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Timing of testing and treatment for asymptomatic diseases ☆

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ABSTRACT

Many papers in the medical literature analyze the cost-effectiveness of screening for diseases by comparing a limited number of *a priori* testing policies under estimated problem parameters. However, this may be insufficient to determine the best timing of the tests or incorporate changes over time. In this paper, we develop and solve a Markov Decision Process (MDP) model for a simple class of asymptomatic diseases in order to provide the building blocks for analysis of a more general class of diseases. We provide a computationally efficient method for determining a cost-effective dynamic intervention strategy that takes into account (i) the results of the previous test for each individual and (ii) the change in the individual's behavior based on awareness of the disease. We demonstrate the usefulness of the approach by applying the results to screening decisions for Hepatitis C (HCV) using medical data, and compare our findings to current HCV screening recommendations.

1. Introduction

Recommended testing protocols to determine the presence of a disease have two major components. First they must specify the population to be tested (i.e., universal testing or targeting). Second, they must specify the timing and frequency of testing, that is, one-time testing, routine testing, or intermittent testing. If it is the latter, they must also specify the time interval between tests and whether the interval should be constant or varying. Although current guidance typically (though not always) specifies the population to be tested, it is often silent as to the frequency and the timing of testing. Timing can be important because it can have an impact on whether testing is cost-effective in a population.

Several criteria are considered when determining the optimal testing protocol. These include the prevalence of the disease, accuracy of the test, whether awareness of disease status reduces costs, the associated costs of the disease and test, and how the disease progresses. As disease prevalence decreases, more persons must be tested to identify one case and thus targeting tests to at-risk persons may be more efficient. However, if the cost of the condition is high relative to the cost of the test, universal testing may be more cost-effective. Awareness of disease status will influence costs if an effective intervention to treat the disease is available or if changes in personal behavior can reduce future morbidity, mortality, or probability of transmission to others. For example, individuals who learn that they have HCV may reduce their alcohol intake, which would reduce the probability of future liver damage. In addition, if they were injection drug users (IDU), they could participate in a needle exchange program, which would reduce the likelihood of transmission to others.

Our motivation is to study testing and treatment protocols from a societal perspective. We specifically focus on *when* to test an individual one or more times for a disease. We use a Markov Decision Processes (MDP) approach to model the disease progression and testing decision, where the reward function (or utility) is based on testing and treatment costs, quality adjusted life years (QALY) defined in different stages of disease, and the cost of infecting other individuals. We also allow the awareness of the presence of the disease to affect behavior, which can change the transition probabilities and secondary infection costs after testing. For a specific class of asymptomatic diseases, we analyze the model for structural results and find sufficient conditions to establish when testing (and treating) the disease is cost-effective, and provide insights for healthcare practice. Most Markov models of diseases are typically analyzed by employing Monte Carlo simulations or

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iterative procedures, however, our goal in this paper is to provide a computationally efficient dynamic testing strategy that can be determined by calculating a simple expression rather than requiring simulation or iteration. Moreover, since the testing strategy is individual based, it incorporates results of previous tests and/or treatments, rather than producing a policy for an entire population. We demonstrate the results for Hepatitis C (HCV) using medical data, and compare our findings to current HCV screening recommendations. We also solve for the threshold incidence for a population group beyond which testing is cost-effective.

The paper is organized as follows. A brief literature review is given in the next section. In Section 3, we describe the Markov model for a general disease setting, and present structural results for the MDP. In Section 4, we perform a numerical study for HCV using data obtained from patient studies and health databases. Finally, we discuss the implications of our results and several directions for future research in the last section.

2. Literature

We briefly summarize past work in the screening and treatment of diseases (particularly HCV) as it relates to our work; this is in no way a complete review of the literature. There have been numerous papers in the medical literature using Monte Carlo simulation of Markov models to study disease progression or screening for other diseases (e.g., [1–3]). In most of these papers, the progression of the disease is modeled as Markovian, and cost-effectiveness of a specified testing policy is calculated using simulation across a population group with particular risk characteristics. These medical papers that utilize simulation often address *whether* to screen the risk group in question; few address *when* the screening should be performed, which can affect cost-effectiveness. The definition of the risk group may include an age range (which is an implicit way of capturing timing), but this may not be sufficient to capture the progression of the disease and behavior over time. Example papers that examine cost-effectiveness of repeated screenings where a limited number of testing policies are specified *a priori* include [4–7]. A paper that studies a large number of screening policies for disease is [8], where the authors evaluate over 1000 testing policies for breast cancer and identify those in the efficient frontier using sample path enumeration over a Markov chain.

Analytical approaches may complement the simulations and help to provide additional insight on the characteristics of the testing policies. There are a few relevant papers that have used analytics for screening decisions. Some of these papers relate to scheduling examinations or replacements for machines in a production system, although papers in this area may have different assumptions than those that focus on medical decisions. Early operations research approaches to this problem include [9,10], both of which have perfect testing information and stationary parameters; the first is an early example of partially observable MDPs (POMDP) with medical implications. Ref. [11] finds that the optimal screening policy is equally spaced if tests have perfect reliability, although other papers have found that spacing may not be equal if parameters vary over time. Examples of papers that primarily focus on inspection of production systems include [12–16]. One key assumption in these papers is that the testing procedure does not impact the performance of the machine unless a corrective action is taken. An important aspect of our problem is the behavioral change brought on by awareness of the disease gained through testing, i.e., we can have "partial" treatment at no cost.

One of the more relevant papers from the inspection literature is [17], which uses a simplified version of a POMDP that the authors then transform into an MDP with complete information. The authors include false positives and negatives for the test but allow no death from causes other than disease and no recurrence of disease (thus no testing after disease has been treated). Ref. [18] allows death from causes other than disease and formulates a screening problem where the disease progression can be modeled with a discrete-time Markov chain. He gives guidelines for calculating the costs as well as the transition probabilities and applies the model to a disease but does not study structural results of the problem.

Ref. [19] focuses on medical screening timing along with follow-on papers [20,21]. These papers focus on a weighted utility function that is linear in the probability of finding a case between tests and the incidence rate; they focus on testing when probabilities are stationary over time, or not age-dependent, while in our case risk behaviors or disease progression may depend on age. Other papers that study screening problems but have stationary parameters include [22,23]. An interesting approach is taken in [24], where the authors use an analytical model similar to inventory modeling to show that the interval between screenings depends on the prevalence in the population, and apply the model to HIV.

Ref. [25] uses a non-Markovian stochastic model to solve for test timing and takes into account the effect of age on disease progression. Ref. [26] finds an exact solution with fallible tests and two disease states. As in our case, the first paper only gains information about disease presence by use of a test, although in the second paper tests take a random amount of time and do not alter the state of the system. We also use a higher number of disease states and allow recurrence of the disease and death from causes other than disease. Special cases with two (or even three) states have also been considered in other papers including a few listed previously, e.g., [27,28], although under different assumptions than the ones we use. Specifically, Ref. [28] considers a production system and the only states are "good" or "bad", and the actions available are to replace the machine or not. Others have considered the special case of one or two tests over the time horizon, such as in [22,25,29]. In our case we are able find explicit conditions for a dynamic testing and/or treating strategy to be beneficial. That is, we do not restrict the number of tests beforehand.

The subject of using MDPs and POMDPs to model medical screening problems is discussed in [30], where POMDPs may be used to capture informational aspects. As the authors state, even the definition of the POMDP may be difficult for a disease, and the number of transitions and probabilities to define can become "practically impossible". They use a hybrid POMDP with an MDP and use approximations to solve it with data from ischemic heart disease, but they point out that other structural refinements are possible to make the models reasonable to define and solve.

Several researchers have modeled the *treatment* of HCV and have, in general, found it to be cost-effective for persons who are known to have the disease [31,32]. The literature on *testing* for HCV is much less clear. For example, Ref. [33] uses a decision analytic model to determine that testing is cost-effective in injection drug users; Ref. [34] also reports that testing can be cost-effective for high-risk groups. However, Ref. [35] finds screening of asymptomatic pregnant women for HCV infection is not cost-effective. In addition, Ref. [36] found that routine HCV testing was not cost-effective in asymptomatic, average-risk adults. Ref. [37] used a Markov simulation model to show that although testing blood donors for HCV was cost-saving for the health care system, screening of post-transfusion patients was not; this is likely because most HCV infections due to transfusions have already been identified. Note that the literature on cost-effectiveness for screening of HCV does not explicitly consider the age as part of the decision process, which is a factor we will consider in this paper.

Most of the papers mentioned above (apart from HCV papers mentioned in the previous paragraph and [7,24] who study HIV)

concentrate on non-infectious diseases. The two main differences between infectious and non-infectious diseases are (i) secondary infection related costs and (ii) the changes in the incidence rate of the disease as a result of the screening policies. In this work, we include the secondary infection costs (whenever necessary), however, we assume that the incidence rate of the disease is not a function of the screening policy as in [35,36,38].

Testing recommendations from public health agencies can also differ. For example, the US Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA) recommend testing of all HIV positive persons for HCV [39]. The US Preventive Services Task Force (USPSTF) recommends against routine testing for HCV in the general population and makes no recommendation for populations with high risk for infection [40]. The Centers for Disease Control and Prevention (CDC), on the other hand, does recommend routine testing for population groups with a high risk for acquiring HCV such as drug users or commercial sex workers [41]. However, none of these agencies make recommendations about the frequency or timing of testing. Explicit consideration of timing could change the recommendations.

Our work in HCV testing and treatment differs from previous work in that we explicitly model the timing decision of the HCV test and explicitly consider behavior change as a result of knowledge of infection from the test. The former is possible because of the MDP model that we develop and study. In addition, we compare different strategies for the number of tests.

To summarize, our research contributes to the literature on medical screening by developing and analyzing a special case of a POMDP model for the timing of a screening test for an infectious disease that may have a long asymptomatic phase. Key aspects include a transition probability matrix that changes with the actions and states to model behavioral changes. We find some analytical results on the timing of disease screening and interpret these for policy implications.

3. Model and structural results

3.1. The mathematical model

We formulate the progression of the disease as well as the testing and treatment decisions as a finite-horizon, discrete time, discounted MDP model. We allow the health states to be partially observable, with the test providing the only update in information regarding the current health state. In the description of the model we will focus on the maximization of utility. The utility is based on QALYs for the different states of health of a person as well as the cost of testing, treating, and corresponding complications. Note that costs may be converted to QALYs using a cost-effectiveness threshold, e.g., $50,000 per QALY [42]. We assume that false positive tests can result but a second test is available with higher accuracy, which reflects common practice. In our base model we will analyze the model with a test that has high sensitivity but we will describe how the model and results extend to tests with false negatives. Moreover, we will provide the formulation for a general state space, but in our results we will concentrate on diseases with a particular state space structure.

Let $S \subset S'$ be the state space of our stochastic process, where

$$S' = \{(i,k) | i \in \{0,\dots,H\}, k \in \{0,1\}\}. \quad (1)$$

We use $i \in \{0,\dots,H\}$ to denote the health state of the individual (note that in the remainder of the paper we will use "health state" to refer to the first component of the state space). 0 is the state in which the individual is healthy and H is the state in which the individual is dead, with the other states representing disease stages that may have different utilities, transition probabilities, or other characteristics. Individuals' belief about whether or not they are healthy is denoted by k; 0 is used for the case that they thinks they are healthy and 1 for the case that they know that they have the disease. The beliefs of the individuals about their health state (e.g., determined by the prevalence in the population to which the individuals belong) are only updated by the use of a screening test. This simpler representation of a POMDP is used to capture the issue of awareness of disease, and it reflects testing as the primary way to determine presence of a disease.

$A = \{NT, T_1, T_2, T_1T_2\}$ denotes the action set and A_s denotes the feasible actions for every $s \in S$, where $A_s \subseteq A$. The action NT denotes "do not test" option, T_1 denotes "test but do not treat if the individual is sick" option, T_2 denotes "treat the individual if that is already known to be sick" option, and T_1T_2 is used for "test and treat if the individual is sick" option. In our model, T_1 is treated differently than T_1T_2, because in some cases the treatment may not exist, is expensive, is not very effective, or may have side effects (in which case the patient might choose not to be treated). Testing without treatment (T_1) is a reasonable option (i.e., an improvement over not testing) only if the awareness of the disease implies benefits other than treatment and cure. These may include changes in utility, changes in probability of infecting others, or changes in progression rates (see below). This also allows for partial treatments. Furthermore, the action T_2 allows the patient to delay the treatment (e.g., when the patient cannot be treated immediately due to an existing health condition or when a patient who did not want the treatment just after the test result decides to have the treatment at a later time). We assume that the test results are immediately available and the length of the treatment is negligible compared to the decision epoch (otherwise the transition probabilities are modified, however, the solution approach is still valid). Hence, we allow transitions to occur at the beginning of the decision epoch when a test and/or treatment action is taken.

$T = \{0,\dots,N\}$ is the set of (finite) decision epochs. Decision epochs can be years, months or even days depending on the disease. In addition, the number of decision epochs might change with respect to the problem. For example, when modeling certain diseases, decisions are made every year (e.g., annual exams) and the number of decision epochs is chosen in accordance with the age after which an individual's utility is negligible, while in other cases shorter time periods are desirable.

$r_t(s,a)$ is defined to be the utility of taking decision a in state s and decision epoch t. It includes the QALYs of different health states and the cost associated with the likelihood of infections to other people (if the disease under consideration is infectious). The cost associated with infections would be primarily for secondary infections, since for many diseases this captures the majority of the reduction of QALYs. It is also a standard way of including QALYs for diseases like HCV as in [36] and HIV as in [7]. Finally, we assume that the costs of a test are only immediate costs. $p(s'|s,a)$ denotes the probability of going to state s' from state s, when decision a is taken. The non-stationary probability transitions are considered in the numerical results section. Moreover, we assume that the transition rate from a healthy state to a sick state is not a function of the screening policy. Note that in the long term, disease prevalence also depends on the screening policy for infectious diseases. This dependency would be important in circumstances where the screening policy greatly reduced the prevalence in a short period of time or if the model were used to predict future prevalence. The model contained herein is not appropriate for either case.

Let $\pi = \{\pi_0,\dots,\pi_N\} \in \Pi$ be a policy where Π denotes the set of all policies and π_t is the action at time $t \in \{0,\dots,N\}$. We assume $\pi_N = NT$ for all $\pi \in \Pi$. We are interested in finding a policy that maximizes the total discounted expected utility over the horizon. The objective function is thus

$$\max_{\pi\in\Pi}\mathbb{E}_{\pi}\left\{\sum_{t=1}^{N}\lambda^{t}r_{t}(s,\pi_{t})\right\}, \tag{2}$$

where $0\leqslant\lambda\leqslant 1$ is the discount factor. Note that the discount factor λ is used to account for the time value of rewards, and it is commonly used in Markov decision models [43]. More specifically, a unit reward received at period $t+1$ has the value of λ at period t (hence, the reward r received at period t has a value of $r\lambda^{t}\leqslant r$ at time 0). Let $u_t^{\pi}(s)=r_t(s,\pi_t)+\sum_{j\in S}\lambda p(j|s,\pi_t)u_{t+1}^{\pi}(j)$. In other words, $u_t^{\pi}(s)$ is the total utility from decision epoch t onwards under policy π if the system is in state s at that time. Let $b_t^{\pi}(s)$ denote the probability that the system is in state s at time t when policy π is used. Then, $\mathbb{E}[u_t^{\pi}]$ can be calculated as $\sum_s b_t^{\pi}(s)u_t^{\pi}(s)$. Furthermore, it should be noted that $\mathbb{E}[u_0^{\pi}]=\mathbb{E}_{\pi}\left\{\sum_{t=1}^{N}\lambda^{t}r_t(s,\pi_t)\right\}$.

In the remainder of this paper we study a special class of diseases with two disease stages (in addition to healthy and death states). By considering this simpler class of diseases, we are able to find closed-form expressions in terms of the problem parameters that determine whether or not it is beneficial to test and/or treat the person at a specific time. This type of Markov model might be appropriate for a disease such as HCV or Chlamydia, which has an earlier asymptomatic stage and a later symptomatic stage in many patients.

The state space for the special class of diseases that we are considering is

$$S=\{(0,0),(1,0),(1,1),(2,1),(3,0)\}. \tag{3}$$

State (0,0) denotes the healthy state, state (3,0) denotes the death state, and the other states represent the different stages of the disease as well as the awareness of the patient as described previously. We assume that once the disease reaches stage 2, the individual is aware of it and the condition causes some irreversible damage (e.g., blindness due to glaucoma or decompensated cirrhosis due to HCV). The feasible actions are as follows:

$$A_s=\begin{cases}\{NT,T_1,T_1T_2\} & \text{if } s\in\{(0,0),(1,0)\},\\ \{NT,T_2\} & \text{if } s=(1,1),\\ \{NT\} & \text{if } s\in\{(2,1),(3,0)\}.\end{cases} \tag{4}$$

Note that testing is a feasible option if the patient is not aware of the condition and treating is a feasible option if the disease is in a reversible stage. Since $r_t(s,a)$ is composed of QALYs, cost of interferon therapy, cost of testing, and other HCV related costs which do not vary significantly with age, $r_t(s,a)=r(s,a)$ for all $t\in\{0,\ldots,N\}$. The discount factor $\lambda<1$ applied to $r(s,a)$ acts on both the QALYs and costs equally which is the standard way to ensure present QALYs and costs are valued more than future QALYs and costs (see, e.g., [7,44]). We let $r(s,NT)=R_s$, and we subtract the cost of testing and/or treatment from this value whenever any action other than NT is chosen. In other words, R_s denotes the utility of being in state s when there are no testing and treatment costs. We let $R_{(3,0)}=0$, hence $u_t^{\pi}((3,0))=0$, for all $t\in\{0,\ldots,N\}$ and $\pi\in\Pi$ (i.e., if the patient dies before the end of the last decision epoch, the remaining utility associated with the rest of the patient's life is equal to zero). Let c_0 be the cost of testing, c_1 be the cost of treating the patient (in disease stage 1), v_1 be the success probability of the treatment (in disease stage 1). If the treatment is successful, the health state of the patient becomes 0; if the treatment is not successful, the health state of the patient stays the same (stage 1) and the awareness element of the state space takes the value 1. The elements of the probability transition matrix under action NT are as follows:

$$P_{s,s'}=\begin{cases}p_{ij} & \text{if } s=(i,0),\ s'\in\{(j,0),(j,1)\} \text{ for } j\geqslant i,\\ q_{ij} & \text{if } s=(i,1),\ s'=(j,1) \text{ for } j\geqslant i.\end{cases} \tag{5}$$

We assume that there is no direct transition to disease stage 2 from the healthy state.

In addition to the diseases mentioned above (Chlamydia, HCV, and glaucoma), some examples of diseases that could be potentially modeled using our state space and the irreversible damage associated with each disease (if the disease is not caught in the earlier stages) are as follows: (i) gonorrhea causing sterility, (ii) human papilloma virus causing cervical cancer, (iii) neurosyphilis causing mental disorders, (iv) diabetes causing retinopathy and blindness, and (v) Hepatitis B causing cirrhosis. Note that our model is particularly useful because these diseases are asymptomatic for a long period in some of the patients. Although our state space is more appropriate for the diseases with simple state spaces, the progression of diseases with more complex structures can also be translated into our state space by simply collapsing multiple states into a single state. However, the main problem in this case is the availability of the medical data and several approximations need to be made in order to determine the prevalence and the transition probabilities.

Moreover, note that we modeled the awareness about the disease as a binary variable. Although this is an appropriate way of modeling many diseases, it does not capture the diseases with obvious symptoms. For example, a person with syphilis may be aware of the presence of the condition even before a formal diagnosis (which would consequently result in changes of behavior). Hence, for diseases with more obvious symptoms or for easily self-diagnosable diseases, our model may not be appropriate since a continuous awareness variable would be needed. Furthermore, for diseases that cause partial awareness in the patient (for example, HCV causing some liver problems but patient is not sure about the actual reason), it is possible to model the awareness by using fuzzy sets [45]. In the case of HCV, despite being in the same disease stage and having the same symptoms, a patient from a high-risk group may be aware of the condition (which would result in behavioral changes) while a patient in low-risk group may not be aware of the condition. Hence the set of people that are aware of the condition and the set of people that are not aware of the condition can be considered as fuzzy sets, and a probability associated with being in each set can be a function of risk group, age, or the previous history. However, for the sake of computational efficiency, we limit ourselves to the binary variable description of the disease awareness without taking into account partial awareness and the fuzzy set description of the awareness.

The following lemma is used throughout the paper and its proof is immediate from backwards induction.

Lemma 1. *Consider a disease with state space S' given in (1). Let π and π' be two policies that might differ after time t but agree otherwise. If $\mathbb{E}[u_t^{\pi}]\geqslant\mathbb{E}[u_t^{\pi'}]$, then $\mathbb{E}[u_0^{\pi}]\geqslant\mathbb{E}[u_0^{\pi'}]$. In other words, the policy that is better at time t is a better policy.*

In the remainder of this section, we determine sufficient conditions for interventions (testing and/or treatment) to be cost-effective. Let us define $f_l(t_i,t_j)$ for $l\in\{1,\ldots,6\}$ and $t_i,\ t_j\in\{0,\ldots,N\}$ as follows[2]:

$$f_1(t_i,t_j)=-c_0\left(\frac{p_{00}^{t_j-t_i}(p_{11}-p_{00}-p_{01})+p_{11}^{t_j-t_i}p_{01}}{p_{01}\left(p_{11}^{t_j-t_i}-p_{00}^{t_j-t_i}\right)}\right)+(R_{11}-R_{10})\left(\frac{1-(\lambda p_{11})^{N-t_j+1}}{1-\lambda p_{11}}\right), \tag{6}$$

[2] For simplicity, we only provide the following expressions under the assumption $p_{00}\neq p_{11}\neq q_{22}$ (which holds in our numerical results section). The derivations provided later in the paper can be used to obtain similar expressions when $p_{00}=p_{11},\ p_{11}=p_{22}$ or $p_{00}=p_{22}$.

$$f_2(t_i,t_j) = -c_1 + v_1R_{00} - v_1R_{11} + v_1\left(R_{00} - R_{10}\frac{p_{01}}{p_{11}-p_{00}}\right)\left(\frac{\lambda p_{00} - (\lambda p_{00})^{N-t_j+1}}{1-\lambda p_{00}}\right) - v_1\left(R_{11} - R_{10}\frac{p_{01}}{p_{11}-p_{00}} + R_{21}\frac{p_{12}}{q_{22}-p_{11}}\right)\left(\frac{\lambda p_{11} - (\lambda p_{11})^{N-t_j+1}}{1-\lambda p_{11}}\right), \quad (7)$$

$$f_3(t_i,t_j) = f_1(t_i,t_j) + f_2(t_i,t_j), \quad (8)$$

$$f_4(t_i,t_j) = -c_0\left(\frac{p_{00}^{t_j-t_i}(p_{11}-p_{00}-p_{01}) + p_{11}^{t_j-t_i}p_{01}}{p_{01}\left(p_{11}^{t_j-t_i} - p_{00}^{t_j-t_i}\right)}\right) + R_{21}\left(\frac{p_{12}}{q_{22}-p_{11}} - \frac{q_{12}}{q_{22}-q_{11}}\right)\left(\frac{\lambda q_{22} - (\lambda q_{22})^{N-t_j+1}}{1-\lambda q_{22}}\right) + \left(R_{10} - R_{21}\left(\frac{p_{12}}{q_{22}-p_{11}} - \frac{q_{12}}{q_{22}-q_{11}}\right)\right) \times \left(\frac{\lambda q_{11} - (\lambda q_{11})^{N-t_j+1}}{1-\lambda q_{11}} - \frac{\lambda p_{11} - (\lambda p_{11})^{N-t_j+1}}{1-\lambda p_{11}}\right), \quad (9)$$

$$f_5(t_i,t_j) = -c_1 + v_1R_{00} - v_1R_{11} + v_1\left(R_{00} - R_{10}\frac{p_{01}}{p_{11}-p_{00}}\right) \times \left(\frac{\lambda p_{00} - (\lambda p_{00})^{N-t_j+1}}{1-\lambda p_{00}}\right) + v_1R_{10}\left(\left(\frac{p_{01}}{p_{11}-p_{00}}\right)\left(\frac{\lambda p_{11} - (\lambda p_{11})^{N-t_j+1}}{1-\lambda p_{11}}\right) - \frac{1-(\lambda q_{11})^{N-t_j+1}}{1-\lambda q_{11}}\right) - v_1R_{21}\left(\frac{q_{12}}{q_{22}-q_{11}}\right) \times \left(\frac{\lambda q_{22} - (\lambda q_{22})^{N-t_j+1}}{1-\lambda q_{22}} - \frac{\lambda q_{11} - (\lambda q_{11})^{N-t_j+1}}{1-\lambda q_{11}}\right), \quad (10)$$

$$f_6(t_i,t_j) = f_4(t_j,t_j) + f_5(t_i,t_j). \quad (11)$$

The expressions above are proportional to differences between the utilities in the remaining decision epochs under different actions at time t_j, given that the last intervention was at time t_i. More details about their calculations are given in the proofs of the propositions below. The following propositions provide conditions for cost-effective testing and treatment strategies when false negatives do not occur.

Proposition 1. *Consider a disease with the state space S given in (3). If the individual was last tested and/or treated at t_i (where $t_0 = 0$) and awareness of the disease affects only the immediate utilities, then the following strategy is cost-effective:*

1. *If the individual was healthy, or treated successfully at time t_i, then it is cost-effective to test the individual (and treat, in the presence of disease) at time t_{i+1} if $f_1(t_i,t_{i+1}) \geqslant 0$ ($f_3(t_i,t_{i+1}) \geqslant 0$).*
2. *If the individual was tested to be in disease stage 1 but not treated at time t_i, then it is cost-effective to treat the individual at time t_{i+1} if $f_2(t_i,t_{i+1}) \geqslant 0$.*

Proof. Let π be a policy that satisfies $\pi_{t_{i+1}} = NT$ for $t > t_i$. Backwards induction shows that

$$u^{\pi}_{t_{i+1}}((0,0)) = R_{(0,0)}\sum_{i=t_{i+1}}^{N}(\lambda p_{00})^{N-i} + R_{(1,0)}p_{01}\sum_{i=t_{i+1}}^{N-1}\lambda^{N-i} \times \sum_{j=0}^{N-i-1}p_{00}^{j}p_{11}^{N-i-j-1} + R_{(2,1)}p_{01}p_{12}\sum_{i=t_{i+1}}^{N-2}\lambda^{N-i} \times \sum_{j=0}^{N-i-2}p_{00}^{j}\sum_{k=0}^{N-i-j-2}p_{11}^{k}q_{22}^{N-i-j-k-2}, \quad (12)$$

$$u^{\pi}_{t_{i+1}}((1,0)) = R_{(1,0)}\sum_{i=t_{i+1}}^{N}(\lambda p_{11})^{N-i} + R_{(2,1)}p_{12}\sum_{i=t_{i+1}}^{N-1}\lambda^{N-i} \times \sum_{j=0}^{N-i-1}p_{11}^{j}q_{22}^{N-i-j-1}, \quad (13)$$

$$u^{\pi}_{t_{i+1}}((1,1)) = R_{(1,1)}\sum_{i=t_{i+1}}^{N}(\lambda q_{11})^{N-i} + R_{(2,1)}q_{12}\sum_{i=t_{i+1}}^{N-1}\lambda^{N-i} \times \sum_{j=0}^{N-i-1}q_{11}^{j}q_{22}^{N-i-j-1}, \quad (14)$$

$$u^{\pi}_{t_{i+1}}((2,1)) = R_{(2,1)}\sum_{i=t_{i+1}}^{N}(\lambda q_{22})^{N-i}. \quad (15)$$

1. First, assume that the individual is healthy at time t_i (either the test result shows that the individual is healthy or the individual is treated successfully). We will compare the policies π and π', where $\pi'_t = \pi_t$ for $t \leqslant t_i$, $\pi'_{t_{i+1}} = T$, $\pi'_t = NT$ for $t > t_i$ and $t \neq t_{i+1}$. When policy π' is used, we obtain the following:

$$u^{\pi'}_{t_{i+1}}((0,0)) = -c_0 + u^{\pi}_{t_{i+1}}((0,0)), \quad (16)$$

$$u^{\pi'}_{t_{i+1}}((1,0)) = -c_0 + u^{\pi}_{t_{i+1}}((1,1)), \quad (17)$$

$$u^{\pi'}_{t_{i+1}}((2,1)) = u^{\pi}_{t_{i+1}}((2,1)). \quad (18)$$

We then find the expected values of utilities in the remaining decision epochs as

$$\mathbb{E}\left[u^{\pi}_{t_{i+1}}\right] = \left(p_{00}^{t_{i+1}-t_i}\right)u^{\pi}_{t_{i+1}}((0,0)) + \left(p_{01}\sum_{j=0}^{t_{i+1}-t_i-1}p_{00}^{j}p_{11}^{t_{i+1}-t_i-j-1}\right)u^{\pi}_{t_{i+1}}((1,0)) + \left(p_{01}p_{12}\sum_{j=0}^{t_{i+1}-t_i-2}p_{00}^{j}\sum_{k=0}^{t_{i+1}-t_i-j-2}p_{11}^{k}p_{22}^{t_{i+1}-t_i-j-k-2}\right)u^{\pi}_{t_{i+1}}((2,1)), \quad (19)$$

$$\mathbb{E}\left[u^{\pi'}_{t_{i+1}}\right] = \left(p_{00}^{t_{i+1}-t_i}\right)u^{\pi'}_{t_{i+1}}((0,0)) + \left(p_{01}\sum_{j=0}^{t_{i+1}-t_i-1}p_{00}^{j}p_{11}^{t_{i+1}-t_i-j-1}\right)u^{\pi'}_{t_{i+1}}((1,1)) + \left(p_{01}p_{12}\sum_{j=0}^{t_{i+1}-t_i-2}p_{00}^{j}\sum_{k=0}^{t_{i+1}-t_i-j-2}p_{11}^{k}p_{22}^{t_{i+1}-t_i-j-k-2}\right)u^{\pi'}_{t_{i+1}}((2,1)). \quad (20)$$

Some algebra shows that $\mathbb{E}\left[u^{\pi'}_{t_{i+1}}\right] \geqslant \mathbb{E}\left[u^{\pi}_{t_{i+1}}\right]$ if $f_1(t_i,t_{i+1}) \geqslant 0$. Since π and π' agree before time t_{i+1}, Lemma 1 shows that $\mathbb{E}\left[u^{\pi'}_0\right] \geqslant \mathbb{E}[u^{\pi}_0]$. Similarly, we compare two policies π and π'', where $\pi''_t = \pi_t$ for $t \leqslant t_i$, $\pi''_{t_{i+1}} = T_1T_2$, $\pi''_t = NT$ for $t > t_i$ and $t \neq t_{i+1}$. When policy π'' is used, we obtain the following:

$$u^{\pi''}_{t_{i+1}}((0,0)) = -c_0 + u^{\pi}_{t_{i+1}}((0,0)), \quad (21)$$

$$u^{\pi''}_{t_{i+1}}((1,0)) = -c_0 - c_1 + v_1u^{\pi}_{t_{i+1}}((0,0)) + (1-v_1)u^{\pi}_{t_{i+1}}((1,1)), \quad (22)$$

$$u^{\pi''}_{t_{i+1}}((2,1)) = u^{\pi}_{t_{i+1}}((2,1)). \quad (23)$$

We then find the expected values of utilities in the remaining decision epochs as above and some algebra shows that $\mathbb{E}\left[u^{\pi''}_{t_{i+1}}\right] \geqslant \mathbb{E}\left[u^{\pi}_{t_{i+1}}\right]$ if $f_3(t_i,t_{i+1}) \geqslant 0$. Since π and π'' agree before time t_{i+1}, Lemma 1 shows that $\mathbb{E}\left[u^{\pi''}_0\right] \geqslant \mathbb{E}\left[u^{\pi}_0\right]$.

2. We compare two policies π and π''', where $\pi'''_t = \pi_t$ for $t \leqslant t_i$, $\pi'''_{t_{i+1}} = T_2$, $\pi'''_t = NT$ for $t > t_i$ and $t \neq t_{i+1}$. When policy π''' is used, we obtain the following:

$$u^{\pi'''}_{t_{i+1}}((1,1)) = -c_1 + v_1 u^{\pi}_{t_{i+1}}((0,0)) - v_1 u^{\pi}_{t_{i+1}}((1,1)), \tag{24}$$

$$u^{\pi'''}_{t_{i+1}}((2,1)) = u^{\pi}_{t_{i+1}}((2,1)). \tag{25}$$

Some algebra shows that $\mathbb{E}[u^{\pi'''}_{t_{i+1}}] \geqslant \mathbb{E}\left[u^{\pi}_{t_{i+1}}\right]$ if $f_2(t_i, t_{i+1}) \geqslant 0$. Since π and π''' agree before time t_{i+1}, Lemma 1 shows that $\mathbb{E}\left[u^{\pi'''}_0\right] \geqslant \mathbb{E}\left[u^{\pi}_0\right]$. □

The proof of the following proposition is similar to the proof of Proposition 1, hence it is omitted.

Proposition 2. *Consider a disease with the state space S given in (3). If the individual was last tested and/or treated at t_i (where $t_0 = 0$) and awareness of the disease affects only the disease's progression, then the following strategy is cost-effective:*

1. *If the individual was healthy, or treated successfully at time t_i, then it is cost effective to test the individual (and treat, in the presence of disease) at time t_{i+1} if $f_4(t_i, t_{i+1}) \geqslant 0$ ($f_6(t_i, t_{i+1}) \geqslant 0$).*
2. *If the individual was tested to be in disease stage 1 but not treated at time t_i, then it is cost-effective to treat the individual at time t_{i+1} if $f_5(t_i, t_{i+1}) \geqslant 0$.*

The proof of the propositions above show that if there exists a time t_1 such that it is cost-effective to test (and/or treat) the individual, assuming that there will be no other interventions later on, then this action should be taken at time t_1. Furthermore, if there exists a time t_2 after time t_1 such that the intervention at time t_2 is better than doing nothing, then this intervention should be done as well. Similarly, at every t_{i+1}, the decision is based on the health state at the time of previous intervention and the remaining time until N. Note that the dynamic testing strategy of the propositions above does not assume that t_i and t_{i+1} are consecutive years, hence we are able to study the cost-effectiveness of policies that are more general than annual or monthly exams.

Propositions 1 and 2 provide computationally efficient methods for determining the cost-effectiveness of interventions. The computational effort associated with applying Propositions 1 and 2 consist of calculating f_1 for some $l \in \{1, \ldots, 6\}$. When using an iterative procedure on two policies that differ at time t_0, instead of Propositions 1 and 2, one needs to determine the remaining utility at time t_0 (which consequently requires finding the remaining utility for all $t_0 \geqslant t$). Moreover, if two policies differ from each other by more than one action, then one needs to repeat this procedure multiple times. More specifically, when finding a cost-effective policy, the number of policies that need to be compared with each other grows exponentially in iterative procedures.

Moreover, note that the testing strategy provided in Propositions 1 and 2 is dynamic and changes according the patient's history. These features provide a further improvement over current policies that consider equally spaced tests for all members of a (sub) population.

Note that the previous propositions assumed that awareness of the disease affects either the immediate rewards or the progression of the disease, which is true of many of the diseases. Simultaneous changes of rewards and progression can also be incorporated into our model, but for the sake of simplicity, exact expressions for that case are not provided here.

Next, we consider the case when false negatives may occur. Specifically, let n_1 denote the probability that the test result is negative even though the person's health state is 1. In this case, for the sake of simplicity, we will provide the solution methodology for different cases instead of exact expressions.

1. If the person's test result is negative at time t_i and the individual has not been tested since time t_{i-1}, we can find the real probabilities of being at each state under policy π as follows:

$$b^{\pi}_{t_i}((0,0)) = \frac{p_{00}^{t_i - t_{i-1}} b^{\pi}_{t_{i-1}}((0,0))}{p_{00}^{t_i - t_{i-1}} b^{\pi}_{t_{i-1}}((0,0)) + n_1 \frac{p_{01}\left(p_{11}^{t_i - t_{i-1}} - p_{00}^{t_i - t_{i-1}}\right)}{p_{11} - p_{00}} b^{\pi}_{t_{i-1}}((1,0))}, \tag{26}$$

$$b^{\pi}_{t_i}((1,0)) = 1 - b^{\pi}_{t_i}((0,0)). \tag{27}$$

Note that $b^{\pi}_{t_i}((0,0)) + b^{\pi}_{t_i}((1,0)) = 1$ because if the person is not aware of the presence of the disease, the health state is either 0 or 1. Now, let us compare two policies π and π', where $\pi_t = \pi'_t$ for $t \leqslant t_i$, $\pi_{t_{i+1}} = NT$, $\pi'_{t_{i+1}} = T_1$, $\pi_t = \pi'_t = NT$ for $t > t_i$ and $t \neq t_{i+1}$. $u^{\pi}_t(s)$ are the same as in the proof of Proposition 1 for every $s \in S$. When policy π' is used, we obtain the following:

$$u^{\pi'}_{t_{i+1}}((0,0)) = -c_0 + u^{\pi}_{t_{i+1}}((0,0)), \tag{28}$$

$$u^{\pi'}_{t_{i+1}}((1,0)) = -c_0 + (1 - n_1) u^{\pi}_{t_{i+1}}((1,1)) + n_1 u^{\pi}_{t_{i+1}}((1,0)), \tag{29}$$

$$u^{\pi'}_{t_{i+1}}((2,1)) = u^{\pi}_{t_{i+1}}((2,1)). \tag{30}$$

We then find the expected values of utilities in the remaining decision epochs for π as

$$\begin{aligned}\mathbb{E}\left[u^{\pi}_{t_{i+1}}\right] = {} & b^{\pi}_{t_i}((0,0))\left\{\left(p_{00}^{t_{i+1}-t_i}\right) u^{\pi}_{t_{i+1}}((0,0)) \right. \\ & + \left(p_{01} \sum_{j=0}^{t_{i+1}-t_i-1} p_{00}^{j} p_{11}^{t_{i+1}-t_i-j-1}\right) u^{\pi}_{t_{i+1}}((1,0)) \\ & \left. + \left(p_{01} p_{12} \sum_{j=0}^{t_{i+1}-t_i-2} p_{00}^{j} \sum_{k=0}^{t_{i+1}-t_i-j-2} p_{11}^{k} p_{22}^{t_{i+1}-t_i-j-k-2}\right) u^{\pi}_{t_{i+1}}((2,1))\right\} \\ & + b^{\pi}_{t_i}((1,0))\left\{\left(p_{11}^{t_{i+1}-t_i}\right) u^{\pi}_{t_{i+1}}((1,0)) \right. \\ & \left. + \left(p_{12} \sum_{j=0}^{t_{i+1}-t_i-1} p_{11}^{j} p_{22}^{t_{i+1}-t_i-j-1}\right) u^{\pi}_{t_{i+1}}((2,1))\right\},\end{aligned} \tag{31}$$

and the expected value of utility in the remaining decision epochs for π' can be calculated similarly. Then, we can find a condition which guarantees that $\mathbb{E}\left[u^{\pi'}_{t_{i+1}}\right] \geqslant \mathbb{E}\left[u^{\pi}_{t_{i+1}}\right]$ will hold. Similarly, if the test result at time t_i indicates that the person is healthy and we want to compare two policies π and π'', where $\pi_t = \pi''_t$ for $t \leqslant t_i$, $\pi_{t_{i+1}} = NT$, $\pi''_{t_{i+1}} = T_1 T_2$, $\pi_t = \pi''_t = NT$ for $t > t_i$ and $t \neq t_{i+1}$. $u^{\pi}_{t_{i+1}}(s)$ are as in the proof of Proposition 1, when policy π'' is used, we obtain the following:

$$u^{\pi''}_{t_{i+1}}((0,0)) = -c_0 + u^{\pi}_{t_{i+1}}((0,0)), \tag{32}$$

$$\begin{aligned}u^{\pi''}_{t_{i+1}}((1,0)) = {} & -c_0 - c_1 + (1 - n_1)\left(v_1 u^{\pi}_{t_{i+1}}((0,0)) \right. \\ & \left. + (1 - v_1) u^{\pi}_{t_{i+1}}((1,1))\right) + n_1 u^{\pi}_{t_{i+1}}((1,0)),\end{aligned} \tag{33}$$

$$u^{\pi''}_{t_{i+1}}((2,1)) = u^{\pi}_{t_{i+1}}((2,1)). \tag{34}$$

Then, we can find the utilities in the remaining decision epochs and a condition that guarantees that $\mathbb{E}\left[u^{\pi''}_{t_{i+1}}\right] \geqslant \mathbb{E}\left[u^{\pi}_{t_{i+1}}\right]$ will hold.

2. If the individual is tested and found to be in disease stage 1 and the treatment is successful, then it is similar to the previous case, assuming that after the treatment, the individual's health

state can be determined accurately. We use $b^{\pi}_{t_i}((0,0)) = 1$, and $b^{\pi}_{t_i}((1,0)) = 0$ when finding the expected utilities in the remaining decision epochs and otherwise proceed as in case 1.

3. If the individual is tested and found to be in disease stage 1 and the treatment is not successful (or the individual is not treated) at time t_i, then it is similar to the case without false negatives when the person is known to be in disease stage 1 at time t_i.

As mentioned earlier, the results of this section are applicable for modeling a broad class of diseases that have an asymptomatic phase followed by a phase where the harm caused by the disease is irreversible. Due to the curse of dimensionality, closed-form expressions for determining effective intervention strategies were only provided for the specific state space we considered. However, the MDP formulation and solution methodology provided in this section can be used for modeling diseases even with more complex progression structures. More specifically, the backwards induction algorithm together with the idea provided in the proof of Proposition 1 can be easily adopted to larger state spaces. In the following section, we implement our dynamic strategy on HCV and provide testing and treatment suggestions for different subpopulations.

4. Applications of the model to HCV

Hepatitis C virus (HCV) is a blood-borne disease present in 3.9 million people in the US (48% are unaware) that can cause end stage liver disease [46]. It is the leading cause for liver transplants and the 10th leading cause of death in the US. It is generally asymptomatic for decades, and many people are unaware of the presence of the disease until end stage liver disease begins and treatment is no longer effective. HCV can be transmitted during the asymptomatic period. There is currently no vaccine, and treatments are somewhat effective if caught early enough. Once infected about 85% will go onto chronic HCV which leads to liver cirrhosis in over 20% of patients [47]. The risk of hepatocellular carcinoma is 17 times higher in patients with HCV [48]. 8000–10000 deaths per year in the US are attributed to chronic liver disease, 40–60% of which are caused by HCV [49]. Prevalence in the overall population is 2% and as high as 40–60% in injection drug users, which is twice that for HIV [50]. The high cost of treating the advanced disease, combined with the infectivity and long asymptomatic period make HCV a candidate for screening programs.

Recall that Propositions 1 and 2 make the assumption that awareness of HCV infection affects only the disease progression *or* the rewards. The propositions can be joined into one where the progression and rewards can change simultaneously (although this new expression is simple to calculate numerically, its parametric description is omitted here for the sake of brevity). For the computational results that follow we use the results from Section 3.1 allowing disease progression and rewards to change simultaneously. We populate the model with parameters specific to HCV. The state space in this case is defined as:

- (0,0) = Healthy
- (1,0) = Infected (unaware)
- (1,1) = Infected (aware)
- (2,1) = Decompensated cirrhosis including associated complications (hepatocellular carcinoma, liver transplant)
- (3,0) = Death

This is a simplified natural history of the disease obtained from Refs. [36,44,51,52]. We develop a Monte Carlo simulation of the disease progression in MATLAB. Individuals enter the system uninfected at age 15. We then implement the following testing strategy: for ages 15 to 35, in each period, we check whether taking any action is cost-effective by using the conditions in Propositions 1 and 2. Whenever it is cost-effective to take an action, the respective action is taken at that time (i.e., test, test and treat, treat). Ages 15–35 constitute the decision epochs which is a conservative estimate of the at-risk ages. After age 35, we add a final reward which represents the continued disease progression (or lack thereof) until age 80 (or death) based on modified model parameters that reflect a higher natural death rate and a lower incidence.

The model is based on QALYs and costs, which are associated with each health state as summarized in Table 1. The utility in each period is calculated by converting the QALY associated with that period to a cost where one QALY corresponds to $50,000, and then subtracting the dollar costs of the screening test, treatment, and annual HCV related health costs. The values for the transition probabilities were taken from the literature. Some of the transitions depend on the population considered. For example, injection drug users (IDUs) are at higher risk for initially acquiring HCV, while those who drink more than 50 g of alcohol per day have faster progression rates to decompensated cirrhosis, see Table 1 for the details on the probabilities and rates. Whenever simplifications were made due to the nature of the model contained herein, we used conservative estimates so that the results would not be biased towards increased testing.

Due to limited HCV incidence data in the literature, it is difficult to assess the age period during an individual's life when they are susceptible to HCV. According to Refs. [53,54], most of the current HCV infections in the US occur due to injection drug use. Hence, we will use the statistics related to injection drug users to extrapolate the ages at which individuals are at most risk for the overall population. According to [55], percent drug use rises dramatically from age range 12–13 to age range 14–15 and remains high until age range 50–54. Consequently, we assume individuals are susceptible to HCV infection during the entire time horizon of ages 15–35, making it a conservative assumption that does not bias towards testing. Note that the model is not sensitive to small changes in

Table 1
Parameter values for model.

	Value	Reference
Parameter		
Time horizon of decision	Ages 15–35	Model assumption
Probability of infection for IDU population	0.014	[50]
Probability of infection for general population	0.0004	[46]
Probability of infection after age 33 (all pops)	0	Model assumption
Progression to decompensated cirrhosis (alcohol)	0.0115	[58]
Progression to decompensated cirrhosis (no alcohol)	0.0025	[58]
Death rate in decompensated cirrhosis	0.22	[52]
Death rate due to other causes (ages 13–33)	0.0016	[59]
Death rate due to other causes (age > 33)	0.015	[59]
Probability of treatment success	54%	[60]
% population heavy drinkers	4.9%	[61]
Discount factor for QALYs	0.97	[36]
Discount factor for costs	0.97	[62]
Costs		
Decompensated cirrhosis	$25,691	[63]
Test	$24.42	[38]
Treatment	$22,896	[64]
Secondary infections	$50,939	Calculated from model
QALYs		
Infected aware	0.98	[36]
Disease complications	0.48	[44]

the time horizon. Table 1 also indicates the probabilities of infection for each risk group.

The cost of infecting others with HCV is calculated using the given data as the *additional* total discounted lifetime cost of an individual as a result of acquiring HCV. We do this by subtracting the total discounted cost of an individual with no possibility of acquiring HCV from the total discounted cost of an individual who acquires HCV at age of 23 (since this data do not exist for HCV, the value is based on the average age of HIV infection from [56] because they have similar behavioral factors). Both calculations are made assuming no screening. The cost of infecting others is thus calculated to be $50,939, which is equivalent to a reduction of 1.1 QALYs in our model. The expected cost of a secondary infection must be multiplied by the probability of infecting someone else at each time step, which will depend on the behavioral characteristics of the individual in question and his age. Hence, we will assume that the probability of infecting others is identical to the patient's probability of acquiring HCV himself.

The aforementioned HCV screening papers [33,35,36,38] have not taken into account varying disease progressions due to alcohol consumption, although medical studies have found there can be a significant effect [57,58]. We define a person as a heavy drinker if the person has two or more drinks per day (greater than 50 g of alcohol). We assume that once a person becomes aware of his infection, the person reduces his drinking below the 50 g threshold (we also study sensitivity to this factor), and reduces his probability of infecting others by half [36]. Behavioral change, then, not only affects the progression of the disease in a patient, but also the rate of transmission to others.

Fig. 1 and Table 2 show the average rewards obtained through the Monte Carlo simulations using the aforementioned testing strategy. Several scenarios are considered including testing the overall and IDU populations under different alcohol and test acceptance assumptions. In the case of the overall and IDU populations we assume 4.9% of the population drink excessively (estimated using the 2001–2004 National Health and Nutrition Examination Survey) as the base case. Since it may not be feasible to conduct an HCV test at the date specified by our testing strategy, we also consider cases where there is a 70% chance of the test occurring when it is cost-effective to do so. We refer to this scenario in the results as 70% test acceptance, where we assume 4.9% of the population consumes alcohol excessively. We consider cases where individuals who drink excessively and become aware of an HCV infection reduce alcohol consumption to less than 50 g/day only 50% of the time, rather than the base case of always reducing alcohol consumption. Finally, in the last column, we consider only individuals who do not consume alcohol excessively. Note that our results for the base case differs from [36] which recommends against routine testing for average risk adults. Our study differs from [36] not only in that we consider the overall population, which contains some high-risk individuals, but we also consider the effects of alcohol consumption and timing/age. Because it may be difficult to know which individuals are at high risk for HCV *a priori,* we believe that considering testing the overall population is more relevant from the public health perspective.

Table 2
Results for the overall and IDU populations from implementing the dynamic testing policy (standard errors are shown in parenthesis).

	Mean QALYs gained	Mean cost	Mean number of tests
Overall population			
Base case (4.9% alcohol)	0.0026 (0.00027)	$116.82 (3.1)	1.9826 (0.00026)
0.7 test accept rate	0.0028 (0.00026)	$119.39 (3.2)	1.9701 (0.00032)
IDU population			
Base case (4.9% alcohol)	0.1625 (0.0028)	$3548.9 (42.4)	17.591 (0.0045)
0.7 test accept rate	0.1503 (0.0029)	$3214.5 (40.9)	12.269 (0.0062)
50% alcohol reduction	0.1622 (0.0028)	$3551.1 (42.5)	17.591 (0.0045)
No alcohol consumption	0.1401 (0.0023)	$3663.6 (42.0)	17.591 (0.0045)

Testing is never cost-effective for members of the overall population who do not consume alcohol excessively or when there is a only 50% alcohol reduction, and consequently the mean number of tests for those is 0 (as is the mean QALY gain and cost). Testing occurs at ages 20 and 25 for the overall population base case (i.e., where 4.9% of the population consumes alcohol excessively and the HCV test is administered when it is cost-effective to do so). When we use a 70% acceptance rate and the first test is missed, the testing strategy then recommends tests at ages 21 and 26. If the test at age 21 is also missed, then the testing recommends testing at age 22 only. For an IDU population, testing is cost-effective every year of the decision epochs (i.e., ages 16–35), regardless of whether any tests are missed. It is clear from the figure that the largest QALY gains are a result of high incidence and alcohol consumption.

Note that our model and results seem to be robust in the case of HCV. More specifically, our results demonstrate that for variables such as the alcohol consumption reduction rate and the test acceptance rate, the model is robust. Only slight changes in the results are observed for changes in these values. Moreover, our analysis revealed that the model is most sensitive to the infection rate of the population. This sensitivity is intuitive since infection is a binary event and is the driver of the health costs and QALY changes. As the most sensitive parameter, the results in the paper show only a 2-fold change in the cost/QALY result due to a 35-fold increase in the incidence rate parameter (when comparing the IDU versus overall populations), suggesting that the model is not overly sensitive to this parameter. The remaining parameters do not depend on the population considered. Moreover, note that we study the testing and treatment decisions for an individual (rather than a population) and we assume that the incidence rate is not a function of the screening policy. Hence, our results do not provide information on the future incidence rate of the disease.

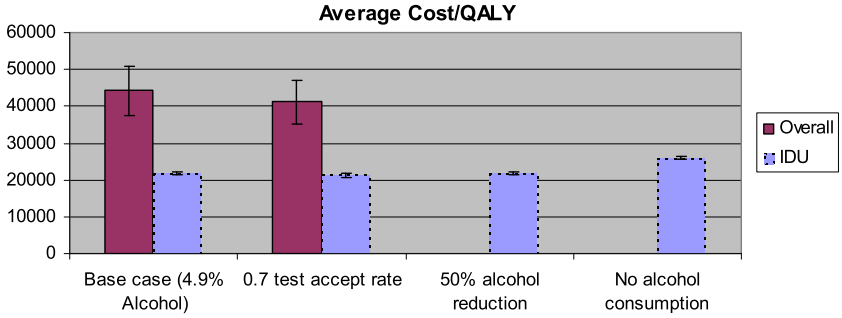

Fig. 1. Mean cost/QALY for the overall and IDU populations from implementing the dynamic policy. Confidence intervals calculated using standard errors.

The threshold incidence for testing (and treating when necessary) is 0.021% when 4.9% of the population consumes alcohol excessively. In that case testing becomes cost-effective for age 27. When no excessive alcohol consumption is assumed, the threshold incidence is 0.066% and testing becomes cost-effective for age 24.

5. Conclusions

In this paper, we have developed a Markov Decision Process (MDP) model for examining the timing of testing with treatment as an option where the action can result in disease awareness that changes the progression of the disease, and the MDP has partial updating of disease presence based on testing. In particular, we consider diseases with two disease stages (in addition to healthy and dead states) and we find sufficient conditions for testing (and treating) to be cost beneficial from a societal perspective. We consider dynamical screening and treatment policies that are determined by the result of the individual's previous test result as well as the disease's progression and infectivity characteristics. Using the results developed in this paper, the cost-effectiveness of testing and/or treatment can be determined by evaluating a closed-form expression rather than requiring a simulation or an iterative procedure. Although our screening and treatment policies have been devised for diseases with simple state spaces, our solution methodology can be adapted (at least numerically) for diseases with more complicated structures.

We use the MDP model in the case of Hepatitis C to study the timing of test and treatment actions for various populations. We use a simplified natural history for HCV that is compatible with the state space employed for the theoretical results. We use medical data to estimate the progression of the disease, prevalence, health costs, and infectivity. We find that both test-only and test-and-treat options are cost-effective for IDU populations. The additional QALYs gained as compared to no testing can be as high as 0.15 for test-and-treat option for IDUs. Regarding the general population, our recommendations find that testing and treating meets the $50,000/QALY cost-effectiveness threshold, albeit not by much.

We also find that uniform times between tests is not necessarily the best strategy when multiple testing is used; this can be driven by risk behaviors that change over time as well as the health costs. We find that incorporating behavior has an impact on recommendations, but that the IDU population should be tested even if there are no behavioral changes from awareness of having HCV. We also find that the number of actions tends to decrease with the effectiveness of behavioral changes in drinking, and that the effectiveness of alcohol behavior change can impact whether test and treat is better.

Our analysis also supports the CDC recommendations to test-and-treat groups with high risk of acquiring HCV. The overall population group is not currently addressed by CDC recommendations since most analysis has not incorporated the effect of alcohol behavior change on progression of Hepatitis C. We also add to the literature by specifying ages for testing of other populations. We have also studied cost-effectiveness using cost minimization (including productivity losses) as the objective or examining the ratio of cost paid to utility gained, and we find similar recommendations on which groups should be tested and how often.

For future work, it would be useful to apply our MDP for determining when to test or treat to other diseases with different characteristics. The research also suggests that examining dynamic screening policies (e.g., as in [8]) could be beneficial for some diseases. Further analysis of MDPs could also suggest other types of policies to consider, and we believe that our work provides an initial building block for the future work.

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