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MAJOR ARTICLE

Cost-Effectiveness and Population Outcomes of General Population Screening for Hepatitis C

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Background. Current US guidelines recommend limiting hepatitis C virus (HCV) screening to high-risk individuals, and 50%–75% of infected persons remain unaware of their status.

Methods. To estimate the cost-effectiveness and population-level impact of adding one-time HCV screening of US population aged 20–69 years to current guidelines, we developed a decision analytic model for the screening intervention and Markov model with annual transitions to estimate natural history. Subanalyses included protease inhibitor therapy and screening those at highest risk of infection (birth year 1945–1965). We relied on published literature and took a lifetime, societal perspective.

Results. Compared to current guidelines, incremental cost per quality-adjusted life year gained (ICER) was $7900 for general population screening and $4200 for screening by birth year, which dominated general population screening if cost, clinician uptake, and median age of diagnoses were assumed equivalent. General population screening remained cost-effective in all one-way sensitivity analyses, 30 000 Monte Carlo simulations, and scenarios in which background mortality was doubled, all genotype 1 patients were treated with protease inhibitors, and most parameters were set unfavorable to increased screening. ICER was lowest if screening was applied to a population with liver fibrosis similar to 2010 estimates. Approximately 1% of liver-related deaths would be averted per 15% of the general population screened; the impact would be greater with improved referral, treatment uptake, and cure.

Conclusions. Broader screening for HCV would likely be cost-effective, but significantly reducing HCV-related morbidity and mortality would also require improved rates of referral, treatment, and cure.

Chronic hepatitis C (CHC) is a neglected disease. More than 4 million US residents have been infected with hepatitis C virus (HCV), 2.9–3.7 million have CHC, and 49%–75% of infected persons are unaware of their infection [1, 2]. Most Americans with CHC acquired their infections decades ago and the current incidence is low [3]. However, CHC-associated liver fibrosis progresses with age, and CHC now results in approximately 14 000 deaths in the United States annually [1] and is the underlying cause for 37%–41% of all liver transplants [4]. In the absence of treatment, CHC is predicted to result in nearly 300 000 deaths between 2020 and 2029 [3]. Despite the scale of the problem and the availability of increasingly effective therapy [5], national guidelines established when treatment was less efficacious recommend testing only persons with identified risk factors (eg, injection drug use, blood transfusions before 1992, unexplained liver function abnormalities) [6]. The objectives of this study are to compare the cost-effectiveness of adding one-time CHC screening of the adult US population to the current risk factor-based approach to improve treatment of advancing fibrosis, and to estimate the impact of increased screening on CHC-related morbidity and mortality.

METHODS

Given the low incidence of CHC in the United States, we modeled screening and management of prevalent infection under 2010 practice standards. Our primary analysis compared risk factor-based screening, the

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current standard of care, to risk factor-based screening plus one-time screening of the general adult US population 20–69 years of age. Screening was considered a one-time intervention in the decision analytic model, followed by a Markov model (built in Microsoft Excel 2010) defining the natural history, costs, and quality-adjusted life years (QALYs) of CHC. Markov models are matrix-based mathematical models used to represent decision problems over time with repeated measures; patients are always in one of a finite number of discrete health states with events represented as transitions from one state to another. Table 1 presents parameters and citations used for our base case and optimal screening and management analyses, generally selected to be unfavorable to the hypothesis that broadened screening would be cost-effective. A detailed rationale for the selection of each base-case parameter, range, and citation is available as an online supplemental methods section (Supplemental Table). Figure 1 depicts the decision analytic and simplified Markov models (for the complete Markov model, see Supplemental Figure 1).

Decision Analytic Model

We used the add-in "TreePlan" (Decision Toolworks, San Francisco, CA) to develop a decision model reflecting the choice of screening strategies. As a conservative estimate of the proportion of CHC detected through current screening approaches, we used National Health and Nutrition Examination Survey (NHANES) data that 49% of the general US population is unaware of their infection [14]. The intervention branch of the model added one-time screening of the general US population (aged 20–69 years). In our base-case model, we conservatively estimated that 15% of the general population would be screened based on surveys reporting 5%–60% uptake of screening recommendations [72]. Because CHC prevalence in the United States is highest among the 35.5% of US adults born from 1945 to 1965 [73], we also conducted a subanalysis of screening 15% of this age group versus the general population.

In the decision model, the total proportion of persons initially treated for CHC was the product of the proportion referred for treatment evaluation, the proportion attending such a visit, the proportion without absolute contraindications to treatment, and the proportion accepting therapy based on genotype. In our base-case model, 14% of persons detected through screening and 26% of persons receiving specialty evaluation received treatment initially, an estimate consistent with authors' clinical experience and extant literature [25–27]. We estimated that 70% of genotype 1 patients without an absolute contraindication to treatment received a liver biopsy, a possible overestimate given the adoption of new approaches to gauge liver fibrosis and determine suitability for treatment [31, 32]. Five health state outcomes from the decision tree were stratified to populate the Markov model: (1) uninfected, (2) unknown infected (including those who were diagnosed but not seen by a specialist), (3) known infected with absolute contraindication to treatment, (4) known infected by genotype, and (5) known infected in treatment by genotype.

Markov Model

The Markov model was stratified by absorbed health states and followed a person 45 years of age (consistent with a peak CHC prevalence at 40–49 years of age in the 2007–2008 data [7]) with annual transitions and standard mortality. A review of recent epidemiologic [33], modeling [3], and trial data of referred patients [5] generated a variety of possible distributions for stage of fibrosis at the time of diagnosis; overall, fibrosis was fairly evenly distributed among each stage, and thus we assumed that one fifth of these persons would be in each stage of fibrosis for our baseline model. We relied on a recent meta-analysis for the rate of progression through each stage [34] and allowed for spontaneous presentation outside of screening [15]. We did not consider benefits of transmission risk reduction, re-treatment, or screening for complications, but we did estimate a nominal reduction in fibrosis progression for those in specialty care based on the impact of alcohol use on fibrosis progression [35], the estimated rate of alcohol use among NHANES respondents with CHC [8, 36], and the expected reduction in alcohol use after counseling [37, 38]. Because treatment of genotype 1 patients with no fibrosis is generally deferred [74], we excluded those patients from the initial treatment cohort but allowed treatment in subsequent years at an overall rate of 4% per year [39]. Rates of sustained viral response ([SVR] considered a cure and associated with improved quality of life and reduced mortality [75]) were taken from major studies for genotype 1 [28], genotype 2/3 [28, 43], and patients with cirrhosis [44]. Risk for progressive liver disease was eliminated for SVR for those with no to moderate fibrosis, and risk was reduced for those with severe fibrosis [46] or cirrhosis [50].

Progression to end-stage liver disease events was primarily based on an older, retrospective study [76]; recent studies included some estimates that would strongly favor general population screening and were thus used as upper limits [47]. Progression from severe fibrosis to end-stage liver disease events was estimated based on recent data [46]. A well-established expert panel review [52] was used as a single source for multiple parameters, including progression from decompensated cirrhosis to liver transplantation; the rate of progression from hepatocellular carcinoma to liver transplantation was assumed equivalent. Liver transplants were capped at 4000 per year based on current estimates that only 6000–7000 livers are available for transplant annually [77]. Progression from liver transplant

Table 1. Hepatitis C Screening Model Parameters

Parameter	Base-Case (Range)	References
Population prevalence		
Proportion of US general adult population HCV EIA+	0.016 (0.013–0.020)	[1, 7–10]
Proportion of injection drug users EIA+	0.60 (0.40–0.80)	[1, 11–13]
Proportion of EIA + unaware of infection	0.50 (0.49–0.75)	[1, 14–16]
Screening and referral		
Proportion EIA-false negative	0.010 (0.000–0.016)	[17–19]
Proportion EIA + chronically infected	0.800 (0.778–0.822)	[1, 20]
Proportion referred to specialty care	0.7700 (0.3850*–0.8269)	[20, 21]
Proportion attend specialty care	0.66 (0.59–0.73)	[20, 21]
Proportion genotype 1 (not 2 or 3)	0.78 (0.76–0.80)	[20, 22–24]
Proportion attending specialty care initially treated	0.26 (calculated)	[25–27]
Proportion absolute contraindications to treatment	0.127 (0.042–0.165*)	[15, 28]
Proportion genotype 2 or 3 accepting treatment	0.605 (0.550*–0.890)	[6, 25, 28–30]
Proportion genotype 1 receiving liver biopsy	0.70 (0.50–0.75*)	[20, 29, 31, 32]
Proportion genotype 1 offered and accepting treatment	0.2435 (0.1948*–0.3740)	[20, 27]
Stage of fibrosis at diagnosis		
None (F0)	0.2 (0.16–0.24)	[3, 5, 33]
Mild (F1)	0.2 (0.16–0.24)	[3, 5, 33]
Moderate (F2)	0.2 (0.16–0.24)	[3, 5, 33]
Severe (F3)	0.2 (0.16–0.24)	[3, 5, 33]
Cirrhosis (F4)	0.2 (0.16–0.24)	[3, 5, 33]
Health-state transition frequencies		
Fibrosis progression		
F0->F1	0.1170 (0.0936*–0.1404)	[34]
F1->F2	0.0850 (0.0680*–0.1020)	[34]
F2->F3	0.1200 (0.1090*–0.1330)	[34]
F3->F4	0.1160 (0.1040*–0.1290)	[34]
Reduction in rate of progression for alcohol use reduction	0.0008 (0.0016–0.0000*)	[8, 15, 35–38]
Transition from unknown to known CHC		
F0–F2	0.0100 (0.0000–0.0500*)	[15]
F3–F4	0.0380 (0.0280–0.0500*)	[15]
Proportion in care treated each subsequent year		
F0	0.0100 (0.0080–0.0120)	[39]
F1	0.0200 (0.0160–0.0240)	[39]
F2	0.0600 (0.0480–0.0720)	[39]
F3	0.0800 (0.0640–0.0960)	[39]
F4	0.0300 (0.0240–0.0420)	[39]
Proportion stopping treatment at 12 weeks due to poor response		
Genotype 1	0.19 (0.15–0.23)	[40, 41]
Genotype 2/3	0.10 (0.09–0.13)	[42]
Progression from treatment to SVR		
Genotype 1	0.46 (0.41*–0.50)	[43]
Genotype 2/3	0.80 (0.72*–0.88)	[28]
Genotype 1 cirrhosis	0.20 (0.16*–0.24)	[44, 45]
Genotype 2/3 cirrhosis	0.43 (0.35*–0.52)	[44]
Progression to advanced liver disease		
Compensated cirrhosis to decompensated cirrhosis	0.0390 (0.0300*–0.0480)	[46–49]
F3 to decompensated cirrhosis (product of parameter x cirrhosis to decompensated cirrhosis)	x0.3077 (0.0000–0.3692)	[46]
Advanced fibrosis SVR to decompensated cirrhosis (product of parameter × [cirrhosis or F3 to decompensation])	x0.0857 (0.0686–0.1028)	[45, 50]
Compensated cirrhosis to HCC	0.0190 (0.0170*–0.0550)	[46–50]

Table 1 continued.

Parameter	Base-Case (Range)	References
F3 to HCC (product of parameter × cirrhosis to HCC)	x0.3818 (0.0000–0.4582)	[46]
Advanced fibrosis SVR to HCC (product of parameter × [cirrhosis or F3 to HCC])	x0.6552 (0.5242–0.7862)	[45, 50, 51]
Decompensated cirrhosis to HCC	0.0140 (0.0060*–0.0200)	[47–49]
Decompensated cirrhosis or HCC to liver transplant	0.0310 (0.0248–0.0372)	[52]
Decompensated cirrhosis to death	0.1290 (0.1032*–0.1548)	[47, 48]
HCC to death	0.4270 (0.341*6–0.5124)	[47, 48]
First year of liver transplantation to death	0.1350 (0.0980*–0.2100)	[4]
Subsequent years of liver transplantation to death	0.0300 (0.0270*–0.0570)	[4, 53]
Costs		
CHC	$174.30 (82.51–509.36)	[49, 52, 54, 55]
Compensated cirrhosis	$1159.52 (678.61*–1640.44)	[49, 52, 54]
Decompensated cirrhosis	$14 864.57 (11 891.66*–36 740.30)	[49, 52, 56]
Hepatocellular carcinoma	$46 529.56 (23 949.35*–69 109.77)	[49, 52]
Liver transplantation, 1st year	$284 221 (227 377*–341 065)	[52, 57–59]
Liver transplantation, subsequent years	$43 074.84 (34 459.87*–51,689.80)	[52, 58]
Provider fees		
Counseling visit for positive EIA (CPT#99211)	$19.54 (15.63–21.50*)	[55]
Initial visit with specialist (CPT#99204)	$140.37 (112.29–168.44*)	[55]
Established visit with specialist (CPT#99214)	$87.98 (70.38–105.57*)	[55]
Liver biopsy (including complications)	$1501.06 (1125.49–1876.62*)	[60]
Laboratory costs		
HCV EIA test	$20.44 (16.35–24.53*)	[55]
Quantitative HCV RNA	$61.35 (49.08–73.62*)	[55]
HCV genotype assay	$368.73 (294.98–442.48*)	[55]
Complete blood count with differential	$11.14 (8.91–13.37*)	[55]
Comprehensive metabolic panel	$15.14 (12.11–18.17*)	[55]
Thyroid stimulating hormone	$24.06 (19.25–28.87*)	[55]
Drug costs (weekly)		
Ribavirin	$141.925 (50.23–387.50*)	2010 WAC, [61, 62],
Average pegylated interferon	$521.5175 (233.23–588.07*)	2010 WAC, [61, 62],
Growth factor therapy (12 doses)	$26 256 (21 005–31,507*)	2010 WAC, [63]
Proportion requiring growth factor therapy	0.16 (0–0.2)	[28]
Total mean treatment cost genotype 1	$32 662	Calculated value
Total mean treatment cost genotype 2/3	$20 233	Calculated value
Utilities		
CHC	0.79 (0.77–0.81)	[64, 65]
Relative added utility of no to moderate fibrosis (value × [1-CHC utility])	0.3 (0–0.36)	[64]
Reduced utility of not knowing diagnosis	−0.02 (0.00–0.02)	[66]
Reduced utility of genotype 1 treatment	−0.07 (0.06–0.08)	[67]
Reduced utility of genotype 2/3 treatment	−0.035 (0.03–0.04)	[67]
SVR	0.86 (0.84*–0.88)	[64, 68]
Cirrhosis	0.76 (0.70–0.79*)	[64, 65, 68]
Decompensated cirrhosis	0.69 (0.44–0.69*)	[64, 65, 69, 70]
Hepatocellular carcinoma	0.67 (0.60–0.72*)	[64, 68]
Liver transplant year 1	0.50 (0.40–0.69*)	[52, 69, 71]
Liver transplant subsequent years	0.77 (0.57–0.77*)	[64, 65, 70]
Parameters for additional analyses		
Age-based screening		
Proportion US population born 1945–1965 EIA+	0.0327	[86]
Proportion of US population born 1945–1965	0.355	2009 US Census

Table 1 continued.

Parameter	Base-Case (Range)	References
Protease inhibitor therapies (telaprevir and boceprevir)		
Proportion discontinuing treatment at 12 weeks	0.10	Package inserts
Proportion requiring growth factor therapy (darbopoeitin)	0.36	Package inserts, [28, 63]
Telaprevir		
Genotype 1 to SVR	0.72	Package insert
Genotype 1 cirrhosis to SVR	0.377	Package insert
Mean weeks of pegylated interferon and ribavirin	34	Package insert
Weekly cost of telaprevir (12-week course)	$4004	2011 WAC
Total mean cost of telaprevir-based therapy	$79 670	Calculated
Total mean cost of telaprevir-based therapy for cirrhosis	$88 029	Calculated
Boceprevir		
Genotype 1 to SVR	0.66	Package insert
Genotype 1 cirrhosis to SVR (48 weeks of therapy)	0.42	Package insert
Mean weeks of boceprevir	28	Package insert
Mean weeks of pegylated interferon and ribavirin	37	Package insert
Weekly cost of boceprevir	$1074	2011 WAC
Total mean cost of boceprevir-based therapy	$61 773	Calculated
Total mean cost of boceprevir-based therapy for cirrhosis	$88 248	Calculated

Abbreviations: CHC, chronic hepatitis C; CPT, current procedural terminology; EIA, enzyme immunoassay; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; RNA, ribonucleic acid; SVR, sustained viral response; WAC, wholesale acquisition cost.

*, Value selected for ''Least favorable scenario'' to broadened screening; all values are annual unless otherwise noted; liver fibrosis (F0, none; F1, mild; F2, moderate; F3, severe; F4, cirrhosis).

to death has declined in recent years, with nearly 88% survival at 1 year and 75% at 5 years as of 2008 [4].

Costs

We considered only direct medical costs and used 2010 Medicare prices for all laboratory and office visits. Those costs derived from previous research were adjusted to the 2010 consumer price index medical costs component.

All screened patients had an HCV antibody (enzyme immune assay); those who tested positive had a medical visit and quantitative ribonucleic acid (RNA) polymerase chain reaction test; those who attended referral care had a new patient visit, complete blood count with differential, comprehensive metabolic panel, and HCV genotype assay. CHC and end-stage liver disease management costs were adjusted to 2010 costs from expert panel review [52], whereas those who did not attend care did not engender costs for CHC. The cost during the first year of liver transplantation was taken from a 2010 assessment of procedural costs [57], and the cost of subsequent years after liver transplantation was adjusted from a 1999 analysis of societal costs [58].

American Association for the Study of Liver Disease (AASLD) guidelines recommend medical visits for patients on antiviral treatment at weeks 0, 4, 12, 24, and 48 for genotype 2/3 with additional visits at weeks 36 and 72 for genotype 1; complete blood count with differential, comprehensive metabolic panel, and quantitative HCV RNA are checked each visit after baseline, and thyroid-stimulating hormone is checked every 12 weeks [6]. We used randomized trial data of significant anemia [28, 63] and wholesale acquisition cost to estimate the average cost of growth factor therapy. Antiviral drug costs were based on wholesale acquisition costs, with Veterans Administration costs [78] as the lower limit and www.drugstore.com prices [40] as the upper limit. Drug costs were adjusted to account for estimated rates of treatment discontinuation at week 12 [40, 42]. Liver biopsy cost incorporating complications was adjusted from the estimate by Wong et al [60]. Those achieving SVR after cirrhosis continued to incur annual costs for cirrhosis management.

QALYs Associated With Each Health State

Where possible, we relied upon a recent systematic review of Short Form 36 Health Survey data for CHC patients [64]. We added utility for those with no to moderate fibrosis given the reduced likelihood of symptoms [64] and for those who were unaware of their infection based on the hypothesis that knowing about CHC reduces quality of life [66]. For utility during the first year of liver transplant, we used standard expert opinion [52], which is consistent with a more recent United Kingdom estimate [69]. The decreased utility of being

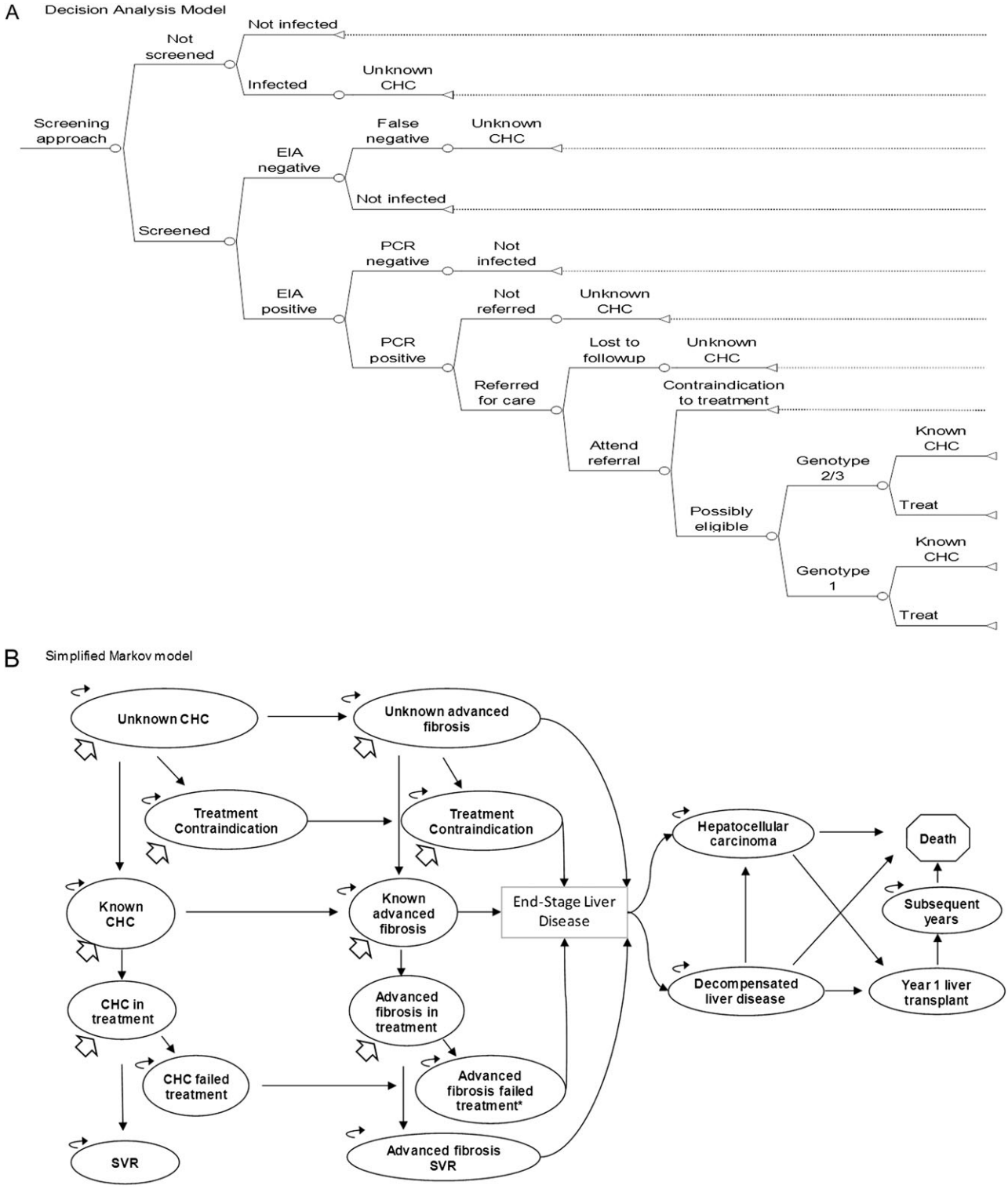

Figure 1. Decision analysis and Markov model for adding one-time general population screening to hepatitis C guidelines. Endpoints of (*A*) decision analysis tree are stratified to (*B*) Markov model, with entry points denoted by large arrows. Chronic hepatitis C infection (CHC) is further stratified by no, mild, or moderate fibrosis; advanced fibrosis is stratified by severe fibrosis or cirrhosis. All stages are stratified by genotype (1 or 2/3). The model allows patients who fail treatment before developing cirrhosis to be re-treated after developing cirrhosis. EIA, enzyme immunoassay; PCR, polymerase chain reaction; SVR, sustained viral response.

Table 2. Cost-Effectiveness of Adding One-Time Screening to Current Hepatitis C Testing Guidelines

Screening Modality	% CHC Initially Detected	% of All CHC Cured	Cost/CHC	QALY/CHC	Cost/QALY	Incremental Cost/QALY
Risk factor screening	50%	10.9%	$59 938	13.50	$4439	—
General population screening						
15% screened	58%	12.1%	$60 269	13.54	$4450	$7900 over risk factor
60% screened	80%	15.0%	$61 337	13.63	$4500	$10 900 over risk factor
						$12 400 over 15%
Age-based (born 1945–1965), 15%	62%	12.6%	$60 180	13.56	$4438	$5400 over risk factor
						Dominates general population
Double background mortality						
Risk factor	50%	5.9%	$77 533	9.62	$8057	—
General population, 15%	58%	6.6%	$77 979	9.65	$8077	$14 200 over risk factor
Least favorable scenario						
Risk factor	50%	8.6%	$46 504	14.18	$3280	—
General population, 15%	58%	9.0%	$46 994	14.19	$3312	$49 000 over risk factor
Telaprevir therapy for genotype 1						
Risk factor		15.3%	$64 864	13.60	$4768	—
General population, 15%		17.0%	$65 505	13.66	$4794	$10 700 over risk factor
Boceprevir therapy for genotype 1						
Risk factor		14.8%	$63 589	13.59	$4679	—
General population, 15%		16.3%	$64 121	13.65	$4698	$9300 over risk factor

Abbreviations: CHC, chronic hepatitis C infection; QALY, quality-adjusted life year.

See Table 1 for values selected for ''Least favorable scenario.''

in treatment for genotype 1 was taken from the results of the ACHIEVE trial, and one-half of that value was applied for genotype 2/3 given that treatment is only 6 months [67].

Analysis

The model estimated costs and lifetime QALYs under each screening approach, discounted at the recommended rate of 3% per annum. Results are presented as incremental cost-effectiveness ratios expressed as incremental cost/QALY gained. In a subanalysis, we compared screening the general population to screening only those born from 1945 to 1965, assuming that implementation costs, uptake, and median age of diagnosed cases would be similar to general population screening. We estimated the impact of newly released protease inhibitors, assuming protease inhibitor therapy for all treatment-naive genotype 1 patients, based on phase 3 evidence and the US Food and Drug Administration-approved data as summarized in the package inserts (Table 1); newly released AASLD practice guidelines recommend protease inhibitor-based therapy for genotype 1 patients but do not provide further guidance on which patients should receive a biopsy or which patients should be treated [79].

We conducted one-way sensitivity analyses for all inputs. Given data suggesting high rates of background mortality among patients with CHC [80], we modeled double background mortality. We generated 30 000 Monte Carlo simulations, in which all parameters were randomly selected from predefined ranges, by using beta distribution for health state transitions, lognormal distribution for costs, and truncated normal distribution for all other variables. We also generated a scenario unfavorable to the hypothesis that general population screening would be cost-effective by selecting lower or upper limits of multiple variables found to be unfavorable on one-way sensitivity analyses (Table 1). To examine the role of advancing fibrosis, we produced a modified Markov model, which included estimated incidence [9] and no screening or treatment; the distribution of fibrosis at each cycle of this model was inserted as parameters into the full model. We evaluated the impact of screening on health outcomes by adjusting the uptake of screening, the rate of referral and attendance for specialty care, the proportion of genotype 1 patients initially treated, and the proportion achieving SVR with new protease inhibitors [81].

RESULTS

Cost-Effectiveness

The addition of general adult population screening to current guidelines was cost-effective in the base-case model (Table 2) and all one-way sensitivity analyses (Figure 2; Supplemental Figure 2). The incremental cost/QALY of general population

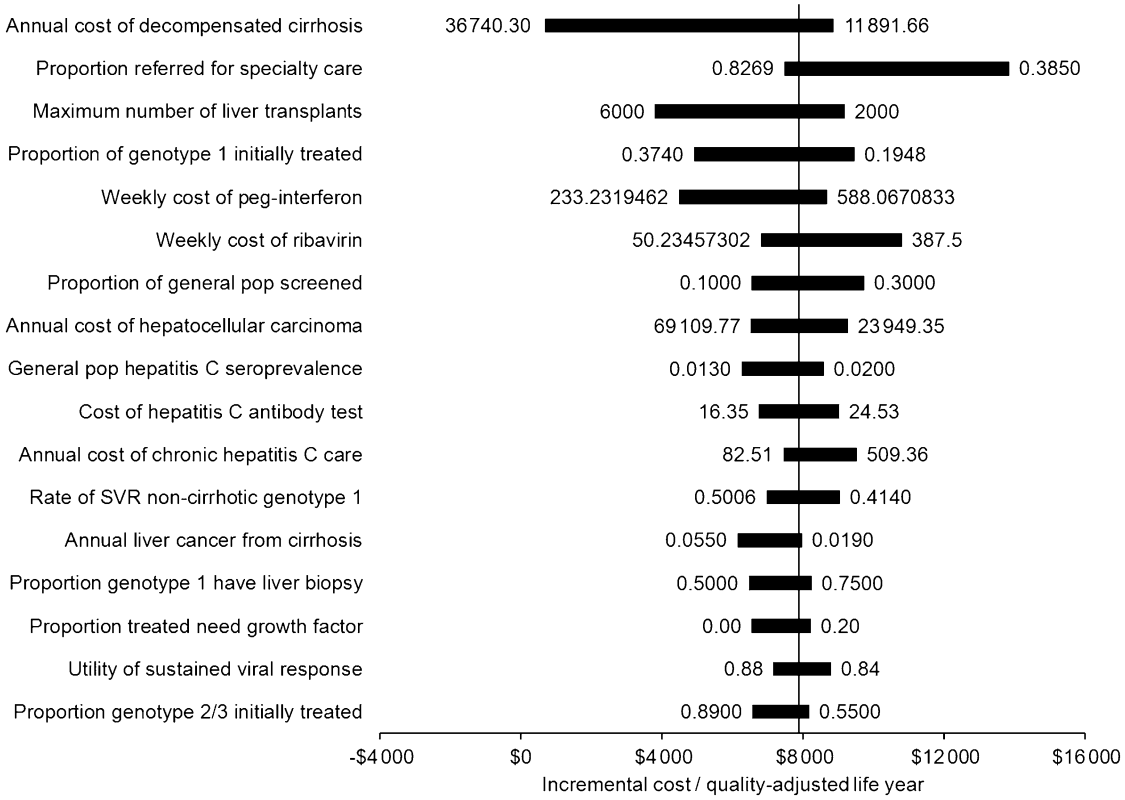

Figure 2. One-way sensitivity analyses of adding one-time general population screening to hepatitis C guidelines. Only variables affecting outcome by at least 1% were included; full panel available online as Supplemental Figure 2. peg, pegylated; pop, population; SVR, sustained viral response.

screening was modestly increased in the setting of doubled background mortality and if protease inhibitor-based regimens were used for all genotype 1 patients. Age-based screening was also cost-effective compared with risk factor screening and dominated general population screening (ie, screening was both less expensive and resulted in more QALYs), assuming that both interventions achieve similar levels of screening coverage in their targeted population.

Sensitivity Analyses

The incremental cost/QALY of general population screening remained under $50 000, a widely used threshold for cost-effectiveness, as long as HCV seropositivity in the tested population remained over 0.53% (Figure 3). In a probabilistic sensitivity analysis in which model parameters were varied across ranges defined in Table 1, the 95% confidence range of the incremental cost/QALY of general population screening was at or below $13 200 (Figure 4; Supplemental Figure 3). In a sensitivity analysis designed to be least favorable to broadened screening, general population screening remained marginally cost-effective ($49 000/QALY). General population screening was modestly sensitive to extremes in the distribution of fibrosis stage at the time of diagnosis: the incremental cost/QALY was highest when most infected persons had no fibrosis at the time of diagnosis, lowest when the plurality had minimal fibrosis, then rose again as more of the population developed cirrhosis (Figure 5).

Population Outcomes

Screening 15% of the general population averted an additional 2% of decompensated cirrhosis events, 1.7% of hepatocellular carcinoma, and 1.1% of liver-related deaths (Figure 6). We adjusted the model to allow 60% of the general population to be screened, then to allow 90% of diagnosed patients to be referred to specialty care, 90% to attend, and 60.5% of genotype 1 to be initially treated (''referral and treatment''); finally, we increased the rate of SVR for genotype 1 patients to 70% (''referral, treatment, and cure''). Screening 60% of the general population reduced the total number of liver-related deaths by 3.8% compared with risk factor screening; the addition of improved rates of referral and treatment averted an additional 4.0% of deaths, and the addition of improved SVR averted an additional 6.9% of deaths. In the setting of optimal referral, treatment, and SVR, screening 60% of the general population averted an additional 7.1% of

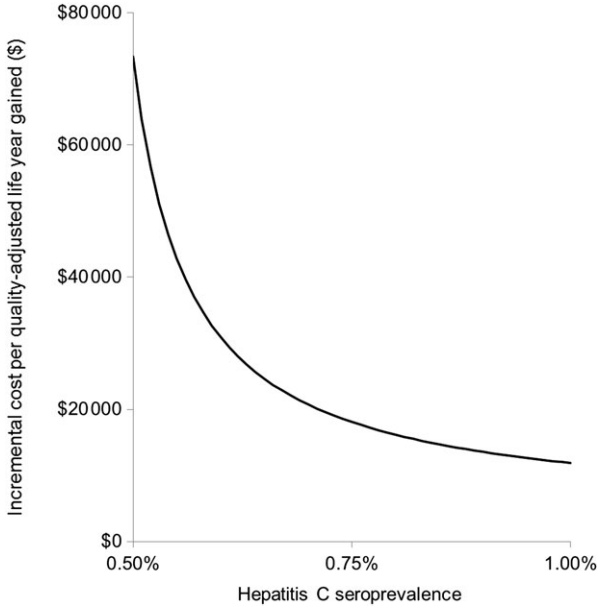

Figure 3. Incremental cost-effectiveness of adding one-time general population screening to hepatitis C guidelines by seroprevalence. Figure represents the additional cost per additional quality-adjusted life year gained if one-time screening of a population with a given hepatitis C seroprevalence is added to current guidelines.

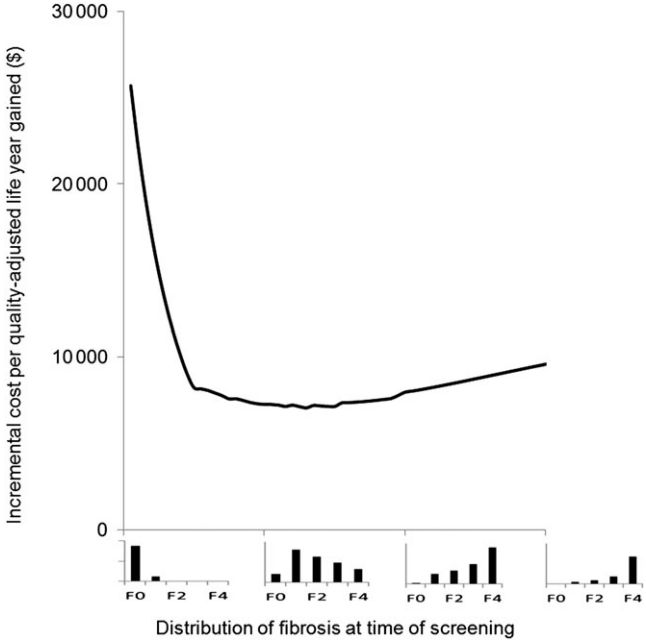

Figure 5. Effect of fibrosis at the time of screening on the cost-effectiveness of adding general population screening to hepatitis C guidelines. *x*-axis represents distribution of fibrosis at time of screening from 60 cycles of a Markov model including incidence and no hepatitis C treatment; current distribution in the United States estimated to be near first mark on *x*-axis. F0, no fibrosis; F2, moderate fibrosis; F4, cirrhosis.

liver-related deaths (approximately 200 000 deaths over the lifetime of the model) compared with risk factor screening.

DISCUSSION

The United States now confronts the sequelae of an HCV transmission epidemic that peaked many years ago, and the absolute cost of managing CHC is increasing as hepatic fibrosis advances in the infected population. As a result, we now have a limited window of time in which to confront the CHC epidemic. We found that the addition of one-time HCV screening of the general adult US population is likely to be cost-effective relative to the current practice of screening based on risk factors. Targeted screening of those born between 1945 and 1965 may be more cost-effective, although results may be different if such an approach costs more to implement, results in inferior clinician uptake, or identifies substantially older infected persons than general population screening. The population-level impact of improved screening would be modest, although improved referral and treatment could approximately double the impact of broadened screening strategies.

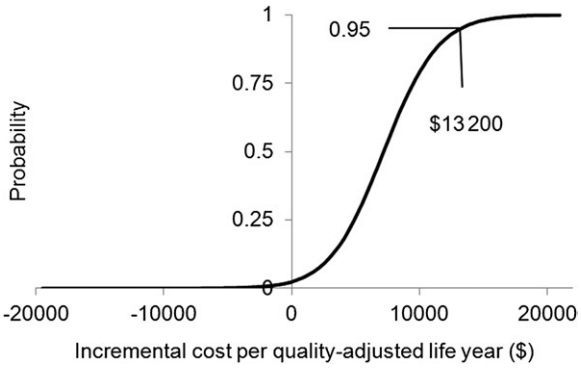

Figure 4. Cost-effectiveness acceptability curve of adding one-time general population screening to hepatitis C guidelines. Figure represents the likelihood that the program would be cost-effective at various thresholds of willingness to pay; in this case, based on 30 000 Monte Carlo simulations, there is a 95% chance that the incremental cost per quality-adjusted life year gained of adding one-time screening to current guidelines would be at or below $13 200.

As therapy improves and our understanding of the effect of fibrosis on response to treatment evolves [82], clinicians are likely to treat CHC in earlier stages of disease. Such a change in practice would marginally increase the incremental cost/QALY of screening in our baseline model (see Supplemental Figure 2), but it would be cost-neutral if response to therapy for those with stage 3 fibrosis were considered equivalent to response for those with cirrhosis (data not shown). Whereas other analyses would be needed to determine the

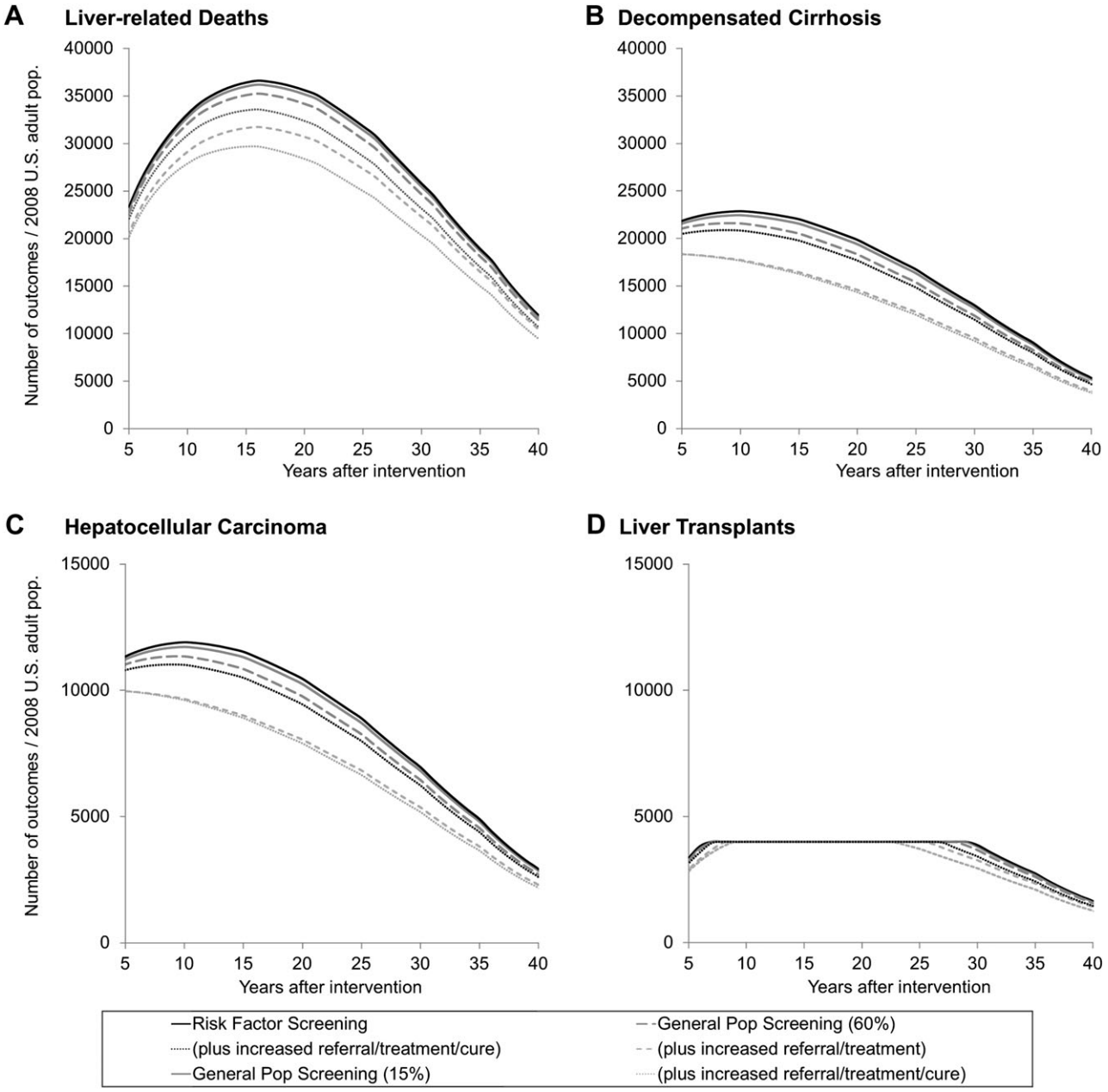

Figure 6. Impact of increased screening, referral, and treatment of hepatitis C on related morbidity. End-stage liver disease outcomes under (1) risk factor-based screening plus (1a) improved referral, treatment, and cure rates; (2) addition of screening of 15% of the general population or (3) addition of screening 60% of the general population plus (3a) improved referral and treatment rates; and (3b) improved cure rates, starting at year 0.

economically optimal timing of CHC treatment, broadened screening is likely to remain cost-effective in the current US population of infected persons.

Model Validation

Our model compares well to prior studies. Health-state outcomes in our model are predicted similar to an established model of HCV natural history [3]. Multiple other models have also found that cost-effectiveness varies based on degree of fibrosis in the population [15, 83, 84] and the overall prevalence of CHC [85]. To compare results to Singer et al's 2001 model [66], we adjusted stage of fibrosis to 10 years earlier and cure and relapse rates to those of nonpegylated interferon, circumstances under which risk factor screening dominated general population screening, consistent with those earlier results. Finally, a recently published cost-effectiveness analysis of birth cohort screening reached conclusions similar to those reported

here, although the methodology, assumptions, parameters, and analysis used differed from our approach [86].

Limitations

Our results have several important limitations. First, the model included a large number of parameters related to the natural history of CHC, the healthcare delivery system, and costs, many of which are not precisely defined. We attempted to address this with extensive one-way sensitivity analyses, probabilistic analyses in which we varied parameter estimates across a range of plausible values, and a "least favorable" scenario designed to favor risk factor screening. Second, we did not stratify by sex, although the parameters we selected should minimize any potential impact on the results of the model. Third, due to the absence of practice standards, we did not formally address novel diagnostic tests (eg, interleukin 28 [31]) and liver imaging procedures (eg, transient elastography [32]) that might reduce costs by guiding therapeutic decisions. Furthermore, our evaluation of new protease inhibitor therapies was preliminary because there was limited clinical experience with these agents and treatments are rapidly changing; although plausible scenarios exist in which the costs of new treatments exceed the benefit, such analyses would be more appropriate for investigations comparing different treatment modalities. Fourth, the model allows a large number of patients to be screened and treated in the initial year, whereas the actual process is likely to take several years and may blunt the discounted cost-effectiveness. Finally, we did not consider the cost of scaling up clinical services for CHC management, an expensive proposition, but one that might be mirrored by the increased capacity needed to treat advanced liver disease if current screening and management strategies continue unchanged.

In conclusion, the addition of one-time screening of the general adult US population for CHC would be cost-effective over the current practice of only screening high-risk individuals. Targeted age-based screening, equivalent to screening only high-risk birth cohorts in our model, may be more cost-effective than general population screening if implementation costs, pace of adoption by clinicians, and median age of diagnosis were similar. Because the cost of managing CHC increases as the disease progresses, from an economic perspective the optimal time to implement broadened screening is now. Similar to recent experience with human immunodeficiency virus, broadened screening is only the first step in a comprehensive public health effort: successfully limiting HCV-associated morbidity and mortality will require initiatives to identify infected persons and ensure their treatment.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Author contributions. P. O. C. takes responsibility for the integrity of the analysis. Conception and design: P. O. C., M. R. G., and S. D. S. Acquisition of data: P. O. C. and J. D. S.. Analysis and interpretation of data: P. O. C., J. D. S., M. R. G., and S. D. S.. Drafting of article: P. O. C. Critical revision of the article for important intellectual content: P. O. C., J. D. S., M. R. G., and S. D. S.. Final approval of the article: P. O. C., J. D.S., M. R. G., and S. D. S.

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All authors have completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and deny any additional conflicts of interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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