Economic Model of a Birth Cohort Screening Program for Hepatitis C Virus

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Recent research has identified high hepatitis C virus (HCV) prevalence among older U.S. residents who contracted HCV decades ago and may no longer be recognized as high risk. We assessed the cost-effectiveness of screening 100% of U.S. residents born 1946-1970 over 5 years (birth-cohort screening), compared with current risk-based screening, by projecting costs and outcomes of screening over the remaining lifetime of this birth cohort. A Markov model of the natural history of HCV was developed using data synthesized from surveillance data, published literature, expert opinion, and other secondary sources. We assumed eligible patients were treated with pegylated interferon plus ribavirin, with genotype 1 patients receiving a direct-acting antiviral in combination. The target population is U.S. residents born 1946-1970 with no previous HCV diagnosis. Among the estimated 102 million (1.6 million chronically HCV infected) eligible for screening, birth-cohort screening leads to 84,000 fewer cases of decompensated cirrhosis, 46,000 fewer cases of hepatocellular carcinoma, 10,000 fewer liver transplants, and 78,000 fewer HCV-related deaths. Birth-cohort screening leads to higher overall costs than risk-based screening ($80.4 billion versus $53.7 billion), but yields lower costs related to advanced liver disease ($31.2 billion versus $39.8 billion); birth-cohort screening produces an incremental cost-effectiveness ratio (ICER) of $37,700 per quality-adjusted life year gained versus risk-based screening. Sensitivity analyses showed that reducing the time horizon during which health and economic consequences are evaluated increases the ICER; similarly, decreasing the treatment rates and efficacy increases the ICER. Model results were relatively insensitive to other inputs. Conclusion: Birth-cohort screening for HCV is likely to provide important health benefits by reducing lifetime cases of advanced liver disease and HCV-related deaths and is cost-effective at conventional willingness-to-pay thresholds. (HEPATOLOGY 2012;55:1344-1355)

Hepatitis C virus (HCV) is the most common blood-borne viral infection in the United States,[1] affecting an estimated 3.6 million U.S. residents.[2] The majority of infected individuals develop chronic hepatitis; persistent liver injury leads to cirrhosis in 5%-30% of cases[3] and may progress to advanced liver disease (AdvLD), which includes decompensated cirrhosis or hepatocellular carcinoma (HCC), leading to liver transplant and premature death. Costs of HCV in the United States are estimated to exceed $5 billion per year,[4] with projected HCV-related societal costs for the years 2010-2019 estimated to total $54.2 billion.[5]

For the last decade, the standard of care for treating HCV has been the combination of pegylated interferon (Peg-IFN) and ribavirin (RBV),[6] which successfully eradicates virus (sustained virologic response; SVR) in 40%-80% of treated patients.[7] This response is 40%-50% in patients with HCV genotype 1 and 80% for patients infected with HCV genotypes 2 and 3. However, the recent approval of newer direct-acting antiviral (DAA) drugs, such as protease inhibitors,

Abbreviations: AdvLD, advanced liver disease; CDC, Centers for Disease Control and Prevention; DAA, direct-acting antiviral; ELISA, enzyme-linked immunosorbent assay; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; IV, intravenous; PCR, polymerase chain reaction; Peg-IFN, pegylated interferon; QALY, quality-adjusted life year; RBV, ribavirin; REF, reference; SVR, sustained virologic response; USD, U.S. dollars.

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used in combination with the Peg-IFN and RBV regimen has the potential to increase SVR in treatment-naïve patients with genotype 1 disease to levels similar to those achieved in genotypes 2 and 3.[8,9]

Clinical guidelines for the screening of HCV published by the Centers for Disease Control and Prevention (CDC) state that all persons should be screened for behaviors that put them at high risk for HCV infection and that those with identified risk factors should be screened for HCV antibodies. The at-risk population includes injection drug users (current or past), recipients of a blood transfusion or organ transplant before July 1992 or clotting factor concentrates produced before 1987, long-term dialysis patients, children born to HCV-positive women, and health care, emergency medical, and public safety workers exposed to HCV.[10] However, recent data suggest that up to three quarters of the prevalent HCV population remain unaware of their condition.[11-14] Factors contributing to low screening rates likely include limited physician awareness, reluctance of patients to admit to unsafe past behaviors, and perception of limited efficacy and poor tolerability of treatments.[13,15-17]

Recent reviews of the economics of HCV screening in several countries concluded that screening was likely to be cost-effective only in populations with high HCV prevalence (i.e., prevalence of 7%-80%) and not in the average-risk or general population (i.e., prevalence from 1% to 3.8%).[18,19] Epidemiologic data[20] suggest that HCV prevalence is highest among U.S. residents born from 1946 to 1970 (including Baby Boomers born from 1946 to 1964). Because the majority of infected individuals in this birth cohort contracted the virus decades ago,[20] they may not be aware of their risk status, even if they fit the risk profile for HCV screening, and are unlikely to be diagnosed until symptoms of liver disease appear. In addition to their high prevalence of infection, as they age, they are at growing risk of developing AdvLD and may have limited time to be diagnosed and successfully treated to avoid potential future complications.

The aim of this study therefore was to assess the clinical and cost implications as well as cost-effectiveness of one-time, targeted screening for HCV in the 1946-1970 birth cohort in the United States (birth-cohort screening), compared with current risk-based screening.

Patients and Methods

We developed a Markov model of the natural history of HCV to assess the potential costs and benefits of a birth-cohort screening program by considering screening, diagnosis, treatment, and outcomes of HCV in the U.S. population. We assessed the clinical and economic effect of implementing a targeted birth-cohort screening program, compared to risk-based screening, based on reported real-world implementation. We focused on the long-term benefits of early diagnosis and treatment on survival and the long-term costs of managing AdvLD. It was assumed that the targeted screening program would temporarily replace the current risk-based screening protocol only in the relevant birth cohort for a limited time (i.e., 5 years), after which the current policy of risk-based screening would resume. The base-case perspective was of a payer; therefore, we considered only direct medical-care costs. Health outcomes evaluated were cases of AdvLD avoided and HCV-related deaths averted; the incremental cost-effectiveness ratio (ICER) was calculated for incremental cost per quality-adjusted life year (QALY) gained.

Model Population. The model population for the primary analysis comprised all individuals born from 1946 to 1970 in the United States currently eligible for screening, based on having no current diagnosis of HCV or documented liver disease. The birth-cohort screening program was assumed to be a supplemental program in the target birth cohort. The population outside of this birth cohort (i.e., born before 1946 or after 1970) was assumed to continue to be screened based on risk-based screening protocols and thus be unaffected by the birth-cohort screening program; therefore, they were not included in this analysis.

Because the current underlying prevalence of chronic HCV and HCV fibrosis distribution in the target population are unknown, we estimated these values in a preliminary analysis using our model (described in the Supporting Materials), where

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Additional Supporting Information may be found in the online version of this article.

Table 1. Screening-Eligible Birth Cohort Born 1946-1970 by HCV Infection, Fibrosis Stage, and Age Group in 2010

	Age Group (2010) (Years)					
Screening-Eligible Population	**40-44**	**45-49**	**50-54**	**55-59**	**60-64**	**All Ages (40-64)**
Total*	20,922,500	22,563,700	22,065,400	19,404,800	16,593,100	101,549,300
No chronic HCV	20,703,700	22,242,900	21,685,100	19,042,800	16,289,300	99,963,700
Spontaneously cleared	127,100	195,100	225,200	197,700	153,700	898,900
Chronic HCV-infected	218,800	320,800	380,300	362,000	303,800	1,585,600
By fibrosis stage, n (% of HCV infected)						
F0	56,700 (25.9)	67,300 (21.0)	62,300 (16.4)	45,300 (12.5)	30,100 (9.9)	261,700 (16.5)
F1	82,200 (37.6)	114,300 (35.6)	121,500 (32.0)	98,200 (27.1)	69,500 (22.9)	485,800 (30.6)
F2	42,000 (19.2)	66,000 (20.6)	79,900 (21.0)	73,900 (20.4)	57,600 (19.0)	319,500 (20.1)
F3	24,400 (11.2)	44,300 (13.8)	62,700 (16.5)	67,400 (18.6)	58,800 (19.4)	257,600 (16.2)
F4	13,400 (6.1)	29,000 (9.0)	53,800 (14.2)	77,100 (21.3)	87,800 (28.9)	261,100 (16.5)

*Generated from preliminary model used to estimate infection and progression of HCV; totals are estimated after excluding 22% of the chronically HCV-infected population (including all with advanced liver disease) assumed to be previously diagnosed; those spontaneously cleared were assumed to retain HCV antibodies and screen false positive for HCV.

incident HCV cases among persons born from 1946 to 1970 were followed until 2010 to track HCV infection, development of chronic HCV, and subsequent HCV progression. Those infected and spontaneously clearing HCV were assumed to retain HCV antibodies. Screening, diagnosis, and treatment were not explicitly modeled during this prescreening period, but we assumed that 22% of individuals with chronic HCV in 2010, including all with AdvLD, were aware of their infection status (i.e., diagnosed) and therefore ineligible for screening.[13] The results of this analysis were used to identify the screening-eligible population and its underlying age-specific distribution across the fibrosis stages (i.e., METAVIR F0-F4) and HCV-antibody status[21] in 2010 (Table 1).

Model Structure. The structure of the model is illustrated in Fig. 1. The model population is categorized into Markov states based on HCV infection status and stage, screening history, treatment for HCV, and death (not depicted). The population is further stratified by age group, gender, and genotype (genotype 1 versus genotypes 2 and 3, grouped). Patients can progress from less-severe fibrosis stages to more-severe fibrosis stages; those in F3 and F4 can progress to HCC and those in F4 are at risk of progression to decompensated cirrhosis. Progression is also allowed

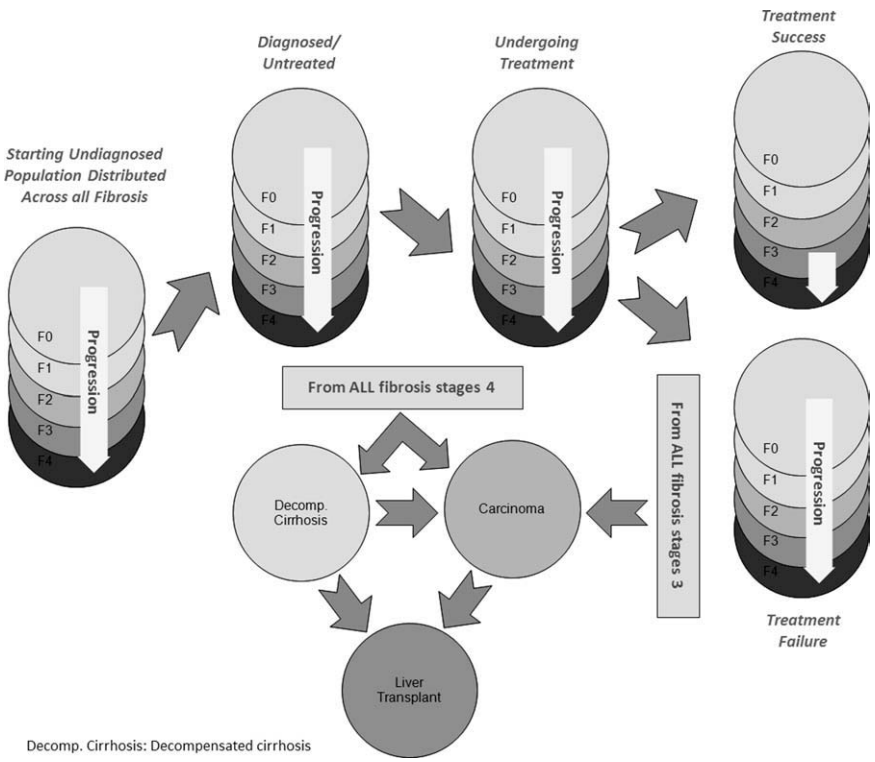


Fig. 1. Overview of the model of HCV diagnosis, treatment, and progression.

from decompensated cirrhosis to HCC and from decompensated cirrhosis or HCC to liver transplant. It has been suggested that a portion of HCV patients may progress slowly or may not be at risk of progression[2]; therefore, the model was programmed such that a subset of patients could be assumed to progress more slowly than others or not progress at all. Progression is modeled by assigning state-specific transition probabilities that differ by gender, age at infection, and current age. The model is stratified into 1-year age bands, with individuals transitioning 1 year in age each cycle.

Screening history is tracked for HCV-uninfected individuals to ensure that they are screened only once. The model allows for false-positive screening tests for the HCV-uninfected population; these patients are those who have spontaneously cleared HCV infection, but still carry antibodies for the disease. It was assumed that individuals with a false-positive test would undergo confirmatory testing and receive a negative diagnosis; therefore, the state is treated as transient.

All patients with undiagnosed disease begin the model in one of five undiagnosed HCV fibrosis states. Movement from the undiagnosed to diagnosed states is governed by the probability of screening. Persons who are not diagnosed may progress through the disease stages from F0-F4 to AdvLD. Once diagnosed, patients are eligible for treatment; however, we assumed that a portion of patients will never be eligible for treatment because of medical contraindications. For treatment-eligible patients, we assumed that a portion undergo treatment at diagnosis, whereas the remainder initiate treatment at a constant yearly probability until death or progression to AdvLD. Untreated patients progress through the fibrosis stages, and the treatment-eligible patients may receive treatment at any point before progression to AdvLD. Treated patients may achieve SVR based on stage- and genotype-specific efficacy of treatment.

Successfully treated patients are tracked in recovered states (F0-F4) to account for morbidity and mortality complications of potential liver scarring associated with previous HCV infection. Patients who recover from fibrosis stages F0-F2 remain in the recovered state until death from other causes or for the remainder model time horizon, whereas those who recover from F3 or F4 may still develop AdvLD. Patients who fail treatment transition to "previously treated" health states (i.e., F0-F4) and progress similarly to untreated patients, but are assumed to be ineligible for retreatment or second-line therapy. Patients may both succeed or fail therapy and progress in the same cycle to ensure that merely receiving treatment is not protective against progression. In any cycle, patients can remain in their current health state, HCV-infected patients can die from HCV complications, and both infected and uninfected patients can die from other causes.

Model Estimation. Default model parameters for costs, utilities, and screening- and treatment-related inputs (Table 2) were estimated from published literature, other secondary sources, and expert opinion. Disease progression and mortality rates from AdvLD by gender, age at infection, and current age were derived mainly from a published model that synthesized data from primary sources[2] and are detailed in Supplementary Table 1. Background mortality for those without AdvLD was estimated from age-specific U.S. population averages.[22] An administrative claims analysis was used to estimate the population proportion screened and the probability of infection among screened individuals under current risk-based screening practice.[2] Treatment eligibility was estimated from follow-up studies[14,28,29] and treatment efficacy from clinical trials.[30,31] Utility multipliers for each health state were derived from published studies of HCV disease, treatment, liver failure, and liver transplant[19,39-41] and were applied to age-specific U.S. national norms[23] to arrive at the age-specific utility for each health state. A transient QALY decrement was associated with a positive diagnosis, including false positive. Costs associated with HCV diagnosis, management, and treatment were estimated from a recent claims study[38] and Medicare reimbursement[34]; undiagnosed HCV disease was assumed to accrue no HCV-related costs. All costs are expressed in 2010USD (U.S. dollars) and, where appropriate, were inflated to 2010USD using the Bureau of Labor Statistics consumer price index for medical-care services.[24]

HCV Screening Strategies. The birth-cohort screening strategy assumes that 100% of the target population will be screened over a 5-year period, in equal numbers each year; this assumption implies that the proportion of unscreened undergoing screening will be 20% in year 1, 25% in year 2, 33.3% in year 3, 50% in year 4, and 100% in year 5. Screening coverage under current risk-based screening was estimated from a published analysis of claims data from an insured population[25] and was assumed to occur at the same yearly probability for the model population until age 70; no screening was assumed for those older than 70. All screened patients were assumed to receive antibody testing with enzyme-linked immunosorbent assay (ELISA), followed by confirmatory polymerase chain reaction (PCR) in those testing antibody positive.

Table 2. Model Inputs

Parameter	Base-Case Estimate	Alternative Values Used in Sensitivity Analyses	References
Proportion of genotype 1	0.75		Blatt et al., 2000; Nainan et al., 2006[26,27]
Proportion of genotypes 2 and 3	0.25		
Screening-eligible target population in 2010* (years)	40-64	45-64, 50-64, 40-59	
Screening parameters			
Risk-based screening†			
Annual proportion screened			
Among those without HCV infection (%)			
Male	0.62	1.25	
Female	0.72	1.44	Shatin et al., 2004[25]
Among those with HCV infection (%)			
Male	2.83	5.66	
Female	2.92	5.85	
Birth-cohort screening‡			
Birth-cohort screening coverage (over 5 years)	1.00	0.20, 0.40	
Proportion of eligible population screened by model year			
Year 1	0.20		
Year 2	0.25		
Year 3	0.33		Assumption
Year 4	0.50		
Year 5	1.00		
HCV treatment-related parameters			
Proportion eligible for treatment§	0.67	0.50 and 0.90	Stepanova et al., 2011[28]
Proportion of patients treated upon diagnosis‖	0.24	0.12	Volk et al., 2009[14]
Annual proportion treated (postdiagnoses among treatment-eligible patients)¶	0.10	0.05	Boccato et al., 2006[29]
Efficacy by HCV-related fibrosis (genotype 1/genotypes 2 and 3)#			
F0-F2	0.78/0.76	Reduced by 5% and 15%	Jacobson et al., 2011; Bruno et al., 2010[30,31]
F3	0.62/0.61		
F4	0.62/0.57		
Costs			
Screening related			
ELISA**	$30		Centers for Medicare & Medicaid Expenses[32]
PCR test**	$83		Centers for Medicare & Medicaid Expenses[32]
Biopsy (genotype 1/genotypes 2 and 3)††	$571/$0		MAG Mutual Healthcare Solutions[33]
Diagnosis-related (genotype 1/genotypes 2 and 3)‡‡	$1,231/$660		MAG Mutual Healthcare Solutions[33]
Treatment related			
Treatment successes (genotype 1/genotypes 2 and 3)			
Treatment costs§§	$70,740/$14,245		
Monitoring costs‖‖	$1,094/$813		Younossi et al., 1999; Genentech, 2010; First Bank Database, 2010; Vertex Pharmaceuticals Incorporated[34,35-37]
Treatment failures			
Treatment costs (genotype 1/genotypes 2 and 3)§§	$56,784/$7,123		
Monitoring costs‖‖	$266		
Annual health state costs			
No HCV	$0		Singer et al., 2001; Younossi et al., 1999[19,34]
Undiagnosed HCV	$0		Singer et al., 2001; Younossi et al., 1999[19,34]
Diagnosed HCV (F0-F3)¶¶	$209		MAG Mutual Healthcare Solutions; Younossi et al., 1999[33,34]
HCV-related compensated cirrhosis##	$557		MAG Mutual Healthcare Solutions; Younossi et al., 1999[33,34]

(Continued)

TABLE 2. *Continued*

Parameter	Base-Case Estimate	Alternative Values Used in Sensitivity Analyses	References
Decompensated cirrhosis	$27,918		McAdam et al., 2011[38]
Carcinoma	$43,725		McAdam et al., 2011[38]
Liver transplant (first year)	$168,375		McAdam et al., 2011[38]
Liver transplant (subsequent years)	$38,016		McAdam et al., 2011[38]
Utilities			
Fibrosis stages F0-F3	0.96		
Fibrosis stage F4	0.80		
Treatment (resulting from side effects)	0.90		
Failed treatment	0.00		
Decompensated cirrhosis	0.56		Singer et al., 2001; Kim et al., 1997; Younossi et al., 2001; Rodger et al., 1999[19,39-41]
Carcinoma	0.25		
Liver transplant (first year)	0.80		
Liver transplant (after first year)	0.95		
Disutility associated with diagnosis of HCV infection	0.02		
Proportion that are slow/nonprogressors (%)	0	10 and 24	Assumption
Discount rate (%)	3.00		
Time horizon, years	Lifetime	10 and 25	

*Obtained from preliminary model used to estimate infection and natural progression of HCV infection for birth cohort.

†Overall RBS rate in the population estimated from Shatin et al., 2004. Proportion of population screened estimated: female, 0.75%; male, 0.67% (calculated as female population tested [14,849] divided by total female study population [1,984,173] and male population tested [13,022] divided by total male study population [1,955,350], respectively); probability of a positive test given screening: female, 4.82%; male, 8.86% (calculated as total females with a positive result [725] divided by number of females tested and total males with a positive result [1,144] divided by number of males tested, respectively). Furthermore, annual proportion screened was estimated by first calculating the odds ratio of being screened for those with versus those without HCV infection and applying to odds ratio for the calculated proportion of persons without HCV infection that are screened.

‡Birth-cohort screening defined as 100% of the Baby Boomer population screened over a 5-year period, in equal numbers each year.

§Stepanova et al., 2011.

‖Volk et al., 2009, based on 24% treated in study of National Health and Nutrition Examination Survey Hepatitis C Follow-up Questionnaire. Applied to overall population.

¶Assumed treated upon progression (proxy for treatment); 55.7% progress over 7.8 mean follow-up years.

#Genotype 1: obtained from the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial (ADVANCE) trial (Jacobson et al., 2011) presented at the American Association for the Study of Liver Diseases 2010. Genotypes 2 and 3: meta-analysis of three clinical trials of IFN-α 2a+RBV; based on proportion of SVR with genotype 1 and for F0-F2: without bridging fibrosis/cirrhosis; F3: with bridging fibrosis; F4: with cirrhosis.

**Component codes for ELISA: 85306; PCR: 82726. Applied at time of screening; those with HCV incur costs of both tests. Those without HCV incur only the cost of ELISA. Those who spontaneously resolve and still retain antibodies incur the cost of both tests.

††For genotype 1, includes biopsy of liver (code: 47000), needle; ultrasonic guidance for needle placement (code: 76942), imaging supervision and interpretation; and preparation of pathology samples, staining and pathology reading/interpretation (code: 88162). For genotypes 2 and 3, assumed to be 0. Applied as one fifth the cost of biopsy each year, because diagnosed patients were assumed to incur biopsy costs every 5 years.

‡‡Includes one office visit–level 4 (code: 99215), liver profile (code: 80076), complete blood count (CBC) (code: 85027), and genotype testing (code: 87902) for genotypes 2 and 3 and, in addition, also includes liver biopsy (codes: 47000, 76942, and 88162) for genotype 1. These costs are applied as a one-time cost at the time of diagnosis.

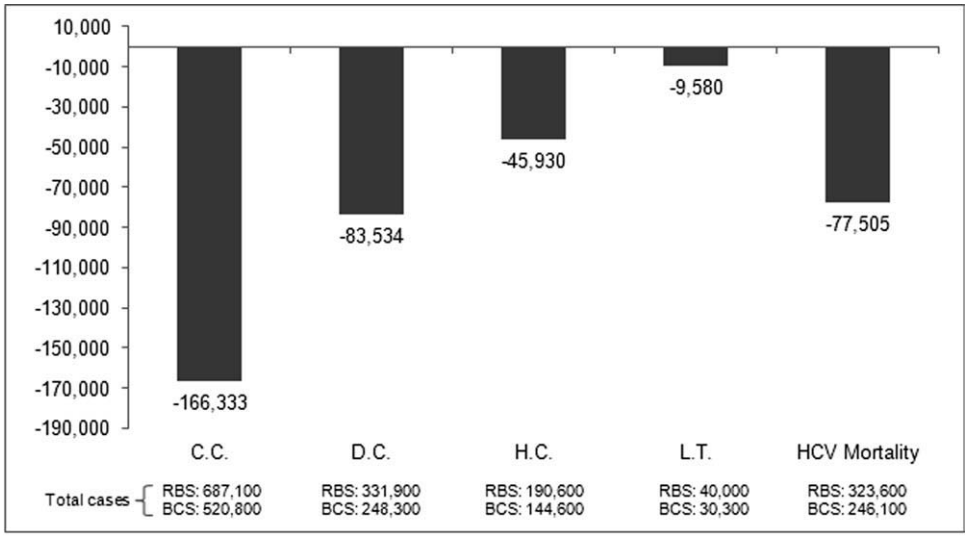
§§Treatment costs for successes for genotype 1 and genotypes 2 and 3 were estimated as sum of Peg-IFN (price/week: $491, obtained from First Bank Database, and assuming 48 weeks of treatment, the cost is $23,565; 24 weeks: $11,782) and RBV (for genotype 1, assumed equal distribution of dosages of 1,000 and 1,200 mg/day, with average weekly price being $18.33 and $21.99, respectively; hence, price per week for 48 weeks = 0.5*$18.33*48*7 + 0.5*$21.99*48*7 = $6,773. For genotypes 2 and 3, average weekly price for 800 mg/day = $14.66; hence, for 24 weeks, $14.66*24*7 = $2,463) for 34 (for genotype 1, assume 58% receive 24 weeks of treatment and 42% receive 48 weeks of treatment [from the ADVANCE trial] to calculate an average of 34 weeks of Peg-IFN+RBV treatment) and 24 weeks, respectively, assigned as a one-time cost to all patients. A cost of $49,200 was added for telaprevir for 12 weeks for all treated patients. Similar calculations were done for treatment failures, assuming 12 weeks of treatment of combination of Peg-IFN, RBV, and telaprevir for genotype 1 and combination of Peg-IFN and RBV for genotypes 2 and 3.

‖‖Estimated from Younossi et al., 1999; unit costs from Medicare RBVRS: liver profile ($16) and CBC ($13) at weeks 2,4,8,12,16, and 24 of treatment for genotypes 2 and 3 and at weeks 32, 40, and 48 for genotype 1; HCV RNA ($35) at end of treatment; level 4 office visit ($98) at weeks 6, 12, and 24 for genotypes 2 and 3 and an additional two office visits for genotype 1; CBC and liver profile at 4, 12, and 24 weeks post-treatment; HCV RNA and office visit at 24 weeks post-treatment. Follow-up costs not assigned to treatment failures. Monitoring costs were assigned as a one-time cost to everyone on treatment.

¶¶Resource use based on Younossi et al., 1999; includes one office visit, one CBC, one liver profile, and 1 HCV RNA test each year. Unit costs from Physician's Fee and Coding Guide.

##Resource use based on Younossi et al., 1999; includes two office visits, two ultrasound and alpha-fetoprotein tests, one CBC, one liver profile, and one HCV RNA test each year. Unit costs from Physician's Fee and Coding Guide.

Model Outputs. The primary clinical outcomes of the model are decompensated cirrhosis, HCC, liver transplant, and mortality. Costs of screening and the yearly costs of HCV diagnosis, management, and treatment, as well as the costs associated with HCV-related complications, were summed to calculate the lifetime



CC: Compensated Cirrhosis; DC: Decompensated Cirrhosis; HC: Hepatocellular Carcinoma; LT: Liver Transplant
RBS: Risk-based Screening Strategy; BCS: Birth-cohort Screening Strategy
Total Screened: 11,379,708 (RBS); 99,490,322 (BCS)
Total Diagnosed: 532,496 (RBS); 1,527,937 (BCS)
Total Treated: 295,423 (RBS); 873,942 (BCS)

Fig. 2. Lifetime incremental reductions in major clinical outcomes associated with targeted birth-cohort HCV screening versus risk-based HCV screening of U.S. residents born 1946-1970.

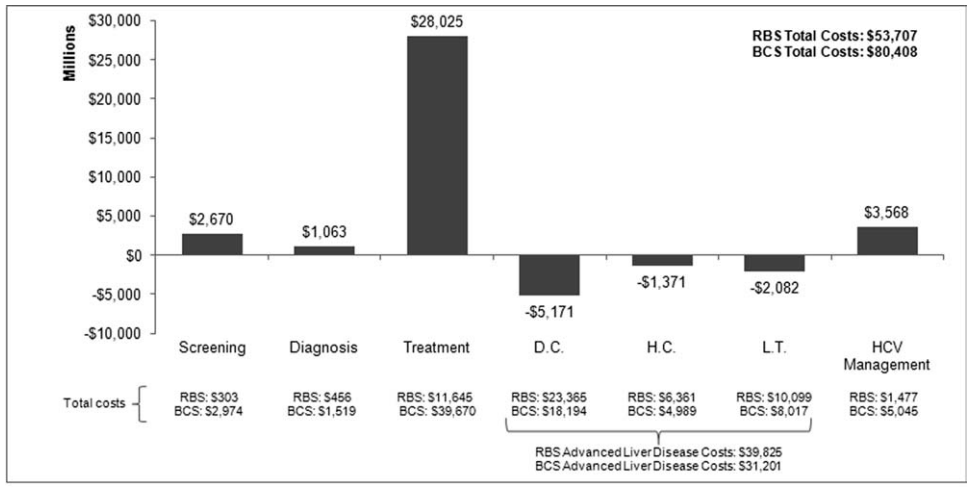
costs for each strategy. All costs and outcomes were discounted at a rate of 3% per year. QALYs were calculated by summing state-specific utilities associated with cycles spent in each health state and subtracting any utility decrements.

Analyses. The target population in the model was U.S. residents born from 1946 to 1970 (40-64 years of age in 2010) for both the current risk-based and birth-cohort screening strategies. An age-group analysis was conducted to identify an optimal birth cohort to include in the targeted screening program by evaluating more limited age ranges, such as the birth cohorts with age ranges of 45-64, 50-64, and 40-59 in 2010. In all analyses, age groups within the 1946-1970 birth cohort not included in the screening program were assumed to have the same probability of being screened as those in the risk-based screening arm.[25] ICERs are estimated by first running the model for all screening strategies and then rank ordering these strategies by increasing cost and comparing each strategy to the next less-costly strategy. If the more-costly strategy provides additional benefit, the two strategies are compared by dividing the additional cost by the additional benefit, yielding an ICER. A strategy is excluded from consideration by "dominance" if it is more costly and less effective than another strategy (i.e., strong dominance) or if it is incrementally less cost-effective than a more-expensive strategy (i.e., weak dominance). Once dominated strategies have been excluded, the ICERs of the remaining (i.e., "nondominated") strategies are compared against willingness-to-pay threshold values, such as $50,000 or $100,000, per QALY gained. The most effective birth-cohort screening strategy with an ICER of less than $100,000 per QALY was chosen as our base case and was used in sensitivity analyses.

To address uncertainty in the estimation of key model parameters and to consider potential future changes in the management of HCV, several sensitivity analyses were conducted to assess how changes in these parameters change results. These included testing alternative assumptions regarding the following: (1) 5-year coverage for birth-cohort screening at 20%, and 40%, to reflect levels more achievable in clinical practice; (2) treatment eligibility at 50% and 90%; (3) treatment rates (base case 24% at diagnosis, then 10% per year afterward) halved to a treatment rate at diagnosis of 12% and annually of 5%; (4) efficacy rates reduced by 5% and 15%; (5) model time horizon of 10 and 25 years; (6) progression rates for those >50 years set equal to rates for those ≤50; and (7) the fraction (varied from 10% to 24%) of chronic infections that progress at a slower rate than normal or do not progress at all. All parameters used in sensitivity analyses were based on plausible estimates from the literature and expert opinion.

Results

Selection of Target Birth Cohort. In incremental analyses to determine the optimal birth cohorts to include in a targeted screening program, current risk-based screening for all 40-64 years old in 2010 was



Note: All costs are in millions of dollars. DC: Decompensated Cirrhosis; HC: Hepatocellular Carcinoma
LT: Liver Transplant; RBS: Risk-based Screening Strategy; BCS: Birth-cohort Screening Strategy
Total lifetime costs for each cost category (by screening strategy) are displayed below their respective labels
HCV Management: includes costs of managing chronic HCV

Fig. 3. Lifetime incremental costs associated with targeted birth-cohort HCV screening versus risk-cohort HCV screening of U.S. residents born 1946-1970. Please confirm disclosure statement as accurate.

the least-costly strategy, whereas targeted birth-cohort screening for all 40-64 years old yielded the most benefits in terms of QALYs. Targeted screening of the older subgroups (i.e., 45-64 and 50-64) were both dominated strategies and so were removed from consideration. Targeted screening of the subset (40-59) and the larger group (40-64) were compared; because screening of the entire 40-64 birth cohort was found to provide additional benefit at a reasonable additional cost ($55,000 per QALY gained), it was chosen as the base-case strategy for reporting results. Based on results of the preliminary model (Table 1), we estimated 102 million screening-eligible individuals (i.e., those with no previous HCV diagnosis) in the relevant birth cohort, of whom an estimated 1.6 million are HCV-infected.

Base-Case Analyses

Clinical outcomes and associated costs. Lifetime differences in clinical outcomes and costs associated with moving from risk-based to birth-cohort screening in the 40- to 64-year-old screening-eligible population are reported in Figs. 2 and 3. A 5-year program of birth-cohort screening led to fewer cases of compensated cirrhosis and AdvLD in this population. Mortality associated with HCV was also reduced by approximately 77,500 deaths (Fig. 2). Although overall costs associated with birth-cohort screening were higher than with risk-based screening ($80.4 billion versus $53.7 billion) as a result of the costs associated with diagnosis and treatment, birth-cohort screening yielded lower AdvLD-related costs ($31.2 billion versus $39.8 billion in the risk-based strategy).

Cost-effectiveness analysis. Cost-effectiveness of the birth-cohort versus risk-based screening strategy in the 40- to 64-year-old birth cohort is reported in Table 3. Results are per person for all persons eligible for screening in 2010 and indicate that birth-cohort screening is more costly than risk-based screening, but provides additional quality-adjusted survival at a cost of $37,700 per QALY gained.

Sensitivity analysis. Results of the sensitivity analyses are reported in Table 3. Because the advantage of birth-cohort over risk-based screening derives from the assumed higher coverage, decreasing screening coverage led to a less-favorable cost-effectiveness profile for birth-cohort screening; however, at screening levels above 20%, this strategy remained below $45,000 per QALY gained. Decreasing the treatment eligibility and reducing the treatment rate assumptions by 50% led to an increase in the ICER, whereas increasing base-case assumptions regarding the risk-based screening rate had a minimal effect on the ICER. Likewise, there was little difference in results when a fraction of patients was assumed not to be at risk of disease progression or had slower than normal disease progression (not reported in Table 3). Reducing treatment efficacy by 5% and 15% led to an increase in the ICER. Assuming the progression rates for patients 50 years and older is equal to the progression rates for patients less than 50 years of age also yielded an increased ICER as a result of slower progression to AdvLD in the older age group. In both cases, the results remained cost-effective at <$50,000 per QALY gained. The effect of changing the model time horizon was more pronounced: Reducing the lifetime horizon to a 25-year time horizon nearly doubled the ICER per QALY gained estimated in the base case, and reducing the time horizon to 10 years increased the ICER by more than 15-fold.

Table 3. Cost-Effectiveness and Sensitivity Analyses Results for Birth Cohort Compared With the Risk-Based HCV Screening Strategy

Strategy	Cost Per Person	QALY Per Person	Incremental Cost	Incremental QALY	Cost/QALY
Base-case analysis					
Risk-based screening	$529	14.995	–	–	REF
Birth-cohort screening	$792	15.002	$263	0.007	$37,720
Sensitivity analyses					
Screening coverage assumptions*					
40% for BCS	$611	14.998	$82	0.002	$38,742
20% for BCS	$551	14.996	$22	0.001	$43,451
Screening rate					
Twice the current screening rate					
RBS	$599	15.000	–	–	REF
BCS	$792	15.000	$193	0.005	$37,581
Treatment eligibility assumptions					
50% for RBS and BCS					
RBS	$514	14.995	–	–	REF
BCS	$742	15.000	$228	0.005	$43,389
90% for RBS and BCS					
RBS	$549	14.996	–	–	REF
BCS	$861	15.006	$312	0.009	$33,281
Treatment rate assumptions					
12% at diagnosis and 5% annual for RBS and BCS					
RBS	$509	14.994	–	–	REF
BCS	$729	14.999	$220	0.004	$49,101
Efficacy					
Reduce efficacy by 5%					
RBS	$530	14.995	–	–	REF
BCS	$796	15.002	$266	0.007	$40,483
Reduce efficacy by 15%					
RBS	$532	14.995	–	–	REF
BCS	$804	15.001	$272	0.006	$47,168
Model time horizon					
10 Years					
RBS	$179	7.068	–	–	REF
BCS	$489	7.069	$310	0.0005	$602,079
25 Years					
RBS	$435	12.897	–	–	REF
BCS	$722	12.901	$287	0.005	$63,664
Transition probabilities					
Equal for age >50 and ≤50 years					
RBS	$474	14.999	–	–	REF
BCS	$751	15.005	$277	0.006	$45,307

Abbreviations: RBS, risk-based screening; BCS, birth-cohort screening.

*Incremental costs and QALY compared with the base-case RBS strategy. BCS scenarios in which <100% of the population was screened at the end of the 5-year BCS program assume that screening of the unscreened population resumes at the same probability as in the RBS arm.

Discussion

This study estimates that there are approximately 1.6 million undiagnosed HCV-infected U.S. residents 40-64 years in age. Under current screening practices, approximately two-thirds will remain undiagnosed until they progress to AdvLD or die. We estimate that a screening program targeting the birth cohort born from 1946 to 1970 (i.e., 40-64 years old in 2010), including the Baby Boomer population, is likely to be cost-effective at U.S. and European willingness-to-pay thresholds of <$50,000 per QALY gained. The birth-cohort screening program provides benefit over risk-based screening by identifying HCV-infected persons who would not otherwise have been screened. At similar levels of screening, birth-cohort screening is less efficient than risk-based screening, because the infected and uninfected are equally likely to be screened under the birth-cohort assumptions. At a 5-year birth-cohort screening level of 13% or lower, risk-based screening is the dominant strategy; at levels above 14%, birth-cohort screening provides more benefit than risk-based screening; and at screening levels above 17%, birth-cohort screening is cost-effective at a willingness-to-pay threshold of $50,000/QALY. Previous studies that found HCV screening to be cost-effective in high-risk groups (e.g., active intravenous [IV] drug users),[18] but

not in the general asymptomatic population,[11,18,19] did not examine specific age groups at elevated, but moderate, risk of HCV; however, our results are consistent with targeted screening for chronic HIV infection in older patients[42] and patients at moderate risk of HIV.[43]

The clinical effect of an HCV screening program over the lifetime of the population is substantial, with reductions of approximately 25% in cases of AdvLD and liver transplants. Birth-cohort screening is expected to lead to diagnosis and, potentially, treatment, of >900,000 prevalent cases of HCV—an important finding for treatment of the disease.[44] When compared to analyses we had conducted before the approval of DAAs, in which we assumed treatment with Peg-IFN and RBV only, we found the benefits of screening, in terms of AdvLD prevented and deaths averted, increased substantially with the addition of DAAs. However, the cost per QALY also increased (from approximately $25,000 with conventional therapy) as a result of increased drug costs. Treatment rates and clinical effectiveness of HCV therapies in the community setting are unknown. However, sensitivity analyses showed birth-cohort screening to be cost-effective, even using relatively pessimistic assumptions for treatment rates and efficacy. Threshold analysis indicated that the ICER for birth-cohort screening remains below $50,000 per QALY gained, even if treatment efficacy is 18% lower than that observed in the clinical trials.

The benefits of screening in the study accrue from effective treatment and cure of HCV; therefore, cost-effectiveness of the birth-cohort screening program is improved by increasing treatment eligibility and is worsened by reducing treatment rates and efficacy. We estimated the likelihood of treatment based on data for conventional Peg-IFN and RBV therapy; however, as treatment continues to improve and becomes more tolerable, we might anticipate that the number of infected patients who seek and qualify for treatment will increase, thus increasing the benefits of the birth-cohort screening program. Because the costs of the screening program are borne in the first 5 years after implementation while the benefits accrue throughout the successfully treated patients' remaining life, the cost-effectiveness of birth-cohort screening is improved when the outcomes in the target cohort are considered over their lifetime, instead of 10 or 25 years.

Under both screening strategies considered, the majority of the screening in the population 40-64 years in age occurs at <65 years and therefore would likely be covered by commercial health insurance and, to a lesser extent, by Medicaid, Medicare, or the Department of Veterans Affairs.[28] Because the clinical benefits of screening accrue in later years, a large portion of the potential cost savings would be realized in patients ≥65 years, enrolled in the Medicare program[28]—although Medicaid and commercial insurance have financial exposure as secondary insurers and would share in the savings. Stratifying costs accrued to patients <65 years versus ≥65 years shows that birth-cohort screening results in a 14% or $1.5 billion reduction in AdvLD-related costs for patients <65 years and a 24.5% or $7.1 billion reduction for patients ≥65 years.

The model is subject to the usual limitations of disease models, which are necessarily simplifications of the disease and treatment process. Our analysis was intended to examine the economics of a fully implemented birth-cohort screening program; therefore, 100% of the target population is assumed to be screened over the 5-year implementation period. In fact, implementation of birth-cohort screening is likely to be limited in populations that are incarcerated, IV drug users, homeless, or lacking insurance. More limited implementation in the target population would be expected to decrease both the screening costs and potential benefits of the birth-cohort screening program.

Results are also dependent on assumptions made in designing the model and estimating inputs. Estimates of HCV prevalence and proportion diagnosed and treated were derived by modeling and combining data from a variety of sources; therefore, the validity and precision of these estimates cannot be verified. In addition, the cost estimates used in the model are derived and synthesized from multiple data sources and may not reflect the actual cost of diagnosis and management of HCV. We did not consider indirect and nonmedical costs of HCV infection, including patient time, transportation, and other out-of-pocket costs for treatment. Because these costs are more likely to occur in diagnosed patients, including them may have reduced the cost-effectiveness of the intervention.

Because we assumed most patients in our population were infected long ago, we did not model new infections resulting from disease transmission in this population. To the extent that screening and successful treatment would reduce transmission and thus prevent new cases of HCV, the benefits of birth-cohort screening are underestimated in our analysis.

Similarly, we did not allow for immigration, which would potentially expand the screening-eligible population; the effect on cost-effectiveness of birth-cohort screening would depend on the prevalence of infection,

disease progression, and previous diagnosis in this population. We did not allow for age-specific risk-based screening rates or rescreening of those previously screened because of limited data. Because rescreening increases costs, but provides no benefit, and is more likely to occur in the risk-based screening arm, inclusion of rescreening would favor birth-cohort screening.

Our analysis assumes that screening of an additional 88 million U.S. residents over 5 years is within the capacity of the U.S. health care system and would have no effect on the cost or availability of screening and treatment. Although capacity constraints are not addressed in our analysis, we note that other large-scale screening programs are already in place; for example, states routinely test all newborns (approximately 4 million/year in the United States) for up to 30 metabolic and genetic diseases.[45] Moreover, it is expected that large-scale screening may promote wider use of technologies, such as robotic ELISA and PCR, resulting in expanded capacity as well as lower unit costs of screening. Capacity planning to ensure the availability of HCV treatment may be required, including possible adoption of alternative treatment delivery models[46]; however, consideration of these health-system changes is beyond the scope of the current analysis.

In summary, model results demonstrate that implementation of a supplemental, targeted, one-time birth-cohort screening program over a limited period (i.e., 5 years) in the U.S. residents born from 1946 to 1970 is likely to provide important health benefits versus current risk-based screening by reducing lifetime cases of AdvLD, liver transplant, and deaths resulting from liver disease and is cost-effective at conventional willingness-to-pay thresholds.

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