Supplementary Material*

Chhatwal J, Kanwal F, Roberts MS, Dunn MA. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. Ann Intern Med. doi:10.7326/M14-1336

 © 2015 American College of Physicians

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

Figure 8. **Incremental cost-effectiveness ratio of sofosbuvir/ledipasvir-based therapies in treatment-naive, interferon-intolerant patients.**

Figure 9. **Incremental cost-effectiveness ratio of sofosbuvir/ledipasvir-based therapies in treatment-experienced patients.**

***** This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.

© 2015 American College of Physicians
Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

Appendix 1: Model Inputs

S1.1. Technical notes about our Markov-based microsimulation model

Our model was developed using C++, a general-purpose computer programming language (1). We used a weekly cycle length to advance time in the model. Patients could discontinue treatment because of adverse events or futility rules (only in the old standard of care arm). At the end of treatment, patients were followed-up for 12 weeks to determine if they achieve a sustained virologic response (SVR). In all modeling arms, we determined SVR at week 12 even though efficacy of the old standard of care was determined at week 24 after treatment. Our assumption was based on a recently published study that showed that the SVR rates at week 12 and 24 were similar (2). We used common random numbers to reduce simulation noise across the two scenarios (3). For each patient profile, we ran 10 000 iterations of our model to reduce first-order variability in the outcomes (4).

S1.2. Demographics and Disease Stage Distribution of Chronic Hepatitis C Virus (HCV) Patients in the United States

Since cost-effectiveness of HCV treatment depends on the patient's age and fibrosis scores, we estimated mean age by fibrosis scores of the HCV patients in the United States (US) at the beginning of 2014 by simulating the effect of disease progression, age, and treatment opportunities from 2001 to 2013. For that purpose, we used a previously validated model of the US population that simulated the clinical practice from 2001 to 2013. The model was validated using data from two NHANES studies (5, 6). The model simulated treatment with peginterferon-ribavirin from 2002 until 2011 and with first-generation protease inhibitors from 2012 onward. We defined a total of 120 patient profiles based on patients' treatment history (naive or experienced); IFN-tolerance (yes or no; for treatment-naive patients only); HCV genotype (G1, G2, G3, or G4), sex (male or female), and METAVIR fibrosis score (no fibrosis [F0], portal fibrosis without septa [F1], portal fibrosis with few septa [F2], numerous septa without fibrosis [F3], or cirrhosis [F4]). There were 80 treatment-naïve profiles calculated as 2 (IFN-tolerance: year or no) X 4 (HCV genotype: G1-G4) X 2 (sex: male or female) X 5 (METAVIR fibrosis scores: F0–F4). The remaining 40 patient profiles belonged to treatment-experienced patients calculated as 4 (HCV genotype: G1-G4) X 2 (sex: male or female) X 5 (METAVIR fibrosis scores: F0–F4). The model also predicted the number of HCV infected patients in the beginning of 2014 who are eligible for HCV treatment, distribution of HCV genotype in 2014, mean age by fibrosis level (**Table 1**). We defined treatment ineligibility due to interferon-intolerance as one or more of the following conditions: bipolar disorder, anemia (Hgb < 10 g/d), pregnancy and neutropenia (neutrophils <750 cells/mm3; 1.2%) (7). According to this study, 17.3% (7903 / 45680) HCV patients had at least one contraindication for interferon.

Table 1. Baseline Population Distribution of HCV-Infected Patients in the United States

Parameter	Distribution (%)	Age (years)
Fibrosis score (8)		
F0	6%	49.9
F1	24%	56.2
F2	21%	57.6
F3	21%	58.3
F4	28%	58.7
Genotype (9)		
G1	80%	--
G2	13%	--
G3	6%	--
G4	1%	--
Sex (6)		
Male	64%	--
Female	36%	--

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

Treatment experienced (8)	39%	--
Interferon Tolerance (7)	17%	--

Abbreviations: HCV, hepatitis C virus; F, METAVIR fibrosis score; G, genotype

S1.3. Efficacy Data for Treatment-Naive Patients Who are Interferon Tolerant

Abbreviations used: PEG, peginterferon; RBV, ribavirin; BOC, boceprevir; TEL, telaprevir; SOF, sofosbuvir; LDV, ledipasvir; AASLD, American Association for the Study of Liver Diseases; IDSA, Infectious Diseases Society of America.

Genotype 1
oSOC: Response-guided or fixed-duration therapy based on BOC + PEG + RBV or TEL + PEG + RBV
We assumed that 50% of the patients used BOC-based treatment and 50% used TEL-based treatment. The duration of treatment was dependent on the baseline fibrosis score.
BOC-based treatment: Non-cirrhotic patients were administered response-guided therapy (RGT), and cirrhotic patients were treated with 48 weeks fixed-duration therapy (10). We used SPRINT-2 trial to estimate efficacy that was used for the approval of boceprevir by the FDA.
The duration of RGT treatment: 78% of patients in SPRINT-2 clinical trial were assigned 28-week treatment, and 22% of patients in SPRINT-2 were assigned 48-week treatment. We estimated the weighted average of the length of duration equal to 32 weeks. For 48-week treatment, SPRINT-2 reported the probability of discontinuation of 42% (11). We also estimated the probability of discontinuation was estimated to be equal to 28% for 32-week treatment. Finally, we estimated the probability and duration of anemia equal to 0.49 and 15 weeks. In non-cirrhotic patients, the probability of discontinuation was 42%, and the probability and duration of anemia were 49% and 21 weeks, respectively.
TEL-based treatment: We used ADVANCE trial to estimate efficacy, which was used for the approval of telaprevir by the FDA. The duration of treatment: 58% of patients in ADVANCE clinical trial were assigned 24-week treatment, and 42% were assigned 48-week treatment. We estimated the weighted average of the length of duration equal to 34 weeks. We also estimated the probability of discontinuation to be equal to 21% for 34-week treatment. The probability and duration of anemia were estimated as 37% and 11.6 weeks, respectively.

SOF-based regimens: SOF+LDV for either 8 or 12 weeks
We used ION-1 and ION-3 studies to estimate efficacy data for SOF and LDV-based treatments because they were used by the FDA for drug approval (12, 13). In non-cirrhotic treatment-naïve patients, the duration of LDV+SOF depends on patient's baseline HCV RNA. Those with HCV RNA less than 6 million IU/mL were considered for 8 weeks of treatment, and 12 weeks otherwise. Among this patient group, 57% (=123/215) of patients were eligible for 8 weeks of treatment (14). In cirrhotic patients, the duration of treatment was 12 weeks, irrespective of HCV RNA level. The discontinuation rates and probability of anemia were 1% in all patients. We assumed that the duration of anemia was 1 week in 8-week regimen and 2 weeks in 12-week regimen. We extracted SVR rates in genotype 1 patients as follow:

- SVR rates of genotype 1 patients *without* cirrhosis and HCV RNA < 6 million IU/mL = 119 / 123 = **97%**
- SVR rates of genotype 1 patients *without* cirrhosis and HCV RNA > 6 million IU/mL = 126 / 131 **96%**
- SVR rates of genotype 1 patients *with* cirrhosis = **97%**

Genotype 2
oSOC: PEG + RBV for 24 weeks
We used the comparator arm of the FISSION study to extract efficacy data for PEG and RBV in genotype 2 patients (15).

SOF-based regimens: SOF + RBV for 12 weeks
We estimated efficacy data of SOF-based treatment using FISSION study (15).

Genotype 3

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

oSOC: PEG + RBV for 24 weeks
We used historic data to estimate efficacy data for genotype 3 patients (16).
SOF-based regimens: SOF + RBV for 24 weeks
We used VALENCE study to estimate efficacy data of SOF-based treatment (17). We assumed the duration of anemia equal to 7 weeks for 24 weeks of RBV-based treatment.

Genotype 4
oSOC: PEG + RBV for 48 weeks
We used a meta-analysis of six randomized control trials to estimate efficacy data for genotype 4 patients (18).
SOF-based regimens: SOF + PEG + RBV for 12 weeks
We used NEUTRINO study to estimate efficacy data for SOF-based treatment (15). The study provided the combined SVR rates of genotype 4 cirrhotic and non-cirrhotic patients equal to 96%. In addition, the study reported the SVR rates of combined genotype 1 and 4 equal to 90% for all patients, 80% for cirrhotic patients, and 92% for non-cirrhotic patients. Using this information, we estimated separate SVR rates in genotype 4 patients by cirrhosis status as follow:

- SVR rates of genotype 4 patients *without* cirrhosis = (92% / 90%) x 96% = **98%**
- SVR rates of genotype 4 patients *with* cirrhosis = (80% / 90%) x 96% = **85%**

Note that NEUTRINO study did not report the proportion of cirrhotic patients by genotype. Because the SVR rates of both genotype 1 and 4 patients were not substantially different using old drugs (PEG-RBV), the proportion of cirrhotic patients may not differ substantially in the US population. Therefore, we assumed that the proportion of cirrhotic patients in genotype 1 and 4 was identical.

S1.4. Efficacy Data for Treatment-Naive Patients Who are Interferon Intolerant

Genotype 1
oSOC: We assumed that no treatment option is available in patients who are interferon intolerant.
SOF-based regimens: SOF+LDV for either 8 or 12 weeks
We used ION-1 and ION-3 studies to estimate efficacy data for SOF and LDV-based treatments, which were used by the FDA for drug approval (12, 13). In non-cirrhotic treatment-naïve patients, the duration of LDV+SOF depends on patient's baseline HCV RNA. Those with HCV RNA less than 6 million IL/mL were considered for 8 weeks of treatment, and 12 weeks otherwise. Among this patient group, 57% of patients were eligible for 8 weeks of treatment (14) . In cirrhotic patients, the duration of treatment was 12 weeks, irrespective of HCV RNA level. The discontinuation rates and probability of anemia were 1% in all patients. We assumed that the duration of anemia was 1 week in 8-week regimen and 2 weeks in 12-week regimen. We extracted SVR rates in genotype 1 patients as follow:

- SVR rates of genotype 1 patients *without* cirrhosis and HCV RNA < 6 million IU/mL = **97%**
- SVR rates of genotype 1 patients *without* cirrhosis and HCV RNA > 6 million IU/mL = **96%**
- SVR rates of genotype 1 patients *with* cirrhosis = **97%**

Genotype 2
oSOC: We assumed that no treatment option is available in patients who are interferon intolerant.
SOF-based regimens: SOF + RBV for 12 weeks
We used POSITRON study to estimate efficacy data in interferon-intolerant genotype 2 patients (19). The study provided SVR rates by presence of cirrhosis: 92% in non-cirrhotic and 94% in cirrhotic patients.

Genotype 3
oSOC: We assumed that no treatment option is available in patients who are interferon intolerant.
SOF-based regimens: SOF + RBV for 24 weeks
We used VALENCE study to estimate efficacy data of SOF-based treatment (17). We assumed the duration of anemia equal to 7 weeks for 24 weeks of RBV-based treatment.

Genotype 4
oSOC: We assumed that no treatment option is available in patients who are interferon intolerant.
SOF-based regimens: SOF + RBV for 24 weeks

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

We used a study of genotype 4 patients from Egyptian Ancestry Study to estimate efficacy data of SOF-based treatment (20), which was used by the AASLD-IDSA for their guidelines. The study reported 100% SVR rates in a small number of patients; however, we assumed the SVR rates of 93%, which were similar to the reported values in other genotypes. The duration of anemia was based on the other RBV-based treatments for 24 weeks. The probability of anemia was assumed to be same as reported in VALENCE study (17).

S1.5. Efficacy Data for Treatment-Experienced Patients

Genotype 1

oSOC: Response-guided or fixed-duration therapy based on BOC + PEG + RBV or TEL + PEG + RBV

We assumed that 50% of the patients used BOC-based treatment and 50% used TEL-based treatment.

BOC-based treatment: Since the RESPOND-2 study did not include previous null-responders to HCV treatment, we combined the results of RESPOND-2 and PROVIDE studies of boceprevir in previously treated patients to derive SVR rates for our analysis (by cirrhosis status). From RESPOND-2, we used the combined results of group 2 and group 3 patients because the individual groups were not powered to detect differences by cirrhosis stage. Below calculations provide our approach. Using percentage of null-responders (i.e. 28%) (21), and the combined SVR rates of (39%) x (28%) + (66.6%) x (72%) = 58.9%, we estimated SVR rates by cirrhosis as follows:

- SVR rates of genotype 1 patients *without* cirrhosis = (58.9% / 66.6%) x (65.4%) = **57.8%**
- SVR rates of genotype 1 patients *with* cirrhosis = (58.9% / 66.6%) x (59.0%) = **52.2%**

TEL-based treatment: We used REALIZE study to estimate efficacy data of TEL-based therapy. The study provided SVR rates by presence of cirrhosis: 70% in non-cirrhotic patients and 58% in cirrhotic patients. The overall discontinuation rate was 29%. We derived separate SVR rates in non-cirrhotic and cirrhotic patients based on their SVR rates as: 23% in non-cirrhotic and 36% in cirrhotic patients.

SOF-based regimens: SOF+LDV for either 12 or 24 weeks

We used ION-2 study to estimate efficacy data for SOF and LDV-based treatments (22), which was used by the FDA for drug approval. In non-cirrhotic treatment-experienced patients, the recommended duration of LDV+SOF is 12 weeks. In cirrhotic patients, the duration of treatment is 24 weeks. The discontinuation rates were 0% in all patients. In non-cirrhotic patients, no patient had anemia. In non-cirrhotic patients, 1% patients had anemia. We assumed that the duration of anemia was 4 week in this subgroup. We extracted SVR rates in genotype 1 patients as follow:

- SVR rates of genotype 1 patients *without* cirrhosis (12-week regimen) = **95%**
- SVR rates of genotype 1 patients *with* cirrhosis (24-week regimen) = **99%**

Genotype 2

oSOC: PEG + RBV for 24 week

The SVR rates of oSOC were derived from ECPIC study (23), which is the largest study to date to evaluate the efficacy of retreatment with peginterferon-ribavirin The SVR rates of non-cirrhotic and cirrhotic genotype 2/3 patients using interferon-based therapies were 61% and 48% respectively. In addition the study provided SVR rates separately for genotype 2 equal to 59%. The combined SVR of genotype 2 and 3 patients was 55%. Using these values, we derived the SVR rates for genotype 2 patients by cirrhosis as follows:

- SVR rates of genotype 2 patients *without* cirrhosis = (61% / 55%) x 59% = **65%**
- SVR rates of genotype 2 patients *with* cirrhosis = (48% / 55%) x 59% = **51%**

SOF-based regimens: SOF + RBV for 12 weeks

We used FUSION study to estimate efficacy data for genotype 2 treatment-experienced patients.(19)

Genotype 3

oSOC: PEG + RBV for 24 week

The SVR rates of oSOC were derived from ECPIC study (23), which is the largest study to date to evaluate the efficacy of retreatment with peginterferon-ribavirin. The SVR rates of non-cirrhotic and cirrhotic genotype 2/3 patients using interferon-based therapies were 61% and 48% respectively. In addition the study provided SVR rates separately for genotype 3 patients equal to 54%. The combined SVR of genotype 2 and 3 patients was 55%. Using these values, we derived the SVR rates for genotype 3 patients by cirrhosis as follows:

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

- SVR rates of genotype 3 patients *without* cirrhosis = (61% / 55%) x 54% = **60%**
- SVR rates of genotype 3 patients *with* cirrhosis = (48% / 55%) x 54% = **47%**

SOF-based regimens: SOF+RBV for 24 weeks
We used VALENCE study to estimate efficacy data of SOF-based treatment in previously treated genotype 3 patients, which was used by the AASLD-IDSA for their guidelines (17). We assumed the duration of anemia equal to 7 weeks for 24 weeks of RBV-based treatment.

Genotype 4
oSOC: PEG + RBV for 48 weeks
The SVR rates of oSOC were derived from ECPIC study, which is the largest study to date to evaluate the efficacy of retreatment with peginterferon-ribavirin (23). For genotype 4 patients, the study did not provide separate SVR rates by cirrhosis. Using SVR rates of cirrhosis versus no-cirrhosis of genotype 2/3 patients, we derived SVR rates of genotype 4 patients as follows:

- SVR rates of genotype 4 patients *without* cirrhosis = (61% / 55%) x 28% = **31%**
- SVR rates of genotype 4 patients *with* cirrhosis= (48% / 55%) x 28% = **24%**

SOF-based regimen: *SOF + PEG + RBV* for 12 weeks
To our knowledge, no clinical study evaluated the combination of sofosbuvir with peginterferon and ribavirin in genotype 4 patients. Therefore, we derived SVR rates of this combination using data from another study that used sofosbuvir and ribavirin for 24 weeks in genotype 4 patients.(20) We assumed that the addition of peginterferon would increase the SVR rates by another 10%, i.e. from 59% to 69%.

S1.6. Discount on Drug Costs

We estimated the average discount on drugs given to payers based on the discounts given to sofosbuvir. Discounts given to private, VA, Medicare and Medicaid were 14%, 44%, 0% and 23%, respectively (24, 25). Using the number of HCV patients under each insurance type, we estimated the average discount on sofosbuvir was 11%. We applied equal discount to all drugs costs because drug-specific discounts were not available for other drug combinations.

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

Table 2. Meta-Regression Equations of Fibrosis Progression

Transition	Equation Providing Transition Probability(26)
F0 to F1	$\exp[-2.0124 - (0.07589 \times duration) + (0.3247 \times 0.9009) + (0.5063 \times f(\text{male})) + (0.4839 \times f(\text{G1}))]$
F1 to F2	$\exp[-1.5387 - (0.06146 \times duration) + (0.8001 \times 0.19)]$
F2 to F3	$\exp[-1.6038 + (0.0172 \times \text{age at HCV}) - (0.05939 \times duration) + (0.4539 \times 0.19)]$
F3 to F4	$\exp[-2.2898 + (0.01689 \times \text{age at HCV}) - (0.03694 \times duration) + (0.5963 \times 0.41) + (1.1682 \times 0.31) - (0.4652 \times f(\text{G1}))]$

Duration of infection was based on fibrosis score at the time of treatment.(26) *duration* = 4.27 if base state is F0; 14.43 if base state is F1; 24.48 if base state is F2, and 32.95 if base state is F3
f(male) = 1, if patient is male; and 0 if patient is female.
f(G1) = 1, if patient has hepatitis C virus (HCV) genotype 1; and 0 otherwise.

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

Table 3. Clinical, Cost, and Quality of Life Inputs and SVR Rates: Baseline Values, Ranges, and Parameters for Distributions Used in Deterministic and Probabilistic Sensitivity Analyses for a Cost-Effectiveness Analysis of Sofosbuvir and Ledipasvir to Treat Hepatitis C

Input	Base Case	Range	Distribution	Parameter 1[a]	Parameter 2[b]
Transition Probabilities (annual)					
F0 to F1 (26)	0.117	0.104–0.130	Beta	274.98	2,075.30
F1 to F2 (26)	0.085	0.075–0.096	Beta	210.06	2,261.18
F2 to F3 (26)	0.120	0.109–0.133	Beta	288.05	2,112.38
F3 to F4 (26)	0.116	0.104–0.129	Beta	270.61	2,062.22
F4 to DC (27)	0.039	0.010–0.079	Beta	3.51	86.48
F4 to HCC (27)	0.014	0.010–0.079	Beta	0.18	12.38
Post F4-SVR to DC (28)	0.008	0.002–0.036	Beta	0.31	38.58
Post F4-SVR to HCC (28)	0.005	0.002–0.013	Beta	1.49	297.13
DC to HCC (29)	0.068	0.030–0.083	Beta	73.58	1008.49
DC to transplantation (30, 31)	0.023	0.010–0.062	Beta	1.31	55.44
DC (first year) to death from liver disease (29)	0.182	0.065–0.190	Beta	1626.40	7309.88
DC (subsequent year) to death from liver disease (29)	0.112	0.065–0.190	Beta	7.03	55.77
HCC to transplantation (32, 33)	0.040	0.000–0.140	Beta	0.59	14.16
HCC to death from liver disease (27)	0.427	0.330–0.860	Beta	2.14	2.87
Liver transplantation (first year) to death from liver disease (34)	0.116	0.060–0.420	Beta	1.37	6.88
Post-Liver transplantation to death from liver disease (34)	0.044	0.024–0.110	Beta	1.63	35.46
Health State Costs (annual)					
F0, F1 (35, 36)	728	±25%	Gamma	15.37	47.37
F2 (35, 36)	737	±25%	Gamma	15.37	47.98
F3 (35, 36)	1496	±25%	Gamma	15.37	97.34
Compensated Cirrhosis (36)	1745	±25%	Gamma	15.37	113.59
DC (36)	19 389	±25%	Gamma	15.37	1261.79
HCC (36)	35 655	±25%	Gamma	15.37	2320.34
Liver transplant (first year) (36)	103 102	±25%	Gamma	15.37	6703.71
Post Liver transplant (36)	27 057	±25%	Gamma	15.37	1760.79
Health State Quality-of-Life Weights					
IFN-based therapy-related multiplier(37)	0.90	0.84–0.96	Beta	86.44	9.60

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

IFN-free therapy-related multiplier	0.95	0.90–1.00	Beta	108.34	5.70
Anemia multiplier (38)	0.83	0.75–0.97	Beta	22.95	4.70
F0, F1 (39)	0.93	0.84–0.99	Beta	47.47	3.57
F2, F3 (39)	0.93	0.84–0.99	Beta	47.47	3.57
Compensated Cirrhosis (39)	0.90	0.81–0.99	Beta	31.12	3.46
DC (39)	0.80	0.57–0.99	Beta	12.29	3.07
HCC (39)	0.79	0.54–0.99	Beta	11.42	3.03
First-year, Post Liver transplant (39)	0.84	0.77–0.93	Beta	53.54	10.20
Post SVR	1.00	0.92–1.00	Beta	3833.92	3.84
SVR decrement					
SVR decrement oSOC (40)	0%	0%–20%	Uniform	--	--
SVR decrement SOF/LDV (40)	0%	0%–15%	Uniform	--	--

Abbreviations: SVR, sustained virologic response; F0–F4, METAVIR fibrosis score; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; F4-SVR. Post-SVR state of cirrhotic patient; IFN, interferon; oSOC, old standard of care; SOF, sofosbuvir; LDV, ledipasvir

[a] Parameter 1 corresponds to α parameter for beta distribution and k (shape) parameter for gamma distribution

[b] Parameter 2 corresponds to β parameter for beta distribution and θ (scale) parameter for gamma distribution

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

Table 4. Health-Related Quality-of-Life Utilities of the United States Population

Age Group	Male	Female
20–29	0.928	0.913
30–39	0.918	0.893
40–49	0.887	0.863
50–59	0.861	0.837
60–69	0.84	0.811
70–79	0.802	0.771
80–89	0.782	0.724

Source: Hammer et al.(41)

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

Appendix 2: Model Validation

We cross-validated our model's natural history predictions with previously published modeling studies (37, 42, 43). These studies reported a 20-year probability of cirrhosis in mild chronic hepatitis C virus (HCV) patients between 27%–29%. Assuming that 28% of patients with mild fibrosis have a fibrosis score F0 and 72% have a fibrosis score F1 (8), the **Markov-based analyses of treatments for chronic hepatitis C** (MATCH*)* model predicted a 20-year cirrhosis probability of 27.3%. We further validated our *MATCH* model with a recently published multicenter follow-up study of patients with advanced fibrosis (44). Since van der Meer et al. used Ishak scoring system and our study used METAVIR scoring system, a direct comparison of results was not possible. We presented the cumulative incidence separately for METAVIR score F4. In patients who failed to achieve sustained virologic response (SVR), the predicted 10-year cumulative incidence rates for HCC, and the combined liver-related death (LRDs) and liver transplants (LTs) were within the reported confidence limits of that study; however, the predicted decompensated cirrhosis (DC) incidence was lower than the reported values (**Table 5**). In patients who achieved SVR, the predicted 10-year cumulative incidence rate of hepatocellular carcinoma (HCC) was within the reported confidence intervals (CIs); however, the incidences of DC and LRD plus LT were higher than the reported values. Our model underestimated the benefits of new therapies. However, part of the differences could potentially be attributed to differences in baseline patients' histologic status between our model and van der Meer et al. because of the use of a different scoring system (Ishak score versus METAVIR).

Table 5. Validation of the Natural History of our Model used to Analyze the Cost-effectiveness of Sofosbuvir and Ledipasvir to Treat Hepatitis C

Treatment Response	Disease Stage	10-year cumulative incidence	
		van der Meer et al.	Model
Patients Who Failed to Achieve SVR	DC	29.9% (CI: 24.3–35.5%)	28.8%
	HCC	21.8% (95% CI: 16.6–27.0%)	16.9%
	LRD plus LT	27.4% (95% CI: 22.0–32.8%)	25.5%
Patients Who Achieved SVR	DC	2.1% (95% C.I.: 0–4.5%)	8.2%
	HCC	5.1% (95% C.I.: 1.3–8.9%)	7.7%
	LRD plus LT	1.9% (95% C.I.: 0–4.1%)	9.8%

Abbreviations: SVR, sustained virologic response; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LRD, liver-related death; LT, liver transplant; CI, confidence interval

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

Appendix 3: Additional Results

Table 6. Lifetime cost-effectiveness of sofosbuvir and ledipasvir in interferon tolerant and *in*tolerant patients

	QALY: oSOC	QALY: SOF-based	Cost: oSOC ($)	Cost: SOF-based ($)	ICER ($/QALY)	pCE at $50K	pCE at $100K
Treatment-Naive Interferon-Tolerant Patients							
Genotype 1							
Non-cirrhotic	10.751	11.056	60 582	68 228	25 067	0.88	0.99
Cirrhotic	8.525	9.447	91 571	96 498	5347	0.92	0.96
Genotype 2							
Non-cirrhotic	10.853	11.051	22 396	78 080	281 397	<0.01	0.03
Cirrhotic	8.644	9.120	44 783	95 979	107 540	0.12	0.40
Genotype 3							
Non-cirrhotic	10.721	11.015	25 286	154 649	440 276	<0.01	<0.01
Cirrhotic	8.333	9.354	49 481	167 634	115 680	0.05	0.28
Genotype 4							
Non-cirrhotic	10.533	11.075	45 296	83 592	70 765	0.17	0.68
Cirrhotic	7.960	9.168	72 519	101 191	23 729	0.74	0.89
Genotypes 1-4							
Non-cirrhotic	10.760	11.053	53 226	75 122	74 733	0.23	0.72
Cirrhotic	8.522	9.395	82 628	100 964	21 003	0.79	0.91
All patients	**10.210**	**10.645**	**60 449**	**81 471**	**48 270**	**0.37**	**0.77**
Treatment-Naive Interferon-*In*tolerant Patients							
Genotype 1							
Non-cirrhotic	9.894	11.056	22 171	68 228	39 635	0.62	0.99
Cirrhotic	7.078	9.447	53 917	96 498	17 977	0.82	0.93
Genotype 2							
Non-cirrhotic	9.770	10.988	24 392	78 963	44 805	0.41	0.94
Cirrhotic	7.078	9.359	53 917	91 446	16 455	0.83	0.94
Genotype 3							
Non-cirrhotic	9.770	11.015	24 392	154 649	104 628	0.04	0.31
Cirrhotic	7.078	9.354	53 917	167 634	49 959	0.37	0.76
Genotype 4							
Non-cirrhotic	9.770	11.015	24 392	155 392	105 227	0.04	0.31
Cirrhotic	7.078	9.379	53 917	168 025	49 592	0.38	0.76
Genotypes 1-4							
Non-cirrhotic	9.868	11.044	22 604	75 144	44 727	0.48	0.96
Cirrhotic	7.078	9.429	53 917	100 366	19 755	0.79	0.92
All patients	**9.183**	**10.647**	**30 298**	**81 341**	**34 872**	**0.56**	**0.95**

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

QALY = quality-adjusted life years; SOF = sofosbuvir; oSOC = old standard of care; LDV = ledipasvir; ICER = incremental cost-effectiveness ratio; pCE at $50K= probability of cost-effectiveness at $50 000 willingness to pay threshold using probabilistic sensitivity analysis; pCE at $100K= probability of cost-effectiveness at $100 000 willingness to pay threshold probabilistic sensitivity analysis.

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

Table 7. Scenario analysis using 10-year time horizon

	QALY: oSOC	QALY: SOF-based	Cost: oSOC ($)	Cost: SOF-based ($)	ICER ($/QALY)
Treatment-Naive (TN) Patients					
Genotype 1					
Non-cirrhotic	6.332	6.565	54 397	76 160	93 522
Cirrhotic	5.650	6.189	77 339	100 306	42 552
Genotype 2					
Non-cirrhotic	6.388	6.557	19 883	87 131	398 461
Cirrhotic	5.712	6.067	34 414	96 312	174 243
Genotype 3					
Non-cirrhotic	6.337	6.537	20 991	172 556	758 237
Cirrhotic	5.603	6.143	36 950	179 375	263 778
Genotype 4					
Non-cirrhotic	6.254	6.564	37 551	107 143	224 324
Cirrhotic	5.459	6.082	54 716	116 056	98 375
Genotypes 1-4					
Non-cirrhotic	6.339	6.562	47 620	84 000	163 006
Cirrhotic	5.653	6.169	68 965	104 941	69 628
All TN	**6.170**	**6.466**	**52 864**	**89 145**	**122 863**
Treatment-Experienced (TE) Patients					
Genotype 1					
Non-cirrhotic	6.343	6.553	74 901	94 401	92 966
Cirrhotic	5.739	6.209	93 946	192 753	210 096
Genotype 2					
Non-cirrhotic	6.371	6.561	23 787	87 191	334 481
Cirrhotic	5.718	5.819	37 508	102 500	643 601
Genotype 3					
Non-cirrhotic	6.354	6.494	24 143	173 242	1062 993
Cirrhotic	5.674	5.833	38 340	186 747	935 802
Genotype 4					
Non-cirrhotic	6.180	6.427	39 383	92 781	216 524
Cirrhotic	5.454	5.901	55 430	103 174	106 834
Genotypes 1-4					
Non-cirrhotic	6.346	6.549	64 668	98 413	166 104
Cirrhotic	5.729	6.131	82 682	179 657	240 996
All TE	**6.194**	**6.446**	**69 094**	**118 374**	**195 473**
Treatment-Naive and Experienced Patients					
All patients	**6.180**	**6.458**	**59 190**	**100 538**	**148 487**

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

Table 8. Scenario analysis using 20-year time horizon

	QALY: oSOC	QALY: SOF-based	Cost: oSOC ($)	Cost: SOF-based ($)	ICER ($/QALY)
Treatment-Naive (TN) Patients					
Genotype 1					
Non-cirrhotic	9.450	9.811	57 718	76 439	51 860
Cirrhotic	7.763	8.745	88 516	105 087	16 873
Genotype 2					
Non-cirrhotic	9.513	9.799	22 895	87 547	226 362
Cirrhotic	7.851	8.506	45 139	102 655	87 803
Genotype 3					
Non-cirrhotic	9.426	9.777	24 828	173 202	423 214
Cirrhotic	7.638	8.667	48 875	184 656	131 934
Genotype 4					
Non-cirrhotic	9.306	9.816	42 487	107 411	127 329
Cirrhotic	7.381	8.542	69 136	122 268	45 775
Genotypes 1-4					
Non-cirrhotic	9.455	9.808	50 951	84 320	94 750
Cirrhotic	7.763	8.707	80 166	109 973	31 558
All TN	**9.040**	**9.537**	**58 129**	**90 622**	**65 286**
Treatment-Experienced (TE) Patients					
Genotype 1					
Non-cirrhotic	9.493	9.793	77 796	94 848	56 894
Cirrhotic	7.946	8.795	104 087	197 164	109 696
Genotype 2					
Non-cirrhotic	9.495	9.805	27 038	87 532	195 103
Cirrhotic	7.858	8.024	48 120	111 889	382 986
Genotype 3					
Non-cirrhotic	9.463	9.699	27 736	174 578	620 061
Cirrhotic	7.776	8.062	49 481	196 204	513 370
Genotype 4					
Non-cirrhotic	9.164	9.567	45 591	95 562	123 907
Cirrhotic	7.370	8.194	69 833	111 417	50 477
Genotypes 1-4					
Non-cirrhotic	9.488	9.786	67 689	98 928	104 743
Cirrhotic	7.918	8.642	92 994	185 074	127 162
All TE	**9.102**	**9.505**	**73 906**	**120 093**	**114 643**
Treatment-Naive and Experienced Patients					
All patients	**9.064**	**9.525**	**64 279**	**102 110**	**82 109**

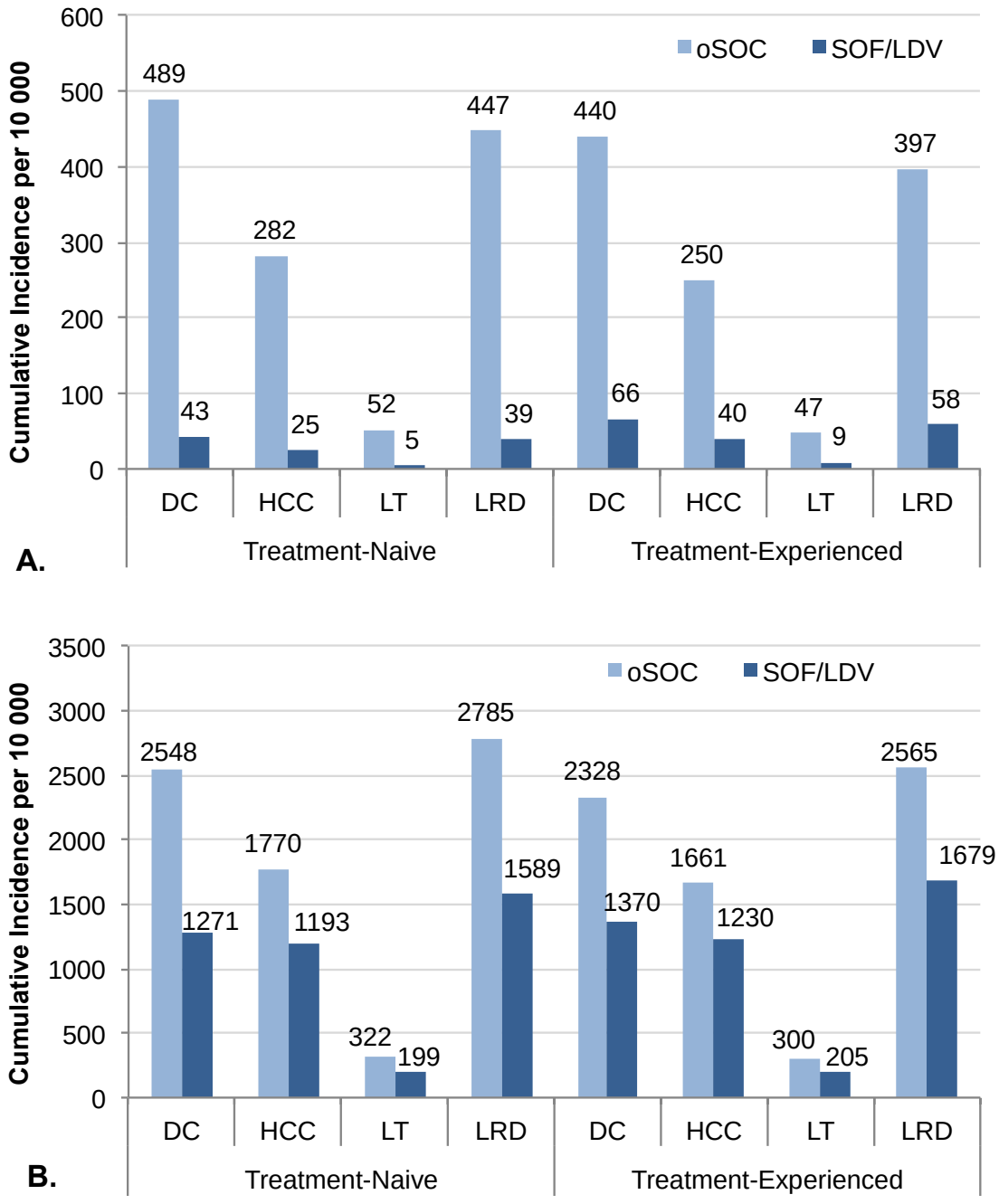
Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

Table 9. Scenario analysis using 30-year time horizon

	QALY: oSOC	QALY: SOF-based	Cost: oSOC ($)	Cost: SOF-based ($)	ICER ($/QALY)
Treatment-Naive (TN) Patients					
Genotype 1					
Non-cirrhotic	10.444	10.877	59 296	76 551	39 860
Cirrhotic	8.234	9.381	91 395	106 599	13 260
Genotype 2					
Non-cirrhotic	10.507	10.862	24 282	87 733	178 787
Cirrhotic	8.331	9.100	47 874	104 524	73 618
Genotype 3					
Non-cirrhotic	10.400	10.837	26 629	173 504	336 489
Cirrhotic	8.077	9.290	51 793	186 328	110 956
Genotype 4					
Non-cirrhotic	10.251	10.884	44 828	107 530	99 054
Cirrhotic	7.775	9.142	72 600	124 096	37 656
Genotypes 1-4					
Non-cirrhotic	10.447	10.872	52 527	84 454	75 089
Cirrhotic	8.232	9.336	83 036	111 544	25 820
All TN	**9.903**	**10.495**	**60 023**	**91 110**	**52 513**
Treatment-Experienced (TE) Patients					
Genotype 1					
Non-cirrhotic	10.502	10.856	79 207	95 041	44 759
Cirrhotic	8.451	9.441	106 810	198 653	92 800
Genotype 2					
Non-cirrhotic	10.485	10.869	28 576	87 685	154 070
Cirrhotic	8.333	8.529	50 819	114 307	323 628
Genotype 3					
Non-cirrhotic	10.443	10.743	29 447	175 218	485 188
Cirrhotic	8.239	8.572	52 252	198 680	439 632
Genotype 4					
Non-cirrhotic	10.072	10.567	48 533	96 856	97 643
Cirrhotic	7.761	8.736	73 262	113 720	41 531
Genotypes 1-4					
Non-cirrhotic	10.492	10.848	69 153	99 156	84 318
Cirrhotic	8.415	9.260	95 725	186 755	107 729
All TE	**9.981**	**10.457**	**75 681**	**120 678**	**94 528**
Treatment-Naive and Experienced Patients					
All patients	**9.934**	**10.480**	**66 126**	**102 635**	**66 770**

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

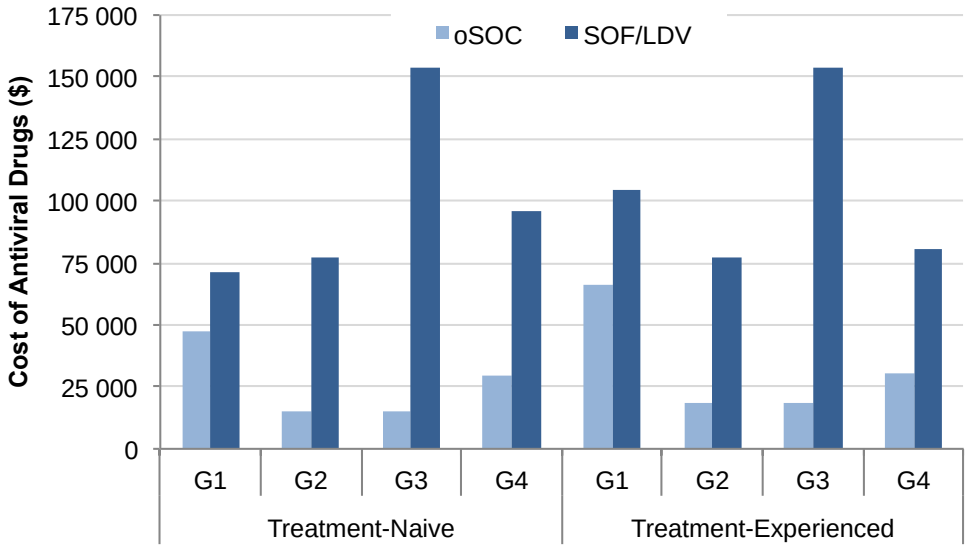
Figure 1. Cumulative Incidence of Advanced Liver Diseases with the Old Standard of Care (oSOC) and Sofosbuvir/Ledipasvir-Based Therapies (SOF/LDV) per 10 000 (A) non-cirrhotic patients treated, and (B) cirrhotic patients treated



Abbreviations: SOF/LDV, sofosbuvir- and ledipasvir-based therapies; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplants; LRD, liver-related deaths.

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

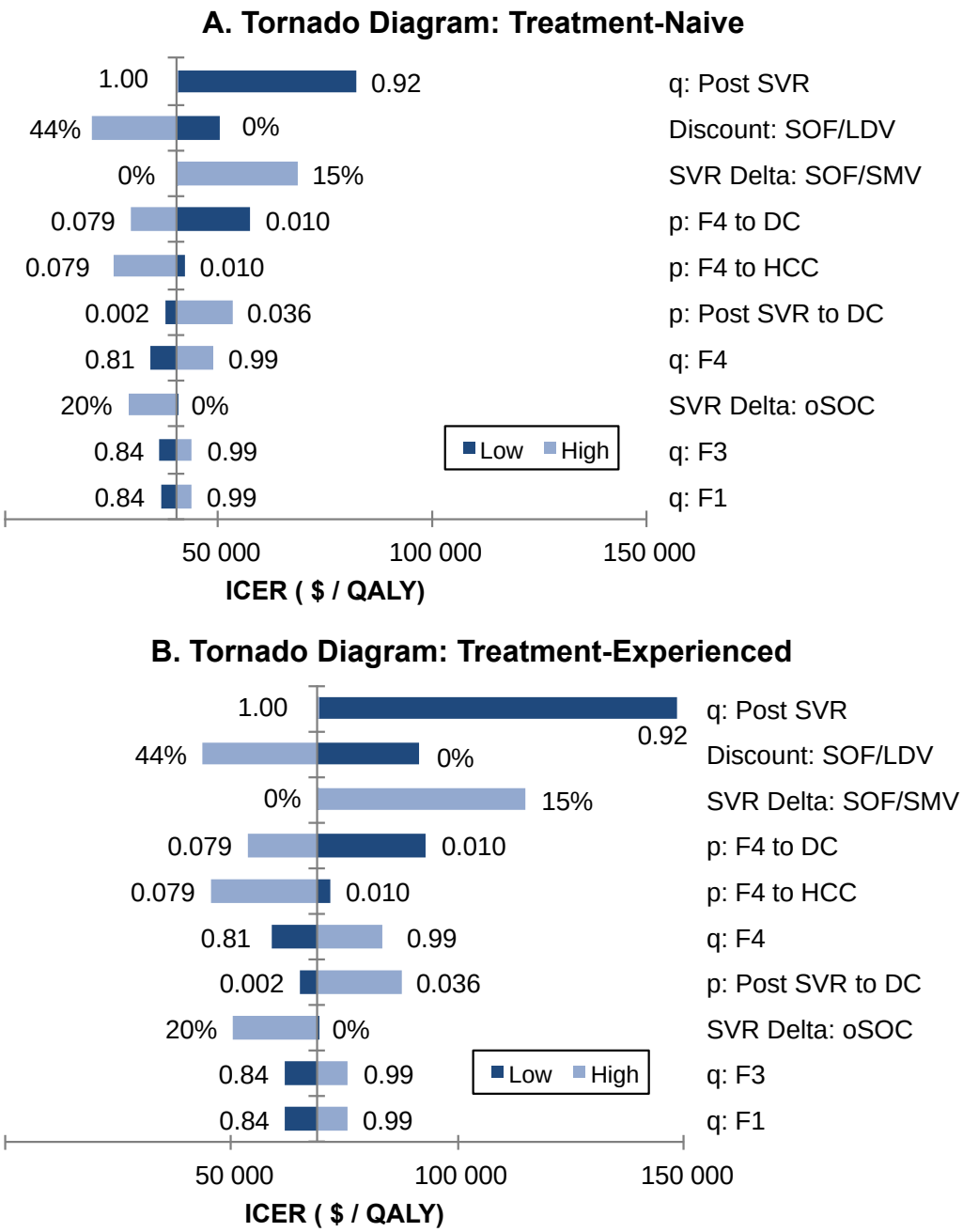
Figure 2. Cost of Antiviral Therapy by Hepatitis C Treatment by Genotype and Prior Treatment History



Abbreviations: G1-G4, genotype 1–4; oSOC, old standard of care; SOF/LDV, sofosbuvir- and ledipasvir-based therapies;

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

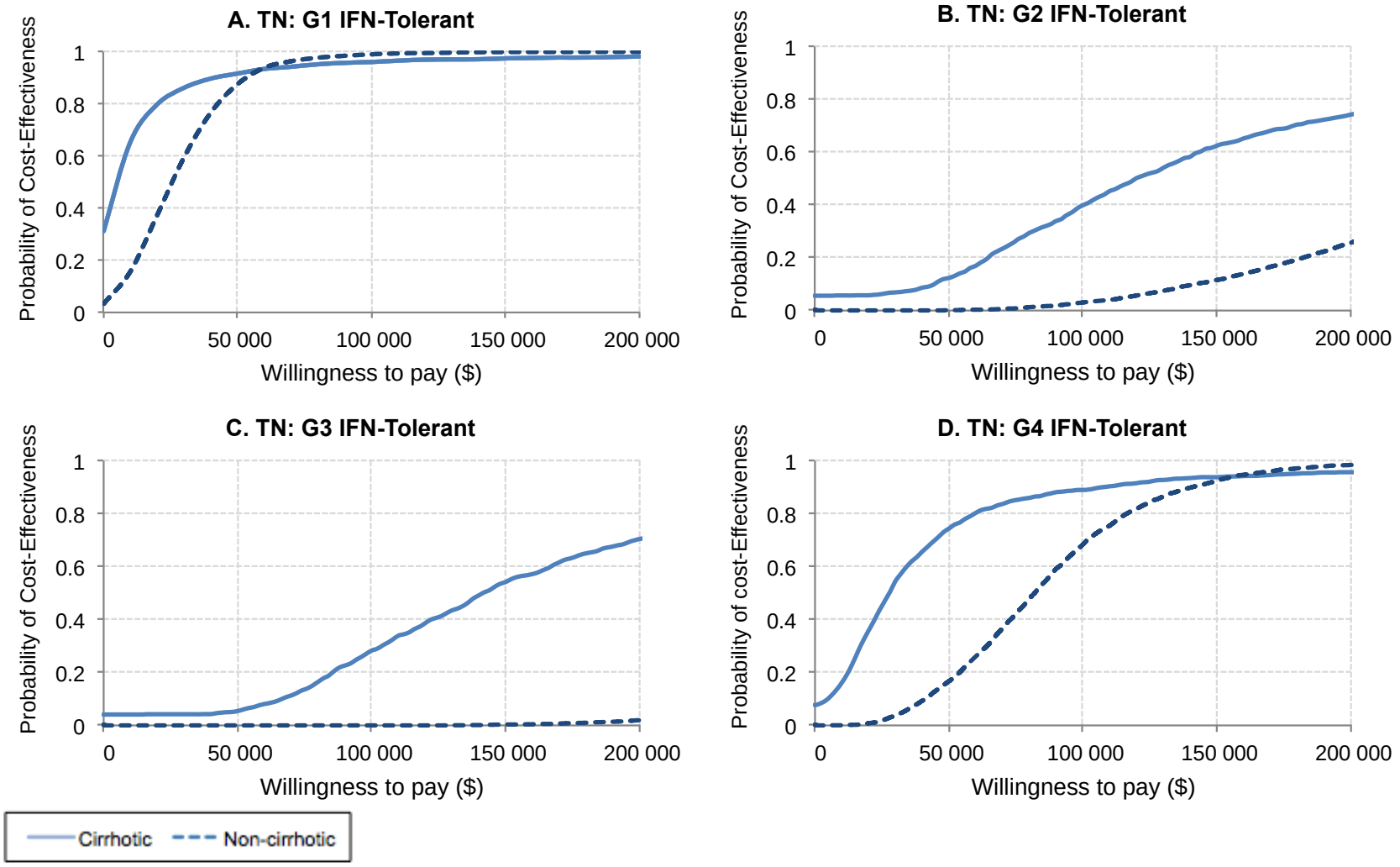
Figure 3 One-way Sensitivity Analysis Showing Top 10 Most Sensitive Parameters in (A) Treatment-Naive Patients, and (B) Treatment-Experienced Patients



Abbreviations: q: Post SVR, quality of life after achieving sustained virologic response (SVR); SVR Delta: SOF/LDV, Reduction in SVR in sofosbuvir (SOF)- and ledipasvir (LDV)-based therapies; p: F4 to DC, probability of developing decompensated cirrhosis (DC) from fibrosis score F4; q: F4, quality-of-life (QOL) weight associated with F4; p: F4 to HCC, probability of developing hepatocellular carcinoma (HCC) from F4; SVR Delta: oSOC, Reduction in SVR in the old standard of care (oSOC); p: Post SVR to DC, probability of developing DC in F4 patients who achieved SVR; q: F3, QOL weight associated with fibrosis score F3; q: F2, QOL weight associated with fibrosis score F2; q: F1, QOL weight associated with fibrosis score F1

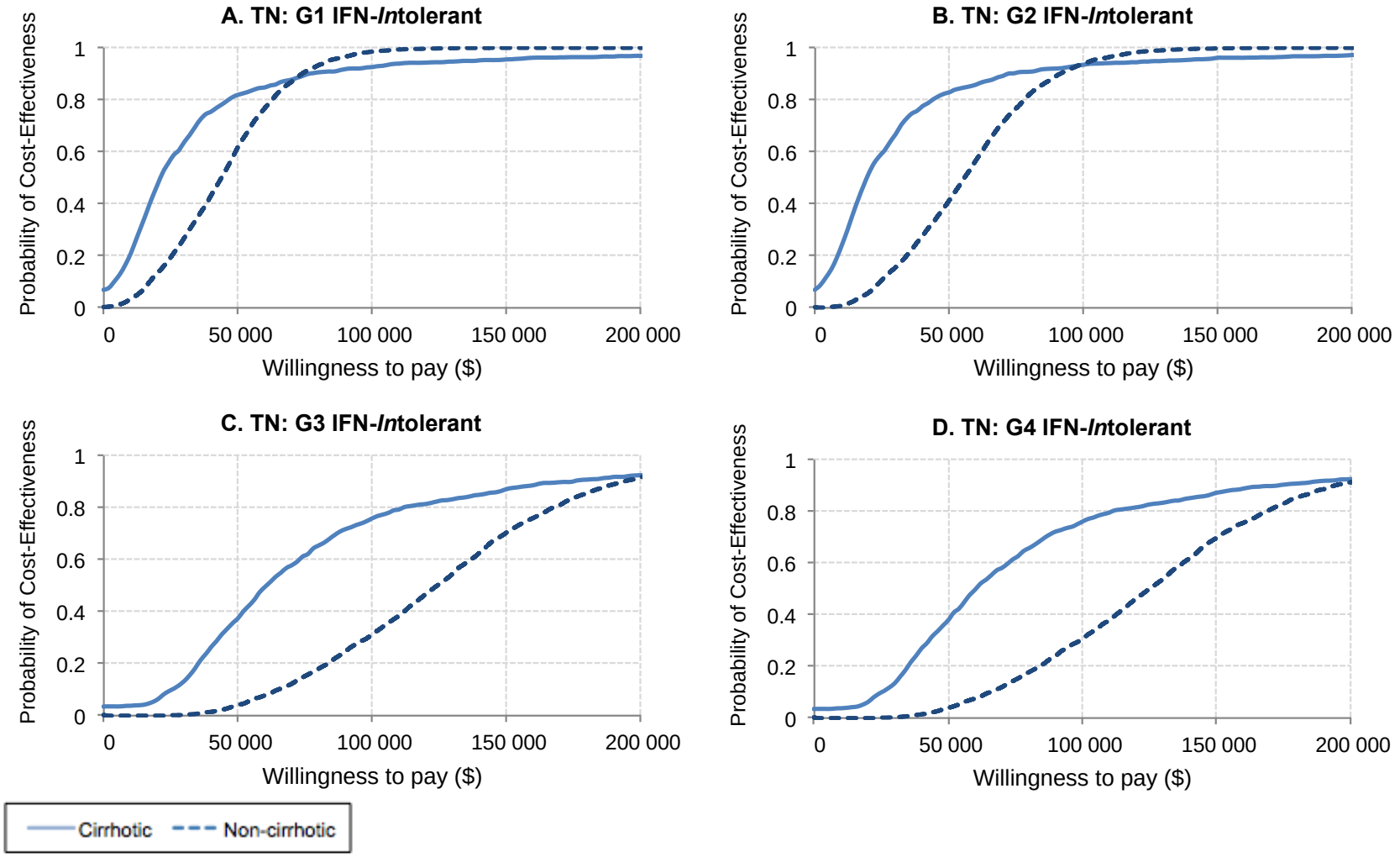
Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

Figure 4. Cost-effectiveness acceptability curves in treatment-naive interferon-tolerant patients



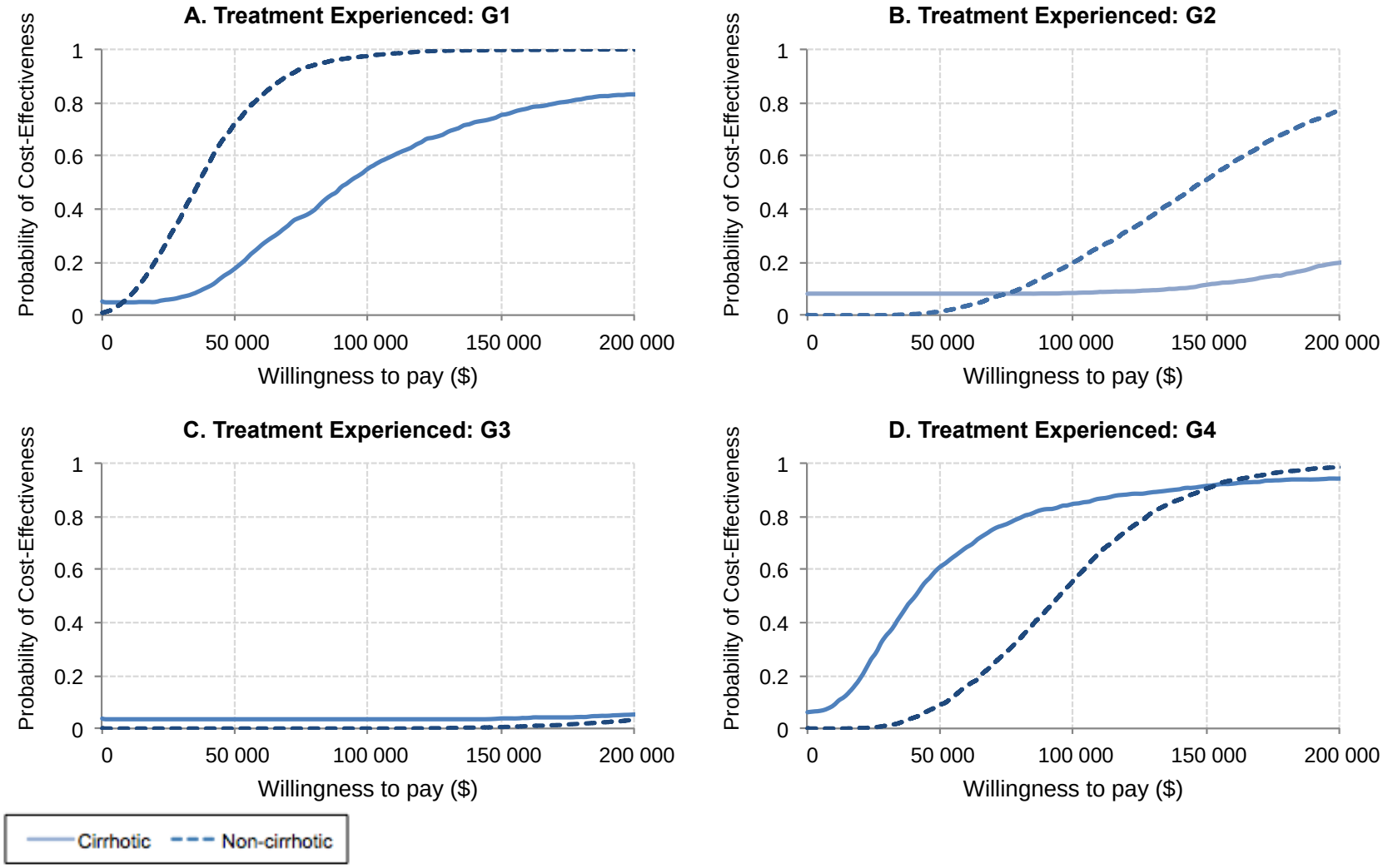
Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

Figure 5. Cost-effectiveness acceptability curves in treatment-naive interferon-intolerant patients



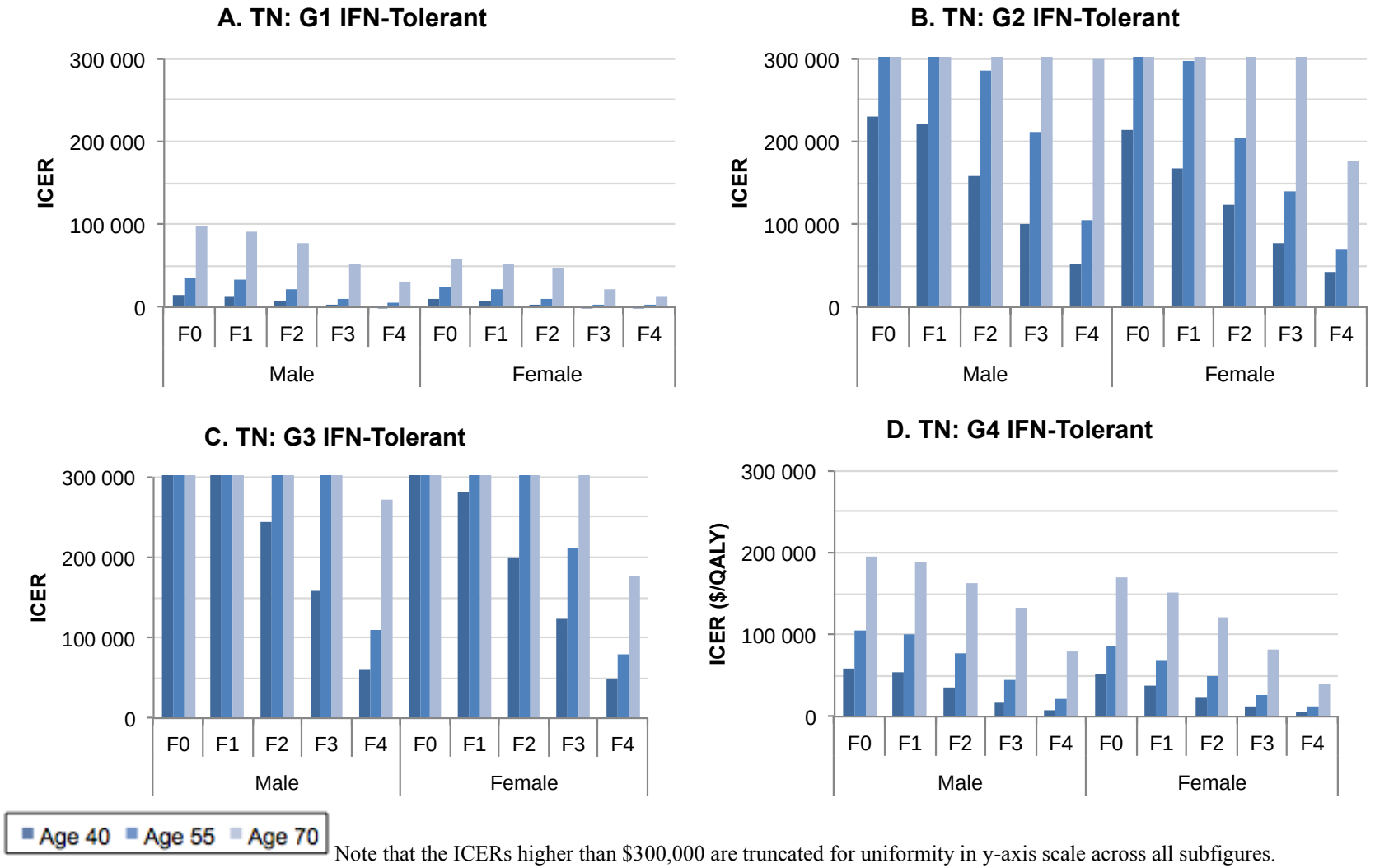
Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

Figure 6. Cost-effectiveness acceptability curves in treatment-experienced patients



Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

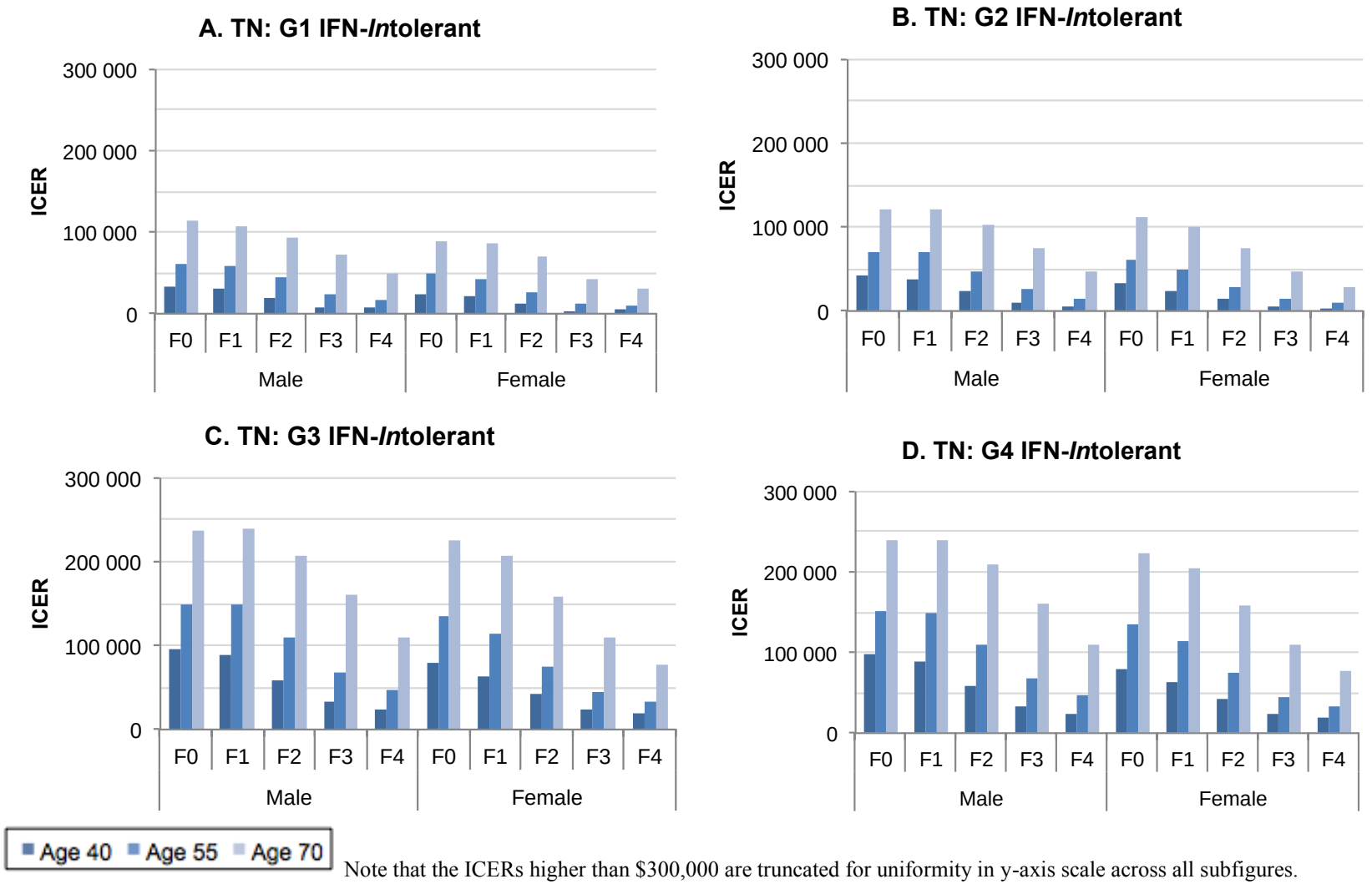
Figure 7. Incremental cost-effectiveness ratio of sofosbuvir- and ledipasvir-based therapies in treatment naive interferon-tolerant patients



Note that the ICERs higher than $300,000 are truncated for uniformity in y-axis scale across all subfigures.

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

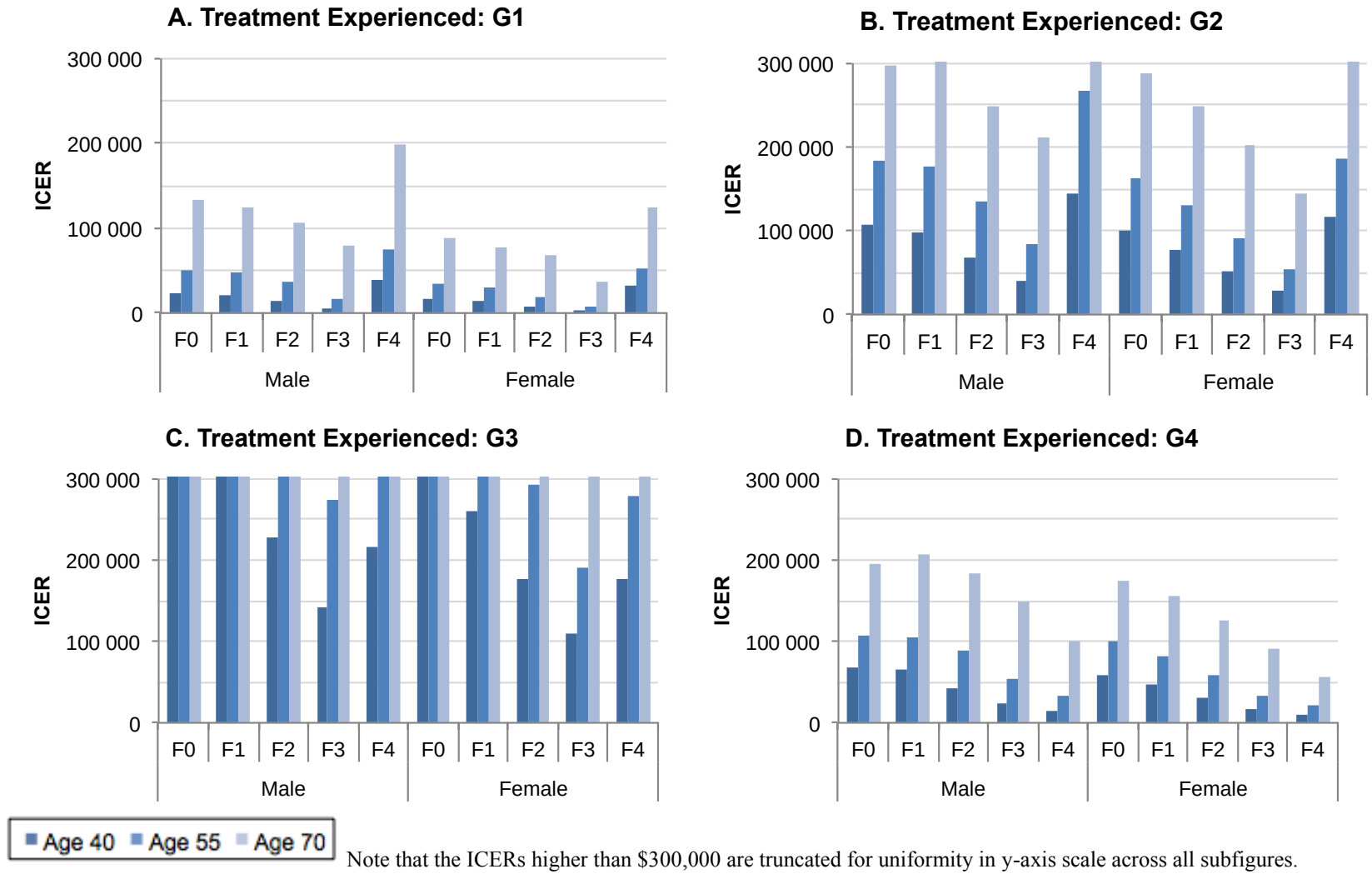
Figure 8: Incremental cost-effectiveness ratio of sofosbuvir- and ledipasvir-based therapies in treatment naive interferon-*in*tolerant patients



Note that the ICERs higher than $300,000 are truncated for uniformity in y-axis scale across all subfigures.

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

Figure 9. Incremental cost-effectiveness ratio of sofosbuvir and ledipasvir-based therapies in treatment experienced patients



Note that the ICERs higher than $300,000 are truncated for uniformity in y-axis scale across all subfigures.

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

References

1. Stroustrup B**.** *The C++ Programming Language*. Reading, MA: Addison-Wesley; 2000.
2. Chen J, Florian J, Carter W, Fleischer RD, Hammerstrom TS, Jadhav PR, et al. Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. Gastroenterology. 2013;144(7):1450-5.e2.
3. Shechter SM, Schaefer AJ, Braithwaite RS, Roberts MS**.** Increasing the efficiency of Monte Carlo cohort simulations with variance reduction techniques. Medical Decision Making. 2006;26(5):550-3.
4. Siebert U, Alagoz O, Bayoumi AM, Jahn B, Owens DK, Cohen DJ, et al. State-transition modeling: A report of the ISPOR-SMDM Modeling Good Research Practices Task Force. Medical Decision Making. 2012;32(5):690-700.
5. Armstrong G, Wasley A, Simard E, McQuillan G, Kuhnert W, Alter M**.** The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Annals of Internal Medicine. 2006;144(10):705.
6. Denniston MM, Jiles RB, Drobeniuc J, Klevens RM, Ward JW, McQuillan GM, et al. Chronic Hepatitis C Virus Infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. Annals of Internal Medicine. 2014;160(5):293-300.
7. Talal A, LaFleur J, Hoop R, Pandya P, Martin P, Jacobson I, et al. Absolute and relative contraindications to pegylated-interferon or ribavirin in the US general patient population with chronic hepatitis C: results from a US database of over 45 000 HCV-infected, evaluated patients. Alimentary pharmacology & therapeutics. 2013;37(4):473-81.
8. Kabiri M, Jazwinski AB, Roberts MS, Schaefer AJ, Chhatwal J**.** The changing burden of hepatitis C in the United States: Model-based predictions. Annals of Internal Medicine. 2014;161(3):170-80.
9. Nainan OV, Alter MJ, Kruszon-Moran D, Gao FX, Xia G, McQuillan G, et al. Hepatitis C virus genotypes and viral concentrations in participants of a general population survey in the United States. Gastroenterology. 2006;131(2):478-84.
10. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB**.** An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011.
11. Poordad F, McCone Jr J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. New England Journal of Medicine. 2011;364(13):1195-206.

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

12. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014;370(20):1889-98.
13. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. 2014;370(20):1879-88.
14. Prescription information of HARVONI in the United States. Retrieved from: http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/harvoni/harvoni_pi.pdf (last accessed on November 4, 2014). 2014.
15. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. New England Journal of Medicine. 2013;368(20):1878-87.
16. Shiffman ML, Suter F, Bacon BR, Nelson D, Harley H, Solá R, et al. Peginterferon Alfa-2a and Ribavirin for 16 or 24 Weeks in HCV Genotype 2 or 3. New England Journal of Medicine. 2007;357(2):124-34.
17. Zeuzem S, Dusheiko G, Salupere R, Mangia A, Flisiak R, Hyland R**.** Sofosbuvir+ ribavirin for 12 or 24 weeks for patients with HCV genotype 2 or 3: the VALENCE Trial. Hepatology. 2013;58(Supp 1):733A.
18. Khuroo MS, Khuroo MS, Dahab ST**.** Meta-analysis: a randomized trial of peginterferon plus ribavirin for the initial treatment of chronic hepatitis C genotype 4. Alimentary Pharmacology & Therapeutics. 2004;20(9):931-8.
19. Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. New England Journal of Medicine. 2013;368(20):1867-77.
20. Ruane P, Ain D, Riad J**.** Sofosbuvir plus ribavirin in the treatment of chronic HCV genotype 4 infection in patients of Egyptian ancestry [abstract no. 1090]. Hepatology. 2013;58(4 Suppl):736A.
21. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. New England Journal of Medicine. 2011;364(25):2417-28.
22. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014;370(16):1483-93.
23. Poynard T, Colombo M, Bruix J, Schiff E, Terg R, Flamm S, et al. Peginterferon alfa-2b and ribavirin: effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy. Gastroenterology. 2009;136(5):1618-28.

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

24. Tricia Neuman, Jack Hoadley a, Cubanski J**.** The cost of a cure: Medicare's role in treating hepatitis C. Retrieved from: http://healthaffairs.org/blog/2014/06/05/the-cost-of-a-cure-medicares-role-in-treating-hepatitis-c/ (Accessed: November 4, 2014). Health Affairs Blog; 2014.
25. Alonso-zaldivar R**.** $1,000-a-pill Sovaldi jolts US health care system. Retrieved from: http://bigstory.ap.org/article/1000-pill-sovaldi-jolts-us-health-care-system (Accessed: November 4, 2014). 2014.
26. Thein H, Yi Q, Dore G, Krahn M**.** Estimation of stage specific fibrosis progression rates in chronic hepatitis C virus infection: A meta analysis and meta regression. Hepatology. 2008;48(2):418-31.
27. Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology. 1997;112(2):463-72.
28. Cardoso AC, Moucari R, Figueiredo-Mendes C, Ripault MP, Giuily N, Castelnau C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. Journal of Hepatology. 2010;52(5):652-7.
29. Planas R, Ballesté B, Antonio Álvarez M, Rivera M, Montoliu S, Anton Galeras J, et al. Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients. Journal of Hepatology. 2004;40(5):823-30.
30. Davis G, Alter M, El-Serag H, Poynard T, Jennings L**.** Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology. 2010;138(2):513-21.
31. Thuluvath P, Guidinger M, Fung J, Johnson L, Rayhill S, Pelletier S**.** Liver transplantation in the United States, 1999–2008. American Journal of Transplantation. 2010;10(4p2):1003-19.
32. Lang K, Danchenko N, Gondek K, Shah S, Thompson D**.** The burden of illness associated with hepatocellular carcinoma in the United States. Journal of Hepatology. 2009;50(1):89-99.
33. Saab S, Hunt DR, Stone MA, McClune A, Tong MJ**.** Timing of hepatitis C antiviral therapy in patients with advanced liver disease: A decision analysis model. Liver Transplantation. 2010;16(6):748-59.
34. Wolfe R, Roys E, Merion R**.** Trends in Organ Donation and Transplantation in the United States, 1999–2008. American Journal of Transplantation. 2010;10(4p2):961-72.

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015

35. Davis KL, Mitra D, Medjedovic J, Beam C, Rustgi V**.** Direct economic burden of chronic hepatitis C virus in a United States managed care population. Journal of Clinical Gastroenterology. 2011;45(2):e17.
36. McAdam-Marx C, McGarry LJ, Hane CA, Biskupiak J, Deniz B, Brixner DI**.** All-cause and incremental per patient per year cost associated with chronic hepatitis C virus and associated liver complications in the United States: A managed care perspective. J Manag Care Pharm. 2011;17(7):531-46.
37. Siebert U, Sroczynski G, Rossol S, Wasem J, Ravens-Sieberer U, Kurth B, et al. Cost effectiveness of peginterferon-2b plus ribavirin versus interferon -2b plus ribavirin for initial treatment of chronic hepatitis C. Gut. 2003;52(3):425.
38. Wilson J, Yao G, Raftery J, Bohlius J, Brunskill S, Sandercock J, et al. A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment. Health Technology Assessment. 2007;11(13):1-202.
39. Chong CAKY, Gulamhussein A, Heathcote EJ, Lilly L, Sherman M, Naglie G, et al. Health-state utilities and quality of life in hepatitis C patients. The American Journal of Gastroenterology. 2003;98(3):630-8.
40. Kanwal F, El-Serag HB**.** HCV treatment: The unyielding chasm between efficacy and effectiveness. Clin Gastroenterol Hepatol. 2014.
41. Hanmer J, Lawrence WF, Anderson JP, Kaplan RM, Fryback DG**.** Report of nationally representative values for the noninstitutionalized US adult population for 7 health-related quality-of-life scores. Medical Decision Making. 2006;26(4):391-400.
42. Bennett W, Inoue Y, Beck J, Wong J, Pauker S, Davis G**.** Estimates of the cost-effectiveness of a single course of interferon- 2b in patients with histologically mild chronic hepatitis C. Annals of Internal Medicine. 1997;127(10):855.
43. Chhatwal J, Ferrante SA, Brass C, El Khoury AC, Burroughs M, Bacon B, et al. Cost-Effectiveness of boceprevir in patients previously treated for chronic hepatitis C genotype 1 Infection in the United States. Value in Health. 2013;16(6):973-86.
44. van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012;308(24):2584-93.

Downloaded From: http://annals.org/ by Jules Levin on 05/28/2015