The Wider Public Health Value of HCV Treatment Accrued by Liver Transplant Recipients

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ABSTRACT

Objectives: Organs for transplantation are scarce, but new medical therapies can prevent organ failure and the need for transplants. We sought to describe the unique value created by treatments that spare organs from failure and thus conserve donated organs for transplant into others, using hepatitis C virus (HCV) as a case study.

Study Design: Epidemiologic-economic model.

Methods: Using data on trends in chronic liver disease, liver disease progression, and liver transplant allocation models, as well as the effectiveness of new HCV treatments, we estimate the potential effects of systematic HCV screening and treatment on the demand for liver transplants in the United States. We estimate the spillover benefits to patients with all-cause liver disease in terms of increased availability of transplants and life-years gained.

Results: We estimated that systematic HCV screening and treatment could spare 10,490 liver transplants to HCV-infected patients from 2015 to 2035. An estimated 7321 transplants would accrue to patients with end-stage liver disease without HCV and 3169 transplants to those with uncured HCV, providing approximately 52,700 and 22,800 additional life-years, respectively.

Conclusions: Treatment advances for HCV have the potential to generate considerable spillover benefits to patients awaiting transplants for non–HCV-mediated liver failure. For other diseases in which organ transplants are in short supply, our study provides a novel pathway by which positive spillovers may accrue from treatments that prevent end-stage organ disease.

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Medical treatments can offer value to society that extends beyond the patients who are directly treated. For example, vaccinations not only reduce the likelihood of infection in those who are vaccinated, they also reduce the spread of infection. Such positive spillovers generate considerable value.[1,2] These spillovers may also result from the treatment of diseases that would otherwise lead to organ damage and transplantation. For example, improvements in nephropathy treatment within diabetes reduce the incidence of end-stage renal disease, thus sparing kidneys for use in patients with end-stage renal disease who do not have diabetes.

The availability of organs for transplantation is scarce. In the United States alone, more than 7000 individuals die awaiting organ transplantation each year.[3] In this study, we explored this idea by applying it to recently introduced therapies for hepatitis C virus (HCV) infection. An estimated 3 million individuals in the United States are affected by chronic HCV, a condition associated with long-term injury to the liver and with complications including cirrhosis, hepatocellular carcinoma, and, ultimately, liver failure (see **eAppendix**, available at **www.ajmc.com**, for further details).[4,5] The most common reason for liver transplantation in the United States is end-stage liver disease (ESLD), and currently, nearly 50% (14,000/29,000) of ESLD cases among transplant recipients are due to HCV.[3]

Until recently, treatments for HCV were neither particularly effective nor well tolerated.[6] However, newer HCV therapies suppress the virus in more than 90% of patients, making an effective cure of HCV highly likely for the majority of those affected.[7-9] Curing patients of HCV obviates their need for future liver transplantation due to HCV, thus creating opportunities for transplantation into patients with other forms of ESLD.

Currently, only one-third of Americans who need liver transplants receive them,[10] and shortages are expected to rise as the transplant waiting list continues to grow while the supply of organs remains flat.[11] Obesity and the aging of the popula-

tion are reducing the quality of deceased donor livers, while obesity-related liver disease is also increasing the demand for them.[12]

We simulated the effect of a systematic HCV screening and treatment program in the United States on the number of livers spared from transplantation into patients with HCV-mediated ESLD. We estimated the number of these spared livers that could be transplanted into patients with other forms of ESLD, as well as the resulting benefits to both groups. Our analysis takes a broader perspective than do existing models of HCV burden[5,13-17] because it recognizes that treatment of patients with HCV creates positive spillovers for non-HCV patients with ESLD.

Take-Away Points

- Organs for transplantation are scarce, but innovative hepatitis C virus (HCV) therapies can prevent liver failure and the need for transplants.
- Systematic HCV screening and treatment would spare 10,490 livers for transplant over 20 years, with almost 70% of these livers benefitting patients with non–HCV-mediated liver failure.
- The increased availability of donor livers will lead to 52,700 additional life-years for patients without HCV infection and 22,800 life-years for patients with HCV, providing economic values of $7.9 billion and $3.5 billion, respectively.
- Such spillover benefits to untreated populations underscore the value of innovative therapies in preventing organ failure.

METHODS

Overview of Data Sources

Our study relied on 2 main data sources: first, the National Health and Nutrition Examination Survey (NHANES), a biennial survey administered to a nationally representative sample of the US population. Along with a survey of health and healthcare utilization, participants also give blood samples and undergo other diagnostic tests. This data set was used to generate trends over time in liver disease and in key risk factors. Our second data source was the United Network for Organ Sharing (UNOS) database, which holds information on every patient on the waiting list for organ transplantation in the United States since 1987, including patient characteristics, primary disease, source of organ, and time spent on waiting list.

Overview of Approach

We developed an epidemiologic-economic model to estimate how a systematic HCV screening and treatment program would: a) reduce the number of livers transplanted into patients with HCV with ESLD and b) increase the number of spared livers that could be transplanted into patients with other forms of ESLD. We converted livers spared into life-years by using prior literature on life expectancy gained from transplants. Finally, we transformed these longevity benefits into economic values using conventional estimates of the value of a statistical life-year.[18,19]

We compared the effects of 2 types of HCV screening and treatment interventions ("real-world" and "comprehensive") with a baseline in which screening and treatment did not change from the status quo. First, we simulated the baseline annual demands for liver transplants from 2015 to 2035, for patients with ESLD, according to underlying disease (ie, HCV, alcohol-related, and nonalcoholic fatty liver disease [NAFLD]). Second, using historical data on national liver transplantation rates, we projected the supply of livers available for transplantation from 2015 to 2035. Third, we performed a simulation of how 2 different interventions in HCV screening and treatment would reduce the demand for liver transplantation among patients with HCV-mediated ESLD during 2015 to 2035. Together, these steps estimated, year-by-year, the impact of systematic HCV screening and treatment on the number of livers newly spared for transplantation.

Projected Annual Baseline Demand for HCV-Mediated Liver Transplants

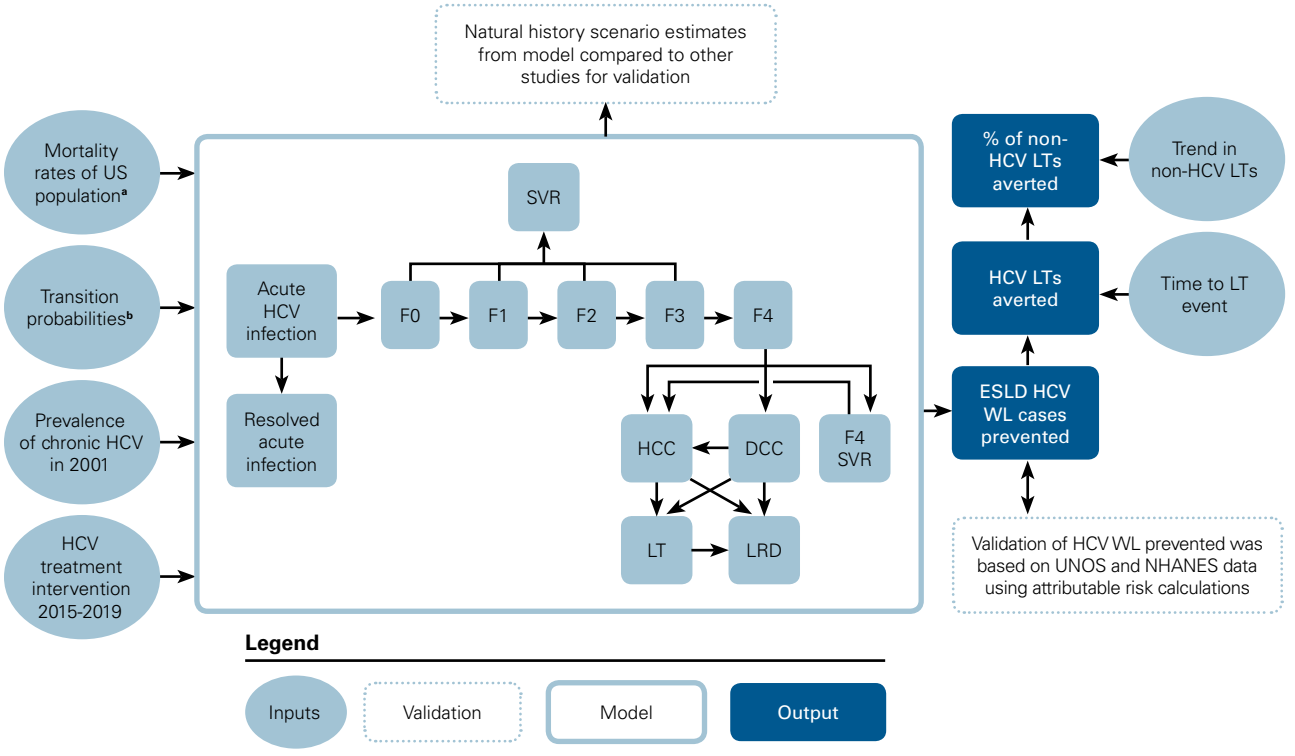
We obtained HCV prevalence data from 2001 to 2012 from NHANES and annual HCV incidence data from 2001 to 2010 from the CDC.[20] The incidence of HCV was estimated to be 17,000 cases in 2010 (see eAppendix).[20] In our baseline scenario, we assumed constant incidence of 18,000 cases per year from 2011 onward.

To estimate the baseline demand for transplants among patients with HCV-mediated ESLD, we adapted previous HCV modeling studies[21] to develop a Monte Carlo Markov simulation model that transitioned patients through each stage of liver disease, from chronic infection without liver fibrosis to decompensated cirrhosis or hepatocellular carcinoma. The latter 2 states comprise candidacy for liver transplantation (**Figure 1** describes the Markov model). The conceptual flow diagram highlights the inputs to the model, steps taken to validate key model assumptions, and the model outputs: a) livers spared from transplantation into patients with HCV as a result of a systematic HCV screening and treatment intervention, and b) the allocation of these spared livers to patients without HCV and patients with uncured HCV on the transplant list.

Projected Annual Baseline Demand for Non–HCV-Mediated Liver Transplants

To project the baseline demand for liver transplants among individuals with non–HCV-mediated ESLD, we

Figure 1. Flow Diagram of Markov Model to Estimate Chronic Liver Disease by Stage in the HCV Population and to Demonstrate Liver Transplants Prevented by Treatment



DCC indicates decompensated cirrhosis; ESLD, end-stage liver disease; F0-F4, stages of liver disease severity marked by fibrosis level in the liver; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LRD, liver-related death at each stage other than DCC and HCC; LT, liver transplant; NHANES, National Health and Nutrition Examination Survey; SVR, sustained viral response; UNOS, United Network for Organ Sharing; WL, waitlist.
[a]Subjects were assumed to have the background mortality rate of the population.
[b]The transition probabilities per year are shown in the eAppendix.

used data from UNOS. We counted the number of individuals on the liver transplant waiting list with a primary diagnosis of NAFLD or liver disease due to alcohol, iron deposition, or copper deposition. As illustrated in Figure 2, the incidence of NAFLD on the transplant waitlist increased significantly in the last decade. From historical data, we linearly extrapolated the annual incidence of NAFLD from 2015 to 2035, and we assumed that rates of liver disease due to alcohol or iron/copper deposition increased linearly until 2025. Based on prior studies,[22] we allowed for a "leveling off" between 2025 and 2035 by reducing the linearly extrapolated rates by 1.5% per year.

Projected Annual Number of Patients Receiving Transplant

Using our incidence forecasts, we projected the annual number of patients with HCV-mediated and non–HCV-mediated ESLD receiving liver transplants. Not all patients on the waiting list receive transplants; the likelihood of transplant varies by etiology of liver disease and clinical severity. UNOS data record whether and when a patient receives a liver transplant, as well as time spent on the waitlist. Using individual-level data from UNOS, we estimated the likelihood of liver transplantation as a function of time spent on the waitlist, adjusting for patient age, sex, and body mass index (BMI). Empirically, the probability of transplantation varied by sex and BMI among patients with HCV-mediated liver disease, but not among those without it. We applied sex- and BMI-specific transplant probabilities to HCV-mediated ESLD incidence estimates to project transplants for patients with HCV from 2015 to 2035. For non–HCV-mediated patients with ESLD, we used unadjusted Kaplan-Meier estimates of the probability of transplantation at a given year (45.7%, 52.3%, 54.8%, 56.4%, and 57.3%, after 1, 2, 3, 4, and 5 years, respectively).

Projected Supply of Livers Available for Transplantation

The supply of livers available for transplanta-

tion, at approximately 6700 per year (2.25 per 100,000 population), remained the same from 2005 to 2013. We conservatively assumed the liver supply would grow proportionately with the population from 2015 to 2035. We conducted several sensitivity analyses around this assumption, as described below.

Effect of HCV Screening and Treatment on Rates of HCV-Mediated ESLD and Liver Transplants

We simulated the annual impact of implementing two 5-year policies to screen for and treat HCV. We assumed that treatment with novel HCV therapies leads to sustained virologic response (SVR) rates of 90% among patients with liver disease fibrosis in stages F0 to F4 where severity of diseases increases with fibrosis stage.[21,23] Subjects achieving SVR at stage F4 were assumed to either remain in SVR or to transition to either decompensated liver disease (at an annual probability of 0.008) or hepatocellular carcinoma (at an annual probability of 0.005).[24]

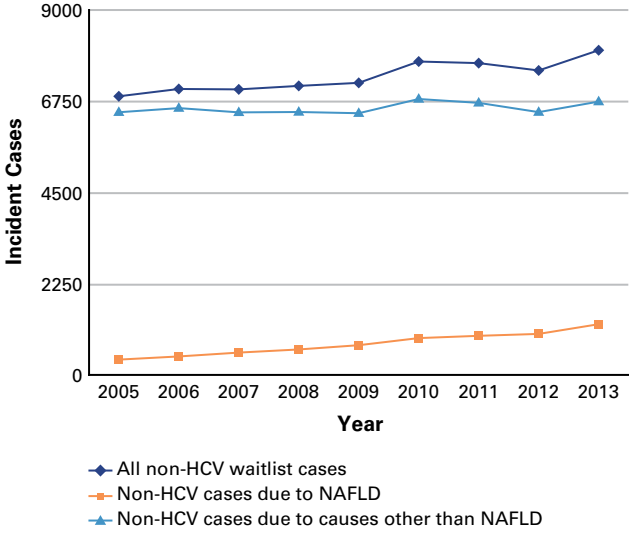
In reality, some patients may not accept screening, others may not receive their results, and still others who are aware of their HCV infection may not initiate treatment. Our real-world screening and treatment intervention rate relies on prior studies to assume that the percent of patients accepting HCV screening is 91%[25] and the percent of those screened positive who initiate treatment is 80% (regardless of liver fibrosis stage).[21,22,26,27]

We calculated the difference in the transplant waitlist size between the real-world scenario and a baseline scenario in which HCV screening and treatment remained at current rates from 2015 to 2035. In the real-world scenario, screening would take place over 5 years during 2015 to 2019, with 100% of patients with HCV aware of their disease status by 2019. In the baseline scenario, we assumed that 25% of subjects between F0 and F3 would be aware of their HCV status, and 75% of subjects would be aware of it at F4.[21] In both scenarios, we used Markov models to project the annual number of patients with and without HCV on the liver transplantation waitlist from 2015 to 2035. Finally, we calculated the number of livers spared and the number of additional patients receiving transplants in the real-world scenario. Additional details are available in the eAppendix.

Measuring Spillovers in Terms of Number and Value of Life-Years Gained

To estimate the economic value of these gains, we applied a value of $150,000 per life-year.[18,19] We computed life-years gained from newly available liver transplants using prior research, estimating that each new transplant adds 7.2 years of life.[28] To calculate social value as life-years gained multiplied by $150,000, we utilized prior research estimating the value of a quality-adjusted life-year.[29-31]

Figure 2. Annual Number of Patients With Non–HCV-Mediated End-Stage Liver Disease on Liver Transplantation Waitlist, 2005-2013, United States



HCV indicates hepatitis C virus; NAFLD, nonalcoholic fatty liver disease.

Sensitivity Analyses

We conducted 3 additional sensitivity analyses. First, we simulated the impact of a comprehensive HCV screening and treatment scenario, with 100% take-up of screening and treatment and 90% effectiveness for those treated. This exercise assessed the potential maximum impact of a systematic screening and treatment program. Second, we assumed a rising, rather than constant, incidence of liver disease due to alcohol, iron deposition, or copper deposition. Third, we simulated the impact of an opt-out organ donation policy, which allows organs from deceased donors to be used unless the deceased has officially requested otherwise.[32-34] Under current law, individuals must opt in and officially request to make their organs available for potential transplants in the event of death. Based on recent meta-analyses, we estimated that an opt-out policy in the United States would increase the supply of livers by 45%.[34]

RESULTS

The impact of a systematic HCV screening and treatment program on the total number of livers spared from 2015 to 2035 is shown in Table 1. The projected numbers of patients with HCV with each stage of liver fibrosis were lower under a systematic HCV screening and treatment

Table 1. Projected Effect of HCV Screening and Treatment on Livers Spared in the United States 2015-2035[a]

Liver Disease Stages	Prevalence		Difference (intervention – baseline)
	Baseline	Real-World Intervention	
Fibrosis stage, patients with HCV			
F0	3,024,066	2,918,313	
F1	7,205,978	6,792,897	
F2	6,722,864	6,194,018	
F3	7,849,909	7,005,057	
F4	14,938,881	10,269,691	
Decompensated liver failure, patients with HCV	1,379,700	1,059,004	
Hepatocellular carcinoma, patients with HCV	554,831	437,000	
Liver-related deaths, patients with HCV	485,935	379,752	
New patients on liver transplant waitlist, all patients	89,477	69,813	
Livers transplanted, all patients	125,992	125,992	
Livers transplanted, patients with HCV	45,541	35,052	10,490
Spared liver transplants newly allocated to patients without HCV			7321
Spared liver transplants newly allocated to patients with uncured HCV			3169
Total life-years gained due to transplant of patients without HCV			123,725
Total life-years gained due to transplant of patients with HCV			53,556

F0-F4 indicates stages of liver disease severity marked by fibrosis level in the liver; HCV, hepatitis C virus.
[a]Results presented for "real-world" screening and treatment scenario

program (our real-world scenario) relative to baseline. For example, the projected number of patients with HCV and decompensated liver failure was 30% lower under a systematic HCV screening and treatment program, and deaths from liver disease fell by 22%. The projected total number of new patients with HCV to be added to the liver transplant list between 2015 and 2035 was 28% lower under a systematic HCV screening and treatment program.

Our model predicted that 45,541 livers would be transplanted into patients with HCV during the 2015-to-2035 period under the baseline scenario compared with 35,052 under the real-world HCV screening and treatment program. The 10,490 spared livers were projected to be primarily allocated to individuals on the waitlist with non–HCV-mediated ESLD (7321 liver transplants), with a lower proportion allocated to those with uncured HCV-mediated ESLD (3169 transplants). Table 2 shows these spared livers broken down by subsets of patient characteristics.

The total life-years gained from additional transplants in each group were projected to be 52,711 years (7321 × 7.2 years) and 22,817 years (3169 × 7.2 years), respectively. This amounts to $7.9 billion in economic value accrued to patients with non–HCV-mediated liver disease over this time period, with an additional $3.5 billion accruing to patients with HCV. Of note, the total number of transplants and life-years gained from newly allocated transplants to patients with non–HCV-mediated ESLD were approximately twice as large as those gained by patients with uncured HCV ESLD requiring transplantation. This is due to the larger projected prevalence of patients who do not have HCV on the transplant waiting list after implementation of the HCV screening and treatment program.

Figure 3 shows the projected year-by-year cumulative number of liver transplants to patients without HCV and those with uncured HCV on the liver transplant list. At each year, the cumulative number of spared livers transplanted into patients with non–HCV-mediated ESLD is roughly twice that among those with uncured HCV on the transplant list. From 2015 to 2035, our model projected 80,451 liver transplantations to patients without HCV, of which the 7321 newly allocated spared livers would account for approximately 9% of the total.

Additional Analyses

Table 3 shows how our projections were affected by not only various sensitivity analyses regarding future trends in NAFLD and other liver disease, but by a comprehensive HCV screening and treatment scenario, in which both screening uptake and treatment rates were 100%, and by an opt-out organ donation policy in the United States that was estimated to increase the supply of transplantable livers by 45%.

We found that increasing trends in NAFLD and liver disease due to alcohol or iron/copper deposition would increase the total number of spared livers allocated to these patients from 7321 to 7653 between 2015 and 2035. The use of an opt-out policy for organ donation would further increase the number of livers spared from 7653 to 10,953, and a comprehensive HCV screening and treatment intervention would further raise the number of spared livers from 10,953 to 16,557.

Table 2. Projected Cumulative Number of Liver Transplants Newly Allocated to Patients, by Select Patient Characteristics

Primary Disease	Sex	BMI	Age Band (years) 18 to 30	30 to 50	50 to 70	Over 70	Totals
Non-HCV	Male	BMI <30	6	371	1177	20	1574
		BMI 30 to 40	2	214	554	4	774
		BMI >40	0	20	35	0	56
	Female	BMI <30	4	101	365	14	485
		BMI 30 to 40	1	57	184	4	246
		BMI >40	0	11	23	0	35
HCV	Male	BMI <30	188	815	1783	98	2884
		BMI 30 to 40	24	345	992	32	1392
		BMI >40	5	57	102	2	166
	Female	BMI <30	195	581	1049	58	1883
		BMI 30 to 40	40	196	582	26	844
		BMI >40	11	41	99	2	153
Totals			475	2809	6946	260	10,490

BMI indicates body mass index; HCV, hepatitis C virus.

DISCUSSION

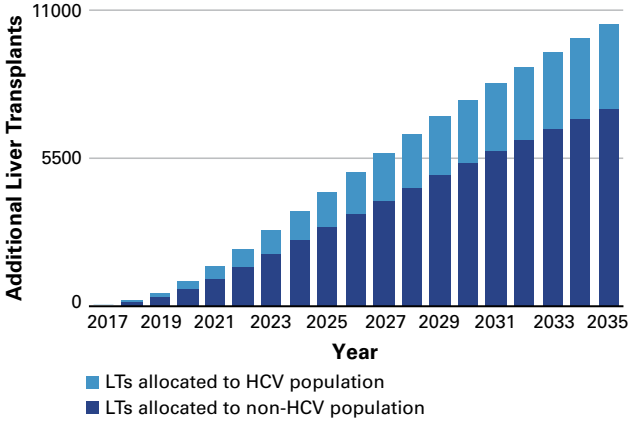
Our findings highlight a novel mechanism by which positive disease spillovers occur when the same scarce resource—in this case transplantable organs—is used for treatment. We estimated that the treatment of HCV by novel direct-acting antiviral therapies may have large, positive spillovers by reducing the future number of liver transplants to patients with HCV, thus sparing livers for transplants into other patients with ESLD. We projected that 10,490 liver transplants to patients infected with HCV could be prevented over a 20-year period, with 7321 of these spared livers going to patients without HCV. Over this period, HCV screening or treatment would make nearly 1 in 10 liver transplants possible. Additionally, this intervention would provide approximately 52,000 additional life-years for patients with ESLD without HCV (valued at $7.9 billion).[28] Because not all patients with HCV will be screened and successfully treated under the real-world scenario, the remaining 3169 spared livers would be allocated to patients with uncured HCV, generating an additional 22,817 life-years (valued at $3.5 billion).

Although our analysis focused on HCV, the disease spillover that we identified applies to other medical advances that reduce the demand for organ transplantation. This has important implications for how society values new treatments that may reduce the demand for future organ transplantation in the disease that is treated. For example, current policy debates around new HCV therapies and HCV screening policies revolve around the question of costs and benefits for patients given an HCV diagnosis and patients with undiagnosed HCV. Although that question is of utmost importance, this study demonstrates that these and other therapies may have an impact that extends beyond the population of patients who are directly treated. In countries with scarce liver supplies, for example, our analysis suggests that patients with ESLD who do not have HCV may still benefit from widespread HCV screening and treatment. To our knowledge, this point has not found its way into the broader public policy debate over HCV or other therapies that reduce the future demand for organ transplantation.

More generally, our research highlights an important mechanism through which organ shortages may be alleviated. This mechanism may be particularly significant, given the limited success of prior efforts to improve transplant supply rates (eg, improving the effectiveness of liver donor transplants,[35] or expanding the supply of deceased donor livers by increasing the number of individuals signing up as organ donors[10,12,36]).

Our study also highlights the negative impact that the growing burden of a single disease can have on outcomes in other diseases. For example, it is widely recognized that increasing rates of obesity lead to higher population rates

Figure 3. Projected Year-by-Year Cumulative Number of Liver Transplants Newly Allocated to Patients Without HCV and Patients With Uncured HCV on Liver Transplant List[a]



HCV indicates hepatitis C virus; LT, liver transplant.
[a]Results presented for real-world screening and treatment scenario.

Table 3. Sensitivity Analyses of the Projected Effect of HCV Screening and Treatment on Livers Spared in the United States, 2015-2035

	ASSUMPTIONS				RESULTS			
Scenario	Future trend in NAFLD	Future trend in other non-HCV liver disease[a]	Organ donation policy	HCV screening and treatment	Total livers spared transplantation into patients with HCV due to screening and treatment intervention	Total spared livers allocated to patients without HCV	Total life-years gained by patients without HCV due to available livers for transplant	Economic value of life-years gained by patients without HCV due to available livers for transplant (in billions, US$)
1	—	—	Opt-in	Real-world	10,490	6886	49,579	7.4
2[b]	↑	—	Opt-in	Real-world	10,490	7321	52,711	7.9
3	—	↑	Opt-in	Real-world	10,490	7300	52,560	7.9
4	↑	↑	Opt-in	Real-world	10,490	7653	55,102	8.3
5	—	—	Opt-out	Real-world	14,995	9846	70,891	10.6
6	↑	—	Opt-out	Real-world	14,995	10,473	75,406	11.3
7	—	↑	Opt-out	Real-world	14,995	10,447	75,218	11.3
8	↑	↑	Opt-out	Real-world	14,995	10,953	78,862	11.8
9	—	—	Opt-in	Comprehensive	15,182	10,519	75,737	11.4
10	↑	—	Opt-in	Comprehensive	15,182	11,107	79,970	12.0
11	—	↑	Opt-in	Comprehensive	15,182	11,082	79,790	12.0
12	↑	↑	Opt-in	Comprehensive	15,182	11,558	83,218	12.5
13	—	—	Opt-out	Comprehensive	21,712	15,057	108,410	16.3
14	↑	—	Opt-out	Comprehensive	21,712	15,872	114,278	17.1
15	—	↑	Opt-out	Comprehensive	21,712	15,911	114,559	17.2
16	↑	↑	Opt-out	Comprehensive	21,712	16,557	119,210	17.9

ESLD indicates end-stage liver disease; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease.
[a]Other non-HCV liver disease primarily includes alcohol-related liver disease and NAFLD.
[b]Scenario 2 reflects the assumptions underlying our main result in the manuscript. It assumes "real-world" intervention parameters, rising (↑) NAFLD trend, flat (—) trends in other liver disease, and the current US opt-in organ donation policy.

of hypertension, diabetes, hyperlipidemia, obstructive sleep apnea, and other diseases. Less well-appreciated is the resulting increase in the demand for liver and kidney transplants stemming from obesity-related complications.

Limitations

Our study had several limitations. First, our analyses were based on predictive modelling. Although model parameters were based on published evidence, there is uncertainty in every parameter. To limit the uncertainty, a number of sensitivity analyses were performed around key parameters. Second, HCV screening and treatment were modelled according to existing evidence on rates of screening and treatment uptake (ie, a real-world scenario). Increases in providers offering HCV treatment would likely raise screening and treatment rates, which is why the upper-bound comprehensive scenario, with 100% screening and treatment uptake, was modelled. Third, our model did not account for infectious disease dynamics, namely that the treatment of patients with HCV reduces overall transmission rates. Fourth, our analysis did not account for the impact of HCV treatment on potential organ donation by individuals cured of HCV.

CONCLUSIONS

We identified a novel mechanism by which positive disease spillovers can occur when the same scarce treatment—in this case transplantable organs—applies to multiple diseases. Illustrating this mechanism in ESLD, our analyses suggest that because the outcomes of patients with various forms of ESLD are linked by the scarcity of liver transplants, a systematic HCV screening and treatment program in the United States could substantially improve transplant opportunities and outcomes for patients with ESLD from causes other than HCV.

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Authorship Information: Concept and design (YSG, ABJ, TJ, DNL, SEM, TP, WS); acquisition of data (WS); analysis and interpretation of data (YSG, ABJ, TJ, DNL, SEM, TP, WS); drafting of the manuscript (YSG, ABJ, TJ, SEM, WS); critical revision of the manuscript for important intellectual content (YSG, ABJ, TJ, DNL, SEM, TP, WS); statistical analysis (ABJ, TJ); obtaining funding (YSG, TJ); and supervision (YSG, ABJ, TJ, DNL, WS).

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eAppendix. The Wider Public Health Value of HCV Treatment Accrued by Liver Transplant Recipients

This appendix describes details that underlie our projection model of the impact of a systematic HCV screening and treatment program on: a) the number of livers spared transplantation into patients with end-stage liver disease (ESLD) due to HCV; b) the number of livers subsequently allocated to patients with ESLD from causes other than HCV; and c) the number of livers subsequently allocated to patients with ESLD from HCV that were either not screened or successfully treated as a result of the HCV intervention.

Exhibit 1. Actual and Projected Annual[a] Incidence of Hepatitis C Virus, United States

Year	Incidence
2001	24,000
2002	29,000
2003	28,000
2004	26,000
2005	21,000
2006	19,000
2007	17,000
2008	18,000
2009	16,000
2010	17,000
2011-2035	18,000 (projected)[b]

[a]Source of annual HCV incidence from 2001 to 2010 is the CDC.[1]
[b]In our baseline scenario, absent widespread treatment with new HCV therapies, we projected an annual HCV incidence of 18,000 cases per year from 2011 onwards.

Exhibit 2 below describes transition probabilities that govern transitions between states in the disease-progression model. For example, 11.7% of patients in fibrosis stage F0 progress to F1 annually. The table also lists sources for each transition probability.

Exhibit 2. Transition Probabilities for the Markov Model

Transition	Probability (per year)	References
Resolution of acute infection (self-cure)	0.22	Armstrong et al (2006)[2]
F0 to F1	0.117	Thein et al (2008)[3]
F1 to F2	0.085	Thein et al (2008)[3]
F2 to F3	0.12	Thein et al (2008)[3]
F3 to F4	0.116	Thein et al (2008)[3]
F4 to DCC	0.029	Fattovich et al (1997)[4]
F4 to HCC	0.013	Fattovich et al (1997)[4]
DCC to HCC	0.068	Planas et al (2004)[5]
DCC to waitlist	0.038	UNOS/OPTN
HCC to waitlist	0.067	UNOS/OPTN
DCC to LRD	0.182	Planas et al (2004)[5]
HCC to LRD	0.427	Fattovich et al (1997)[4]

DCC indicates decompensated cirrhosis; F0-F4, stages of liver disease severity marked by fibrosis level in the liver; HCC, hepatocellular carcinoma; LRD, liver-related death at each stage other than DCC and HCC; UNOS/OPTN, United Network for Organ Sharing/Organ Procurement and Transplantation Network.

Subjects were also assumed to have the background mortality rate of the population (see **Exhibit 3**).

As subjects progress through the stages of the model, their background mortality rates vary according to the age-dependent mortality rates shown in Exhibit 3 below.[6]

Exhibit 3. Background Annual Mortality Rates by Age Band and Sex (per 100,000 person years) Used in the Markov Model as life tables.

Age Band (years)	Female (Deaths per 100,000 person years)	Male (Deaths per 100,000 person years)
18-19	40	110
20-29	51	126
30-39	98	182
40-49	275	455
50-59	492	811
60-69	1108	1709
70+	5274	5905

Source: US National Center for Health Statistics.

Outline of Markov simulation to project HCV-mediated end-stage liver disease incidence

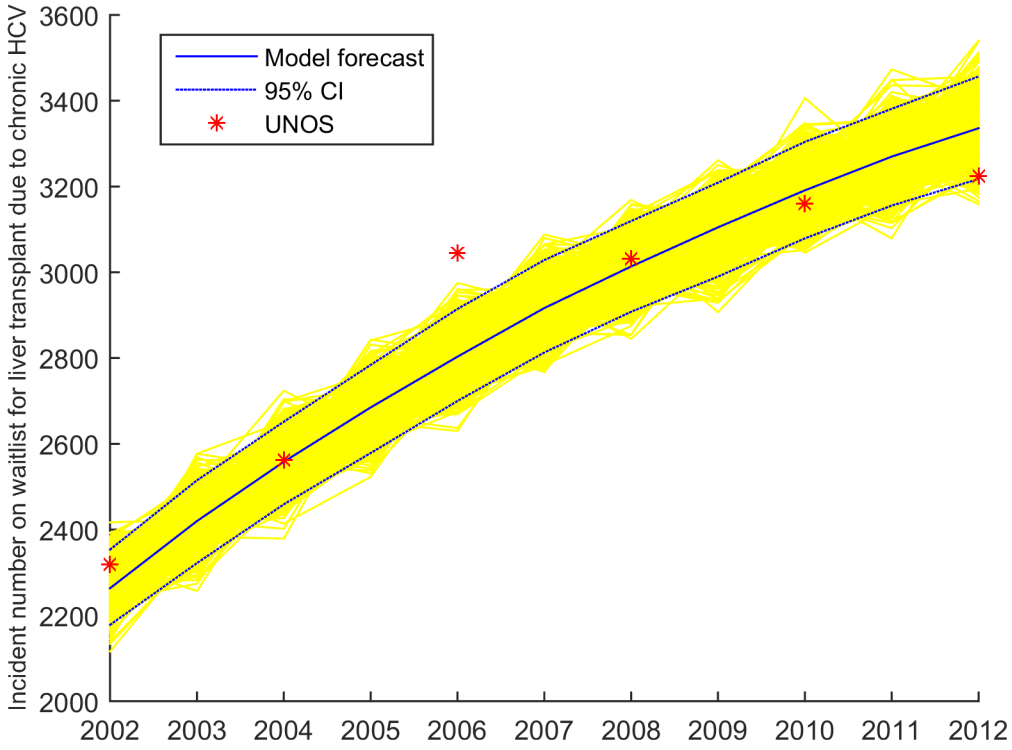
Our model was first initialized with baseline hepatitis C virus (HCV) prevalence in each liver-disease stage in year 2001. Subsequently, Markov transitions were simulated for 1000 sets (using a seeded randomization for repeatability) of the 2001 chronic HCV population of 3.2 million (CDC) with assumed yearly HCV incidence of 18,000 estimated from existing data.[7] The execution of multiple simulation scenarios provided us with an estimated distribution of model outcomes. This allowed us to estimate expected prevalence along with 95% CIs that account for random sampling variation within the population. The population was stratified into both males and females, and across 7 age groups (in years: 18-19, 20-29, 30-39, 40-49, 50-59, 60-69, over 70).

The primary purpose of the Markov model was to forecast how changes in chronic HCV influenced trends in end-stage liver disease (ESLD) requiring transplantation from 2015 to 2035. The fit of the model to existing data was validated by comparing ESLD incidence due to HCV with actual United Network for Organ Sharing (UNOS) waitlist data. A parameter sensitivity analysis has been previously performed,[8] and transition probabilities both from and to F4, decompensated cirrhosis, and hepatocellular carcinoma are the most sensitive.

For purposes of validation, the Markov model was executed for 1000 runs from 2002 to 2012 (latest date for both UNOS and National Health and Nutrition Examination Survey data) and the forecast trends are shown in **Exhibit 4** below. Solid lines indicate the projected trend and the dashed lines a 95% CI for the trend. Importantly, note that the trend is consistent with UNOS

data (red dots). Note that some of the currently HCV-positive patients would remain on the liver transplant waitlist even if their HCV were cured, because of background rates of other forms of liver disease (eg, alcohol liver disease and HCV-mediated liver disease are sometimes concomitant in the same individual).

Exhibit 4. Comparison of Projected HCV-Mediated Demand for Liver Transplant With Actual Transplant Waitlist Data From United Network of Organ Sharing and Organ Procurement Transplant Network

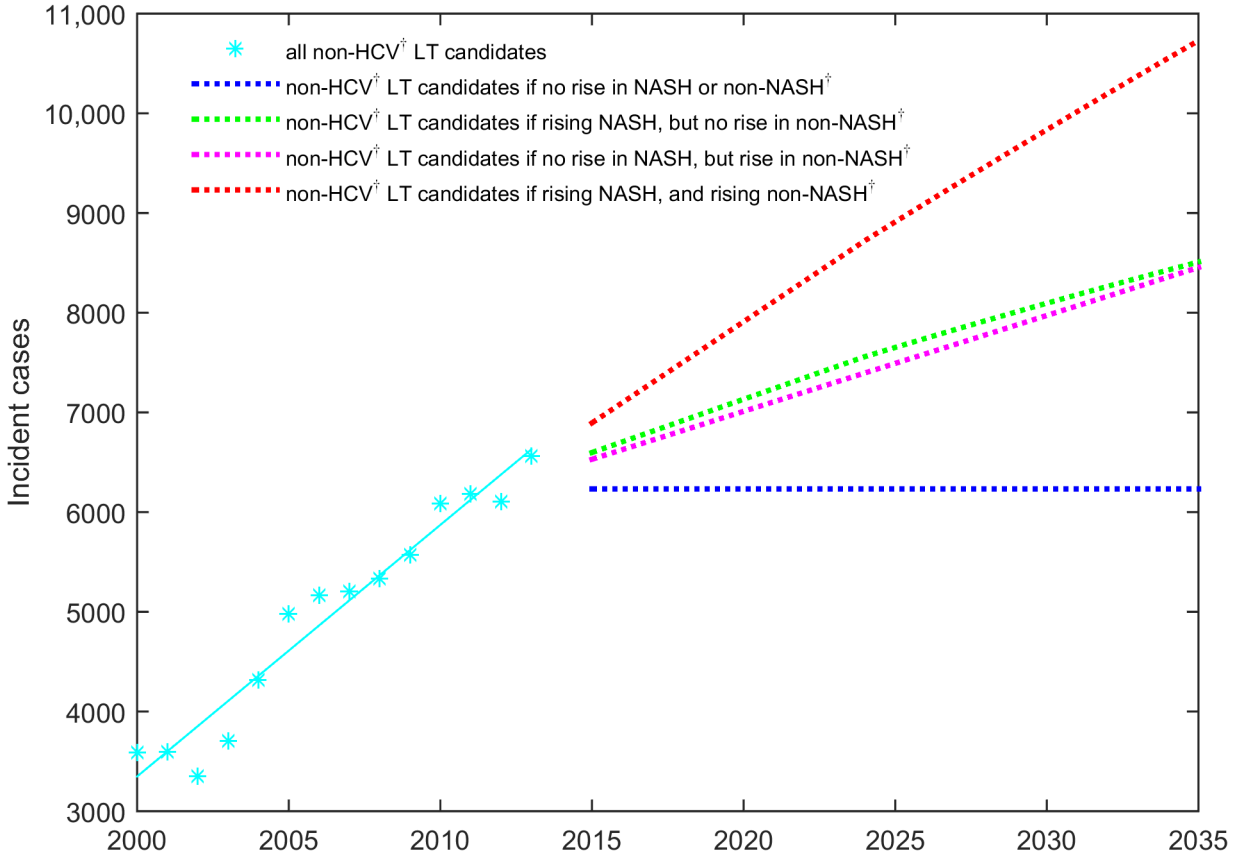


HCV, hepatitis C virus; UNOS, United Network for Organ Sharing.

Projection of non–HCV-mediated end-stage liver disease incidence

We considered several different models projecting incidence of non–HCV-mediated end-stage liver disease from 2015 to 2035. These models are shown graphically in Exhibit 5. Briefly, we categorized individuals with non–HCV-mediated liver disease into 1 of 2 categories: (a) those with nonalcoholic fatty liver disease, or (b) those with neither nonalcoholic fatty liver disease nor HCV (eg, liver disease due to alcohol, iron deposition [hemochromatosis], or copper deposition [Wilson's disease]). Trends for each of these categories are shown in the main manuscript. As shown in **Exhibit 5** below, our sensitivity analyses assumed various projections for each of these 2 categories from 2013 to 2035.

Exhibit 5. Four Trends for Incident Cases on the Waitlist for Subjects With No HCV Diagnosis



†Includes alcoholic liver disease and cryptogenic cirrhosis.

HCV indicates hepatitis C virus; LT, liver transplant; NASH, nonalcoholic steatohepatitis (also known as nonalcoholic fatty liver disease).

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