Clinical Infectious Diseases

MAJOR ARTICLE

Population-level Outcomes and Cost-Effectiveness of Expanding the Recommendation for Age-based Hepatitis C Testing in the United States

Joshua A. Barocas,[1,a] Abriana Tasillo,[2] Golnaz Eftekhari Yazdi,[2] Jianing Wang,[2] Claudia Vellozzi,[3] Susan Hariri,[3] Cheryl Isenhour,[3] Liisa Randall,[4] John W. Ward,[3] Jonathan Mermin,[5] Joshua A. Salomon,[6] and Benjamin P. Linas[2,7,a]

[1]Division of Infectious Diseases, Massachusetts General Hospital, and [2]Division of Infectious Diseases, Boston Medical Center, Massachusetts; [3]Division of Viral Hepatitis, US Centers for Disease Control and Prevention, Atlanta, Georgia; [4]Massachusetts Department of Public Health, Boston; [5]National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia; [6]Stanford University Department of Medicine, California; and [7]Boston University School of Medicine, Massachusetts

Background. The US Centers for Disease Control and Prevention and the U.S. Preventive Services Task Force recommend one-time hepatitis C virus (HCV) testing for persons born 1945–1965 and targeted testing for high-risk persons. This strategy targets HCV testing to a prevalent population at high risk for HCV morbidity and mortality, but does not include younger populations with high incidence. To address this gap and improve access to HCV testing, age-based strategies should be considered.

Methods. We used a simulation of HCV to estimate the effectiveness and cost-effectiveness of HCV testing strategies: 1) standard of care (SOC) – recommendation for one-time testing for all persons born 1945–1965, 2) recommendation for one-time testing for adults ≥40 years (≥40 strategy), 3) ≥30 years (≥30 strategy), and 4) ≥18 years (≥18 strategy). All strategies assumed targeted testing of high-risk persons. Inputs were derived from national databases, observational cohorts and clinical trials. Outcomes included quality-adjusted life expectancy, costs, and cost-effectiveness.

Results. Expanded age-based testing strategies increased US population lifetime case identification and cure rates. Greatest increases were observed in the ≥18 strategy. Compared to the SOC, this strategy resulted in an estimated 256,000 additional infected persons identified and 280,000 additional cures at the lowest cost per QALY gained (ICER = $28,000/QALY).

Conclusions. In addition to risk-based testing, one-time HCV testing of persons 18 and older appears to be cost-effective, leads to improved clinical outcomes and identifies more persons with HCV than the current birth cohort recommendations. These findings could be considered for future recommendation revisions.

Keywords. hepatitis C virus; testing, cost-effectiveness.

Half of the estimated 3.5 million people with chronic hepatitis C virus (HCV) are unaware of their status [1]. HCV treatments provide cure rates that are >90% [2], highlighting the importance of diagnosis. Current US HCV testing recommendations by the Centers for Disease Control and Prevention (CDC) and US Preventive Services Task Force include routine 1-time testing of persons born between 1945 and 1965, "referred to as the birth cohort," and concurrent targeted testing for high-risk persons [3, 4]. While prevalence remains highest among those in the birth cohort [5], incidence is rising in younger persons [6] exposed primarily through injection drug use (IDU).

The current strategy targets the high-prevalence population with advanced liver disease at near-term risk of HCV-associated mortality and is cost-effective [7] but it misses younger, more recently infected persons. Risk-based strategies are currently used to identify persons with HCV not in the birth cohort. Risk-based testing in addition to birth cohort testing is more effective than either strategy alone [8]. The value of expanding routine HCV testing among adults born after 1965 in the United States is unknown. In this study, we used a simulation model of HCV disease to investigate population-level outcomes and cost-effectiveness of expanding HCV testing recommendations to age-based testing that could replace birth cohort testing.

METHODS

Analytic Overview

We used the hepatitis C cost-effectiveness model, a Monte Carlo microsimulation model of HCV infection, screening, and treatment [9], to estimate the cost-effectiveness of the following 4 recommended strategies for HCV testing: 1-time testing for all persons born between 1945 and 1965 (standard of care [SOC]), 1-time testing for adults aged ≥40 years (≥40 strategy), 1-time testing for adults aged ≥30 years (≥30 strategy), and 1-time

Received 18 September 2017; editorial decision 27 January 2018; accepted 3 February 2018; published online February 6, 2018.

[a]J.A.S. and B.P.L. contributed equally to this work.

Correspondence: J. A. Barocas, Massachusetts General Hospital, 55 Fruit St, GrJ-504, Boston, MA 02114 (jbarocas@mgh.harvard.edu).

Clinical Infectious Diseases® 2018;67(4):549–56

© The Author(s) 2018. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.

DOI: 10.1093/cid/ciy098

testing for adults aged ≥18 years (≥18 strategy). All strategies assumed targeted testing of people who inject drugs (PWID). We chose to compete these strategies because age-based strategies may enhance national implementation [10] and because the effectiveness and costs of early screening are unknown.

We simulated outcomes including HCV cases identified, linked to care, initiated treatment, and cured over a lifetime; fibrosis stage at diagnosis; liver-attributable mortality; and quality-adjusted life years (QALYs). We projected lifetime medical costs assuming a healthcare system perspective and a 3% discount rate to both costs and benefits [11].

We used standard methods to calculate the incremental cost-effectiveness ratio (ICER) of each testing strategy as the additional cost per person for the total population divided by the QALYs gained compared to the next less expensive strategy [11]. We assumed a willingness-to-pay (WTP) threshold of $100 000/QALY [11].

We used data from national databases, clinical trials, and observational cohorts to inform parameter values (Table 1). We repeated the analysis under the following alternative scenarios: inefficient testing, in which identifying the same number of cases as were identified in the base case requires twice as much testing among uninfected persons, and payer restrictions on HCV treatment such that individuals must have at least Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) stage F2 fibrosis and ≥6 months of sobriety prior to being treated. With regard to the inefficient testing strategy, an argument against recommending routine testing is that such an approach generally requires a greater number of persons tested to find 1 infected person. Since our base case testing rates assumed targeting that improves yield, we varied assumptions about the efficiency of such targeting to reflect the possibility of lower yield with broader testing strategies. Second, payer restrictions continue to exist in most states; therefore, it is important to explore these real-world scenarios. We conducted 1-way deterministic sensitivity analyses on the base case.

Hepatitis C Cost-Effectiveness Model Structure and Inputs

Model Structure

The model is a closed cohort microsimulation, meaning that there are no new entrants to the simulation. It simulates the lifetime course of a hypothetical cohort that has the same demographics and HCV epidemiology of the US population (see Supplementary Appendix) [12]. The model includes several modules, which are described below.

HCV Infection, Risk Factors, and Natural History

HCV prevalence is stratified by age, sex, and risk behaviors. We simulated initiation, duration, and cessation of IDU behavior. Incidence of HCV, mortality from non-HCV causes, healthcare costs, and quality of life (QoL) depend on current drug use status (Supplementary Appendix). There is an incidence of new infections among simulated people that is conditional on current IDU. In the model, this corresponds to higher HCV incidence among young people due to higher prevalence of IDU in that group and the tendency for individuals to leave IDU as they age.

As individuals advance through METAVIR stages of fibrosis, QoL decreases and healthcare costs increase. Liver-attributable mortality occurs only among individuals who have reached METAVIR stage F4 (cirrhosis). Individuals with decompensated cirrhosis face a higher mortality probability than those with compensated cirrhosis, which reflects real-world findings [13].

HCV Testing

Individuals have a monthly probability of HCV testing that varies by age, sex, and drug use status. We modeled the effect of a recommendation for routine HCV testing as an increase in the monthly probability that a person in a group is tested. Recommending routine 1-time testing does not ensure that all receive an HCV test nor does it prevent some individuals from being tested multiple times in a lifetime.

HCV Treatment

When an individual is identified as HCV infected, that individual is first linked to HCV care, with a probability according to age. Individuals who do not link to care upon diagnosis may do so in the future (Supplementary Appendix). After successful linkage, individuals have a probability of accepting and completing HCV treatment.

HCV cure halts fibrosis progression [14, 15], HCV-attributable costs decrease by 50% of the individual's disease stage-specific cost before therapy [16], and HCV-related health utility reverts to that for the previous untreated stage. Finally, following cure, liver-related mortality among cirrhotic individuals is reduced by 94% [17]. Residual risk of liver death reflects ongoing risk of decompensation or hepatocellular carcinoma (HCC) [13].

Costs

During each month, persons accrue age- and sex-stratified "background costs" attributable to non-HCV–related healthcare [18], HCV-specific costs that vary by disease state [16], and IDU in PWID [19].

Utilities

"Background" utility, a function of age and unrelated to HCV, was derived from the Medical Expenditure Panel Survey (MEPS) [20. It is multiplied by HCV-specific utility [21, 22], IDU-related utility, and, when applicable, temporary disutility from treatment-ending major toxicity events (see Supplementary Appendix).

Model Data

HCV Infection, Risk Factors, and Natural History

Using published literature, we estimated age- and sex-stratified HCV prevalence among active PWID. Prevalence for

Table 1. Selected Model Inputs for Analysis of Cost-Effectiveness of Expanding Recommendations for Age-based Hepatitis C Virus Testing[a]

Parameter	Estimate	Range	Reference
Population			
Median age (years)	38	25–55	[12]
Mean age at time of infection (years)	23	18–28	[41, 42]
SMR, active PWID	11	4.8–17	[43]
SMR, former PWID	6.5	4.8–17	[44–46]
HCV infection			
Liver mortality (deaths/100 person-years)			
F4	3	1–5	[13]
Decompensation	21	3–30	[13]
Infection, PWID (cases/100 person-years)	12	1.7–35	[47]
Testing, linkage, and treatment			
Background testing (tests per 100 person-years)	…	…	[24]
Birth cohort	2.7	1–5	…
Complement	2.6	1–5	…
PWID	33.1	15–50	[23]
Linkage (%)			[48]
<30	17.9	8.5–86	…
≥30	28.9	8.5–86	…
Relink[b]	…	…	[48]
<30	17.9	8.5–86	…
≥30	28.9	8.5–86	…
Voluntary relink	0.00142	0–0.01	Expert opinion[c]
Treatment completion (%)	96.7–96.8	…	[25]
Hepatotoxicity (%)	0.08	…	[25]
SVR[d] after completion, noncirrhotic (%)	99	50–99	[25]
SVR after completion, cirrhotic (%)	93	93–96	[25]
Post-SVR mortality multiplier	0.06	0.01–1	[17]
Healthcare costs			
Cost with active infection ($/month)			[16]
f0	256	128–384	
f1	256	128–384	
f2	256	128–384	
f3	256	128–384	
f4	455	228–683	
Decompensated	867	434–1301	
Cost with SVR ($/month)			[16]
f0	128	64–192	
f1	128	64–192	
f2	128	64–192	
f3	128	64–192	
f4	227	114–341	
Decompensated	433	217–650	
Testing and eligibility costs ($)			
HCV antibody test	19	10–30	[28]
HCV RNA test	78	50–100	[28]
Fibroscan	135	…	[28, 49]
False positive[e]	683	300–1000	…
Treatment costs ($)			…
Sofosbuvir/velpatasvir (per month)	23026	0–38000	[50]
Health state utilities[f]			
Age-specific utility for persons without infection or injection drug use	0.76–0.92		
Utility for active injection drug	0.68	0.54–0.8	[29]
Utility for former injection drug use	0.82	0.71–0.93	[29]
Utility for active HCV infection, by METAVIR fibrosis stage			[51]
f0	0.94	0.9–1.0	…
f1	0.94	0.9–1.0	…
f2	0.94	0.9–1.0	…
f3	0.94	0.9–1.0	…
f4	0.75	0.6–0.9	[21]
Decompensated	0.60	0.48–0.75	…
Utility for HCV infection after effective treatment, by stage			Expert opinion
f0	0.97	0.94–1.0	…
f1	0.97	0.94–1.0	…
f2	0.97	0.94–1.0	…
f3	0.97	0.94–1.0	…
f4	0.94	0.75–0.97	…
Decompensated	0.75	0.60–0.94	…
Utility with hepatotoxicity	0.75	0.50–0.99	…

Abbreviations: f, fibrosis; HCV, hepatitis C virus; METAVIR, meta-analysis of histological data in viral hepatitis; PWID, people who inject drugs; SMR, standardized mortality rate; SVR, sustained virologic response.

[a]Baseline estimates used in the analysis are reported, with ranges used for sensitivity analysis, when applicable. Costs are in 2016 US dollars.

[b]Individuals identified as HCV infected for the first time have a probability of linking to care (ie, "linkage"). If such individuals do not link to care at that time, they may be identified with subsequent testing. Therefore, they have a probability of linking to care with each subsequent identification. The "relink" parameter refers to this subsequent linkage probability.

[c]Expert opinion includes methodological consultation with the Center for Health Economics of Treatment Interventions for Substance Use Disorders, HCV, and HIV (CHERISH).

[d]SVR is a commonly accepted marker of HCV cure. It is measured 12 weeks following completion of treatment.

[e]False positive costs include HCV genotype, two physician visits, CBC, liver panel, and HCV RNA.

[f]All individuals are subject to an age-adjusted utility without injection drug use or HCV infection. Active or former injection drug use and active or treated HCV infection are then applied multiplicatively. Final absolute utilities are relative to a hypothetical individual in perfect health (utility = 1.0).

other risk behavior groups was derived from the National Health and Nutrition Examination Survey (see Supplementary Appendix).

We modeled movement between IDU states over the course of the simulation using AIDS Linked to the Intravenous Experience (ALIVE) cohort data (see Supplementary Appendix).

HCV Testing

We estimated HCV testing rates among active PWID using data from cohorts of PWID [23] and assigned a constant testing rate to all active PWID in the simulation. We estimated testing rates and the effect of recommendation changes in the non-drug-using cohort using the MarketScan claims database (see Supplementary Appendix) [24].

HCV Treatment

We modeled an oral, pan-genotypic HCV regimen for all genotypes and fibrosis stages [25]. In the base case, there were no treatment restrictions. Duration and treatment outcomes were derived from cohort studies and clinical trials [25, 26].

Costs

We assessed costs from the healthcare system perspective in 2016 US dollars. We derived costs from the 2016 laboratory and physician fee schedules from the Centers for Medicare and Medicaid Services for reimbursement [27, 28]. HCV treatment costs were derived by using the average wholesale price minus 23%. We explored HCV-attributable costs in sensitivity analysis (Supplementary Tables 4 and 5).

Utilities

We used a combination of MEPS data and published health utility literature estimates to derive health state-related utilities [18, 21, 29].

Monte Carlo Variance Reduction

We developed a strategy that enabled us to improve the precision of estimates since results would otherwise be subject to substantial Monte Carlo error (Supplementary Appendix). Briefly, we simulated a large cohort and noted infection status over time for each individual. For those individuals who never became infected, we recorded key health and economic outcomes and did not resimulate their life courses under each of the comparator strategies in the analysis. We deterministically calculated life expectancy and healthcare costs for this subgroup. For those who were infected, we simulated life courses following infection under each of the various screening strategies to determine health outcomes, life expectancy, and costs. For all cost and health outcomes used in the cost-effectiveness calculations, we computed population-weighted averages that combined outcomes among the never-infected group and the infected group.

Study Approval

This secondary analysis of published literature and deidentified data sources did not require institutional review board approval.

RESULTS

In the SOC strategy, 71% of all HCV-infected persons were identified and 44% of HCV-infected persons were cured over a lifetime (Figure 1). The proportion of individuals in the total US population diagnosed prior to cirrhosis was 58%, and 32% of those who were HCV infected ultimately died from liver disease (data not shown). Among HCV-infected persons born outside the birth cohort, 67% of cases were diagnosed prior to developing cirrhosis, and liver-related mortality among HCV-infected persons was 27% (Table 2).

Clinical Outcomes

Expanded age-based testing strategies increased lifetime case identification and cure rates in the US population, with the greatest increases observed in the ≥18 strategy (Figure 1). Compared to the SOC, the ≥18 strategy resulted in an estimated 256 000 additional infected persons identified, 280 000 additional cures, and an estimated 4400 fewer cases of HCC in the United States (assuming an HCC incidence rate of 2.49 per 100 person-years with cirrhosis) [30] over the lifetime of this cohort. The average number of lifetime tests increased

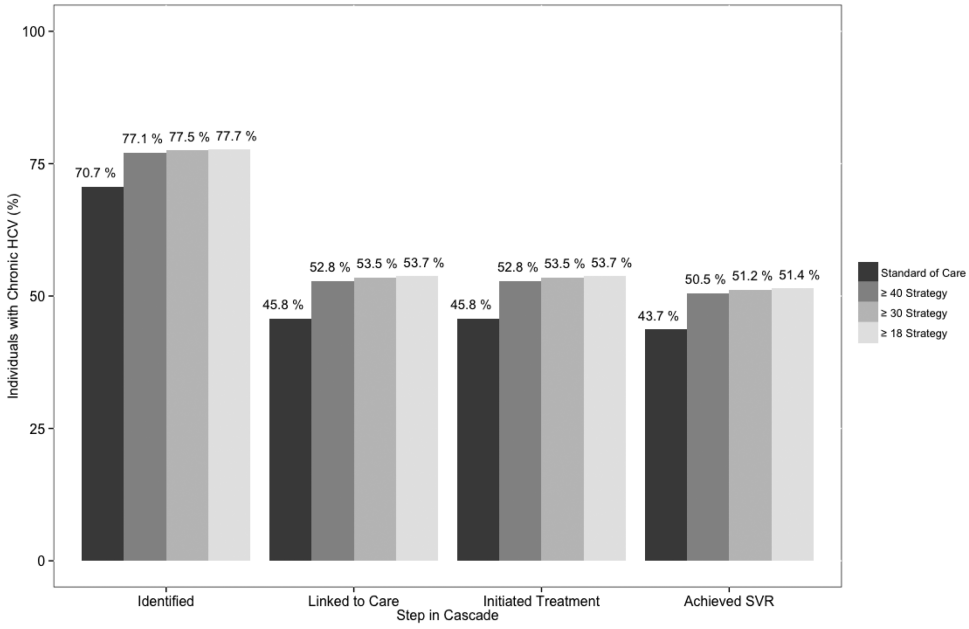

Figure 1. Hepatitis C virus (HCV) continuum of care over the lifetime by strategy. The bar graph illustrates the percent of the HCV-infected population that attains clinical outcomes along the HCV continuum of care. Each bar shading represents a specific testing strategy. Abbreviation: SVR, sustained virologic response.

Table 2. Selected Cost and Clinical Outcomes by Strategy for Various Populations

	Total US Population			HCV-Infected Persons		HCV-Infected Persons Born Outside Birth Cohort			
Strategy[a]	Average Lifetime Healthcare Cost,[b] $	Life Expectancy (LY)	Quality-Adjusted Life Expectancy (QALY)	Life Expectancy (LY)	Quality-Adjusted Life Expectancy (QALY)	Life Expectancy (LY)	Quality-Adjusted Life Expectancy (QALY)	Proportion Identified Prior to Cirrhosis (%)	Proportion With HCV-Attributable Death (%)
Standard of care	$287 760	81.319	74.476	69.888	62.411	67.157	58.162	66.5	27.0
Test ≥40	$287 880	81.326	74.482	70.414	62.896	67.976	58.918	75.4	22.1
Test ≥30	$287 900	81.327	74.483	70.517	62.994	68.136	59.070	76.5	21.4
Test ≥18	$287 900	81.327	74.484	70.564	63.038	68.209	59.138	76.8	21.3

All values are undiscounted; averages of costs and life expectancy are per person.

Abbreviations: HCV, hepatitis C virus; LY, life years; QALY, quality-adjusted life years.

[a]Additional details of the sensitivity analyses as well as the inefficient testing and payer restriction alternative scenarios are provided in the Supplementary Appendix.

[b]Values that appear the same differed beyond the third decimal place

from 2.35 tests per person to 4.63 in the SOC strategy and the ≥18 strategy, respectively (Supplementary Table 2 and Supplementary Figure 1). Clinical outcomes over different time horizons are included in the Supplementary Appendix (Supplementary Figures 2 and 3).

Among the HCV-infected population born outside of the birth cohort, case detection rates increased from 74% to 85% and cure rates increased from 49% to 61%, which resulted in a 31% reduction in the proportion reaching cirrhosis before diagnosis and a 21% reduction in liver-attributable mortality in the ≥18 strategy compared to the SOC (Table 2).

The ≥18 strategy resulted in an increase in life expectancy from 67.2 to 68.2 years compared to the SOC in this population (Table 2) and 1 discounted quality-adjusted life day across the general population (Table 3).

Cost Outcomes

As testing began at younger ages, HCV-related costs comprised a smaller portion of the incremental cost of each strategy compared to the next most inclusive (Figure 2). All strategies resulted in decreased costs related to managing chronic HCV and advanced liver disease including HCC. The cost of HCV testing in the SOC strategy corresponds to approximately $2500 per case diagnosed. In the ≥18 strategy, the cost of testing increased to $4400 per case diagnosed. The additional cost of testing per case diagnosed was $1900.

Incremental Cost-Effectiveness Ratio

In the base case, the ≥18 strategy provided the greatest quality-adjusted life expectancy and the lowest cost/QALY gained. This strategy dominated all other expanded testing strategies by extended dominance with an ICER compared to the SOC of $28 000/QALY (Table 3).

Scenario Analysis

In the inefficient testing scenario that required twice as much testing among uninfected persons to identify the same cases, the average discounted cost of the ≥18 strategy increased minimally to $126 170 (from $126 150 in the base case). That strategy remained cost-effective, with an ICER compared to ≥30 strategy of $44 000. In the treatment restriction scenario, the ≥18 strategy ICER remained cost effective but increased to $34 000/QALY (Supplementary Tables 22 and 23).

Sensitivity Analysis

In 1-way sensitivity analyses, the ≥18 strategy had an ICER <$100 000/QALY compared to its next best alternative across broad parameter ranges (Supplementary Tables 4–21), except for the scenario when an individual could only link to care when first identified as infected and never again (Supplementary Table 20). In other scenarios, specifically, when there was no improvement in QoL and costs decreased following early-stage cure, when cost of early-stage disease was $0, and when treatment costs were varied, the ≥30 strategy dominated the ≥40 strategy by extended dominance, but the ≥18 strategy remained cost-effective (Supplementary Tables 6, 12–13, 21). We note that the ≥18 strategy remained cost-effective, with an ICER of $30 000 when there was no mortality benefit from sustained virologic response (SVR; Supplementary Table 8).

DISCUSSION

We used a simulation model of HCV to investigate the clinical outcomes, costs, and cost-effectiveness of age-based strategies for routine HCV testing that could replace current cohort-based guidance in the United States. We found that a recommendation for 1-time testing of all adults, with continued risk-based testing throughout life, improved clinical outcomes and was cost-effective in the United States.

The birth cohort recommendation focuses the testing effort among the group that has had the highest HCV prevalence [31]. The HCV epidemic is changing, with an increasing proportion of persons with HCV outside of this cohort. The shift is multifactorial, including premature mortality in the birth cohort [32], persons in the birth cohort treated and cured of their infection [33], and higher incidence of new HCV infections among younger PWID [6]. A substantial number of undiagnosed cases

Table 3. Results of Cost-Effectiveness Analysis

Strategy[a]	Average Discounted Cost[b] ($)	Incremental Average Discounted Cost ($)	Discounted QALY	Incremental Discounted Quality-Adjusted Life Days (QALD)	Incremental Cost-Effectiveness Ratio[c] ($/QALY)
Standard of Care	$126 080	…	56.840	…	…
Test ≥40	$126 140	…	56.842	…	Dominated[d]
Test ≥30	$126 150	…	56.843	…	Dominated
Test ≥18	$126 150	$74.50	56.843	0.964	$28 000

Abbreviation: QALY, quality-adjusted life years.

[a]Additional details of the sensitivity analyses as well as the inefficient testing and payer restriction alternative scenarios are provided in the Supplementary Appendix.

[b]The overall incremental cost-effectiveness ratio was calculated as the difference in the average discounted costs for the total US population divided the difference in the discounted quality-adjusted life expectancy for the total US population, all discounted at 3% per year.

[c]Values that appear the same differed beyond the third decimal place.

[d]Dominated = extended dominance means that the strategy was more costly and more effective but had a lower incremental cost-effectiveness ratio compared to other strategies.

exist outside of the birth cohort and might never be diagnosed under the current strategy [8]. Expansion of the recommendation for routine testing to include all adults would increase the probability of testing and identify more people with HCV.

Other analyses have demonstrated that HCV testing is cost-effective in high-prevalence settings such as among baby boomers [7], in substance use disorder treatment programs [34], and in prisons and jails [35], as well as in subpopulations that include adolescents and young adults [36] and human immunodeficiency virus–infected men who have sex with men [37]. Our study takes the next step in this evolution of thought and policy about HCV testing to consider routine HCV testing for all adults.

The value of screening all adults lies in the value of early diagnosis. In our base case, routine testing of adults aged ≥18 years dominated the other age-based strategies by extended dominance. The ≥18 strategy identifies cases sooner than the other strategies, thereby increasing QoL and decreasing costs associated with HCV, since there is disutility and cost for the years that a person lives with HCV, even with early-stage disease. When we assume no QoL improvement or cost decrease associated with treating early-stage HCV, the ≥18 strategy no longer

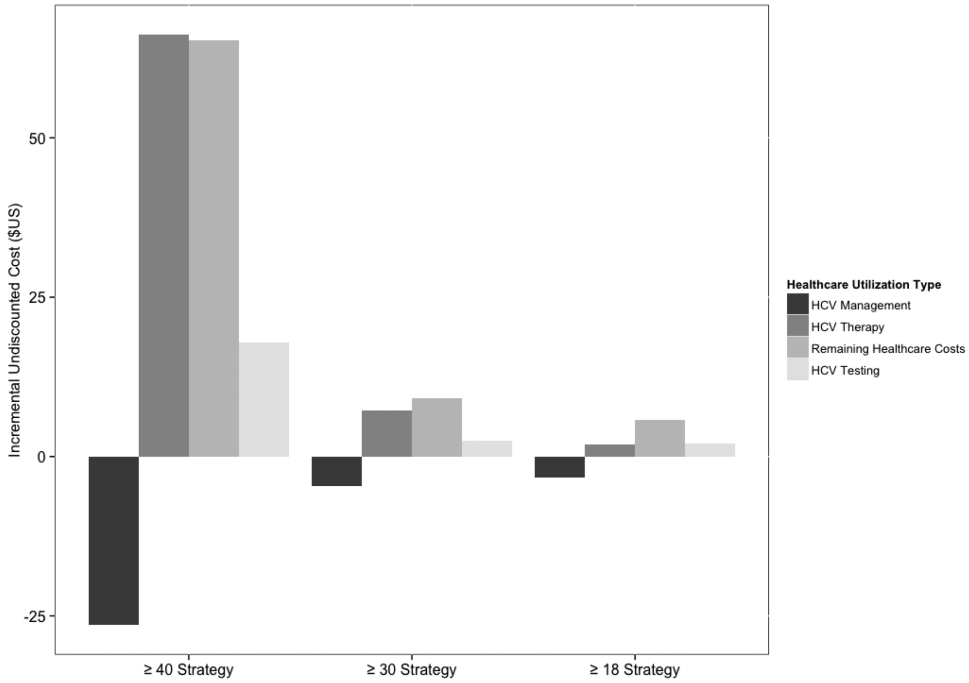

Figure 2. Incremental healthcare use costs by strategy over the lifetime. The bar graph illustrates the incremental costs relative to the previous strategy by type of healthcare expenditure for each testing strategy. The first grouping of bars is the incremental costs of 1-time testing for adults aged ≥40 years (≥40 strategy) compared to the standard of care (1-time testing for all persons born between 1945 and 1965). Next are incremental costs for 1-time testing for adults aged ≥30 years (≥30 strategy) compared to the costs for the ≥40 strategy followed by the incremental costs of the 1-time testing for adults aged ≥18 years compared to costs for the ≥30 strategy. In all 3 strategies, hepatitis C virus (HCV) testing, HCV therapy, and other non-HCV healthcare are costs (positive value) that outweighed the cost savings from HCV management (negative value). Non-HCV healthcare costs become a larger proportion of the overall incremental costs in younger testing strategies. Abbreviation: HCV, hepatitis C virus.

dominates the ≥30 strategy but does prevent enough liver-attributable morbidity and mortality to remain cost-effective. Ultimately, the cost-effectiveness of expanding testing to ≥18 is driven by reductions in cirrhosis and liver-related mortality, including HCC, while the reason it dominates other strategies is driven by QoL improvements and cost reductions associated with treating early-stage HCV. New recommendations should continue to include targeted testing among PWID, which effectively serves as a "backstop" to catch later incident cases missed by the ≥18 strategy.

Findings from our alternative scenarios deserve discussion. First, while an argument against routine testing is that it is a resource-intensive effort to find a small number of cases, our findings demonstrate that routine testing was cost-effective even when we tested twice as much to find the same number of cases. Second, though testing in our treatment restriction scenario was cost-effective, this conclusion is not an endorsement of these restrictive policies. Rather, this scenario recognizes the status quo in many states and demonstrates that even if patients are treated only once they reach advanced fibrosis, it remains cost-effective to test all adults.

There were limitations to our study. First, the use of cohort studies and large national databases to derive estimates may not be representative of the overall US population; however, our detailed analysis of testing rates in MarketScan [24] are in line with previously published reports [38–40]. Second, there is relatively little evidence on the cost of early-stage HCV and the magnitude of the change in health-related utilities derived from treating early-stage HCV. Our sensitivity analyses demonstrated that earlier testing remained cost-effective even in the setting in which treating early-stage disease had no implications for cost or QoL. Third, differences between strategies are small and could be suspected to reflect Monte Carlo variance. We anticipated this because the life expectancy change in the general population attributable to expanded HCV testing is expected to be small, even at a high general population prevalence of 3%, because the majority remain uninfected and get no benefit from testing. We minimized Monte Carlo error in our results with a variance reduction strategy outlined in the Methods section and in the Supplementary Appendix. We empirically assessed the degree of variance between runs to ensure that the difference between strategies expected from random variance is smaller than the difference in outcomes seen between strategies (Supplementary Figures 4–12). Fourth, we used a closed cohort but allowed individuals who were aged <18 years into guidance. Using a closed cohort in this way will be biased by omitting some future consequences of different screening strategies. Because the omitted consequences will occur 2 decades or more into the future, the impact of the omission will be relatively small compared to the overall magnitude of the population-level cumulative outcomes, especially given uncertainties about long-term changes in demography and HCV epidemiology and in the presence of a positive discount rate, as in our main analyses. Fifth, the rate of fibrosis progression with HCV is uncertain. We used one appropriate estimate of fibrosis progression rates and performed sensitivity analyses to ensure that such uncertainty did not have a major impact on the qualitative conclusions. Finally, while we did not incorporate incident infection explicitly related to factors such as tattoos, HCV incidence in the United States due to these risk factors is small in comparison to IDU [6]. We explored the impact of nondrug use–related HCV on cost-effectiveness conclusions, and our results remained robust.

In conclusion, in addition to risk-based testing, routine, 1-time HCV testing of persons aged ≥18 years is cost-effective, could lead to improved clinical outcomes, and is likely to identify more persons with HCV than the current birth cohort recommendations. These findings should be considered for future recommendation revisions.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. J. A. B. conceived of the design of the work; led the acquisition, analysis, and interpretation of the data; and drafted the initial and revised manuscript. A. T. conceived of the design of the work; performed the acquisition, analysis, and interpretation of the data; and contributed to the initial and revised manuscript. G. E. Y. implemented the computer simulation model and assisted with model design, analysis of data, and manuscript revision. J. W. assisted with acquisition, analysis, and interpretation of data and with manuscript revision. C. V. assisted with project design, interpretation of data, and manuscript revision. S. H. assisted with project design, interpretation of data, and manuscript revision. C. I. assisted with interpretation of data and manuscript revision. L. R. assisted with project conception, analysis and interpretation of data, and manuscript revision. J. W. W. assisted with analysis and interpretation of data and manuscript content and revision. J. M. assisted with analysis and interpretation of data and manuscript content and revision. J. A. S. conceived of the design of the work; was involved with the acquisition, analysis, and interpretation of data; and assisted with drafting the initial and revised manuscript. B. P. L. conceived of the design of the work; was involved with the acquisition, analysis, and interpretation of data; and assisted with drafting the initial and revised manuscript.

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

Financial support. This work was supported by the National Institute on Drug Abuse at the National Institutes of Health (5T32DA013911-15 and 1R25DA037190-01 to J. A. B.) and (R01DA031059 and P30DA040500 to B. P. L. and J. A. S.], the Massachusetts General Hospital Fund for Medical Discovery (to J. A. B.), and the CDC (5U38PS004642 to J. A. B., J. W., G. E. Y., A. T., J. A. S., and B. P. L.).

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Denniston MM, Klevens RM, McQuillan GM, Jiles RB. Awareness of infection, knowledge of hepatitis C, and medical follow-up among individuals testing positive for hepatitis C: National Health and Nutrition Examination Survey 2001–2008. Hepatology **2012**; 55:1652–61.

2. D'Ambrosio R, Degasperi E, Colombo M, Aghemo A. Direct-acting antivirals: the endgame for hepatitis C? Curr Opin Virol **2017**; 24:31–7.
3. Moyer VA; U.S. Preventive Services Task Force. Screening for hepatitis C virus infection in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med **2013**; 159:349–57.
4. Smith BD, Morgan RL, Beckett GA, et al. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945–1965. MMWR Recomm Rep **2012**; 61:1–32.
5. Klevens RM, Canary L, Huang X, et al. The burden of hepatitis C infection-related liver fibrosis in the United States. Clin Infect Dis **2016**; 63:1049–55.
6. Lansky A, Finlayson T, Johnson C, et al. Estimating the number of persons who inject drugs in the United States by meta-analysis to calculate national rates of HIV and hepatitis C virus infections. PLoS One **2014**; 9:e97596.
7. 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.
8. Mahajan R, Liu SJ, Klevens RM, Holmberg SD. Indications for testing among reported cases of HCV infection from enhanced hepatitis surveillance sites in the United States, 2004–2010. Am J Public Health **2013**; 103:1445–9.
9. Linas BP, Barter DM, Leff JA, et al. The hepatitis C cascade of care: identifying priorities to improve clinical outcomes. PLoS One **2014**; 9:e97317.
10. Eccles MP, Grimshaw JM, Shekelle P, Schünemann HJ, Woolf S. Developing clinical practice guidelines: target audiences, identifying topics for guidelines, guideline group composition and functioning and conflicts of interest. Implement Sci **2012**; 7:60.
11. Neumann PJ, Russell LB, Sanders GD, Siegel JE, Ganiats TG. Cost effectiveness in health and medicine. 2nd ed. Oxford (NY): Oxford University Press, **2017**.
12. US Census Bureau. ACS demographic and housing estimates, table DP05. **2016**.
13. Bruno S, Zuin M, Crosignani A, et al. Predicting mortality risk in patients with compensated HCV-induced cirrhosis: a long-term prospective study. Am J Gastroenterol **2009**; 104:1147–58.
14. Gonzalez HC, Duarte-Rojo A. Virologic cure of hepatitis C: impact on hepatic fibrosis and patient outcomes. Curr Gastroenterol Rep **2016**; 18:32.
15. Zator ZA, Chung RT. After the cure: management of HCV after achievement of SVR. Curr HIV/AIDS Rep **2013**; 10:428–35.
16. Davis KL, Mitra D, Medjedovic J, Beam C, Rustgi V. Direct economic burden of chronic hepatitis C virus in a United States managed care population. J Clin Gastroenterol **2011**; 45:e17–24.
17. 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.
18. Agency for Healthcare Research and Quality. Total health services-mean and median expenses per person with expense and distribution of expenses by source of payment: medical expenditure panel survey household component data. Generated interactively. Available at: http://meps.ahrq.gov/mepsweb/. Accessed 15 July.
19. Coffin PO, Sullivan SD. Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal. Ann Intern Med **2013**; 158:1–9.
20. Sullivan PW, Ghushchyan V. Preference-based EQ-5D index scores for chronic conditions in the United States. Med Decis Making **2006**; 26:410–20.
21. McLernon DJ, Dillon J, Donnan PT. Health-state utilities in liver disease: a systematic review. Med Decis Making **2008**; 28:582–92.
22. Chong CA, Gulamhussein A, Heathcote EJ, et al. Health-state utilities and quality of life in hepatitis C patients. Am J Gastroenterol **2003**; 98:630–8.
23. Coffin PO, Jin H, Huriaux E, Mirzazadeh A, Raymond HF. Trends in use of health care and HIV prevention services for persons who inject drugs in San Francisco: results from National HIV Behavioral Surveillance 2005–2012. Drug Alcohol Depend **2015**; 146:45–51.
24. Barocas JA, Wang J, White LF, et al. Substantial impact of the 2012 CDC HCV screening guidelines in the U.S. among persons born 1945–1965: an interrupted-time series analysis. Health Aff **2017**; 36:2142–50.
25. Feld JJ, Jacobson IM, Hézode C, et al; ASTRAL-1 Investigators. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. N Engl J Med **2015**; 373:2599–607.
26. Younossi ZM, Park H, Gordon SC, et al. Real-world outcomes of ledipasvir/sofosbuvir in treatment-naive patients with hepatitis C. Am J Manag Care **2016**; 22:SP205–11.
27. U.S. Department of Health and Human Services Centers for Medicare and Medicaid Services. 2016 Physician Fee Schedule. **2016**.
28. U.S. Department of Health and Human Services Centers for Medicare and Medicaid Services. 2016 Laboratory Fee Schedule. **2016**.
29. Pyne JM, French M, McCollister K, Tripathi S, Rapp R, Booth B. Preference-weighted health-related quality of life measures and substance use disorder severity. Addiction **2008**; 103:1320–9; discussion 1330–2.
30. Hallager S, Ladelund S, Christensen PB, et al. Liver-related morbidity and mortality in patients with chronic hepatitis C and cirrhosis with and without sustained virologic response. Clin Epidemiol **2017**; 9:501–16.
31. Smith BD, Beckett GA, Yartel A, Holtzman D, Patel N, Ward JW. Previous exposure to HCV among persons born during 1945–1965: prevalence and predictors, United States, 1999–2008. Am J Public Health **2014**; 104:474–81.
32. US Centers for Disease Control and Prevention. Surveillance for viral hepatitis United States, 2014. **2015**.
33. Tapper EB, Bacon BR, Curry MP, et al. Real-world effectiveness for 12 weeks of ledipasvir-sofosbuvir for genotype 1 hepatitis C: the Trio Health study. J Viral Hepat **2017**; 24:22–7.
34. Schackman BR, Leff JA, Barter DM, et al. Cost-effectiveness of rapid hepatitis C virus (HCV) testing and simultaneous rapid HCV and HIV testing in substance abuse treatment programs. Addiction **2015**; 110:129–43.
35. He T, Li K, Roberts MS, et al. Prevention of hepatitis C by screening and treatment in U.S. prisons. Ann Intern Med **2016**; 164:84–92.
36. Assoumou SA, Tasillo A, Leff JA, et al. The cost-effectiveness of one-time hepatitis C screening strategies among adolescents and young adults in primary care settings. Clin Infect Dis **2017**; 66:376–384.
37. Linas BP, Wong AY, Schackman BR, Kim AY, Freedberg KA. Cost-effective screening for acute hepatitis C virus infection in HIV-infected men who have sex with men. Clin Infect Dis **2012**; 55:279–90.
38. Isenhour CJ, Hariri SH, Hales CM, Vellozzi CJ. Hepatitis C antibody testing in a commercially insured population, 2005–2014. Am J Prev Med **2017**; 52:625–31.
39. Linas BP, Hu H, Barter DM, Horberg M. Hepatitis C screening trends in a large integrated health system. Am J Med **2014**; 127:398–405.
40. Flanigan CA, Leung SJ, Rowe KA, et al. Evaluation of the impact of mandating health care providers to offer hepatitis C virus screening to all persons born during 1945–1965—New York, 2014. Morb Mortal Wkly Rep **2017**; 66:1023–6.
41. Hagan H, Thiede H, Des Jarlais DC. Hepatitis C virus infection among injection drug users: survival analysis of time to seroconversion. Epidemiology **2004**; 15:543–9.
42. Suryaprasad AG, White JZ, Xu F, et al. Emerging epidemic of hepatitis C virus infections among young nonurban persons who inject drugs in the United States, 2006–2012. Clin Infect Dis **2014**; 59:1411–9.
43. Mathers BM, Degenhardt L, Bucello C, Lemon J, Wiessing L, Hickman M. Mortality among people who inject drugs: a systematic review and meta-analysis. Bull World Health Organ **2013**; 91:102–23.
44. McAnulty JM, Tesselaar H, Fleming DW. Mortality among injection drug users identified as "out of treatment." Am J Public Health **1995**; 85:119–20.
45. Miller CL, Kerr T, Strathdee SA, Li K, Wood E. Factors associated with premature mortality among young injection drug users in Vancouver. Harm Reduct J **2007**; 4:1.
46. Degenhardt L, Larney S, Randall D, Burns L, Hall W. Causes of death in a cohort treated for opioid dependence between 1985 and 2005. Addiction **2014**; 109:90–9.
47. Sacks-Davis R, Grebely J, Dore GJ, et al; InC3 Study Group. Hepatitis C virus reinfection and spontaneous clearance of reinfection–the InC3 study. J Infect Dis **2015**; 212:1407–19.
48. Viner K, Kuncio D, Newbern EC, Johnson CC. The continuum of hepatitis C testing and care. Hepatology **2015**; 61:783–9.
49. U.S. Department of Health and Human Services Center for Medicare Services. Clinical Diagnostic Laboratory Fee Schedule. **2016**.
50. Micromedex Solutions. Drug Topics Red Book Online. Available at: http://www.micromedexsolutions.com/. Accessed 15 December 2017.
51. Sullivan PW, Ghushchyan V. Preference-based EQ-5D index scores for chronic conditions in the United States. Med Decis Making **2006**; 26:410–20.