

# Timing of Testing and Treatment of Hepatitis C and other Diseases\*

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June 2007

## Abstract

Many papers in the medical literature analyze the cost-effectiveness of screening by simulating the disease and a limited number of *a priori* testing policies. However, this may be insufficient to determine the best timing of the tests or incorporate changes over time. In this paper, we study this problem with a dual approach, both analytical and simulation. We develop a Markov Decision Process (MDP) model for diseases where our goal is to determine the best timing for testing (and treatment) decisions when the presence of the disease is not known in advance; our model allows for the awareness of a disease to change behavior. We analyze the model for structural results and find that under certain assumptions the utilities determine a condition that is sufficient to establish that testing (and treating) the disease is cost-effective, and we discuss the insights for healthcare practice. Using medical data, we use simulation to solve for the optimal timing for a limited number of tests and treatments for the case of Hepatitis C. We compare our findings to current Hepatitis C screening recommendations.

## 1 Motivation

Hepatitis C virus (HCV) is a blood-borne virus that typically leads to a slow progression of chronic liver disease. In the US, an estimated 3.9 million people are currently infected (Centers for Disease Control and Prevention, 2006b), making it the most common chronic blood-borne infection in the country, although the majority of people are asymptomatic for decades before the negative health effects first become noticeable. HCV can cause liver cell damage, cancer, and cirrhosis, and is the

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\*Research supported in part by the AT&T Labs Fellowship Program, NASA Harriet G. Jenkins Predoctoral Fellowship, and DMI-0348532. The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the views of the National Science Foundation or other sponsors.

leading cause for liver transplants; it is the 10<sup>th</sup> leading cause of death in the US. Most people are unaware they have the disease until they develop end stage liver disease but they may spread the disease to others even when they are asymptomatic. There is currently no vaccine for HCV, although treatments exist that can cure with a 42% rate if applied early enough. The high cost of treating the advanced disease, combined with the infectivity and long asymptomatic period make HCV a candidate for screening programs. In this paper, we analyze models for the testing and treatment of HCV and other diseases.

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 impact 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 and utilities 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, a person who learns she has HCV may reduce her alcohol intake, which would reduce the probability of future liver damage. In addition, if she were an injection drug user (IDU), she 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 for HCV from a societal perspective. Although HCV is our initial goal, we generalize our model so that it can be used to analyze testing for other infectious and non-infectious diseases. We specifically focus on the optimal *times* to test

an individual for a disease over a lifetime. Important characteristics of our model are that testing may result in future benefits even if a complete cure is not possible, a diseased person may infect others, disease may recur after treatment, and death may occur from causes other than disease. The assumption that testing may result in positive benefit is important, since it not only includes partial treatments but allows us to incorporate behavioral changes that may result from awareness of a disease.

In this paper, we focus on testing when there is a single optimization function of interest to society or a payor, similar to Houshyar (1991); Parmigiani (1993); Hauskrecht and Fraser (2000); the advantage of doing so allows one to choose one policy as clearly better over another. One example of such an objective function applied to medical problems is to measure the gain in quality adjusted life years (QALYs) in the population from testing and/or treatment. For screening decisions, measuring QALYs without also including cost is not sufficient since this would simply result in policies that recommend testing very frequently at very high cost. Costs can be incorporated in the objective based on a cost-effectiveness threshold for QALYs. One could also minimize societal cost incorporating productivity losses due to the disease; we found similar results using either objective function. Another alternative is to examine trade-off curves of cost and utility; we are examining policies under this framework in Faissol et al. (2007).

We use a Markov Decision Process (MDP) to model the disease progression and testing decision, where the reward function is based on testing and treatment costs/utility, QALYs defined in different stages of the disease, and the disutility of infecting other individuals. We use a special case of a Partially Observable MDP (POMDP), where information on whether someone has the disease can only be obtained from testing and if disease presence is known then the disease state is also. The latter is reasonable since a secondary test would provide information on the exact disease state but would be performed immediately after all positive tests, so a second decision is not needed in the model. The former is reasonable since we study asymptomatic diseases and from the society or payor perspective there is unlikely to be regular updating of probabilities without testing. Differences in incidences can also be captured by segmenting the population according to risky behaviors. We assume there are a finite number of health states and a finite lifespan of each person, and we allow reward functions to be non-stationary, because disease incidence or progression may change with age. Since awareness of the presence of the disease can affect behavior, testing can change

the transition probabilities and immediate rewards (through reduced secondary infections). We analyze the disease screening problem for structured policies, finding that some exist under certain assumptions on utility or the progression of health states. We interpret how these results could affect not only policy recommendations but also physician practice. Numerically, we also identify certain structured policies that may not exist for the general problem setting. Finally, we solve the optimal timing problem for the case of HCV based on medical data and simulations of the population. Our goals are to introduce modeling characteristics important for some diseases and inform policymaking and medical practice with results and insights from the model.

## 2 Literature

We briefly summarize past work in HCV screening and treating as it relates to our work; this is in no way a complete review of the literature. Several researchers have modeled *treatment* of HCV and have in general found it to be cost-effective for populations who are known to have the disease (Kim et al., 1997; Salomon et al., 2003). In addition, some researchers have studied treatment cost-effectiveness for recurrent HCV (Neumann et al., 2006; Saab et al., 2002). Based on this work, we assume that patients can have recurrent HCV and be treated again. The literature on *testing* for HCV is much less clear. For example, Castelnovo et al. (2006) find based on a decision analytic model that testing is cost-effective in injection drug users; Gordon (1999) also reports that testing can be cost-effective for high-risk groups. However Plunkett and Grobman (2005) find screening of asymptomatic pregnant women for Hepatitis C virus infection is not cost-effective. In addition, Singer and Younossi (2001) found that routine HCV testing was not cost-effective in asymptomatic, average-risk adults. Pereira and Sanz (2000) 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, while we find that age can affect whether a particular policy is cost-effective.

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 (Centers for Disease Control and Prevention, 1999). 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 (U.S. Preventive Services Task Force, 2004). 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 (Centers for Disease Control and Prevention, 2004). 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 treating differs from previous work in that we explicitly model the timing decision of the testing and explicitly consider behavior change as a result of knowledge of infection from testing. The former is possible because of the Markov decision process model that we develop and study. In addition, we compare different strategies for the number of tests.

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., Goldie and Kuntz (2003); Rosenquist and Lindfors (1994); Sonnenberg et al. (2000)) 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. The simulation medical papers often address *whether* to screen the risk group in question, although fewer 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 Brenner et al. (2006); Michaelson et al. (1999); Vijan et al. (2000); Paltiel et al. (2005). A paper that studies a large number of screening policies for disease is Diehl et al. (2006), 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 be able to provide additional insight on the characteristics of the testing policies, and there are also relevant papers that have used analytics for screening decisions. Some of these papers also 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 Smallwood and Sondik (1973) and Kirch and Klein (1974), both of which have perfect testing information and stationary parameters; the first is an early example of POMDPs with medical implications. Lee and Pierskalla (1988) find that the optimal screening 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 White (1978); Milioni and Pliska (1988a,b); Ozekici and Papazyan (1988); Yang and Klutke (2000). 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 Ozekici and Pliska (1991), 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). Houshyar (1991) 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.

Zelen (1993) focuses on medical screening timing along with follow-on papers Lee and Zelen (1998) and Lee et al. (2004). These papers focus on a weighted utility function that is linear in the probability of finding a case and being incident between tests; 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 Monahan (1980) and Parmigiani (1997). An interesting approach is taken in Kaplan and Satten (2000), 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.

Parmigiani (1993) uses a non-Markovian stochastic model to solve for test timing, and Parmigiani (1996) finds an exact solution with fallible tests and two disease states. As in our case, the

latter 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 general number of disease states in most of our results and allow recurrence of the disease and death from causes other than disease.

The subject of using MDPs and POMDPs to model medical screening problems is discussed in Hauskrecht and Fraser (2000), 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.

In some of our results we address the special case of two disease states. Special cases with two (or even three) disease states have also been considered in other papers including some above but also others, e.g., Eddy et al. (1988) and GrosfeldNir (1996), although under different assumptions than the ones we use. Others have considered the special case of one or two tests over the time horizon, such as in Parmigiani (1993); Parmigiani and Skates (2001); Monahan (1980) with different assumptions than ours. In our case we are able find explicit conditions for testing to be beneficial with one test allowed and two disease states, which may apply to some diseases. Other assumptions are as before, where testing can impact transition probabilities and parameters may be non-stationary.

To summarize, our research contributes to the literature on medical screening by developing and analyzing a special case of a POMDP model for the optimal timing of a screening test for a disease that may have secondary infections. 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. We apply the model to HCV using medical data and also provide examples of the model applied to Chlamydia, comparing our results to existing recommendations.

The remainder of the paper is organized as follows. We describe the Markov model for a general disease setting in the next section, and present structural results for the MDP. Then in Section 4, we perform a numerical study 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.

### 3 Model and Structural Results

#### 3.1 The Mathematical Model

We formulate the progression of the diseases as well as the testing and treatment decisions as a finite-horizon, discrete time discounted MDP model. We allow one state to be partially observable, with the test providing the only update in information regarding that state. In the description of the model we will focus on the maximization of societal 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 (Chapman et al., 2004). 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 write the model with a test that has high sensitivity but we will describe how the model and results extend to tests with false negatives.

The following are the elements of our formulation:

1. **Decision Epochs**  $T = \{1, 2, \dots, N\}$  is the set of (finite) decision epochs. Decision epochs might be years, months or even days depending on the disease; also the number of decision epochs might change with respect to the problem. When modeling some diseases, decisions are made every year (e.g., annual exams) and the number of decision epochs is chosen to be an age after which an individual's utility is negligible while in other cases shorter time periods are desirable.
2. **State and Action Sets**  $S = \{(h, i) | h \in \{1, \dots, H\}, i \in \{0, 1\}\}$ , where  $\{1, \dots, H\}$  denotes the set of health states of the individual. Unless indicated otherwise, 1 is the state of being healthy and  $H$  is the death state, with the other states representing disease states that may have different utilities, transition probabilities, or other characteristics. An individual's awareness about whether or not he has the health condition is denoted by state  $i$ ; 0 is used for the case that he thinks he is healthy and 1 for the case that he knows that he has the disease.

The probability of having the disease (e.g., determined by the prevalence in the population to which the individual belongs) is only updated by the use of a screening test. This simpler representation of a partially-observable MDP is used to capture the issue of awareness of disease but reflect testing as the primary way used to determine presence of a disease.

$A = \{NT, T, TT\}$  denotes the actions and  $A_s$  denotes the feasible actions for each state  $A_s \subseteq A$  for every  $s \in S$ .  $NT$  is used for “do not test”,  $T$  is used for “test but do not treat”,  $TT$  is used for “test and treat”. In our model,  $T$  is treated differently than  $TT$ , since in some cases the treatment may not exist, is expensive or not very effective, or may have many side effects (in which case the patient might choose not to be treated). Testing without treatment ( $T$ ) 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 infectivity probability, or changes in progression rates (see below). This also allows for partial treatments. Note that if  $i = 1$  or  $h = H$ , i.e., a person is known to be sick or he is dead, then the only possible action is  $NT$ , and there is no decision to be made.

### 3. Utility and Transition Probabilities

$r_t(s, a)$  is defined to be the immediate utility of taking decision  $a$  at state  $s$  and decision epoch  $t$ . It includes the cost of testing (and treating) and QALYs of different health states. Note that utility may change with age. Finally, this utility may include the likelihood of infections to other people. This value would be primarily for secondary infections, since for many diseases this captures the majority of the infection QALYs. It is also a standard way of including infection QALY for diseases like HCV (Singer and Younossi, 2001) and HIV (Paltiel et al., 2005). While this is an appropriate way for modeling infectivity for many diseases, it does not appropriately capture the growth aspects for a localized outbreak of a highly contagious disease such as Ebola. Finally, we assume that the costs of a test are only immediate costs and that the test does not cause future harm to the individual. While this is not true for all tests (e.g., radioactive ones), it is true for many such as the saliva test used for HCV.

$p_t(s'|s, a)$  is the probability of going to state  $s'$  from state  $s$  at decision epoch  $t$ , when decision  $a$  is taken at decision epoch  $t$ . This allows transition probabilities to change with time (or age)

due to both disease progression rates and risk behavior. Since the probabilities depend on the state, this also implies that the probabilities can change when a testing decision indicates the presence of the disease. These probabilities determine the length of the disease as well as the morbidity since the transition to the death state is included. Transitions to the death state  $H$  may also occur for reasons other than the disease being studied. The probabilities also incorporate the probability of success of the treatment, which aids in modeling several types of diseases as presented in the taxonomy.

- 4. Policies** A policy is composed of actions at each time. Since the decision maker makes the decision without knowing the actual state with certainty, actions are only based on the time. If  $\pi$  is a policy, we use  $\pi_t$  to denote the action at time  $t$ , where  $t \in \{1, \dots, N-1\}$ . We assume there is no decision at time  $N$ .

We are interested in finding a policy that will maximize the total discounted expected utility over the horizon. The objective function is thus

$$\max_{\pi} E_{\pi} \left\{ \sum_{t=1}^N \lambda^{t-1} r_t(s, \pi_t) \right\}.$$

Let  $u_t^{\pi}(s) = r_t(s, \pi_t) + \sum_{j \in S} \lambda p_t(j|s, \pi_t) u_{t+1}^{\pi}(j)$ . In other words,  $u_t^{\pi}(s)$  is the total utility from decision epoch  $t$  onwards if the system is at state  $s$  at that time, policy  $\pi$  is used and  $\lambda$  is the discount factor where  $0 \leq \lambda \leq 1$ . Let  $b_t^{\pi}(s)$  denote the probability that the system is at state  $s$  at time  $t$  when policy  $\pi$  is used. Then,  $E[u_t^{\pi}]$  can be calculated as  $\sum_s b_t^{\pi}(s) u_t^{\pi}(s)$ . It should be noted that  $E[u_1^{\pi}] = E_{\pi} \left\{ \sum_{t=1}^N \lambda^{t-1} r_t(s, \pi_t) \right\}$ .

### 3.2 Structural Results

In this section, we will analyze the MDP for the timing of testing and treatment decisions for structural results. In some cases the structural results will help to solve the problem, and they can also provide additional insight for practitioners or policymakers as to when certain policies might be appropriate based on disease characteristics. .

We will use the following assumptions in some of our results:

**Assumption 1**  $r_t((h, i), a)$  is nonincreasing in  $h$ , for  $i \in \{0, 1\}$ , for  $t \in \{1, \dots, N-1\}$  and for every  $a \in A_{(h,i)}$ .  $r_N((h, i))$  is nonincreasing in  $h$ , for  $i \in \{0, 1\}$ .

**Assumption 2**  $q_t((k, i)|s, a) = \sum_{j=k}^H p_t((j, i)|s, a)$  is nondecreasing in  $s$  for every  $k \in \{1, \dots, H\}$ ,  $i \in \{0, 1\}$ ,  $t \in \{1, \dots, N - 1\}$ , for  $s \in S$  and for every  $a \in A_s$ .

Assumption 1 says that advanced disease states have lower utility, which is the case in many diseases. If the objective function is to maximize overall utility then this assumption is reasonable. However, if the objective is instead to minimize cost, there may be some exceptions to this, such as when the disease causes organ failure. In that case, the cost of transplantation is very high but the cost of the disease after transplantation (including death) may be less than the cost of the transplant.

Assumption 2 is the “increasing failure rate” assumption. It can be interpreted as, “the worse a patient’s health state is, the quicker it becomes even worse”. This assumption also holds when the rate of progression of disease is thought to be constant between states.

**Proposition 1.** *Let  $\pi$  and  $\pi'$  be two policies that might differ after time  $t$  and agree otherwise. If  $E[u_t^\pi] \geq E[u_t^{\pi'}]$ , then  $E[u_1^\pi] \geq E[u_1^{\pi'}]$ . In other words, the policy that is better at time  $t$  is a better policy.*

This result is a use of the backwards induction algorithm when the decision maker does not know what the state is, and the proof of the result above is immediate. If the policy maker is allowed to test (and treat) the person at most once, this result shows that if there exists a time when expected utility onwards is more when we test (and treat) the person, then it is beneficial to test (and treat) the person. The result does not say anything about the optimality of the testing time; it just tells if it is better to test than not to test. In practice this result implies that if someone visits a physician at a time other than the “optimal” time, then it may still be beneficial to screen the individual. This also matches with our numerical results, which indicate that there may be a wide range of ages where testing is beneficial for at-risk populations.

**Lemma 1.** *Under Assumptions 1 and 2, for any policy  $\pi$ ,  $u_t^\pi((h, i))$  is nonincreasing in  $h$ , for  $i \in \{0, 1\}$  and for every  $t$ .*

The proof of this result follows directly from Lemma 4.7.2 of Puterman (1994). This result states that under any policy, being at a worse health state has a lower utility-to-go function. This may not be true for all diseases, since in some cases the cost of treating the disease may be more costly (in units of utility) than being in worse health states, e.g., the death state. If the objective

function is to maximize utility, the assumptions (and thus the result) often hold, since the death state has a lower utility compared to other states. For diseases where it applies, the result may also help to motivate prevention or educational programs, where funds may be used to help reduce progression to the more advanced disease states, since it is known the utility of the progressed disease will be lower.

We incorporate behavioral changes (e.g., from awareness of the disease or among different risk groups) of individuals by altering the immediate rewards and/or the probability transition matrices. Let  $\bar{p}_t(s'|s, a)$  be the probability of going from state  $s$  to state  $s'$  at time  $t$  when action  $a$  is taken for a less risky person (as compared to  $p_t(s'|s, a)$  for the base case). Let us define  $\bar{r}_t(s, a)$ ,  $\bar{q}_t(s'|s, a)$  and  $\bar{u}_t^\pi(s)$  for the less risky person in a similar way as before.

If a person changes his behavior positively, we assume that  $\bar{q}_t((k, i)|s, a) \leq q_t((k, i)|s, a)$  for every  $k \in \{1, \dots, H\}$ ,  $i \in \{0, 1\}$ ,  $t \in \{1, \dots, N-1\}$ , for  $s \in S$  and for every  $a \in A_s$ . Intuitively, this means that progression of the disease is slower for a less risky person, which also corresponds with evidence from the literature for diseases where behavior has an impact. Also, since the less risky person also has a lower probability of infecting other people because of the behavioral changes, we assume that  $\bar{r}_t(s, a) \geq r_t(s, a)$  for all periods  $t$ .

**Lemma 2.** *Under Assumptions 1 and 2, for any policy  $\pi$ ,  $\bar{u}_t^\pi(s) \geq u_t^\pi(s)$  for every  $s \in S$ , and for every  $t$ .*

The proof again uses Lemma 4.7.2 of Puterman (1994), and it is immediate. This lemma tells us that a less risky person has a higher utility-to-go function no matter which health state he is in. Under these conditions, educational programs to reduce risky behavior may be desirable. Further, using this result we obtain a helpful theorem that gives a sufficient condition to decide if it is beneficial to test a person at a given time or not.

**Theorem 1.** *If Assumptions 1 and 2 hold, policy  $\pi$  is used before time  $t$  and  $E_\pi[r_t(s, T)] \geq E_\pi[r_t(s, NT)]$ , then at time  $t$  it is better to test than not to test.*

This theorem gives an easy way to make testing decisions for some diseases (see appendix for the proof). Since the person becomes less risky after testing, the only disadvantage of testing is the immediate testing utility. If the immediate decrease in the utility from secondary infections is more than the utility loss from testing (i.e., cost of testing), then it is beneficial to test the person.

Our result also does not put any restrictions on the number of tests already performed. But for example if a person has already been tested the previous year, chances are high that testing the person again this year does not result in a significant increase in utility. So, the sufficient condition for utility in the theorem is more likely to hold if enough time has passed since the last test.

A similar idea can also be used to compare the no-test decision with the test-and-treat decision. But since  $TT$  is more expensive than  $T$  (and thus loses utility), and some of the benefits of  $TT$  are encountered in the time following the testing period (i.e., if the treatment is successful and the person gets better), then an additional time period needs to be considered. Using the same reasoning as above, we obtain the following theorem.

**Theorem 2.** *Assume that policies  $\pi$  and  $\pi'$  agree except after time  $t$ , when  $\pi$  uses action  $NT$  whereas  $\pi'$  uses action  $TT$ . If Assumptions 1 and 2 hold and  $E_{\pi'}[r_t(s, T)] + \lambda E_{\pi'}[r_{t+1}(s, \pi'_{t+1})] \geq E_{\pi}[r_t(s, NT)] + \lambda E_{\pi}[r_{t+1}(s, \pi_{t+1})]$ , then at time  $t$  it is better to test the person (and treat if he is sick) than not to test.*

The proof uses the same idea as for Theorem 1, so it is omitted. This theorem states that if the QALYs gained by the person at times  $t$  and  $t + 1$  are more than the utility loss from testing and treating, then we can conclude that it is better to use action  $TT$  than do nothing, since we already know that after time  $t + 1$  the objective is improved by the  $TT$  action. In the cases addressed by both theorems, clearly there can be diseases for which  $T$  or  $TT$  are beneficial but the condition does not hold, e.g., if most of the benefit is not in the next period but in future periods.

If false negatives occur, our results still hold as long as a negative test does not make a person become riskier. In that case the expected values of the immediate utilities in Theorems 1 and 2 decrease, and the sufficient conditions become less likely to hold.

In the next result we look at a special class of diseases where there are only two health states to consider. By considering this simpler class of diseases, we are able to find a closed-form expression in terms of the problem parameters that determines whether or not it is beneficial to test the person at a specific time if he can be tested only once. We assume that we are modeling a short time period relative to a person's lifetime, or that the disease is not fatal so that the death state can be disregarded. This type of Markov model might be appropriate for a disease such as Chlamydia, which is not fatal and has a limited number of health states, especially for males.

**Theorem 3.** *Consider a disease with two states, namely healthy and sick. Let  $\lambda$  be the discount factor,  $c_1$  be the cost of testing and  $c_2$  be the cost of treating the patient,  $q$  be the success probability of the treatment,  $p$  be the probability of a healthy person getting the disease at each time period, and  $r_1(r_2)$  be the utility per period of being at the healthy (sick) state in QALYs. Then assuming that the person is healthy at time 0, and at most one test is allowed, it is beneficial to test and treat the person at time  $N - t$ , if*

$$\frac{c_1}{(1 - p^{N-t})} + c_2 \geq \lambda q[(r_2 - r_1) \frac{1 - (\lambda p)^t}{1 - \lambda p} - r_1(\lambda p)^t]. \quad (1)$$

The proof of this result is in the appendix. In this theorem, the assumption that the individual is healthy at the beginning of the horizon and he is not tested before time  $t$  can be relaxed without loss of generality. For this case, when we are finding  $E[u_{N-t}^\pi]$  and  $E[u_{N-t}^{\pi'}]$  we need to replace  $p^t$  and  $1 - p^t$  by  $b_{N-t}^\pi$  and  $1 - b_{N-t}^\pi$ . Again we can get a closed form expression for whether it is beneficial to test at time  $N - t$ , but the condition will be depend on  $\pi$ .

Theorem 3 provides an easy way to calculate whether it is beneficial to test an individual at the current time based on their risk level, the benefit of the testing, and the costs. While testing at the optimal time would offer an overall improvement, in practice it may be easier to use a policy in which an individual is tested when they arrive for a doctor's appointment (if it is an appropriate time) than to hope that they come back at the optimal time to test. This is particularly true for diseases for which there may be less awareness among the public regarding screening, or if only certain risk groups would have high enough prevalence to warrant testing. It also provides an easy way to do a first cut at examining a disease (or a disease under new conditions) to see if it will be cost-effective to screen. As an example, we applied the condition to data for Chlamydia, which is a sexually transmitted disease that does not cause death and can be represented with two health states without significant loss; in that case, using estimates from the medical literature, we found that women aged 20 should be screened for Chlamydia, which corresponds with recommendations of the CDC (see Faissol (2007) for details).

It is also worth pointing out some structural results that do not hold in general. For example, numerical tests indicate that multiple tests to screen for a disease should not necessarily be evenly spaced. This is consistent with Diehl et al. (2006), who found that dynamic screening policies

could be but were not always in the efficient frontier. For the diseases we study, the interval may depend not only on the utilities of the disease states and disease progression (both which may be non-stationary) but also the risk behaviors for the disease.

Further, numerical experiments have also shown that the benefit is not necessarily concave in the number of tests. For example, it may be beneficial to screen once for a disease over the horizon, less beneficial to screen twice, and more beneficial to screen three times. Both this result and the result about dynamic screening suggest that simply simulating a few intervals for screening may not be sufficient to capture the maximum benefit for screening, and that either many types of policies should be considered in the simulation or using the MDP model can be useful. However, in our numerical results we found that the differences among the (non-concave) different policies were quite small, so it is reasonable to consider a limited number of tests.

## 4 Applications of the Model to HCV

In this section, we use the model developed in Section 3.1, and we populate the parameters of the model with medical data specific to HCV. We solve the full model to optimality for a limited number of tests, and we show how aspects such as behavioral changes may be important in testing and treatment decisions.

### 4.1 Disease Background and Statistics on HCV

Once infected with HCV, virtually all patients develop liver cell damage. About 85% will go on to chronic HCV which leads to liver cirrhosis in over 20% of patients, and hepatocellular carcinoma (HCC) in 1-5% of patients within 20 years of infection (National Institutes of Health, 1997). The risk of HCC is 17 times higher in patients with HCV (Donato et al., 1998). Chronic liver disease leads to approximately 8,000 to 10,000 deaths per year in the U.S., 40-60% of which are caused by HCV (Centers for Disease Control and Prevention, 2005b). The states of the natural history of HCV are shown in Figure 1 (e.g., Bennett et al. (1997); Singer and Younossi (2001); Stein et al. (2004)).

The primary mode of transmission of HCV is through blood and blood products. Prevalence in the general U.S. population is approximately 2%, though it can be much higher in specific groups.

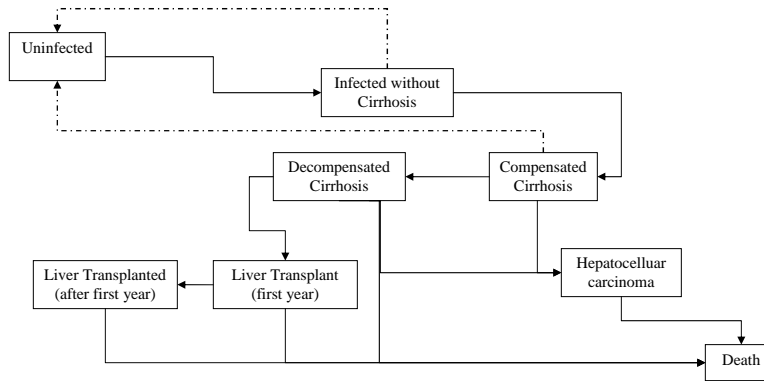


Figure 1: The states of HCV where solid lines represent natural history transitions and dashed lines represent transitions due to treatment success. Not shown in the diagram but included in the model are transitions to death from all states due to causes other than HCV.

For example, the overall prevalence among injection drug users who have used drugs for at least 5 years is estimated to be 60-80% (Centers for Disease Control and Prevention, 2006c), which is more than double that of HIV. HCV is rarely if at all transmitted sexually; however, commercial sex workers have a prevalence (6%) three times higher than that of the overall population (National Network of STD-HIV Training Centers, 2005). The higher prevalence could be due to injection drug use among this population. In addition, the incarcerated population has a prevalence of 15% (Centers for Disease Control and Prevention, 2003).

The current treatment for HCV is combination therapy of peginterferon and ribivirin which consists of once weekly dosing for 48 weeks (National Network of STD-HIV Training Centers, 2005). This treatment has a sustained response (i.e., success) rate of approximately 42% in patients with non-cirrhotic HCV. The likelihood of success depends on the genotype of the individual. Patients of genotype 1 (G1) have a treatment success rate of 29% while non-genotype 1 (G2) patients have a treatment success rate of 62%, where 60% of the population is G1 (Hornberger et al., 2006). In the case of sustained viral response, the patient is assumed cured, but still remains susceptible to another HCV infection. In the case where there is no sustained viral response to the therapy, the natural progression of HCV infection occurs.

## 4.2 Markov Decision Process for Screening and Treatment of HCV

To apply the MDP model to HCV we first define the elements of the model for this disease using the notation from Section 3.1. Note that throughout this section we assume that the threshold for

cost-effectiveness is \$50,000 per QALY; thus we convert costs to utility with this value (Chapman et al., 2004).

For HCV, the decision epochs are  $T = \{1, 2, \dots, 100\}$  where each period represents one year of life. The states in the HCV model are defined as  $S = \{(h, i)\}$  where  $h \in \{\text{uninfected, infected without cirrhosis, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant (first year), liver transplanted (after first year), death}\}$  and  $i \in \{\text{unaware of infection status, aware of infection status}\}$ . The actions in HCV are  $A_s = \{\{\text{NT, T, TT}\}\}$ , whenever  $h = \text{“uninfected,” “infected without cirrhosis,” or “compensated cirrhosis”}$ , and  $i = \text{“unaware of infection status”}$ , otherwise  $A_s = \{\text{NT}\}$ , where NT, T, and TT correspond to “do nothing”, “test for HCV”, and “test for HCV and treat if necessary”, respectively. In the numerical results below, we look at not only the optimal decisions but also decisions in other times periods, so as to build insight on the impact of timing on cost-effectiveness.

The results of the model will be based on QALYs and costs. QALYs are associated with each health state as summarized in Table 1 (tables for cost values are available in supplemental documentation). For each screening policy, the utility is calculated by converting the resulting QALYs associated with the policy to a cost where 1 QALY represents \$50,000, and then subtracting the dollar costs of the screening test, treatment, and annual HCV related health costs. Consequently, policies that result in utilities greater than zero are considered cost-effective.

Health State	QALY Value	Reference
Uninfected	1.00	Singer and Younossi (2001)
Infected without Cirrhosis	0.96	Singer and Younossi (2001)
Compenstated Cirrhosis	0.80	Singer and Younossi (2001)
Decompensated Cirrhosis	0.56	Singer and Younossi (2001)
Transplantation (1st year)	0.80	Singer and Younossi (2001)
Transplantation (after 1st year)	0.95	Singer and Younossi (2001)
Hepatocellular Carcinoma	0.25	Singer and Younossi (2001)
Treatment	0.93	Bennett et al. (1997)

Table 1: QALY values for various health states

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 probability of acquiring HCV equal to zero from the total discounted cost of an individual who acquires HCV at age of 23 (since this data does not

exist for HCV, the value is based on the average age of HIV infection from Rosenberg et al. (1994) 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. The expected cost of a secondary infection must be multiplied by the probability of infecting someone else at each time step, which will depend greatly 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. Note that an annual discount rate of 3% is used for both cost and QALY values (Lipscomb et al., 1996; Singer and Younossi, 2001).

The values for the transition probabilities were taken from the literature. Some of the transitions depend greatly on the age of the individual as well as the risk characteristics of the person. For example, injection drug users (IDUs) are at higher risk for initially acquiring HCV, while those who drink more than 50 grams of alcohol per day have faster progression rates to cirrhosis. Progression to cirrhosis also increases with age and male gender. Death rates are taken to be a function of age as reported by the CDC. See Table 2 for the details on the probabilities and rates. Efforts were made to use values from the same paper when possible.

<b>Base case transition probabilities</b>	<b>Value</b>	<b>References</b>
Progression rate to Compensated Cirrhosis for heavy drinkers	0.0072	Freeman et al. (2001)
Progression rate to Compensated Cirrhosis without heavy drinking	0.0036	Poynard et al. (2001)
Progression rate to Decompensated Cirrhosis	0.0390	Bennett et al. (1997)
Progression rate to HCC from Cirrhosis or Decompensated Cirrhosis	0.0268	Degos et al. (2000)
Rate of liver transplant from Decompensated Cirrhosis	0.0300	Bennett et al. (1997)
Death rate from Decompensated Cirrhosis	0.2180	Fattovich et al. (1997)
Death rate from HCC	0.4270	Fattovich et al. (1997), Bennett et al. (1997)
Death rate after liver transplant first year	0.1370	Forman et al. (2002)
Death rate after liver transplant after first year	0.0520	Forman et al. (2002)
Death rate from other causes		CDC, Deaths (2006)

Table 2: Parameter values for transition probabilities (reported in annual terms)

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. Therefore, since the HCV risk groups

are very similar to that of HIV, we examined HIV incidence data to extrapolate the ages at which individuals are at most risk for the overall population. According to the Centers for Disease Control and Prevention (2005a), children under age 13 constitute less than 1% of persons living with HIV through the year 2000 (mostly acquired through mother-to-infant transmission, which is not studied in this model), and after age 55 HIV infection rates drop dramatically. Consequently, we set the probability of acquiring HCV before age 13 and after age 55 to zero for the overall population. According to the Department of Health and Human Services (2005), percent drug use rises dramatically from age range 12-13 to age range 14-15 and remains high until age range 50-54. Consequently, for IDUs we used an age range of 15-50 as the period in which the probability of acquiring HCV is higher (with other probabilities of infection as above). For a commercial sex worker, we used an age range of 15-45 for their higher risk of infection period with values outside of this range as above (Brewer et al., 2000). Table 3 indicates the probabilities of infection for each risk group.

<b>Risk Group</b>	<b>Annual Probability of Infection</b>	<b>References</b>
Overall population	0.0004	CDC, Hep Surv (2006)
Injection drug users	0.014	CDC, Viral Hep C (2006)
Incarcerated individuals	0.0016	CDC, Viral Hep C (2006)
Commercial sex workers	0.0012	National Network (2005)
STD clinic attendees (non-IDU)	0.0008	National Network (2005)

Table 3: Annual probability of HCV infection by type of risk group

Most of the existing screening papers have not taken into account varying progressions due to alcohol, although medical studies have found there can be a significant effect. We define a person as a heavy drinker if she has 2 or more drinks per day (greater than 50g or alcohol). We assume that once a person becomes aware of his infection, she reduces her drinking below the 50g threshold (we also study sensitivity to this factor), and she reduces her probability of infecting others by half (Singer and Younossi, 2001). Behavioral change, then, not only affects the progression of the disease in a patient, but also the rate of transmission to others. Sensitivity is performed on these values.

### 4.3 Numerical Results

We first present a set of graphs illustrating the results for two populations: IDUs and the general population. In each of these graphs, the  $x$ -axis is the age of the individual at the time of the test and the  $y$ -axis is the additional discounted utility as compared to the do-nothing option. Therefore, any value above the do-nothing line is cost-effective. For example, if test-only at age 35 has a utility of 1000, then this is equivalent to an additional 0.02 QALYs compared to do nothing assuming the \$50,000/QALY threshold value. For each population we consider different amounts of behavioral change due to reduction in alcohol consumption (if they drink) and/or reduction to risky behavior (if they engage in it). Each of the graphs is only for a single test and/or treat.

The results for IDUs are shown in Figures 2(a) and 2(b). In (a) the IDUs are assumed to be heavy drinkers and in (b) the IDUs drink less than 50g/day. For almost all age ranges, test-only and test-and-treat are cost-effective for this population, even when there are no behavioral changes. Note that test-and-treat dominates test-only for all situations. In addition, test-only or test-and-treat has approximately twice the additional discounted utility for heavy drinkers than for non-drinkers. Finally, the age range that is most cost-effective for test or test-and-treat is approximately 25-35 years of age, although the range of ages where test or test-and-treat is cost-effective are smaller for non-drinkers since there is less impact from a behavior change of a non-drinker. It should be mentioned that since IDUs are engaging in illegal activities, it is not clear if they would be likely to change risky behavior or alcohol consumption based on knowledge of being HCV-positive. Therefore the most likely plots that would apply to this group would be the ones for no infection reduction and no alcohol reduction.

Figure 3(a) shows the results of a single test for the overall general population. In this figure, we use the value that 4.90% of the general population for the U.S. has 2 or more alcoholic drinks per day, obtained from the Behavioral Risk Factor Surveillance System (BRFSS) (National Center for Chronic Disease Prevention and Health Promotion). As is the case for IDUs, it is more cost-effective to test-and-treat than to test-only. In addition, test-only is not cost-effective for the general population. Although all test-and-treat possibilities are cost-effective even when there is no change in behavior for risk or alcohol consumption, the additional discounted utility is fairly small—over two orders of magnitude less cost-effective than test-and-treat for IDUs.

Clearly, using a single test over a lifetime for test-only and test-and-treat may not be the most

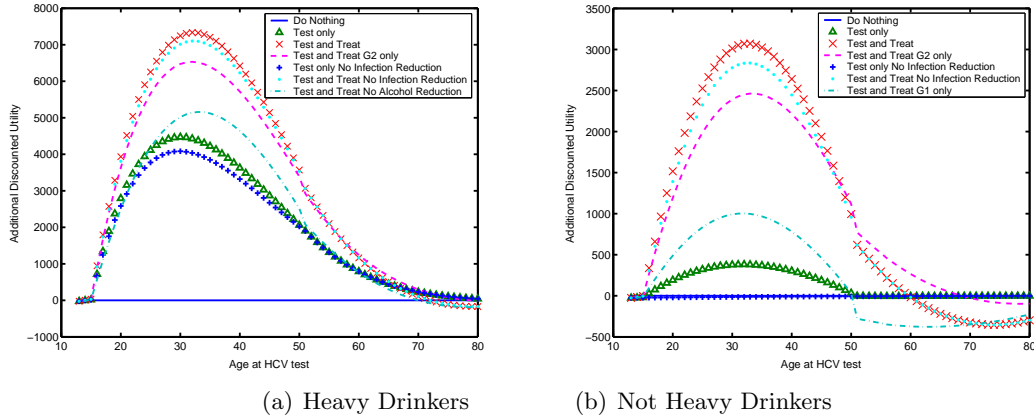
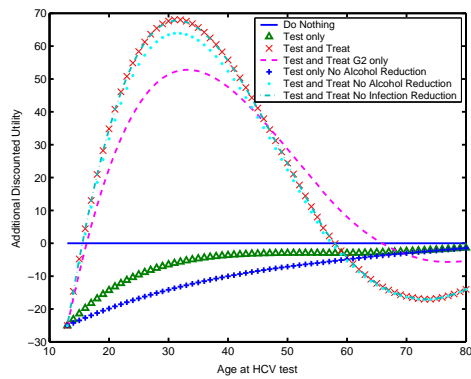


Figure 2: Additional discounted utility for various test and test-and-treat alternatives for IDUs.

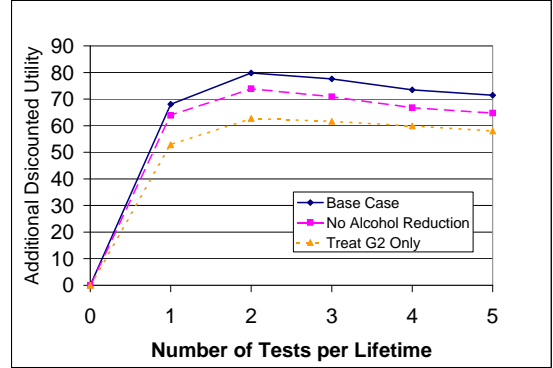
cost-effective policy. We considered actions up to five times over the horizon for both test-only and test-and-treat policies. In Figure 3(b) we show the discounted additional utility over doing nothing for different numbers of tests for the general population. As can be seen from this figure, testing twice over the lifetime is best for all cases in this population, although this assumes that the best timing of tests is chosen. Additional results for both IDUs and the general population are shown in Table 4. In this table both the additional discounted utility and the optimal test times are presented. The range of cost-effective ages for single tests are also included for comparison. Notice that a higher number of tests is more cost-effective for IDUs than for the general population, which is due to the higher risk for this group. Figure 4(a) shows the sensitivity of the optimal results for the IDU population to the change in alcohol behavior effectiveness (from 100% to 0%) on progression to cirrhosis, since this factor is not well-known for HCV.

It is interesting to note from Table 4 that for cases where multiple testing was used, the most cost-effective implementation was not uniform spacing of the test. In the table, as age increases, the time between tests tends to increase. As mentioned in Section 2, other researchers that have studied multiple testing strategies in general employ uniform policies.

It is useful to examine timing and comparison of number of tests in more detail. Figure 4(b) displays the utility gained by testing (and treating) the overall population 3 times over the lifetime based on the age of the first test. The best and worst cases are shown along with points corresponding to evenly spaced tests; the value of a single test over the lifetime is also shown for comparison.



(a) Single Test



(b) Multiple Tests

Figure 3: Additional discounted utility for various test and test-and-treat alternatives for the overall population.

For the first part of a lifetime (about 35 years), the best evenly spaced three tests do as well as the best intervals of any length, although evenly spaced intervals can also be as bad as the worst three tests. It is also interesting to note that a single test over a lifetime is dominated by most evenly spaced 3 tests for the first part of the lifetime, but in the second half of the lifetime one screening is better. This makes sense, since there is less risk of contracting the disease in the latter part of the lifetime and less benefit gained from finding a positive test, however it suggests that timing is important towards determining how many screenings are appropriate. The graph also shows that usually longer intervals between tests are better for HCV; longer intervals may be more likely to balance costs and gains. These results provide further evidence that timing and intervals between tests are important. In Faissol et al. (2007) we explore policy recommendations related to timing and frequency of tests and identify implementable policies that are cost-effective.

#### 4.4 Comparison of Results to Other Studies/Recommendations

Our results fall in line with CDC recommendations (although these do not explicitly consider age or alcohol). For all groups studied with a high risk of acquiring HCV, both testing (and test-and-treat) were cost-effective over a wide age range compared to doing nothing. We do not find, however, that testing alone is cost-effective for the general population at this point. Of course, conditions such as the cost of an HCV test, prevalence of disease, and treatment costs/effectiveness could change in

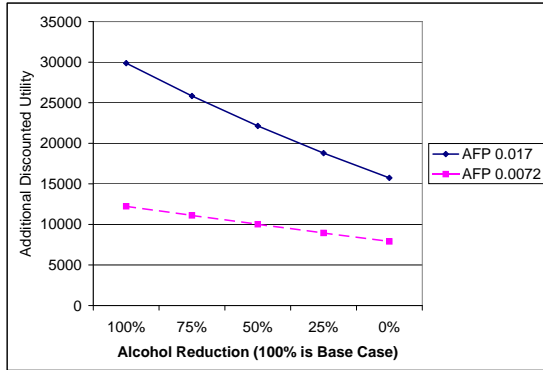
Risk Group	Case	Additional Discounted Utility	Optimal Ages to Test	Single Test Cost-Effective Age Range
<b>General</b>	Base Case	79.8	26, 41	16-57
	Treat G2 Only	62.7	28, 41	17-65
	No Alcohol Reduction	73.9	27, 41	16-57
<b>IDU</b>	No Alcohol Base Case	3806.3	21, 27, 33, 41, 49	16-59
	No Alcohol Treat G2 Only	4648.0	21, 27, 33, 39, 45	16-69
	Alcohol Base Case	12234.0	21, 27, 33, 41, 49	14-71
	Alcohol Treat G2 Only	11236.0	21, 27, 33, 41, 49	14-78
	75 % Alcohol Reduction	11112.0	21, 27, 33, 41, 49	14-70
	50 % Alcohol Reduction	10017.0	21, 27, 33, 41, 49	15-70
	25 % Alcohol Reduction	8947.9	21, 27, 33, 41, 49	15-70
	0 % Alcohol Reduction	7904.6	21, 27, 33, 41, 49	15-70

Table 4: Optimal policies where up to 5 test and test-and-treat per lifetime are considered.

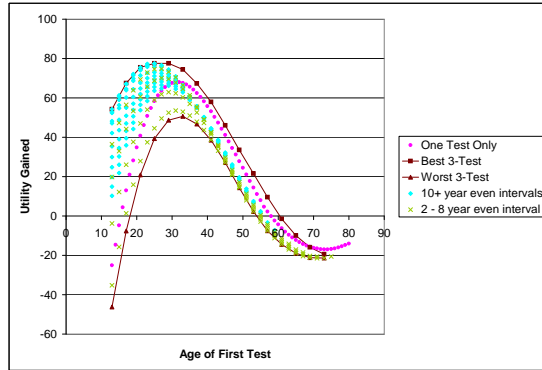
the future. We did find that test-and-treat was cost-effective for the general population, but only very slightly.

New HCV testing technologies are being developed that could impact the recommendation regarding universal screening. OraSure Technologies Inc. ([www.orasure.com](http://www.orasure.com)) is commercializing a rapid HCV test that uses a saliva sample, which should bring down costs and be easier to administer. If the per test cost could be reduced to \$1.50, test-only would be cost-effective for the overall population. The probability of infection is also a key issue in testing. We find that if the probability were to increase from 0.0004 to 0.0017, *ceteris paribus*, universal screening of the general population even without treatment would be cost-effective.

Our findings do vary significantly from the USPSTF (U.S. Preventive Services Task Force, 2004) who recommend against screening of the general population and make no recommendation for high-risk populations such as IDUs. The USPSTF believes that the “psychological harm” of screening such as anxiety or the impact on partner relationships can be an important factor. In addition, they argue that the natural progression of HCV is unclear in that treatment is only effective for a subset of the population and it is difficult to determine who these individuals are *a priori*. We do explicitly model the disutility to the individual of ineffective treatment, though we did not explicitly consider the potential psychological harm from the screening process since there are not good estimates of this cost for HCV. Due to the large additional utility of test-only and test-and-treat for the IDU population, the psychological harm would have to be quite large to not recommend testing this



(a) Sensitivity on the effect that alcohol reduction has on disease progression with the best timing for five test-and-treat actions for IDUs



(b) Three tests for overall population compared to one test as function of age of first test

Figure 4: Additional discounted utility for various test and test-and-treat alternatives

group. It is the case that if this cost were significant, we would not recommend test-and-treat for the general population, although we expect that the harm is likely much less than that for HIV, for which universal screening of the general population is now recommended.

Finally, we should mention that when alternative values for QALYs, transition probabilities, or costs were found in the literature, we used the most conservative or tested the sensitivity of the results to both. For example if the QALY values for HCV reported in Chong et al. (2003) were used rather than those in Singer and Younossi (2001), we find that the exact value changes but that the overall conclusions about which policies are best agree and ages when testing is cost-effective are close to the same.

## 5 Conclusions

In this paper we have developed a Markov Decision Process (MDP) for examining the timing and frequency of testing with treatment as an option where the action can result in disease awareness that changes the progression of the disease, where the MDP has partial updating of disease presence based on testing. We show monotonicity results and find some conditions that are sufficient to determine whether testing (and treating) is a good decision. In particular, we find sufficient conditions for testing (and treating) to be beneficial from a cost-minimization perspective for society.

Furthermore, when the disease can be modeled by two states (e.g., healthy and sick), we show the conditions under which it is cost-saving to test (and treat).

We use the MDP model in the case of HCV to study the timing of test and treatment actions for various populations. 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 are cost effective for IDU populations. The additional QALYs gained as compared to do nothing can be as high as 0.245 for test-and-treat for IDUs. We also found 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.

Regarding the general population who does not drink excessively, our recommendations find testing and treating is at the boundary of cost-effectiveness; 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 HCV. We also add to the literature by specifying ages for testing of other populations. We have further 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 Diehl et al. (2006) could be beneficial for some diseases. Further analysis of MDPs could also suggest other types of policies to consider.

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