{b_t}^N(s')}\Big)\alpha_{b_t,t+1}^N + \sum_{s'\in S\setminus S^{PO}} p_t^N(s'|s) V_{t+1}^*(s')\Big)
\end{aligned}$$

Since $\sum_{s\in S^{PO}} b_t(s) = 1$ we get:

$$\begin{aligned}
V_t(b_t,N) &= \sum_{s\in S^{PO}} b_t(s) r_t^N(s) + \gamma \sum_{s\in S^{PO}} b_t(s)\Big(\sum_{s'\in S^{PO}} p_t^N(s'|s)\alpha_{b_t,t+1}^N + \sum_{s'\in S\setminus S^{PO}} p_t^N(s'|s) V_{t+1}^*(s')\Big) \\
&= \sum_{s\in S^{PO}} b_t(s) r_t^N(s) + \sum_{s\in S^{PO}} b_t(s)\gamma\Big(\sum_{s'\in S^{PO}} p_t^a(s'|s)\alpha_{b_t,t+1}^N + \sum_{s'\in S\setminus S^{PO}} p_t^N(s'|s) V_{t+1}^*(s')\Big)
\end{aligned}$$

Hence we can write the optimal value function as follows:

$$V_t^*(b_t) = \max_{a \in A}\{V_t(b_t, a)\} = \max_{a \in A} \sum_{s \in S^{PO}} b_t(s)\alpha^a_{b_t,t}(s)$$

where

$$\alpha^a_{b_t,t}(s) = \begin{cases} r_t^a(s) + \gamma \sum_{o \in O} q_t^a(o|s)\Big(\sum_{s' \in S^{PO}} p_t^{a,o}(s'|s)\alpha^{a,o}_{b_t,t+1} \\ + \sum_{s' \in S \setminus S^{PO}} p_t^{a,o}(s'|s)V^*_{t+1}(s')\Big), & \text{for } a = Y \\ r_t^a(s) + \gamma\Big(\sum_{s' \in S^{PO}} p_t^a(s'|s)\alpha^a_{b_t,t+1} + \sum_{s' \in S \setminus S^{PO}} p_t^a(s'|s)V^*_{t+1}(s')\Big), & \text{for } a = N \end{cases}$$

□

B Transition probability matrices

$$p_0^N(.|.) = \begin{pmatrix} 0.9892 & 0.0067 & 0 & 0.0001 & 0 & 0.0041 \\ 0 & 0.9529 & 0 & 0.0430 & 0 & 0.0041 \\ 0 & 0 & 0.9959(1-g_t) & 0.9959g_t & 0 & 0.0041 \\ 0 & 0 & 0 & 0.8465 & 0.1494 & 0.0041 \\ 0 & 0 & 0 & 0 & 0.9959 & 0.0041 \\ 0 & 0 & 0 & 0 & 0 & 1.0000 \end{pmatrix}$$

$$p_5^N(.|.) = \begin{pmatrix} 0.9847 & 0.0067 & 0 & 0.0001 & 0 & 0.0086 \\ 0 & 0.9486 & 0 & 0.0428 & 0 & 0.0086 \\ 0 & 0 & 0.9914(1-g_t) & 0.9914g_t & 0 & 0.0086 \\ 0 & 0 & 0 & 0.8427 & 0.1487 & 0.0086 \\ 0 & 0 & 0 & 0 & 0.9914 & 0.0086 \\ 0 & 0 & 0 & 0 & 0 & 1.0000 \end{pmatrix}$$

$$p_{15}^N(.|.) = \begin{pmatrix} 0.9753 & 0.0066 & 0 & 0.0001 & 0 & 0.0180 \\ 0 & 0.9396 & 0 & 0.0424 & 0 & 0.0180 \\ 0 & 0 & 0.9820(1-g_t) & 0.9820g_t & 0 & 0.0180 \\ 0 & 0 & 0 & 0.8347 & 0.1473 & 0.0180 \\ 0 & 0 & 0 & 0 & 0.9820 & 0.0180 \\ 0 & 0 & 0 & 0 & 0 & 1.0000 \end{pmatrix}$$

$$p_{25}^N(.|.) = \begin{pmatrix} 0.9265 & 0.0277 & 0 & 0.0011 & 0 & 0.0448 \\ 0 & 0.8884 & 0 & 0.0669 & 0 & 0.0448 \\ 0 & 0 & 0.9552(1-g_t) & 0.9552g_t & 0 & 0.0448 \\ 0 & 0 & 0 & 0.8106 & 0.143 & 0.0464 \\ 0 & 0 & 0 & 0 & 0.9536 & 0.0464 \\ 0 & 0 & 0 & 0 & 0 & 1.0000 \end{pmatrix}$$

$$p_{30}^N(.|.) = \begin{pmatrix} 0.8337 & 0.1143 & 0 & 0.0072 & 0 & 0.0448 \\ 0 & 0.8481 & 0 & 0.1072 & 0 & 0.0448 \\ 0 & 0 & 0.9552(1-g_t) & 0.9552g_t & 0 & 0.0448 \\ 0 & 0 & 0 & 0.8106 & 0.1430 & 0.0464 \\ 0 & 0 & 0 & 0 & 0.9536 & 0.0464 \\ 0 & 0 & 0 & 0 & 0 & 1.0000 \end{pmatrix}$$

$$p_{35}^N(.|.) = \begin{pmatrix} 0.7617 & 0.1045 & 0 & 0.0065 & 0 & 0.1273 \\ 0 & 0.7748 & 0 & 0.0979 & 0 & 0.1273 \\ 0 & 0 & 0.8727(1-g_t) & 0.8727g_t & 0 & 0.1273 \\ 0 & 0 & 0 & 0.7349 & 0.1297 & 0.1354 \\ 0 & 0 & 0 & 0 & 0.8646 & 0.1354 \\ 0 & 0 & 0 & 0 & 0 & 1.0000 \end{pmatrix}$$

$$p_0^{(Y,+)}(.|.) = \begin{pmatrix} 0 & 0 & 0.9959(1-g_t) & 0.9959g_t & 0 & 0.0041 \\ 0 & 0 & 0.9959(1-g_t) & 0.9959g_t & 0 & 0.0041 \\ 0 & 0 & 0.9959(1-g_t) & 0.9959g_t & 0 & 0.0041 \\ 0 & 0 & 0 & 0.8465 & 0.1494 & 0.0041 \\ 0 & 0 & 0 & 0 & 0.9959 & 0.0041 \\ 0 & 0 & 0 & 0 & 0 & 1.0000 \end{pmatrix}$$

$$p_5^{(Y,+)}(.|.) = \begin{pmatrix} 0 & 0 & 0.9914(1-g_t) & 0.9914g_t & 0 & 0.0086 \\ 0 & 0 & 0.9914(1-g_t) & 0.9914g_t & 0 & 0.0086 \\ 0 & 0 & 0.9914(1-g_t) & 0.9914g_t & 0 & 0.0086 \\ 0 & 0 & 0 & 0.8427 & 0.1487 & 0.0086 \\ 0 & 0 & 0 & 0 & 0.9914 & 0.0086 \\ 0 & 0 & 0 & 0 & 0 & 1.0000 \end{pmatrix}$$

$$p_{15}^{(Y,+)}(.|.) = \begin{pmatrix} 0 & 0 & 0.9820(1-g_t) & 0.9820g_t & 0 & 0.0180 \\ 0 & 0 & 0.9820(1-g_t) & 0.9820g_t & 0 & 0.0180 \\ 0 & 0 & 0.9820(1-g_t) & 0.9820g_t & 0 & 0.0180 \\ 0 & 0 & 0 & 0.8347 & 0.1473 & 0.0180 \\ 0 & 0 & 0 & 0 & 0.9820 & 0.0180 \\ 0 & 0 & 0 & 0 & 0 & 1.0000 \end{pmatrix}$$

$$p_{25}^{(Y,+)}(.|.) = \begin{pmatrix} 0 & 0 & 0.9552(1-g_t) & 0.9552g_t & 0 & 0.0448 \\ 0 & 0 & 0.9552(1-g_t) & 0.9552g_t & 0 & 0.0448 \\ 0 & 0 & 0.9552(1-g_t) & 0.9552g_t & 0 & 0.0448 \\ 0 & 0 & 0 & 0.8106 & 0.1430 & 0.0464 \\ 0 & 0 & 0 & 0 & 0.9536 & 0.0464 \\ 0 & 0 & 0 & 0 & 0 & 1.0000 \end{pmatrix}$$

$$p_{30}^{(Y,+)}(.|.) = \begin{pmatrix} 0 & 0 & 0.9552(1-g_t) & 0.9552g_t & 0 & 0.0448 \\ 0 & 0 & 0.9552(1-g_t) & 0.9552g_t & 0 & 0.0448 \\ 0 & 0 & 0.9552(1-g_t) & 0.9552g_t & 0 & 0.0448 \\ 0 & 0 & 0 & 0.8106 & 0.1430 & 0.0464 \\ 0 & 0 & 0 & 0 & 0.9536 & 0.0464 \\ 0 & 0 & 0 & 0 & 0 & 1.0000 \end{pmatrix}$$

$$p_{35}^{(Y,+)}(.|.) = \begin{pmatrix} 0 & 0 & 0.8727(1-g_t) & 0.8727g_t & 0 & 0.1273 \\ 0 & 0 & 0.8727(1-g_t) & 0.8727g_t & 0 & 0.1273 \\ 0 & 0 & 0.8727(1-g_t) & 0.8727g_t & 0 & 0.1273 \\ 0 & 0 & 0 & 0.7349 & 0.1297 & 0.1354 \\ 0 & 0 & 0 & 0 & 0.8646 & 0.1354 \\ 0 & 0 & 0 & 0 & 0 & 1.0000 \end{pmatrix}$$

$$p_t^{(Y,-)}(.|.) = p_t^N(.|.), \quad \forall t$$

C Probabilities associated with expected total cost computations of implementing screening policies

In order to compute the expected total cost of screening policies, transition probability matrices will need to be updated taking into consideration the configuration of each case along with the sensitivity (ω) and specificity (σ) of the screening test. Let $M \neq 0$ represent the total number of screening periods provided by a policy up to time t and m_k be the number of "No screen" epochs between $k-1^{st}$ and k^{th} screening epoch. There are $M+1$ cases that might be realized at time t with the following transition probability matrices for an individual in State 0 or State 1 at the beginning of the horizon:

– Case 1: First screening test result is positive. This means that from epoch 0 to epoch $m-1$ the transitions are based on $p_k^N(.|.)$ screening matrices, then there is a positive result at epoch m_1 with related matrix $p^{Y,+}(.|.)$ after which the individual is in completely observable states.

$$\textit{State 0: } (1-\sigma) \prod_{k=0}^{m_1-1} p_k^N(.|.) p_{m_1}^{Y,+}(.|.) \prod_{k=m_1+1}^{t} p_k^N(.|.) \tag{1}$$

$$\textit{State 1: } \omega \prod_{k=0}^{m_1-1} p_k^N(.|.) p_{m_1}^{Y,+}(.|.) \prod_{k=m_1+1}^{t} p_k^N(.|.) \tag{2}$$

– Case 2: Second screening test result is positive. In this case the first screening test result is negative and the second is positive.

$$\textit{State 0: } (1-\sigma)\sigma \prod_{k=0}^{m_1-1} p_k^N(.|.) p_{m_1}^{Y,-}(.|.) \prod_{k=m_1+1}^{m_1+m_2} p_k^N(.|.) p_{m_1+m_2+1}^{Y,+}(.|.) \prod_{k=m_1+m_2+2}^{t} p_k^N(.|.) \tag{3}$$

$$\textit{State 1: } \omega(1-\omega) \prod_{k=0}^{m_1-1} p_k^N(.|.) p_{m_1}^{Y,-}(.|.) \prod_{k=m_1+1}^{m_1+m_2} p_k^N(.|.) p_{m_1+m_2+1}^{Y,+}(.|.) \prod_{k=m_1+m_2+2}^{t} p_k^N(.|.) \tag{4}$$

– Case M: M^{th} screening test result is positive. In this case the first $M-1$screening test results are negative and the last is positive.

$$\begin{aligned} \textit{State 0: } & (1-\sigma)\sigma^{M-1} \prod_{k=0}^{m_1-1} p_i^N(.|.) p_{m_1}^{Y,-}(.|.) \prod_{k=m_1+1}^{m_1+m_2} p_i^N(.|.) p_{m_1+m_2+1}^{Y,-}(.|.) \ldots \\ & \prod_{k=m_1+m_2+\ldots+m_{M-1}+M-1}^{m_1+m_2+\ldots+m_M+M-2} p_k^N(.|.) p_{m_1+m_2+\ldots+m_M+M-1}^{Y,+}(.|.) \prod_{k=m_1+m_2+\ldots+m_M+M}^{t} p_k^N(.|.) \end{aligned} \tag{5}$$

$$\begin{aligned} \textit{State 1: } & \omega(1-\omega)^{M-1} \prod_{k=0}^{m_1-1} p_i^N(.|.) p_{m_1}^{Y,-}(.|.) \prod_{k=m_1+1}^{m_1+m_2} p_i^N(.|.) p_{m_1+m_2+1}^{Y,-}(.|.) \ldots \\ & \prod_{k=m_1+m_2+\ldots+m_{M-1}+M-1}^{m_1+m_2+\ldots+m_M+M-2} p_k^N(.|.) p_{m_1+m_2+\ldots+m_M+M-1}^{Y,+}(.|.) \prod_{k=m_1+m_2+\ldots+m_M+M}^{t} p_k^N(.|.) \end{aligned} \tag{6}$$

– Case M+1: All screening test results are negative.

$$\begin{aligned} \textit{State 0: } & \sigma^M \prod_{k=0}^{m_1-1} p_k^N(.|.) p_{m_1}^{Y,-}(.|.) \prod_{k=m_1+1}^{m_1+m_2} p_k^N(.|.) p_{m_1+m_2+1}^{Y,-}(.|.) \ldots \\ & \prod_{k=m_1+m_2+\ldots+m_{M-1}+M-1}^{m_1+m_2+\ldots+m_M+M-2} p_k^N(.|.) p_{m_1+m_2+\ldots+m_M+M-1}^{Y,-}(.|.) \prod_{k=m_1+m_2+\ldots+m_M+M}^{t} p_k^N(.|.) \end{aligned} \tag{7}$$

$$\textit{State 1:}\quad (1-\omega)^M \prod_{k=0}^{m_1-1} p_k^N(.|.) p_{m_1}^{Y,-}(.|.) \prod_{k=m_1+1}^{m_1+m_2} p_k^N(.|.) p_{m_1+m_2+1}^{Y,-}(.|.) \ldots$$
$$\prod_{k=m_1+m_2+\ldots+m_{M-1}+M-1}^{m_1+m_2+\ldots+m_M+M-2} p_k^N(.|.) p_{m_1+m_2+\ldots+m_M+M-1}^{Y,-}(.|.) \prod_{k=m_1+m_2+\ldots+m_M+M}^{t} p_k^N(.|.) \tag{8}$$

D Monahan's algorithm with Eagle's reduction

This algorithm proceeds as follows: first, all α-vectors are initialized, being equal to the reward vector for each belief-action-observation tuple. At each decision epoch all possible α-vectors are generated. The idea of the reduction and elimination phases is to eliminate dominated vectors as much as possible. Basically, the algorithm eliminates the vectors depending on whether there exists a belief point where that specific vector is dominant or not. These vectors are identified using a linear programming (LP) approach [32]. If the LP yields a feasible solution, then the corresponding vector is dominated and hence can be eliminated. The pseudo-code of this algorithm as given in [27] is given below.

Algorithm 1 Monahan's Algorithm with Eagle's reduction

1: Step 1: Initialization: $\alpha^\iota(b,a,o)(s) = r(s)\ \forall b$, $a \in A$, and $o \in O$ where A, O and $r(s)$ for $s \in S^{PO}$ are defined as in 2.1.
2: Step 2: Generation: Generate all possible α-vectors. Mark each of the generated α-vectors and add them to a list.
3: Step 3: Eagle's Reduction phase
   – Selection: Choose a marked α-vector from the list. If none exists, then go to Step 4. Otherwise,
   – Elimination: Unmark the selected α-vector and delete it from the list if it is components are completely dominated by any other α-vector. Go to selection phase.
4: Step 4: Monahan's Elimination phase
   – Mark: Mark all of the remaining α-vectors in the list.
   – Selection: Choose a marked α-vector from the list. If none exists, then terminate. Otherwise,
   – LP construction: Unmark the selected α-vector and construct the LP for that vector.
   – Elimination: If the LP yields a solution $\sigma \leq 0$, then remove this α-vector from the list. Go to LP construction.