September 2011

The Cost-Effectiveness of Birth Cohort and Universal Hepatitis C Antibody Screening in U.S. Primary Care Settings

Technical Report

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1. MODEL INITIATION

1.1 Starting Population

Before the model is run, the model sets the initiation parameters. These settings include

- population size,
- proportional demography of the population, and
- prevalence of injecting drug use risk behaviors (risk of infection) and disease progression risk factors.

For "The Cost-Effectiveness of Birth Cohort and Universal Hepatitis C Antibody Screening in U.S. Primary Care Settings," we set the population aged 20 or older in 2006 to the starting values shown in Table 1-1, based on data derived from the National Health and Nutrition Examination Survey.

Table 1-1. Model Starting Population Values

Birth Year	Race/Ethnicity/ Injecting History	Gender	Insurance	Number
1945–1955	African American	Female	Yes	1,201,543
1945–1955	African American	Female	No	217,313
1945–1955	African American	Male	Yes	1,107,066
1945–1955	African American	Male	No	121,299
1945–1955	Injecting drug use history, race/ethnicity not specified	Female	Yes	176,823
1945–1955	Injecting drug use history, race/ethnicity not specified	Female	No	0
1945–1955	Injecting drug use history, race/ethnicity not specified	Male	Yes	487,075
1945–1955	Injecting drug use history, race/ethnicity not specified	Male	No	108,657
1945–1955	White, Hispanic	Female	Yes	831,837
1945–1955	White, Hispanic	Female	No	229,955
1945–1955	White, Hispanic	Male	Yes	1,006,781
1945–1955	White, Hispanic	Male	No	266,003
1945–1955	White, Non-Hispanic or other race	Female	Yes	10,667,127
1945–1955	White, Non-Hispanic or other race	Female	No	803,135
1945–1955	White, Non-Hispanic or other race	Male	Yes	10,744,349
1945–1955	White, Non-Hispanic or other race	Male	No	702,508

(continued)

Table 1-1. Model Starting Population Values (continued)

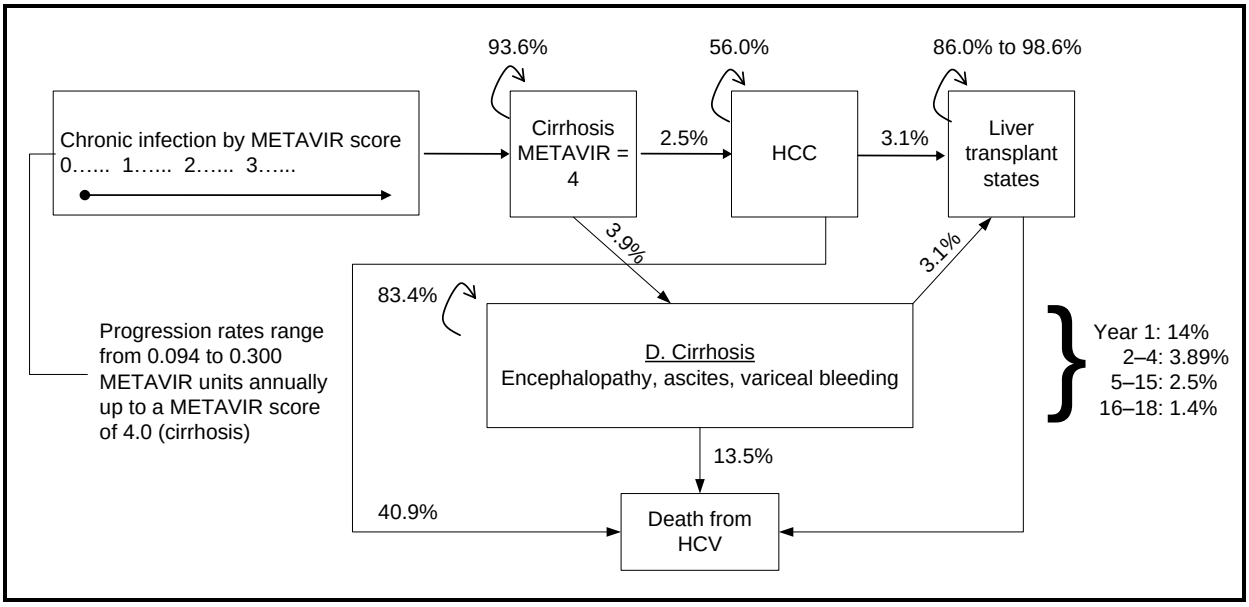
Birth Year	Race/Ethnicity/ Injecting History	Gender	Insurance	Number
1956–1965	African American	Female	Yes	1,923,698
1956–1965	African American	Female	No	326,994
1956–1965	African American	Male	Yes	1,419,368
1956–1965	African American	Male	No	509,968
1956–1965	Injecting drug use history, race/ethnicity not specified	Female	Yes	443,681
1956–1965	Injecting drug use history, race/ethnicity not specified	Female	No	56,378
1956–1965	Injecting drug use history, race/ethnicity not specified	Male	Yes	241,060
1956–1965	Injecting drug use history, race/ethnicity not specified	Male	No	163,497
1956–1965	White, Hispanic	Female	Yes	1,582,011
1956–1965	White, Hispanic	Female	No	658,089
1956–1965	White, Hispanic	Male	Yes	1,517,261
1956–1965	White, Hispanic	Male	No	622,383
1956–1965	White, Non-Hispanic or other race	Female	Yes	12,779,095
1956–1965	White, Non-Hispanic or other race	Female	No	1,238,274
1956–1965	White, Non-Hispanic or other race	Male	Yes	13,267,878
1956–1965	White, Non-Hispanic or other race	Male	No	1,519,995

1.2 Disease Progression

Based on the assignment of initiation parameters, our model calculates the prevalence of infection, the infection duration for prevalent cases, and the degree of disease progression in each duration group. All prevalent cases then progress from their baseline severity group forward to cirrhosis based on their progression rate and their progression risk behaviors. Disease progression is re-estimated in time steps of 1 year moving forward from the year of model initiation.

As illustrated by Figure 1-1, the model incorporates two chronic infection states (mild disease corresponding to a METAVIR score of 0 or 1, and moderate disease corresponding to a METAVIR score of 2 or 3), cirrhosis (corresponding to a METAVIR score of 4), a grouped category to describe the symptoms associated with decompensation, hepatocellular carcinoma (HCC), and post-liver transplant states. Probabilities of death are not shown. Patients can die from causes unrelated to hepatitis C. From hepatitis C, patients can die from decompensated cirrhosis, HCC, or as a result of complications or failure of their liver transplant. Parameters governing these transitions are presented in Table 1 of the manuscript.

Figure 1-1. Hepatitis C Natural History Model



Note: HCC = hepatocellular carcinoma; HCV = hepatitis C virus. Transitions to death from other causes are omitted from the diagram to reduce visual clutter. In each state an additional arrow could be drawn from that state to an additional rectangle representing death from causes other than HCV.

Notes on Interpreting the diagram: In this diagram, rectangles represent health states in which modeled individuals reside at the end of one time period (in this model, a time period is 1 year). Arrows represent probabilities of moving from one state to another state between any two time periods. All arrows in the model except the arrow from "Chronic infection by METAVIR score" to "Cirrhosis METAVIR = 4" represent the probability that any cohort in that state will move to another state in that year assuming that they did not die from non-HCV-related causes in that year first. Curved arrows that point back into the same state represent the probability that that state is unchanged between two time periods, which is equal to 1 minus the sum of the probabilities of moving to other health states.

An explanation of how chronic infection progression is computed in the model: In our model, individuals move linearly through the stages of chronic infection until they reach a METAVIR score of 4. Computationally, this is achieved at the model's initiation by creating mutually exclusive categories for each combination of fibrosis progression rate (see Table 3.1 of http://www.rti.org/pubs/hepcmorbidity_rein.pdf) by years of duration (see Table 2.2 of this document) for people in state less than 4. Each of these categories is assigned an annual progression increment based on the gender, age, and alcohol consumption level represented by the category. In each year, the probability of that group progressing by their annual increment is set to 1 until that group reaches cirrhosis (a METAVIR score of 4).

2. BASELINE PATIENT CHARACTERISTICS

2.1 Prevalence of Hepatitis C Virus

To match our starting population, we estimated hepatitis C virus (HCV) prevalence by age group, gender, race/ethnicity, and history of injecting drugs (Alter et al., 1999; Armstrong et al., 2006; CDC, 1998). For people without a history of injecting drugs, we used data for the U.S. noninstitutionalized population from the National Health and Nutrition Examination Survey (NHANES) for the years 2001 to 2006. We defined disease prevalence as the presence of any HCV antibodies, which includes patients with ongoing chronic infection (approximately 75%) and patients whose infection spontaneously cleared (25%). We estimated the prevalence of HCV by age group, gender, and race/ethnicity for patients with no disclosed injecting drug use history. Tables 2-1 through 2-6 present our analytic results for people who do not disclose a history of injecting drugs.

For those who reported a history of injecting drugs, NHANES contained an insufficient sample to estimate prevalence by age group, gender, and race/ethnicity. Tables 2-7 and 2-8 present data stratified by age group and gender only for those with injecting drug use history, and Table 2-9 presents data by age group alone. A history of injecting drug use was defined as disclosing on the NHANES behavioral questionnaire ever using a needle to shoot illegal street drugs.

Table 2-1. Non-Injecting Drug Use History HCV Prevalence by Age Group: White Male

Age Group	N	HCV Prevalence	CI Low	CI High
40–49	357	0.035	0.015	0.055
50–59	332	0.014	0.002	0.025

Note: HCV = hepatitis C virus; CI = confidence interval

Table 2-2. Non-Injecting Drug Use History HCV Prevalence by Age Group: White Female

Age Group	N	HCV Prevalence	CI Low	CI High
40–49	320	0.017	0.005	0.038
50–59	327	0.007	0.001	0.038

Note: HCV = hepatitis C virus; CI = 95% confidence interval

Table 2-3. Non-Injecting Drug Use History HCV Prevalence by Age Group, Gender, and Race/Ethnicity: Black Male

Age Group	N	HCV Prevalence	CI Low	CI High
40–49	162	0.070	0.037	0.103
50–59	93	0.040	0.003	0.077

Note: HCV = hepatitis C virus; CI = 95% confidence interval

[a] The small sample size for some subgroups did not include any positive cases. Instead of setting this value to zero, by assumption we set the value equal to the prevalence observed in the most similar subgroup, white male, age 20–29.

Table 2-4. Non-Injecting Drug Use History HCV Prevalence by Age Group, Gender, and Race/Ethnicity: Black Female

Age Group	N	HCV Prevalence	CI Low	CI High
40–49	154	0.006	0.011	0.015
50–59	97	0.020	0.005	0.040

Note: HCV = hepatitis C virus; CI = 95% confidence interval

Table 2-5. Non-Injecting Drug Use History HCV Prevalence by Age Group, Gender, and Race/Ethnicity: Hispanic Male

Age Group	N	HCV Prevalence	CI Low	CI High
40–49	194	0.019	0.005	0.033
50–59	101	0.015	0.011	0.018

Note: HCV = hepatitis C virus; CI = 95% confidence interval

Table 2-6. Non-Injecting Drug Use History HCV Prevalence by Age Group, Gender, and Race/Ethnicity: Hispanic Female

Age Group	N	HCV Prevalence	CI Low	CI High
40–49	187	0.027	0.004	0.086
50–59	—	0.007[a]	—	—

Note: HCV = hepatitis C virus; CI = 95% confidence interval

[a] The small sample size for some subgroups did not include any positive cases. Instead of setting this value to zero, by assumption we set the value equal to the prevalence observed in the most similar subgroup, white female, age 50–59.

Table 2-7. Injecting Drug Use History HCV Prevalence by Age Group and Gender: Male

Age Group	N	HCV Prevalence	CI Low	CI High
40–49	30	0.619	0.471	0.767
50–59	39	0.686	0.613	0.759

Note: HCV = hepatitis C virus; CI = 95% confidence interval

Table 2-8. Injecting Drug Use History HCV Prevalence by Age Group and Gender: Female

Age Group	N	HCV Prevalence	CI Low	CI High
40–49	26	0.623	0.486	0.760
50–59	13	0.578	0.003	0.999

Note: HCV = hepatitis C virus; CI = 95% confidence interval

Table 2-9. Injecting Drug Use History HCV Prevalence by Age Group: All IDU

Age Group	N	HCV Prevalence	CI Low	CI High
40–49	56	0.621	0.539	0.703
50–59	52	0.656	0.567	0.745

Note: HCV = hepatitis C virus; CI = 95% confidence interval

2.2 Infection Duration for Those with Chronic Infection

In our model, the infection duration (the number of years since a patient has been infected with HCV) partially (along with progression rate) governed the disease severity at model start time. We assigned duration of infection using incidence data developed to generate a published model (Armstrong et al., 2000). We developed a specialized model to estimate duration based on estimated past HCV incidence trends adjusting for past trends in mortality and the difference in infection rates between population subgroups. The models apply estimates of past incidence and mortality to past cohorts and have been calibrated to accurately reproduce current anti-HCV prevalence. Table 2-10 shows the estimated proportional distribution of infection in years of duration among the total population. Based on available data, we explored whether duration varied by gender, race/ethnicity, age, or injecting drug use status and found no support for stratifying on those characteristics.

Table 2-10. Duration of Infection by Age Group

	Duration of Infection (Years)				
Age Group	**0 to 4**	**5 to 9**	**10 to 14**	**15 to 20**	**20+**
20–29	0.6	0.25	0.08	0.04	0.03
30–39	0.27	0.32	0.24	0.11	0.06
40–49	0.08	0.14	0.21	0.24	0.33
50–59	0.04	0.05	0.08	0.13	0.7
60+	0.03	0.04	0.04	0.06	0.83

2.3 Probability of Other Baseline Characteristics

HIV infection status and alcohol intake are other characteristics that are assigned at model baseline that affect the progression of HCV. The estimates in Table 2-11 were derived from NHANES. The use of heavy alcohol was assumed to be the average of the NHANES and NSDUH estimates (0.10).

Table 2-11. Other Baseline Characteristics of Patients with HCV/IDU Drug Users

Parameter	Parameter	Source

HIV infection	0.0205	NHANES
Heavy alcohol (more than four drinks per day)	0.089	NHANES

Note: National Health and Nutrition Examination Survey (NHANES) estimates are among patients with hepatitis C virus (HCV).

2.4 Background Mortality Rates

Background mortality rates were estimated using the 2003 National Vital Statistics Life Tables (Arias, 2006). For the model, these rates were used to assign mortality risks for non-injecting drug users (IDUs) stratified by age, gender, and race/ethnicity. Active IDUs experience an elevated risk of death compared with non-IDUs, and the failure to include this elevated risk of mortality might lead to substantial bias in our results in favor of testing and treatment of HCV (Davoli et al., 1997; Joe et al., 1982; Miller et al., 2007; Spittal et al., 2006; Vlahov et al., 2004). We incorporated the elevated risk of mortality into the model by assigning people with a disclosed past injecting drug use risk a higher relative risk (RR) of death compared with others in the same demographic group (defined by age and gender, but not race/ethnicity). We calculated this elevated RR as follows:

1. To best stratify risk of HCV infection, our model defines IDU status as individuals who responded yes to the NHANES question "Have you ever, even once, used a needle to inject a drug not prescribed by a doctor?" However, not all of these people are active IDUs, and thus they do not all experience an elevated risk of mortality. We controlled for this using a second NHANES question to divide active users (i.e., those who reported using a needle to inject illegal street drugs in the past 12 months) from inactive users (i.e., those who did not). Using NHANES data from 2002 to 2006, we found that 24.5% of people who admitted to ever injecting illegal street drugs had done so in the past 12 months and thus were defined as active users.

2. We assumed the RR of mortality for inactive users was the same as for the general population, a common assumption used in prior cost-effectiveness models (Bennett, et al., 1997; Wong et al., 2000; Salomon et al., 2003).

3. We estimated the RR of mortality for active IDUs as 4.89, the average value for the two latest waves of data from a study of new onset IDUs (Vlahov et al., 2004). This value is somewhat conservative as many other studies report a higher RR. However, we think it is appropriate given that many previous cost-effectiveness models use no additional risk of mortality for people who inject drugs.

4. Because we did not assume that primary care physicians would be able to distinguish active from inactive drug users, we calculated a single RR of mortality for all IDUs equal to the weighted average of the RR for active and inactive users. We stratified this by age group. This was equal to the probability of being an inactive user times the RR of an inactive user plus the probability of being an active user times the RR of an active user. For people aged 40 or older, this was equal to $0.8909 \times 1.0 + 0.1091 \times 4.89 = 1.42$.

5. Because we do not stratify IDUs by race/ethnicity, the annual probability of mortality for an IDU was equal to the average mortality probability of blacks, whites, and

Hispanics of the same age and gender times the RR value. When this method resulted in probabilities greater than 1, the probabilities were reset to 1.00.

3. EFFECTIVENESS OF ANTIVIRAL THERAPY

3.1 SVR Rates Used in the Model

We assumed that all patients treated with antiviral therapy received pegylated interferon alpha 2a with weight-based dosage of ribavirin. We set SVR rates to the average of four studies of antiviral therapy administered in nonclinical trial settings in primary care settings (Antonucci et al., 2007; Dudley, O'Donnell, Haydon, & Mutimer, 2006; Roblin, 2010; Vlahov et al., 2004). This yielded an SVR rate of 0.33 for genotypes 1 and 4 and 0.69 for genotypes 2 and 3.

For direct acting antiviral (DAA) medication plus pegylated interferon alpha 2a with weight-based dosage of ribavirin we set the SVR rate to a conservative value of 0.535. This value is equal to to the ratio of the average SVR rate of standard therapy (0.33) divided by the SVR of standard therapy observed in clinical trials (0.46) multiplied by the SVR rate observed for 12-week telaprevir treatment plus peginterferon-ribavirin in clinical trial data (0.747).

4. MEDICAL TREATMENTS FOR HEPATITIS C BY STAGE AND THEIR ASSOCIATED COSTS

We estimated the costs of clinical services used to treat patients in each disease stage by converting the procedures associated with each disease stage outlined in medical guidelines into their corresponding procedure codes and assigned these codes medical reimbursement costs based on the Medicare fee schedule. Mentions of the Cleveland Clinic refer to the Carey et al. (2007) monograph, Hepatitis C Management. AASLD refers to the American Association for the Study of Liver Diseases (Strader, Wright, Thomas, & Seeff, 2004) Practice Guideline, Diagnosis, Management, and Treatment of Hepatitis C. MCR refers to the Medicare Reimbursement Relative Value Units (RVU) as obtained from Gray and Parkinson (2003), The Essential RBRVS. References to the VFC/CDC price list refer to the Vaccine for Children Program, Vaccine Price List (which also includes prices for vaccines for adults).

We used literature-based estimates for the costs of treating end-stage liver disease prior to transplantation and for transplant costs themselves. For the costs of end-stage liver disease prior to transplantation, this was because we were unable to identify clear guidelines about how these conditions are managed. For transplantation costs, this was because (unlike costs for other stages in the model) much work has been done estimating these costs using empirical data. We felt these empirical estimates were likely superior to estimates we could develop from practice guidelines.

4.1 Screening Costs

We estimated screening costs from data provided by a federally qualified health center that conducted routine hepatitis B screening of at-risk patients, replacing the reimbursement costs for hepatitis B antibody tests with the costs of a hepatitis C test (Rein et al., 2011). These costs included the costs of testing and program management ($34) for all patients and the cost of delivering positive test results and providing clinical referrals to positive patients ($19).

4.2 Positive Diagnosis

We estimated two costs associated with a positive diagnosis (Tables 4-1 and 4-2). The two costs differ based on the testing costs involved because we assume blood and metabolic tests would be incorporated with treatment for those who immediately receive antiviral therapies.

4.3 Treatment

Treatment costs differ between genotypes based on the duration of therapy. Costs for treatment for genotype 1 are based on an estimated 48 weeks of therapy, whereas costs for genotypes 2 and 3 are based on an estimated 24 weeks of therapy. Elements of treatment

costs include testing costs, outpatient visits, and mental health management in addition to the costs of antiviral medications. Testing schedules are based on clinical recommendations with the exception that we assumed one qualitative RNA test, for amplified detection of virus to be performed at the conclusion of therapy. The costs account for discontinuation as discussed later in this section.

Table 4-1. Positive Diagnosis—Coordinated with Immediate Treatment

Elements	Code	Quantity	Unit Cost	Total Cost	Recommendation Source	Cost Source
Quantitative RNA—for confirmation	87522	1	$59.85	$59.85	AASLD	Gray, 2003; AMA, 2007
By assumption, quantitative is 100% sensitive and qualitative not used at this stage	87521					
One post diagnosis risk reduction counseling session (15 minutes)	99401	1	$42.07	$42.07	AASLD	Gray, 2003; AMA, 2007
Genotype sequencing	87902	1	$359.69	$359.69	AASLD	Gray, 2003; AMA, 2007
Twinrix hepatitis A/B vaccination		3	$37.64	$112.92	Cleveland Clinic	Pediatric/VFC Vaccine Price List. (2007)
HIV EIA screening	86703	1	$19.17	$19.17	Cleveland Clinic	Gray, 2003; AMA, 2007
Outpatient office visit, new patient	99203	1	$92.09	$92.09	Assumption	Gray, 2003; AMA, 2007
Total initial workup cost following diagnosis				$685.79		

Note: AASLD = American Association for the Study of Liver Diseases; EIA = Enzyme-Linked ImmunoSorbent Assay Test; VFC = Vaccines for Children

Table 4-2. Positive Diagnosis—Not Coordinated, Treatment Does Not Immediately Follow

Elements	Code	Quantity	Unit Cost	Total Cost	Recommendation Source	Cost Source
Quantitative RNA—for confirmation	87522	1	$59.85	$59.85	AASLD	Gray, 2003; AMA, 2007
One post diagnosis risk reduction counseling session (15 minutes)	99401	1	$42.07	$42.07	AASLD	Gray, 2003; AMA, 2007
Genotype sequencing	87902	1	$359.69	$359.69	AASLD	Gray, 2003; AMA, 2007
Twinrix hepatitis A/B vaccination		3	$37.64	$112.92	Cleveland Clinic	Pediatric/VFC Vaccine Price List. (2007)
Comprehensive metabolic panel	80053	1	$14.77	$14.77	Cleveland Clinic	Gray, 2003; AMA, 2007
CBC/DIF	85027	1	$9.04	$9.04	Cleveland Clinic	Gray, 2003; AMA, 2007
WBC	85007	1	$4.81	$4.81	Cleveland Clinic	Gray, 2003; AMA, 2007
Hemoglobin	85018	1	$3.31	$3.31	Cleveland Clinic	Gray, 2003; AMA, 2007
Automated platelet count	85049	1	$6.25	$6.25	Cleveland Clinic	Gray, 2003; AMA, 2007
HIV EIA screening	86703	1	$19.17	$19.17	Cleveland Clinic	Gray, 2003; AMA, 2007
Outpatient office visit, new patient	99203	1	$92.09	$92.09	Assumption	Gray, 2003; AMA, 2007
Total initial workup cost following diagnosis				$723.97		

Notes: AASLD = American Association for the Study of Liver Diseases; VFC = Vaccines for Children; CDC/DIF = Complete Blood Count with Differential Related Tests; WBC = white blood cells

We assume that an initial workup that does not involve treatment will require patient health monitoring tests (comprehensive metabolic panel, CBC/DIF, WBC, hemoglobin, automated platelet count) that in this paper we include under the "Tests" value for treatment.

4.4 Estimation of Antiviral Costs for Pegylated Interferon Plus Ribavirin

Costs of hepatitis C treatment are impacted by both the direct cost of the drugs themselves and the likelihood of finishing the full treatment regimen. We collected drug cost estimates from two sources and compared these with the estimates from Red Book. These estimates all used a regimen of pegylated interferon plus ribavirin yet were still significantly lower than estimates from the Red Book because the Red Book does not reflect the discounted price obtained by most health insurers (Table 4-3).

Table 4-3. Average Monthly Costs of Pegylated Interferon plus Ribavirin

Source	Genotype 1 Avg. Monthly Cost	Genotype 2/3 Avg. Monthly Cost
Red Book (2006)	$3,703.88	$3,703.88
Kaiser Outpatient Clinic (Roblin, 2010)	$1,028.30	$1,028.30
Chapko et al. (2005, 2006)	$640.20	$587.00

Note: Represents discount negotiated price for VA facilities.

For this study, we used monthly costs of antiviral therapy supplied by the Kaiser Health System of Georgia because we felt these represented the best match of costs that would be paid in a primary care setting (Roblin, 2010). In addition to prescription drug costs, antiviral therapy involves a number of other services and procedures. Our first step (Table 4-4) in calculating the cost of antiviral therapy was to estimate the total cumulative cost by month of treatment assuming a patient completed the full course of treatment.

Table 4-4. Costs of Peg-IFN + Ribavirin Antiviral Treatment by Month

		Kaiser Drug Costs	
Month	**Cost Item**	**Genotype 1**	**Genotype 2, 3**
1	Peg Interferon	$988.30	$988.30
	Ribavirin	$40.00	$40.00
	Health and Behavior Screen	$23.50	$23.50
	Qualitative RNA	$49.04	$49.04
	Outpatient Visit	$59.50	$59.50
	Fluoxetine	$9.30	$9.30
	Tests	$130.34	$106.87
	Total	**$1299.98**	**$1276.51**
2, 4, 8, 10[a]	Outpatient Visit	$59.50	$59.50
	Fluoxetine	$9.30	$9.30
	Peg Interferon	$988.30	$988.30
	Ribavirin	$40.00	$40.00
	Total	**$1097.10**	**$1097.10**
3, 9[a]	Outpatient Visit	$59.50	$59.50
	Fluoxetine	$9.30	$9.30
	Health and Behavior Screen	$22.74	$22.74
	Tests	$130.34	$106.87
	Peg Interferon	$988.30	$988.30
	Ribavirin	$40.00	440.00
	Total	**$1250.18**	**$1226.71**
5, 7, 11[a]	Outpatient Visit	$59.50	$59.50
	Fluoxetine	$9.30	$9.30
	Tests	$130.34	$106.87
	Peg Interferon	$988.30	$988.30
	Ribavirin	$40.00	$40.00

	Total	**$1227.44**	**$1203.97**
6, 12[a]	Outpatient Visit	$59.50	$59.50
	Fluoxetine	$9.30	$9.30
	Health and Behavior Screen	$22.74	$22.74
	Peg Interferon	$988.30	$988.30
	Ribavirin	$40.00	$40.00
	Total	**$1119.84**	**$1119.84**

[a] Costs presented for genotype 2 represent only those for months 1 through 6.

In our second step, we then adjusted the cost of medication to account for expected weeks of therapy. We used a distribution of weeks of treatment taken by patients in methadone versus control settings, where the control setting represented those prospectively matched for traits (sex, age, HCV genotype, and HCV RNA) but who had no history of injecting drug use, illicit drug use, or opioid maintenance therapy for ≤ 5 years (Mauss et al., 2004). For calculation purposes, we assumed that if patients did not drop out in the first 11 months (for genotype 1) or 5 months (for genotypes 2 or 3), they discontinued treatment at the conclusion of their treatment regimen, shown in the last month of treatment. While Mauss et al. (2004) presented costs for both a control and methadone sample, discontinuation rates used to calculate the costs of treatment for the model used the control sample for all settings (Table 4-5).

Table 4-5. Proportion of Patients Discontinuing Treatment by Month

Month	Proportion Who Discontinued, Control Genotype 1	Proportion Who Discontinued, Control Genotype 2/3
1	0.04	0.04
2	0	0
3	0.04	0.04
4	0.08	0.08
5	0.02	0.02
6	0	0.82
7	0	
8	0.04	
9	0	
10	0	
11	0	
12	0.78	

We calculated monthly costs weighted by the proportion of patients reaching that month of treatment. Total costs were calculated by summing the weighted monthly costs and are shown in Table 4-6.

Table 4-6. Treatment cost, accounting for discontinuation, assuming actual utilization of this therapy outside of randomized controlled trials

	Kaiser Costs	
Treatment Cost Parameter	**Cost, Genotype 1**	**Cost, Genotype 2, 3**
Treatment cost, assuming discontinuation	$12,079.90	$6,446.30
Treatment cost, assuming full treatment regimen with no discontinuation	$14,110.74	$7,021.23

4.5 Estimation of Antiviral Costs for Direct Acting Antivirals Plus Pegylated Interferon Plus Ribavirin

We estimated the costs of DAA's as equivalent to the costs of the drug Telaprevir. The costs of boceprevir are likely to be different. We estimated weekly costs of telaprevir treatment as the average of three estimates obtained through personal communication (Table 4-7).

Table 4-7. Average Weekly Costs of Telaprevir (Teleprevir is usually used for 12 weeks unless lack of response dictates earlier discontinuation).

Source	Genotype 1 Weekly Cost
Weill Cornell Medical College	$4,100.00
University of Alabama Birmingham	$3,333.00
Veterans Administration	$2,917.00
Average	$3,450.00

Note: Weill Cornell Medical College data provided via personal communication with Andrew Talal, Associate Medical Director Center for the Study of Hepatitis C at the Weill Cornell Medical College, 8/29/2011; University of Alabama Birmingham (UAB) data provided via personal communication with Dr. Omar Massoud, Director of Clinical Liver Research for the UAB Liver Center, 8/28/2011; Veterans Administration data provided via personal communication with Yngve Falck-Ytter, Chief, Division of Gastroenterology, Louis Stokes VA Medical Center, Cleveland, August 26,2011.

Using these weekly costs as an input, we estimated expected per patient costs after accounting for treatment abandonment and clinically advised discontinuation using four calculations. Given the total absence of data on actual utilization of this therapy at the time we authored this article, our calculations seek to provide rational assumptions to four questions (future research should seek to estimate answers to these questions using empirical data).

a. What proportion of patients gets each of several types of response guided therapy (with response guided therapy determining the number of weeks of treatment)?

b. How should these proportions be modified if we assumed lower assumed overall probability of SVR than observed in clinical trials?

c. How should we assign the remainder of patients after we transform the SVR probabilities to be lower?

d. What unit costs do we multiply these proportions against to model overall costs treatment?

Question A. What proportion of patients gets each of several types of response guided therapy (with response guided therapy determining the number of weeks of treatment)?

We addressed this question using a response-based treatment algorithm provided by Mount Sinai Medical Center (personal communication, Katherine Krauskopf, Instructor of General Internal Medicine, Mount Sinai School of Medicine) and Clinical Response data found in the Jacobson et al. (2011) Phase 3 clinical trial of telaprevir.

The Mt. Sinai Algorithm has four treatment duration states—4, 12, 24, and 48 weeks—which are driven by response (both good and bad). Using Jacobsen et al. (2011), we divided people into the following treatment states according to the Mt. Sinai Algorithm:

- Treated for 24 weeks in Jacobsen et al. (2011), might be treated for 4, 12, or 24 weeks given the Mt. Sinai algorithm.
- Treated for 24 weeks in Jacobsen et al. (2011), would be treated for 24 weeks given the Mt. Sinai algorithm.
- Treated for 48 weeks in Jacobsen et al. (2011), would be treated for 48 weeks given the Mt. Sinai algorithm.
- Lost to follow-up or unclear information in Jacobsen et al. (2011).

Table 4-8 divides patients in Jacobsen et al. (2011) into their analogous Mt. Sinai Treatment algorithm categories.

Table 4-8. Distribution of Jacobsen et al. (2011) to their Analogous Mount Sinai Treatment Algorithm Categories

Group #	Telaprevir Treatment Duration Group Description	Reason For Duration	Number	Proportion of Those Treated
1	Discontinue treatment after 4 weeks	RNA > 1,000 at 4 weeks	Some portion of group 3	Some portion of group 3
2	Discontinue treatment after 12 weeks	RNA > 1,000 at 12 weeks	Some portion of group 3	Some portion of group 3
3	Discontinue treatment after 24 weeks	Detectable RNA at 24 weeks	38	0.105

4	Treatment with Peg-IFN +Ribavirin for 24 weeks	Undetectable RNA at 4 and 12 weeks	212	0.584
5	Treatment with Peg-IFN +Ribavirin for 48 weeks	RNA 1-1000 at 4 or 12 weeks, undetectable at 24 weeks	102	0.281
6	Partial treatment 0 to 48 weeks	Lost to Follow-up	4	0.011
7	Partial treatment 0 to 48 weeks	Unclear	7	0.019

To use these data in our model, we made the following two adjustments:

- We distributed the 38 patients in the Jacobsen et al. (2011) data who discontinued treatment after 24 weeks into thirds and apportioned them one-third each to 4 weeks, 12 weeks, and 24 weeks of treatment.
- We distributed the 11 patients in lost to follow-up and unclear into groups 1 through five with an equal distribute across the groups.

These adjustments result in the data in Table 4-9.

Table 4-9. Distribution of Jacobsen et al. (2011) to their Analogous Mount Sinai Treatment Algorithm Categories After Making First Set of Adjustments

Group #	Telaprevir Treatment Duration Group Description	Reason For Duration	Number	Proportion of Those Treated
1	Discontinue treatment after 4 weeks	RNA > 1,000 at 4 weeks	14.9	0.041
2	Discontinue treatment after 12 weeks	RNA > 1,000 at 12 weeks	14.9	0.041
3	Discontinue treatment after 24 weeks	Detectable RNA at 24 weeks	14.9	0.041
4	Treatment with Peg-IFN +Ribavirin for 24 weeks	Undetectable RNA at 4 and 12 weeks	214.2	0.59
5	Treatment with Peg-IFN +Ribavirin for 48 weeks	RNA 1-1000 at 4 or 12 weeks, undetectable at 24 weeks	104.2	0.287
6	Partial treatment 0 to 48 weeks	Lost to follow-up	Redistributed	0
7	Partial treatment 0 to 48 weeks	Unclear	Redistributed	0

Question B. How should these proportions be modified if we assumed lower overall probability of SVR than observed in clinical trials?

To account for lower SVR rates expected in clinical settings, we subtracted the difference between the expected effectiveness and the clinical trial efficacy (21.1%) and assigned these patients to categories 1 through 5 in terms of duration of treatment using the assumptions outlined in Question C.

Question C. How should we assign the remainder of patients after we transform the SVR probabilities to be lower?

To assign the expected number of people who would not achieve an SVR in our assumed clinical care setting but who did in achieve an SVR in the clinical trial data (21.1% of the sample), we assumed these patients discontinued at some point during their therapy and then used the discontinuation percentages seen in the Jacobson et al. (2011) data to distribute them to treatment states.

From the Jacobson data:

- 15/210 discontinued treatment in the 24-week arm (7.1%)
- 80/153 discontinued in the 48-week arm (52.3%)

We assumed that the incremental difference between 52.3% in the 48 week arm and 7.1% in the 24 week arm was due to duration. If that assumption were true, then it follows that if all patients were offered a possible 48 weeks of treatment, you would expect 7.1% would discontinue before 24 weeks and an additional 45.2% would discontinue between 24 and 48 weeks. In percentage terms, 13.7% of those that discontinued did so before 24 weeks, and 86.3% did so between 24 and 48 weeks.

Combining the answer from Question B with the assumptions from Question C, we subtracted 21.1% equally across categories 4 and 5 and redistributed that 21.1% into two new categories: (6) discontinued by 24 weeks, and (7) discontinued between 24 and 48 weeks. Based on this, 13.7% and 86.3% of those that discontinued, discontinue at 24 and 48 weeks respectively. In Question D, we will then distribute these people evenly across weeks. This yields Table 4-10.

Table 4-10. Distribution of Jacobsen et al. (2011) to their Analogous Mount Sinai Treatment Algorithm Categories After Making All Adjustments

Group #	Telaprevir Treatment Duration Group Description	Reason For Duration	Number	Proportion of Those Treated
1	Discontinue treatment after 4 weeks	RNA > 1,000 at 4 weeks	14.9	0.041

2	Discontinue treatment after 12 weeks	RNA > 1,000 at 12 weeks	14.9	0.041
3	Discontinue treatment after 24 weeks	Detectable RNA at 24 weeks	14.9	0.041
4	Treatment with Peg-IFN +Ribavirin for 24 weeks	Undetectable RNA at 4 and 12 weeks	175.9	0.485
5	Treatment with Peg-IFN +Ribavirin for 48 weeks	RNA 1-1000 at 4 or 12 weeks, undetectable at 24 weeks	66.1	0.182
6	Partial treatment 0 to 24 weeks	Unknown	10.5	0.029
7	Partial treatment 0 to 48 weeks	Unknown	66.1	0.182

Question D. What unit costs do we multiply these proportions against to model overall costs treatment?

In this step, we distributed patients in the seven states above to weeks of treatment, assigned each week costs, and from these values assigned costs based on the monthly costs of pegylated antiviral therapy including ancillary costs plus the additional costs of telaprevir. From Figure 4-10, we assigned people with known weeks in which they discontinued (e.g., 4 weeks, 12 weeks) to those weeks of treatment. We assigned patients in group 6 of Table 4-9 equally by week across weeks 1 through 24, and we assigned patients in group 7 equally across weeks 25 through 48. Weekly costs were set to expected cost of telaprevir in that week (Table 4-7) plus expected costs of pegylated interferon and other medical costs in that week.

We estimated weekly values of pegylated interferon and other medical costs by dividing the monthly values in Table 4-4 (variable by month) by 30.4, the average number of days in a month multiplied by 7 (days in a week). Table 4-11 presents our work in estimating the costs of telaprevir + pegylated interon plus ribavirin and other treatment medical services.

Table 4-11. Estimation Cost of Expected Cost of Telaprevir Plus Pegylated Interferon Plus Ribaviron Using Discontinuation Distribution and Weekly Cost Data

Weeks of Treatment	Proportion of Those Treated	Telaprevir Cost	Other Costs	Total Cost to This Point for Those Who Complete Treatment	Total Costs Multiplied by Proportion for Average Computation
1	0.001	$3,450	$299	$3,749	$5
2	0.001	$3,450	$299	$7,498	$9
3	0.001	$3,450	$299	$11,248	$14
4	0.041	$3,450	$299	$14,997	$615
5	0.001	$3,450	$252	$18,699	$23
6	0.001	$3,450	$252	$22,402	$27
7	0.001	$3,450	$252	$26,104	$32

8	0.001	$3,450	$252	$29,807	$36
9	0.001	$3,450	$288	$33,544	$41
10	0.001	$3,450	$288	$37,282	$45
11	0.001	$3,450	$288	$41,020	$50
12	0.042	$3,450	$288	$44,757	$1,889
13	0.001	$0	$252	$45,010	$54
14	0.001	$0	$252	$45,262	$55
15	0.001	$0	$252	$45,515	$55
16	0.001	$0	$252	$45,767	$55
17	0.001	$0	$282	$46,050	$56

(continued)

Table 4-11. Estimation Cost of Expected Cost of Telaprevir Plus Pegylated Interferon Plus Ribaviron Using Discontinuation Distribution and Weekly Cost Data (continued)

Weeks of Treatment	Proportion of Those Treated	Telaprevir Cost	Other Costs	Total Cost to This Point for Those Who Complete Treatment	Total Costs Multiplied by Proportion for Average Computation
18	0.001	$0	$282	$46,332	$56
19	0.001	$0	$282	$46,615	$56
20	0.001	$0	$282	$46,897	$57
21	0.001	$0	$258	$47,155	$57
22	0.001	$0	$258	$47,413	$57
23	0.001	$0	$258	$47,670	$58
24	0.534	$0	$258	$47,928	$25,574
25	0.008	$0	$282	$48,211	$366
26	0.008	$0	$282	$48,493	$368
27	0.008	$0	$282	$48,776	$370
28	0.008	$0	$282	$49,058	$372
29	0.008	$0	$252	$49,311	$374
30	0.008	$0	$252	$49,563	$376
31	0.008	$0	$252	$49,815	$378
32	0.008	$0	$252	$50,068	$380
33	0.008	$0	$288	$50,356	$382
34	0.008	$0	$288	$50,643	$384
35	0.008	$0	$288	$50,931	$386
36	0.008	$0	$288	$51,219	$388
37	0.008	$0	$252	$51,471	$390
38	0.008	$0	$252	$51,724	$392
39	0.008	$0	$252	$51,976	$394
40	0.008	$0	$252	$52,229	$396
41	0.008	$0	$282	$52,511	$398

42	0.008	$0	$282	$52,794	$400
43	0.008	$0	$282	$53,076	$402
44	0.008	$0	$282	$53,359	$405
45	0.008	$0	$258	$53,616	$407
46	0.008	$0	$258	$53,874	$409
47	0.008	$0	$258	$54,132	$410
48	0.190	$0	$258	$54,390	$10,311
				Average Cost Per Patient (sum of final column)	**$48,212**

4.6 Post Antiviral Therapy Costs/Post-Treatment, if SVR

Post-therapy costs for patients who achieve an SVR assume ongoing monitoring for virus for the rest of the patient's life. We assume that the intensity of monitoring declines from Year 1 (Table 4-12) to Years 2 through 5 (Table 4-13) and then again from Year 5 to the rest of the patient's life (Table 4-14).

Table 4-12. Post-Treatment, if SVR, Year 1

Elements	Code	Quantity	Unit Cost	Total Cost	Recommendation Source	Cost Source
Qualitative RNA, amplified detection	87521	2	$49.04	$98.08	Assumption	Gray, 2003; AMA, 2007
Outpatient office visit, established patient	99213	2	$59.50	$119.00	Assumption	Gray, 2003; AMA, 2007
Comprehensive metabolic panel	80053	2	$14.77	$29.54	Cleveland Clinic	Gray, 2003; AMA, 2007
Total post-treatment SVR				$246.62		

Note: SVR = sustained viral response

Table 4-13. Post-Treatment, if SVR, Years 2–5

Elements	Code	Quantity	Unit Cost	Total Cost	Recommendation Source	Cost Source
Qualitative RNA, amplified detection	87521	1	$49.04	$49.04	Assumption	Gray, 2003; AMA, 2007
Outpatient office visit, established patient	99213	1	$59.50	$59.50	Assumption	Gray, 2003; AMA, 2007
Comprehensive metabolic panel	80053	1	$14.77	$14.77	Cleveland Clinic	Gray, 2003; AMA, 2007
Total post-treatment SVR				$123.31		

Note: SVR = sustained viral response

Table 4-14. Post-Treatment, if SVR 5-Death

Elements	Code	Quantity	Unit Cost	Total Cost	Recommendation Source	Cost Source
Qualitative RNA, amplified detection	87521	0.5	$49.04	$24.52	Assumption	Gray, 2003; AMA, 2007
Outpatient office visit, established patient	99213	0.5	$59.50	$29.75	Assumption	Gray, 2003; AMA, 2007
Comprehensive metabolic panel	80053	0.5	$14.77	$7.39	Cleveland Clinic	Gray, 2003; AMA, 2007
Total post-treatment SVR				$54.27	Assumes check once every 2 years	

Note: SVR = sustained viral response

4.7 Chronic Carrier State/Post-Treatment if No SVR

We assume an annual cost for patients with chronic disease comprised of outpatient services and testing to monitor the progression of disease and manage a patient's mental health status (Table 4-15). These costs are identical regardless of whether a patient has never undergone therapy or has undergone therapy and not experienced an SVR. We assume identical costs across all METAVIR states prior to decompensation.

Table 4-15. Treatment of Chronic Infection

Elements	Code	Quantity	Unit Cost	Total Cost	Recommendation Source	Cost Source
Outpatient office visit, established patient	99213	1	$59.50	$59.50	Assumption	Gray, 2003; AMA, 2007
Ultrasonic HCC screening	76705	1	$91.33	$91.33	Assumption	Gray, 2003; AMA, 2007
Mental health screening	96151	1	$22.74	$22.74	Assumption	Gray, 2003; AMA, 2007
Comprehensive metabolic panel	80053	1	$14.77	$14.77	Cleveland Clinic	Gray, 2003; AMA, 2007
Liver biopsy	47000	0.2	$225.49	$45.10	One biopsy every 5 years, based on recommendation from New York State Department of Health[a]	Gray, 2003; AMA, 2007
Total post-treatment SVR				$263.00	Assumes annual occurrence until cirrhosis or death	

Note: HCC = hepatocellular carcinoma; SVR = sustained viral response

[a]http://www.health.state.ny.us/diseases/communicable/hepatitis/guidelines/management.htm

4.8 End-Stage Liver Disease, Decompensated Cirrhosis, and Hepatocellular Carcinoma

We used estimated annual medical costs for severe liver complications taken from Davis et al. (2010) for the costs of treating DCC and HCC in years where patients did not undergo transplantation. These costs are equal to $12,433 per year.

4.9 Transplant Costs

Nine studies published between 1995 and 2006 were reviewed to obtain cost estimates for liver transplantation in the initial transplant year. Table 4-16 shows estimates of the cost of liver transplantation from several studies, describes the elements included in each estimate, and then converts the estimates into common 2007 dollar values.

Table 4-16. Cost of Liver Transplantation in the Initial Transplant Year

Type of Estimate	Study	Description	Cost	Year	2007 Estimated Cost
Foreign health systems	Castelnuovo et al. (2006)	English health system costs—translated from Euros (1 e = 1.3 $)	$60,562	2006	$61,734
	Kogure et al. (2006)	Japanese health care system	$97,901	2005	$103,014
Origin of estimate unclear	Jhaveri et al. (2006)	Unclear derivation (most likely Showstack et al.)	$200,000	2005	$210,445
	Salomon et al. (2003)	Unclear derivation	$118,285	2001	$137,331
	Wong et al. (2000)	Unclear derivation	$108,659	1999	$134,040
Updated by same source	Ortner and Cosway (2005)	Older Milliman Report Value	$393,000	2005	$413,525
May exclude procurement costs	Miriti et al. (2008)	Unpublished	$183,268	2007	$183,268
Pediatric costs	Englesbe et al. (2006)	Pediatric (weighted average of those with and without biliary complications). Excludes procurement costs	$154,000	2005	$162,043
Strongest estimates	Haubolt (2007)[a]	Unpublished, 2008 Milliman Report Value	a.$519,600 b.$283,400	2007	$283,400
	Englesbe et al. (2006)	Adults (weighted average of those with and without biliary complications); excludes procurement costs	$191,000	2005	$200,975
	Showstack et al. (1999)	Seminal estimate	$203,434	1995	$275,665
	Average of Strong Estimates Used in Model				**$253,347**

[a] Haubolt estimate includes (a) for billable charges and (b) estimate of payments after Medicare discount is applied to applicable components.

Several of these estimates can be excluded from consideration. Castelnuovo et al. (2006) and Kogure et al. (2006) can be excluded because they are estimates of costs in foreign settings (the United Kingdom and Japan). Ortner and Cosway (2005) can also be excluded, because Haubolt (2007) represents a more up-to-date estimate of the same costs and also provides the ability to estimate the discounted cost to Medicare. Jhaveri et al. (2006), Salomon et al. (2003), and Wong et al. (2000) can be excluded because the origins of their estimates are unclear. Miriti et al. (2008) has not yet been published and their estimate may not include procurement costs. Finally, one of the two estimates contained in Englesbe et al. (2006) are for pediatric costs as opposed to adult costs, costs that would be rare in the treatment of HCV.

After those exclusions, the average liver transplant cost of the three studies with the best estimates—Haubolt (2007), Englesbe et al. (2006), and Showstack et al. (1999)—was $253,347. This cost was used as the baseline estimate of first year costs in the model, the estimate varied as explained below in the probabilistic sensitivity analyses.

After the initial transplant year, patients continue to receive extensive follow-up care. Patients must take daily medications to reduce the risk of organ rejection. Usually, follow-up care is provided by physicians at the transplant center. Various studies have constructed these costs, but no good contemporary study of the costs of maintaining liver transplant patients exists. Table 4-17 presents estimates found in the literature or used in other cost-effectiveness models. Each of these is in turn derived from a source in the early to mid-1990s.

Table 4-17. Annual Cost of Liver Transplantation in Subsequent Transplantation Years

Study	Cost	Year of Estimate	2007 Estimated Cost
Berge et al. (2000)	$21,900	1997	$28,040
Salomon et al. (2003)	$20,657	2001	$23,983
Wong et al. (2000)	$18,976	1999	$23,407

Table 4-18 provides a summary of the medical costs, ranges, and distributions used in our cost-effectiveness model. We assumed ranges for these variables based on guidelines taken from Doubilet et al. (1985), essentially a range of ±50% for all health care costs given our general uncertainty about their actual values. We used the normal distribution for costs that we considered discrete and unlikely to be affected by outlier values (such as screening costs and antiviral therapy) and the lognormal distribution for health care costs (like annual costs per stage of disease) that could contain more variation.

Table 4-18. Summary of Costs and Distribution Parameters Used in Model

Parameter	Value	Range	Source	Distribution
Medical costs				
Screening				
Negative test	34	17–51	Rein et al., 2011	Normal
Positive test, no return for results	34	17–54	Rein et al., 2011	Normal
Cost of returning for results	19	9–28	Rein et al., 2011	Normal
Treatment				
Cost of initial workup, if coordinated with treatment	686	342–1029	Carey et al., 2007; Strader et al., 2004; Gray, 2003; AMA, 2007	Normal
Cost of treatment, genotype 1, pegylated interferon and ribavirin only	12,080	6,040–18,120	Roblin, 2010	Normal
Cost of treatment, genotype 1, telaprevir, pegylated interferon and ribavirin only	47,846	38,277—57,415	Personal communication, assumptions, see text	Normal
Cost of treatment, genotype 2/3	6,446	3,223–9,669	Roblin, 2010	Normal
Cost of year 1 post-treatment	247	123–370	Carey et al., 2007; Strader et al., 2004; Gray, 2003; AMA, 2007	Log normal
Cost of years 2–5 post-treatment	123	62–185	Carey et al., 2007; Strader et al., 2004; Gray, 2003; AMA, 2007	Log normal
Cost of years 6–death post-treatment	54	27–81	Carey et al., 2007; Strader et al., 2004; Gray, 2003; AMA, 2007	Log normal
Non-antiviral Medical Care				
Cost of initial workup, if not treated	724	361–1,086	Carey et al., 2007; Strader et al., 2004; Gray, 2003; AMA, 2007	Normal
Cost for METAVIR stages 0–4	263	132–395	Carey et al., 2007; Strader et al., 2004; Gray, 2003; AMA, 2007	Log normal
Cost of compensated cirrhosis	263	132–395	Carey et al., 2007; Strader et al., 2004; Gray, 2003; AMA, 2007	Log normal
Cost of decompensated cirrhosis	12,433	6,216-18,650	Davis et al., 2011	Log normal
Cost of HCC	12,433	6,216-18,650	Davis et al., 2011	Log normal

(continued)

Table 4-18. Summary of Costs and Distribution Parameters Used in Model (continued)

Parameter	Value	Range	Source	Distribution
Cost of liver transplant (year of)	253,347	126,674–380,021	Englesbe et al., 2006; Haubolt, 2007, personal communication; Showstack et al., 1999	Log normal
Cost of liver transplant (subsequent years)	23,983	11,991–35,975	Salomon et al., 2003	Log normal

Note: AASLD = American Association for the Study of Liver Diseases; CBC/DIF = Complete Blood Count with Differential Related Tests; HCC= hepatocellular carcinoma; HCV= hepatitis C virus; IDU = injecting drug use; MCR = Medicare; SVR = sustained viral response; VFC = Vaccines for Children; *Assumed identical rate for women with high alcohol intake as low because point estimate for this value was slightly lower, likely due to sample variation.

5. PRODUCTIVITY LOSSES

Productivity losses are used to incorporate the costs of lost labor into cost-effectiveness models. This document outlines the parameters used to estimate the productivity losses for patients with hepatitis C during treatment as well as the losses resulting from decompensated cirrhosis and hepatocellular carcinoma (HCC).

Productivity losses were calculated using the number of work hours missed from Perrillo et al. (2004). The hours missed per month of treatment were adjusted using the discontinuation rates from Mauss et al. (2004). In effect, patients were assumed to miss a certain number of hours of work for each month during treatment, but because a proportion of patients will drop out each month, not all of the hours of missed work should be used in estimating productivity losses (Mauss et al., 2004). Hours of work missed were converted into the proportion of the year missed of work. Annual wages by age group from the Bureau of Labor Statistics were adjusted for labor force participation and multiplied by the proportion of the year lost due to hepatitis C virus (HCV) treatment (Bureau of Labor Statistics, 2009). The productivity losses by genotype reflect the different length of time for each treatment regimen.

The productivity losses from decompensated cirrhosis and HCC assume an entire year of work is lost. Annual wages by age group from the Bureau of Labor Statistics were adjusted for labor force participation. Table 5-1 shows the productivity losses from hepatitis C treatment and from decompensated cirrhosis and HCC.

Table 5-1. Productivity Losses

Age Range	Genotype 1 Treatment	Genotype 2/3 Treatment	DC/HCC
20–29	$658	$288	$9,611
30–39	$1,227	$538	$17,929
40–49	$2,075	$909	$30,314
50–59	$1,230	$539	$17,974
60–69	$199	$87	$2,913
70–99	$0	$0	$0
100+	$0	$0	$0

Note: DC = decompensated cirrhosis; HCC = hepatocellular carcinoma

6. UTILITY LOSSES

6.1 Background QALYs

Background quality-adjusted life year (QALY) values refer to the QALYs individuals experience without the given health condition under study. When averaged across an entire population, background QALYs do not equal 1.00 because at least some individuals experience morbidity from other causes. Because the prevalence of other health conditions increases as patients age, background QALYs decrease with increasing age. In this study, we used background QALYs from Gold et al. (1998) (shown in Table 6-1).

Table 6-1. Background QALYs

Age Range	QALY
0–4	0.94
5–17	0.93
18–24	0.915
25–34	0.915
35–44	0.895
45–54	0.865
55–64	0.805
65–74	0.77
75–100	0.695

Note: QALY = quality-adjusted life year

6.2 QALY Losses from Hepatitis C

QALYs are generally measured in one of four ways:

- Visual Analogue Scale (VAS). Patients are asked to draw the value of their health status on a picture of a "feeling thermometer" where 1 represents perfect health and 0 represents death.
- Time-Tradeoff (TT). Patients are asked to evaluate the proportional worth of a year with illness relative to a year of perfect health.
- Standard Gamble (SG) methodologies. Patients are asked what risk of death they would accept in exchange for curing their disease.
- Conversions of Health Utility Indexes, particularly the Short Form 6 Domain (SF-6D) or the EuroQual Five Dimension (EQ-5D) Health Index Questionnaires. Specific combinations of questionnaire responses are associated using regression analysis with a database of health utility values collected from a large randomly selected community survey.

Little consensus exists on which of these methodologies is most appropriate. However, VAS methods are widely considered weaker than the others and should only be used when other estimates do not exist.

Six studies (Chong et al., 2003; Grieve et al., 2006; Mrus et al., 2006; Sherman et al., 2004, 2006; Siebert et al., 2005; Wright et al., 2006) elicited QALYs directly from patients (Table 6-2) using one of these methods. Mrus et al. (2006) and Sherman et al. (2004) are the same study. A fifth study (Thein et al., 2005) used a published conversion algorithm (Nichol et al., 2001) to assess the average QALY value associated with 15 studies that assessed the impact of hepatitis C virus (HCV) on functionality using the SF-36 health survey (Ware and Sherbourne, 1992; Nichol, Sengupta, & Globe, 2001; Thein et al., 2005).

Table 6-2. Major Empirical Studies of Patient Utility Losses from HCV Infection

Study	Location	Sample Characteristics	Methods
Chong et al. (2003)	Toronto	193 current liver and liver transplant clinic patients, former patients with SVR (response rate = 93%)	VAS, TT, SG, HUI-SF-36
Siebert et al. (2005)	Germany	348 consecutive patients at a German liver clinic	VAS
Sherman et al. (2004); Mrus et al. (2006)	Cincinnati	124 outpatients from indigent clinic, private university-based clinic, transplant center, HIV clinic	VAS, TT, SG
Thein et al. (2005)	Literature	15 published studies	HUI-SF-36
Grieve et al. (2006)	London, Newcastle, Southampton	196 patients with mild HCV from RCT, 175 cases with moderate chronic infection, cirrhosis, and decompensated cirrhosis from hospitals	HUI-EQ-5D

Note: VAS = Visual Analogue Scale; TT = Time Trade-off; SG = Standard Gamble; HUI = Health Utility Indexes; SF-36 = Short Form-36 Health Utility Index; and EQ-5D = EuroQoL 5 Dimension Health Utility Index

To summarize these studies, we first eliminated values derived using VAS methods because VAS methods cannot be linked to patient utility and because VAS-estimated qualities have been demonstrated to poorly reproduce values obtained using TT, SG, or HUI methods (Rashidi et al., 2006). This eliminated all results from Siebert et al. (2005) and one set of results from Chong et al. (2003) and from Sherman et al. (2004). We also eliminated QALY values from Mrus et al. (2006) because it was impossible to isolate the types of patients these values referred to or the estimation method used to calculate values.

After this elimination process, seven sets of QALY estimates remained: SG, SF-36, and EQ-5D estimates from Chong et al. (2003); TT and SG estimates from Sherman et al. (2004), for compensated and decompensated cirrhosis only; EQ-5D estimates from Grieve et al. (2006); and the summary set of SF-36 estimates from Thein et al. (2005).

We organized these QALY values according to eight HCV health states:

1. No HCV
2. SVR at least 6 months following treatments
3. Mild chronic infection corresponding to METAVIR score of 0 or 1
4. Moderate chronic infection corresponding to METAVIR score of 2 or 3
5. Compensated cirrhosis corresponding to a METAVIR score of 4
6. Decompensated cirrhosis
7. HCC
8. Liver transplant after transplant year

To compare results, we standardized the remaining QALY values as a proportion of the baseline value by dividing the QALY value for each health state by the QALY value for the no HCV state. This diminishes the impact of the estimation methodology on the utility estimation and presents all estimates in terms of their proportional value of non-HCV health, whatever the background utility value for non-HCV might be. Following this, we calculated the mean, median, minimum, and maximum relative QALY values for each health state (Table 6-3). The mean value is what we used in the cost-effectiveness model.

Table 6-3. Summary of Empirically Estimated QALY Measures

	State	Mean	Median	Min	Max
Rescaled to equal 1.00	QALY state 1: No HCV	1.00	1.00	1.00	1.00
As a proportion of State 1	QALY state 2: SVR	0.93	0.94	0.83	1.01
	QALY state 3: Mild chronic hepatitis	0.86	0.88	0.78	0.94
	QALY state 4: Moderate Chronic hepatitis	0.83	0.80	0.78	0.89
	QALY state 5: Compensated cirrhosis	0.81	0.81	0.67	0.90
	QALY state 6: Decompensated cirrhosis	0.70	0.72	0.55	0.80
	QALY state 7: Hepatocellular carcinoma	0.67	0.72	0.55	0.79
	QALY state 8: Liver transplant, subsequent years	0.78	0.78	0.72	0.84

Note: HCV = hepatocellular carcinoma; QALY = quality-adjusted life year; SVR = sustained viral response

7. VALIDATION

Rein, Wittenborn, et al. (2011) present a demonstration of the validation of this model. That paper tested the external validity of the model by programming it with hepatitis C virus (HCV) prevalence estimates generated using the National Health and Nutrition Examination Survey (NHANES) III data collected between 1988 and 1994. It then set the model's starting cohort population values to those that existed in 1991 and simulated disease progression for 25 years. For validation, the paper compared the average annual number of cases of end-stage liver disease, liver transplants, and deaths predicted by the model from 2000 to 2004 to estimates of those same outcomes drawn from published studies. The validation exercise did not look at cases of cirrhosis or chronic HCV by disease stage. However, the model did accurately recreate the NHANES prevalence data on antibody positivity used to populate it.

For end-stage liver disease, as presented in Table 2 of Rein, Wittenborn, et al. (2011), that paper estimated approximately 33% fewer cases of decompensated cirrhosis (43,423 compared to 65,294 cases) and 68% more cases of liver cancer (12,262 compared to 7,271) compared to the one other estimate of these outcomes, estimates that were also derived from simulation results (Davis et al., 2003). Cumulatively, the paper estimated 55,685 cases of prevalent end-stage liver disease in the United States in 2005.

For the birth cohort, our model produced a population prevalence of HCV antibody of .036. The latest unpublished CDC estimate for the prevalence is 0.033 (unpublished data). Our estimate is 0.003 percentage points/9% higher than this CDC estimate.

Note that although the Rein, Wittenborn, et al. (2011) model predicted relatively more cases of HCC compared with Davis et al. (2003), it predicted virtually the exact number of transplants reported in 2005 (1,697 for the model compared to 1,677, the average number of HCV transplants from United Network for Organ Sharing between the years 2001 and 2006). Because we assume the same annual medical costs for liver cancer as we do for decompensated cirrhosis and because the additional cases of liver cancer are not resulting in greater than observed numbers of liver transplants, the differences relative to Davis et al. (2003) in the distribution of end-stage liver disease cases between liver cancer and decompensated cirrhosis are not likely leading to either substantially increased or decreased costs of HCV in our predictions. Rein, Wittenborn, et al. (2011) also predicted annual deaths from HCV with approximately a 10% variance from observed deaths in 2005.

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