

# Cost-Effectiveness of Novel Regimens for the Treatment of Hepatitis C Virus

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**Background:** New regimens for hepatitis C virus (HCV) have shorter treatment durations and increased rates of sustained virologic response compared with existing therapies but are extremely expensive.

**Objective:** To evaluate the cost-effectiveness of these treatments under different assumptions about their price and efficacy.

**Design:** Discrete-event simulation.

**Data Sources:** Published literature.

**Target Population:** Treatment-naive patients infected with chronic HCV genotype 1, 2, or 3.

**Time Horizon:** Lifetime.

**Perspective:** Societal.

**Intervention:** Usual care (boceprevir-ribavirin-pegylated interferon [PEG]) was compared with sofosbuvir-ribavirin-PEG and 3 PEG-free regimens: sofosbuvir-simeprevir, sofosbuvir-daclatasvir, and sofosbuvir-ledipasvir. For genotypes 2 and 3, usual care (ribavirin-PEG) was compared with sofosbuvir-ribavirin, sofosbuvir-daclatasvir, and sofosbuvir-ledipasvir-ribavirin (genotype 3 only).

**Outcome Measures:** Discounted costs (in 2014 U.S. dollars), quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios.

**Results of Base-Case Analysis:** Assuming sofosbuvir, simeprevir, daclatasvir, and ledipasvir cost \$7000, \$5500, \$5500, and \$875 per week, respectively, sofosbuvir-ledipasvir was cost-effective for genotype 1 and cost \$12 825 more per QALY than usual care. For genotype 2, sofosbuvir-ribavirin and sofosbuvir-daclatasvir cost \$110 000 and \$691 000 per QALY, respectively. For genotype 3, sofosbuvir-ledipasvir-ribavirin cost \$73 000 per QALY, sofosbuvir-ribavirin was more costly and less effective than usual care, and sofosbuvir-daclatasvir cost more than \$396 000 per QALY at assumed prices.

**Results of Sensitivity Analysis:** Sofosbuvir-ledipasvir was the optimal strategy in most simulations for genotype 1 and would be cost-saving if sofosbuvir cost less than \$5500. For genotype 2, sofosbuvir-ribavirin-PEG would be cost-saving if sofosbuvir cost less than \$2250 per week. For genotype 3, sofosbuvir-ledipasvir-ribavirin would be cost-saving if sofosbuvir cost less than \$1500 per week.

**Limitation:** Data are lacking on real-world effectiveness of new treatments and some prices.

**Conclusion:** From a societal perspective, novel treatments for HCV are cost-effective compared with usual care for genotype 1 and probably genotype 3 but not for genotype 2.

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**D**rug therapies for hepatitis C virus (HCV) infection have been available for more than a decade. Despite approval of the protease inhibitors boceprevir and telaprevir in 2011, which have substantially increased rates of sustained virologic response (SVR) for patients infected with HCV genotype 1, many patients do not complete recommended treatment owing to shortcomings of pegylated interferon (PEG) (1).

Several new regimens may represent important improvements over current HCV treatments. The once-daily nucleotide polymerase inhibitor sofosbuvir (Sovaldi, Gilead Sciences) was approved in December 2013 (2) to be used in combination with ribavirin and PEG in treatment-naive patients infected with HCV genotypes 1 and 4 and with ribavirin alone in patients infected with HCV genotypes 2 and 3. Sofosbuvir can achieve higher SVR rates in substantially shorter treatment times than existing regimens (3–6). Shorter treatment durations and higher SVR rates, even among non-responders, also seem possible with other PEG-free regimens consisting of sofosbuvir in combination with simeprevir (7, 8), daclatasvir (9), or ledipasvir (10–13).

Despite their promise, these novel therapies are very expensive and, considering that more than 3 mil-

lion patients (14) may be eligible for these therapies, the budgetary implications have generated widespread concern (15, 16). Little is known about the relative societal health benefit and value of the new treatments for hepatitis C compared with current options. Therefore, we conducted a cost-effectiveness analysis to evaluate the balance between health benefit and health care expenditures for these treatments under different assumptions about their price and efficacy.

## METHODS

We developed a discrete-event simulation (DES) model using Arena, version 12.00 (Rockwell Automation), to simulate the natural history and progression of liver disease among treatment-naive patients infected

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Supplement

**EDITORS' NOTES****Context**

Newer regimens to treat hepatitis C virus (HCV) seem efficacious but are extremely expensive.

**Contribution**

The cost-effectiveness of standard HCV regimens was compared with newer regimens containing sofosbuvir for each HCV genotype. Newer regimens were cost-effective for genotype 1 and probably genotype 3 but were not cost-effective for genotype 2. Some regimens were cost-saving with sufficient reduction in the cost of sofosbuvir.

**Caution**

Data came from clinical trials rather than usual practice.

**Implication**

If prices of newer hepatitis C drugs were reduced, new HCV treatments may not only be cost-effective but may also reduce the cost of HCV treatment over the long term.

with chronic HCV genotype 1, 2, or 3 and compare clinical and economic outcomes of treatment strategies (Figure 1) (17-20). Our modeling approach and assumptions have been explained in the Appendix (available at [www.annals.org](http://www.annals.org)).

**Treatment Strategies and Efficacy Assumptions**

Treatment strategies for each HCV genotype were defined in accordance with current clinical guidelines and proposed indications for new drugs (Supplement Figure 1, available at [www.annals.org](http://www.annals.org)). On the basis of recent clinical trials, we considered 5 treatment strategies for patients infected with HCV genotype 1: usual care consisting of response-guided triple therapy using boceprevir-ribavirin-PEG for 28 to 48 weeks; newly approved triple therapy using sofosbuvir-ribavirin-PEG for 12 weeks; and 12-week PEG-free regimens using sofosbuvir-simeprevir, sofosbuvir-daclatasvir, or sofosbuvir-ledipasvir.

For patients infected with HCV genotype 2, we evaluated 3 treatment strategies: usual care consisting of dual therapy with ribavirin-PEG for 24 weeks, the newly approved PEG-free regimen using sofosbuvir-ribavirin for 12 weeks, and a PEG-free regimen using sofosbuvir-daclatasvir for 12 weeks.

For patients infected with HCV genotype 3, we evaluated 4 treatment strategies: usual care consisting of dual therapy with ribavirin-PEG for 24 weeks and PEG-free regimens using sofosbuvir-ribavirin for 24 weeks, sofosbuvir-daclatasvir for 12 weeks, and sofosbuvir-ledipasvir-ribavirin for 12 weeks.

We modeled treatment efficacy based on SVR, which was defined as an HCV RNA level below the lower limit of quantification measured at 12 weeks after the end of treatment (3).

The SVR rates from different treatment strategies were derived from the results of published clinical trials (Table 1) (3, 6-13, 21-25). We also assumed that alcohol use negatively affects SVR rates in the base-case analysis and varied this in the sensitivity analysis (Table 1) (27, 28).

**Disease Progression**

The assumptions that defined the natural history of the disease in our model are presented in Table 1. We assumed progression of liver disease to be a function of patient-level variables. In accordance with the observed disease progression rates in 3 population-based cohorts of patients with HCV, we assumed that the change in the Meta-analysis of Histologic Data in Viral Hepatitis (METAVIR) score (42) was larger in patients with higher levels of daily alcohol consumption and men (30). We calibrated the model to emulate observed progression rates in community-based cohorts (Appendix Figure 1, available at [www.annals.org](http://www.annals.org)) (31, 32). Annual transition rates from compensated to decompensated cirrhosis or hepatocellular carcinoma were based on natural history models that have been empirically calibrated to epidemiologic data on HCV infection seroprevalence and liver cancer mortality (34, 35).

We modeled increased rates of mortality not related to liver disease among patients with HCV using sex- and race-dependent hazard ratios based on the results of NHANES III (Third National Health and Nutrition Examination Survey) (33). Background mortality rates stratified by sex and race were derived from U.S. life tables published as part of *National Vital Statistics Reports* (36). We assumed that a proportion of patients with decompensated cirrhosis or hepatocellular carcinoma received a liver transplant based on Model for End-Stage Liver Disease criteria (43). A summary of data sources has been provided in the Supplement Table.

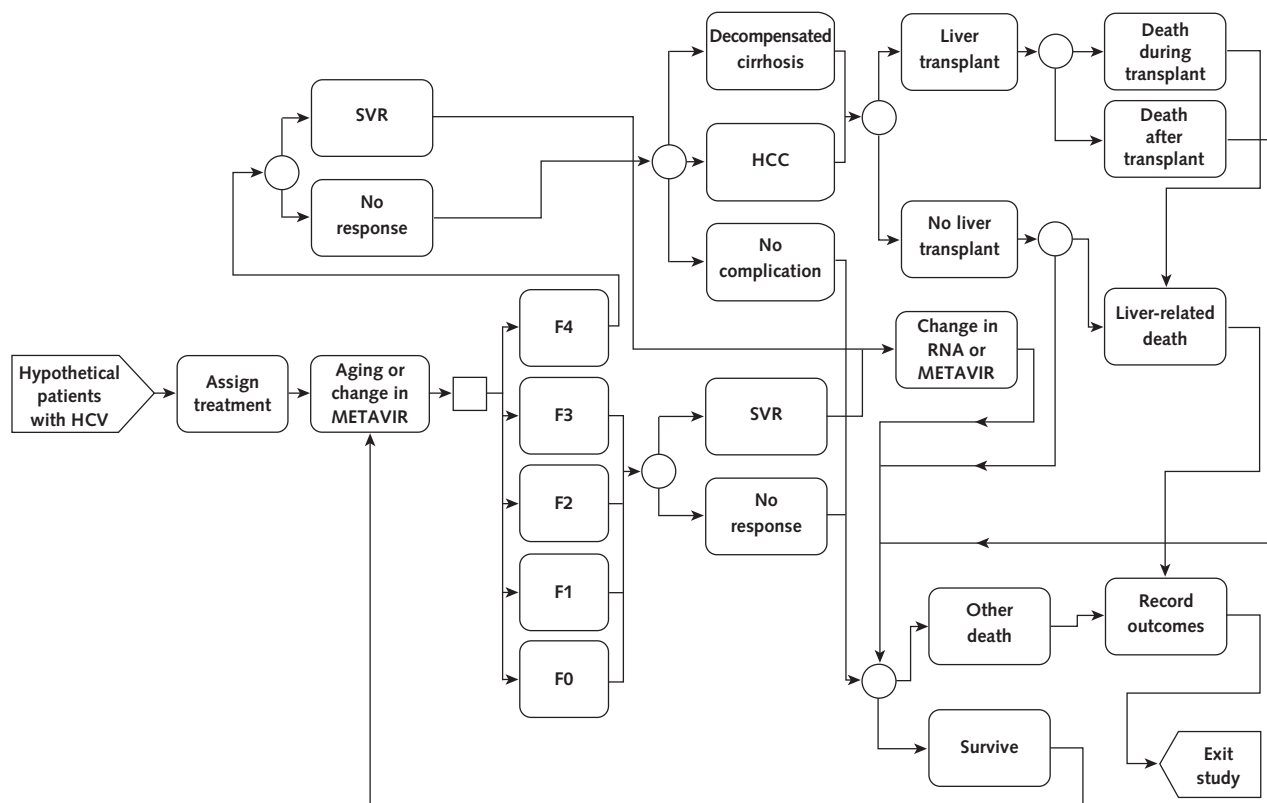
**Quality-of-Life Weights**

Health-related quality-of-life weights associated with each health state in the model were derived from the peer-reviewed literature (Table 1) (33, 38). Age-specific baseline quality-of-life estimates were based on results from the Medical Expenditure Panel Survey (37). We assumed that there was no HCV-related residual effect on quality of life after achieving SVR, and the negative effect of PEG on quality of life was proportional to the length of interferon treatment.

**Costs**

Annual costs of HCV treatment at different stages of disease, cost of treatment drugs, and cost of treatment-related side effects were included in the model. Only direct medical costs were included; indirect costs due to productivity loss or nonmedical costs (for example, cost of seeking medical care) were not included. Annual costs associated with different stages of HCV were derived from previous cost-effectiveness and observational studies comparing the medical costs of patients with HCV at different stages of disease with

**Figure 1.** Model structure for one of the treatment groups.



This diagram shows one of the treatment groups in the model. Other treatment groups have the identical structure but different values for model parameters. The model assigns baseline characteristics (age, sex, race, alcohol use, METAVIR stage score, HCV genotype, IL-28B genotype, and age-specific quality of life) to a hypothetical cohort with HCV. Patients are assigned a treatment strategy and fibrosis stage (F0, F1, F2, F3, or F4) based on their METAVIR score. In each cycle, patients follow different health trajectories depending on whether they have achieved SVR, possible subsequent complications, liver-related death, or background mortality; probabilities of each are a function of patient characteristics in that cycle. If a patient survives in a given year, the quality-adjusted life-year and total cost accrued in that year will be recorded and patient characteristics will be updated for the next cycle. All patients are followed over their lifetime. Patients will receive only 1-time treatment, and re-treatment has not been modeled. HCC = hepatocellular carcinoma; HCV = hepatitis C virus; SVR = sustained virologic response.

control patients without HCV (33, 39, 40, 44-48). The costs of sofosbuvir (\$7000 per week), simeprevir (\$5500 per week), and ledipasvir (\$875 per week) are based on the wholesale acquisition costs (2, 41). Because daclatasvir has not yet been approved for use in the United States and no pricing information is available, we assumed it had the same cost as simeprevir. Whenever necessary, we adjusted unit costs for inflation by using the U.S. Consumer Price Index to reflect 2014 U.S. dollars (49).

**Sensitivity Analysis**

We conducted 1-way sensitivity analyses by changing all of our input parameters one at a time across their possible ranges (Table 1). We then performed a probabilistic sensitivity analysis (50) by varying all of our model parameters simultaneously. For this purpose, we sampled 10 000 independent sets of input parameters from their probability distributions; for each set of parameters, we modeled a cohort of 10 000 hypothetical patients per treatment strategy (51, 52). The results of these probabilistic sensitivity analyses are reported using incremental cost-effectiveness acceptability curves

that reflect the probability of each treatment strategy having the highest net monetary benefit at various willingness-to-pay thresholds. We also compared the novel regimens with no treatment, as well as dual therapy with RBV and PEG alone.

**Role of the Funding Source**

The funding source had no role in the design, conduct, or reporting of this analysis, or in the decision to submit the manuscript for publication.

**RESULTS**

**HCV Genotype 1**

The results of our base-case analysis comparing usual care (boceprevir-ribavirin-PEG) with the new regimens are presented in Table 2, and cost-effectiveness frontiers are shown in Figure 2. With usual care, the average quality-adjusted life expectancy was 11.28 QALYs, and patients incurred average lifetime costs of \$100 926. Treatment with sofosbuvir-ribavirin-PEG increased quality-adjusted life expectancy to 12.19 QALYs and was more costly, with average lifetime costs

**Table 1.** Model Parameters and Assumptions

Input Parameter	Mean (Range)	Distribution (a, b)	Reference
<b>Mean SVR rates for genotype 1</b>			
SOF-LDV for 12 wk	0.99 (0.95 to 1.00)	$\beta$ (211, 3)	10, 11
White			
CC genotype	1.00	$\beta$ (213, 1)	
CT genotype	0.99	$\beta$ (211, 3)	
TT genotype	0.99	$\beta$ (211, 3)	
Black			
CC genotype	1.00	$\beta$ (213, 1)	
CT genotype	0.99	$\beta$ (211, 3)	
TT genotype	0.99	$\beta$ (211, 3)	
SOF-DCV for 12 wk	0.98 (0.95 to 1.00)	$\beta$ (124, 2)	9
White			
CC genotype	0.98	$\beta$ (124, 2)	
CT genotype	0.98	$\beta$ (124, 2)	
TT genotype	0.98	$\beta$ (124, 2)	
Black			
CC genotype	0.98	$\beta$ (124, 2)	
CT genotype	0.98	$\beta$ (124, 2)	
TT genotype	0.98	$\beta$ (124, 2)	
SOF-SMV for 12 wk	0.93 (0.79 to 0.96)	$\beta$ (74, 6)	7, 8
White			
CC genotype	0.91	$\beta$ (21, 2)	
CT genotype	0.96	$\beta$ (100, 4)	
TT genotype	0.85	$\beta$ (33, 6)	
Black			
CC genotype	0.91	$\beta$ (21, 2)	
CT genotype	0.96	$\beta$ (100, 4)	
TT genotype	0.85	$\beta$ (33, 6)	
SOF-RBV-PEG for 12 wk	0.90 (0.87 to 0.93)	$\beta$ (294, 33)	3
White			
CC genotype	0.98	$\beta$ (93, 2)	
CT genotype	0.87	$\beta$ (157, 24)	
TT genotype	0.87	$\beta$ (44, 7)	
Black			
CC genotype	0.98	$\beta$ (93, 2)	
CT genotype	0.87	$\beta$ (157, 24)	
TT genotype	0.87	$\beta$ (44, 7)	
BOC for 24-32 wk + RBV-PEG for 28-48 wk			21, 26
White			
CC genotype	0.70	$\beta$ (211, 92)	
CT genotype	0.82	$\beta$ (63, 14)	
TT genotype	0.65	$\beta$ (67, 36)	
TT genotype	0.55	$\beta$ (23, 19)	
Black			
CC genotype	0.47	$\beta$ (22, 25)	
CT genotype	0.82	$\beta$ (63, 14)	
CT genotype	0.65	$\beta$ (67, 36)	
TT genotype	0.55	$\beta$ (23, 19)	
RR for SVR for METAVIR stage >F2	0.61	-	22
RBV-PEG at 48 wk			8
White			
CC genotype	0.69	$\beta$ (301, 135)	
CT genotype	0.33	$\beta$ (196, 400)	
TT genotype	0.27	$\beta$ (38, 139)	
Black			
CC genotype	0.48	$\beta$ (20, 22)	
CT genotype	0.15	$\beta$ (22, 124)	
TT genotype	0.13	$\beta$ (15, 97)	
<b>Mean SVR rates for genotype 2</b>			
SOF-DCV at 24 wk	0.92 (0.86 to 1.00)	$\beta$ (24, 2)	9
SOF-RBV at 12 wk	0.97 (0.90 to 1.00)	$\beta$ (68, 2)	3
RBV-PEG at 24 wk	0.78 (0.67 to 0.86)	$\beta$ (52, 15)	3
<b>Mean SVR rates for genotype 3</b>			
SOF-LDV-RBV at 12 wk	1.00 (0.90 to 1.00)	$\beta$ (25, 1)	13
SOF-DCV at 24 wk	0.89 (0.86 to 1.00)	$\beta$ (16, 2)	9
SOF-RBV at 24 wk	0.57 (0.48 to 0.63)	$\beta$ (104, 79)	3
RBV-PEG at 24 wk	0.63 (0.57 to 0.70)	$\beta$ (111, 65)	3
<b>RR of SVR in alcohol users</b>	0.80 (0.65 to 1.00)	$\beta$ (67, 13)	27, 28

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Table 1—Continued

Input Parameter	Mean (Range)	Distribution (a, b)	Reference
<b>Cohort characteristics, %</b>			
Baseline age distribution			29
20-29 y	1.2	-	
30-39 y	10.1	-	
40-49 y	40.7	-	
50-59 y	38.3	-	
≥60 y	9.7	-	
Men	63.6	-	29
Black race	25.3	-	29
Proportion with excess alcohol consumption	19.0	-	26
Distribution of METAVIR fibrosis stages at baseline			9, 30
F0	10.2	-	
F1	36.1	-	
F2	20.7	-	
F3	15.2	-	
F4	17.9	-	
Distribution of virus genotype			22, 30
Genotype 1	66.0	-	
Genotype 2	12.0	-	
Genotype 3	19.0	-	
Genotype 4	3.0	-	
Distribution of patients based on IL-28B genotype			24
White			
CC genotype	37.0	-	
CT genotype	51.0	-	
TT genotype	12.0	-	
Black			
CC genotype	14.0	-	
CT genotype	49.0	-	
TT genotype	37.0	-	
<b>Natural history of HCV</b>			
Annual change in METAVIR stage			30-32
Alcohol use in men			
<50 g/d	0.111	Normal (0.111, 0.010)	
≥50 g/d	0.154	Normal (0.154, 0.011)	
Alcohol use in women			
<50 g/d	0.095	Normal (0.095, 0.003)	
≥50 g/d	0.083	Normal (0.083, 0.017)	
Annual rate of decompensated cirrhosis from stage F4 fibrosis	0.0392	$\beta$ (59, 1447)	33-35
Annual rate of HCC from decompensated cirrhosis or stage F4 fibrosis	0.0208	$\beta$ (40, 1887)	33-35
Annual probability of liver transplant			33
Conditional on decompensated cirrhosis	0.05	$\beta$ (1, 18)	
Conditional on HCC	0.15	$\beta$ (2, 13)	
Annual probability of death			33
During liver transplant	0.14	Normal (0.14, 0.004)	
After liver transplant	0.05	Normal (0.05, 0.005)	
Conditional on decompensated cirrhosis	0.26	Normal (0.26, 0.053)	
Conditional on HCC within 1 y after liver transplant	0.72	Normal (0.72, 0.055)	
Conditional on HCC within ≥2 y after liver transplant	0.25	Normal (0.25, 0.035)	
HR for non-liver-related death in patients with HCV			33
Men			
White	2.56	Normal (2.56, 0.375)	
Black	2.75	Normal (2.75, 0.425)	
Women			
White	1.90	Normal (1.90, 0.300)	
Black	2.48	Normal (2.48, 0.375)	
Background mortality			36
Men			
White	-	$0.0001 \times \exp(0.076 \times \text{age})$	
Black	-	$0.0003 \times \exp(0.0681 \times \text{age})$	
Women			
White	-	$0.0001 \times \exp(0.0785 \times \text{age})$	
Black	-	$0.00005 \times \exp(0.0855 \times \text{age})$	
Probability of no EVR at 12 wk for PEG-RBV	0.36	$\beta$ (293, 160)	2, 25

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Table 1—Continued

Input Parameter	Mean (Range)	Distribution (a, b)	Reference
Probability of no virologic response at 28 wk for BOC	0.13	$\beta$ (41, 275)	33
Probability of treatment completion at 28 wk for BOC	0.50	$\beta$ (158, 158)	33
Probability of continuing treatment until 48 wk for BOC	0.37	$1-\beta$ (41, 275)– $\beta$ (158, 158)	33
<b>Utilities</b>			
Age-specific baseline			37
<30 y	0.922	–	
30–39 y	0.901	–	
40–49 y	0.871	–	
50–59 y	0.842	–	
60–69 y	0.823	–	
70–79 y	0.790	–	
≥80 y	0.736	–	
Condition-specific			33, 38
F0	1.000	–	
F1 and F2	0.980 (0.700 to 1.000)	$\beta$ (5.88, 0.12)	
F3	0.850 (0.660 to 1.000)	$\beta$ (38, 7)	
F4	0.790 (0.460 to 1.000)	$\beta$ (40, 11)	
Decompensated cirrhosis	0.720 (0.260 to 0.910)	$\beta$ (36, 14)	
HCC	0.720 (0.150 to 0.950)	$\beta$ (36, 14)	
After liver transplant	0.825 (0.640 to 1.000)	$\beta$ (8, 2)	
Annualized reduction while receiving PEG regimens	–0.165 (–0.400 to 0.000)	$-1 \times \beta$ (2, 11)	
<b>Unit costs, \$*</b>			
Adverse effects of standard therapy	1990 (1344 to 2496)	Normal (1990, 288)	33, 39, 40
Annual maintenance cost†			
F0–F3	1462 (152 to 5870)	Normal (1462, 141)	
F4	4350 (152 to 5330)	Normal (4350, 210)	
Decompensated cirrhosis	11 520 (3681 to 27 845)	Normal (11 520, 2780)	
HCC	45 860 (22 117 to 66 341)	Normal (45 860, 11 054)	
1 y after liver transplant	151 028 (72 825 to 218 455)	Normal (151 028, 36 410)	
>1 y after liver transplant	26 371 (12 715 to 38 156)	Normal (26 371, 6358)	
<b>Treatment costs, \$/wk</b>			
PEG	580	–	33, 41
RBV	371	–	33, 41
BOC	1100	–	33, 41
SOF	7000 (500 to 9500)	–	2, 16
SMV	5500 (500 to 9500)	–	2, 16
DCV	5500 (500 to 9500)	–	Assumption
LDV	875 (500 to 9500)	–	41

BOC = boceprevir; DCV = daclatasvir; EVR = early virologic response; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HR = hazard ratio; IL = interleukin; LDV = ledipasvir; PEG = pegylated interferon; RBV = ribavirin; RR = relative risk; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response.

\* Direct costs per year.

† A 3.7% inflation rate was applied to unit costs in the model to convert 2012 costs to 2014 costs.

of \$120 648 (Table 2). As a result, the incremental cost-effectiveness ratio of sofosbuvir-ribavirin-PEG compared with usual care was \$21 528 per QALY gained.

All 3 PEG-free regimens achieved higher quality-adjusted survival than usual care (12.26, 12.36, and 12.40 QALYs for sofosbuvir-simeprevir, sofosbuvir-daclatasvir, and sofosbuvir-ledipasvir, respectively). But they were also more costly, with lifetime expenditures of \$171 023, \$169 747, and \$115 358, respectively (Table 2). Assuming sofosbuvir-ledipasvir cost \$7875 per week, this regimen results in the largest QALY gain and smallest incremental cost compared with usual care, with an incremental cost-effectiveness ratio of \$12 825 per QALY gained.

Compared with no treatment, the costs per additional QALY gained were \$30 001, \$50 951, \$48 206, and \$25 291 for sofosbuvir-ribavirin-PEG, sofosbuvir-simeprevir, sofosbuvir-daclatasvir, and sofosbuvir-

ledipasvir, respectively (Appendix Tables 1 and 2, available at [www.annals.org](http://www.annals.org)). The costs per additional QALY gained were \$35 836 for usual care (boceprevir-ribavirin-PEG) and \$24 833 for dual therapy (ribavirin-PEG) compared with no treatment.

Because the pricing of daclatasvir has not been determined and that of sofosbuvir, simeprevir, and ledipasvir could change as new drugs enter the marketplace, we varied the weekly cost of all 4 drugs between \$500 and \$9500 and examined the thresholds at which each treatment strategy offered the largest net monetary benefit (Figure 3, top). At a conventional willingness-to-pay threshold of \$50 000 per QALY gained, sofosbuvir-ledipasvir was the optimal strategy, but if ledipasvir cost more than \$2400 per week, sofosbuvir-ribavirin-PEG would be optimal (Figure 3, top). Changing the cost of simeprevir across a range from \$500 to \$9500 did not affect which regimen was

optimal, but if daclatasvir had a weekly price lower than \$700, sofosbuvir-daclatasvir would become optimal. Sofosbuvir-ledipasvir would be cost-saving if sofosbuvir cost less than \$5500 per week (Supplement Figure 2). The sofosbuvir-ribavirin-PEG regimen would be cost-saving if sofosbuvir cost less than \$4500 per week.

The assumed SVR rates from different treatments also influenced their value. Sofosbuvir-ledipasvir was the optimal strategy unless its SVR rate was less than 87% or if the SVR rate of sofosbuvir-ribavirin-PEG exceeded 99% (Figure 4, top). In those cases, sofosbuvir-ribavirin-PEG was the optimal strategy (Appendix Figure 2).

Incremental cost-effectiveness ratios were also sensitive to patient characteristics, including fibrosis stage and age. Overall, all treatment strategies were more economically attractive in patients with higher fibrosis stages (Appendix Figure 3) and in those who were younger at the time of treatment initiation (Appendix Figure 4). With the exception of annual discount rate, utility weight for stage F4 fibrosis, hazard ratio of non-liver-related death, and the costs associated with stages F0 to F3 fibrosis, other parameters had very small effects on our results (Supplement Figure 3).

The results of probabilistic sensitivity analysis suggested that at a willingness-to-pay threshold of \$13 000 per QALY, usual care and sofosbuvir-ledipasvir were equally optimal strategies (Appendix Figures 5 and 6). Above this threshold, sofosbuvir-ledipasvir had a higher likelihood of being the optimal strategy.

### HCV Genotype 2

With usual care (RBV-PEG), quality-adjusted survival was 11.86 QALYs and lifetime expenditures were \$54 005 (Table 2). Sofosbuvir-ribavirin increased expected survival to 12.37 QALYs, with costs of \$109 958, which resulted in an incremental cost-effectiveness ratio of \$110 168 per QALY gained (Figure 2, middle). Treatment with sofosbuvir-daclatasvir did not offer any advantage over sofosbuvir-ribavirin because it resulted in smaller quality-adjusted survival (12.24 QALYs) and was more expensive (\$316 845).

Compared with no treatment, sofosbuvir-ribavirin and sofosbuvir-daclatasvir resulted in incremental cost-effectiveness ratios of \$45 344 and \$137 973 per QALY gained, respectively (Appendix Table 3, available at [www.annals.org](http://www.annals.org)).

At a willingness-to-pay threshold of \$50 000 per QALY, usual care was the optimal strategy for genotype 2, but if sofosbuvir cost less than \$4500 per week (Figure 3, middle), sofosbuvir-ribavirin would be optimal. Sofosbuvir-ribavirin would be cost-saving if sofosbuvir cost less than \$2250 per week. Sofosbuvir-daclatasvir was not cost-saving at any prices of sofosbuvir and daclatasvir analyzed (Supplement Figure 4).

Usual care also remained the optimal strategy in these patients when SVR rates of PEG-free regimens varied between 80% and 100% (Figure 4, middle). Treatment of patients at more severe stages of fibrosis (Appendix Figure 3) and at younger ages (Appendix Figure 4) was relatively more cost-effective. Annual dis-

count rate, utility weight for fibrosis stages, the risk for non-liver-related death, and disutility due to PEG-based regimens had larger effects on incremental cost-effectiveness ratios than other model parameters (Supplement Figure 5).

For genotype 2, our probabilistic sensitivity analysis found that sofosbuvir-ribavirin is most likely to be the optimal strategy at a willingness-to-pay threshold of \$110 000 per QALY or higher (Appendix Figures 5 and 6).

### HCV Genotype 3

Usual care (RBV-PEG) produced quality-adjusted survival of 11.50 QALYs, with lifetime costs of \$58 323 (Table 2). Sofosbuvir-ribavirin would lead to lower quality-adjusted survival (11.37 QALYs), with very large costs (\$207 872) (Figure 2, bottom). Although sofosbuvir-daclatasvir increased expected survival to 12.16 QALYs, it was still very expensive (\$317 830) and resulted in an incremental cost-effectiveness ratio of \$396 229 per QALY gained. The sofosbuvir-ledipasvir-ribavirin regimen increased expected survival to 12.35 QALYs, with a lifetime cost of \$120 464, and resulted in an incremental cost-effectiveness ratio of \$72 236 per QALY gained.

Compared with no treatment, sofosbuvir-ribavirin costs \$108 443, sofosbuvir-daclatasvir costs \$119 664, and sofosbuvir-ledipasvir-ribavirin costs \$27 950 for each additional QALY gained (Appendix Table 3).

At a willingness-to-pay threshold of \$50 000 per QALY, usual care was the optimal strategy for patients with genotype 3, but if sofosbuvir cost less than \$5500 per week (Figure 3, bottom), sofosbuvir-ledipasvir-ribavirin would be optimal. Usual care remained the optimal strategy for SVR rates between 50% and 100% (Figure 4, bottom). Sofosbuvir-ledipasvir-ribavirin would be cost-saving if sofosbuvir cost less than \$1500 per week (Supplement Figure 6).

Sofosbuvir-ledipasvir-ribavirin and sofosbuvir-daclatasvir were more cost-effective in patients at more severe stages of fibrosis (Appendix Figure 3) and in those who were younger (Appendix Figure 4). Compared with usual care, however, the incremental cost-effectiveness ratio of sofosbuvir-daclatasvir remained above approximately \$200 000 per QALY and the newly approved sofosbuvir-ribavirin resulted in fewer QALYs and higher costs than usual care in all situations. As with genotype 2, annual discount rate, utility weight for fibrosis stages, hazard ratio of non-liver-related death, and disutility associated with PEG-based regimens had a larger effect on incremental cost-effectiveness ratios (Supplement Figure 7). In the probabilistic sensitivity analysis, the willingness-to-pay threshold had to be greater than \$75 000 per additional QALY gained for sofosbuvir-ledipasvir-ribavirin to be the optimal strategy over usual care in most simulations (Appendix Figures 5 and 6).

## DISCUSSION

Novel treatments for HCV substantially shorten treatment length, achieve substantially higher SVR

**Table 2. Base-Case Results\***

Treatment Strategy, by Genotype	Cost, \$	Effectiveness, QALYs	Incremental Cost Relative to Usual Care, change in \$
<b>Genotype 1</b>			
BOC-RBV-PEG (usual care)	100 926 (94 766 to 108 470)	11.28 (10.66 to 11.98)	Reference
SOF-RBV-PEG	120 648 (115 949 to 125 548)	12.19 (11.55 to 12.85)	19 722 (13 651 to 24 185)
SOF-SMV (PEG-free regimen)	171 023 (166 580 to 176 401)	12.26 (11.62 to 12.95)	70 097 (64 063 to 74 878)
SOF-DCV (PEG-free regimen)	169 747 (165 406 to 174 669)	12.36 (11.71 to 13.11)	68 821 (62 574 to 73 859)
SOF-LDV (PEG-free regimen)	115 358 (111 095 to 120 379)	12.40 (11.77 to 13.08)	14 432 (8396 to 19 489)
<b>Genotype 2</b>			
RBV-PEG (usual care)	54 005 (48 633 to 60 897)	11.86 (11.20 to 12.61)	Reference
SOF-RBV (PEG-free regimen)	109 958 (105 544 to 114 729)	12.37 (11.70 to 13.09)	55 953 (50 878 to 59 769)
SOF-DCV (PEG-free regimen)	316 845 (311 645 to 322 857)	12.24 (11.53 to 12.99)	262 840 (257 326 to 267 722)
<b>Genotype 3</b>			
RBV-PEG (usual care)	58 323 (52 027 to 65 999)	11.50 (10.90 to 12.23)	Reference
SOF-RBV (PEG-free regimen)	207 872 (201 623 to 215 794)	11.37 (10.74 to 12.09)	149 549 (145 381 to 154 820)
SOF-DCV (PEG-free regimen)	317 830 (312 217 to 325 029)	12.16 (11.43 to 12.94)	259 507 (253 615 to 265 813)
SOF-LDV-RBV (PEG-free regimen)	120 464 (115 543 to 125 573)	12.35 (11.68 to 13.07)	62 141 (53 101 to 70 163)

BOC = boceprevir; DCV = daclatasvir; LDV = ledipasvir; PEG = pegylated interferon; QALY = quality-adjusted life-year; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir.

\* Numbers in parentheses are 95% credible intervals, which reflect the results of probabilistic sensitivity analysis.

rates, and offer interferon-free regimens for patients who cannot tolerate interferon or do not adequately respond to current medications. However, little is known about their economic value compared with the current care. Our study investigated the assumptions under which the new regimens would or would not be considered cost-effective strategies.

From a societal perspective, the newly approved PEG-free regimen of sofosbuvir-ledipasvir for 12 weeks could be very cost-effective relative to usual care (costing \$12 825 per QALY gained) for patients with HCV genotype 1. In probabilistic sensitivity analysis, sofosbuvir-ledipasvir seems to be the optimal treatment strategy in the greatest number of simulations. Other treatment regimens for patients with HCV genotype 1 also provide relatively good value in our base-case models but were less effective and more costly than sofosbuvir-ledipasvir and rarely optimal in probabilistic analysis. For patients with genotype 2, the newly approved regimen of sofosbuvir-ribavirin cost approximately \$110 168 per QALY gained compared with usual care. For patients with genotype 3, sofosbuvir-ledipasvir-ribavirin for 12 weeks cost approximately \$73 000 per QALY gained compared with usual care, which represents relatively good value.

Although we found the sofosbuvir-ribavirin-PEG and sofosbuvir-ledipasvir regimens for genotype 1 and potentially sofosbuvir-ledipasvir-ribavirin for genotype 3 to be cost-effective at their currently assumed prices (\$7000 per week for sofosbuvir and an additional \$875 per week for ledipasvir), the offset savings from avoiding complications related to HCV do not outweigh the cost of the drugs themselves; thus, these strategies do not seem to actually reduce overall spending. This is an exceptionally high bar, however, that is generally not expected when evaluating whether a new strategy represents good value for money. Nevertheless, in our sensitivity analysis, we found that if the price of sofosbuvir was less than \$5500 per week, a regimen of

sofosbuvir-ledipasvir could actually be cost-saving for genotype 1. Similarly, if the cost of sofosbuvir was less than \$4500 per week, sofosbuvir-ribavirin-PEG could be cost-saving. In contrast, for genotype 2, the newly approved regimen of sofosbuvir-ribavirin would be cost-saving only if sofosbuvir cost less than \$2250 per week. For genotype 3, sofosbuvir-ledipasvir-ribavirin would be cost-saving if sofosbuvir cost less than \$1500 per week. This reflects the relative limitations of new therapies for treatment of genotypes 2 and 3. When compared with no treatment, sofosbuvir-ribavirin for genotype 2 and sofosbuvir-ledipasvir-ribavirin for genotype 3 resulted in incremental cost-effectiveness ratios of \$45 344 and \$27 950 per QALY gained, respectively. This is particularly relevant to patients for whom a usual PEG-based regimen is not an option.

An analysis such as ours can measure the additional cost required to achieve an incremental QALY from a societal perspective, but it does not account for the effect of such expenditures on near-term health care budgets nor the fact that the organizations that will pay for these drugs in the near term may not be the ones to primarily benefit from their downstream effects. Regardless of the cost-effectiveness of novel hepatitis C treatments, there is considerable concern that their very high prices could substantially increase short-term overall drug spending for many public and private payers. Further, unpleasant PEG-based regimens are not prescribed to all patients infected with early-stage HCV and HCV screening has not been a routine practice. The far greater tolerability of the newer drugs could mean that HCV screening will become more common, with resultant increases in the demand for these agents.

In the face of this economic reality, payers may give priority to patients for whom treatment is most cost-effective. For example, our analysis suggests that all treatment strategies for genotype 1 were more economically attractive in patients with higher fibrosis stages and in those who were younger at the time of



Table 2—Continued

Incremental QALYs Relative to Usual Care, change in QALYs	Incremental Cost-Effectiveness, change in \$/change in QALYs
Reference	Reference
0.92 (0.51 to 1.33)	21 528 (12 834 to 39 629)
0.98 (0.55 to 1.41)	71 445 (39 615 to 79 956)
1.09 (0.66 to 1.54)	63 355 (43 454 to 108 171)
1.13 (0.69 to 1.59)	12 825 (6 420 to 22 755)
Reference	Reference
0.51 (0.09 to 0.94)	110 168 (56 414 to 573 491)
0.38 (−0.10 to 0.86)	691 574 (−5 085 270 to 6 658 138)
Reference	Reference
−0.13 (−0.53 to 0.25)	Dominated
0.65 (0.09 to 1.16)	396 229 (202 096 to 1 606 541)
0.85 (−0.06 to 1.71)	73 236 (−296 686 to 394 766)

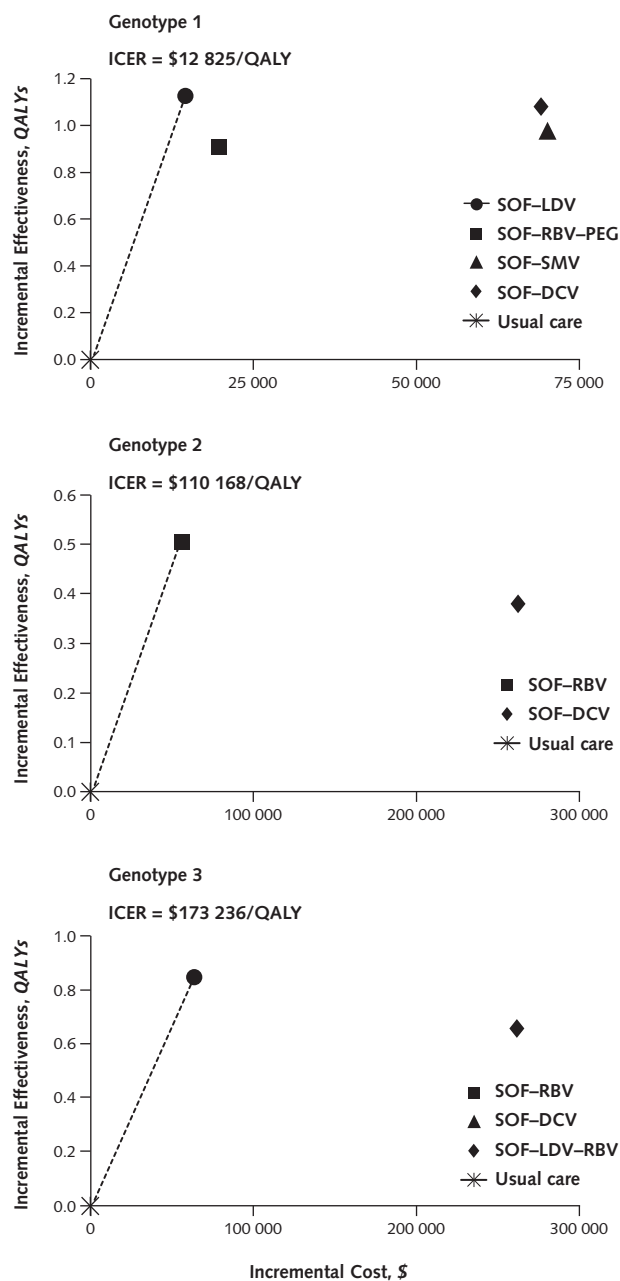
treatment initiation. However, the ethics of resource allocation based on such criteria are far from clear.

Our analysis has several limitations. Our model focused on treatment-naive patients; however, new regimens have also been shown to be effective in nonresponders and patients with relapse after initial SVR. We did not directly include parameters for nonadherence in our model. But overall SVR rates implicitly reflect patients' adherence to response-guided treatments, at least in the clinical trial setting. More detailed modeling of adherence would probably bias the results against usual care and therefore indicate that the new drugs are more cost-effective than is reflected in our trial-based analyses. We did not include other factors, such as insurance coverage and geographic variations, that could influence access to health care. We based our analysis on wholesale acquisition costs, but in reality, prices negotiated between manufacturers and large insurers are often lower than these prices. Because this information is not publicly available, the results of our sensitivity analyses can serve as a tool for understanding the financial impact of lower prices on the economic value of new treatments.

We restricted our analysis to direct medical costs and did not consider the effect of treatment on indirect costs (that is, productivity loss), nonmedical costs (for example, resources spent by patients to seek medical care), or costs accrued from prolonged life expectancy. Our model cannot incorporate all elements of clinical decision making, such as patient preference for oral therapy or risk for decompensation with PEG. We have not accounted for the effect of SVR on transmission rates, although inclusion would probably make the cost-effectiveness results more attractive for treatments with higher rates of SVR. Finally, more regimens for HCV treatment are expected to be approved (53); greater competition may lead to reduced therapy costs, which would alter our findings and probably increase the value of treating hepatitis C over time.

In summary, our analysis suggests that from a societal perspective, sofosbuvir-based treatment regimens

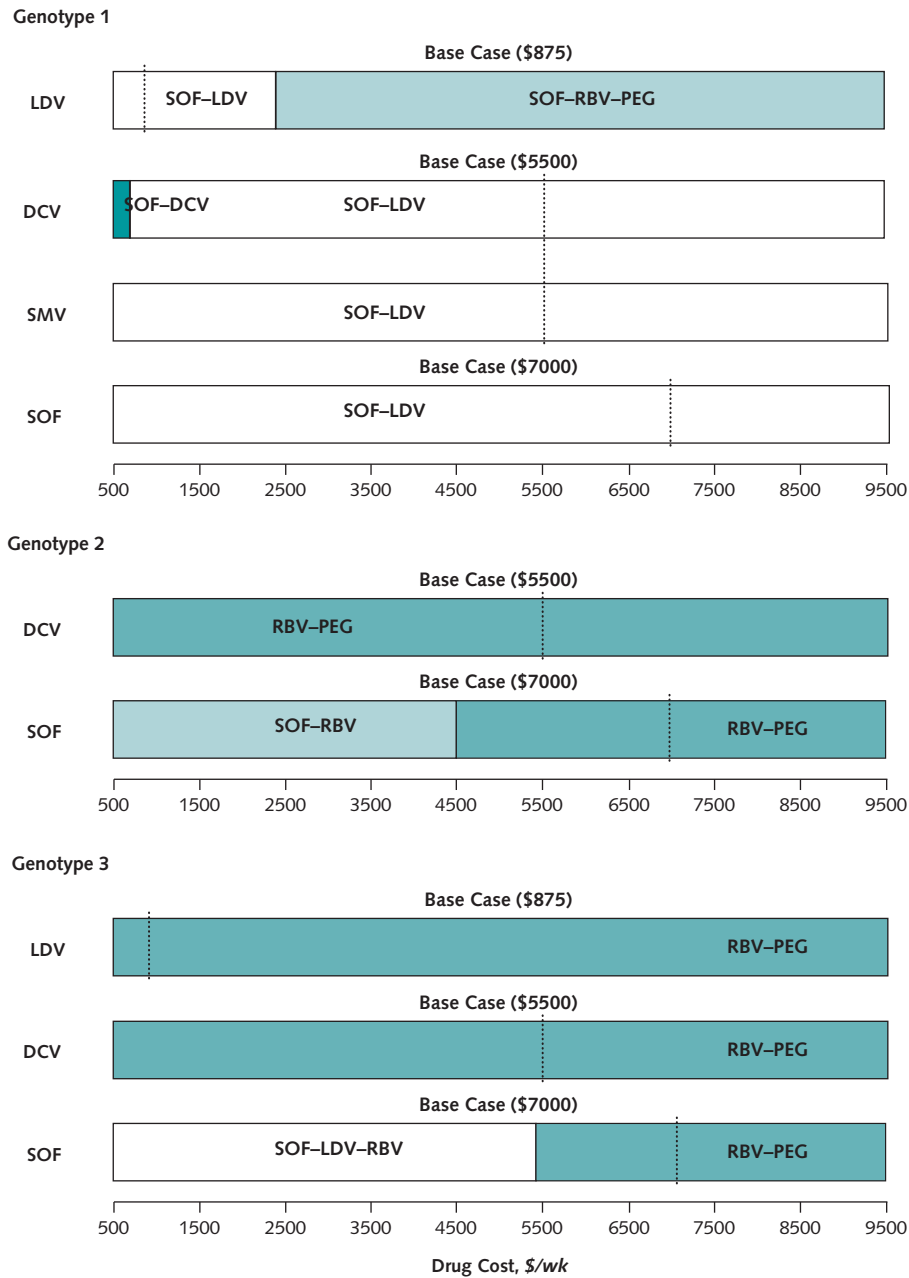
Figure 2. Base-case results of incremental cost-effectiveness of treatment strategies versus usual care for genotypes 1 (top), 2 (middle), and 3 (bottom).



The lines represent the efficient frontier. The ICERs (compared with the next best alternative) have been reported for the points on the efficient frontier. Treatment options that are not on the efficient frontiers result in larger incremental costs and smaller incremental QALYs. DCV = daclatasvir; ICER = incremental cost-effectiveness ratio; LDV = ledipasvir; PEG = pegylated interferon; QALY = quality-adjusted life-year; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir.

seem to represent good long-term economic value in treatment-naive patients with HCV genotypes 1 and potentially genotype 3 but not for those with genotype 2. If these drugs became available at lower prices, they

**Figure 3.** One-way sensitivity analyses on individual drug prices, identifying the threshold at which various treatment strategies become optimal in terms of net monetary benefit for genotypes 1 (top), 2 (middle), and 3 (bottom).



Dotted lines represent the values used in the base-case analyses. This sensitivity analysis assumes a willingness-to-pay threshold of \$50 000 per quality-adjusted life-year. DCV = daclatasvir; LDV = ledipasvir; PEG = pegylated interferon; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir.

could not only improve health outcomes but also reduce long-term health care costs.

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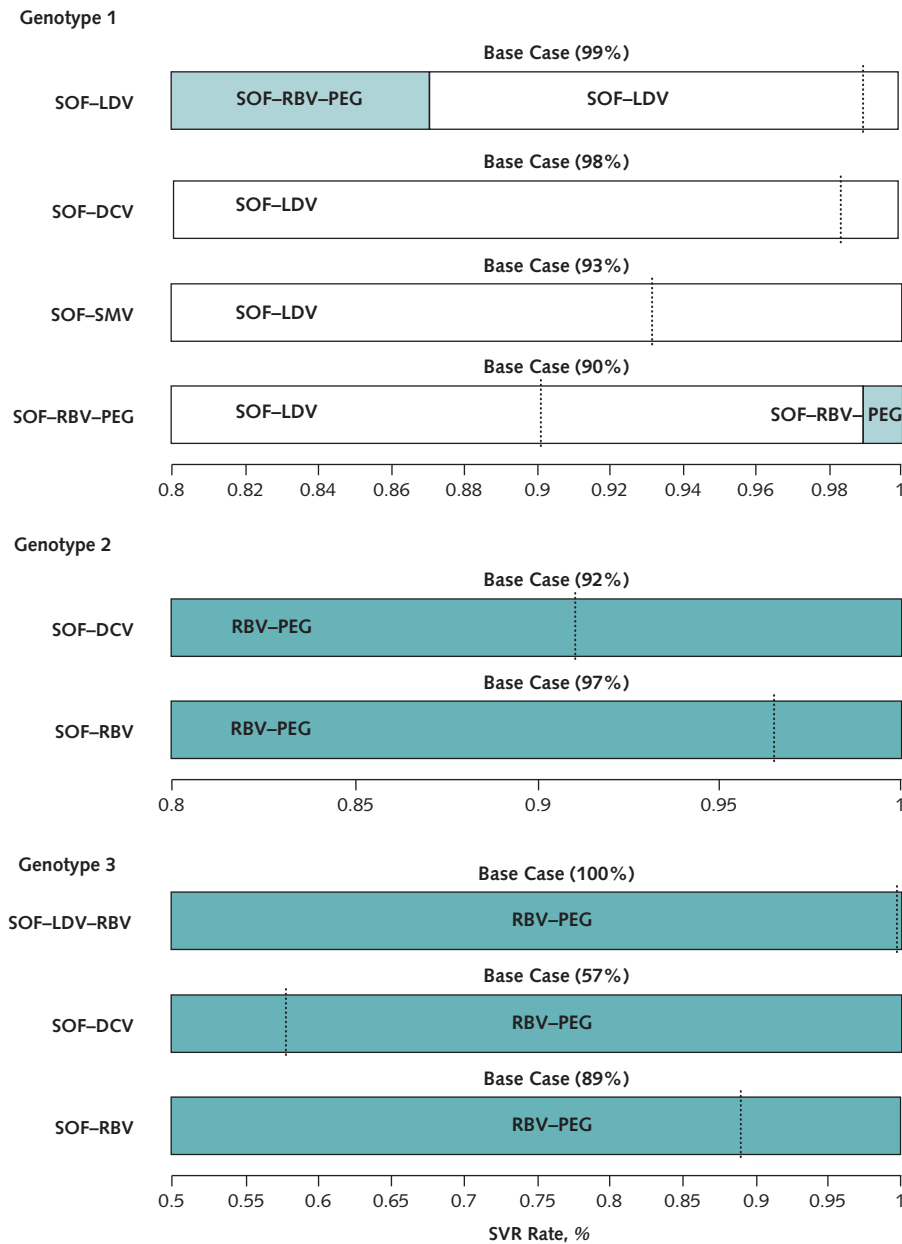
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**Reproducible Research Statement:** *Study protocol:* Not applicable. *Statistical code:* Available from Dr. Najafzadeh (e-mail,

**Figure 4.** One-way sensitivity analyses on SVR, identifying the threshold at which various treatment strategies become optimal in terms of net monetary benefit for genotypes 1 (top), 2 (middle), and 3 (bottom).



Dotted lines represent the values used in the base-case analyses. This sensitivity analysis assumes a willingness-to-pay threshold of \$50 000 per quality-adjusted life-year. DCV = daclatasvir; LDV = ledipasvir; PEG = pegylated interferon; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response.

mnajafzadeh@partners.org). Data set: Input parameters and sources are provided in the text.

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## APPENDIX: MORE DETAILS ON THE MODEL

### Model Structure and Assumptions

We developed a DES model using Arena, version 12.00, to simulate the natural history and progression of liver disease among treatment-naïve patients infected with chronic HCV genotype 1, 2, or 3 and compare clinical and economic outcomes of treatment strategies (Figure 1) (17, 18, 20). To do this, we created a hypothetical cohort of 10 000 patients with baseline characteristics (age, sex, race, alcohol use, disease stage based on METAVIR score (42), IL-28B genotype status, virus genotype, and age-specific quality of life) chosen to emulate the actual distribution of patients with HCV in the United States (Table 1). Individual patients were tracked throughout their life as their liver disease progressed, and survival, quality-adjusted survival (measured in QALYs), and costs were calculated. Health trajectories in the model were defined on the basis of the epidemiology and progression of chronic HCV as documented in the literature (Table 1). Patients started the model with different levels of fibrosis; each subsequent year, they could progress to a higher METAVIR stage (from F0 to F4) or develop compensated cirrhosis, decompensated cirrhosis, or hepatocellular carcinoma. Because of the substantially different treatment options and efficacies, we modeled patients infected with each HCV genotype separately.

By creating identical clones of our cohort and assigning them to different treatment strategies, we com-

pared treatment-related differences in outcomes. Both costs and QALYs were discounted at a rate of 3% per year in accordance with U.S. Public Health Service guidelines for cost-effectiveness analyses (19); sensitivity analyses were also conducted with 0% and 5% discount rates. The analysis was conducted from a societal perspective. Costs and QALYs of different treatment strategies compared with usual care were presented in a cost-effectiveness plane to facilitate comparison among treatment strategies based on cost-effectiveness frontiers (Figure 2).

We modeled treatment efficacy based on SVR, which we defined as an HCV RNA level below the lower limit of quantification measured at 12 weeks after the end of treatment (3). Consistent with previously published cost-effectiveness analyses of HCV treatments, we assumed that after achieving SVR, a patient would no longer have progression of liver disease but would still be at increased risk for non-liver-related death (33, 47, 48).

The SVR rates from the different treatment strategies were derived from the results of published clinical trials (Table 1). For genotype 1, SVR rates were based on results from SPRINT-2 (Serine Protease Inhibitor Therapy 2) (21, 26) for boceprevir-ribavirin-PEG, NEUTRINO (3) for sofosbuvir-ribavirin-PEG, COSMOS (6, 7) for sofosbuvir-simeprevir (6, 7), AI444040 trial (9) for sofosbuvir-daclatasvir, and studies by Afdhal and colleagues and Kowdley and colleagues (10, 11) and LONESTAR (12) for sofosbuvir-ledipasvir. For genotypes 2 and 3, SVR rates were based on results from FISSION for ribavirin-PEG and sofosbuvir-ribavirin (3), the AI444040 trial (9) for sofosbuvir-daclatasvir, and ELECTRON 2 (13) for sofosbuvir-ledipasvir-ribavirin. Further, additional data from POSITRON (6), ELECTRON (23), and a study by Fried and colleagues (22) were used to model possible ranges for efficacy of treatment strategies. Because there are no data on variation of daclatasvir efficacy based on IL-28B genotype or race, all subgroups were assumed to have the same SVR rates. We also assumed that alcohol use negatively affects SVR rates in the base-case analysis and varied this in the sensitivity analysis (27, 28).

Consistent with previously published cost-effectiveness analyses of HCV treatments, we assumed that after achieving SVR, a patient would no longer have progression of liver disease but would still be at increased risk for non-liver-related death (33, 35, 47, 48).

We modeled increased rates of mortality not related to liver disease among patients with HCV using sex- and race-dependent hazard ratios based on the results of the NHANES III (33). We derived from published data the probability of liver-related death in patients with decompensated cirrhosis and early- and

late-stage hepatocellular carcinoma during and after liver transplant (Table 1).

Background mortality rates stratified by sex and race were derived from U.S. life tables published as part of *National Vital Statistics Reports* (36). Exponential functions were fitted to probabilities of dying between age  $x$  and  $x + 1$  ( $q_x$ ) in each population stratum, and the resulting values were incorporated into our model to predict the age-, sex-, and race-specific probability of background mortality for each patient at different time points of the simulation.

We assumed that a proportion of patients with decompensated cirrhosis or hepatocellular carcinoma received a liver transplant based on the Model for End-Stage Liver Disease criteria (43). Death as a result of advanced liver disease, failed liver transplant, and background mortality were the 3 possible competing events defined as absorbing health states in the model. A summary of data sources has been provided in the Supplement Table.

Annual costs associated with different stages of HCV were derived from observational studies that compared the medical costs of patients with HCV at different stages of disease with control patients without HCV (39, 40). In the base-case analyses, we used unit costs that were consistent with recent cost-effectiveness studies to increase the comparability of our findings (33). We varied these assumptions extensively in sensitivity analyses.

An individual-level DES model was used to facilitate modeling of event probabilities as a function of individual patient characteristics (for example, age) and model-level variables (such as time). For example, patients' METAVIR score was simulated over time as a function of their individual characteristics. This model allowed us to model the history of disease for individual patients and changes in their characteristics (for example, age) over time. We recorded the sequence of events using patient-specific variables and therefore avoided the proliferation of health states in the model. Considering that most epidemiologic data are reported as rates and annual probabilities, events were modeled on the basis of probabilities in a cycle rather than sampling from time-to-event distributions. Outcomes were assessed at weeks 8, 12, 24, and 48 and yearly afterward. A nested Monte Carlo simulation was used to account for first- and second-order uncertainties (17, 51, 52). For the probabilistic sensitivity analysis, we sampled 10 000 independent sets of input parameters from their probability distributions in the outer loop; for each set of parameter realizations, we modeled a cohort of 10 000 hypothetical patients per treatment strategy in the inner loop. We fixed the seed number when simulating different treatment strategies

to ensure that observed variations in outcomes were the result of differences in treatment effect rather than variation of simulation cohort or chance.

### Model Validation

To ensure that our model produced plausible values, we first simulated a cohort of treatment-naive patients with HCV aged 50 years, assuming no increased risk for non-liver-related death, and examined whether the life expectancy in this cohort matched that seen in life tables for this age group. We then simulated a cohort of patients with no evidence of fibrosis (that is, F0) at baseline to compare their average progression rates to cirrhosis, with the rates estimated on the basis of various observational studies (31, 32) (Appendix Figure 1). We then used model inputs from previously published cost-effectiveness studies (33) for currently approved treatment strategies (that is, boceprevir-ribavirin-PEG for genotype 1 and RBV-PEG for genotypes 2 and 3) to verify that our model achieved similar results (Appendix Table 1) (33, 47, 48). The characteristics of the simulated cohort and model parameters under the no-treatment and dual-therapy strategies were identical to our base-case assumptions.

Estimated progression rates vary widely based on study setting (31, 32). Review of estimated progression rates in different clinical settings suggests that a 7% likelihood of progression to cirrhosis after 20 years seems to be a realistic estimate based on community-based studies. Because Poynard and colleagues' study (30) is based on a liver clinic series, the overall estimated progression rates tend to be relatively high. However, these high rates are mainly derived by those who have contracted HCV at ages older than 40 years. As seen in Poynard and colleagues' study (30), expected duration for progression to cirrhosis is substantially lower for those who were infected at ages younger than 40 years. We have assumed that all patients in our model have contracted HCV before age 40 years. Therefore, the lower rates in Poynard and colleagues' study (30) were applied to all ages in our model.

To compare the progression rates in the model with the rates reported in studies by Thein and colleagues (31) and Freeman and colleagues (32), we simulated a cohort of recently infected patients (that is, F0 stage at baseline) over their lifetime and recorded progression rates to cirrhosis over time. Under our base-case assumptions, 6.4% developed cirrhosis over 25 years since infection (Appendix Figure 1). This suggests that progression rates in our model are slightly less than the rates observed in community-based cohorts and very similar to the calibrated model by Salomon and colleagues (34).

**Appendix Figure 1.** Proportion of patients with no evidence of stage F0 fibrosis who developed stage F4 cirrhosis over time in the calibrated model.



A cohort of recently infected patients (i.e., at stage F0 fibrosis at baseline) were simulated over their lifetime, and their progression rates to cirrhosis over time were recorded. The characteristics of this cohort were identical to our assumptions in the base-case analysis, assuming that they received no treatment for hepatitis C virus. Under the base-case assumptions, 6.4% of patients developed cirrhosis over 25 y since infection.

**Appendix Table 1.** Results of Base-Case Analysis for Model Validation for Genotype 1\*

Variable	No Treatment	Dual Therapy (RBV-PEG)	Current Care (BOC-RBV-PEG)
<b>Estimated distribution of outcomes, %</b>			
METAVIR stage at end of life			
F0	0.5	4.7	7.7
F1	4.6	15.1	25.5
F2	11.2	15.2	17.6
F3	16.9	19.4	14.1
F4	30.0	25.3	19.0
Decompensated cirrhosis	20.6	11.0	8.6
HCC	9.9	5.9	3.8
Liver transplant	6.3	3.4	3.7
Liver-related death	30.7	16.5	12.3
Patients with SVR	0.1	37.5	61.2
<b>Cost-effectiveness results</b>			
Life expectancy, y	69.1	70.2	70.2
QALYs	9.94 (9.15-10.69)	10.85 (10.18-11.59)	11.27 (10.65-11.98)
Cost, \$	53 257 (42 792-67 263)	75 745 (65 658-87 025)	100 926 (94 765-108 469)
Incremental QALYs	Reference	0.90 (0.51-1.37)	1.33 (0.85-1.92)
Incremental cost, U.S. \$	Reference	22 488 (13 085-31 437)	47 669 (39 024-54 048)
ICER relative to no treatment, change in \$/change in QALYs	Reference	24 883 (12 299-47 749)	35 836 (23 827-56 568)
Incremental QALYs	-	Reference	0.43 (0.06-0.84)
Incremental cost, \$	-	Reference	25 181 (16 762-33 390)
ICER relative to usual care, change in \$/change in QALYs	-	Reference	59 048 (24 718-286 555)

BOC = boceprevir; HCC = hepatocellular carcinoma; ICER = incremental cost-effectiveness ratio; PEG = pegylated interferon; QALY = quality-adjusted life-year; RBV = ribavirin; SVR = sustained virologic response.

\* Numbers in parentheses are 95% credible intervals, which reflect the results of probabilistic sensitivity analysis. All estimates are over the patients' lifetime.



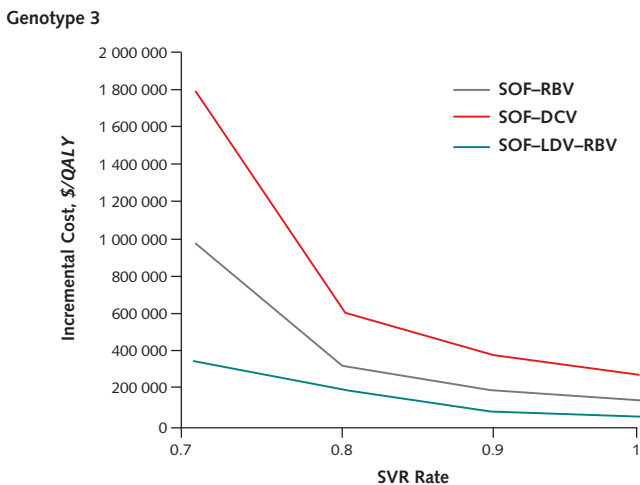
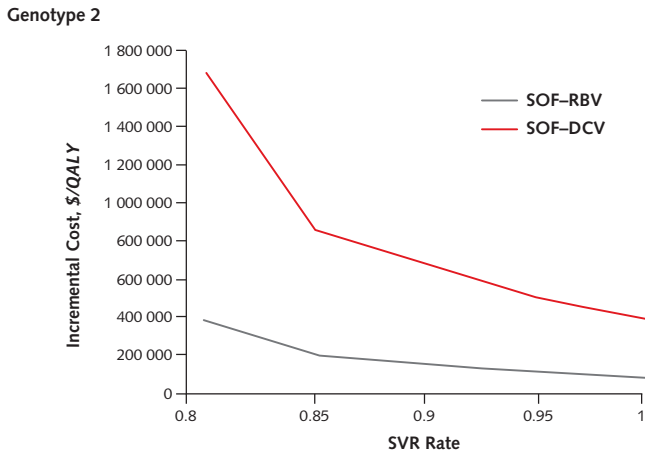
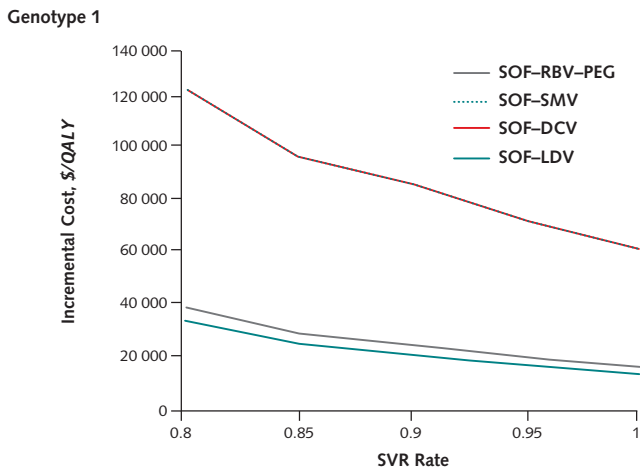
**Appendix Table 2. Base-Case Results for Treatment Strategies for Genotype 1\***

Variable	No Treatment	Dual Therapy (RBV-PEG)	Current Care (BOC-RBV-PEG)	SOF-RBV-PEG	SOF-SMV	SOF-DCV	SOF-LDV-RBV
<b>Estimated distribution of outcomes, % of life</b>							
METAVIR stage at end of life							
F0	0.5	4.7	7.7	10.2	0.7	0.5	0.1
F1	4.6	15.1	25.5	30.2	42.4	45.2	46.7
F2	11.2	15.2	17.6	20.9	21.5	21.6	22.6
F3	16.9	19.4	14.1	15.1	14.6	14.6	14.6
F4	30.0	25.3	19.0	18.8	16.8	16.2	15.4
Decompensated cirrhosis	20.6	11.0	8.6	2.8	2.1	1.2	0.2
HCC	9.9	5.9	3.8	1.3	1.4	0.3	0.4
Liver transplant	6.3	3.4	3.7	0.7	0.5	0.4	0.0
Liver-related death	30.7	16.5	12.3	3.7	3.6	1.3	0.5
Patients with SVR	0.1	37.5	61.2	86.4	91.3	96.2	99.2
<b>Cost-effectiveness results</b>							
Life expectancy, y	69.1	70.2	70.2	71.5	71.9	71.7	71.9
QALYs	9.94 (9.15-10.69)	10.85 (10.18-11.59)	11.27 (10.65-11.98)	12.19 (11.55-12.85)	12.27 (11.62-12.95)	12.36 (11.71-13.11)	12.40 (11.77-13.08)
Cost, \$	53 257 (42 792-67 263)	75 745 (65 658-87 025)	100 926 (94 765-108 469)	120 648 (115 949-125 548)	171 022 (166 580-176 401)	169 747 (165 406-174 669)	115 358 (111 095-120 379)
Incremental QALYs relative to no treatment, change in QALYs	Reference	0.90 (0.51-1.37)	1.33 (0.85-1.92)	2.25 (1.94-3.43)	2.31 (1.65-3.14)	2.42 (1.75-3.29)	2.46 (1.81-3.29)
Incremental cost relative to no treatment, change in \$	Reference	22 488 (13 085-31 437)	47 669 (39 024-54 048)	67 392 (55 519-76 854)	117 766 (105 257-127 299)	116 490 (104 305-126 072)	62 101 (49 114-72 058)
ICER relative to no treatment, change in \$/change in QALYs	Reference	24 883 (12 299-47 749)	35 836 (23 827-56 568)	30 001 (21 405-42 019)	50 951 (36 355-70 853)	48 206 (34 956-66 833)	25 291 (17 619-35 576)
Incremental QALYs relative to current care, change in QALYs	-	-	Reference	0.92 (0.51-1.33)	0.98 (0.55-1.41)	1.09 (0.66-1.54)	1.13 (0.69-1.59)
Incremental cost relative to usual care, change in \$	-	-	Reference	19 722 (13 651-24 185)	70 097 (64 063-74 878)	68 821 (62 574-73 859)	14 432 (8396-19 489)
ICER relative to usual care, change in \$/change in QALYs	-	-	Reference	21 528 (12 834-39 629)	71 445 (39 615-79 956)	63 355 (43 454 -108 171)	12 825 (6420-22 755)

BOC = boceprevir; DCV = daclatasvir; HCC = hepatocellular carcinoma; ICER = incremental cost-effectiveness ratio; LDV = ledipasvir; PEG = pegylated interferon; QALY = quality-adjusted life-year; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response.

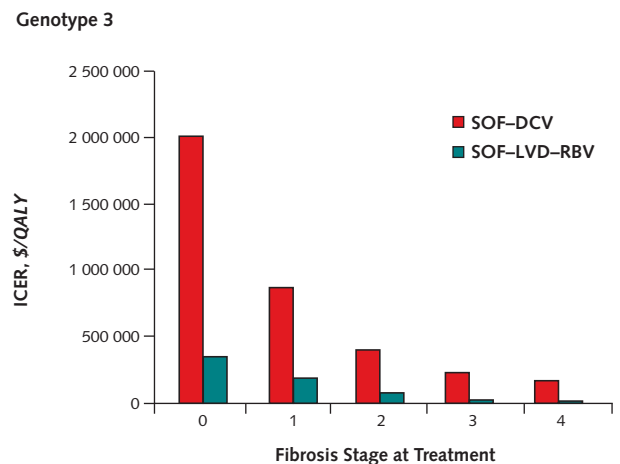
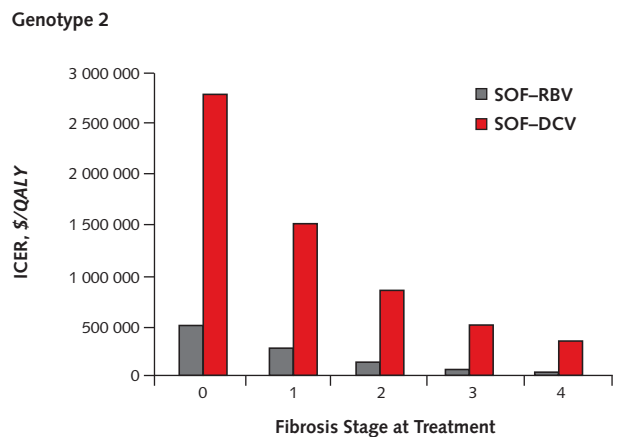
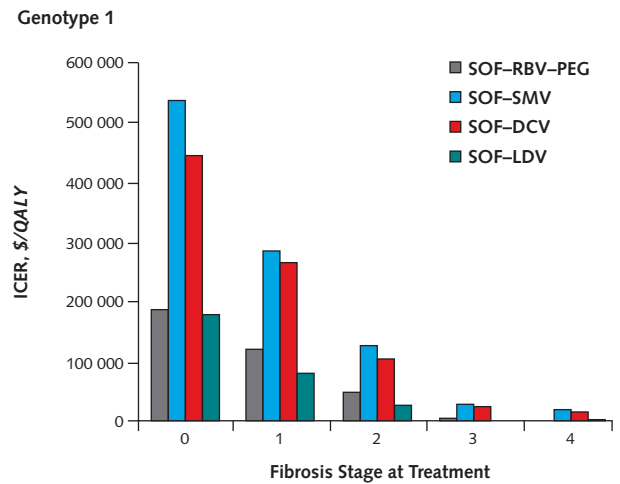
\* Numbers in parentheses are 95% credible intervals, which reflect the results of probabilistic sensitivity analysis. All estimates are over the patients' lifetime.

**Appendix Figure 2.** Incremental cost-effectiveness ratio of treatment strategies versus usual care as a function of SVR rate for genotype 1 (top), 2 (middle), and 3 (bottom).



Usual care for genotype 1 consisted of response-guided triple therapy using boceprevir-RBV-PEG for 28 to 48 wk. Usual care for genotypes 2 and 3 consisted of dual therapy with RBV-PEG for 24 wk. DCV = daclatasvir; LDV = ledipasvir; PEG = pegylated interferon; QALY = quality-adjusted life-year; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response.

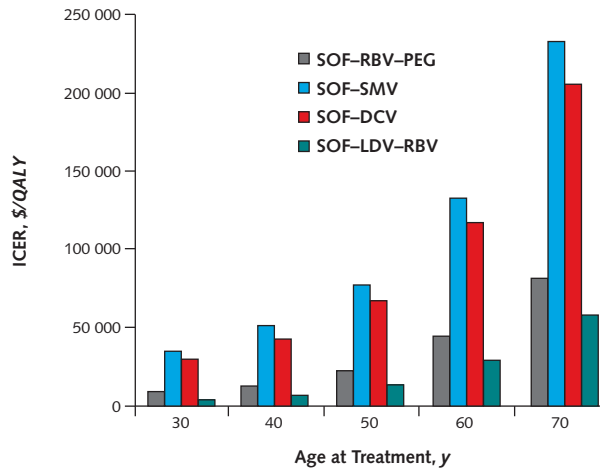
**Appendix Figure 3.** ICERs as a function of baseline fibrosis stage, with results of a 1-way sensitivity analysis for genotypes 1 (top), 2 (middle), and 3 (bottom).



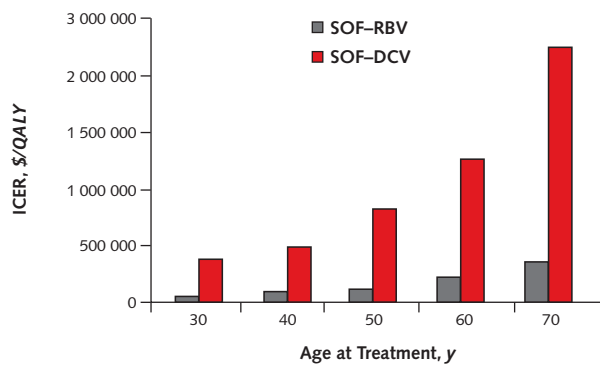
Usual care for genotype 1 consisted of response-guided triple therapy using boceprevir-RBV-PEG for 28 to 48 wk. Usual care for genotypes 2 and 3 consisted of dual therapy with ribavirin-PEG for 24 wk. DCV = daclatasvir; ICER = incremental cost-effectiveness ratio; LDV = ledipasvir; PEG = pegylated interferon; QALY = quality-adjusted life-year; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir.

**Appendix Figure 4.** ICER of treatment strategies versus usual care as a function of age at treatment initiation for genotypes 1 (top), 2 (middle), and 3 (bottom).

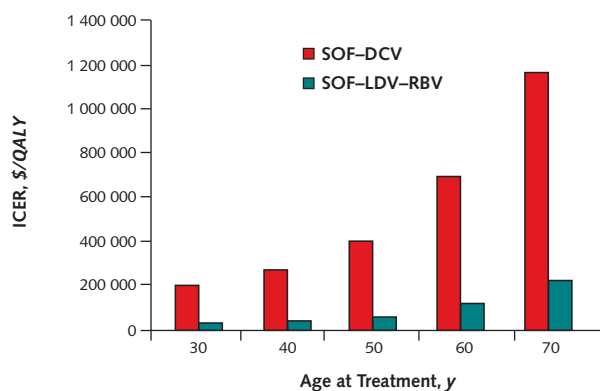
**Genotype 1**



**Genotype 2**

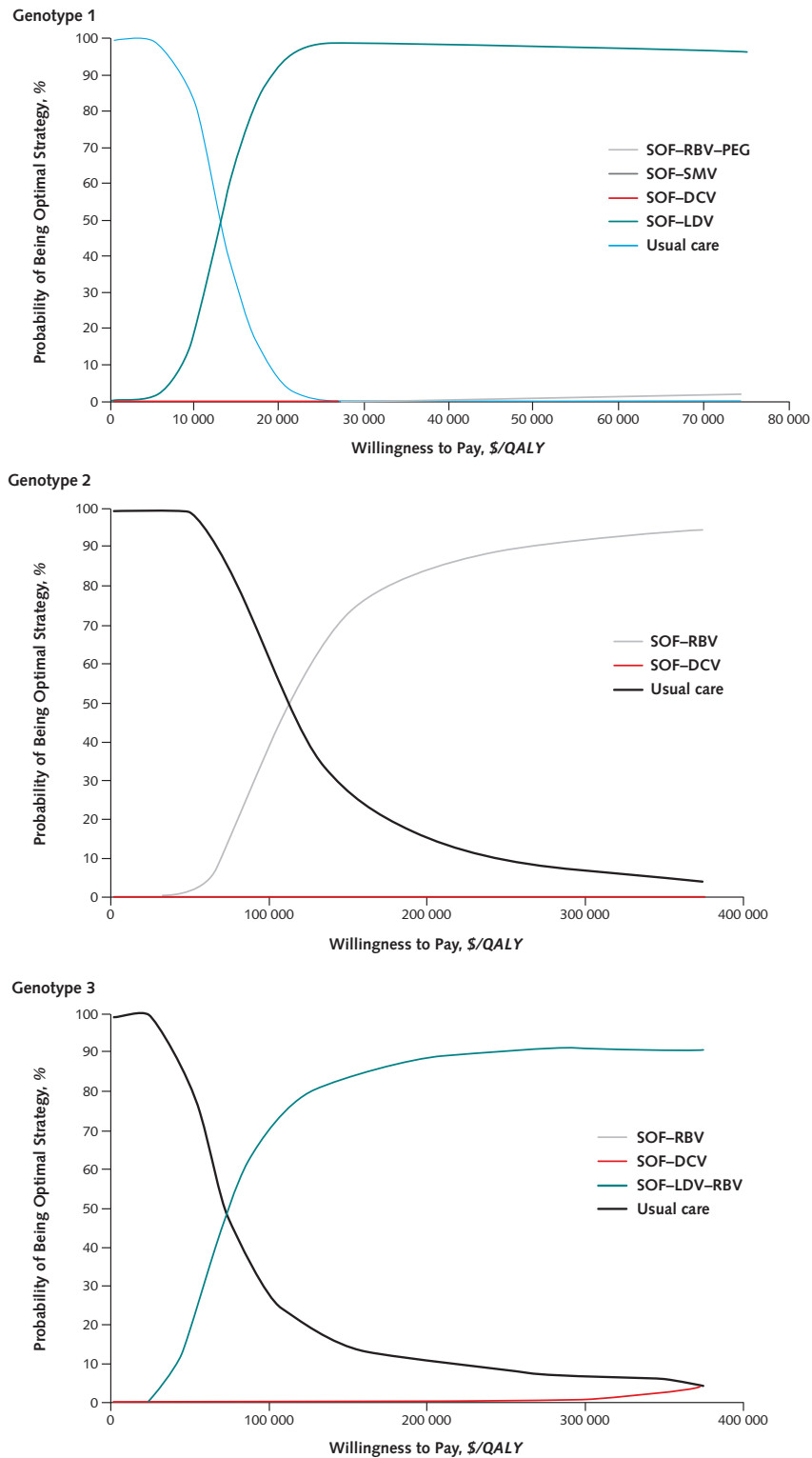


**Genotype 3**



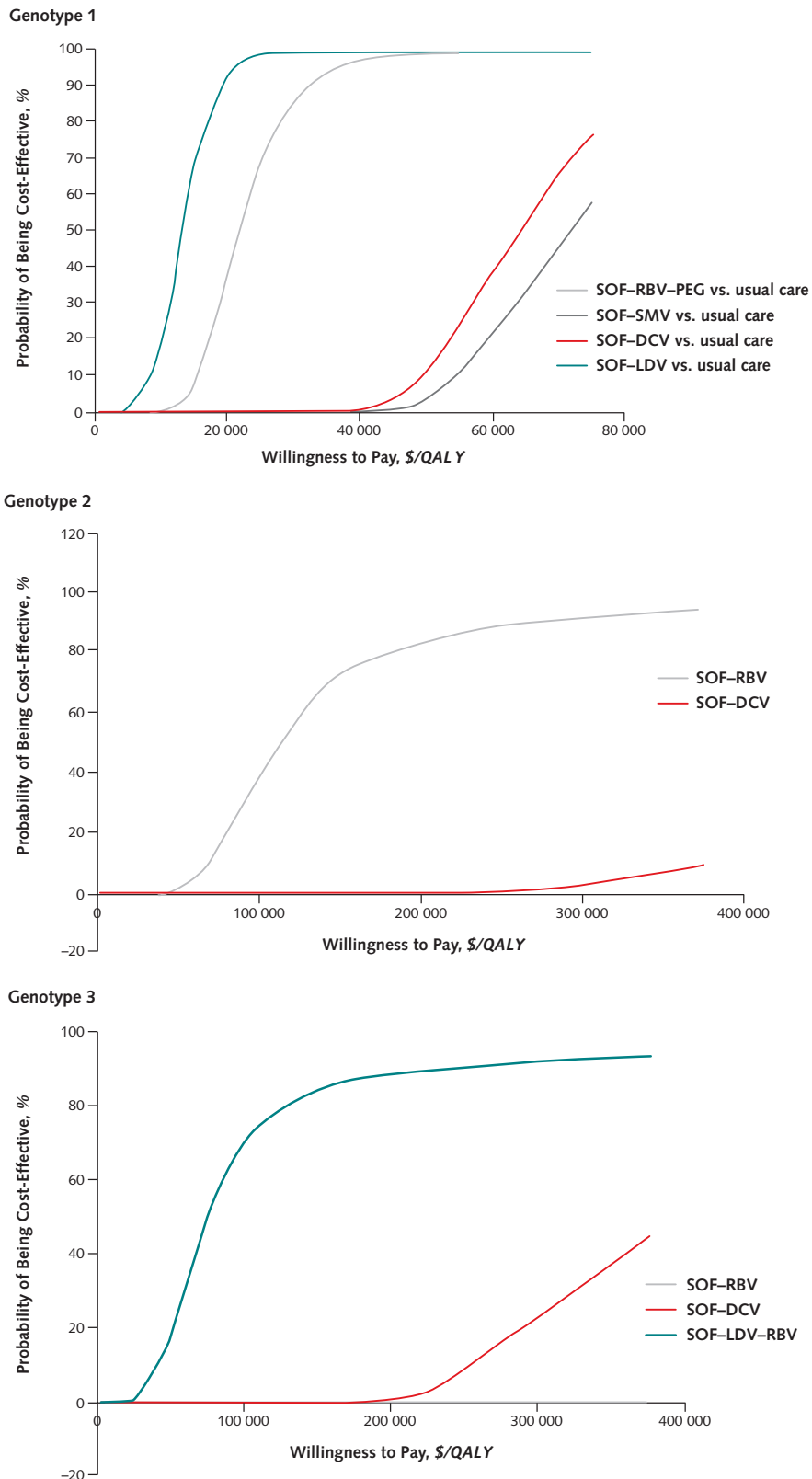
Usual care for genotype 1 consisted of response-guided triple therapy using boceprevir-RBV-PEG for 28 to 48 wk. Usual care for genotypes 2 and 3 consisted of dual therapy with ribavirin-PEG for 24 wk. Because SOF-RBV is a dominated strategy for all ages, it has not been included. DCV = daclatasvir; ICER = incremental cost-effectiveness ratio; LDV = ledipasvir; PEG = pegylated interferon; QALY = quality-adjusted life-year; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir.

**Appendix Figure 5.** Cost-effectiveness acceptability curve showing the optimal choices at various willingness-to-pay thresholds for genotypes 1 (top), 2 (middle), and 3 (bottom).



The plots represent the results of probabilistic sensitivity analyses using a Monte Carlo simulation, and the lines show the percentage of iterations in which each strategy would be optimal at various willingness-to-pay thresholds. Usual care for genotype 1 consisted of response-guided triple therapy using boceprevir-RBV-PEG for 28 to 48 wk. Usual care for genotypes 2 and 3 consisted of dual therapy with RBV-PEG for 24 wk. DCV = daclatasvir; LDV = ledipasvir; PEG = pegylated interferon; QALY = quality-adjusted life-year; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir.

Appendix Figure 6. Results of probabilistic sensitivity analysis.



Cost-effectiveness acceptability curves of treatment strategies vs. usual care. Usual care for genotype 1 consisted of response-guided triple therapy using boceprevir-RBV-PEG for 28 to 48 wk. Usual care for genotypes 2 and 3 consisted of dual therapy with RBV-PEG for 24 wk. DCV = daclatasvir; LDV = ledipasvir; PEG = pegylated interferon; QALY = quality-adjusted life-year; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir.

**Appendix Table 3. Base-Case Results for Treatment Strategies for Genotypes 2 and 3\***

Variable	No Treatment			Genotype 2			Genotype 3			
	Current Care (RBV-PEG)	SOF-RBV	SOF-DCV	Current Care (RBV-PEG)	SOF-RBV	SOF-DCV	Current Care (RBV-PEG)	SOF-RBV	SOF-DCV	SOF-LDV-RBV
<b>Estimated distribution of outcomes, %</b>										
METAVIR stage at end of life										
F0	0.5	9.0	10.4	10.9	10.4	10.4	7.1	7.9	10.1	10.4
F1	4.6	27.0	32.1	33.1	32.1	32.1	22.2	20.7	20.3	32.2
F2	11.2	19.1	19.9	20.3	19.9	19.9	19.1	17.8	20.3	20.5
F3	16.9	15.0	15.1	15.4	15.1	15.1	16.2	16.5	16.1	16.9
F4	30.0	19.8	18.3	18.3	18.6	18.6	21.6	21.8	19.2	17.6
Decompensated cirrhosis	20.6	6.5	2.3	1.1	2.3	2.3	7.2	8.5	1.9	1.1
HCC	9.9	1.9	0.7	0.6	0.7	0.7	4.1	4.1	1.7	0.9
Liver transplant	6.3	1.7	0.9	0.3	0.9	0.9	2.5	2.7	0.7	0.4
Liver-related death	30.7	8.2	2.8	1.8	2.8	2.8	10.8	12.5	3.5	1.8
Patients with SVR	0.5	75.1	90.1	94.6	90.1	90.1	61.1	57.6	86.1	93.2
<b>Cost-effectiveness results</b>										
Life expectancy, y	69.1	71.3	72.1	71.8	72.1	72.1	70.1	70.2	71.6	72.3
QALYs	10.96 (10.02 to 11.80)	11.86 (11.20 to 12.61)	12.37 (11.70 to 13.09)	12.37 (11.70 to 13.09)	12.24 (11.53 to 12.99)	12.24 (11.53 to 12.99)	11.50 (10.90 to 12.22)	11.37 (10.73 to 12.08)	12.16 (11.43 to 12.94)	12.35 (11.68 to 13.07)
Cost, \$	53 257 (42 791 to 67 263)	54 004 (48 633 to 60 897)	109 958 (105 544 to 114 729)	109 958 (105 544 to 114 729)	316 845 (311 645 to 322 857)	316 845 (311 645 to 322 857)	58 323 (52 027 to 65 999)	207 872 (201 623 to 215 794)	317 830 (312 217 to 325 029)	120 464 (115 543 to 125 573)
Incremental QALYs relative to no treatment, change in QALYs	Reference	1.92 (1.32 to 2.67)	2.42 (1.76 to 3.27)	2.42 (1.76 to 3.27)	2.30 (1.58 to 3.07)	2.30 (1.58 to 3.07)	1.56 (1.05 to 2.22)	1.43 (0.93 to 2.01)	2.21 (1.48 to 3.00)	2.40 (1.47 to 3.44)
Incremental cost relative to no treatment, change in \$	Reference	53 955 (48 588 to 60 851)	109 908 (105 499 to 114 685)	109 908 (105 499 to 114 685)	316 795 (311 583 to 322 812)	316 795 (311 583 to 322 812)	5066 (-4342 to 12 670)	154 616 (145 803 to 161 561)	264 573 (252 013 to 274 672)	67 207 (52 745 to 78 049)
ICER relative to no treatment, change in \$/change in QALYs	Reference	28 160 (19 823 to 42 004)	45 344 (33 437 to 62 433)	45 344 (33 437 to 62 433)	137 973 (102 252 to 202 091)	137 973 (102 252 to 202 091)	3256 (-2883 to 8700)	108 443 (77 584 to 164 803)	119 664 (87 044 to 181 878)	27 950 (18 768 to 46 706)
Incremental QALYs relative to usual care, change in QALYs	-	Reference	0.51 (0.09 to 0.94)	0.51 (0.09 to 0.94)	0.38 (-0.10 to 0.86)	0.38 (-0.10 to 0.86)	Reference	-0.13 (-0.53 to 0.25)	0.65 (0.09 to 1.16)	0.85 (-0.06 to 1.71)
Incremental cost relative to usual care, change in \$	-	Reference	55 953 (50 878 to 59 769)	55 953 (50 878 to 59 769)	262 840 (257 326 to 267 722)	262 840 (257 326 to 267 722)	Reference	149 549 (145 381 to 154 820)	259 507 (253 615 to 265 813)	62 141 (53 101 to 70 163)
ICER relative to usual care, change in \$/change in QALYs	-	Reference	110 168 (56 414 to 573 491)	110 168 (56 414 to 573 491)	691 574 (-5085.270 to 6 658 138)	691 574 (-5085.270 to 6 658 138)	Reference	Dominated	396 229 (202 096 to 1 606 541)	73 236 (-269 686 to 394 766)

DCV = daclatasvir; HCC = hepatocellular carcinoma; ICER = incremental cost-effectiveness ratio; LDV = ledipasvir; PEG = pegylated interferon; QALY = quality-adjusted life-year; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response.

\* Numbers in parentheses are 95% credible intervals, which reflect the results of probabilistic sensitivity analysis. All estimates are over the patients' lifetime.