Costs and Spillover Effects of Private Insurers' Coverage of Hepatitis C Treatment

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ABSTRACT

Objectives: Hepatitis C virus (HCV) treatment incentives for private payers may be misaligned because payers must bear immediate costs and may not realize long-term benefits. However, these benefits may accrue to future payers, including Medicare. We examined how and to what extent private payers' current HCV treatment coverage decisions impact Medicare's and private payers' future costs.

Study Design: Discrete-time Markov model.

Methods: We modelled HCV disease progression and transmission to simulate the economic and social effects of different private-payer HCV treatment scenarios on Medicare. The model examined differences between a baseline scenario (current practice guidelines) and 2 alternative scenarios that expand treatment coverage. Spillover effects were measured as reduced HCV treatment costs and medical expenditures in Medicare. We calculated the spillover effects and net social value of each scenario (total value of quality-adjusted life-years accrued over time minus cumulative treatment and medical costs).

Results: With expanded HCV treatment coverage, private payers experience reduced medical expenditures in the 3-to-5-year time horizon; however, they still face higher treatment costs. Over a 20-year horizon, private payers experience overall savings of $10 billion to $14 billion after treatment costs. The expansion of coverage by private payers generates positive spillover benefits to Medicare of $0.3 billion to $0.7 billion over a 5-year horizon, and $4 billion to $11 billion over a 20-year horizon.

Conclusions: When private payers increase HCV treatment coverage, they may achieve significant savings while inducing spillover benefits to Medicare. Future savings, however, may not motivate immediate treatment investments among private payers who experience high beneficiary turnover.

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Hepatitis C virus (HCV) infection is a slowly progressing disease that often remains asymptomatic for at least 10 years post exposure. Left untreated, HCV infection can lead to serious hepatic complications, liver failure, and death.[1-5] Through recent pharmaceutical breakthroughs, short courses of treatment with direct-acting antivirals (DAAs) provide a high likelihood of cure.[6,7] DAAs are the current standard of care in the United States, but they generate higher upfront costs relative to previous treatments.

The higher cost and efficacy of DAAs present a quandary for health system decision makers: treatment costs are borne in the short term, yet a significant portion of the benefits, including reduced disease transmission and HCV-related costs, accrue over the longer term. Few doubt that patients with HCV should be treated with these highly effective novel therapies; the salient policy question is when treatment should occur. A growing body of research indicates that early HCV treatment likely generates the greatest value for patients and society[7]; however, it is much less clear that early treatment generates benefits for the private payers providing this treatment to patients with HCV. Private payers retain enrollees less than 10 years on average,[8] which discourages investments in therapies with long-term benefits. These incentives may conflict with the value other payers receive when they enroll patients who were treated earlier in their disease state, before complications arose.[7]

The misalignment between short-term costs and long-term benefits is of particular concern for Medicare, which insures individuals 65 or older.[9] An estimated 75% of individuals currently infected with HCV in the United States are baby boomers (born between 1945 and 1965)—most of whom will be enrolled in Medicare within the next 10 to 15 years.[10] Further, the majority of HCV-positive baby boomers was likely infected decades ago, and therefore, is at serious risk of disease complications when entering Medicare.[11]

Because private insurers currently cover a large population of HCV-positive baby boomers, their HCV coverage

decisions today will impact their own costs, as well as the long-term costs borne by the publicly funded Medicare system.[12] In this article, we simulate the transmission and progression of HCV under various private-payer HCV treatment coverage policies, quantify how these polices affect healthcare costs and benefits borne by private insurers and Medicare, and compute the social impact of these policies.

Take-Away Points

Although the treatment costs for hepatitis C virus (HCV) are borne immediately, many benefits of treatment (eg, improved quality of life, longer survival) accrue in the future. Private payers with high beneficiary turnover may be reluctant to cover HCV treatment today, but foregoing treatment today results in larger future healthcare costs for both Medicare and private payers.

- Expanding private coverage of HCV treatments would generate $10 billion to $14 billion in private-payer savings and $4 billion to $11 billion in spillover benefits to Medicare after 20 years.
- Costs of private-coverage expansion exceed benefits for private payers in the short term; however, this investment would break even after 16 to 17 years.
- Total social value of comprehensive HCV treatment is positive for society, but private insurers do not have the incentive to provide comprehensive HCV treatment.

METHODS

Overview of the Markov Model of HCV Transmission and Disease Progression

We developed a discrete-time Markov model (Microsoft Excel 2010/VBA, Microsoft Corporation, Redmond, Washington) that incorporates patient insurance status, categorized as Medicare, Medicaid, private, or uninsured. We quantified the downstream indirect effects on Medicare from earlier private-insurer investment in HCV treatment, which we refer to as "spillover effects"[13,14] (see **Figure 1**; a detailed description of the model is available in the **eAppendix** [available at **www.ajmc.com**]).

The model categorizes patients into 3 subpopulations by risk of HCV exposure: 1) people who inject drugs (PWID); 2) HIV-infected men who have sex with men (MSM-HIV); and 3) all other adults born before 1992, when systematic testing of the blood supply for HCV began ("Other Adults"), of which baby boomers account for approximately 39%.[15] The model assumes that individuals belong to the same risk group throughout the simulation. The risk groups of infected patients are further stratified by HCV genotypes 1, 2, and 3, which account for 70%, 16%, and 12% of the HCV-infected populations in the United States, respectively.[16]

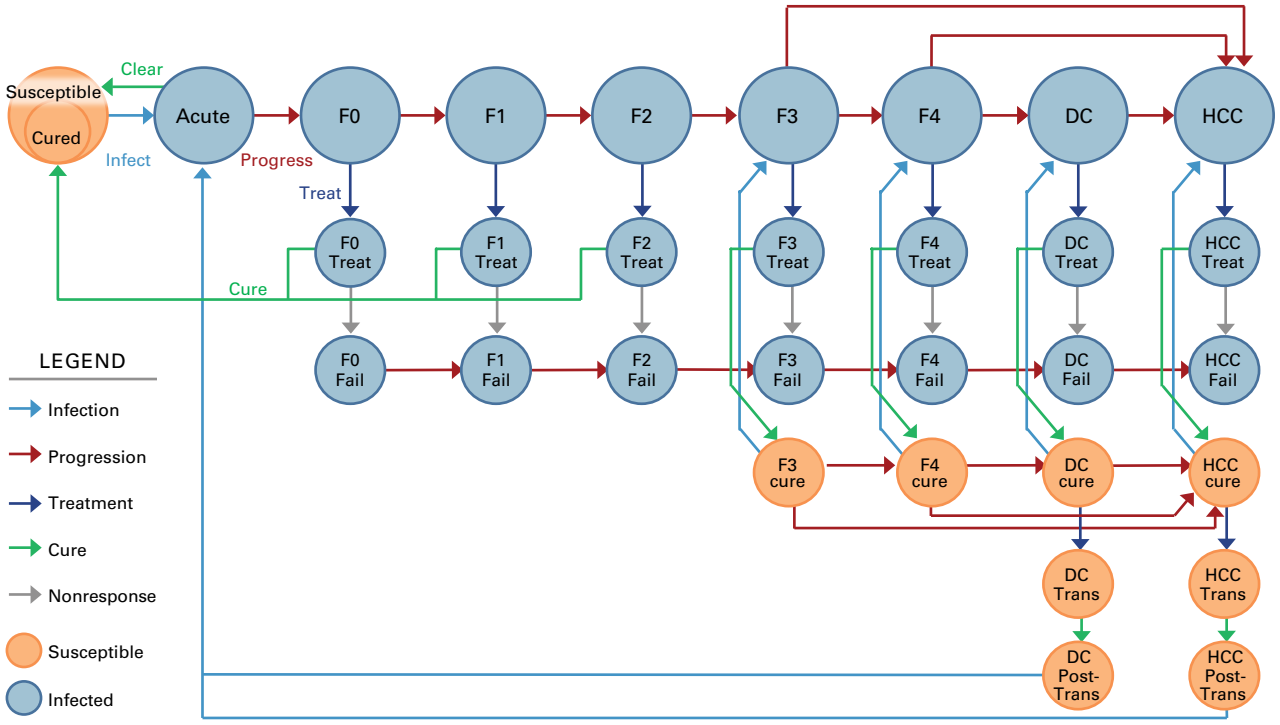
The model assumes Other Adults is a closed cohort in which infected individuals do not transmit HCV to uninfected individuals.[17-19] This assumption is based on the introduction of mandatory HCV screening of blood products in 1992 and the observed low disease-transmission risk among adults who are not PWID or MSM-HIV.[17,20] HCV can be transmitted by an infected individual in the PWID or MSM-HIV groups to an uninfected individual in the same group; uninfected individuals and those previously cured of HCV are at risk of becoming infected. Furthermore, patients can only be infected with 1 genotype at a time, but can become re-infected with any genotype after being cured.

Once infected with HCV, patients progress through disease states based on transition probabilities obtained from the literature (see eAppendix). The initial distribution of fibrosis stages is assumed independent of age and insurance status.[21] We use the METAVIR scoring system to categorize liver fibrosis stages from F0 (no fibrosis) to F4 (most severe). Successfully treated patients return to the pool of susceptible individuals and have the same reinfection probability as individuals who were never infected.

Patients are eligible for treatment if they meet the treatment coverage criteria specified by their insurance type. For the PWID and Other Adults groups, we computed the population's initial insurance distribution and HCV prevalence by age, using the 5 most recent waves of the National Health and Nutrition Examination Survey (NHANES) (2003-2004 through 2011-2012), applying appropriate weights to generate nationally representative estimates.[15,22] Due to the small sample of NHANES respondents in the MSM-HIV exposure group, we used prevalence estimates from the published literature.[16,23,24] For all groups, insurance type was assumed constant throughout the simulation, except when patients entered Medicare at age 65. Only diagnosed patients may receive treatment, and based on published estimates of diagnosis rates, we assumed 50% of patients infected with HCV were diagnosed during any given model cycle.[25]

HCV treatment costs, medical expenditures (nontreatment medical costs), quality-adjusted life-year (QALY) weights, and mortality rates were derived from estimates in the published literature.[26,27] All cost parameters were inflated to 2015 US dollars, and future costs and QALYs were discounted at an annual 3% rate.[28] Treatment costs vary by genotype and fibrosis stage, while medical expenditures and QALY weights vary by disease state. Treatment efficacy, treatment costs, and medical expenditures do not vary by insurance status or over time, with the exception of treatment costs, which are discounted after 2 years to account for future market competition[29] (see eAppendix for full details).

Figure 1. Schematic of HCV Transmission and Progression Model[a,b]



DC indicates decompensated cirrhosis; F0-F4, fibrosis stages of HCV, F4 being most severe; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; trans, transplant.

[a]This schematic represents a single 1-year cycle in the simulation of the HCV model developed in this paper. The model is simulated repeatedly over a given time period, and population outcomes are recorded after each cycle. At the start of the model, individuals are classified by HCV disease state: susceptible (uninfected), infected with acute HCV, or infected with chronic HCV. Chronically infected patients are distributed across fibrosis stages F0-F4, DC, or HCC. In each model cycle, patients can transition across disease states and chronically infected patients can initiate treatment. Patients who receive treatment and are cured return to the susceptible pool of individuals. All states have transitions to "dead." (See the eAppendix for full details about model states and transitions.)

[b]Adapted from the appendix of Van Nuys (2015)[7] and reproduced by permission of the authors.

Treatment Scenarios

We simulated 3 treatment coverage scenarios over a 20-year period: a baseline scenario and 2 alternative scenarios with varying degrees of expanded treatment coverage. All scenarios assume that patients with Medicare, Medicaid, or private insurance coverage who meet the fibrosis stage criteria are treated with DAAs, while uninsured patients have no access to treatment.[30-32]

In the baseline scenario, we assumed all diagnosed publicly and privately insured patients infected with HCV in fibrosis stages F3 or F4 would receive treatment, following the American Association for the Study of Liver Diseases and Infectious Diseases Society of America guidelines for "highest priority for treatment," which is consistent with general trends regarding payer coverage of HCV treatment.[30,33-36] The alternative scenarios assumed that private insurers expand treatment coverage to either fibrosis stages F2-F4 or F0-F4.

Baseline Distribution of Insurance Status

Table 1 presents the baseline distribution of insurance status by risk group. Although more than 40% of the PWID and MSM-HIV groups are uninsured or covered by Medicaid, the majority (53%) of the Other Adults group has private insurance coverage. Even though treatment scenarios assume uninsured patients do not receive treatment, these patients may benefit from expanded private insurance treatment coverage through lower HCV transmission rates since fewer patients will transmit the disease after treatment.

Alternative Simulations

In addition to the treatment scenarios described above, we conducted 3 additional simulations. First, we assessed the spillover effects to Medicare solely driven by individuals transitioning into Medicare at age 65, by measuring Medicare spillovers for the Other Adults risk group only,

Table 1. Baseline Distribution of Insurance Status by Risk Group

Payer Type	Percent of Risk Group (%)		
	Other Adult[a]	PWID	MSM-HIV
Private	53.3	40.4	42.9
Medicare	19.8	7.5	16.8
Medicaid[b]	8.2	13.0	25.6
Uninsured	18.7	39.1	14.7

MSM-HIV indicates men infected with HIV who have sex with men; PWID, people who inject drugs.
[a]"Other Adult" indicates all other adults born prior to 1992.
[b]The Medicaid payer type includes Medicaid and other state and local programs.
Source: National Health and Nutrition Examination Survey, 2003-2012.

which has no disease transmission in the model. Second, we calculated the impact of Medicare treatment coverage expansion on Medicare costs and computed spillover effects to private insurers, while holding constant private treatment coverage at the baseline. Finally, we explored the impact on Medicare if Medicaid expands treatment coverage simultaneously with private insurers.

Model Outputs

Across all scenarios, the spillover effects on Medicare are computed as the change in HCV cost burden resulting from private payers expanding HCV treatment coverage minus the change in annual total healthcare expenditures (ie, medical and HCV treatment costs), relative to the baseline scenario. This captures the net benefit from the payer perspective.

To capture the impact from patients' perspectives, we computed the change in net social value of HCV treatment relative to the baseline scenario. We define net social value as the total value of QALYs accrued over time (ie, value of health gains from treatment) minus cumulative treatment and medical costs. We assumed a $150,000 value per QALY, given the range of values cited in the literature.[37,38] We focused on outcomes for 5- and 20-year horizons, but results for 10 years are presented in the eAppendix.

RESULTS

Effects of Private Insurance Treatment Expansion

Table 2 shows the impact on private payers and on Medicare 5 and 20 years after private payers expand treatment from the baseline (F3-F4) to either F2-F4 or F0-F4. When treatment is expanded to F2-F4, private payers, as a class, realize net savings from reduced medical expenditures within 20 years. Relative to the baseline scenario, Medicare's cumulative costs are reduced by $0.25 billion ($74 per HCV-positive Medicare beneficiary) after 5 years and $4.4 billion ($427 per HCV-positive Medicare beneficiary) after 20 years. These cost reductions represent the spillover effect on Medicare from private payers' treatment expansion even though Medicare does not expand coverage. In other words, if private payers restrict treatment coverage to F3-F4, Medicare would face an additional $4.4 billion cost burden over 20 years, relative to F2-F4 treatment coverage.

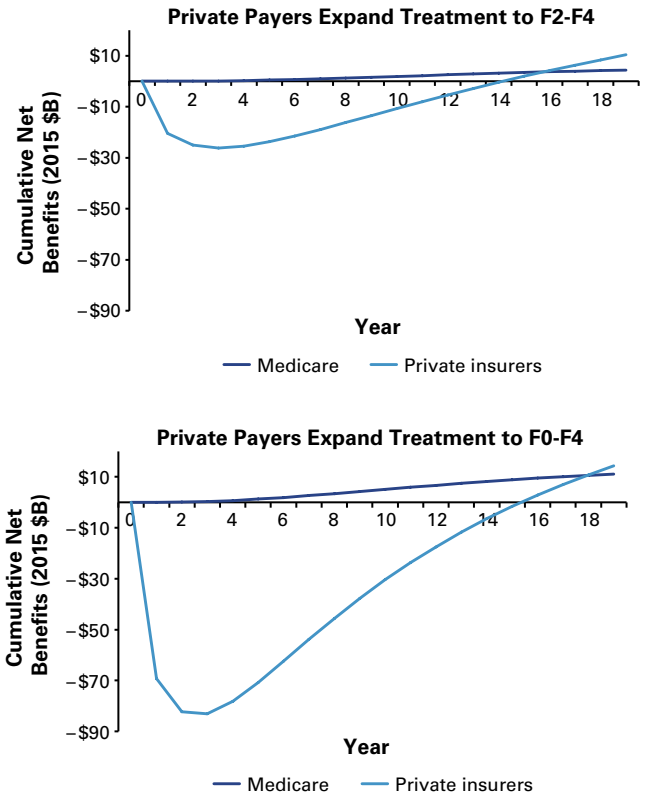
Medicare receives a larger net benefit if private treatment coverage is expanded to F0-F4. After 20 years, Medicare's medical expenditures declined by $9 billion and treatment costs declined by $2 billion, for a net benefit of $11 billion

Table 2. Change in Costs[a] When Private Insurers Expand Treatment Coverage

	Treat F2-F4		Treat F0-F4	
	Cost Effect on Private Insurers	Cost Effect on Medicare "Spillovers"	Cost Effect on Private Insurers	Cost Effect on Medicare "Spillovers"
5-year horizon				
Change in medical expenditures ($B)	–$6.81	-$0.20	–$21.82	–$0.67
Change in HCV treatment costs ($B)	$32.28	–$0.04	$100.03	–$0.05
Change in total costs ($B)	$25.47	–$0.25	$78.21	–$0.72
Change in total costs per capita	$7641	–$74	$23,646	–$217
20-year horizon				
Change in medical expenditures ($B)	–$44.33	–$3.00	–$104.43	–$9.03
Change in HCV treatment costs ($B)	$34.00	–$1.40	$90.15	–$2.03
Change in total costs ($B)	–$10.33	–$4.40	–$14.28	–$11.06
Change in total costs per capita	–$1002	–$427	–$1465	–$1134

$B indicates US dollars in billions; F0-F4, fibrosis stages of HCV (F4 being most severe); HCV, hepatitis C virus.
[a]Costs are changes that result from expanding from the baseline scenario (treat F3-F4) and are reported in 2015 US dollars. Future costs are discounted at a rate of 3% per year. Per capita costs are calculated as total cost per HCV-positive Medicare beneficiary at the given time horizon.

Figure 2. Cumulative Net Benefits to Payers[a] From Private Treatment Expansion Relative to Treat F3-F4



$B indicates US dollars in billions; F0-F4, fibrosis stages of HCV (F4 being most severe).
[a]Net benefits to payer = medical expenditure savings – treatment costs.

($1134 per HCV-positive Medicare beneficiary). In both alternative scenarios, private payers with time horizons of less than 20 years have the incentive to restrict treatment coverage, even though this policy harms both Medicare and private insurers in the long term. Figure 2 makes clear, however, that private payers do not enjoy the same net benefit as Medicare in the short term, because they bear the upfront treatment costs. Private payers face increased total costs of $25 billion to $78 billion after 5 years of expanding treatment. It takes roughly 16 to 17 years for private payers to break even on their upfront investment in treatment; after 20 years, they enjoy net savings of $10 billion to $14 billion. When treatment is expanded to F0-F4, net benefits to Medicare are 2.5 times higher compared with expanding to F2-F4. In addition, despite 5-year costs that are almost 3 times larger compared to expansion to F2-F4, expanding to F0-F4 results in an additional $4 billion in savings to private payers over a 20-year period.

Expanding HCV treatment coverage also greatly benefits society, through both reduced mortality and improved health-related quality of life for treated patients.[39] Relative to treating at stages F3-F4, expanding treatment to F2-F4 generates 0.9 million additional discounted life-years over a 20-year period, and this figure increases to 1.17 million discounted QALYs after applying health utilities to the model population. Similarly, expansion to F0-F4 generates 1.7 million discounted life-years and 2.35 million QALYs over 20 years, relative to treating F3-F4.

QALY gains represent considerable value for society (see Figure 3). The cumulative net social value for each treatment expansion scenario is positive within 8 years. However, expanding treatment to F0-F4 provides the largest societal benefits after 20 years, at $382 billion, compared with only $192 billion generated by only expanding to F2-F4.

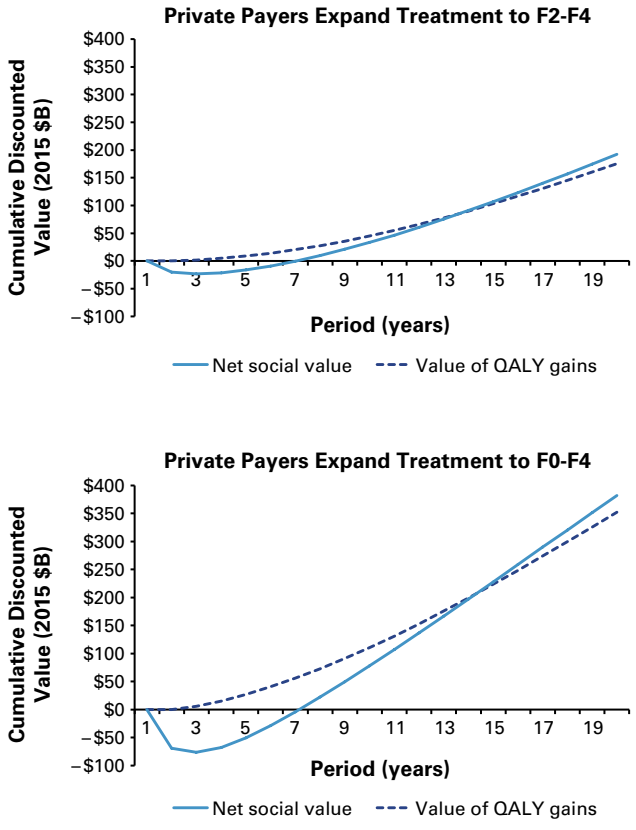
Alternative Simulation Results

In the simulation of the private-payer treatment expansion for the Other Adults group only, we assessed the Medicare spillovers driven solely by individuals transitioning into Medicare at age 65. We found that the Other Adults group accounts for 88% of the 20-year spillover effect when treatment is expanded to F2-F4 and 84% when treatment is expanded to F0-F4. This suggests that the majority of the net benefits to Medicare result from improved health of currently infected patients rather than reduced transmission.

Next, we assessed the impact on private payers' costs, attributable to Medicare expanding treatment coverage from F3-F4 to F2-F4, holding private-insurer treatment coverage constant at the baseline. In this simulation, because individuals do not transition from Medicare to private insurance, private insurers benefit from reduced treatment costs and medical expenditures exclusively due to a reduced transmission effect. Therefore, the spillovers generated by expanded Medicare treatment coverage are smaller than those generated by expanded private insurance treatment. After 20 years, private insurers experience cost savings of $0.97 billion compared with the $4.4 billion Medicare saves in the analogous private expansion scenario. Additionally, Medicare requires 25 years to reach positive net benefits of expanding treatment coverage to F2-F4.

Finally, we explored the impact of expanding Medicaid treatment coverage simultaneously with private insurance coverage. If both Medicaid and private payers expand treatment from F3-F4 to F2-F4, Medicare saves $5.1 billion over 20 years—an additional $0.6 billion in savings, relative to a private-payer expansion alone. Simultaneous expansion by Medicaid and private insurers from F3-F4 to F0-F4 saves Medicare $12.8 billion in total costs—an additional $1.2 billion in savings. Given the significantly larger size of the

Figure 3. Social Value[a,b] of More Generous Hepatitis C Virus Treatment by Private Insurers Relative to Treat F3-F4



$B indicates US dollars in billions; F0-F4, fibrosis stages of HCV (F4 being most severe); QALY, quality-adjusted life-year.
[a]Values calculated for all insurance types combined.
[b]Net social value = (QALYs x $150,000) – medical expenditures – treatment costs.

privately insured population relative to the Medicaid population, it is not surprising that private insurance treatment expansion generates the majority of spillovers to Medicare.

Expanding Medicaid treatment coverage also has a small effect on costs to private payers through reduced transmission rates. Over 20 years, private payers experience an additional $0.3 billion in total cost savings when Medicaid expands treatment to F2-F4 and an additional $0.82 billion in total cost savings when Medicaid expands treatment to F0-F4.

The eAppendix presents additional sensitivity analyses conducted on model parameters and assumptions; specifically, sensitivities to changes in treatment costs and in the value of a QALY. Our findings suggest that increasing treatment costs by 50% does not substantively change spillovers to Medicare.[6] For example, when treatment costs increase by 50%, expanding treatment to F2-F4 results in a $5.1-billion savings to Medicare compared with a $4.4-billion savings in the main analysis. We also found that reducing the value of a QALY to $50,000 yields a positive net social value by year 10 compared with year 8 in the main analysis.

DISCUSSION

Investments in HCV treatment pay off over the long term; unfortunately, however, private payers face patient turnover, which makes it difficult for them to enjoy the long-term return on their investment. Although most enrollees switch insurers within 10 years, it takes roughly 15 years for private-payer treatment investments to pay off, from their own individual perspective. Therefore, enrollee turnover creates a short-term focus among private payers that might discourage HCV treatment and other similar long-term investments. The costs of this incentive problem are borne by all future payers—including Medicare and private payers.

The vast majority of HCV-positive baby boomers will transition from private insurance coverage to Medicare within the next decade. Our analysis shows that when private payers expand treatment coverage to fibrosis stages F2-F4, they accrue cost savings over the next 20 years and save Medicare $4.4 billion over the same period. However, if private insurers expand coverage to all fibrosis stages (F0-F4), the spillover benefits to Medicare increase to $11.1 billion over 20 years.

Future costs are also borne by private payers. This may seem counterintuitive since these costs result from private payers' own decisions; however, this is a classic economic problem of "free-riding." Private payers recognize that other firms today cover the enrollees they will cover in 15 years; thus, they understand that their current treatment decisions have a smaller impact on the health of their enrollee population 15 years from now. Consequently, a single insurer can only hope that other payers will treat its future beneficiaries. Unfortunately, all private payers face the same harsh calculus, which discourages short-term treatment investments and imposes long-term costs on everyone.

This study adds to the growing evidence that earlier HCV treatment generates considerable value to patients and society, contributing to the ongoing debate about when to initiate HCV treatment, given its costs. Although treatment guidelines do not recommend limiting treatment by fibrosis stage, insurers must balance the increasing evidence for early treatment against their actuarial costs.[30] Additionally, this study demonstrates the magnitude of the wedge between payer incentives today,

and when patients infected with HCV age into Medicare in the future. Decision makers charged with allocating limited healthcare resources are faced with difficult tradeoffs between short-term costs and long-term benefits. Although this issue is salient in the treatment of HCV, it applies to numerous other clinical settings as well.

Our results present a challenge to policy makers regarding who should be responsible for HCV treatment coverage decisions. Although the socially optimal strategy is for private insurers to expand treatment coverage, this conflicts with their short-term financial incentives. A blunt solution would subsidize HCV treatments directly, since their long-term social benefits exceed the benefits internalized by private payers.

A more nuanced solution would allow private payers to capture the long-term benefits they create from expanded treatment, even if patients switch coverage. An insurer who treats a patient lowers the actuarial cost of covering that patient in the future, which could be rebated to the original insurer as a "handoff payment" if the patient were to switch coverage.[40] Alternatively, an explicit credit could be granted to each payer that treats a patient.[41] An example is the idea of "Healthcoins," or a similar market-based tradable asset pegged at the value society derives from treatment (benefits of treatment minus costs).[41] These and other policy options remain an open area of further research and discussion.

Limitations

As in any modeling-based analysis, our approach has some limitations. Markov models are designed to capture cohort-level effects and therefore cannot forecast individual disease processes and outcomes.[42,43] We assumed individuals belong to a single risk group to avoid double counting, but some overlap is likely to exist in reality. We also assumed no retreatment for individuals who initially failed treatment, but this limitation likely results in a small impact on cost estimates, since existing research indicates that the number of nonresponders is low.[6,44-46]

Although NHANES provides reliable population-level estimates, subpopulation estimates are less reliable due to small sample sizes. Additionally, due to NHANES' self-reporting design, it is possible that stigmatized behaviors, such as sexual activities and intravenous drug use, are underreported, which would affect subpopulation estimates. However, NHANES-based estimates are similar to other estimates reported in the literature.[47] Finally, NHANES also does not capture homeless and incarcerated populations, both of which have high HCV prevalence and limited treatment access.[15,48]

Lastly, our model was designed to examine spillover effects of private coverage policies to Medicare; thus, transitions between insurance types are not modeled, except for individuals aging into Medicare at 65. Spillovers to Medicaid and uninsured populations are limited in our model to the impact of reduced disease transmission. Incorporating insurance transitions could generate additional positive spillover effects from healthier individuals switching among Medicaid, private plans, and uninsured. Additionally, our model assumes uniform coverage among private insurers and does not capture variation in insurance coverage levels. We did not, therefore, study the effects of private insurers who offer different levels of coverage. Differences in coverage may be relevant in a competitive private market or one in which employers and beneficiaries vary in their demand for benefit generosity. Differences in benefit design and competition among insurers present valuable questions for further research.

CONCLUSIONS

Expanding HCV treatment coverage significantly benefits patients and society through a reduced disease burden; however, the optimal approach to paying for these treatments is less clear. As our results demonstrate, expanding private insurance coverage of HCV treatments reduces treatment costs and medical expenditures for Medicare over all time horizons. It also generates net savings for private insurers in the longer term and benefits to society in terms of QALYs. The misalignment between short-term treatment costs and long-term benefits that private payers face, however, may not promote socially optimal treatment strategies. Public policies may be required to realize the benefits of expanding HCV treatment coverage.

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content (GAM, KM, CRH, MTL, DD, TJ, SEM, YSG, RB, DNL); statistical analysis (KM,DD, TJ); obtaining funding (TJ, YSG); administrative, technical, or logistic support (GAM, KM, MTL); and supervision (GAM, TJ, YSG, DNL).

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REFERENCES

1. Razavi H, ElKhoury AC, Elbasha E, et al. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. *Hepatology.* 2013;57(6):2164-2170. doi: 10.1002/hep.26218.

2. Butt AA, Yan P, Lo Re V 3rd, et al; ERCHIVES (Electronically Retrieved Cohort of HCV Infected Veterans) Study Team. Liver fibrosis progression in hepatitis C virus infection after seroconversion. *JAMA Intern Med.* 2015;175(2):178-185. doi: 10.1001/jamainternmed.2014.6502.

3. Institute of Medicine (US) Committee on the Prevention and Control of Viral Hepatitis Infection; Colvin HM, Mitchell AE (eds). *Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C.* Washington, DC: National Academies Press; 2010.

4. Eckman MH, Talal AH, Gordon SC, Schiff E, Sherman KE. Cost-effectiveness of screening for chronic hepatitis C infection in the United States. *Clin Infect Dis.* 2013;56(10):1382-1393. doi: 10.1093/cid/cit069.

5. Moorman AC, Gordon SC, Rupp LB, et al; Chronic Hepatitis Cohort Study Investigators. Baseline characteristics and mortality among people in care for chronic viral hepatitis: the chronic hepatitis cohort study. *Clin Infect Dis.* 2013;56(1):40-50. doi: 10.1093/cid/cis815.

6. Leidner AJ, Chesson HW, Xu F, Ward JW, Spradling PR, Holmberg SD. Cost-effectiveness of hepatitis C treatment for patients in early stages of liver disease. *Hepatology.* 2015;61(6):1860-1869. doi: 10.1002/hep.27736.

7. 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 Aff (Millwood).* 2015;34(10):1666-1674. doi: 10.1377/hlthaff.2014.1193.

8. Cunningham PJ. Few Americans switch employer health plans for better quality, lower costs [NIHCR research brief No. 12]. National Institute for Health Care Reform website. http://www.nihcr.org/Health-Plan-Switching. Published January 2013. Accessed April 8, 2015.

9. Original Medicare (Part A and B) eligibility and enrollment. CMS website. https://www.cms.gov/medicare/eligibility-and-enrollment/origmedicarepartabeligenrol/index.html. Updated November 3, 2015. Accessed December 10, 2015.

10. Smith BD, Morgan RL, Beckett GA, et al; Centers for Disease Control and Prevention. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *MMWR Recomm Rep.* 2012;61(RR-4):1-32.

11. Davis GL, Alter MJ, El–Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology.* 2010;138(2):513-521, 521.e1-6. doi: 10.1053/j.gastro.2009.09.067.

12. Stepanova M, Kanwal F, El-Serag HB, Younossi ZM. Insurance status and treatment candidacy of hepatitis C patients: analysis of population-based data from the United States. *Hepatology.* 2011;53(3):737-745. doi: 10.1002/hep.24131.

13. Chernew M, Baicker K, Martin C. Spillovers in health care markets: implications for current law projections. CMS website. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/ReportsTrustFunds/downloads/spillovereffects.pdf. Published April 16, 2010. Accessed November 25, 2015.

14. Romley JA, Axeen S, Lakdawalla DN, Chernew ME, Bhattacharya J, Goldman DP. The relationship between commercial health care prices and Medicare spending and utilization. *Health Serv Res.* 2015;50(3):883-896. doi: 10.1111/1475-6773.12262.

15. National Health and Nutrition Examination Survey. CDC website. http://www.cdc.gov/nchs/nhanes.htm. Accessed May 25, 2015.

16. Manos MM, Shvachko VA, Murphy RC, Arduino JM, Shire NJ. Distribution of hepatitis C virus genotypes in a diverse US integrated health care population. *J Med Virol.* 2012;84(11):1744-1750. doi: 10.1002/jmv.23399.

17. Coffin PO, Reynolds A. Ending hepatitis C in the United States: the role of screening. *Hepat Med.* 2014;6:79-84. doi: 10.2147/HMER.S40940.

18. Henderson DK. Managing occupational risks for hepatitis C transmission in the health care setting. *Clin Microbiol Rev.* 2003;16(3):546-568.

19. Williams IT, Bell BP, Kuhnert W, Alter MJ. Incidence and transmission patterns of acute hepatitis C in the United States, 1982-2006. *Arch Internal Med.* 2011;171(3):242-248. doi: 10.1001/archinternmed.2010.511.

20. Hepatitis C FAQs for health professionals. CDC website. http://www.cdc.gov/hepatitis/hcv/hcvfaq.htm. Updated March 11, 2016. Accessed November 5, 2015.

21. Hagan LM, Sulkowski MS, Schinazi RF. Cost analysis of sofosbuvir/ribavirin versus sofosbuvir/simeprevir for genotype 1 hepatitis C virus in interferon-ineligible/intolerant individuals. *Hepatology.* 2014;60(1):37-45. doi: 10.1002/hep.27151.

22. Annual estimates of the resident population by single year of age and sex for the United States, states. and Puerto Rico commonwealth: April 1, 2010 to July 1, 2014. US Census Bureau website. http://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=PEP_2014_PEPSYASEX&prodType=table. Accessed April 6, 2015.

23. Denniston MM, Jiles RB, Drobeniuc J, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. *Ann Intern Med.* 2014;160(5):293-300. doi: 10.7326/M13-1133.

24. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 dependent areas—2011 [HIV Surveillance Supplemental Report]. CDC website. http://www.cdc.gov/hiv/pdf/2011_monitoring_hiv_indicators_hssr_final.pdf. Published October 2013. Accessed January 16, 2015.

25. Yehia BR, Schranz AJ, Umscheid CA, Lo Re V 3rd. The treatment cascade for chronic hepatitis C virus infection in the United States: a systematic review and meta-analysis. *PLoS One.* 2014 ;9(7):e101554. doi: 10.1371/journal.pone.0101554.

26. Mathers BM, Degenhardt L, Bucello C, Lemon J, Wiessing L, Hickman M. Mortality among people who inject drugs: a systematic review and meta-analysis. *Bull World Health Organ.* 2013;91(2):102-123. doi: 10.2471/BLT.12.108282.

27. Whiteside YO, Selik R, An Q, et al. Comparison of rates of death having any death-certificate mention of heart, kidney, or liver disease among persons diagnosed with HIV infection with those in the general US population, 2009-2011. *Open AIDS J.* 2015;9:14-22. doi: 10.2174/1874613601509010014.

28. Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-Effectiveness in Health and Medicine: Report of the Panel on Cost-Effectiveness in Health and Medicine. New York: Oxford University Press; 1996.

29. Friedman SL, Bansal MB. Reversal of hepatic fibrosis—fact or fantasy? *Hepatology.* 2006;43(2, suppl 1):S82-S88.

30. AASLD IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology.* 2015;62(3):932-954. doi: 10.1002/hep.27950.

31. Ditah I, Al Bawardy B, Gonzalez HC, et al. Lack of health insurance limits the benefits of hepatitis C virus screening: insights from the National Health and Nutrition Examination Hepatitis C Follow-Up Study. *Am J Gastroenterol.* 2015;110(8):1126-1133. doi: 10.1038/ajg.2015.31.

32. McGowan CE, Fried MW. Barriers to hepatitis C treatment. *Liver Int.* 2012;32(suppl 1):151-156. doi: 10.1111/j.1478-3231.2011.02706.x.

33. Pharmacy clinical policy bulletins Aetna non-Medicare prescription drug plan: subject: hepatitis C. 2015. Aetna website. http://www.aetna.com/products/rxnonmedicare/data/2014/GI/hepatitis_c.html. Accessed May 21, 2015.

34. Canary LA, Klevens RM, Holmberg SD. Limited access to new hepatitis C virus treatment under state Medicaid programs. *Ann Intern Med.* 2015;163(3):226-228. doi: 10.7326/M15-0320.

35. Prior authorization criteria: United American—essential (PDP). United American website. https://www.uamedicarepartd.com/PDF/Formulary/UA_Essential_PriorAuthorization_2016.pdf. Updated May 1, 2015. Accessed September 30, 2015.

36. Clinical pharmacy programs [program number 2014 P 2023-4]. United Healthcare website. https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Pharmacy%20Resources/Sovaldi_Medical%20Necessity.pdf. Published September 1, 2014. Accessed March 5, 2014.

37. Hirth RA, Chernew ME, Miller E, Fendrick AM, Weissert WG. Willingness to pay for a quality-adjusted life year: in search of a standard. *Med Decis Making.* 2000;20(3):332-342.

38. Neumann PJ, Cohen JT, Weinstein MC. Updating

cost-effectiveness—the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med.* 2014;371(9):796-797. doi: 10.1056/NEJMp1405158.

39. Younossi ZM, Stepanova M, Afdhal N, et al. Improvement of health-related quality of life and work productivity in chronic hepatitis C patients with early and advanced fibrosis treated with ledipasvir and sofosbuvir. *J Hepatol.* 2015;63(2):337-345. doi: 10.1016/j.jhep.2015.03.014.

40. Bhattacharya J, Chandra A, Chernew M, et al. Best of both worlds uniting universal coverage and personal choice in health care. American Enterprise Institute website. https://www.aei.org/wp-content/uploads/2014/09/-best-of-both-worlds-uniting-universal-coverage-and-personal-choice-in-health-care_105214167938.pdf. Published August 2013. Accessed November 25, 2015.

41. Basu A. Financing cures in the United States. *Expert Rev Pharmacoecon Outcomes Res.* 2015;15(1):1-4. doi: 10.1586/14737167.2015.990887.

42. Briggs MA, Sculpher M. An introduction to Markov modelling for economic evaluation. *Pharmacoeconomics.* 1998;13(4):397-409.

43. Amiri M, Kelishadi R. Comparison of models for predicting outcomes in patients with coronary artery disease focusing on microsimulation. *Int J Prev Med.* 2012;3(8):522-530.

44. Gutierrez JA, Lawitz EJ, Poordad F. Interferon-free, direct-acting antiviral therapy for chronic hepatitis C. *J Viral Hepat.* 2015;22(11):861-870. doi: 10.1111/jvh.12422.

45. Younossi ZM, Singer ME, Mir HM, Henry L, Hunt S. Impact of interferon free regimens on clinical and cost outcomes for chronic hepatitis C genotype 1 patients. *J Hepatol.* 2014;60(3):530-537. doi: 10.1016/j.jhep.2013.11.009.

46. Tice JA, Ollendorf DA, Pearson SD; Institute for Clinical and Economic Review. The comparative clinical effectiveness and value of simperevir and sofosbuvir in the treatment of chronic hepatitis C infection. California Technology Assessment Forum website. http://ctaf.org/sites/default/files/assessments/CTAF_Hep_C_Apr14_final.pdf. Published April 15, 2014. Accessed October 8, 2014.

47. Denniston MM, Klevens RM, McQuillan GM, Jiles RB. Awareness of infection, knowledge of hepatitis C, and medical follow-up among individuals testing positive for hepatitis C: National Health and Nutrition Examination Survey 2001-2008. *Hepatology.* 2012;55(6):1652-1661. doi: 10.1002/hep.25556.

48. Edlin BR, Eckhardt BJ, Shu MA, Holmberg SD, Swan T. Toward a more accurate estimate of the prevalence of hepatitis C in the United States. *Hepatology.* 2015;62(5):1353-1363. doi: 10.1002/hep.27978. ■

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eAppendix. Investing in the Future: Costs and Spillover Effects of Private Insurers' Coverage of Hepatitis C Treatment

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]

1.1. Model States

We developed a discrete time Markov model in Excel to simulate HCV progression and treatment as depicted in the schematic in the **Figure**,[7] which represents a single 1-year cycle in the simulation of the HCV model developed in this paper. The model is simulated repeatedly (eg, each year for 20 years), and population outcomes, such as the number of people in each disease 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 model includes states in which the population is not infected (ie, "susceptible") or cured and states in which the population is infected. We define the infection disease states as acute or chronic, where chronic consists of 7 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.[8]

Table A1. METAVIR Stage Descriptions[8]

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 3 cohorts or subpopulations, defined by their level of risk of HCV exposure: (a) people who inject drugs (PWID), (b) men infected with the human immunodeficiency virus (HIV) who have sex with men (MSM-HIV), and (c) adults who were born prior to 1992 when systematic testing of the blood supply for HCV began (Other Adults). The PWID group includes individuals who self-identify as using intravenous drugs. The MSM-HIV group includes individuals who self-identify as MSM and have tested positive for HIV. The Other Adult group

includes all other adults born before 1992 who do not report being in the PWID or MSM-HIV group.[9] In the manuscript we refer to these 3 cohorts as "risk groups."

The 3 risk groups are modeled independently—an individual belongs to 1 risk group for the duration of the simulation, and risk groups do not interact. Outside of the PWID and MSM-HIV groups, the risk of HCV transmission is low,[10-13] and we therefore make the simplifying assumption of no ongoing transmission in the Other Adult risk group. Because it is a closed cohort, the Other Adult population shrinks over time.[14] We assume that the PWID and MSM-HIV risk groups experience ongoing entry and exit such that their cohort size remains constant over the simulation. Mortality rates for the risk groups are discussed in more detail in section 3.2.

Within each risk group, we model the 3 HCV genotypes most common in the United States (genotypes 1, 2 and 3).[15] 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,[16] may progress at different rates,[17,18] and face different mortality risks.[19] Patients can only be infected with 1 genotype at a time, but once cured, a patient can be re-infected with any of the 3 genotypes.

In order to track insurance status in the simulation, we further stratify the population in each risk group into 4 insurance status categories and 1-year age cohorts. The 4 insurance status categories are private, Medicare, Medicaid, and uninsured. We assume that insurance status does not depend on disease state and does not change over time, except when the population transitions into Medicare at age 65 years. In other words, the proportion of the population who turns 65 during the simulation switches insurance status from private, Medicaid, or uninsured to Medicare. The population that is under age 65 years during the entire simulation retains its initial insurance status.

1.3. Model Transitions

In each disease state, there are a number of possible transitions, which are represented by arrows in the schematic in **Figure 1**. 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. 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 1 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.[20,21] Patients may stay in any disease state, except acute, for more than 1 cycle.

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.[22,23] 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 still may progress to additional liver damage, albeit more slowly than patients with uncured HCV.[24] They

are susceptible to 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 1 cycle, after which patients move to a posttransplant 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.[25,26]

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:

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

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 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 ($t = 0$):

$$K = \frac{(incidence\ rate_{t_0})(N_{t0}^{infected} + N_{t0}^{susceptible})}{N_{t0}^{infected}} \quad (2)$$

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. 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, that risk of infection is proportional to prevalence. This implicitly assumes that within a risk group, newly infected people do not change their behaviors and are equally likely to transmit the disease as previously infected people, even though previously infected people may be more likely to be higher risk.

Table A2. Starting Annual Incidence Rates and Values of *K*

	Annual Incidence Rate	Calculated *K*
Other Adult[a]		
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

K is the proportionality constant for incidence rate; HIV, human immunodeficiency virus; MSM-HIV, HIV-positive men who have sex with men; PWID, people who inject drugs.
[a]Other Adults, US residents born before 1992 who are not members of the PWID or MSM-HIV groups
Source: Williams et al (2011)[11] and authors' calculations.

2. Analysis of Policy Scenarios

All scenarios assume that HCV treatment consists of the most effective direct-acting antiviral (DAA) regimens available. Regimens by fibrosis stage and genotype are selected based on the most recent treatment guidelines of the American Association for the Study of Liver Diseases (AASLD).[27] When multiple regimens are recommended for a genotype or fibrosis stage, the average efficacy is calculated and used. Treatment costs for genotype 1 are based on the 12-week DAA cost estimate of $100,000 (2012 USD) cited by Leidner et al.[28] This estimate is inflated to 2015 dollars and adjusted for treatment duration.[28] For genotype 2, we assume a treatment duration of 16 weeks, and for genotype 3, we assume a duration of 24 weeks. Regimen drugs, duration, efficacy, and costs differ by infection genotype, as detailed in **Table A3**.

The treatments used in all scenarios include drugs that are currently protected under patent, but that have seen price competition from recent market entrants. To account for these pricing dynamics, the model reduces treatment costs by 46%[29] in years 2-20 to account for branded competition.[30]

Table A3. Regimens, Duration, and Efficacy

Drugs used						
Genotype 1	LED/SOF for 12 weeks (F0-F3) or 24 weeks (F4) ABT-450/r for 12 weeks (F0-F3) or 24 weeks (F4 only) 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 plus RBV for 24 weeks (no IFN used)					
Treatment costs						
	Year 1[28]			*Years 2+*[28]		
Genotype 1	$103,799			$56,051		
Genotype 2	F0-F2: $103,799 F3-HCC: $138,398			F0-F2: $56,051 F3-HCC: $74,735		
Genotype 3	$207,598			$112,103		
Efficacy						
	F0-F2		**F3**		**F4, DC, HCC**	
	Other Adult[a] *& PWID*	*MSM-HIV*	*Other Adult*[a] *& PWID*	*MSM-HIV*	*Other Adult*[a] *& PWID*	*MSM-HIV*
Genotype 1	F0: 0.98 F1-F2: 0.97	0.96	0.97	0.96	F4: 0.93 DC-HCC: 0.82	F4: 0.91 DC-HCC: 0.82
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

ABT-450/r refers to paritaprevir with ritonavir; LED/SOF, ledipasvir and sofosbuvir combination, SOF/SIM, sofosbuvir and simeprevir combination; SOF plus RBV is sofosbuvir plus ribaviran; DC indicates decompensated cirrhosis; F0-F4, METAVIR fibrosis stages (F4 is most severe); HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; IFN, interferon; ; MSM-HIV, HIV-positive men who have sex with men; PWID, people who inject drugs.

[a]Other Adults, US residents born before 1992 who are not members of the PWID or MSM-HIV groups.

2.1. Treatment Policies

The scenarios involve treating a fixed proportion of the prevalent population in *each* model cycle. Once treated in the first model cycle, many of the currently diagnosed patients are cured and removed from the prevalent population, yet in subsequent model cycles, the same proportion of the remaining prevalent patients are treated. Thus, aggressive treatment scenarios implicitly assume that prevalent patients continue to be diagnosed at the same constant rate and that the same proportion of diagnosed patients is available for treatment.

We evaluate treatment policies and the spillover impact on Medicare by comparing 2 alternative scenarios with a status quo scenario. The status quo scenario reflects current access to treatment and AASDL guidelines for "highest priority for treatment" and assumes that all insurance types provide treatment for fibrosis stages F3 and F4. We assume the uninsured population does not receive treatment.

We consider 2 alternative scenarios. The first assumes that private payers expand treatment from the status quo to include the population in fibrosis stages F2-F4. The second alternative scenario assumes private payers expand treatment to the population in fibrosis stages F0-F4. We compute the impacts of this increased private-payer generosity on Medicare as the differences in outcomes between the alternative scenarios and the status quo for the population in Medicare.

2.2. Model Outputs

The model outputs the number of people, treatment costs, medical expenditures (nontreatment costs) in each year, disease-treatment state, risk group, genotype, and insurance-status category. We use these outputs to compute changes in costs to Medicare in the 2 alternative scenarios relative to status quo, described above.

To obtain the social value of treatment under the alternative scenarios relative to the status quo, we multiply the number of people in each disease state, risk group, genotype, and insurance-status group by published estimates of annual per-person values for quality-adjusted life-years (QALYs). Each QALY is valued at $150,000 to generate the total value of QALYs produced by a treatment scenario.[31] Other annual per-person estimates of economic measures, including treatment costs and medical expenditures, are similarly applied to disease-state populations to generate population-wide estimates. Dollar values are discounted at 3% per year to produce present discounted values of future value streams.[32]

Patients who die within a cycle are assumed to transition out of the simulation following a uniform probability distribution with a mean of 6 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 Adult risk group represents the largest number of HCV-infected patients, and is defined as US residents born before 1992 who are not members of the PWID or MSM-HIV groups. Model parameters for the Other Adult risk group and their sources are provided in **Table A4**.

The PWID risk group has the highest incidence rate, reflecting the greatest transmission among the 3 risk groups. The PWID cohort also has the highest starting mortality rates for both the infected and uninfected populations.[33] Model parameters for the PWID cohort and their sources are provided in **Table A5**.

The MSM-HIV risk group is composed of HIV-positive men who have sex with men. This co-infection affects the progression of HCV.[34] Model parameters for the MSM-HIV risk group and their sources are provided in **Table A6**.

Table A4. Model Parameters for "Other Adult"[a] Risk Group by Genotypes 1-3 and Disease States[b]

Disease State	HCV Genotype		
	Genotype 1	Genotype 2	Genotype 3
Annual Mortality Rate[c]			
Susceptible (background)		0.042[35]	
Acute, F0-F2	0.0834[36]	0.0709[19,36]	0.0776[19,36]
F3, F4	0.2390[19,36]	0.2032[19,36]	0.2223[19,36]
DC	0.1350[37-39]	0.1148[19,37-39]	0.1256[19,37-39]
HCC	0.4270[37,40,41]	0.3630[19,37,40,41]	0.3971[19,37,40,41]
Transplant[d]		0.1650[42]	
Post transplant[e]		0.1249[19,35]	
Annual Transition Probability			
Acute → spontaneous clearance		0.18[20]	
F0 → F1		0.076[43-45]	
F1→ F2		0.095[43-45]	
F2 → F3		0.108[43-45]	
F3 → F4		0.134[43-45]	
F3 → HCC	0.008[37,46]	0.008[37,46]	0.0144[17,37,46]
F4 → DC	0.039[37,38,47]	0.0265[17,37,47]	0.0507[17,37,47]
F4 → HCC	0.025[37,38]	0.0138[17,37,38]	0.045[17,37,38]
DC → HCC	0.025[37,38]	0.0138[17,37,38]	0.045[17,37,38]
DC → transplant		0.031[48,49]	
HCC → transplant		0.103[47,48]	
F3 cure → F4 cure		0.0375[24]	
F3 cure → HCC cure		0.0029[24]	
F4 cure → DC cure		0.0109[24]	
F4 cure → HCC cure		0.009[24]	
DC cure → HCC cure		0.007[24]	
QALY Weights			
Susceptible, acute		0.86[48,50]	
Acute, F0-F1		0.79[49,50]	
F2, F3, F3 cure		0.79[49,50]	
F4, F4 cure		0.76[48,51]	
DC, DC cure		0.69[48,51]	
DC transplant[d]		0.50[48,51]	
DC post transplant[e]		0.71[26,52]	
HCC, HCC cure		0.67[48,51]	
HCC transplant[d]		0.50[48,51]	
HCC post transplant[e]		0.71[26,52]	

Annual Medical Expenditures[f]	
Susceptible	$6984[53]
Acute, F0, F1, F2, F3	$16,904[54]
F0 fail, F1 fail, F2 fail, F3 fail, F3 cure	$10,988[54,55]
F4	$20,052[54]
F4 fail, F4 cure	$15,239[54,55]
DC	$56,020[54]
DC fail, DC cure	$39,214[54,55]
DC transplant[d]	$161,108[54]
DC post transplant[e]	$161,108[54]
HCC	$124,229[54]
HCC fail, HCC cure	$86,961[54,55]
HCC transplant[d]	$161,108[54]
HCC post transplant[e]	$161,108[54]

DC indicates decompensated cirrhosis; F0-F4, METAVIR fibrosis stages (F4 is most severe); HCC, hepatocellular carcinoma; QALY, quality-adjusted life-year.

[a]Other Adults, US residents born before 1992 who are not members of the groups of people who use intravenous drugs or men infected with HIV who have sex with other men.

[b]The table reports the average mortality.

[c]Model relies on mortality rates by 1-year age group, as reported by the National Vital Statistics Report and adjusted for risk.[14]

[d]Year of liver transplant.

[e]All subsequent years after liver transplant.

[f]All medical expenditures are inflated to 2015 dollars.

Table A5. Model Parameters for PWID Risk Group by Genotypes 1-3 and Disease States[a]

Disease State	HCV Genotype		
	Genotype 1	Genotype 2	Genotype 3
Annual Mortality Rate[b]			
Susceptible	0.0161[33]		
Acute, F0-F2	0.2520[33,36]	0.2142[19,33,36]	0.2344[19,33,36]
F3, F4	0.4481[19,33,36]	0.3809[19,33,36]	0.4167[19,33,36]
DC	0.1350[37-39]	0.1148[19,37-39]	0.1256[19,37-39]
HCC	0.4270[37-39]	0.3630[19,37-39]	0.3971[19,37-39]
Transplant[c]	0.1650[42]		
Post transplant[d]	0.3169[19,33]		
Annual Transition Probability			
Acute → spontaneous clearance	0.18[56]		
F0 → F1	0.116[43,57-62]		
F1 → F2	0.085[43,57-62]		
F2 → F3	0.085[43,57-62]		
F3 → F4	0.13[43,57-62]		
F3 → HCC	0.008[37,46]	0.008[37,46]	0.0144[17,37,46]
F4 → DC	0.039[37,38,47]	0.0265[17,37,47]	0.0507[17,37,47]
F4 → HCC	0.025[37,38,47]	0.0138[17,37,38]	0.045[17,37,38]
DC → HCC	0.025[37,38,47]	0.0138[17,37,38]	0.045[17,37,38]
DC → transplant	0.031[48,49]		
HCC → transplant	0.103[47,48]		
F3 cure → F4 cure	0.0364[24]		
F3 cure → HCC cure	0.0029[24]		
F4 cure → DC cure	0.0109[24]		
F4 cure → HCC cure	0.009[24]		
DC cure → HCC cure	0.007[24]		
QALY weights	Same as for Other Adult[e] risk group. See Table A4 for values.		
Annual medical expenditures[f]	Same across risk groups and genotype. See Table A4 for values.		

DC indicates decompensated cirrhosis; F0-F4, METAVIR fibrosis stages (F4 is most severe); HCC, hepatocellular carcinoma; PWID, people who inject drugs; QALY, quality-adjusted life-year.

[a]The table reports the average mortality.

[b]Model relies on mortality rates by 1-year age group, as reported by the National Vital Statistics Report and adjusted for risk.[14]

[c]Year of liver transplant.

[d]All subsequent years after liver transplant.

[e]Other Adults, US residents born before 1992 who are not members of the groups PWID or men infected with the HIV who have sex with other men.

[f]All medical expenditures inflated to 2015 dollars.

Table A6. Model Parameters for MSM-HIV Risk Group by Genotypes 1-3 and Disease States[a]

Disease State	HCV Genotype		
	Genotype 1	**Genotype 2**	**Genotype 3**
Annual Mortality Rate[b]			
Susceptible	0.0860 [63]		
Acute, F0-F2	0.1821[36,63]	0.1548[19,36,63]	0.1693[19,36,63]
F3, F4	0.3716[19,36,63]	0.3158[19,36,63]	0.3456[19,36,63]
DC	0.1350[37-39]	0.1148[19,37-39]	0.1256[19,37-39]
HCC	0.4270[37-39]	0.3630[19,37-39]	0.3971[19,37-39]
Transplant[c]	0.1650[64,65]		
Post transplant[d]	0.2459[64,65]		
Annual Transition Probability			
Acute → spontaneous clearance	0.130[21]		
F0 → F1	0.122[34]		
F1 → F2	0.115[34]		
F2 → F3	0.124[34]		
F3 → F4	0.115[34]		
F3 → HCC	0.016[26,37,46,66]	0.016[26,37,46,66]	0.0288[17,37,46,66]
F4 → DC	0.078[26,37,38,47,67]	0.053[17,37,38,47,67]	0.1014[37,38,47,67]
F4 → HCC	0.050[26,37,38,66]	0.0275[17,37,38,66]	0.0900[37,38,66]
DC → HCC	0.050[26,37,38,66]	0.0275[17,37,38]	0.0900[37,38]
DC → transplant	0[26]		
HCC → transplant	0[26]		
F3 cure → F4 cure	0.0322[24]		
F3 cure → HCC cure	0.0058[24]		
F4 cure → DC cure	0.0218[24]		
F4 cure → HCC cure	0.018[24]		
DC cure → HCC cure	0.014[24]		

QALY Weights	
Susceptible	0.87[25,64]
Acute, F0-F1	0.81[25,49,64]
F2, F3, F3 cure	0.80[25,49,64]
F4, F4 cure	0.68[25,64]
DC, DC cure	0.48[25,64]
DC transplant[c]	0.81[25,64]
DC post transplant[d]	0.81[25,64]
HCC, HCC cure	0.23[25,64]
HCC transplant[c]	0.81[25,64]
HCC post transplant[d]	0.81[25,64]
Medical expenditures[e]	Same across risk groups and genotype. See Table A4 for values.

DC indicates decompensated cirrhosis; F0-F4, METAVIR fibrosis stages (F4 is most severe); HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; MSM-HIV, HIV-positive men who have sex with other men; QALY, quality-adjusted life-year.
[a]The table reports the average mortality.
[b]Model relies on mortality rates by 1-year age group, as reported by the National Vital Statistics Report and adjusted for risk.[14]
[c]Year of liver transplant.
[d]All subsequent years after liver transplant.
[e]All medical expenditures are inflated to 2015 dollars.

3.1. Starting Populations

At model start, the size of the total infected population across all disease stages is 3,640,847.[68] This includes 22,304 incident patients,[69] who are distributed across the 3 risk groups according to estimates from Williams et al,[11] and within each risk group across 3 genotypes according to the prevalence of each genotype in the overall population, as estimated by Manos et al (2012).[15] These incident patients make up the populations in the acute phases at the start of the simulation. The remaining 3,618,543 non-incident infected population at model start are distributed across risk groups and genotypes following the same logic. These patients are then further distributed across chronic disease stages as in Hagan (2014).[10,43,70] 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[a]

		Other Adult	PWID	MSM-HIV
Uninfected/Susceptible		197,404,127[35]	2,242,594[71]	461,600[72]
Genotype 1	*Acute*	0	14,514	1545
	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	5832
	DC	47,859	27,386	2916
	HCC	47,859	27,386	2916
Genotype 2	*Acute*	0	3225	343
	F0	60,267	34,486	3672
	F1	124,078	71,000	7560
	F2	77,992	44,629	4752
	F3	49,631	28,400	3024
	F4	21,271	12,171	1296
	DC	10,635	6086	648
	HCC	10,635	6086	648
Genotype 3	*Acute*	0	2419	258
	F0	45,200	25,864	2754
	F1	93,059	53,250	5670
	F2	58,494	33,471	3564
	F3	37,223	21,300	2268
	F4	15,953	9129	972
	DC	7976	4564	486
	HCC	7976	4564	486

DC indicates decompensated cirrhosis; F0-F4, METAVIR fibrosis stages (F4 is most severe); HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; MSM-HIV, HIV-positive men who have sex with other men; Other Adults, US residents born before 1992 who are not members of the PWID or MSM-HIV groups; PWID, people who inject drugs.

[a]We computed the initial insurance status distributions for each risk group based on self-reported insurance status from National Health and Nutrition Examination Survey (NHANES).

Source: Authors' analysis[68] and CDC (2014)[73]; Manos (2012)[15]; Williams (2011)[11]; and Hagan (2014).[70]

Table A8 reports the distribution of insurance status by risk group.

Table A8. Starting Distribution of Insurance Type by Risk Group

	Risk Group		
Insurance Status	**Other Adult[a]**	**PWID**	**MSM-HIV**
Private Insurance	106,437,282	1,419,979	255,941
	53.32%	40.45%	42.86%
Medicare	39,444,874	262,933	100,229
	19.76%	7.49%	16.83%
Medicaid[b]	16,388,786	456,359	152,730
	8.21%	13.00%	25.56%
Uninsured	37,348,866	1,371,184	87,700
	18.71%	39.06%	14.74%
Total	199,619,808	3,510,456	596,600

HIV, human immunodeficiency virus; MSM-HIV, HIV-positive men who have sex with other men; PWID, people who inject drugs.
[a]Other Adults, US residents born before 1992 who are not members of the PWID or MSM-HIV groups.
[b]The Medicaid group includes the population covered under other local and state programs designed for low-income, disabled, or disadvantaged individuals.
Source: NHANES 2003-2012.

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,

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

where M_0(a) is the US base annual mortality rate,[14] 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. We derive the proportionality constants R_r, R_g, R_s based on estimates from the literature and given in **Table A9**, below.

Table A9. Mortality Adjustment Factors by Disease State and Genotype

Disease State	Mortality Factor R_s	Viral Genotype	Mortality Factor R_g
Uninfected	1.000	Genotype 1	1.000
Acute, F0-F2	2.370	Genotype 2	0.850
F3, F4[a]	8.935	Genotype 3	0.930
Post transplant and cured states	3.770		

F0-F4, METAVIR fibrosis stages (F4 is most severe).
[a]F3-F4 is a multiple of the F2 factor, so the total is 2.370 (El-Kamary et al, 2011) x 3.770 (McCombs et al, 2012) = 8.935.[19,36] F3, F4, decompensated cirrhosis, hepatocellular carcinoma, and cured are 3.770 times base mortality.

We assume the proportionality constant for the Other Adult 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.[33] The paper provides a mortality rate ratio (standardized mortality ratio) 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 with the general population. To estimate R_r, we expressed 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:

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

where $P(I)$ is the initial proportion infected in the PWID risk group, $P(NI) = 1–P(I)$ is the proportion uninfected, and $P(g,s)$ is the proportion of the infected persons 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) give estimates of $P(g, s)$, $P(I)$, and $P(NI) = 1–P(I)$, and using the values of R_g and R_s given above we solved equation 5 for R_r to get $R_r = 4.15$.[74] This implies that the mortality rate for HCV-uninfected PWIDs is approximately 4.15 times that of the baseline rate in the United States (accounting for age).

We used a similar approach for the MSM-HIV group using the mortality rate ratios for HIV-infected men (Karch et al, 2015), which estimates that HIV-infected men have about 3.4 times the mortality rate of the baseline mortality in the United States.[75] The 3.4 figure accounts for excess mortality from HCV infection, and thus (as explained above) 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 group from Van Nuys et al (2015) and obtained $R_r = 2.04$ for the MSM-HIV group.[74]

These adjustment factors are applied to age-based base mortality rates based on 2010 Census data.[14] The age-based base mortality rates reported by HHS are adjusted using the multiplicative mortality model described above to account for disease state, genotype, and risk group.

4. Additional Results

4.1. Results for 10-year time horizon

We report results at the 5- and 20-year horizon in the main text. Results for our primary simulation at the 10 year horizon are presented in **Table A10**.

Table A10. Change in Costs when Private Payers Expand Treatment Coverage (10-year horizon)[a]

	Treat F2-F4		Treat F0-F4	
	Cost Effect on Private Insurers	**Cost Effect on Medicare "Spillovers"**	**Cost Effect on Private Insurers**	**Cost Effect on Medicare "Spillovers"**
	10-year horizon			
Change in medical expenditures ($B)	–$21.59	–$0.20	–$38.83	–$2.53
Change in HCV treatment costs ($B)	$35.04	–$0.04	$63.13	–$0.13
Change in total costs ($B)	$13.45	–$0.25	$24.30	–$2.66
Change in total costs per capita	$2184	–$73.68	$4105	–$449

B indicates billions (US dollars); F0-F4, METAVIR fibrosis stages (F4 is most severe); HCV indicates hepatitis C virus.

[a]Costs are changes that result from expanding from the baseline scenarios ("Treat F3-F4") and are reported in 2015 US dollars. Future costs are discounted at a rate of 3% per year. Per capita costs are calculated as total cost per HCV-positive Medicare beneficiary.

4.2. Sensitivity Analyses

We conducted sensitivity analyses to test the effect of several key assumptions on our results.

First, we tested the sensitivity of results to varying the economic value of a QALY. A wide range of values are used, so we varied our value from a low of $50,000/QALY to a high of $300,000/QALY to reflect the range of values seen in the literature (see **Table A11**).

Table A11. Sensitivity Analysis: QALY Values[a]

	Private Insurance Expansion from Baseline (F3-F4) to F2-F4			**Private Insurance Expansion from Baseline (F3-F4) to F0-F4**		
	Assumed Value of a QALY			**Assumed Value of a QALY**		
	50K	**150K**	**300K**	**50K**	**150K**	**300K**
	5-year horizon					
Total QALYs	$3.0	$8.9	$17.8	$9.1	$27.2	$54.4
Cumulative net value	–$22.2	–$16.3	–$7.4	–$68.3	–$50.2	–$23.0
	20-year horizon					
Total QALYs	$116.9	$350.6	$701.3	$176.4	$529.1	$1058.3
Cumulative net value	$133.7	$367.5	$718.1	$206.3	$559.1	$1088.2

F0-F4 indicates the METAVIR fibrosis stages (F4 is most severe); QALY, quality-adjusted life-year.
[a]Total QALYs and net value are in billions (2015 US dollars).

Next, we examined the effects of varied treatment costs on our results. We varied treatment cost in each year by 50% to simulate low-cost (-50%) and high-cost (+50%) scenarios. Results are presented in **Table A12**.

Table A12. Sensitivity Analysis: Treatment Costs over 20-year horizon[a]

	Private Insurance Expansion from Baseline (F3-F4) to F2-F4		**Private Insurance Expansion from Baseline (F3-F4) to Treat F0-F4**	
	Effect on Private Insurers	**Effect on Medicare ("Spillovers")**	**Effect on Private Insurers**	**Effect on Medicare ("Spillovers")**
Low Treatment Costs				
Medical expenditures	–$44.3	–$3.0	–$104.4	–$9.0
HCV treatment costs	$27.6	–$1.4	$73.1	–$1.9
Total costs	–$16.7	–$4.3	–$31.3	–$11.0
Per-capita total[b] costs	–$1622.6	–$421.3	–$3210.2	–$1125.7
High Treatment Costs				
Medical expenditures	–$44.3	–$3.0	–$104.4	–$9.0
HCV treatment costs	$51.0	$2.1	$135.2	–$3.0
Total costs	$6.7	–$5.1	$30.8	–$12.1
Per-capita total costs[a]	$646.6	–$494.9	$3156.4	–$1238.3

F0-F4 indicates METAVIR fibrosis stages (F4 is most severe); HCV, hepatitis C virus.
[a]Medical expenditures, HCV treatment costs, and total costs are in billions (2015 US dollars).
[b]Per-capita costs are calculated as total cost per HCV-positive Medicare beneficiary.

Finally, we test the effect of simultaneous expansion of treatment by both Medicaid and private payers on Medicare, as opposed to holding Medicaid's treatment policy constant (see **Table A13**).

Table A13. Alternative Simulation: Impact of Simultaneous Private and Medicaid Expansion over a 20-year horizon[a]

	Private and Medicaid Expansion from Baseline (F3-F4) to F2-F4		**Private and Medicaid Expansion from Baseline (F3-F4) to F0-F4**	
	Effect on Private Insurers	**Effect on Medicare ("Spillovers")**	**Effect on Private Insurers**	**Effect on Medicare ("Spillovers")**
Medical expenditures	–$44.6	–$3.5	–$105.0	–$10.4
HCV treatment costs	$34.0	–$1.6	–$89.9	–$2.3
Total costs	–$10.6	–$5.1	–$15.1	–$12.8
Per-capita total costs[b]	–$1036.7	–$496.0	–$1568.8	–$1328.3

F0-F4 indicates METAVIR fibrosis stages (F4 is most severe); HCV, hepatitis C virus.
[a]Medical expenditures, HCV treatment costs, and total costs are in billions (2015 US dollars.
[b]Per-capita costs are calculated as total cost per HCV-positive Medicare beneficiary.

eAPPENDIX REFERENCES

1. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med.* 2006;144(10):705-714.
2. Biggins SW, Bambha KM, Terrault NA, et al. Projected future increase in aging hepatitis C virus-infected liver transplant candidates: a potential effect of hepatocellular carcinoma. *Liver Transpl.* 2012;18(12):1471-1478.
3. Centers for Disease Control. Hepatitis C information for health professionals. 2014; http://www.cdc.gov/hepatitis/HCV/. Accessed January 20, 2015.
4. Yehia BR, Schranz AJ, Umscheid CA, Lo Re V III. The treatment cascade for chronic hepatitis C virus infection in the United States: A systematic review and meta-analysis. *PLoS ONE*. 2014;9(7):e101554. doi:10.1371/journal.pone.0101554
5. Denniston MM, Klevens RM, McQuillan GM, Jiles RB. Awareness of infection, knowledge of hepatitis C, and medical follow-up among individuals testing positive for hepatitis C: National Health and Nutrition Examination Survey 2001-2008. *Hepatology.* 2012;55(6):1652-1661.
6. Smith BD, Morgan RL, Beckett GA, et al. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports / Centers for Disease Control.* 2012;61(RR-4):1-32.
7. Sonnenberg FA, Beck JR. Markov models in medical decision making a practical guide. *Medical decision making.* 1993;13(4):322-338.
8. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology.* 2009;49(4):1335-1374.
9. HCV Advocate. A Brief History of Hepatitis C. 2015; http://hcvadvocate.org/hepatitis/factsheets_pdf/Brief_History_HCV.pdf. Accessed October 16, 2015.
10. Coffin PO, Scott JD, Golden MR, Sullivan SD. Cost-effectiveness and population outcomes of general population screening for hepatitis C. *Clin Infect Dis.* 2012;54(9):1259-1271.
11. Williams IT, Bell BP, Kuhnert W, Alter MJ. Incidence and transmission patterns of acute hepatitis C in the United States, 1982-2006. *Archives of internal medicine.* 2011;171(3):242-248.
12. Henderson DK. Managing occupational risks for hepatitis C transmission in the health care setting. *Clinical microbiology reviews.* 2003;16(3):546-568.
13. Centers for Disease Control. Hepatitis C FAQs for Health Professionals. 2015; http://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#b4. Accessed November 5, 2015.
14. Arias E. United States life tables, 2010. *National vital statistics reports: from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System.* 2014;63(7):1-64.15. Manos MM, Shvachko VA, Murphy RC, Arduino JM, Shire NJ. Distribution of hepatitis C virus genotypes in a diverse US integrated health care population. *J Med Virol.* 2012;84(11):1744-1750.
16. Tice JA, Ollendorf DA, Pearson SD. The comparative clinical effectiveness and value of simperevir and sofosbuvir in the treatment of chronic hepatitis c infection. 2014; http://ctaf.org/sites/default/files/assessments/CTAF_Hep_C_Apr14_final.pdf. Accessed October 8, 2014.

17. Kanwal F, Kramer JR, Ilyas J, Duan Z, El-Serag HB. HCV genotype 3 is associated with an increased risk of cirrhosis and hepatocellular cancer in a national sample of U.S. Veterans with HCV. *Hepatology.* 2014;60(1):98-105.
18. Probst A, Dang T, Bochud M, Egger M, Negro F, Bochud PY. Role of hepatitis C virus genotype 3 in liver fibrosis progression--a systematic review and meta-analysis. *Journal of viral hepatitis.* 2011;18(11):745-759.
19. McCombs J, Matsuda T, Tonnu-Mihara I, et al. The risk of long-term morbidity and mortality in patients with chronic hepatitis C: results from an analysis of data from a Department of Veterans Affairs Clinical Registry. *JAMA internal medicine.* 2014;174(2):204-212.
20. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. *Journal of viral hepatitis.* 2006;13(1):34-41.
21. Schnuriger A, Dominguez S, Guiguet M, et al. Acute hepatitis C in HIV-infected patients: rare spontaneous clearance correlates with weak memory CD4 T-cell responses to hepatitis C virus. *AIDS (London, England).* 2009;23(16):2079-2089.
22. Friedman SL, Bansal MB. Reversal of hepatic fibrosis -- fact or fantasy? *Hepatology.* 2006;43(2 Suppl 1):S82-88.
23. Wright TL. Treatment of patients with hepatitis C and cirrhosis. *Hepatology.* 2002;36(5 Suppl 1):S185-194.
24. Kabiri M, Jazwinski AB, Roberts MS, Schaefer AJ, Chhatwal J. The changing burden of hepatitis C virus infection in the United States: model-based predictions. *Ann Intern Med.* 2014;161(3):170-180.
25. Kuehne FC, Bethe U, Freedberg K, Goldie SJ. Treatment for hepatitis C virus in human immunodeficiency virus-infected patients: clinical benefits and cost-effectiveness. *Archives of internal medicine.* 2002;162(22):2545-2556.
26. Saab S, Gordon SC, Park H, Sulkowski M, Ahmed A, Younossi Z. Cost-effectiveness analysis of sofosbuvir plus peginterferon/ribavirin in the treatment of chronic hepatitis C virus genotype 1 infection. *Alimentary pharmacology & therapeutics.* 2014;40(6):657-675.
27. AASLD IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology.* 2015:n/a-n/a.
28. Leidner AJ, Chesson HW, Xu F, Ward JW, Spradling PR, Holmberg SD. Cost-effectiveness of hepatitis C treatment for patients in early stages of liver disease. *Hepatology.* 2015.
29. Tirrell M. Pricing wars heat up over hepatitis C drugs. *CNBC* 2015; http://www.cnbc.com/id/102396903. Accessed April 8, 2015.
30. Grabowski HG, Vernon JM. Brand loyalty, entry, and price competition in pharmaceuticals after the 1984 Drug Act. *J Law Econ.* 1992;35(2):331-350.
31. Hirth RA, Chernew ME, Miller E, Fendrick AM, Weissert WG. Willingness to pay for a quality-adjusted life year: in search of a standard. *Med Decis Making.* 2000;20(3):332-342.
32. Gold MR, Siegel J, Russell L, Weinstein M. Cost-effectiveness in health and medicine: report of the panel on cost-effectiveness in health and medicine. *New York: Oxford Univ Pr.* 1996.
33. Mathers BM, Degenhardt L, Bucello C, Lemon J, Wiessing L, Hickman M. Mortality among people who inject drugs: a systematic review and meta-analysis. *Bulletin of the World Health Organization.* 2013;91(2):102-123.

34. Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. *AIDS (London, England).* 2008;22(15):1979-1991.
35. U.S. Census Bureau. Annual Estimates of the Resident Population by Single Year and Sex for the Unites States: April 1, 2010 to July 1, 2013. 2013; http://factfinder2.census.gov. Accessed February 25, 2015.
36. El-Kamary SS, Jhaveri R, Shardell MD. All-cause, liver-related, and non-liver-related mortality among HCV-infected individuals in the general US population. *Clin Infect Dis.* 2011;53(2):150-157.
37. Younossi ZM, Singer ME, Mir HM, Henry L, Hunt S. Impact of interferon free regimens on clinical and cost outcomes for chronic hepatitis C genotype 1 patients. *Journal of hepatology.* 2014;60(3):530-537.
38. Rein DB, Smith BD, Wittenborn JS, et al. The cost-effectiveness of birth-cohort screening for hepatitis C antibody in U.S. primary care settings. *Ann Intern Med.* 2012;156(4):263-270.
39. Planas R, Balleste B, Alvarez MA, et al. Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients. *Journal of hepatology.* 2004;40(5):823-830.
40. Singer ME, Younossi ZM. Cost effectiveness of screening for hepatitis C virus in asymptomatic, average-risk adults. *Am J Med.* 2001;111(8):614-621.
41. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology.* 1997;112(2):463-472.
42. Best JH, Veenstra DL, Geppert J. Trends in expenditures for Medicare liver transplant recipients. *Liver Transpl.* 2001;7(10):858-862.
43. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology.* 2008;48(2):418-431.
44. Shin JL, Teitel J, Swain MG, et al. A Canadian multicenter retrospective study evaluating transjugular liver biopsy in patients with congenital bleeding disorders and hepatitis C: is it safe and useful? *American journal of hematology.* 2005;78(2):85-93.
45. Hamada H, Yatsuhashi H, Yano K, et al. Impact of aging on the development of hepatocellular carcinoma in patients with post-transfusion chronic hepatitis C. *Cancer.* 2002;95(2):331-339.
46. Dienstag JL, Ghany MG, Morgan TR, et al. A prospective study of the rate of progression in compensated, histologically advanced chronic hepatitis C. *Hepatology.* 2011;54(2):396-405.
47. McGarry LJ, Pawar VS, Panchmatia HR, et al. Economic model of a birth cohort screening program for hepatitis C virus. *Hepatology.* 2012;55(5):1344-1355.
48. McEwan P, Ward T, Yuan Y, Kim R, L'Italien G. The impact of timing and prioritization on the cost-effectiveness of birth cohort testing and treatment for hepatitis C virus in the United States. *Hepatology.* 2013;58(1):54-64.
49. Salomon JA, Weinstein MC, Hammitt JK, Goldie SJ. Cost-effectiveness of treatment for chronic hepatitis C infection in an evolving patient population. *Jama.* 2003;290(2):228-237.
50. Chong CA, Gulamhussein A, Heathcote EJ, et al. Health-state utilities and quality of life in hepatitis C patients. *The American journal of gastroenterology.* 2003;98(3):630-638.
51. Thein HH, Krahn M, Kaldor JM, Dore GJ. Estimation of utilities for chronic hepatitis C from SF-36 scores. *The American journal of gastroenterology.* 2005;100(3):643-651.
52. McLernon DJ, Dillon J, Donnan PT. Health-state utilities in liver disease: a systematic review. *Med Decis Making.* 2008;28(4):582-592.

53. Davis KL, Mitra D, Medjedovic J, Beam C, Rustgi V. Direct economic burden of chronic hepatitis C virus in a United States managed care population. *Journal of clinical gastroenterology.* 2011;45(2):e17-24.
54. Gordon SC, Pockros PJ, Terrault NA, et al. Impact of disease severity on healthcare costs in patients with chronic hepatitis C (CHC) virus infection. *Hepatology.* 2012;56(5):1651-1660.
55. Gordon SC, Hamzeh FM, Pockros PJ, et al. Hepatitis C virus therapy is associated with lower health care costs not only in noncirrhotic patients but also in patients with end-stage liver disease. *Alimentary pharmacology & therapeutics.* 2013;38(7):784-793.
56. Villano SA, Vlahov D, Nelson KE, Cohn S, Thomas DL. Persistence of viremia and the importance of long-term follow-up after acute hepatitis C infection. *Hepatology.* 1999;29(3):908-914.
57. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. *Hepatology.* 1999;30(4):1054-1058.
58. Cournot M, Glibert A, Castel F, et al. Management of hepatitis C in active drugs users: experience of an addiction care hepatology unit. *Gastroenterologie clinique et biologique.* 2004;28(6-7 Pt 1):533-539.
59. Grando-Lemaire V, Goisset P, Sorge F, et al. [Hepatitis C virus screening in drug users in an addiction out-patient unit]. *Gastroenterologie clinique et biologique.* 2002;26(12):1091-1096.
60. Puoti M, Bonacini M, Spinetti A, et al. Liver fibrosis progression is related to CD4 cell depletion in patients coinfected with hepatitis C virus and human immunodeficiency virus. *The Journal of infectious diseases.* 2001;183(1):134-137.
61. Rai R, Wilson LE, Astemborski J, et al. Severity and correlates of liver disease in hepatitis C virus-infected injection drug users. *Hepatology.* 2002;35(5):1247-1255.
62. Wilson LE, Torbenson M, Astemborski J, et al. Progression of liver fibrosis among injection drug users with chronic hepatitis C. *Hepatology.* 2006;43(4):788-795.
63. Centers for Disease Control and Prevention. HIV surveillance report, 2011, vol 23. 2013; http://www.cdc.gov/hiv/topics/surveillance/resources/reports/. Accessed July 25, 2015.
64. Hornberger J, Torriani FJ, Dieterich DT, et al. Cost-effectiveness of peginterferon alfa-2a (40kDa) plus ribavirin in patients with HIV and hepatitis C virus co-infection. *J Clin Virol.* 2006;36(4):283-291.
65. Forman LM, Lewis JD, Berlin JA, Feldman HI, Lucey MR. The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology.* 2002;122(4):889-896.
66. Razavi H, Elkhoury AC, Elbasha E, et al. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. *Hepatology.* 2013;57(6):2164-2170.
67. Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology.* 2010;138(2):513-521, 521 e511-516.
68. Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey. In: National Center for Health Statistics, ed. Hyattsville, MD: U.S. Department of Health and Human Services,; 2015.
69. Centers for Disease Control and Prevention. Surveillance for viral hepatitis - United States, 2012. 2015; http://www.cdc.gov/hepatitis/Statistics/2012Surveillance/Commentary.htm#hepC. Accessed January 16, 2015.

70. Hagan LM, Sulkowski MS, Schinazi RF. Cost analysis of sofosbuvir/ribavirin versus sofosbuvir/simeprevir for genotype 1 hepatitis C virus in interferon-ineligible/intolerant individuals. *Hepatology.* 2014;60(1):37-45.
71. Mathers BM, Degenhardt L, Phillips B, et al. Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review. *Lancet.* 2008;372(9651):1733-1745.
72. Centers for Disease Control and Prevention. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 dependent areas—2011. *HIV Surveillance Supplemental Report* 2013; http://www.cdc.gov/hiv/library/reports/surveillance. Accessed January 16, 2015.
73. Centers for Disease Control. Viral hepatitis statistics & surveillance. 2014; http://www.cdc.gov/hepatitis/Statistics/2012Surveillance/index.htm. Accessed October 10, 2014.
74. 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):1666-1674.
75. Karch D, Hall H, Tang T, Hu X, Mermin J. Comparative Mortality Among People Diagnosed with HIV Infection or AIDS in the US, 2001-2010. *Public health reports (Washington, DC: 1974).* 2014;130(3):253-260.