Value of Expanding HCV Screening and Treatment Policies in the United States

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ABSTRACT

Objectives: To investigate the value of expanding screening and treatment for hepatitis C virus (HCV) infection in the United States.

Study Design: Discrete-time Markov model.

Methods: We modeled HCV progression and transmission to analyze the costs and benefits of investment in screening and treatment over a 20-year time horizon. Population-level parameters were estimated using National Health and Nutrition Examination Survey data and published literature. We considered 3 screening scenarios that vary in terms of clinical guidelines and physician awareness of guidelines. For each screening scenario, we modeled 3 approaches to treatment, varying the fibrosis stage of treatment initiation. Net social value was the key model outcome, calculated as the value of benefits from improved quality-adjusted survival and reduced transmission minus screening, treatment, and medical costs.

Results: Expanded screening policies generated the largest value to society. However, this value is constrained by the availability of treatment to diagnosed patients. Screening all individuals in the population generates $0.68 billion in social value if diagnosed patients are treated in fibrosis stages F3-F4 compared with $824 billion if all diagnosed patients in stages F0-F4 are treated. Moreover, increased screening generates cumulative net social value by year 8 to 9 under expanded treatment policies compared with 20 years if only patients in stages F3-F4 are treated.

Conclusions: Although increasing screening for HCV may generate some value to society, only when paired with expanded access to treatment at earlier disease stages will it produce considerable value. Such a "test and treat" strategy is likely to entail higher short-term costs but also yield the greatest social benefits.

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Chronic infection with hepatitis C virus (HCV) is estimated to affect at least 3.5 million individuals in the United States,[1] and the incidence is increasing.[2] Chronic HCV infection can lead to hepatic damage, including cirrhosis and hepatocellular carcinoma, and is the most common cause of liver transplantation in the United States.[3,4]

Because symptoms of HCV infection are usually absent or nonspecific until late stages of the disease, an estimated 50% to 75% of infected individuals are unaware of their HCV status and get tested only after significant symptoms develop.[5-7] Prior research suggests that earlier identification and treatment of patients infected with HCV generates benefits for patients and society, but the potential social value of increased screening, whether alone or in combination with early treatment, is not well understood.[3,8-12] Novel HCV regimens, including direct-acting antivirals (DAAs), have increased cure rates dramatically, which may affect the value of expanded screening.[13,14] For example, rates of sustained virologic response (SVR) observed in clinical trials of DAA treatments generally exceed 98% for patients infected with genotype 1 HCV without cirrhosis or prior treatment failure.[15-19]

Despite rapid innovation in HCV treatment, however, unmet need remains significant. Only 13% to 36% of patients diagnosed with chronic HCV infection have received treatment,[3] and even fewer patients completed the treatment regimen and achieved SVR.[20] Failures to screen, diagnose, and treat all contribute to this current state of affairs.

Broad consensus exists on the need for inclusive screening. In 2012, the CDC updated its guidelines and recommended expanding screening to include all individuals born between 1945 and 1965 (baby boomers)—a cohort comprising an estimated 75% of existing HCV infections.[21] Similarly, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) updated their guidelines in 2015 to recommend one-

time screening for asymptomatic baby boomers.[3] Unfortunately, more than 40% of physicians are unaware of current guidelines,[21,22] and many individuals infected with HCV may have limited contact with the healthcare system. For these and other reasons, HCV screening rates remain below recommended levels.

It remains unclear whether and to what extent expanded screening benefits society. All-oral DAA regimens present considerable up-front costs[23]; yet recent research suggests the value of their long-term health benefits is likely to be even higher.[12] Screening can identify potentially treatable patients, with implications for both healthcare costs and health benefits. In this article, we explore whether and to what extent expanded screening policies provide net value to society and assess the net social value of varying levels of access to treatment after diagnosis.

Take-Away Points

We developed a discrete-time Markov model to simulate the effects of expanding screening for hepatitis C virus (HCV) infection and initiating treatment at different fibrosis stages. We compare screening and treatment policies in terms of net social value over a 20-year horizon.

- Increased screening generates positive social value in 20 years, but this benefit is reduced without concurrent expansion of treatment.
- Investments in HCV screening and treatment are expected to "break even" from a social perspective after 20 to 22 years when treatment is limited to fibrosis stages F3-F4 and after only 8 to 9 years when treatment is expanded to include stages F0-F2.

METHODS

Overview of the Markov Model of HCV Transmission and Progression

In this article, we present results of a discrete-time Markov simulation model (Microsoft Excel 2010/VBA, Microsoft Corporation, Redmond, Washington) that simulates the detection, treatment, and progression of populations susceptible to HCV infection, as well as associated costs and health benefits, under different screening and treatment policies. The model builds on previous work that simulates the effects of treatment policies (without screening) on population-level costs, health benefits, and disease dynamics.[12]

The model tracks infected and uninfected individuals in 3 groups, stratified by risk of HCV exposure: a) people who inject drugs (PWID), b) HIV-positive men who have sex with men (MSM-HIV), and c) all other adults born before 1992, when systematic testing of the blood supply for HCV began (Other Adults). Of the last group, approximately 39% were baby boomers.[5] The model further stratifies the infected population in each risk group by HCV genotypes 1, 2, and 3, which account for 70%, 16%, and 12% of the US population infected with HCV, respectively.[24]

Once infected, individuals progress through disease states according to transition probabilities drawn from the literature (see **eAppendix**, available at **www.ajmc.com**). Undiagnosed patients face some probability of screening, which varies across the 3 scenarios described below. Diagnosed patients face a probability of treatment that varies according to 3 treatment policy scenarios. If successfully treated, cured patients return to the pool of susceptible, uninfected individuals and experience the same probability of reinfection as those without a previous infection.

The 3 HCV risk groups were modeled independently, such that individuals do not switch among risk groups and cannot infect individuals in a different risk group. Although patients are infected with only 1 genotype at a time, once cured they can be re-infected with any genotype. HCV transmission in the MSM-HIV and PWID risk groups is based on the number of infected individuals in each risk group and genotype, and is described in detail in the eAppendix.[25] Outside of the PWID and MSM-HIV groups, the risk of HCV transmission is low.[8,25-27] Therefore, we made the simplifying assumption of no further transmission of HCV in the Other Adults group.

Key model inputs included starting population size, transmission probabilities, and progression rates in each risk group; genotype and disease state at diagnosis; HCV treatment costs; nontreatment medical expenditures; screening costs; quality-adjusted life-year (QALY) utility weights; and mortality rates. Model parameters were obtained from the published literature or computed from National Health and Nutrition Examination Survey (NHANES) data for the years 2003 through 2012.[5] All cost estimates were adjusted to 2015 US dollars, and all future costs and QALYs were discounted at 3% per year.

Base drug costs reflect wholesale acquisition costs as of December 2014. However, since treatment duration varies by genotype, this results in different treatment costs by genotype. All treatments considered are currently patent-protected and face price competition from other branded products. To account for branded competition, the model reduced treatment costs by 46% in years 2 to 20 of the simulation.[28,29] Screening costs included the cost of an HCV antibody test (enzyme-linked immunoassay) and a level-1 outpatient visit.[4] Medical expenditures for diagnosed patients were computed by disease state and diagnosis status.[9,10,30]

QALY weights were assigned based on disease state and diagnosis status. We assumed that individuals diagnosed

Table 1. Description of HCV Screening Scenarios[a,b,c]

Screening Scenarios	Description
Current Screening	Offer screening to the baby boomer subpopulation in Other Adults group each year; after they accept once, do not offer again.
	Offer screening to PWID and MSM-HIV annually; screen if accept.
	58% of primary care physician/clinicians offer screening.
Physician Education	Offer screening to the baby boomer subpopulation in Other Adults group each year; after they accept once, do not offer again.
	Offer screening to PWID and MSM-HIV annually; screen if accept.
	100% of primary care physician/clinicians offer screening.
Screen All	Offer screening to everyone in the Other Adults group annually until they accept; after they accept once, do not offer again.
	Offer screening to PWID and MSM-HIV annually, and screen if accept.
	100% of primary care physician/clinicians offer screening.

HCV indicates hepatitis C virus; MSM-HIV, HIV-positive men who have sex with men; PWID, people who inject drugs.
[a]Screening scenarios are consistent across treatment policies in our analysis.
[b]Individuals in the PWID and MSM-HIV groups who reject the offer of screening or test negative for HCV will be offered screening in all subsequent years. Adjusting for the probability of visiting a doctor, the proportion of physicians offering screening, and the screening acceptance rate, individuals in the MSM-HIV and PWID groups are, on average, offered screening every 1.9 years and screened every 2 years in Current Screening. On average, they are offered screening every 1.1 years in Physician Education and Screen All and are screened every 1.2 years.
[c]Other Adults, individuals born before 1992 who are not in the PWID and MSM-HIV groups.

with HCV incur associated psychological costs; therefore, patients who are HCV-infected, but undiagnosed, have QALY weights 2% higher than their diagnosed and untreated counterparts.[23] For details on model parameters, dynamics, and assumptions, see the eAppendix.

Scenarios Analyzed

HCV screening. The model explores 3 scenarios for the frequency and inclusiveness of screening in clinical practice (see Table 1). We used AASLD/IDSA screening guidelines to define screening practice,[3] adjusting for 2 important realities. First, screening can occur only if a patient interacts with a healthcare provider. NHANES data were used to determine the annual rate at which patients received healthcare services. Second, patients might decline offered screening. In all scenarios, we assumed that 91% of those offered screening would accept it.[7]

Real-world screening rates also depend on physician awareness of, and adherence to, screening guidelines. The baseline scenario (Current Screening) assumes that 58% of clinicians are aware of HCV screening guidelines based on data reported in the literature.[22] To assess the effects of expanded screening on costs and patient outcomes, we considered 2 alternative scenarios: Physician Education explores the effect of increasing physician awareness of screening guidelines to 100%, with no change in the guidelines themselves, and Screen All assumes that, in addition to increasing physician awareness of guidelines to 100%, guidelines are expanded to provide one-time HCV screening to all individuals born before 1992. Because data for guideline adherence were not available, we made the simplifying assumption in all scenarios that all physicians aware of screening guidelines also adhere to them. In practice, physician adherence to clinical guidelines is likely to be imperfect[31]; however, assuming full adherence yields the maximum possible value that could be generated by screening. We examined the sensitivity of screening rates to physician adherence in the eAppendix.

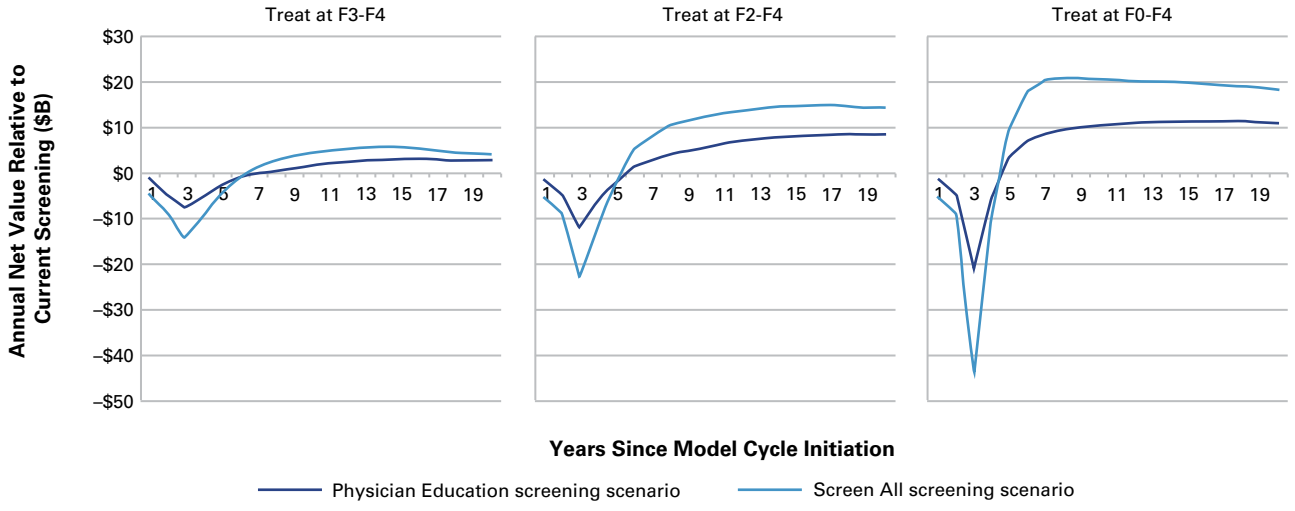
Treatment practices. The effect of HCV screening on patient health depends on whether a diagnosed patient is subsequently treated. To better understand the relationship between screening and treatment access, we varied the fibrosis stages at which treatment would be available to diagnosed individuals in each screening scenario. Using the METAVIR scoring system to categorize liver fibrosis stages from F0 (no fibrosis) to F4 (most severe), we considered 3 levels of treatment access: a) treatment at fibrosis stages F3-F4, which reflects current practice[32-34] and serves as the baseline; b) treatment at F2-F4; and c) treatment at F0-F4. We assumed that all screened and diagnosed individuals receive all-oral DAAs if they are insured (see eAppendix).

Key Model Outputs

The key model output was net social value, defined as the difference between: a) the economic value of clinical benefits from improved quality-adjusted survival and reduced transmission, which is calculated as total QALYs multiplied by $150,000[35,36]; and b) total healthcare costs, measured as the sum of treatment costs, screening costs, and other medical expenditures. We reported results as changes relative to the baseline scenario (ie, Current Screening with treatment at F3-F4). Therefore, net social value is reported as the difference between a given alternative scenario and the baseline. We also examined the value of expanding screening while treatment remained constant. In this case, Current Screening serves as the baseline for comparing expanded screening scenarios.

In addition to net social value, we reported incremental cost-effectiveness ratios relative to the baseline. Also, since HCV treatment incurs short-term costs but generates long-term benefits, we calculated the break-even point (ie, the

Figure 1. Annual Net Value of Expanded Screening Policies Relative to Current Screening, by Treatment Access Policy[a]



$B indicates US dollars in billions; F0-F4 indicate fibrosis stages, F4 being most severe.
[a]Annual net value is the difference between the value of benefits and costs in a given year. Results are presented as the net value of each screening scenario relative to the Current Screening scenario, holding treatment constant.

years required to switch from negative to positive cumulative net social value) for each screening and treatment combination. Cumulative social value and cost-effectiveness results are presented for a 20-year time horizon. For results at the 10-year time horizon, see the eAppendix.

Sensitivity Analyses

Each parameter in our model is characterized by some degree of uncertainty. For example, estimates for disease and transmission dynamics vary in the literature. Additionally, our model includes a number of important assumptions that affect our results.

To test the sensitivity of our model to disease progression and transmission parameters, we conducted sensitivity tests of key model parameters within each scenario. For each key parameter, we varied the parameter across a range and report how the scenario's value changes in percentage terms when using the upper and lower bounds of the range. We also examined several key assumptions, including physician adherence to screening guidelines, future reductions in treatment costs, and others. For details, see the eAppendix.

RESULTS

Annual Net Value

Figure 1 reports the annual net value of screening scenarios stratified by treatment scenario. More inclusive screening policies involve net costs in the short term, but generate positive net value after 5 to 7 years. More comprehensive treatment policies cause inclusive screening policies to rise in value more quickly, but also make them more costly in the short run. Relative to Current Screening, annual net values in Screen All are approximately double those in Physician Education.

Cumulative Net Value

Costs and QALY gains used to calculate cumulative net social value over the 20-year time horizon are presented in Table 2. Total cost is driven primarily by medical expenditures and treatment costs. In both expanded screening scenarios, medical expenditures increase under treatment at F3-F4. By contrast, savings from reduced medical expenditures exceed the costs of treatment in all scenarios under treatment at F0-F4.

Over a 20-year time horizon, Screen All generates the greatest cumulative net social value at all levels of treatment access compared with the baseline (see Table 3). In general, however, screening expansion has a relatively small effect on cumulative net social value, unless treatment is similarly expanded. Relative to Current Screening, Screen All generates a net gain of $0.68 billion under the most restrictive access to treatment (F3-F4) and Physician Education generates a net loss in social value of $1.76 billion. The relative gain from increased screening rises with more comprehensive access to treatment. Under treatment at F2-F4, Physician Education generates net social value of $421 billion and Screen All generates net social value of $464 billion over 20 years, relative to

Table 2. Incremental Changes in Cost and QALYs Relative to Baseline Over 20-Year Time Horizon[a,b]

Screening Scenarios		Incremental Cost (2015 US$, millions)				Incremental QALYs
		Total Change in Cost	Components of Cost Calculation			
			Medical Expenditures	Screening Costs	HCV Treatment Costs	
Current Screening	Treat F3-F4	–	–	–	–	–
	Treat F2-F4	–$12,008.70	–$64,462.69	$46.94	$52,407.05	2,426,958
	Treat F0-F4	–$34,896.72	–$158,889.00	$104.27	$123,888.00	4,223,819
Physician Education	Treat F3-F4	$20,688.93	$13,833.73	$950.67	$5904.54	126,204
	Treat F2-F4	$5644.79	–$56,679.79	$1022.25	$61,302.32	2,844,402
	Treat F0-F4	–$22,905.26	–$160,313.61	$1109.93	$136,298.42	4,861,810
Screen All	Treat F3-F4	$39,405.21	$27,167.71	$1541.78	$10,695.73	267,230
	Treat F2-F4	$21,860.64	–$48,152.48	$1613.36	$68,399.75	3,240,048
	Treat F0-F4	–$11,816.73	–$159,943.80	$1701.04	$146,426.02	5,411,407

F0-F4 indicate fibrosis stages, F4 being most severe; HCV, hepatitis C virus; QALY, quality-adjusted life-year.
[a]All results are relative to baseline, which is Current Screening with treatment of fibrosis stages F3-F4.
[b]All future values are discounted at a rate of 3%.

baseline. These gains increase to $752 billion (Physician Education) and $824 billion (Screen All) under more comprehensive treatment (F0-F4).

Under any given treatment strategy, Screen All is the highest-value screening strategy (see Figure 2). With treatment at F2-F4, Screen All generates nearly twice the value generated by Physician Education over 20 years. The value of screening approximately doubles when treatment is expanded to F0-F4, under which Physician Education and Screen All generate $83.7 billion and $155.1 billion, respectively, in cumulative discounted social value. Broader treatment increases the costs and benefits by roughly the same proportion. Therefore, even though net social value doubles with wider treatment, incremental cost-effectiveness ratios (ICERs) for screening do not vary ($42,000/QALY for treatment at F2-F4 and $19,000/QALY for F0-F4).

Incremental Cost-Effectiveness

All screening strategies are highly cost-effective after 20 years when combined with treatment at F2 or earlier (Table 3). In these expanded treatment scenarios, Screen All exhibits the highest ICER under treatment at F2-F4, at $6747/QALY gained, and 4 of the 6 scenarios are cost-saving. Expanded screening is less cost-effective when treatment is restricted to F3-F4, however, with ICERs reaching $163,933/QALY for Physician Education.

Break-Even Analysis

Varying screening policy has little impact on the number of years required to break even (see Table 3). The accompanying treatment scenario has a much larger effect. For example, with treatment restricted to F3-F4, Screen All breaks even in 20 years—just slightly earlier than Physician Education (22 years). With expansion of treatment to either F2-F4 or F0-F4, all screening scenarios break even in 8 or 9 years.

Table 3. Cumulative Social Value and Incremental Cost-Effectiveness Relative to Baseline Over 20-Year Time Horizon[a,b]

Screening Scenario		Treatment Access		
		Treat F3-F4	Treat F2-F4	Treat F0-F4
Current Screening	Cumulative social value ($B)	–	$376.05	$668.47
	ICER[c] ($/QALY)	–	Cost-saving[d]	Cost-saving[d]
	Break-even point[e] (years)	–	8	8
Physician Education	Cumulative social value ($B)	–$1.76	$421.02	$752.18
	ICER[c] ($/QALY)	$163,933	$1985	Cost-saving[d]
	Break-even point[e] (years)	22	9	8
Screen All	Cumulative social value ($B)	$0.68	$464.15	$823.53
	ICER[c] ($/QALY)	$147,458	$6747	Cost-saving[d]
	Break-even point[e] (years)	20	9	8

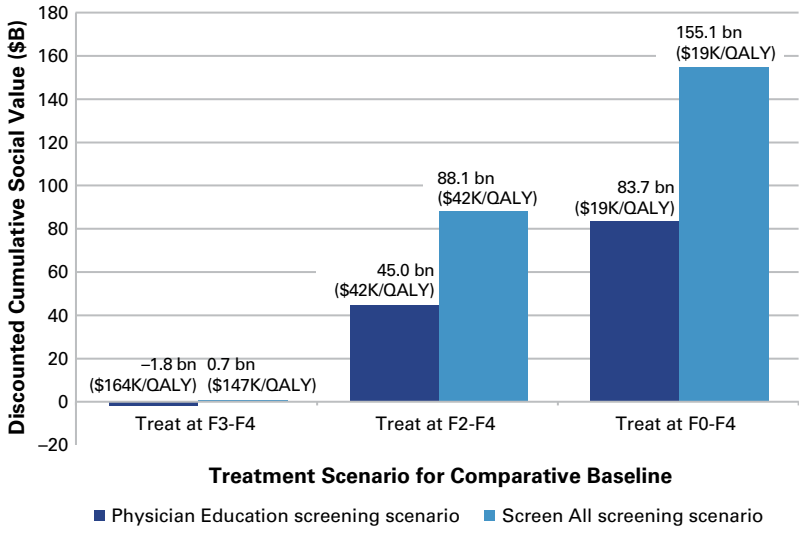
$B indicates US dollars in billions; F0-F4 indicate fibrosis stages, F4 being most severe; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
[a]All results are relative to baseline, which is Current Screening with treatment of fibrosis stages F3-F4.
[b]Values are in 2015 US dollars. All future values are discounted at a rate of 3%.
[c]ICER values represent change in overall cost divided by change in cumulative QALYs.
[d]Cost-saving indicates a reduction in cumulative costs relative to baseline.
[e]Break-even points indicate the time required for a scenario to break even (ie, switch from negative to positive cumulative net social value) relative to the baseline scenario. If the break-even point occurred beyond the 20-year time horizon, the model was run for 50 years to determine the break-even point.

Sensitivity Analyses

Sensitivity tests within screening/treatment combinations highlight 4 key drivers of uncertainty in our results: starting size of the total Other Adult population, QALY utility weights, discount rate, and economic value of QALYs. Combining the maximum and minimum values from these parameters' ranges generates 16 permutations that allow us to approximate the upper and lower bounds on our results, given uncertainty in model parameters.

For scenarios with expanded treatment, net social value always remains positive after 20 years and all scenarios remain cost-effective or cost saving. For screening expansion under treatment at F3-F4, however, cumulative social value ranges from –$27 billion, at the minimum, to $69 billion at the maximum (both under the Screen All scenario); cost-effectiveness under treatment at F3-F4 ranges from $114,819 to $206,992/QALY gained. This result highlights the interdependence between screening and treatment policies. For detailed results and additional sensitivity analyses, see the eAppendix.

Figure 2. Cumulative Net Social Value and ICER of Expanding Screening Only Over 20 Years, Holding Treatment Constant[a]



$B indicates billions of 2015 US dollars; bn, billion; F0-F4, fibrosis stages, F4 being most severe; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
[a]Within each treatment scenario, results are relative to the "Current Screening" screening scenario under the given level of treatment.

DISCUSSION

Both expanded screening and expanded treatment are valuable. However, they are each more valuable when used together. Screening is more effective when diagnosed patients are treated earlier, and treatment expansions generate greater benefits when more patients are diagnosed. Conversely, increasing screening without expanding treatment leads to minimal gains or net losses to society. Newly diagnosed patients derive less benefit and some may even be harmed by the knowledge of their HCV infection if they remain untreated.

For example, the strategy of expanding both screening and treatment breaks even after 8 to 9 years, but expanding screening alone takes 20 to 22 years to break even. The strong complementarity between screening and treatment policies remains over a wide range of cost estimates. Even under the most optimistic screening scenario sensitivities, expanding screening alone takes a minimum of 16 years to break even. One might see greater returns from screening alone, if diagnosed and untreated patients reduce risky transmission behaviors. We do not investigate this possibility, which should be considered in future research.

Our findings suggest that screening expansions are robustly cost-effective and socially valuable, but only when paired with expanded treatment. This is consistent with previous research suggesting that screening for HCV is cost-effective when paired with treatment, even when treating with more expensive DAAs; Rein et al (2012), for example, reported an ICER of $35,700/QALY saved by birth-cohort screening policies focused on the baby boomer population.[7] A more recent study of novel DAAs suggest ICERs ranging from $24,921 to $72,169/QALY saved.[37] At the 10-year time horizon, our results suggest similar levels of cost-effectiveness (see eAppendix).

The pursuit of both expanded screening and treatment for HCV is consistent with current trends in HIV management, where public health agencies and experts have increasingly supported a "test and treat" strategy, as the value of aggressive screening and early treatment for patients with HIV has become clear.[38,39] Existing research, including this study, suggests that such a policy may be beneficial in HCV management as well.[11-13]

Policy makers and payers in a fiscally constrained environment face a conundrum highlighted by our results. Expanding screening and treatment pays off in as few as 8 years, but the up-front costs are high in the scenarios examined. Because of patient turnover, private payers and state Medicaid systems may not retain patients long enough to directly benefit from their investments in HCV treatment.

Furthermore, whereas the costs of screening and treatment are borne by insurers and other payers, only a small portion of the benefits accrue directly to them (in the form of reduced future medical costs).[40] The vast majority of the benefits from treatment accrue to patients and society in longer lives and higher quality of life,[12,40] potentially resulting in a "race to the bottom" in which public and private payers make decisions based on short-term costs alone.

Limitations

Although Markov modeling as a tool for understanding chronic disease management policies is well established in the literature,[41] the approach has limitations. First, as with any simulation, Markov models are not designed to generate predictions or forecasts. Similarly, as with all population-level studies, results from a Markov simulation cannot inform individual-level understanding of disease processes and outcomes.[41,42] The results of our model should be approached as a guide for decision making rather than being predictive of real-world outcomes.

Second, each parameter carries a degree of uncertainty. We present sensitivity analyses and alternative model scenarios in the eAppendix in order to characterize this uncertainty. The model also assumes that parameter estimates are stable for the duration of the simulation and that this is a reasonable representation of HCV disease progression in the modeled risk groups.

Third, the model does not capture some important dynamics of the HCV epidemic. For example, the model does not account for the recent outbreak of HCV due to the increase in intravenous drug use among rural youth.[43,44] In addition, the model does not capture the "treatment cascade" that occurs as patients are lost to follow-up between screening, treatment, and, ultimately, the achievement of SVR.[20] We also lack concrete data on the extent to which physicians adhere to treatment guidelines.[31,45] Our results are therefore an upper bound on the value of increased screening.

Fourth, while NHANES provides reliable population-level estimates, it is subject to several limitations. Small sample sizes make subpopulation estimates less reliable. NHANES also excludes the incarcerated and homeless populations, each of which is thought to have high rates of HCV.[1,46,47] In addition, because NHANES relies on self-reported behavioral data, such as sexual behavior and injection drug use, there is a risk of underreporting. Nonetheless, use of NHANES is preferable to parameters from the literature because its sample is representative of the housed, civilian population of the United States.

Finally, more than half of new HCV infections occur in the PWID population, and evidence suggests that combining increased outreach efforts with prevention, testing, and antiviral treatment may have considerable effects on incidence and prevalence in this group.[48] Effective prevention includes outreach, education, testing, needle and syringe access, and access to opioid substitution therapy.[48,49] Our model does not incorporate the effect of outreach or prevention efforts, however, and assumes that effects on transmission are due to treatment effects alone. Future research should explicitly model the additional effects of programs that offer targeted outreach, screening, prevention, treatment, and wraparound services for high-risk populations.

CONCLUSIONS

Increasing screening for HCV infection may generate considerable value for society, but only when paired with access to treatment at earlier stages of the disease. This result highlights the importance of implementing policies to ensure patients who receive an HCV-positive diagnosis remain in the healthcare system until they receive treatment and achieve SVR. Resource constraints in the healthcare system require difficult allocation decisions, and HCV has been at the center of many recent debates. Our findings suggest that expansions in screening coupled with treatment of all infected patients could break even within 8 years and accrue an additional $823.53 billion in discounted net social benefits over a 20-year horizon. Thus, expanded screening and treatment may pay substantial dividends, but only when effective mechanisms are in place to ensure that patients are retained in care and able to access treatment.

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eAppendix. Value of Expanding HCV Screening and Treatment Policies in the United States

1. Conceptual Model

Hepatitis C (HCV) is a transmissible viral infection that is often asymptomatic in the early stages of the disease, but can progress to serious liver complications, including cirrhosis and hepatocellular carcinoma, over years or decades and lead to a significant healthcare and cost burden. [1-3] Approximately half of HCV-infected patients are unaware they have the disease, which complicates treatment of the virus.[4-6] Recently published guidelines from American Association for the Study of Liver Diseases (AASLD) recommend one-time screening of baby boomers[a] and annual screening of individuals with other high exposure risks, specifically persons who inject drugs (PWID) and HIV-infected men who have sex with men (MSM-HIV).[7]

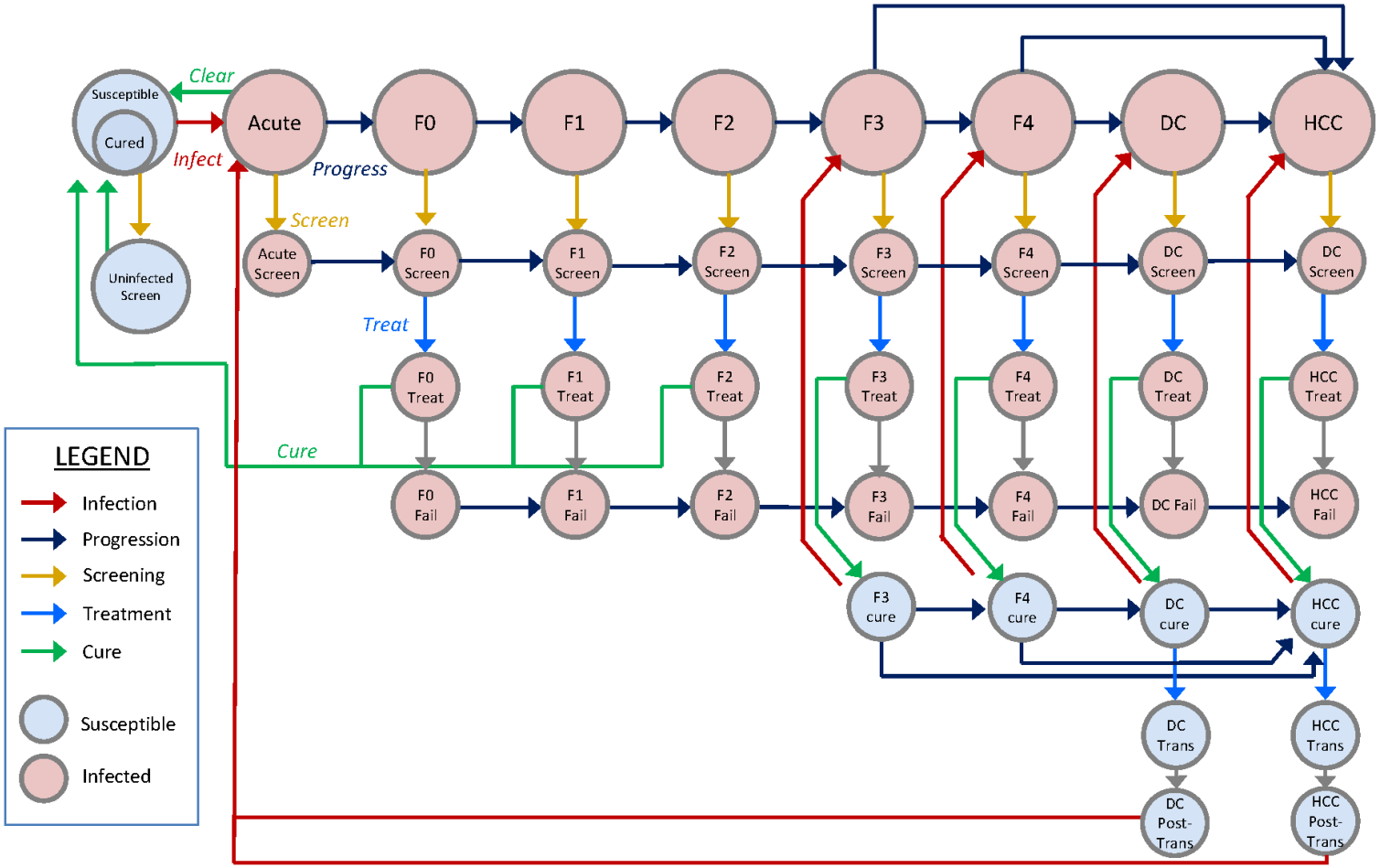
1.1. Model States

We developed a discrete time Markov model in Excel to simulate HCV detection through screening, progression and treatment as depicted in the schematic in **Figure A1**.[8] The schematic in **Figure A1** represents a single one-year cycle in the simulation. The model is simulated repeatedly (eg, 20 years), and population outcomes, such as the number of people in each disease and screening state, are collected at the end of each cycle. In each cycle over which the model is simulated, the population transitions through each disease state at assumed probabilities.

The states modeled include states in which the population is not infected (ie, "susceptible") or cured, states in which the population is infected, and disease detection (ie, "screen") states. The model defines the infection disease states as acute or chronic, where chronic consists of seven stages of liver damage: fibrosis stages F0-F4 using the METAVIR scoring system, decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC). **Table A1** summarizes the METAVIR scoring system, which quantifies the degree of liver fibrosis in patients with liver diseases such as HCV.[9]

[a] About three-fourths of patients in the United States living with the HCV infection were born between 1945 and 1965, "baby boomers."[7,8]

Figure A1. Hepatitis C Screening and Transmission Simulation Model Schematic



F0-F4: METAVIR fibrosis stage (F4 is most severe); DC: decompensated cirrhosis; HCC: hepatocellular carcinoma; Trans: transplant. "Screen" indicates screening offered. All states have transitions to "dead." Adapted from: Van Nuys K, Brookmeyer R, Chou JW, Dreyfus D, Dieterich D, Goldman DP. Broad Hepatitis C Treatment Scenarios Return Substantial Health Gains, But Capacity Is A Concern. *Health Affairs.* 2015;34(10):1666-167.

Table A1. METAVIR Stage Descriptions[9]

Stage	Description
0	No fibrosis
1	Periportal fibrotic expansion
2	Periportal septae (septum)
3	Porto-central septae
4	Compensated cirrhosis

1.2. Populations Modeled

We model three distinct subpopulations, defined by the risk of disease exposure. These 3 subpopulations are: (1) people who inject drugs ("PWID"), (2) HIV-infected men who have sex with men ("MSM-HIV"), and (3) all other US adults born prior to 1992 ("Other Adults"). In the paper we refer to these three cohorts as "risk groups." Of the three groups, PWID is at most risk of HCV infection (a reported 60% of new HCV infections occur in individuals who report recent injection drug use).[10,11] Studies have demonstrated that MSM-HIV are at increased risk of HCV infection through sexual transmission.[12-14]

Of the Other Adults group, approximately 39% are "baby boomers" born between 1945-1965, a population at high risk of prior infection, but low risk of new infection.[12,15,16] The remainder of the Other Adults group is also at low risk of new infection and consists of adults who were born prior to 1992 (when the blood supply started to be systematically tested for HCV) but are not baby boomers.[15] We do not differentiate between baby boomers and non-baby boomers in the Other Adults group, but the proportion of the Other Adults risk group who are baby boomers impacts the derivation of screening scenario parameters (discussed in more detail in section 2.1).

The three risk groups are modeled independently—an individual belongs to one risk group for the duration of the simulation, and risk groups do not interact. Since the risk of transmission is low for the Other Adults group,[17-20] we make a simplifying assumption of no ongoing transmission in the Other Adults risk group. Because it is a closed cohort, the Other Adults population shrinks over time, and is assumed to have increasing mortality rates over the course of a simulation.[21] We assume that the PWID and MSM-HIV risk groups have constant mortality rates and experience ongoing entry and exit such that their size and age distribution remains constant over the simulation. Mortality rates are discussed in more detail in section 3.2.

Within each risk group, we model the three HCV genotypes most common in the US (genotypes 1, 2 and 3).[22] This permits us to model HCV prevalence and transmission with greater nuance, and to account for the fact that different genotypes respond differently to treatment [23], may progress at different rates [24,25], and involve different mortality risks.[26]

1.3. Model Transitions

In each disease state, there are a number of possible transitions, which are represented by arrows in the schematic.[2] The probability of transition along these arrows is assumed, based on the literature, or calculated.

Upon initial infection, patients enter an "acute" phase, which they must leave after one model cycle. They may die, spontaneously clear the disease without treatment, or progress to "chronic" disease. The model assumes that 13% of acute infections for MSM-HIV and 18% of acute infections for PWID and Other Adults clear spontaneously.[27,28] Patients may stay in any disease state, except acute, for more than one cycle.

In the model, patients may be screened at any stage, from susceptible through all chronic stages. Patients in stage F0 or higher may receive HCV treatment during the simulation, depending on the treatment scenario; if not cured, treated patients may progress or die at the same rates as infected and untreated patients. If HCV is cured in stages F0-F2, patients are no longer infectious, and the model assumes that liver damage is reversed.[29,30] These patients return to the susceptible population with healthy livers; if re-infected, they re-commence disease progression at the acute stage.

Patients cured of HCV in stages F3 and higher are no longer infectious, but they may progress to additional liver damage more slowly than patients with uncured HCV.[31] They are susceptible for re-infection at the same rate as patients without liver damage, but if re-infected, re-enter the infected population with their existing level of liver damage. Patients with DC or HCC who are cured of HCV are no longer infectious and become eligible for liver transplants. The transplant stage lasts exactly one cycle, after which patients move to a post-transplant state. If these patients are re-infected, they re-enter the infected population with healthy livers at the acute stage. Consistent with current clinical practice, patients who are co-infected with HIV (all patients in the MSM-HIV risk group, see below) are not eligible for liver transplants.[32,33]

1.4. Transmission Function

In the PWID and MSM-HIV risk groups, for each genotype, the rate at which individuals are infected is modeled dynamically as a function of the number in the risk group who are currently infected with the given genotype. Individuals who are uninfected (susceptible) at the beginning of a year *t* are at risk of becoming HCV infected, and the probability of becoming infected during year *t* (ie, the annual incidence rate) is given by:

$$Pr(infected_{t+1}|susceptible_t) = K \times \frac{N_t^{infected}}{N_t^{infected} + N_t^{susceptible}} \qquad (1)$$

where *t* is the year, $N_t^{infected}$ is the number of people infected at the beginning of year *t*, and $N_t^{susceptible}$ is the number of people susceptible at the beginning of year *t*. The transmission

[2] The model assumes that transition to death is possible from all states, but to simplify the schematic, Figure 1 suppresses arrows representing the transition to death.

model specified by equation (1) assumes that the incidence rate is proportional to the fraction of individuals in a risk group who are infected. The proportionality constant *K* is calibrated to ensure that the incidence rate (the left side of equation (1) matches the empirical estimate of disease incidence rate at model start (*t*=0):

$$K = \frac{(incidence\ rate_{t_0})(N_{t_0}^{infected} + N_{t_0}^{susceptible})}{N_{t_0}^{infected}} \quad (2)$$

The incidence rates and proportionality constants *K* for each risk group by genotype are reported in **Table A2**. We assume *K* only varies across risk groups and is the same for each genotype within a risk group. Patients may only be infected with one genotype at a time, but once cured, a patient can be re-infected with any of the three genotypes. This model assumes a constant ratio between incidence (left-hand side of equation (1)) and prevalence (the ratio on the right-hand side of equation (1)), that is, the risk of infection is proportional to prevalence. This implicitly assumes that within a risk group, newly infected people are equally likely to transmit the disease as previously infected people.

Table A2. Starting Annual Incidence Rates and Values of K

	Annual Incidence Rate	Calculated *K*
Other Adults		
Genotype 1	0	0
Genotype 2	0	0
Genotype 3	0	0
PWID		
Genotype 1	0.0065	0.025
Genotype 2	0.0014	0.025
Genotype 3	0.0011	0.025
MSM-HIV		
Genotype 1	0.0034	0.021
Genotype 2	0.0007	0.021
Genotype 3	0.0006	0.021

SOURCE: Williams et al. (2011) [20] and authors' calculations.

2. Analysis of Policy Scenarios

We model 3 screening and 3 treatment scenarios, for a total of 9 combined scenarios. The manuscript focuses on the impacts of expanding screening and treatment policies relative to the status quo screening and treatment policies.

Our model assumes individuals must be screened and diagnosed as HCV positive before receiving treatment. However, we assume 41.5% of all infected individuals in the starting population are aware of their diagnosis in the initial model cycle and therefore do not receive screening. These individuals receive treatment in the second cycle. Our diagnosis awareness percentage is derived from the NHANES follow-up survey, which includes a question for all HCV-positive individuals regarding whether they have previously been told that they have HCV.

The NHANES HCV follow-up survey is limited by a low response rate, but we find that the NHANES diagnosis rates are similar to findings in the literature.[34]

2.1. Screening Scenario Parameter Estimates

All screening scenarios rely on the patient interacting with the healthcare system in order to receive screening. We estimate the annual rate at which patients utilize healthcare services using NHANES data (NHANES variable name HUQ050). For the infected population, the rate of heath care services utilization is 76.9.% for baby boomers in the Other Adults group, 83.5% for non-baby boomers in the Other Adults group, 89.7% for the PWID group, and 95.1% for MSM-HIV group.[3] All screening scenarios assume a constant screening rate across acute and all chronic states. For the susceptible population, the rate of healthcare services utilization is 85.5% for baby boomers in the Other Adults group, 84.1% for non-baby boomers in the Other Adults group, 85.6% for the PWID group, and 95.1% for MSM-HIV group.

In all scenarios, we adjust screening rates to account for some patients' preferences against screening, and adopt the assumption from Rein et al (2012) that 91% of people offered screening accept it.[35]

Screening costs are equal to $41.37 per person. Our cost is taken from Eckman (2013) and inflated to 2015 dollars; it includes a hepatitis C antibody EIA test and a level 1 office outpatient visit.[36]

2.1.1. Baseline Screening Scenario

In characterizing the baseline screening scenario ("Current Screening"), we attempt to capture the key features of current HCV screening policy. AASLD screening guidelines recommend one-time screening of baby boomers and annual screening of PWIDs and MSM-HIV.[37] We assume that individuals will only be screened if they utilize the healthcare system and their physician adheres to the AASLD guidelines. Therefore, in Current Screening, all individuals in the PWID and MSM-HIV groups and baby boomers in the Other Adults group who visit a doctor or clinic *and* whose physician adheres to screening guidelines are offered screening. The undiagnosed Other Adults population receives screening only once and the undiagnosed PWID and MSM-HIV populations are offered screening every cycle, with acceptance occurring about once every 15-18 months.

Based on estimates in Kallman (2009), we assume that 58% of physicians are aware of guidelines.[38] Since data for adherence is not available, we assume 100% of physicians who are aware of guidelines adhere to them.

[3] This estimate is based on 5 waves of NHANES data from 2004-2012.

2.1.2. Alternative Screening Scenarios

We consider two alternative screening scenarios in the manuscript:

(1) "Physician Education" assumes 100% physician awareness of screening guidelines compared with 58% in Current Screening; this increase in awareness could result from physician education outreach efforts.

(2) "Screen All" assumes all patients unaware of their HCV status are offered screening when they visit a doctor or clinic. Relative to Current Screening, this scenario relaxes the condition that only baby boomers in the Other Adults group are offered screening, and offers one-time screening to all members of the Other Adults group, and additionally assumes 100% physician awareness of screening guidelines

2.2. Treatment Scenario Parameter Estimates

Treatment early in the course of HCV infection decreases the risk of fibrosis progression and long-term hepatic complications, and AASLD 2015 treatment guidelines recommend that all patients with chronic HCV infection (excluding those with limited life expectancy due to non-hepatic causes) receive antiviral treatment. However, the guidelines additionally note that if resources are limited, prioritization should be given to those with more advanced disease and the highest risk of liver-related complications. [7]

Regimens by fibrosis stage and genotype are selected based on the AASLD's most recent treatment guidelines. Therefore, all scenarios assume that HCV treatment consists of the most effective direct-acting antiviral regimens available. When multiple regimens are recommended for a genotype or fibrosis stage, the average efficacy is calculated and used. Regimen drugs, duration, efficacy and costs differ by infection genotype, as detailed in **Table A3**. All costs are inflated to 2015 dollars.

The treatments used in all scenarios include drugs that are currently protected under patent, but have seen price competition from recent market entrants. To account for these pricing dynamics, the model reduces treatment costs by 46% [39] in years 2-20 to account for branded competition.[40]

The model assumes that treatment is only available to patients with insurance, and insurance status does not depend on fibrosis stage. We rely on NHANES to estimate the proportion of each risk group with insurance, and we adjust the estimates to incorporate the impact of the ACA on insurance rates, which results in an 8.5 percentage point increase in the percentage of individuals who have insurance.[41] The final percentage of each risk group with insurance for individuals infected with genotype 1 is 80.3% for Other Adults, 66.5% for PWID, and 94.2% for MSM-HIV; the percentage of each risk group with insurance for genotypes 2 and 3 is 70.4% for Other Adults, 71.7% for PWID, and 94.2% for MSM-HIV.

Table A3. Treatment Regimens, Duration and Efficacy

Drugs used						
Genotype 1	LED/SOF for 12 weeks OMB/PTV/r plus DSV with or without RBV for 12 weeks (F0-F3) or 24 weeks (F4) SOF/SIM with or without RBV for 12 weeks (F0-F3) or 24 weeks (F4)					
Genotype 2	No cirrhosis: SOF and RBV for 12 weeks Cirrhosis: SOF and RBV for 16 weeks					
Genotype 3	SOF and RBV for 24 weeks					
Treatment costs						
	Yr 1[42]		Yrs 2+[42]			
Genotype 1	$103,799		$56,051			
Genotype 2	F0-F2: $103,799 F3-F4: $138,398		F0-F2: $56,051 F3-F4: $74,735			
Genotype 3	$207,598		$112,103			
Efficacy						
	F0-F2		**F3**		**F4**	
	Other Adults PWID	MSM-HIV	Other Adults PWID	MSM-HIV	Other Adults PWID	MSM-HIV
Genotype 1	F0: 0.98 F1-F2: 0.97	0.96	0.97	0.96	0.93	0.91
Genotype 2	0.97	0.88	0.97	0.88	0.97	0.88
Genotype 3	0.91	0.67	0.91	0.67	0.68	0.67

LDV, ledipasvir; SOF, sofosbuvir; OMB, ombitasvir; PTV, paritaprevir; r, ritonavir; DSV, dasabuvir; RBV, ribavirin; SMV, simeprevir; PWID, people who inject drugs; MSM-HIV, HIV-infected men who have sex with men.

2.2.1. Treatment Scenarios

The baseline treatment scenario "Treat F3-F4" was selected according to the AASLD's guidelines' "highest priority" population for treatment, and also aligns with coverage policies observed today.[7] Therefore, the status quo scenario treats patients with fibrosis stages F3 and F4. The alternative treatment scenarios are as follows:

(1) "Treat F2-F4" expands the baseline to include fibrosis stages F2-F4

(2) "Treat F0-F4" further expands treatment to include fibrosis stages F0-F4

2.3. Model Outputs

Each year, the model produces the number of people in every disease, screening, and treatment state. These disease-state populations are then multiplied by published estimates of annual per-person values for quality-adjusted life years (QALYs) in each disease state; each QALY is valued at $150,000 to generate the total value of QALYs produced by a screening-treatment scenario combination.[43] Other annual per-person estimates of economic measures, including treatment costs and non-treatment medical expenditures, are similarly applied to disease-state populations to generate population-wide estimates. These estimates are assumed to be constant

over the duration of the simulation. Dollar values are discounted at 3% per year to produce present discounted values of future value streams.[44]

Patients who die within a cycle are assumed to transition out of the simulation following a uniform probability distribution with a mean of six months. Model outputs for such patients are calculated as half the values as for those who do not die during the cycle.

3. Model Parameter Estimates

Model parameters are taken from the published literature, with efforts made to find risk group- and genotype-specific values wherever possible. The Other Adults risk group contains the largest number of HCV-infected patients, and is defined as US residents born prior to 1992 who are not in the PWID or MSM-HIV risk groups. It is modeled with a mortality rate that increases 8% per year as the closed cohort ages over time.[45] Model parameters for the Other Adults cohort and their sources are provided in Table A4.

The PWID risk group has the highest incidence rate, reflecting the greater transmission among the three risk groups. The PWID cohort also has the highest starting mortality rates for both the infected and uninfected populations.[46] Model parameters for the PWID cohort and their sources are provided in Table A5.

The MSM-HIV risk group is characterized by co-infection with HIV, which affects the progression of HCV [47], and in our analysis is composed of men who have sex with men. Model parameters for the MSM-HIV group and their sources are provided in Table A6.

Table A4. Model Parameters for the Other Adults Risk Group, Genotypes 1-3

Disease State	Genotype 1	Genotype 2	Genotype 3
Annual Mortality Rate			
Susceptible (Background)		0.0083 [48]	
Acute, F0-F2	0.0197 [49]	0.0167 [26,49]	0.0183 [26,49]
F3, F4	0.0742 [26,49]	0.0631 [26,49]	0.0690 [26,49]
DC	0.1350 [35,50,51]	0.1148 [26,35,50,51]	0.1256 [26,35,50,51]
HCC	0.4270 [50,52,53]	0.3630 [26,50,52,53]	0.3971 [26,50,52,53]
Transplant[a]		0.1650 [54]	
Post-Transplant[b]		0.0313 [26,48]	
Annual Background Mortality Growth Rate		0.08 [45]	
Annual Transition Probability			
Acute → Spontaneous Clearance		0.18 [27]	
F0 → F1		0.076 [55-57]	
F1→ F2		0.095 [55-57]	
F2 → F3		0.108 [55-57]	
F3 → F4		0.134 [55-57]	
F3 → HCC	0.008 [50,58]	0.008 [50,58]	0.0144 [24,50,58]
F4 → DC	0.039 [35,50,59]	0.0265 [24,50,59]	0.0507 [24,50,59]
F4 → HCC	0.025 [35,50]	0.0138 [24,35,50]	0.045 [24,35,50]
DC → HCC	0.025 [35,50]	0.0138 [24,35,50]	0.045 [24,35,50]
DC → Transplant		0.031 [60,61]	
HCC → Transplant		0.103 [59,60]	
F3 Cure → F4 Cure		0.0375 [31]	
F3 Cure → HCC Cure		0.0029 [31]	
F4 Cure → DC Cure		0.0109 [31]	
F4 Cure → HCC Cure		0.009 [31]	
DC Cure → HCC Cure		0.007 [31]	
QALY Weights[d]			
Susceptible		0.86 [60,62]	
Acute, F0-F1		0.79 [61,62]	
F2, F3, F3 Cure		0.79 [61,62]	
F4, F4 Cure		0.76 [60,63]	
DC, DC Cure		0.69 [60,63]	
DC Transplant[a]		0.50 [60,63]	
DC Post-Transplant[b]		0.71 [33,64]	
HCC, HCC Cure		0.67 [60,63]	
HCC Transplant[a]		0.50 [60,63]	
HCC Post-Transplant[b]		0.71 [33,64]	

Disease State	Genotype 1	Genotype 2	Genotype 3
Annual Medical Expenditures[c]			
Susceptible	$6,984 [65]		
Acute, F0, F1, F2, F3	$16,904 [66]		
F0 Fail, F1 Fail, F2 Fail, F3 Fail, F3 Cure	$10,988 [66,67]		
F4	$20,052 [66]		
F4 Fail, F4 Cure	$15,239 [66,67]		
DC	$56,020 [66]		
DC Fail, DC Cure	$39,214 [66,67]		
DC Transplant[a]	$161,108 [66]		
DC Post-Transplant[b]	$ 161,108 [66]		
HCC	$124,229 [66]		
HCC Fail, HCC Cure	$86,961 [66,67]		
HCC Transplant[a]	$161,108 [66]		
HCC Post-Transplant[b]	$161,108 [66]		

[a]Year of liver transplant; [b]All subsequent years after liver transplant; [c]All Medical Expenditures inflated to 2015 dollars; [d]QALY weights for individuals who are HCV positive but undiagnosed are 2% higher than those shown in the table.

Table A5. Model Parameters for the PWID Risk Group, Genotypes 1-3

Disease State	Genotype 1	Genotype 2	Genotype 3
Annual Mortality Rate			
Susceptible	0.0139 [46]		
Acute, F0-F2	0.0330 [46,49]	0.0281 [26,46,49]	0.0307 [26,46,49]
F3, F4	0.1246 [26,46,49]	0.1059 [26,46,49]	0.1159 [26,46,49]
DC	0.1350 [35,50,51]	0.1148 [26,35,50,51]	0.1256 [26,35,50,51]
HCC	0.4270 [35,50,51]	0.3630 [26,35,50,51]	0.3971 [26,35,50,51]
Transplant[a]	0.1650 [54]		
Post-Transplant[b]	0.0526 [26,46]		
Annual Transition Probability			
Acute → Spontaneous Clearance	0.18 [68]		
F0 → F1	0.116 [55,69-74]		
F1 → F2	0.085 [55,69-74]		
F2 → F3	0.085 [55,69-74]		
F3 → F4	0.13 [55,69-74]		
F3 → HCC	0.008 [50,58]	0.008 [50,58]	0.0144 [24,50,58]
F4 → DC	0.039 [35,50,59]	0.0265 [24,50,59]	0.0507 [24,50,59]
F4 → HCC	0.025 [35,50,59]	0.0138 [24,35,50]	0.045 [24,35,50]

Disease State	Genotype 1	Genotype 2	Genotype 3
DC → HCC	0.025 [35,50,59]	0.0138 [24,35,50]	0.045 [24,35,50]
DC → Transplant	0.031 [60,61]		
HCC → Transplant	0.103 [59,60]		
F3 Cure → F4 Cure	0.0364 [31]		
F3 Cure → HCC Cure	0.0029 [31]		
F4 Cure → DC Cure	0.0109 [31]		
F4 Cure → HCC Cure	0.009 [31]		
DC Cure → HCC Cure	0.007 [31]		
QALY Weights	Same as for Other Adults risk group. See Table A4 for values.		
Annual Medical Expenditures[c]	Same across risk groups and genotype. See Table A4 for values.		

[a]Year of liver transplant; [b]All subsequent years after liver transplant; [c]All medical expenditures inflated to 2015 dollars.

Table A6. Model Parameters for the MSM-HIV Risk Group, Genotypes 1-3

Disease State	Genotype 1	Genotype 2	Genotype 3
Annual Mortality Rate			
Susceptible	0.0071 [75]		
Acute, F0-F2	0.0168 [49,75]	0.0156 [26,49,75]	0.0156 [26,49,75]
F3, F4	0.0632 [26,49,75]	0.0538 [26,49,75]	0.0588 [26,49,75]
DC	0.1350 [35,50,51]	0.1148 [26,35,50,51]	0.1256 [26,35,50,51]
HCC	0.4270 [35,50,51]	0.3630 [26,35,50,51]	0.3971 [26,35,50,51]
Transplant[a]	0.1650 [76,77]		
Post Transplant[b]	0.0267 [76,77]		
Annual Transition Probability			
Acute → Spontaneous Clearance	0.130 [28]		
F0 → F1	0.122 [47]		
F1 → F2	0.115 [47]		
F2 → F3	0.124 [47]		
F3 → F4	0.115 [47]		
F3 → HCC	0.016 [33,50,58,78]	0.016 [33,50,58,78]	0.0288 [24,50,58,78]
F4 → DC	0.078 [33,35,50,59,79]	0.053 [24,35,50,59,79]	0.1014 [35,50,59,79]
F4 → HCC	0.050 [33,35,50,78]	0.0275 [24,35,50,78]	0.0900 [35,50,78]
DC → HCC	0.050 [33,35,50,78]	0.0275 [24,35,50]	0.0900 [35,50]
DC → Transplant	0 [33]		
HCC → Transplant	0 [33]		

Disease State	Genotype 1	Genotype 2	Genotype 3
F3 Cure → F4 Cure	0.0322 [31]		
F3 Cure → HCC Cure	0.0058 [31]		
F4 Cure → DC Cure	0.0218 [31]		
F4 Cure → HCC Cure	0.018 [31]		
DC Cure → HCC Cure	0.014 [31]		
QALY Weights[d]			
Susceptible	0.87 [32,76]		
Acute, F0-F1	0.81 [32,61,76]		
F2, F3, F3 Cure	0.81 [32,61,76]		
F4, F4 Cure	0.68 [32,76]		
DC, DC Cure	0.48 [32,76]		
DC Transplant[a]	0.81 [32,76]		
DC Post-Transplant[b]	0.81 [32,76]		
HCC, HCC Cure	0.23 [32,76]		
HCC Transplant[a]	0.81 [32,76]		
HCC Post-Transplant[b]	0.81 [32,76]		
Medical Expenditures[c]	Same across risk groups and genotype. See Table A4 for values.		

[a]Year of liver transplant; [b]All subsequent years after liver transplant; [c]All Medical Expenditures inflated to 2015 dollars; [d]QALY weights for individuals who are HCV positive but undiagnosed are 2% higher than those shown in the table

3.1. Starting Populations

At model start, the size of the total infected population across all disease stages is 3,618,543 people.[80] This includes 22,304 incident patients,[81] who are distributed across the three risk groups according to estimates from Williams et al. (2011),[20] and within each risk group across three genotypes according to the prevalence of each genotype in the overall population, as estimated by Manos et al. (2012).[22] These incident patients make up the populations in the acute phases at the start of the simulation. The remaining 3,596,239 non-incident infected population at model start are then distributed across risk groups and genotypes following the same logic. These patients are then further distributed across chronic disease stages as in Hagan (2014).[18,55,82] The distribution of the infected population by risk group, genotype, and disease stage is given in Table A7.

Table A7. Size and distribution of model populations at start of simulation

	Other Adults	PWID	MSM-HIV

Uninfected/Susceptible		197,404,132 [48]	2,242,594 [83]	461,600 [84]
Genotype 1	*Acute*	0	14,514	1,545
	F0	271,199	155,186	16,524
	F1	558,352	319,501	34,020
	F2	350,964	200,829	21,384
	F3	223,341	127,801	13,608
	F4	95,717	54,772	5,832
	DC	47,859	27,386	2,916
	HCC	47,859	27,386	2,916
Genotype 2	*Acute*	0	3,225	343
	F0	60,267	34,486	3,672
	F1	124,078	71,000	7,560
	F2	77,992	44,629	4,752
	F3	49,631	28,400	3,024
	F4	21,271	12,171	1,296
	DC	10,635	6,086	648
	HCC	10,635	6,086	648
Genotype 3	*Acute*	0	2,419	258
	F0	45,200	25,864	2,754
	F1	93,059	53,250	5,670
	F2	58,494	33,471	3,564
	F3	37,223	21,300	2,268
	F4	15,953	9,129	972
	DC	7,976	4,564	486
	HCC	7,976	4,564	486

SOURCE: Authors' analysis and CDC (2014);[85] Manos (2012);[22] Williams (2011);[20] and Hagan (2014)[82]

3.2. Annual Mortality Rates

To appropriately account for mortality risk by risk group, age, genotype and disease state, we estimate mortality rates that account for differential risks using the multiplicative model,

$$M(a,r,g,s) = M_0(a)R_rR_gR_s \quad (3)$$

where M_0(a) is the US base annual mortality rates[21], for a person at age a and R_r, R_g, R_s are proportionality constants that account for a person's risk group, HCV genotype, and stage of liver disease, respectively.[4] We derive the proportionality constants R_r, R_g, R_s based on estimates from the literature and given in Table A8, below.

[4]Age is computed as the population-weighted average age, based on Census population estimates [21].

Table A8. Mortality Adjustment Factors by Disease State and Genotype

Disease State	Mortality Factor R_g
Uninfected	1.000
Acute, F0-F2	2.370
F3, F4	8.935
Post-Trans, cured states	3.770

Viral Genotype	Mortality Factor R_g
Genotype 1	1.000
Genotype 2	0.850
Genotype 3	0.930

F3-F4 is a multiple of the F2 factor, so the total is 2.370 x 3.770 = 8.935. F3, F4, DC, HCC cured are 3.770 times base mortality.

We assume the proportionality constant for the Other Adults risk group, R_r, is 1.0. For the PWID group we rely on Mathers et al. (2013), which provides a systematic review of the mortality of intravenous drug users.[46] The paper provides a mortality rate ratio (standardized mortality ratio, SMR) of 11.19 in North America (see page 109, figure 3). This means that the death rates of PWIDs are approximately 11.9 times that of the US base annual mortality rate after adjusting for age; however, directly using the 11.9 estimate overcounts mortality in this group because some of the excess mortality among PWID is attributable to HCV infection and thus is already accounted for by our other proportionality constants in the model in equation (3), namely R_s and R_g. Thus, we need to parse out the effect of risk group that is independent from the effects of HCV infection. Specifically, R_r represents the age adjusted mortality rate ratio for HCV *uninfected* PWIDs compared to the general population. To estimate R_r, express the mortality rate for the PWIDs at age a (called $M(a,r)$ in the equation below) as a weighted average of the mortality rates for HCV-infected PWIDs (stratified by genotype and disease stage) and uninfected PWIDS:

$$M(a,r) = P(I)\sum_{g,s} M(a,r,g,s)P(g,s) + P(NI)M(a,r,NI) \quad (4)$$

where $P(I)$ is the initial proportion infected in the PWID risk group, $P(NI) = 1\text{-}P(I)$ is the proportion uninfected, and $P(g,s)$ is the proportion of the infected person who are infected with genotype g and are in stage s. Dividing the above equation by the baseline mortality rate for a person in the United States at age a we obtain,

$$\frac{M(a,r)}{M_0(a)} = 11.19 = P(I)\sum_{g,s} R_r R_g R_s P(g,s) + P(NI)R_r \quad (5)$$

Van Nuys et al. (2015) gives estimates of $P(g, s)$, $P(I)$ and $P(NI=)=1\text{-}P(I)$, and using the values of R_g and R_s given above we solved equation (2) for R_r to get R_r= 4.15.[86] This implies that the

mortality rate for HCV uninfected PWIDs is approximately 4.15 times that of the baseline rates in the US (accounting for age).

We used a similar approach for the MSM-HIV risk group using the mortality rate ratios for HIV-infected men (Karch et al, (2015), which says HIV infected men have about 3.4 times the mortality rate of the baseline mortality in the US.[87] The 3.4 figure accounts for excess mortality from HCV infection, and thus (as explained above) it also needs to be adjusted downward so as not to double count the effects of HCV on mortality. We used the above equation (5) replacing 11.19 with 3.4 and using the input values for $P(g,s)$ and P(I) for the MSM-HIV risk group from Van Nuys et al. (2015) and obtained R_r= 2.04 for the MSM-HIV risk group.[86]

Since the Other Adults risk group is a closed cohort whose average age increases over the simulation, we assume that the background mortality rate grows at 8% per year in this group.[45] For the other two risk groups, we assume a stable age distribution, or that the exiting of older individuals is offset by ongoing entry of younger individuals into these risk groups, and assume a constant background mortality computed by average age, risk group and genotype. While it is possible that improved treatments might lead to the slight aging of these two risk groups, these effects could be offset by younger ages at entry into the groups (eg, younger age at initiation of drug use or sexual activity). Accordingly, in the absence of clear trends on the ages of initiation for these risk behaviors, we have opted for the simplest plausible assumption of a stable (stationary) age distribution in the PWID and MSM-HIV groups over the time span of our simulation.

4. Additional Results

4.1. Results of main analysis: 10-year time horizon

In this section, we report results for our primary analysis, relative to baseline (Current Screening and treatment at F3-F4), at the 10-year time horizon.

Table A9: Results for components of social value (incremental costs and QALYs) relative to baseline, 10 year time horizon

Scenario		Incremental Costs ($)				Incremental QALYs
Screening	**Treatment**	**Total**	**Med. Expend**	**Screening Cost**	**Treatment Cost**	
	F3-F4	---	---	---	---	---
Current	F2-F4	20,563,786,061	(30,546,777,372)	18,838,220	51,091,725,214	499,079
	F0-F4	48,853,220,537	(85,933,986,218)	50,646,003	134,736,560,752	1,103,804
	F3-F4	18,006,899,946	10,926,690,247	1,272,328,012	5,807,881,687	(7,574)
Physician Ed.	F2-F4	38,465,017,869	(24,035,257,780)	1,303,221,108	61,197,054,541	571,129
	F0-F4	64,787,996,453	(87,393,189,004)	1,355,247,576	150,825,937,882	1,277,068
	F3-F4	34,748,759,839	21,747,794,370	1,986,977,550	11,013,987,920	21,925
Screen All	F2-F4	54,105,329,184	(17,554,909,383)	2,017,870,645	69,642,367,922	680,326
	F0-F4	76,888,570,742	(88,785,234,915)	2,069,897,114	163,603,908,544	1,467,665

Table A10. Cumulative Social Value and Incremental Cost-Effectiveness Relative to Baseline, 10-year Time Horizon

Screening Scenarios		Treatment Access		
		Treat F3-F4	**Treat F2-F4**	**Treat F0-F4**
Current Screening	**Cumulative Social Value (2015 USD)**	---	$54 bn	$117 bn
	ICER ($/QALY)	---	$41,203	$44,259
Physician Education	**Cumulative Social Value (2015 USD)**	-$19 bn	$47 bn	$127 bn
	ICER ($/QALY)	Strongly Dominated	$67,349	$50,732
Screen All	**Cumulative Social Value (2015 USD)**	-$31 bn	$48 bn	$143 bn
	ICER ($/QALY)	$1,584,885	$79,529	$52,388

All results are relative to baseline, which is Current Screening with treatment of fibrosis stages F3-F4. ICER values represent change in overall cost divided by change in cumulative QALYs. "Cost-saving" indicates a reduction in cumulative costs relative to baseline. Dollar values in $US 2015. All future values are discounted at a rate of 3%. ICER = incremental cost-effectiveness ratio.

4.2. Cost Effectiveness

Using our results, we generate a cost effectiveness frontier to facilitate comparison of alternative approaches. Figures A2 and A3 present the cost-effectiveness frontiers at 10 years and 20 years, respectively.

Figure A2: Cost efficiency frontier at 10-year horizon

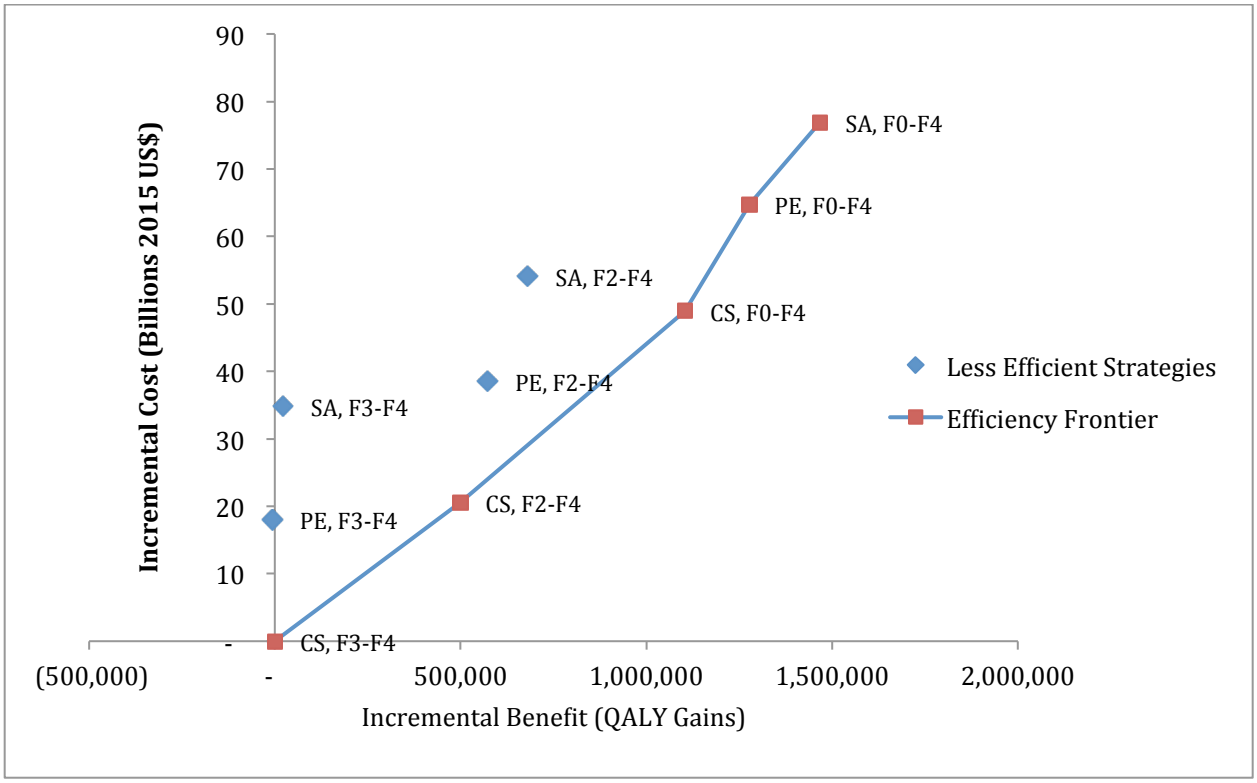
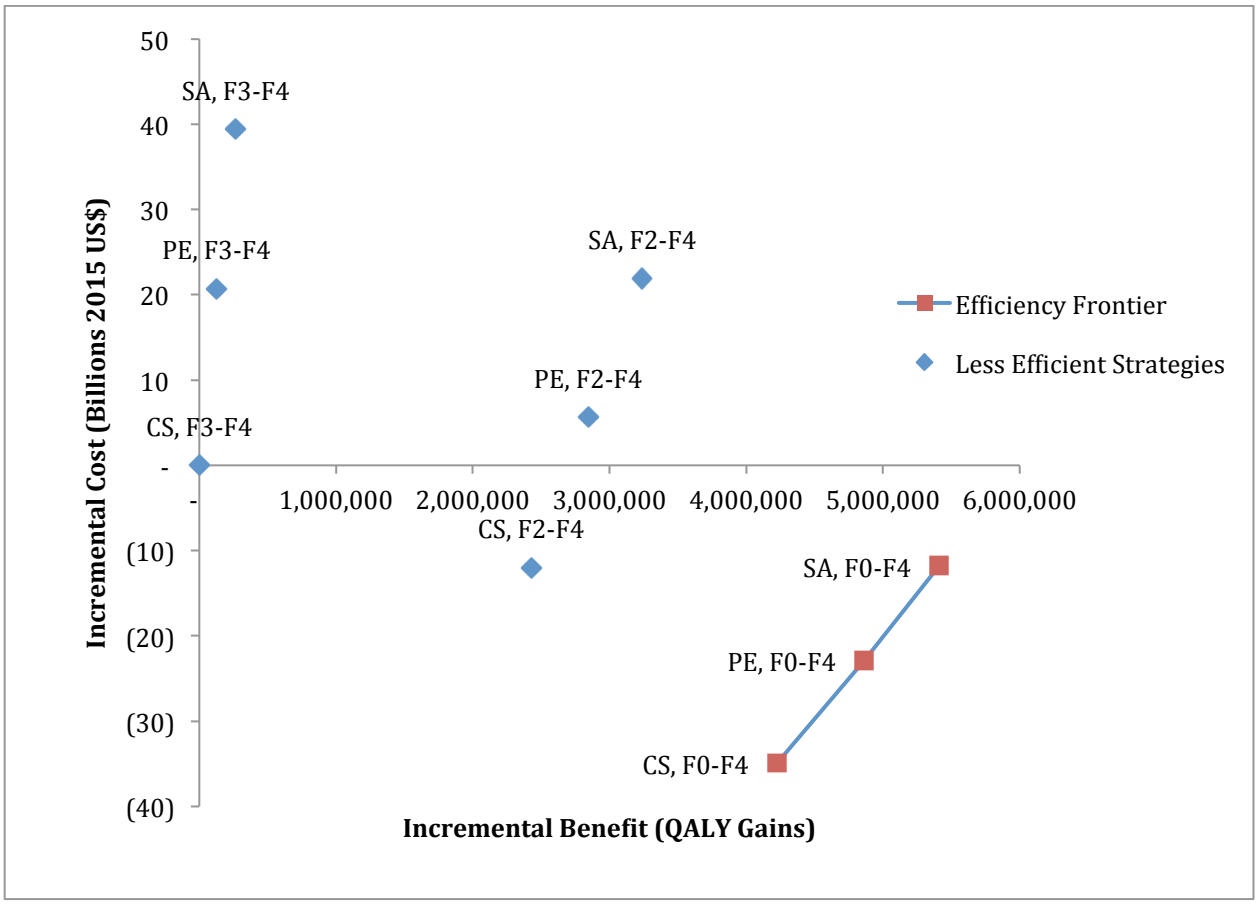


Figure A3: Cost efficiency frontier at 20-year horizon



5. Sensitivity Analyses

We conducted several sensitivity analyses to better characterize uncertainty inherent in the model. We explore the individual impact of a number of changes in key variables within screening/treatment combinations. We then examine the effects of varying the most sensitive parameters on results for cumulative net social value and ICERs. The results of these sensitivities are presented below.

5.1. Sensitivity Analyses

We conducted sensitivity tests of 21 key variables, identified as bearing a high level of uncertainty due to uncertainty in the parameter itself, a range of values offered in differing sources, or subjective assessment of the uncertainty of a given assumption. For each variable, the model was run with the parameter value set at maximum and minimum values, holding all other variables constant (at levels used in primary analyses).

5.1.1. One-way Sensitivities: Ranges

We ran sensitivities around the model inputs presented in Table A12.

Table A12. Sensitivity Analysis Parameters of Interest

Parameter	Definition/Notes	Range
Starting Infected Population PWID	Number of individuals from the PWID group who are chronically infected with HCV at the start of the model	1,077,683 – 1,458,041
Starting Infected Population MSM-HIV	Number of individuals from the MSM-HIV group who are chronically infected with HCV at the start of the model	114,750 – 155,250
Starting Infected Population Other Adult	Number of individuals from the Other Adult group who are chronically infected with HCV at the start of the model	1,883,329 – 2,548,033
Total Starting Population PWID	Total number of individuals in the PWID group at the start of the model, where total = susceptible + infected	2,983,888 – 4,037,024
Total Starting Population MSM-HIV	Total number of individuals in the MSM-HIV group at the start of the model, where total = susceptible + infected	507,110 – 686,090
Total Starting Population Other Adult	Total number of individuals in the Other Adult group at the start of the model, where total = susceptible + infected	169,676,841 – 229,562,785
Medical Expenditures PWID	Total (annual) non-treatment medical expenditures for the PWID group. This value varies by disease state.	See Table A14
Medical Expenditures MSM-HIV	Total (annual) non-treatment medical expenditures for the MSM-HIV group. This value varies by disease state.	See Table A14
Medical Expenditures Other Adult	Total (annual) non-treatment medical expenditures for the Other Adult group. This value varies by disease state.	See Table A14
QALY Weights	Quality of life (utility) values associated with each disease state. For this sensitivity check, values for PWID, MSM-HIV, and Other Adult were adjusted simultaneously.	See Table A14
Fibrosis distribution: F0	Proportion of chronically infected individuals with fibrosis stage F0. For this sensitivity check, values for PWID, MSM-HIV, and Other Adult were adjusted simultaneously.	0.15- 0.19 [82]
Fibrosis distribution: F1	Proportion of chronically infected individuals with fibrosis stage F1. For this sensitivity check, values for PWID, MSM-HIV, and Other Adult were adjusted simultaneously.	0.32- 0.39 [82]

Parameter	Definition/Notes	Range
Fibrosis distribution: F2	Proportion of chronically infected individuals with fibrosis stage F2. For this sensitivity check, values for PWID, MSM-HIV, and Other Adult were adjusted simultaneously.	0.20- 0.24 [82]
Fibrosis distribution: F3	Proportion of chronically infected individuals with fibrosis stage F3. For this sensitivity check, values for PWID, MSM-HIV, and Other Adult were adjusted simultaneously.	0.13- 0.15 [82]
Fibrosis distribution: F4	Proportion of chronically infected individuals with fibrosis stage F4. For this sensitivity check, values for PWID, MSM-HIV, and Other Adult were adjusted simultaneously.	0.055- 0.065 [82]
Physician Awareness	Probability that physicians are aware of screening guidelines. For this sensitivity check, values for PWID, MSM-HIV, and Other Adult were adjusted simultaneous.	0.496-0.67
Healthcare Interaction	Probability that individuals interact with the healthcare system. Specifically, the probability of being insured impacts the treatment probability, and the probability of seeing a doctor in the past year impacts screening probabilities. For this sensitivity check, values for PWID, MSM-HIV, and Other Adult were adjusted simultaneously.	See Table A13
Treat/Screen Cost	Cost of screening and treatment. For this sensitivity check, values for PWID, MSM-HIV, and Other Adult were adjusted simultaneously.	Treatment costs: ±50% Screening costs: $21.24-$528.63
QALY Decrement	QALY decrement for individuals who are diagnosed with HCV but untreated. For this sensitivity check, values for PWID, MSM-HIV, and Other Adult were adjusted simultaneously.	0-4%
Discount Rate	Discount rate for costs and QALYs	1-5%
QALY Value ($)	Dollar value assigned to a quality adjusted life year (QALY)	$50,000-$300,000

When varying the proportion of the fibrosis distribution for a given fibrosis stage, changes are uniformly distributed across the adjacent fibrosis stages. For example, if the proportion in F1 increases by 2%, the proportion in F0 decreases by 1% and the proportion in F3 decreases by 1%. DC and HCC ranges were not included in the sensitivity analyses.

Table A13. Screening and Treatment Baseline Parameter and Ranges for Healthcare Interaction Sensitivity

	Other Adult			PWID		MSM-HIV	
Annual Screening Probabilities by Screening Scenario							
	Current Screening	Physician Education	Screen All	Current Screening	Physician Education & Screen All	Current Screening	Physician Education & Screen All
Susceptible	0.178 (0.176-0.180)	0.305 (0.301-0.309)	0.778 (0.769-0.787)	0.454 (0.448-0.489)	0.779 (0.768-0.838)	0.505 (0.470 – 0.531)	0.866 (0.805-0.910)
Infected	0.16 (0.145 – 0.174)	0.274 (0.249-0.299)	0.699 (0.635-0.763)	0.476 (0.420-0.504)	0.816 (0.720-0.865)	0.505 (0.470 – 0.531)	0.866 (0.805-0.910)
Annual Treatment Probabilities							
	0.803 (0.635-0.885)			0.665 (0.597-0.773)		0.942 (0.818-1.0)	

Parameter ranges are derived from NHANES. Treatment probabilities only apply to patients who are eligible by fibrosis stage. For example, in Treat F3-F4, diagnosed PWID patients in fibrosis stages F0-F2 have zero probability of treatment, and stages F3-F4 have 0.665 probability of treatment.

Table A14. Sensitivity Analyses: Range of Parameter Values

QALY Weights –Other Adult and PWID	
Susceptible	0.84- 0.88 [18,60]
Acute, F0-F1	0.77-0.81 [18,60]
F2, F3, F3 Cure	0.77-0.81 [18,60]
F4, F4 Cure	0.70- 0.79 [18,60]
DC, DC Cure	0.44- 0.69 [18,60]
DC Transplant	0.44- 0.69 [18,60]
DC Post-Transplant	0.60-0.82 [33,64]
HCC, HCC Cure	0.60-0.72 [18,60]
HCC Transplant	0.40- 0.69 [18,60]
HCC Post-Transplant	0.60-0.82 [33,64]
QALY Weights – MSM-HIV	
Susceptible	0.74- 1.0[76]
Acute, F0-F1	0.69-0.93[76]
F2, F3, F3 Cure	0.69-0.93[76]
F4, F4 Cure	0.58- 0.78[76]
DC, DC Cure	0.41-0.55[76]
DC Transplant	0.69- 0.93[76]
DC Post-Transplant	0.69- 0.93[76]
HCC, HCC Cure	0.2-0.26[76]
HCC Transplant	0.69- 0.93[76]
HCC Post-Transplant	0.69- 0.93[76]
Annual Medical Expenditures – Other Adult, PWID, MSM-HIV	
Susceptible	$6753 - 7127 [65]
Acute, F0, F1, F2, F3	$16,210 – 17,597 [66]
F0 Fail, F1 Fail, F2 Fail, F3 Fail, F3 Cure	$10,537 – 11,439 [66,67]
F4	$17,866 – 22,238 [66]
F4 Fail, F4 Cure	$13,578 – 16,900 [66,67]
DC	$50,362 – 61,678 [66]
DC Fail, DC Cure	$35,253 – 43,175 [66,67]
DC Transplant, DC Post-Transplant	$144,836 – 177,380 [66]
HCC	$116,651 – 131,807 [66]
HCC Fail, HCC Cure	$81,656 – 92,265 [66,67]
HCC Transplant, HCC Post-Transplant	$151,280 – 170,936 [66]

5.1.2. Model Sensitivity Analysis: Results

We present results of sensitivity tests on cumulative social value at the 20-year time horizon (Tables A15-A23). Results are presented as a percent change relative to the output from using the parameter input value assumed for our main analysis. Because each combination of screening and treatment scenarios employs a unique set of baseline assumptions, nine separate sets of sensitivity results are included, one for each scenario. In general, the social value results across scenarios are most sensitive to the same model inputs.

Table A15: One-way Sensitivity results: Current Screening with Treatment at F3-F4

Parameter	%Difference in Cumulative Social Value	
	Low	High
QALY Value ($)	-68.460%	102.689%
Discount Rate	-14.178%	18.307%
Total Starting Population Other Adult	-6.791%	6.791%
QALY weights	-5.857%	5.850%
Total Starting Population PWID	-0.117%	0.117%
Medical Expenditures Other Adult	-0.071%	0.071%
Starting Infected population Other Adult	-0.030%	0.030%
Total Starting Population MSM-HIV	-0.022%	0.022%
Starting Infected population PWID	-0.021%	0.021%
Treat/Screen Cost	-0.005%	0.005%
QALY Decrement	-0.003%	0.003%
Medical Expenditures PWID	-0.002%	0.002%
Starting Infected population MSM-HIV	-0.002%	0.002%
Fibrosis Distribution: F0	-0.001%	0.001%
Healthcare Interaction	-0.001%	0.001%
Fibrosis Distribution: F2	-0.001%	0.001%
Fibrosis Distribution: F3	-0.001%	0.001%
Fibrosis Distribution: F4	-0.0004%	0.0004%
Medical Expenditures MSM-HIV	-0.0004%	0.0004%
Physician Awareness	-0.0001%	0.0001%
Fibrosis Distribution: F1	0.000%	0.000%

Parameter definitions and ranges for sensitivity parameters are given in Tables A12-A14.

Table A16: One-way Sensitivity results: Current Screening with Treatment at F2-F4

Parameter	%Difference in Cumulative Social Value	
	Low	High
QALY Value ($)	-68.458%	102.686%
Discount Rate	-14.183%	18.314%
Total Starting Population Other Adult	-6.788%	6.788%
QALY weights	-5.854%	5.848%
Total Starting Population PWID	-0.117%	0.117%
Medical Expenditures Other Adult	-0.071%	0.071%
Starting Infected population Other Adult	-0.025%	0.025%
Total Starting Population MSM-HIV	-0.022%	0.022%
Starting Infected population PWID	-0.018%	0.020%
Healthcare Interaction	-0.004%	0.003%
QALY Decrement	-0.003%	0.003%
Fibrosis Distribution: F2	-0.002%	0.002%
Medical Expenditures PWID	-0.002%	0.002%
Starting Infected population MSM-HIV	-0.002%	0.002%
Physician Awareness	-0.002%	0.002%
Fibrosis Distribution: F3	-0.001%	0.001%
Fibrosis Distribution: F0	-0.001%	0.001%
Fibrosis Distribution: F4	-0.0004%	0.0004%
Medical Expenditures MSM-HIV	-0.0003%	0.0003%
Fibrosis Distribution: F1	-0.0004%	0.0003%
Treat/Screen Cost	0.0000%	0.0000%

Parameter definitions and ranges for sensitivity parameters are given in Tables A12-A14.

Table A17: One-way Sensitivity results: Current Screen with Treatment at F0-F4

Parameter	%Difference in Cumulative Social Value	
	Low	High
QALY Value ($)	-68.455%	102.682%
Discount Rate	-14.187%	18.319%
Total Starting Population Other Adult	-6.785%	6.785%
QALY weights	-5.852%	5.846%
Total Starting Population PWID	-0.117%	0.117%
Medical Expenditures Other Adult	-0.070%	0.070%
Starting Infected population Adult	-0.023%	0.023%
Total Starting Population MSM-HIV	-0.022%	0.022%
Starting Infected population PWID	-0.015%	0.015%
Healthcare Interaction	-0.005%	0.004%
Physician Awareness	-0.003%	0.003%
QALY Decrement	-0.003%	0.003%
Medical Expenditures PWID	-0.002%	0.002%
Fibrosis Distribution: F2	-0.002%	0.002%
Starting Infected population MSM-HIV	-0.002%	0.002%
Fibrosis Distribution: F0	-0.001%	0.001%
Fibrosis Distribution: F3	-0.001%	0.001%
Fibrosis Distribution: F1	-0.0004%	0.001%
Fibrosis Distribution: F4	-0.0004%	0.0004%
Medical Expenditures MSM-HIV	-0.0003%	0.0003%
Treat/Screen Cost	0.0000%	0.0000%

Parameter definitions and ranges for sensitivity parameters are given in Tables A12-A14.

Table A18: One-way Sensitivity results: Physician Education with Treatment at F3-F4

Parameter	%Difference in Cumulative Social Value	
	Low	High
QALY Value ($)	-68.461%	102.692%
Discount Rate	-14.179%	18.307%
Total Starting Population Other Adult	-6.791%	6.791%
QALY weights	-5.856%	5.850%
Total Starting Population PWID	-0.117%	0.117%
Medical Expenditures Other Adult	-0.071%	0.071%
Starting Infected population Other Adult	-0.030%	0.030%
Total Starting Population MSM-HIV	-0.022%	0.022%
Starting Infected population PWID	-0.021%	0.021%
Medical Expenditures PWID	-0.003%	0.003%
Starting Infected population MSM-HIV	-0.002%	0.002%
QALY Decrement	-0.002%	0.002%
Fibrosis Distribution: F0	-0.001%	0.001%
Healthcare Interaction	-0.002%	0.001%
Fibrosis Distribution: F2	-0.001%	0.001%
Fibrosis Distribution: F4	-0.0004%	0.0004%
Fibrosis Distribution: F3	-0.0004%	0.0004%
Medical Expenditures MSM-HIV	-0.0004%	0.0004%
Fibrosis Distribution: F1	-0.0001%	0.0001%
Physician Awareness	0.0000%	0.0000%
Treat/Screen Cost	0.0000%	0.0000%

Parameter definitions and ranges for sensitivity parameters are given in Tables A12-A14.

Table A19: One-way Sensitivity results: Physician Education with Treatment at F2-F4

Parameter	%Difference in Cumulative Social Value	
	Low	High
QALY Value ($)	-68.459%	102.689%
Discount Rate	-14.184%	18.315%
Total Starting Population Other Adult	-6.787%	6.787%
QALY weights	-5.854%	5.848%
Total Starting Population PWID	-0.117%	0.117%
Medical Expenditures Adults	-0.071%	0.071%
Starting Infected population Adults	-0.025%	0.025%
Total Starting Population MSM-HIV	-0.022%	0.022%
Starting Infected population PWID	-0.018%	0.018%
Healthcare Interaction	-0.005%	0.004%
Fibrosis Distribution: F2	-0.003%	0.003%
Medical Expenditures PWID	-0.002%	0.002%
QALY Decrement	-0.002%	0.002%
Starting Infected population MSM-HIV	-0.002%	0.002%
Fibrosis Distribution: F3	-0.001%	0.001%
Fibrosis Distribution: F0	-0.001%	0.001%
Fibrosis Distribution: F1	-0.001%	0.001%
Fibrosis Distribution: F4	-0.0004%	0.0004%
Medical Expenditures MSM-HIV	-0.0004%	0.0004%
Physician Awareness	0.0000%	0.0000%
Treat/Screen Cost	0.0000%	0.0000%

Parameter definitions and ranges for sensitivity parameters are given in Tables A12-A14.

Table A20: One-way Sensitivity results: Physician Education with Treatment at F0-F4

Parameter	%Difference in Cumulative Social Value	
	Low	High
QALY Value ($)	-68.4556%	102.683%
Discount Rate	-14.188%	18.321%
Total Starting Population Other Adult	-6.784%	6.784%
QALY weights	-5.852%	5.846%
Total Starting Population PWID	-0.117%	0.117%
Medical Expenditures Other Adult	-0.070%	0.070%
Total Starting Population MSM-HIV	-0.022%	0.022%
Starting Infected population Other Adult	-0.022%	0.022%
Starting Infected population PWID	-0.014%	0.014%
Healthcare Interaction	-0.006%	0.004%
QALY Decrement	-0.002%	0.002%
Medical Expenditures PWID	-0.002%	0.002%
Fibrosis Distribution: F2	-0.002%	0.002%
Starting Infected population MSM-HIV	-0.001%	0.001%
Fibrosis Distribution: F3	-0.001%	0.001%
Fibrosis Distribution: F0	-0.001%	0.001%
Fibrosis Distribution: F1	-0.0005%	0.001%
Fibrosis Distribution: F4	-0.0004%	0.0004%
Medical Expenditures MSM-HIV	-0.0003%	0.0003%
Physician Awareness	0.0000%	0.0000%
Treat/Screen Cost	0.0000%	0.0000%

Parameter definitions and ranges for sensitivity parameters are given in Tables A12-A14.

Table A21: One-way Sensitivity results: Screen All with Treatment at F3-F4

Parameter	%Difference in Cumulative Social Value	
	Low	High
QALY Value ($)	-68.4631%	102.695%
Discount Rate	-14.179%	18.308%
Total Starting Population Other Adult	-6.791%	6.791%
QALY weights	-5.856%	5.850%
Total Starting Population PWID	-0.117%	0.117%
Medical Expenditures Other Adult	-0.071%	0.072%
Starting Infected population Other Adult	-0.030%	0.030%
Total Starting Population MSM-HIV	-0.022%	0.022%
Starting Infected population PWID	-0.021%	0.021%
Medical Expenditures PWID	-0.003%	0.003%
Starting Infected population MSM-HIV	-0.002%	0.002%
Fibrosis Distribution: F0	-0.001%	0.001%
QALY Decrement	-0.001%	0.001%
Healthcare Interaction	-0.001%	0.001%
Fibrosis Distribution: F2	-0.001%	0.001%
Fibrosis Distribution: F4	-0.0004%	0.0004%
Medical Expenditures MSM-HIV	-0.0004%	0.0004%
Fibrosis Distribution: F3	-0.0003%	0.0003%
Fibrosis Distribution: F1	-0.0002%	0.0001%
Physician Awareness	0.0000%	0.0000%
Treat/Screen Cost	0.0000%	0.0000%

Parameter definitions and ranges for sensitivity parameters are given in Tables A12-A14.

Table A22: One-way Sensitivity results: Screen All with Treatment at F2-F4

Parameter	%Difference in Cumulative Social Value	
	Low	High
QALY Value ($)	-68.4604%	102.691%
Discount Rate	-14.185%	18.316%
Total Starting Population Other Adult	-6.787%	6.787%
QALY weights	-5.853%	5.848%
Total Starting Population PWID	-0.117%	0.117%
Medical Expenditures Other Adult	-0.071%	0.071%
Starting Infected population Other Adult	-0.024%	0.024%
Total Starting Population MSM-HIV	-0.022%	0.022%
Starting Infected population PWID	-0.018%	0.018%
Healthcare Interaction	-0.005%	0.003%
Fibrosis Distribution: F2	-0.003%	0.003%
Medical Expenditures PWID	-0.002%	0.002%
Starting Infected population MSM-HIV	-0.002%	0.002%
QALY Decrement	-0.001%	0.001%
Fibrosis Distribution: F3	-0.001%	0.001%
Fibrosis Distribution: F1	-0.001%	0.001%
Fibrosis Distribution: F4	-0.0004%	0.0004%
Fibrosis Distribution: F0	-0.0004%	0.0004%
Medical Expenditures MSM-HIV	-0.0004%	0.0004%
Physician Awareness	0.0000%	0.0000%
Treat/Screen Cost	0.0000%	0.0000%

Parameter definitions and ranges for sensitivity parameters are given in Tables A12-A14.

Table A23: One-way Sensitivity results: Screen All with Treatment at F0-F4

Parameter	%Difference in Cumulative Social Value	
	Low	High
QALY Value ($)	-68.456%	102.685%
Discount Rate	-14.189%	18.322%
Total Starting Population Other Adult	-6.784%	6.784%
QALY weights	-5.851%	5.846%
Total Starting Population PWID	-0.117%	0.117%
Medical Expenditures Other Adult	-0.071%	0.071%
Total Starting Population MSM-HIV	-0.022%	0.022%
Starting Infected population Other Adult	-0.020%	0.020%
Starting Infected population PWID	-0.014%	0.014%
Healthcare Interaction	-0.006%	0.004%
Fibrosis Distribution: F2	-0.002%	0.002%
Medical Expenditures PWID	-0.002%	0.002%
Starting Infected population MSM-HIV	-0.001%	0.001%
QALY Decrement	-0.001%	0.001%
Fibrosis Distribution: F3	-0.001%	0.001%
Fibrosis Distribution: F1	-0.001%	0.001%
Fibrosis Distribution: F0	-0.001%	0.001%
Fibrosis Distribution: F4	-0.0004%	0.0004%
Medical Expenditures MSM-HIV	-0.0003%	0.0003%
Physician Awareness	0.0000%	0.0000%
Treat/Screen Cost	0.0000%	0.0000%

Parameter definitions and ranges for sensitivity parameters are given in A12-A14.

5.2. Sensitivity of Social Value Gains and ICERs to Key Parameters

The one-way sensitivities presented in section 5.1 highlight four key parameters that may drive uncertainty in the model. To better understand the implications of this uncertainty on our results, which are presented as changes relative to baseline, Tables A24-27 present variations of our main results for both the high and low end of tested ranges for each of the following variables: (1) QALY value ($); (2) discount rate; (3) starting population size for the Other Adults group; and (4) quality of life utility weights.

Table A24. Cumulative Social Value Relative to Baseline for high and low values of QALYs, 20-year Time Horizon

Screening Scenarios	Treatment Access					
	Treat F3-F4		Treat F2-F4		Treat F0-F4	
	$50K	$300K	$50K	$300K	$50K	$300K
Current Screening	---	---	$133.4	$740.1	$246.1	$1,302.0
Physician Education	-$14.4	$17.2	$136.6	$847.7	$266.0	$1,481.5
Screen All	-$26.0	$40.8	$140.1	$950.2	$282.4	$1,635.2

Table A25. Cumulative Social Value ($ billions) and Incremental Cost-Effectiveness ($/QALY) Relative to Baseline for high and low discount rates, 20-year Time Horizon

Screening Scenarios	Discount rate	Treatment Access					
		Treat F3-F4		Treat F2-F4		Treat F0-F4	
		1%	5%	1%	5%	1%	5%
Current Screening	**Cumulative Social Value**	---	---	$497.6	$286.4	$881.2	$510.2
	ICER	---	---	Cost Saving	Cost Saving	Cost Saving	Cost Saving
Physician Education	**Cumulative Social Value**	$3.4	-$5.4	$561.4	$317.5	$993.6	$572.4
	ICER	$130,549	$208,672	Cost Saving	$6,070	Cost Saving	$376
Screen All	**Cumulative Social Value**	$10.8	-$6.6	$620.9	$348.4	$1,088.1	$626.1
	ICER	$119,632	$183,090	$2,724	$11,662	Cost Saving	$3,224

All results are relative to baseline, which is Current Screening with treatment of fibrosis stages F3-F4. ICER values represent change in overall cost divided by change in cumulative QALYs. "cost-saving" indicates a reduction in cumulative costs relative to baseline. Dollar values in $US 2015. ICER = incremental cost-effectiveness ratio.

Table A26. Cumulative Social Value ($ billions) and Incremental Cost-Effectiveness ($/QALY) Relative to Baseline for high and low Other Adult starting population, 20-year Time Horizon

Screening Scenarios	Starting Pop.	Treatment Access: Treat F3-F4 *Low*	Treat F3-F4 *High*	Treat F2-F4 *Low*	Treat F2-F4 *High*	Treat F0-F4 *Low*	Treat F0-F4 *High*
Current Screening	**Cumulative Social Value**	---	---	$376.1	$376.1	$668.5	$668.5
	ICER	---	---	Cost Saving	Cost Saving	Cost Saving	Cost Saving
Physician Education	**Cumulative Social Value**	-$1.7	-$1.9	$421.1	$420.9	$752.3	$752.1
	ICER	$163,116	$164,750	$1,948	$2,021	Cost Saving	Cost Saving
Screen All	**Cumulative Social Value**	$0.9	$0.5	$464.3	$464.0	$823.7	$823.3
	ICER	$146,741	$148,175	$6,688	$6,806	Cost Saving	Cost Saving

All results are relative to baseline, which is Current Screening with treatment of fibrosis stages F3-F4. ICER values represent change in overall cost divided by change in cumulative QALYs. "cost-saving" indicates a reduction in cumulative costs relative to baseline. Dollar values in $U.S. 2015. All future values are discounted at a rate of 3%. ICER = incremental cost-effectiveness ratio.

Table A27. Cumulative Social Value ($ billions) and Incremental Cost-Effectiveness ($/QALY) Relative to Baseline for high and low QALY weights, 20-year Time Horizon

Screening Scenarios	QALY Weight	Treatment Access: Treat F3-F4 *Low*	Treat F3-F4 *High*	Treat F2-F4 *Low*	Treat F2-F4 *High*	Treat F0-F4 *Low*	Treat F0-F4 *High*
Current Screening	**Cumulative Social Value**	---	---	$371.4	$383.6	$659.1	$681.2
	ICER	---	---	Cost Saving	Cost Saving	Cost Saving	Cost Saving
Physician Education	**Cumulative Social Value**	-$1.5	-$0.9	$416.1	$430.3	$741.8	$767.3
	ICER	$161,825	$156,676	$2,008	$1,942	Cost Saving	Cost Saving
Screen All	**Cumulative Social Value**	$1.2	$2.4	$459.2	$474.9	$812.9	$840.4
	ICER	$145,731	$141,349	$6,816	$6,600	Cost Saving	Cost Saving

All results are relative to baseline, which is Current Screening with treatment of fibrosis stages F3-F4. ICER values represent change in overall cost divided by change in cumulative QALYs. "cost-saving" indicates a reduction in cumulative costs relative to baseline. Dollar values in $U.S. 2015. All future values are discounted at a rate of 3%. ICER = incremental cost-effectiveness ratio.

5.3. Establishing Upper and Lower Bounds

Many model parameters are derived from the literature and from other sources where there is disagreement about the appropriate value, making it very challenging to establish confidence intervals, or even distributions, for individual parameters. As a result, probabilistic sensitivity testing of our model is challenging.

By varying the four parameters identified in sections 5.1 and 5.2 simultaneously, we are able to estimate approximate upper and lower bounds on the results generated by our model. To do this, we generated 16 combinations of the maximum and minimum values in the ranges tested for the four key parameters (see Tables A12-14). Table A28 provides a key to the scenarios created by these permutations.

We then report a series of results, leading to estimates of maximum and minimum values (approximate upper and lower bounds) on our net cumulative social value and ICER results.

Table A28: Key to Permutations of four key parameters

Permutation	QALY Value ($)	Discount Rate	Other Adult Starting Population	QALY weight (utility)
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				

	Highest value in parameter range (see Tables A12-14)
	Lowest value in parameter range (see Tables A12-14)

Table A29: Permutations of key parameters: All Scenarios

	% Difference in Cumulative Social Value								
	Current Screen			Phys. Ed			Screen All		
	F3-F4	**F2-F4**	**F0-F4**	**F3-F4**	**F2-F4**	**F0-F4**	**F3-F4**	**F2-F4**	**F0-F4**
1	96.32	96.30	96.28	96.32	96.30	96.28	96.32	96.30	96.28
2	75.71	75.70	75.68	75.71	75.70	75.68	75.71	75.70	75.68
3	71.63	71.62	71.62	71.63	71.62	71.62	71.64	71.63	71.62
4	170.48	170.47	170.47	170.48	170.48	170.47	170.49	170.48	170.47
5	-69.49	-69.49	-69.50	-69.49	-69.50	-69.50	-69.50	-69.50	-69.50
6	52.17	52.17	52.17	52.18	52.17	52.17	52.18	52.18	52.17
7	141.91	141.92	141.92	141.91	141.92	141.92	141.92	141.92	141.92
8	136.84	136.85	136.86	136.84	136.86	136.87	136.85	136.86	136.87
9	-57.93	-57.93	-57.92	-57.94	-57.93	-57.93	-57.94	-57.93	-57.93
10	-73.05	-73.05	-73.05	-73.05	-73.05	-73.05	-73.06	-73.06	-73.05
11	-72.93	-72.93	-72.93	-72.93	-72.93	-72.93	-72.93	-72.93	-72.93
12	109.84	109.86	109.88	109.85	109.87	109.89	109.85	109.88	109.89
13	-76.29	-76.29	-76.29	-76.30	-76.30	-76.29	-76.30	-76.30	-76.29
14	-62.69	-62.69	-62.68	-62.70	-62.69	-62.68	-62.70	-62.69	-62.68
15	-62.78	-62.78	-62.77	-62.78	-62.78	-62.77	-62.79	-62.78	-62.77
16	-67.28	-67.27	-67.27	-67.28	-67.28	-67.27	-67.29	-67.28	-67.27

Parameter definitions and ranges for sensitivity parameters are given in Tables A12-A14; key to parameter permutations is provided in Table A28. Results are percent deviation from total social value under our preferred model assumptions within a given screening/treatment combination, rather than relative to baseline.

Table A30: Permutations of four key parameters: Social Value Relative to Baseline (Current Screening with Treatment at F3-F4)

	% Difference in Cumulative Social Value							
	Current Screen		Phys. Ed			Screen All		
	F2-F4	F0-F4	F3-F4	F2-F4	F0-F4	F3-F4	F2-F4	F0-F4
1	54.44	53.84	636.00	57.37	55.48	3675.60	59.91	56.86
2	49.46	48.72	590.96	52.20	50.24	3431.61	54.76	51.70
3	54.44	53.84	650.42	57.43	55.52	3749.27	60.02	56.92
4	163.75	158.76	1888.02	171.25	162.05	9953.31	176.00	163.98
5	-73.44	-72.90	-721.20	-76.45	-74.26	-4009.56	-78.67	-75.27
6	49.46	48.72	605.38	52.26	50.27	3505.28	54.87	51.76
7	155.20	150.13	1763.02	162.20	153.14	9336.53	166.90	155.17
8	163.75	158.76	1896.31	171.29	162.07	9989.15	176.06	164.01
9	-50.88	-48.66	-677.54	-53.81	-50.20	-3667.36	-56.08	-51.38
10	-73.44	-72.90	-706.78	-76.39	-74.23	-3935.89	-78.56	-75.21
11	-74.27	-73.76	-728.71	-77.31	-75.13	-4050.23	-79.52	-76.13
12	155.20	150.13	1771.31	162.24	153.16	9372.36	166.95	155.20
13	-74.27	-73.76	-714.29	-77.25	-75.10	-3976.56	-79.42	-76.07
14	-52.31	-50.10	-698.37	-55.32	-51.68	-3770.15	-57.60	-52.85
15	-50.88	-48.66	-669.25	-53.78	-50.18	-3631.52	-56.03	-51.35
16	-52.31	-50.10	-690.08	-55.29	-51.66	-3734.31	-57.55	-52.82%

Parameter definitions and ranges for sensitivity parameters are given in Tables A12-A14; key to parameter permutations is provided in Table A28. Results are percent deviation from net cumulative social value under our preferred model assumptions relative to baseline.

	Largest percent increase within scenario combination, relative to baseline
	Largest percent decrease within scenario combination, relative to baseline

Table A31: Permutations of key parameters: ICER Relative to Baseline (Current Screening with Treatment at F3-F4)

	% Difference in ICER							
	Current Screen		Phys. Ed			Screen All		
	F2-F4	**F0-F4**	**F3-F4**	**F2-F4**	**F0-F4**	**F3-F4**	**F2-F4**	**F0-F4**
1	61.28	58.24	22.77	202.24	108.52	20.16	70.61	247.33
2	59.98	56.79	26.27	212.30	108.82	23.42	76.06	252.29
3	61.28	58.24	21.15	196.57	107.14	18.53	67.73	242.07
4	-45.79	-43.73	-23.28	-165.71	-83.85	-21.69	-60.09	-194.72
6	59.98	56.79	24.60	206.44	107.39	21.75	73.09	246.84
7	-50.80	-48.90	-20.03	-167.99	-90.51	-18.62	-58.74	-205.12
8	-45.79	-43.73	-23.77	-167.65	-84.33	-22.13	-60.92	-196.29
12	-50.80	-48.90	-20.55	-170.00	-91.02	-19.08	-59.60	-206.75

Parameter definitions and ranges for sensitivity parameters are given in Tables A12-A14; key to parameter permutations is provided in Table A28. Results are percent deviation from ICER value under our preferred model assumptions relative to baseline. Because ICER calculation does not include economic value of QALYs, reported results are limited to permutations with high QALY values to avoid duplication.

	Largest percent increase within scenario combination, relative to baseline
	Largest percent decrease within scenario combination, relative to baseline

Table A32. Permutations of Key Parameters: Maximum and Minimum Values for Cumulative Social Value and Incremental Cost-Effectiveness Relative to Baseline, 20-year Time Horizon

Screening Scenarios		Treatment Access					
		Treat F3-F4		Treat F2-F4		Treat F0-F4	
	Bound	*Min*	*Max*	*Min*	*Max*	*Min*	*Max*
Current Screening	**Cumulative Social Value**	---	---	$97	$992	$175	$1,730
	ICER	---	---	Cost Saving	Cost Saving	Cost Saving	Cost Saving
Physician Education	**Cumulative Social Value**	-$15	$32	$96	$1,142	$187	$1,971
	ICER	$124,959	$206,992	Cost Saving	$6,198	Cost Saving	$415
Screen All	**Cumulative Social Value**	-$27	$69	$95	$1,281	$197	$2,174
	ICER	$114,819	$181,994	$2,636	$11,879	Cost Saving	$3,325

All results are relative to baseline, which is Current Screening with treatment of fibrosis stages F3-F4. ICER values represent change in overall cost divided by change in cumulative QALYs. "cost-saving" indicates a reduction in cumulative costs relative to baseline. Dollar values in $U.S. 2015. All future values are discounted at a rate of 3%. ICER = incremental cost-effectiveness ratio.

5.4. Alternative Screening Scenarios

5.4.1. High Risk Screening Frequency

Even though AALSD guidelines recommend annual screening for high risk individuals, less frequent screening might provide similar benefits to society at a lower cost. We explore two sensitivity analyses in which, on average, individuals in the PWID and MSM-HIV risk groups receive screening once every 3 years or every 5 years instead of annually. Baby boomers in the Other Adults group still receive a one-time screening.

5.4.2. Screening Outreach for PWID

Over half of new HCV infections are among PWID, and outreach programs have been proposed for reducing incidence. The model in this paper was not designed to explicitly simulate screening outreach policies. We adapt our scenario parameters to approximate the impact of screening outreach in the PWID population. The adaptation does not take into account specific policy features or the transmission and cost dynamics associated with an outreach program.

This scenario increases the percentage of PWIDs screened by relaxing the assumption that PWIDs are screening only when they visit a doctor or clinic. Outreach results in 100% of PWID being offered screening, and 91% accepting screening. This scenario also increases the screening cost for PWID relative to the status quo from $41.37 to $310.55 per screening in order to approximate the additional costs associated with an outreach program.[88]

Table A33. Sensitivity to Alternative Screening Scenarios: Cumulative Social Value Relative to Baseline over 20-year Time Horizon and Years to Policy Break-Even (BE)

		Treatment Scenario		
		Treat F3-F4	**Treat F2-F4**	**Treat F0-F4**
Screening Scenario	**Current Screening**	---	$376.1 bn (8 yrs to BE)	$668.5 bn (8 yrs to BE)
	Screening Outreach (PWID)	-$7.8 bn (29 yrs to BE)	$433.8 bn (8 yrs to BE)	$788.9 bn (7 yrs to BE)
	Screen PWID & MSM-HIV Every 3 Years	-$0.1 bn (21 yrs to BE)*	$391.7 bn (8 yrs to BE)	$689.2 bn (8 yrs to BE)
	Screen PWID & MSM-HIV Every 5 Years	$3.2 bn (15 yrs to BE)*	$412.8 bn (8 yrs to BE)	$714. bn (8 yrs to BE)

*Cumulative Net Value has an inverted u-shaped pattern. Therefore, the net value is initially negative, becomes positive, and then switched back to negative. The break-even year represents the initial switch to positive values.

5.5. Physician Adherence to Screening Guidelines

We assume that individuals will only be screened if they utilize the healthcare system and their physician is aware of clinical guidelines for screening. Following Kallman (2009), we assume that 58% of physicians are aware of guidelines.[38] Since data for adherence is not available, we make the simplifying assumption that 100% of physicians who are aware of guidelines adhere to

them. Real-world adherence to screening guidelines is likely to be less than 100%, however, and lower adherence to guidelines affects the overall probability of a patient being screened.

To test the sensitivity of the screening probabilities in our model to this assumption, we calculate the probability of being screened for a range of adherence levels, presented in Table A34 below.

Table A34. Screening Probabilities by Risk Group and Screening Scenario

	Other Adult			PWID		MSM-HIV	
	Current Screening	**Physician Education**	**Screen All**	**Current Screening**	**Physician Education & Screen All**	**Current Screening**	**Physician Education & Screen All**
100% Adherence							
Susceptible	0.178	0.305	0.778	0.454	0.779	0.505	0.866
Infected	0.160	0.274	0.699	0.476	0.816	0.505	0.866
75% Adherence							
Susceptible	0.133	0.229	0.583	0.341	0.584	0.379	0.649
Infected	0.120	0.206	0.525	0.357	0.612	0.379	0.649
50% Adherence							
Susceptible	0.089	0.152	0.389	0.227	0.389	0.252	0.433
Infected	0.080	0.137	0.359	0.238	0.408	0.252	0.433
25% Adherence							
Susceptible	0.044	0.076	0.194	0.114	0.195	0.130	0.220
Infected	0.004	0.069	0.175	0.119	0.204	0.130	0.220

The probability of screening with 100% physician adherence in the Current Screening scenario ranges from 0.16-0.505. While probabilities of screening are slightly lower with lower rates of physician adherence, the probabilities used in the model (at 100% adherence) are consistent with existing research.[4] Nonetheless, our results should be viewed as an upper bound, dependent on physician implementation of screening guidelines.

5.6. Varying PWID Starting Infected Population

There is no consensus regarding the prevalence of HCV (detected + undetected) in the U.S. population. Edlin (2015) suggest that 1 million additional PWID have been infected by HCV than what a household survey, such as NHANES, can detect.[89] We use estimates from Edlin (2015), Mathers (2008), Tempalski (2013), Tseng (2007), and Edlin (2011) to calculate upper and lower bounds for the PWID infected population size.[83,89-92]

Table A35. Sensitivity to Starting PWID Infected Population Size: Cumulative Social Value Relative to Baseline over 20-year Time Horizon and Years to Policy Break-Even (BE)

		Treatment Scenario					
		Treat F3-F4		Treat F2-F4		Treat F0-F4	
		Low	*High*	*Low*	*High*	*Low*	*High*
Screening Scenario	**Current Screening**	---	---	$317.7 bn (8 yrs to BE)	$435.6 bn (8 yrs to BE)	$550.6 bn (8 yrs to BE)	$792.2 bn (8 yrs to BE)
	Physician Education	-$1.1 bn (22 yrs to BE)	-$2.9 bn (22 yrs to BE)	$357.1 bn (9 yrs to BE)	$485.8 bn (9 yrs to BE)	$621.3 bn (8 yrs to BE)	$889.7 bn (8 yrs to BE)
	Screen All	$1.3 bn (20 yrs to BE)	-$0.5 bn (21 yrs to BE)	$400.2 bn (9 yrs to BE)	$528.9 bn (9 yrs to BE)	$692.7 bn (8 yrs to BE)	$961.1 bn (8 yrs to BE)

5.7. Additional sensitivities

We also conduct sensitivities on other variables of interest in order to better understand the effect of key assumptions on social value results. We conducted the following tests: (1) Vary treatment and screening costs to model "high" and "low" cost scenarios; (2) Remove the assumption that diagnosed, untreated patients receive a 2% decrease in QALY weights; and (3) Remove the treatment discount from price competition. Results are presented in Table A36 below.

Table A36: Sensitivity to Model Assumptions: Cumulative Social Value Relative to Baseline over 20-year Time Horizon and Years to Policy Break-Even (BE)

Screening Scenarios	Sensitivity Analysis: Treatment/Screening Cost *Low*	Sensitivity Analysis: Treatment/Screening Cost *High*	Sensitivity Analysis: Utility Decrement *None*	Sensitivity Analysis: Treatment Cost Discount *None*
		Treat F3-F4		
Current Screening	--	--	--	--
Physician Education	$1.7 bn (19 years to BE)	-$4.8bn (25 years to BE)	$4.8 bn (18 years to BE)	-$6.8 bn (27 years to BE)
Screen All	$6.8 bn (18 years to BE)	-$4.9 bn (23 years to BE)	$12.6 bn (16 years to BE)	-$8.4 bn (26 years to BE)
		Treat F2-F4		
Current Screening	$402.3 bn (6 years to BE)	$349.9 bn (9 years to BE)	$376.2 bn (8 years to BE)	$348.2 bn (9 years to BE)
Physician Education	$452.2 bn (7 years to BE)	$390.3 bn (10 years to BE)	$427.7 bn (8 years to BE)	$385.6 bn (10 years to BE)
Screen All	$499.1 bn (7 years to BE)	$429.8 bn (10 years to BE)	$476.2 bn (9 years to BE)	$422.7 bn (10 years to BE)
		Treat F0-F4		
Current Screening	$730.5 bn (6 years to BE)	$606.6 bn (9 years to BE)	$669.0 bn (8 years to BE)	$620.1 bn (9 years to BE)
Physician Education	$820.9 bn (6 years to BE)	$683.9 bn (10 years to BE)	$759.2 bn (8 years to BE)	$693.2 bn (9 years to BE)
Screen All	$897.6 bn (6 years to BE)	$750.1 bn (10 years to BE)	$835.8 bn (8 years to BE)	$755.9 bn (10 years to BE)

Notes: Baseline is Current Screening with treatment at F3-F4, simulated separately for each sensitivity analysis. Values in parentheses represent the years required for a scenario to "break even" (ie, years required to switch from negative to positive cumulative net social value) relative to the baseline. Dollar values in $U.S. 2015. All future values are discounted at a rate of 3%. QALY: quality-adjusted life year; BE: break even. Low cost sensitivity scenario reduces treatment costs by 50% and assumes screening costs only include the EIA antibody test ($21.24); high cost sensitivity scenario increases treatment costs by 50% and assumes screening for chronically infected individuals includes the cost of an EIA antibody test, RNA quantitative test, genotype test, and three level 1 office visits ($528.63).[36,42] Utility Decrement removes the assumption that diagnosed but untreated individuals experience a 2% QALY decrease. Treatment Cost Discount removes the 46% treatment cost discount in years 2-20 that results from price competition.

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