VALUE IN HEALTH 19 (2016) 326–334

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

ISSUE HIGHLIGHTS
Economic Evaluation

Economic and Public Health Impacts of Policies Restricting Access to Hepatitis C Treatment for Medicaid Patients

Alexis P. Chidi, PhD, MSPH[1,2,*], *Cindy L. Bryce, PhD*[3], *Julie M. Donohue, PhD*[3], *Michael J. Fine, MD, MSc*[1,2], *Douglas P. Landsittel, PhD*[1], *Larissa Myaskovsky, PhD*[1,2], *Shari S. Rogal, MD, MPH*[1,2], *Galen E. Switzer, PhD*[1,2], *Allan Tsung, MD*[1,2], *Kenneth J. Smith, MD, MS*[1]

[1]*University of Pittsburgh School of Medicine, Pittsburgh, PA, USA;* [2]*VA Pittsburgh Healthcare System Pittsburgh, PA, USA;*
[3]*University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, USA*

ABSTRACT

Background: Interferon-free hepatitis C treatment regimens are effective but very costly. The cost-effectiveness, budget, and public health impacts of current Medicaid treatment policies restricting treatment to patients with advanced disease remain unknown. **Objectives:** To evaluate the cost-effectiveness of current Medicaid policies restricting hepatitis C treatment to patients with advanced disease compared with a strategy providing unrestricted access to hepatitis C treatment, assess the budget and public health impact of each strategy, and estimate the feasibility and long-term effects of increased access to treatment for patients with hepatitis C. **Methods:** Using a Markov model, we compared two strategies for 45- to 55-year-old Medicaid beneficiaries: 1) Current Practice—only advanced disease is treated before Medicare eligibility and 2) Full Access—both early-stage and advanced disease are treated before Medicare eligibility. Patients could develop progressive fibrosis, cirrhosis, or hepatocellular carcinoma, undergo transplantation, or die each year. Morbidity was reduced after successful treatment. We calculated the incremental cost-effectiveness ratio and compared the costs and public health effects of each strategy from the perspective of Medicare alone as well as the Centers for Medicare & Medicaid Services perspective. We varied model inputs in one-way and probabilistic sensitivity analyses. **Results:** Full Access was less costly and more effective than Current Practice for all cohorts and perspectives, with differences in cost ranging from $5,369 to $11,960 and in effectiveness from 0.82 to 3.01 quality-adjusted life-years. In a probabilistic sensitivity analysis, Full Access was cost saving in 93% of model iterations. Compared with Current Practice, Full Access averted 5,994 hepatocellular carcinoma cases and 121 liver transplants per 100,000 patients. **Conclusions:** Current Medicaid policies restricting hepatitis C treatment to patients with advanced disease are more costly and less effective than unrestricted, full-access strategies. Collaboration between state and federal payers may be needed to realize the full public health impact of recent innovations in hepatitis C treatment.

Keywords: cost-effectiveness, hepatitis C, interferon-free, Medicaid, Medicare.

Introduction

Hepatitis C affects more than 3.2 million patients in the United States and is a common cause of chronic liver disease worldwide [1,2]. Most infected patients develop chronic disease that can remain asymptomatic for decades. However, left untreated, chronic hepatitis C causes progressive hepatic fibrosis, which can result in severe complications. After developing cirrhosis, patients are at risk for hepatocellular carcinoma, may require liver transplantation, and have an increased risk of early mortality [3–5]. Successful treatment can reduce morbidity and improve patients' quality of life [5–7]. In fact, if recent advances in drug regimens are widely implemented, hepatitis C could become a rare disease as early as 2036 [8].

New hepatitis C treatments are highly effective and have few adverse effects, but high costs could limit access to these medications. The preceding generation of interferon-based treatment regimens were poorly tolerated by patients, and required lengthy treatment durations, so many patients have remained untreated [9]. Recently approved interferon-free drug regimens for patients with genotype 1 disease are more than 94% effective in as few as 8 weeks for many patient subgroups, but can cost up

---

Conflict of interest: S. Rogal receives research funding for unrelated projects from Gilead Sciences. The rest of the authors report no potential conflicts of interest.

[*] *Address correspondence to:* Alexis P. Chidi, 3471 Fifth Avenue, Suite 300, Pittsburgh, PA 15213.

E-mail: apc10@pitt.edu.

http://dx.doi.org/10.1016/j.jval.2016.01.010

to $190,000 per patient [10–12]. Despite their high cost, interferon-free regimens have been demonstrated to be cost-effective at thresholds of $50,000 to $100,000 per quality-adjusted life-year (QALY) [13–15].

Resource-constrained government health insurance programs, including Medicaid and Medicare, cover a substantial proportion of US patients with hepatitis C and are heavily impacted by the high prices of these drugs. Most state Medicaid programs restrict treatment of hepatitis C to patients with advanced liver disease because of medication costs [16]. Because hepatitis C is most prevalent in patients aged 45 years and older, many Medicaid patients with early-stage disease may not develop advanced disease or complications until after becoming eligible for Medicare [17,18].

Restrictive hepatitis C treatment policies are likely to reduce short-term costs to state Medicaid programs. However, it is unclear how these policies might shift the financial burden of hepatitis C management to the Medicare program or impact overall costs to the Centers for Medicare & Medicaid Services (CMS). In addition, the public health impact of delaying treatment for early-stage patients until after disease progression remains unknown. Thus, this study evaluated the cost-effectiveness of current Medicaid policies restricting hepatitis C treatment to patients with advanced disease compared with a strategy providing unrestricted access to hepatitis C treatment. We also assessed the budget and public health impact of each strategy and estimated the feasibility and long-term effects of increased access to treatment for patients with hepatitis C.

Methods

Model Structure and Perspective

Using a Markov state-transition model, we conducted cost-effectiveness, budget, and public health impact analyses from the perspectives of 1) the Medicare program alone, which included costs and effects accrued after patients became eligible for Medicare benefits, and 2) CMS, which incorporated costs and effects accrued during the entire study period. We considered lifetime costs and outcomes, used 3% annual discounting (varied in sensitivity analysis), and adjusted all prices to 2015 US dollars using the Consumer Price Index.

Model Cohort

We modeled hypothetical cohorts of 45-, 50-, and 55-year-old treatment-naive and treatment-experienced Medicaid patients diagnosed with genotype 1 hepatitis C. Our selected age groups comprise approximately 95% of the Medicaid hepatitis C population [19]. Our cohorts excluded patients with any history of decompensated cirrhosis, liver transplantation, or HIV coinfection. Chronic hepatitis C disease severity is measured using the Meta-analysis of Histologic Data in Viral Hepatitis (METAVIR) score, which describes five stages of liver fibrosis: F0, no hepatic fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, many septa without cirrhosis; and F4, cirrhosis [20]. We estimated the baseline distribution of METAVIR scores using model-based predictions of the hepatitis C virus (HCV)-infected population in 2014 (Table 1) [8,13].

Natural History Model

We created a Markov model to simulate the natural history and epidemiology of hepatitis C infection (Fig. 1). Patients accrued liver-related treatment and follow-up costs as well as QALYs for their Markov state at the end of each 1-year cycle. Patients could make one state transition each year. Mortality was possible during each model stage; we estimated age-specific, annual all-cause mortality rates using US life tables [21]. Disease progression and excess liver-related mortality occurred according to stage-specific transition probabilities and relative risks of mortality established in previous studies (Table 1).

We grouped patients into three stages of baseline disease severity: early-stage disease (METAVIR F0-F2), advanced fibrosis (METAVIR F3), and compensated cirrhosis (METAVIR F4). Patients with compensated cirrhosis could later develop complications including decompensated cirrhosis, liver transplantation, and hepatocellular carcinoma. Patients with early-stage disease, advanced fibrosis, or compensated cirrhosis could receive hepatitis C treatment. We assumed that after successful treatment, patients with early-stage disease would return to full health and accrue no further hepatitis C infection–related costs. In contrast, patients with advanced fibrosis or cirrhosis would have markedly reduced risks of disease progression, complications, and mortality, but no reduction in follow-up costs after successful treatment (Table 1).

Treatment

We assumed that all patients would be treated with one of two currently available interferon-free hepatitis C drug regimens: a single-dose two-drug combination of sofosbuvir/ledipasvir (SOF/LDV) or a multidose three-drug combination of ombitasvir, paritaprevir, and ritonavir with dasabuvir (3D). At the time of analysis, the American Association for the Study of Liver Diseases recommended both these treatments for patients with genotype 1 hepatitis C (see Appendix Table 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2016.01.010). Because utility data were not available for the 3D regimen at the time of our analysis, we performed our primary analysis using data for SOF/LDV (Table 2) and used estimates for 3D in sensitivity analyses. We estimated the efficacy of each treatment regimen using data from recently published clinical trials [22–30]. In patient subgroups for which several alternative treatment options have demonstrated similar effectiveness, we chose the least costly drug regimen.

We determined SOF/LDV treatment disutility using data from a quality-of-life study conducted alongside recent clinical trials [31]. Because utility data for the 3D and 3D with ribavirin regimens were not available, we used treatment disutility data for the SOF/LDV and SOF/LDV with ribavirin regimens, respectively, in our sensitivity analysis (Table 2).

Costs and Effectiveness

We estimated treatment and follow-up costs for patients with hepatitis C (Table 1). In the base case, we included a 23.1% discount from the national average drug acquisition price for each drug regimen, which is required as part of the Medicaid drug rebate program; we varied drug prices in sensitivity analysis. We used the Medicare physician fee schedule to calculate the costs of on-treatment medical monitoring [32], including a single pretreatment office visit, complete blood cell count, complete metabolic panel, and viral load measurement; monthly office visits, viral load measurements, and metabolic panels during treatment; and a single post-treatment office visit, viral load measurement, and metabolic panel. We assumed that patients using ribavirin-containing regimens were monitored more frequently, with twice-monthly office visits and complete blood cell counts (Table 2).

From the Medicare perspective, costs and QALYs began to accrue upon Medicare eligibility at age 65 years (or earlier for the share eligible due to disability). From the CMS perspective, costs and QALYs accrued throughout the study period. Because Medicare Part D can involve substantial cost sharing for seniors not receiving low- income subsidies, we subtracted expected patient out-of-pocket costs estimated using current Part D coverage rules [33], but assumed that the prescription drug coverage gap

Table 1 – Hepatitis C cohort characteristics, natural history, costs, and utilities.

Description	Base case	Low	High	Distribution	Source
Cohort characteristics, %					
F0-2	0.51	0.38	0.64	Dirichlet	[8,13]
F3	0.21	0.16	0.26	Dirichlet	[8,13]
F4	0.28	0.21	0.35	Dirichlet	[8,13]
Treatment-naive	0.61	0.46	0.76	Beta	[8,13]
Risk of disease progression, %					
F0-2 to F3	0.12	0.11	0.13	Beta	[65]
F3 to F4	0.12	0.09	0.14	Beta	[65]
F3 to HCC	0.01	0	0.03	Beta	[66]
F4 to DC	0.04	0.01	0.04	Beta	[66,67]
F4 to HCC	0.03	0.01	0.08	Beta	[66,68]
DC to HCC	0.07	0.03	0.08	Beta	[69]
DC to transplant	0.03	0.02	0.06	Beta	[70,71]
HCC to transplant	0.04	0	0.14	Beta	[72,73]
Progression after SVR, %					
F3 to HCC	0.007	0.006	0.008	Beta	[5,74]
F4 to DC	0.005	0.002	0.096	Beta	[34,74]
F4 to HCC	0.007	0	0.019	Beta	[34,74,75]
Mortality rates					
Hepatitis C[*]	2.37	1.28	4.38	Lognormal	[76]
Cirrhosis (RR)[†]	2.50	1.23	5.08	Lognormal	[6]
SVR[*]	1.00	–	–	–	Estimate
SVR after F4 (RR)[‡]	0.39	0.14	0.65	Lognormal	[5–7]
DC, %	0.10	0.04	0.21	Beta	[69]
HCC, %	0.43	0.34	0.51	Beta	[67,77]
Transplant year 1, %	0.14	0.06	0.42	Beta	[40,78]
Transplant year 2+, %	0.03	0.02	0.11	Beta	[78]
Annual follow-up costs (2015 US $)					
F0-3	1,357	89	4,072	Gamma	[34–36]
F4	1,409	729	3,342	Gamma	[34–36]
DC	22,338	12,768	39,446	Gamma	[34,35]
HCC	47,885	25,713	74,200	Gamma	[34,35]
Transplant year 1	228,090	165,537	366,183	Gamma	[34,35,37]
Transplant year 2+	38,662	36,998	55,497	Gamma	[34,35]
SVR (F0-2)	0	–	–	–	Estimate
Utilities before SVR					
F0-2	0.85	0.83	0.87	Beta	[39,40]
F3	0.79	0.77	0.81	Beta	[39,40]
F4	0.76	0.67	0.79	Beta	[39,40]
DC	0.69	0.44	0.69	Beta	[34]
HCC	0.67	0.6	0.72	Beta	[34]
Transplant year 1	0.50	0.30	0.80	Beta	[34]
Transplant year 2+	0.77	0.57	0.77	Beta	[34]
Utilities after SVR					
F0-2	0.92	0.90	0.94	Beta	[34]
F3	0.86	0.84	0.88	Beta	[34]
F4	0.83	0.81	0.85	Beta	[34]

DC, decompensated cirrhosis; F0-2, F3, F4, METAVIR stages of hepatic fibrosis; HCC, hepatocellular carcinoma; METAVIR, Meta-analysis of Histologic Data in Viral Hepatitis; RR, relative risk; SVR, sustained virologic response.

[*] Compared with all-cause mortality.

[†] Compared with F0-2.

[‡] Compared with pretreatment state.

(i.e., "donut hole") would not be in place by the time the oldest cohort becomes eligible for Medicare benefits.

We determined annual follow-up costs for each health state using recent estimates for Medicare and managed care patients [34–37], and used age-specific median utility values for healthy patients [38]. We estimated utility weights for each hepatitis C–related health state on the basis of recent comprehensive reviews of the literature [34,39,40]. Finally, we varied all parameters over feasible ranges in sensitivity analyses (Table 1).

Strategies

We compared two strategies for managing hepatitis C infection in Medicaid beneficiaries: 1) *Current Practice*—only patients with advanced fibrosis or cirrhosis are treated for hepatitis C before becoming eligible for Medicare and treatment for patients with early-stage disease is deferred until disease progression or Medicare eligibility; and 2) *Full Access*—patients with early-stage disease, advanced fibrosis, and cirrhosis are treated before

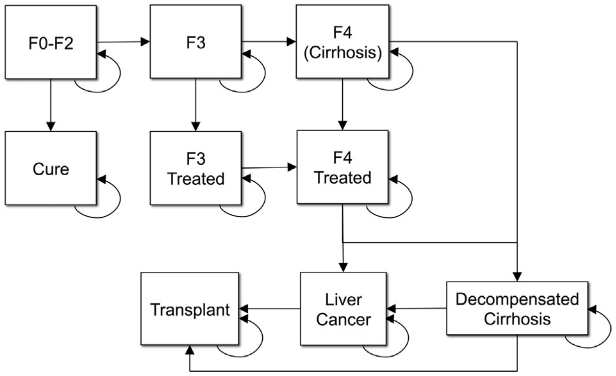

Fig. 1 – Markov state transition model simulating the natural history of hepatitis C. ***Note.*** **Transition probabilities derived from recent population-based studies. F0-2, F3, and F4 represent METAVIR stages of hepatic fibrosis. F3- and F4-treated states involve reduced risks of liver-related morbidity and mortality compared with untreated states. METAVIR, Meta-analysis of Histologic Data in Viral Hepatitis.**

becoming eligible for Medicare benefits (Fig. 2). Because some Medicare Advantage plans are adopting more restrictive treatment strategies, we assumed in the base case that 50% of patients with early-stage disease would be treated on Medicare eligibility (varied 0%–100% in sensitivity analysis).

Assumptions

To perform this analysis, we made a number of simplifying assumptions to systematically bias the model against the Full-Access strategy. We assumed that 1) patients who failed treatment with sofosbuvir- or ombitasvir-based regimens would not be re-treated because guidelines for re-treatment had not yet been developed; 2) only patients 75 years or younger would undergo liver transplantation [41]; 3) Medicare and Medicaid programs would have similar follow-up and treatment costs; 4) patients would become eligible for full Medicare benefits at age 65 years; however, to account for Medicare-Medicaid dual eligibility, we estimated that 14% of Medicaid recipients younger than 65 years would receive Medicare disability benefits while 14% of Medicare beneficiaries older than 65 years received Medicaid benefits [42,43]; and 5) the size of the Medicaid hepatitis C population would remain static over time. We accounted for a one-time Medicaid expansion in a sensitivity analysis.

Cost-Effectiveness Analyses

We completed the analyses separately for cohorts of 45-, 50-, and 55-year-old Medicaid beneficiaries with hepatitis C. In the base case, we calculated the incremental cost-effectiveness ratio (ICER), which reflects the additional investment required to gain an additional QALY. Although a $50,000/QALY threshold has classically been used in cost-effectiveness analyses, ICER thresholds of $100,000/QALY to $150,000/QALY may better reflect contemporary preferences [44,45].

We also conducted sensitivity analyses to determine whether variations in model inputs would change the preferred strategy. First, we varied model inputs individually over a range of plausible values in one-way sensitivity analyses (Table 1). Then, we used Monte-Carlo probabilistic sensitivity analyses in which values are randomly sampled from each variable's probability distribution and repeated over 5000 iterations to determine the likelihood that each strategy is cost-effective [46]. We performed all analyses using TreeAge Pro 2015 (TreeAge Software, Williamstown, MA).

Structural Sensitivity Analyses

Because it is not feasible to treat all Medicaid patients with HCV in a single year, we also conducted structural sensitivity analyses using staged treatment strategies, in which patients would be treated over time. We estimated that 450,000 patients with genotype 1 hepatitis C are currently receiving Medicaid benefits, and up to 600,000 may be enrolled if Medicaid expansion is widely adopted [17,19,47–50].

Table 2 – Hepatitis C treatment parameters.

Parameter	Base case	Low	High	Distribution	Source
Treatment efficacy					
SOF/LDV × 8 wk	0.94	0.90	0.97	Beta	[22]
SOF/LDV × 12 wk (naive)	0.96	0.92	1.00	Beta	[22,23]
SOF/LDV × 12 wk (naive F4)	0.97	0.84	1.00	Beta	[23]
SOF/LDV × 12 wk (experienced)	0.95	0.89	0.99	Beta	[24]
SOF/LDV/RBV × 12 wk (F4)	0.88	0.72	0.92	Beta	[24,25]
Treatment disutilities					
SOF/LDV × 8 wk	0.03	−0.19	0.25	Normal	[31]
SOF/LDV × 12 wk	0.04	−0.20	0.28	Normal	[31]
SOF/LDV/RBV × 12 wk	−0.02	−0.30	0.26	Normal	[31]
Drug costs ($) (weekly)					
SOF/LDV	5874	2500	7875	Gamma	NADAC
Ribavirin	152.78	114.59	190.98	Gamma	[34]
Medical monitoring costs ($) (each, ±25%)					
Office visits (CPT 99213)	72.94	51.13	79.69	Gamma	MPFS
Complete blood cell count	10.58	8.81	14.30	Gamma	MPFS
Complete metabolic panel	14.37	11.51	19.43	Gamma	MPFS
Quantitative HCV PCR	58.29	38.61	78.77	Gamma	MPFS

AWP, average wholesale price; CPT, Current Procedural Terminology, Fourth Edition; HCV, hepatitis C; MPFS, Medicare Physician Fee Schedule 2015; NADAC, National Average Drug Acquisition Cost; PCR, polymerase chain reaction; SOF/LDV, sofosbuvir/ledipasvir; 3D, ombitasvir, ritonavir, and paritaprevir with dasabuvir.

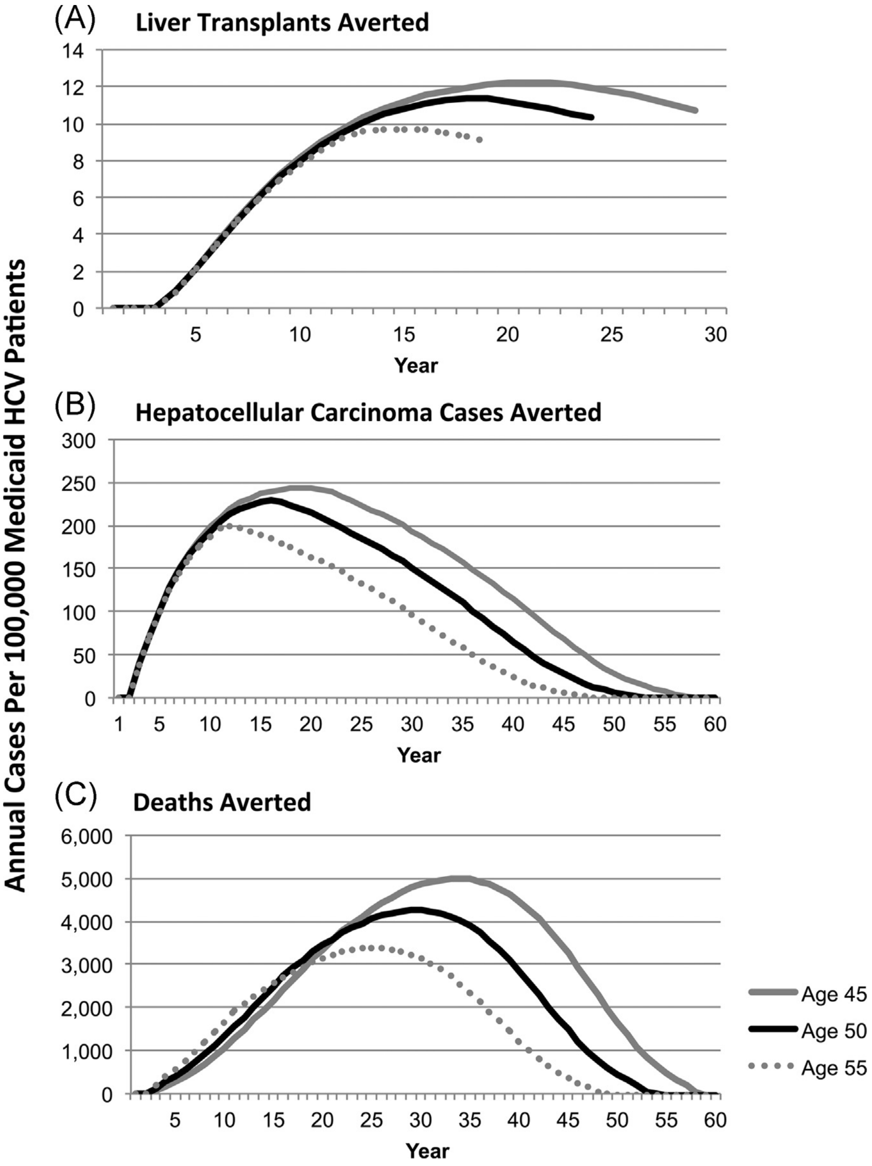

Fig. 2 – Annual public health impact of unrestricted vs. restricted access to hepatitis C treatment among Medicaid beneficiaries. Estimates of: (A) Liver transplants averted, (B) hepatocellular carcinoma cases Averted, and (C) deaths averted per 100,000 Medicaid patients with HCV. HCV, hepatitis C virus.

We also estimated treatment capacity for each strategy. On the basis of total Medicaid hepatitis C drug expenditures in 2014 and previous reports of treatment capacity, we estimated that approximately 30,000 Medicaid patients with hepatitis C could be treated in a given year [51,52]. Because more patients are likely to be treated each year under the Full-Access strategy, we also modeled an expanded Full-Access strategy with an annual treatment capacity of 40,000 patients. Recent developments suggest that increased treatment capacity is likely to be feasible because new drug regimens are now 24 to 36 weeks shorter in duration than interferon-based regimens, allowing more patients to be treated by the same number of physicians in any given year. In addition, a recent study demonstrated that primary care providers can effectively administer hepatitis C treatment in uncomplicated cases [53]. If this practice were widely adopted in the United States, then a much larger physician workforce would be available to treat early-stage patients with hepatitis C. To derive approximate annual treatment probabilities, we estimated that 13% of early-stage patients die or progress each year, whereas the number of patients with advanced-stage disease is reduced by approximately 1% each year, accounting for entry, progression, and death, based on data from our natural history model (see Appendix Table 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2016.01.010). In the Current Practice strategy, treatment would be offered to early-stage patients only after all patients with advanced fibrosis or cirrhosis have been treated. In Full-Access strategies, treatment would be equally allocated across fibrosis stages each year.

Budget and Public Health Impact Analyses

Finally, we compared the budget and public health impact of each treatment strategy. Using a Markov cohort analysis, which describes the costs and utilities associated with each Markov state during each model year, we estimated and compared cost estimates as well as adverse health outcomes for each strategy.

Table 3 – Cost-effectiveness of restricted access to hepatitis C treatment: Base-case results.

Strategy	Medicare perspective			CMS perspective		
	Costs ($)	QALYs	ICER ($/QALY)	Costs ($)	QALYs	ICER ($/QALY)
45-y-old cohort						
Full Access	20,196	5.31		93,151	17.14	
Current Practice	27,707	4.50	Dominated	104,426	14.13	Dominated
50-y-old cohort						
Full Access	21,410	6.31		90,524	15.79	
Current Practice	30,610	**5.47**	Dominated	98,527	13.06	Dominated
55-y-old cohort						
Full Access	22,778	7.58		87,543	14.36	
Current Practice	34,738	6.76	Dominated	92,912	12.05	Dominated

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

We compared the annual and cumulative costs for both treatment strategies in our base-case analysis. Next, we used the model to estimate the annual and cumulative number of cases of adverse health outcomes such as hepatocellular carcinoma, liver transplantation, and mortality, per 100,000 Medicaid recipients.

Results

Base-Case Analyses

In the base case, the Full-Access strategy was cost saving and more effective compared with the Current Practice strategy for all age cohorts from the Medicare perspective (Table 3). For the 50-year-old cohort, which represented the average Medicaid patient with hepatitis C, the Current Practice strategy ($30,610, 5.47 QALYs) cost an additional $9,200 per patient and yielded 0.84 fewer QALYs compared with the Full-Access strategy ($21,410, 6.31 QALYs). Cost savings for the Full-Access strategy increased with cohort age.

From the CMS perspective, the Full-Access strategy was also cost saving for each age cohort, but to a lesser degree. Compared with the Full-Access strategy ($90,524, 15.79 QALYs), the Current Practice strategy cost an additional $8,003 per patient and yielded 2.73 fewer QALYs ($98,527, 13.06 QALYS) for the 50-year-old cohort (Table 3). The Full-Access strategy was more cost saving for younger cohorts from the CMS perspective.

Sensitivity Analyses

In one-way sensitivity analyses from the Medicare perspective, the Full-Access strategy was cost saving for all age cohorts regardless of variations in any individual model input. From the CMS perspective, variations in follow-up costs for patients with early-stage disease and in the discount rate impacted the ICER differently in each age cohort. The Full-Access strategy remained cost saving as long as the cost of follow-up for early-stage patients was more than approximately $200 per year in the 45-year-old cohort, $350 per year in the 50-year-old cohort, and $600 per year in the 55-year-old cohort. In addition, the Full-Access strategy was cost saving for discount rates below 5% to 6%, depending on the age of the cohort. The Full-Access strategy was cost saving over the range of plausible values for all other model inputs.

In probabilistic sensitivity analysis, the Full-Access strategy was cost-effective in 100% of iterations from the Medicare perspective at all willingness-to-pay thresholds. From the CMS perspective, the Full-Access strategy was cost-effective in 93% of iterations at the cost-saving threshold of $0/QALY and in 100% of iterations at $4500/QALY. Including the three-drug regimen instead of SOF/LDV did not change the preferred strategy from either perspective. In our structural sensitivity analysis, the staged Full-Access strategy was cost saving compared with the staged Current Practice strategy for all age cohorts, regardless of annual treatment capacity or the size of the Medicaid hepatitis C population (Table 4).

Budget and Public Health Impact Analyses

Our budget impact analyses revealed that, from the CMS perspective, the Full-Access strategy became cost saving compared with the Current Practice strategy after 13 to 16 years, depending on cohort age. By the end of the study period, the Full-Access strategy saved $10,340 per patient for the 45-year-old cohort, $8,148 for 50-year-olds, and $5,695 for 55-year-old patients. With staged treatment strategies, Full Access became cost saving after 9 years for each age cohort. In the worst-case scenario, with 600,000 hepatitis C patients and 30,000 treated per year, the Full-Access strategy saved $3,197 to $3,568 per patient by the end of the study period, depending on the age of the cohort. For a cohort of 450,000 50-year-old Medicaid patients with hepatitis C, treating 30,000 patients per year using interferon-free regimens would cost Medicaid programs an average of $4,746 per beneficiary annually with the Current Practice strategy and $4,568 per beneficiary annually with the Full-Access strategy. If a total of 600,000 patients required treatment, costs would decrease to $4,640 per beneficiary with Current Practice and $4,428 per beneficiary with Full Access. In comparison, no treatment would cost $2309 per beneficiary.

The public health impact analysis demonstrated that for every 100,000 50-year-old Medicaid beneficiaries, the Full-Access strategy could avert approximately 5,994 cases of hepatocellular carcinoma and 121 liver transplants compared with the Current Practice strategy. The number of cases averted varied over time for each age cohort (Fig. 2).

Conclusions

This cost-effectiveness analysis revealed that for current Medicaid beneficiaries, unrestricted access to hepatitis C treatment is cost saving compared with the current policy restricting treatment to only patients with advanced liver disease. The increased short-term costs of unrestricted access to care can be offset by savings from reduced complications in 9 to 16 years, depending on the treatment strategy and the age of the cohort. Furthermore, increased access to treatment could avert numerous future cases of hepatocellular carcinoma, reduce the need for liver transplantation, and prevent early mortality.

Table 4 – Cost-effectiveness of staged treatment strategies for Medicaid patients with hepatitis C, by number of Medicaid beneficiaries with hepatitis C.

Strategy	450,000 patients with HCV		600,000 patients with HCV	
	Costs ($)	QALYs	Costs ($)	QALYs
45-y-old cohort				
Expanded Full Access	97,138	14.73	97,462	14.20
Full Access	97,462	14.20	97,541	13.64
Current Practice	100,608	14.08	100,833	13.55
50-y-old cohort				
Full Access	92,657	12.98	92,220	12.45
Expanded Full Access	92,775	13.48	92,657	12.98
Current Practice	95,861	12.86	95,601	12.36
55-y-old cohort				
Full Access	86,841	11.68	85,542	11.18
Expanded Full Access	87,778	12.15	86,841	11.68
Current Practice	90,344	11.56	89,190	11.09

Note. Population size estimates reflect current Medicaid HCV population & potential increase in prevalence due to Medicaid expansion. Current Practice and Full Access, 30,000 patients treated per year; Expanded Full Access, 40,000 patients treated per year.
HCV, hepatitis C virus; QALYs, quality-adjusted life-years.

We demonstrated that the Full-Access strategy led to long-term cost savings compared with the more restrictive Current Practice strategy. In fact, under ideal circumstances, the total savings could exceed $3.5 billion for the 450,000 Medicaid beneficiaries with hepatitis C. This is because under both strategies, all patients will ultimately be treated unless they decompensate or die before becoming eligible. An open- access strategy would lead to treatment earlier in the natural history of the disease, substantially reducing follow-up costs for patients with early-stage disease. This interpretation is supported by the results of our sensitivity analysis, which demonstrated that the Full-Access strategy is cost saving only if annual follow-up costs for early-stage patients exceed $600, meaning that it is economically advantageous to avert these costs. In addition, open access to treatment would reduce the number of early-stage patients who progress to advanced fibrosis or cirrhosis before being treated. This is important because even after successful treatment, patients with advanced disease still have high follow-up costs and a small risk of developing costly complications, while successfully treated early-stage patients have similar outcomes to their uninfected age-matched peers. Although the overall budget impact is considerable, we demonstrate that the cost to Medicaid of managing hepatitis C with interferon-free regimens is less than $5000 per capita annually regardless of treatment strategy. This is significantly less than the costs to Medicaid of managing many other major diseases, from respiratory illnesses ($8,100 per capita annually) to diabetes ($13,500 per capita annually) [54,55].

Our results were robust to variations in most model inputs. In sensitivity analyses, the Full-Access strategy was no longer cost saving for very high discount rates ($\geq$5%) or very low follow-up costs for early-stage patients (<$600), both of which are unlikely. Cost-effectiveness guidelines suggest that a 3% discount rate is likely to be appropriate as the Office of Management and Budget recently suggested that a 3.4% nominal 30-year interest rate should be used for cost-effectiveness analyses [56,57]. Similarly, most studies suggest that costs of follow-up for early-stage patients with hepatitis C are much higher than $600. Recently, the rate of hospitalizations for patients with early-stage and advanced hepatitis C has increased, which suggests that the costs of managing these patients are likely to be increasing as well [58].

Because the assumptions made were generally biased against the Full-Access strategy, our estimates are likely to be conservative. The Full-Access strategy was cost saving even if there was no associated increase in treatment capacity. In reality, doubling the pool of eligible patients is likely to increase the absolute number of patients seeking treatment, bounded only by physician availability, patients' knowledge of their disease status, and medical eligibility for treatment. Finally, we assumed that drug prices would be similar for Medicare and Medicaid. However, many state Medicaid programs are negotiating dramatic price discounts for hepatitis C treatment regimens, which could reduce the total cost of the Full-Access strategy [59]. Meanwhile, because the Medicare program cannot negotiate drug prices, the costs of waiting to treat patients after Medicare eligibility are likely to be higher than our estimates, which were based on Medicaid prices.

Our results are consistent with those of recent studies evaluating the impact of novel interferon-free treatment regimens, demonstrating that novel interferon-free drug regimens are cost-effective for many patient subgroups [13,15]. One study in particular demonstrated that the SOF/LDV regimen could be cost saving compared with the previous standard of care if treatment was substantially discounted, but did not evaluate the effects of restrictive versus inclusive treatment strategies [15]. In addition, the results of our public health impact analysis are consistent with findings from Kabiri et al. [8], who also demonstrated that increased access to hepatitis C treatment could result in substantial long-term reductions in morbidity and mortality. This study addresses the dilemma of determining which patients with hepatitis C should be treated first, which has been highlighted in numerous recent editorials [16,60,61]. Here, we offer empiric evidence to inform this debate and demonstrate that, from a government payer perspective, allowing access to treatment for early-stage patients may be the less costly and more effective long-term strategy.

Our analysis is interesting in light of current events in public health. For example, the US Preventive Services Task Force recently recommended birth cohort screening for hepatitis C for adults born between 1945 and 1965 [62]. The analysis demonstrating that screening is cost-effective assumed that patients would be treated after disease was identified, albeit with older drug regimens [63]. It will become important to consider the ethical and economic implications if positive birth cohort screens are not paired with treatment initiation. In addition, although the prevalence is highest among patients aged 45 years and older, the incidence of hepatitis C has recently been rising at an alarming rate among younger injection drug users [64]. Although our analysis focused on older cohorts, we demonstrate that Full Access is increasingly cost saving for younger patients, who would live with the disease for a longer period of time. Treating these patients while they have early-stage disease would reduce the high costs of disease management and potential complications that are likely to occur if treatment is deferred until disease progression. Treating younger patients may also curb the spread of the disease and reduce the duration of the epidemic.

This study has some limitations that must be acknowledged. First, analytic methods that directly account for resource constraints may provide more precise estimates. However, because our assumptions biased the model against the Full-Access strategy, the conclusions are likely to be similar. Second, we estimated treatment efficacy using clinical trial data, which may overestimate real-word effectiveness. Third, some Medicaid managed care plans may receive smaller drug discounts than those mandated by the Medicaid drug rebate program. To account for this, we varied drug prices widely in sensitivity analysis. Finally, our model only included liver-related costs and did not account for potential increases in cumulative health care costs associated with reduced early mortality. This is beyond the scope of this analysis but is an interesting topic for future study.

In conclusion, using cost-effectiveness analyses, we found that current Medicaid policies restricting hepatitis C treatment to patients with advanced disease are more costly and less effective than strategies with unrestricted access to treatment for patients with early-stage and advanced disease. Although our results provide empiric support for providing open access to treatment for hepatitis C, additional factors, including the size of the physician workforce and budgetary limitations, must also be considered. This study also highlights that in a multipayer health care system, efforts to minimize costs for individual payers can result in cost shifting and economic efficiency for the system as a whole. In light of this, collaborative efforts between state and federal payers may be needed to realize the full public health impact of recent advances in hepatitis C therapy.

Source of financial support: A.P.C. was supported by the National Institutes of Health (grant no. TL1TR000145).

Supplementary Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2013.02.008 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

REFERENCES

[1] Mohd Hanafiah K, Groeger J, Flaxman AD, et al. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology 2013;57:1333–42.

[2] Chak E, Talal AH, Sherman KE, et al. Hepatitis C virus infection in USA: an estimate of true prevalence. Liver Int 2011;31:1090–101.

[3] Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology 2015;148:547–55.

[4] Davis GL, Albright JE, Cook SF, et al. Projecting future complications of chronic hepatitis C in the United States. Liver Transplant 2003;9:331–8.

[5] Butt AA, Wang X, Moore CG. Effect of hepatitis C virus and its treatment on survival. Hepatology 2009;50:387–92.

[6] Dieperink E, Pocha C, Thuras P, et al. All-cause mortality and liver-related outcomes following successful antiviral treatment for chronic hepatitis C. Dig Dis Sci 2014;59:872–80.

[7] van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012;308:2584–93.

[8] Kabiri M, Jazwinski AB, Roberts MS, et al. The changing burden of hepatitis C virus infection in the United States: model-based predictions. Ann Intern Med 2014;161:170–80.

[9] Holmberg SD, Spradling PR, Moorman AC, et al. Hepatitis C in the United States. New Engl J Med 2013;368:1859–61.

[10] Liang TJ, Ghany MG. Therapy of hepatitis C—back to the future. New Engl J Med 2014;370:2043–7.

[11] A 4-drug combination (Viekira Pak) for hepatitis C. Med Lett Drugs Ther 2015;57:15–7.

[12] A combination of ledipasvir and sofosbuvir (Harvoni) for hepatitis C. Med Lett Drugs Ther 2014;56:111–2.

[13] Chhatwal J, Kanwal F, Roberts MS, et al. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. Ann Intern Med 2015;162:397–406.

[14] Chidi AP, Rogal S, Bryce CL, et al. Cost-effectiveness of new antiviral regimens for treatment-naive US veterans with hepatitis C. Hepatology 2016;63:428–36.

[15] Najafzadeh M, Andersson K, Shrank WH, et al. Cost-effectiveness of novel regimens for the treatment of hepatitis C virus. Ann Intern Med 2015;162:407–19.

[16] Haque M, Zariat A. Treatment strategy for hepatitis C: a dilemma for the payers and the providers. Am J Gastroenterol 2014;109:1953–4.

[17] 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;160:293–300.

[18] Neuman T, Hoadley J, Cubanski J. The cost of a cure: Medicare's role in treating hepatitis C. Health Affairs Blog.

[19] Centers for Disease Control and Prevention, National Center for Health Statistics. National Health and Nutrition Examination Survey Data. Hyattsville, MD: Centers for Disease Control and Prevention, 2012. Available from: http://wwwn.cdc.gov/Nchs/Nhanes/Search/nhanes11_12.aspx. [Accessed January 12, 2016].

[20] Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology 1996;24:289–93.

[21] Arias E. United States Life Tables, 2009. National Vital Statistics Reports. Hyattsville, MD: National Center for Health Statistics, 2014.

[22] Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. New Engl J Med 2014;370:1879–88: Available from: http://wwwn.cdc.gov/Nchs/Nhanes/Search/nhanes11_12.aspx. [Accessed January 12, 2016]..

[23] Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. New Engl J Med 2014;370:1889–98.

[24] Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. New Engl J Med 2014;370:1483–93.

[25] Lawitz E, Poordad FF, Pang PS, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. Lancet 2014;383:515–23.

[26] Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. New Engl J Med 2014;370:1604–14.

[27] Andreone P, Colombo MG, Enejosa JV, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. Gastroenterology 2014;147:359–65. e1.

[28] Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. New Engl J Med 2014;370:1594–603.

[29] Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. New Engl J Med 2014;370:1983–92.

[30] Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. New Engl J Med 2014;370:1973–82.

[31] Younossi ZM, Stepanova M, Marcellin P, et al. Treatment with ledipasvir and sofosbuvir improves patient-reported outcomes: results from the Ion-1, 2 and 3 clinical trials. Hepatology 2015;61:1798–808.

[32] Centers for Medicare and Medicaid Services. Medicare Physician Fee Schedule Search. US Department of Health & Human Services. 2015. Available from: https://www.cms.gov/apps/physician-fee-schedule/search/search-criteria.aspx. [Accessed July 23, 2015]

[33] Centers for Medicare and Medicaid Services. Closing the Coverage Gap —Medicare Prescription Drugs Are Becoming More Affordable; CMS Product No. 11493. US Department of Health & Human Services. Available from: https://www.medicare.gov/Pubs/pdf/11493.pdf. 2015 [Accessed July 2, 2015].

[34] Coffin PO, Scott JD, Golden MR, et al. Cost-effectiveness and population outcomes of general population screening for hepatitis C. Clin Infect Dis 2012;54:1259–71.

[35] McAdam-Marx C, McGarry LJ, Hane CA, et al. All-cause and incremental per patient per year cost associated with chronic hepatitis C virus and associated liver complications in the United States: a managed care perspective. J Manag Care Pharm 2011;17:531–46.

[36] Younossi ZM, Singer ME, Mir HM, et al. Impact of interferon free regimens on clinical and cost outcomes for chronic hepatitis C genotype 1 patients. J Hepatol 2014;60:530–7.

[37] Schnitzler MA, Skeans MA, Axelrod DA, et al. OPTN/SRTR 2013 Annual Data Report: economics. Am J Transplant 2015;15(Suppl. 2):1–24.

[38] Gold MR, Franks P, McCoy KI, et al. Toward consistency in cost-utility analyses: using national measures to create condition-specific values. Med Care 1998;36:778–92.

[39] Thein HH, Krahn M, Kaldor JM, et al. Estimation of utilities for chronic hepatitis C from SF-36 scores. Am J Gastroenterol 2005;100:643–51.

[40] 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;60:37–45.

[41] Kim WR, Stock PG, Smith JM, et al. OPTN/SRTR 2011 Annual Data Report: liver. Am J Transplant 2013;13(Suppl. 1):73–102.

[42] Medicare-Medicaid Coordination Office, Centers for Medicare & Medicaid Services. Medicare-Medicaid Dual Enrollment from 2006 through 2013. US Department of Health & Human Services. 2014. Available from: https://www.cms.gov/Medicare-Medicaid-Coordination/Medicare-and-Medicaid-Coordination/Medicare-Medicaid-Coordination-Office/Downloads/DualEnrollment20062013.pdf. [Accessed June 25, 2015].

[43] Office of the Actuary, Centers for Medicare & Medicaid Services. Actuarial Report on the Financial Outlook for Medicaid. US Department of Health & Human Services, 2013. Available from: https://www.cms.gov/Medicare-Medicaid-Coordination/Medicare-and-Medicaid-Coordination/Medicare-Medicaid-Coordination-Office/Downloads/DualEnrollment20062013.pdf. [Accessed July 2, 2015].

[44] Braithwaite RS, Meltzer DO, King JT Jr, et al. What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule? Med Care 2008;46:349–56.

[45] Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness–the curious resilience of the $50,000-per-QALY threshold. New Engl J Med 2014;371:796–7.

[46] Doubilet P, Begg CB, Weinstein MC, et al. Probabilistic sensitivity analysis using Monte Carlo simulation: a practical approach. Med Decis Making 1985;5:157–77.

[47] Stepanova M, Younossi ZM. Interferon-free regimens for chronic hepatitis C: barriers due to treatment candidacy and insurance coverage. Dig Dis Sci 2015;60:3248–51.

[48] Kaiser Family Foundation. The Cost of Not Expanding Medicaid. Report #8457. 2013. Available from: https://www.cms.gov/Medicare-Medicaid-Coordination/Medicare-and-Medicaid-Coordination/Medicare-Medicaid-Coordination-Office/Downloads/DualEnrollment20062013.pdf. [Accessed 6/25/2015].

[49] Kaiser Family Foundation. Medicaid expansion under the Affordable Care Act. JAMA 2013;309: 1219–1219.

[50] Buettgens M, Holahan J, Recht H. Medicaid Expansion, Health Coverage, and Spending: An Update for the 21 States That Have Not Expanded Eligibility. Kaiser Family Foundation 2015: Available from: http://files.kff.org/attachment/issue-brief-medicaid-expansion-health-coverage-and-spending-an-update-for-the-21-states-that-have-not-expanded-eligibility. [Accessed September 2, 2015].

[51] Volk ML, Tocco R, Saini S, et al. Public health impact of antiviral therapy for hepatitis C in the United States. Hepatology 2009;50:1750–5.

[52] Centers for Medicare & Medicaid Services. 2014 National Summary State Drug Utilization. US Department of Health & Human Services. 2014. Available from: http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Prescription-Drugs/Downloads/Rx-By-State/NA/NAUTIL14.zip. [Accessed June 1, 2015].

[53] Arora S, Thornton K, Murata G, et al. Outcomes of treatment for hepatitis C virus infection by primary care providers. New Engl J Med 2011;364:2199–207.

[54] Kaiser Family Foundation. The role of Medicaid for people with respiratory disease. 2012. Available from: https://kaiserfamilyfoundation.files.wordpress.com/2013/01/8383_rd.pdf. [Accessed January 2, 2016].

[55] Kaiser Family Foundation. The role of Medicaid for people with diabetes. 2012. Available from: https://kaiserfamilyfoundation.files.wordpress.com/2013/01/8383_d.pdf. [Accessed January 2, 2016].

[56] Office of Management and Budget. Appendix C. Discount Rates for Cost-Effectiveness, Lease Purchase, and Related Analyses. OMB Circular No. A-94. Revised December 2014 ed. Available from: http://www.whitehouse.gov/omb/circulars_a094/a94_appx-c/. [Accessed June 11, 2015]

[57] Gold MR. Cost-Effectiveness in Health and Medicine. New York: Oxford University Press, 1996.

[58] Xu F, Tong X, Leidner AJ. Hospitalizations and costs associated with hepatitis C and advanced liver disease continue to increase. Health Aff (Millwood) 2014;33:1728–35.

[59] Loftus P. States work to strike deals for hep C drug discounts. Wall Street J.

[60] Etzion O, Ghany MG. A cure for the high cost of hepatitis C virus treatment. Ann Intern Med 2015;162:660–1.

[61] Ghany MG. The ongoing debate of who to treat for chronic hepatitis C virus. JAMA Intern Med 2015;175:169–70.

[62] U.S. Preventive Services Taskforce. Final Recommendation Statement: Hepatitis C: Screening. May 2015. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/hepatitis-c-screening. [Accessed July 15, 2015].

[63] 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;156:263–70.

[64] Zibbell JE, Iqbal K, Patel RC. Centers for Disease Control and Prevention. Increases in hepatitis C virus infection related to injection drug use among persons aged ≤30 years—Kentucky, Tennessee, Virginia, and West Virginia, 2006–2012. MMWR Morb Mortal Wkly Rep 2015;64:453–8.

[65] Thein HH, Yi Q, Dore GJ, et al. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology 2008;48:418–31.

[66] 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;54:396–405.

[67] 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;112:463–72.

[68] Alazawi W, Cunningham M, Dearden J, et al. Systematic review: outcome of compensated cirrhosis due to chronic hepatitis C infection. Aliment Pharmacol Therapeut 2010;32:344–55.

[69] Planas R, Balleste B, Alvarez MA, et al. Natural history of decompensated hepatitis C virus-related cirrhosis: a study of 200 patients. J Hepatol 2004;40:823–30.

[70] Thuluvath PJ, Guidinger MK, Fung JJ, et al. Liver transplantation in the United States, 1999–2008. Am J Transplant 2010;10:1003–19.

[71] Davis GL, Alter MJ, El-Serag H, et al. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology 2010;138:513–21, 521. e1-6.

[72] Lang K, Danchenko N, Gondek K, et al. The burden of illness associated with hepatocellular carcinoma in the United States. J Hepatol 2009;50:89–99.

[73] Saab S, Hunt DR, Stone MA, et al. Timing of hepatitis C antiviral therapy in patients with advanced liver disease: a decision analysis model. Liver Transplant 2010;16:748–59.

[74] Morgan TR, Ghany MG, Kim HY, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology 2010;52:833–44.

[75] Smith BD1, Morgan RL, Beckett GA. 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;61:1–32.

[76] 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;53:150–7.

[77] Jain A, Reyes J, Kashyap R, et al. Long-term survival after liver transplantation in 4,000 consecutive patients at a single center. Ann Surg 2000;232:490–500.

[78] Wolfe RA, Roys EC, Merion RM. Trends in organ donation and transplantation in the United States, 1999-2008. Am J Transplant 2010;10:961–72.