Supplement. Data and Supporting Results and Additional Clinical Scenarios

This online supplement accompanies the manuscript entitled, “The Changing Burden of Hepatitis C Infection in the United States: Model-based Predictions.” The supplement provides data and supporting results, including validation, sensitivity analyses, and additional clinical scenarios.

Model implementation

We developed our individual-level state-transition model using C++, a general-purpose programming language, to make computational simulation experiments efficient for the entire hepatitis C virus (HCV)-infected population in the United States (US).

Model Inputs for Patients with Interferon Contraindication

Treatment with regimens that include pegylated interferon and ribavirin (PEG-RBV) is limited by medical and psychiatric contraindications. Some of these contraindications are considered modifiable by medical or psychiatric interventions, such as anemia, depression, and substance abuse. We assumed that 34.6% of patients with HCV infection had contraindications to therapy and that 67% of these contra-indications were modifiable (1), and if there was an urgency to treat a patient's hepatitis C due to advanced fibrosis (F3–F4), those patients could be treated. We were not able to determine a response rate to PEG-RBV treatment in such patients, but assumed that the response rate for patients with modifiable contraindications to interferon would be 20% lower than treatment-naïve patients with similar degrees of fibrosis but no contraindications. Wave 1 and Wave 2 treatment response rates in non-cirrhotic

patients with contraindications to interferon were assumed to be similar to those without the contraindication. However, the response rates in cirrhotic patients with contraindications to interferon were assumed to be lower than those without the contraindication.

Supplement Table 1. **Model Parameter Values**

Variable	Value	References
Natural history transition probabilities*		
F0 to F1	0.117	(2)
F1 to F2	0.085	(2)
F2 to F3	0.120	(2)
F3 to F4	0.116	(2)
F4 to DC	0.029	(3)
F4 to HCC	0.014	(3)
SVR F4 to DC	0.008	(4)
SVR F4 to HCC	0.005	(4)
DC to HCC	0.068	(5)
DC to liver transplantation	0.023	(6, 7)
DC (first year) to liver-related death	0.182	(5)
DC (>1 year) to liver-related death	0.112	(5)
HCC to liver transplantation	0.040	(8, 9)
HCC to liver-related death	0.427	(3)
Liver transplantation (first year) to liver-related death	0.116	(10)
HCV-infected population characteristics		
Total active HCV-infected population in 2001 (million)	3.2	(11)
Chronic-infection ratio (%)†	75	(1)
Percentage of patients unaware of their HCV infection	60	(1, 12-17)
Chronic contraindication (%)‡	34.6	(1)
Sex (%)		(11)
Male	64.22	
Female	35.78	
HCV genotype (%)		(18)
1	73	
2	14	
3	8	
Other	5	
Stage distribution of HCV-infected population in 2001 (%)		(7)
F0	27.20	
F1	33.39	
F2	17.11	
F3	11.08	
F4	9.61	
DC	1.43	
HCC	0.18	
Age distribution of HCV-infected population in 2001 (%)		(11)
18–19	1.78	
20–29	10.67	
30–39	22.67	
40–49	28.89	
50–59	20.44	
60–69	9.33	
70–100	6.22	
Age distribution of the new HCV infections (%)		(19)
18–19	3.2	
20–29	26.3	

30–39	27.7	
40–49	24.9	
50–59	13.4	
60–69	4.4	
70–100	0.1	
Distribution of treatment-experienced patients (%)		
Genotype 1		
Relapsers	53	(20)
Partial responders	19	(20)
Null responders	28	(20)
Genotype 2–6		
Relapsers	47	(21)
Partial responders	16	(21)
Null responders	37	(21)

F0 = METAVIR stage for no fibrosis; F1 = METAVIR stage for portal fibrosis without septa; F2 = METAVIR stage for portal fibrosis with few septa; F3 = METAVIR stage for numerous septa without cirrhosis; F4 = METAVIR stage for cirrhosis; HCV = hepatitis C virus; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; SVR = sustained virologic response.

[*]Reported values are annual transition probabilities.

[†]The percentage of infected patients who develop chronic infection.

[‡]The ratio of patients with contraindication (with modifiable and non-modifiable reasons) amongst chronically infected patients.

Supplement Table 2. **The Estimated Annual Incidence of Hepatitis C in the United States, from 2001–2050**

Year	Estimated Incidence
2001	24 000
2002	29 000
2003	28 000
2004	26 000
2005	21 000
2006	19 000
2007	17 000
2008	18 000
2009	16 000
2010	17 000
2011–2050*	18 000

*Annual HCV incidence in 2001–2010 are based on a report by the Centers for Disease Control and Prevention (22), and we assumed the annual HCV incidence to be constant beyond 2011 at 18 000 cases in all clinical scenarios.

Supplement Table 3. **The Annual Probability of Becoming Aware of Hepatitis C Infection in Each Disease Stage**

Stage	Probability of becoming aware (assumption)	Estimated average years spent in stage	Probability of becoming aware within a year
F0	0.25	4.04	0.06940
F1	0.25	4.99	0.05591
F2	0.25	3.47	0.07891
F3	0.25	3.15	0.08598
F4	0.75	4.47	0.26513
DC	0.95	3.36	0.56489

Note: We assumed that all patients with hepatocellular carcinoma would be aware of their disease. DC = decompensated cirrhosis.

F0 = METAVIR stage for no fibrosis; F1 = METAVIR stage for portal fibrosis without septa; F2 = METAVIR stage for portal fibrosis with few septa; F3 = METAVIR stage for numerous septa without cirrhosis; and F4 = METAVIR stage for cirrhosis.

Supplement Table 4. **The Base-Case Scenario Values and Range of Parameters Used in 1-Way Sensitivity Analyses**

Parameter	Base-case value	Lower value	Upper value	Reference
Natural history transition probabilities*				
F0 to F1	0.117	0.104	0.130	(2)
F1 to F2	0.085	0.075	0.096	(2)
F2 to F3	0.120	0.109	0.133	(2)
F3 to F4	0.116	0.104	0.129	(2)
F4 to DC	0.029	0.010	0.039	(3)
F4 to HCC	0.013	0.010	0.079	(3)
SVR F4 to DC	0.008	0.002	0.036	(4)
SVR F4 to HCC	0.005	0.002	0.013	(4)
DC to HCC	0.068	0.030	0.083	(5)
DC to liver transplantation	0.023	0.010	0.062	(6, 7)
DC (first year) to liver-related death	0.182	0.065	0.190	(5)
DC (>1 year) to liver-related death	0.112	0.065	0.190	(5)
HCC to liver transplantation	0.040	0.000	0.140	(8, 9)
HCC to liver-related death	0.427	0.330	0.860	(3)
Liver transplantation (first year) to liver-related death	0.116	0.060	0.420	(10)
Liver transplantation (>1 year) to liver-related death	0.044	0.024	0.110	(10)
HCV-infected population characteristics				
Total HCV-infected population in 2001 (million)	4.2	3.4	4.9	(11)
Chronic infection ratio (%)†	78	70.4	86.6	(11)
Percentage of patients unaware of their HCV infection	60	50	75	(1)
Chronic contraindication (%)‡	34.6	31.14	38.06	(1)
Other		**-10%**	**+10%**	
Percentage of patients who pursue treatment	80	72	88	
Percentage of patients who accept screening and receive correct results	81.9	73.71	90.09	

F0 = METAVIR stage for no fibrosis; F1 = METAVIR stage for portal fibrosis without septa; F2 = METAVIR stage for portal fibrosis with few septa; F3 = METAVIR stage for numerous septa without cirrhosis; F4 = METAVIR stage for cirrhosis; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; SVR = sustained virologic response; HCV = hepatitis C virus.

*Reported values are annual transition probabilities.

†The percentage of infected patients who develop chronic infection.

‡The ratio of patients with contraindication (with modifiable and non-modifiable reasons) amongst chronically infected patients.

Supplement Table 5. **The Base-Case Scenario Values and Range of Group Parameters in 1-Way Sensitivity Analyses**

Parameter	Base-case value	Lower value (-10%)	Upper value (+10%)	Reference
HCV-infected population characteristics				
Sex (%)				
Male	64.22	58.03	67.90	(11)
Female	35.78	41.97	32.10	
HCV genotype (%)*				(18, 23)
1	73	65	83	
2	14	12.6	15.4	
3	8	7.2	8.8	
Other	5	4.5	5.5	
Stage distribution of HCV-infected population in 2001 (%)†		**-10%**	**+10%**	(7)
F0	27.2	24.48	29.92	
F1	33.39	30.05	36.73	
F2	17.11	15.40	18.82	
F3	11.08	9.97	12.19	
F4	9.61	8.65	10.57	
DC	1.43	1.29	1.57	
HCC	0.18	0.20	0.16	
Age distribution for HCV-infected population in 2001 (%)‡		**-10%**	**+10%**	
18–19	1.78	1.60	1.96	
20–29	10.67	9.60	11.74	
30–39	22.67	20.40	24.94	
40–49	28.89	26.00	31.78	
50–59	20.44	18.40	22.48	
60–69	9.33	8.40	10.26	
70–100	6.22	5.60	6.84	
Age distribution of the new HCV infections (%)		**-10%**	**+10%**	
18–19	3.2	2.88	3.52	
20–29	26.3	23.67	28.93	
30–39	27.7	24.93	30.47	
40–49	24.9	22.41	27.39	
50–59	13.4	12.06	14.74	
60–69	4.4	3.96	4.84	
70-100	6.22	0.09	0.11	
Distribution of treatment-experienced patients (%)§		**-10%**	**+10%**	
Genotype 1				
Relapsers	53	47.7	58.3	(20)
Partial responders	19	17.1	20.9	(20)
Null responders	28	25.2	30.8	(20)
Genotype 2–6				
Relapsers	47	42.3	51.7	(21)
Partial responders	16	14.4	17.6	(21)
Null responders	37	33.3	40.7	(21)

HCV = hepatitis C virus; F0 = METAVIR stage for no fibrosis; F1 = METAVIR stage for portal fibrosis without septa; F2 = METAVIR stage for portal fibrosis with few septa; F3 = METAVIR stage for numerous septa without cirrhosis; F4 = METAVIR stage for cirrhosis; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma.

[*]For sensitivity analyses, all other values in this category were normalized such that the total percentage adds to 100%.

[†]For sensitivity analyses of disease-stage distribution for the infected population, all other values in this category were normalized such that the total percentage adds to 100%.

[‡]For sensitivity analyses of age distribution of the infected population and annual new HCV infections, all other values in this category were normalized such that the total percentage adds to 100%.

[§]For sensitivity analyses, all other values in this category were normalized such that the total percentage adds to 100%.

Supplement Table 6. **Annual Hepatitis C Treatment Capacity in the United States from 2001-2007 and Its Effect on Advanced-Stage Hepatitis C Outcomes**

Year	Treatment capacity in 2001–2007 (24)
2001	126 040
2002	126 040
2003	107 131
2004	144 276
2005	114 197
2006	88 083
2007	83 270
Treatment capacity alternative data estimates	
Baseline: Base-case scenario* with constant treatment capacity beyond 2007	
2008–2050	83 270
Scenario 1: Base-case scenario with an increase in treatment capacity by 10% in 2012 and 50% in 2014	
2008–2011	83 270
2012–2013	91 579 (10% increase)
2014–2050	124 905 (50% increase)
Scenario 2: Base-case scenario with an increase in treatment capacity by 10% in 2012 and 20% decrease in 2014†	
2008–2011	83 270
2012–2013	91 579 (10% increase)
2014–2050	66 616 (20% decrease)
Scenario 3: Base-case scenario with an increase in treatment capacity by 10% in 2012 and unlimited capacity starting in 2014	
2008–2011	83 270
2012–2013	91 579 (10% increase)
2014–2050	Unlimited

	Treatment capacity scenarios			
Advance-stage disease outcomes	**Baseline***	**Scenario 1**	**Scenario 2†**	**Scenario 3**
Decompensated cirrhosis				
Cumulative incidence (2014–2050)	293 900	253 100	318 100	165 100
Peak annual prevalence	62 700	61 300	63 300	55 600
Year of peak annual prevalence	2019	2017	2019	2014
Peak annual incidence	15 300	15 200	15 500	11 900
Year of peak annual incidence	2014	2015	2017	2014
Hepatocellular carcinoma				
Cumulative incidence (2014–2050)	240 200	211 900	255 700	149 200
Peak annual prevalence	23 200	22 800	23 400	21 200
Year of peak annual prevalence	2019	2017	2020	2014
Peak annual incidence	11 400	11 100	11 400	9 800
Year of peak annual incidence	2019	2017	2020	2014
Liver-related deaths				
Total deaths (2014–2050)	433 600	385 900	458 900	280 400
Peak annual deaths	19 300	18 900	19 300	17 500
Year of peak annual deaths	2020	2018	2020	2014
Liver transplants				
Total transplants (2014–2050)	37 900	34 500	40 400	24 500
Peak annual liver transplants	2100	2100	2100	2000
Year of peak annual liver transplants	2016	2015	2017	2014

*Base case scenario = simulation scenario with risk-based and birth-cohort screening, treatment with peginterferon and ribavirin and/or DAAs before 2014, and newly approved and future therapies starting in 2014, and limited treatment capacity.

[†]Scenario 2 simulated decreased capacity beyond 2014 as a result of limited reimbursement of expensive HCV drugs.

Supplement Table 7. **Comparison of Model Estimations to Published Data and Modeling Studies**

Output	Model estimation (year)	Published data (year)	References
Cross-validation with published data			
Chronic HCV cases	2.7 million (average in 2003–2010)	2.7 million (2003–2010)	(25)
Hepatocellular carcinoma prevalence	12 700 (average in 2001–2004)	12 300 (average in 2001–2004)	(26)
Hepatocellular carcinoma incidence	7500 (2005)	6500 (2005)	(8, 27)
Liver-related deaths	11 900 (2005)	11 850 (2005)	(19)
	Model estimation (% of total chronic HCV cases in 2001)	**Previously published modeling study estimation (% of total chronic HCV cases in 2001)**	
Comparison with other modeling study – 2001 projections			
Chronic HCV cases	3.2 million	3.5 million	(7)
F0 cases	864 700 (26.92)	970 000 (27.66)	(7)
F1 cases	1 098 600 (34.20)	1 190 000 (33.93)	(7)
F2 cases	558 800 (17.40)	610 000 (17.39)	(7)
F3 cases	378 600 (11.79)	395 000 (11.26)	(7)
F4 cases	311 400 (9.69)	342 500 (9.76)	(7)
Decompensated cirrhosis cases	33 100 (-)	47 000 (-)	(7)
Liver transplants	2100 (-)	1800 (-)	(7)

HCV = hepatitis C virus; F0 = METAVIR stage for no fibrosis; F1 = METAVIR stage for portal fibrosis without septa; F2 = METAVIR stage for portal fibrosis with few septa; F3 = METAVIR stage for numerous septa without cirrhosis; and F4 = METAVIR stage for cirrhosis.

Supplement Table 8. **Validation of the Natural History of Our Model Predicting Disease Burden of Hepatitis C in the United States**

Initial treatment response	Subsequent liver complication	10-year cumulative incidence	
		van der Meer et al. (28)	Model prediction
Patients who did not achieve SVR			
	DC	29.9% (95% CI: 24.3–35.5%)	33.6%
	HCC	21.8% (95% CI: 16.6–27.0%)	20.7%
	LRD plus LT	27.4% (95% CI: 22.0–32.8%)	29.6%
Patients who achieved SVR			
	DC	2.1% (95% CI: 0–4.5%)	7.5%
	HCC	5.1% (95% CI: 1.3–8.9%)	5.9%
	LRD plus LT	1.9% (95% CI: 0–4.1%)	7.8%

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

Supplement Table 9. **The Effect of Hepatitis C Treatment Efficacies on Advanced-Stage Hepatitis C Outcomes**

Scenario	Advance-stage disease outcomes	Baseline	10% relative decrease* (% change)	5% relative increase† (% change)
Pre-DAA	**Decompensated cirrhosis**			
	Cumulative incidence (2014–2050)	418 100	439 800 (5%)	406 900 (-3%)
	Peak annual prevalence	68 000	70 100 (3%)	67 200 (-1%)
	Year of peak annual prevalence	2022	2022	2022
	Peak annual incidence	16 800	17 500 (4%)	16 400 (-2%)
	Year of peak annual incidence	2020	2019	2019
	Hepatocellular carcinoma			
	Cumulative incidence (2014–2050)	318 900	334 600 (5%)	312 400 (-2%)
	Peak annual prevalence	25 000	26 100 (4%)	24 700 (-1%)
	Year of peak annual prevalence	2021	2022	2021
	Peak annual incidence	12 200	12 800 (5%)	12 100 (-1%)
	Year of peak annual incidence	2021	2021	2021
	Liver-related deaths			
	Total deaths (2014–2050)	560 100	585 000 (4%)	548 400 (-2%)
	Peak annual deaths	20 600	21 400 (4%)	20 300 (-1%)
	Year of peak annual deaths	2023	2023	2023
	Liver transplants			
	Total transplants (2014–2050)	47 800	49 500 (4%)	46 700 (-2%)
	Peak annual liver transplants	2100	2200 (5%)	2100 (0%)
	Year of peak annual liver transplants	2021	2020	2015
Base Case	**Decompensated cirrhosis**			
	Cumulative incidence (2014–2050)	293 900	326 400 (11%)	277 100 (-6%)
	Peak annual prevalence	62 700	65 000 (4%)	61 400 (-2%)
	Year of peak annual prevalence	2019	2019	2019
	Peak annual incidence	15 300	15 900 (4%)	15 100 (-1%)
	Year of peak annual incidence	2014	2016	2015
	Hepatocellular carcinoma			
	Cumulative incidence (2014–2050)	240 200	261 700 (9%)	229 200 (-5%)
	Peak annual prevalence	23 200	24 100 (4%)	23 300 (0%)
	Year of peak annual prevalence	2019	2019	2018
	Peak annual incidence	11 400	11 700 (3%)	11 500 (1%)
	Year of peak annual incidence	2019	2018	2018
	Liver-related deaths			
	Total deaths (2014–2050)	433 600	468 900 (8%)	414 900 (-4%)
	Peak annual deaths	19 300	19 800 (3%)	18 900 (-2%)
	Year of peak annual deaths	2020	2020	2019
	Liver transplants			
	Total transplants (2014–2050)	37 900	41 000 (8%)	36 900 (-3%)
	Peak annual liver transplants	2100	2100 (0%)	2000 (-5%)
	Year of peak annual liver transplants	2016	2017	2018
Ideal	**Decompensated cirrhosis**			

Cumulative incidence (2014–2050)	158 100	193 900 (23%)	139 400 (-12%)
Peak annual prevalence	56 000	57 200 (2%)	55 500 (-1%)
Year of peak annual prevalence	2014	2014	2014
Peak annual incidence	12 000	12 600 (5%)	11 800 (-2%)
Year of peak annual incidence	2014	2014	2014
Hepatocellular carcinoma			
Cumulative incidence (2014–2050)	143 900	167 500 (16%)	130 900 (-9%)
Peak annual prevalence	20 800	21 000 (1%)	20 300 (-2%)
Year of peak annual prevalence	2014	2014	2014
Peak annual incidence	9500	9800 (3%)	9300 (-2%)
Year of peak annual incidence	2014	2014	2014
Liver-related deaths			
Total deaths (2014–2050)	272 100	311 400 (14%)	251 800 (-7%)
Peak annual deaths	17 500	17 800 (2%)	17 400 (-1%)
Year of peak annual deaths	2014	2014	2014
Liver transplants			
Total transplants (2014–2050)	24 000	26 900 (12%)	22 000 (-8%)
Peak annual liver transplants	2000	2100 (5%)	2000 (0%)
Year of peak annual liver transplants	2014	2014	2014

*The treatment efficacy rates of all therapies used under each scenario were decreased relatively by 10%. For example, under the base-case scenario, the treatment efficacy of peginterferon and ribavirin (PEG-RBV) and the treatment efficacy of triple therapy (PRG-RBV plus boceprevir/telaprevir) were relatively reduced by 10% compared with the default values.

†The treatment efficacy rates of all therapies used under each scenario were increased relatively by 5%.

Pre-DAA = simulation scenario with risk-based screening and peginterferon and ribavirin treatment; Base case = simulation scenario with risk-based and birth-cohort screening, treatment with peginterferon and ribavirin and/or DAAs before 2014, and newly approved and future therapies starting in 2014, and limited treatment capacity; Ideal = simulation scenario with universal screening, treatment with peginterferon and ribavirin and/or DAAs before 2014, and newly approved and future therapies starting in 2014, and unlimited treatment capacity; DAA = direct-acting antiviral agent.

Note: The year of peak annual prevalence or incidence is mostly similar in the baseline and sensitivity analyses results. In some cases, the year of peak annual prevalence or incidence in the baseline, though similar, did not fall between the projected values for sensitivity analyses because of first-order uncertainty in the model outcomes.

Supplement Table 10. **The Effect of Possible Delays in the Launch of Future Therapies According to the Base-Case Scenario* on Advanced-Stage Hepatitis C Outcomes**

	Launch of future therapies (start year)			
Outcome (2014–2050)	**2-year early:** Wave 1 (2014) Wave 2 (2015)	**Default:** Wave 1 (2014) Wave 2 (2017)	**2-year delay:** Wave 1 (2014) Wave 2 (2019)	**4-year delay:** Wave 1 (2014) Wave 2 (2021)
Cumulative incidence of decompensated cirrhosis	292 000	293 900	295 600	296 700
Cumulative incidence of hepatocellular carcinoma	240 500	240 200	242 000	242 300
Total liver-related deaths	432 100	433 600	434 700	436 300
Total liver transplants	38 200	37 900	38 300	38 400

*Base case scenario = simulation scenario with risk-based and birth-cohort screening, treatment with peginterferon and ribavirin and/or DAAs before 2014, and newly approved and future therapies starting in 2014, and limited treatment capacity.
Wave 1 = new therapies launched in 2014 for all patients that increased treatment response rates to 90% in non-cirrhotic patients and 60%–80% in cirrhotic patients; Wave 2 = future therapies that we assumed would be launched in 2017 and increase treatment response rates to 90% in cirrhotic patients.

Supplement Table 11. **1-Way Sensitivity Analyses of the Ratio of Patients in F0–F3 States who Choose to Wait for Better Therapies before 2014 According to the Base-Case Scenario***

Combinations	Wait in F0–F2 states (%)	Wait in F3 state (%)	Cumulative incidence in 2014–2050 (Percent difference from base-case)			Peak annual incidence in 2014–2050 (Percent difference from base-case)		
			DC	HCC	LRD	Peak annual DC incidence	Peak annual HCC incidence	Peak annual LRD
1	0	0	327 700	264 400	471 500	63 800	23 700	19 400
2	25	0	326 600	263 600	470 500	63 200	23 600	19 400
3	50	0	326 400	262 500	469 900	63 200	23 400	19 300
4	75	0	324 900	263 200	468 500	62 400	23 700	19 200
5	100	0	323 400	261 900	467 300	62 100	23 300	18 900
6	25	25	326 700	263 200	470 000	63 600	23 600	19 300
7	50	25	325 900	263 000	469 600	62 800	23 500	19 200
8†	75	25	325 500	262 800	469 700	62 700	23 200	19 300
9	100	25	325 100	263 000	468 600	62 100	23 100	19 100
10	50	50	326 200	263 400	470 400	62 800	23 600	19 300
11	75	50	326 300	263 200	469 600	62 800	23 400	19 200
12	100	50	325 700	263 400	469 200	62 300	23 200	19 000
13	75	75	326 800	265 000	471 400	62 500	23 500	19 100
14	100	75	326 200	264 300	470 200	61 700	23 000	18 900
15	100	100	326 600	264 700	471 000	62 200	23 200	18 900

*Base case scenario = simulation scenario with risk-based and birth-cohort screening, treatment with peginterferon and ribavirin and/or DAAs before 2014, and newly approved and future therapies starting in 2014, and limited treatment capacity.

†The results of the base-case scenario.

F0 = METAVIR stage for no fibrosis; F1 = METAVIR stage for portal fibrosis without septa; F2 = METAVIR stage for portal fibrosis with few septa; F3 = METAVIR stage for numerous septa without cirrhosis; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma.

Supplement Table 12. **Results of 1-Way Sensitivity Analyses**

	Cumulative incidence in 2014–2050 (Percent difference from base-case)			Peak annual incidence in 2014–2050 (Percent difference from base-case)		
Parameter	**DC**	**HCC**	**LRD**	**Peak annual DC incidence**	**Peak annual HCC incidence**	**Peak annual LRD**
Base-case results	325 500	262 800	469 700	62 700	23 200	19 300
Natural-history transition probabilities						
F0 to F1, 0.104	320 100 (-2)	258 100 (-2)	461 400 (-2)	61 500 (-2)	23 000 (-1)	18 700 (-3)
F0 to F1, 0.130	330 900 (2)	267 500 (2)	476 400 (1)	63 800 (2)	23 600 (2)	19 400 (1)
F1 to F2, 0.075	314 100 (-4)	253 000 (-4)	452 700 (-4)	60 300 (-4)	22 400 (-4)	18 500 (-4)
F1 to F2, 0.096	338 100 (4)	272 900 (4)	486 300 (4)	65 300 (4)	24 400 (5)	20 200 (5)
F2 to F3, 0.109	316 000 (-3)	254 600 (-3)	454 800 (-3)	60 300 (-4)	22 600 (-3)	18 500 (-4)
F2 to F3, 0.133	335 500 (3)	270 600 (3)	483 900 (3)	65 000 (4)	24 000 (3)	19 700 (2)
F3 to F4, 0.104	314 300 (-3)	253 500 (-4)	452 300 (-4)	60 100 (-4)	22 400 (-4)	18 300 (-5)
F3 to F4, 0.129	335 000 (3)	271 200 (3)	484 100 (3)	65 200 (4)	24 400 (5)	19 800 (3)
F4 to DC, 0.010	201 100 (-38)	257 900 (-2)	370 100 (-21)	29 900 (-52)	21 400 (-8)	13 600 (-30)
F4 to DC, 0.039	368 500 (13)	262 800 (0)	504 900 (7)	76 100 (21)	24 200 (4)	21 400 (11)
F4 to HCC, 0.010	336 300 (3)	244 300 (-7)	456 000 (-3)	64 000 (2)	21 000 (-9)	18 400 (-5)
F4 to HCC, 0.079	180 800 (-44)	448 300 (71)	595 400 (27)	39 700 (-37)	57 700 (149)	31 200 (62)
SVR F4 to DC, 0.002	268 100 (-18)	252 200 (-4)	429 400 (-9)	59 400 (-5)	22 900 (-1)	18 400 (-4)
SVR F4 to DC, 0.036	508 900 (56)	299 400 (14)	599 000 (28)	78 800 (26)	24 700 (6)	21 800 (13)
SVR F4 to HCC, 0.002	328 800 (1)	234 700 (-11)	445 400 (-5)	62 800 (0)	22 200 (-4)	18 600 (-3)
SVR F4 to HCC, 0.013	319 100 (-2)	328 200 (25)	524 400 (12)	62 000 (-1)	26 100 (12)	20 200 (4)
DC to HCC, 0.030	326 500 (0)	215 200 (-18)	464 200 (-1)	74 800 (19)	19 200 (-17)	18 800 (-2)
DC to HCC, 0.083	325 000 (0)	278 000 (6)	470 600 (0)	58 700 (-6)	24 700 (6)	19 400 (0)
DC to liver transplantation, 0.010	325 700 (0)	268 000 (2)	472 100 (0)	65 900 (5)	23 700 (2)	19 200 (0)
DC to liver transplantation, 0.062	326 400 (0)	250 200 (-5)	460 900 (-2)	54 800 (-13)	22 200 (-4)	18 600 (-4)
DC (first year) to liver-related death, 0.065	325 700 (0)	277 000 (5)	466 300 (-1)	70 600 (13)	24 500 (6)	18 900 (-2)
DC (first year) to liver-related death, 0.190	325 900 (0)	262 700 (0)	470 300 (0)	62 000 (-1)	23 400 (1)	19 000 (-2)
DC (>1 year) to liver-related death, 0.065	326 600 (0)	285 600 (9)	460 100 (-2)	74 300 (19)	25 000 (8)	18 300 (-5)
DC (>1 year) to liver-related death, 0.190	325 400 (0)	242 100 (-8)	476 100 (1)	50 900 (-19)	21 600 (-7)	19 900 (3)
HCC to liver transplantation, 0.000	326 200 (0)	262 800 (0)	475 400 (1)	62 500 (0)	25 400 (9)	19 600 (1)
HCC to liver transplantation, 0.140	324 900 (0)	263 000 (0)	459 400 (-2)	62 500 (0)	20 000 (-14)	18 400 (-5)
HCC to liver-related death, 0.330	325 400 (0)	262 700 (0)	466 300 (-1)	62 200 (-1)	29 000 (25)	18 800 (-3)
HCC to liver-related death, 0.860	326 100 (0)	263 100 (0)	474 200 (1)	63 200 (1)	12 400 (-47)	19 600 (2)
Liver transplantation (first year) to liver-related death, 0.060	325 900 (0)	263 300 (0)	469 200 (0)	63 000 (0)	23 200 (0)	19 000 (-1)

Liver transplantation (first year) to liver-related death, 0.420	325 800 (0)	262 900 (0)	473 400 (1)	62 900 (0)	23 400 (1)	19 500 (1)
Liver transplantation (>1 year) to liver-related death, 0.024	325 400 (0)	263 200 (0)	460 900 (-2)	62 600 (0)	23 200 (0)	18 800 (-2)
Liver transplantation (>1 year) to liver-related death, 0.110	326 700 (0)	263 000 (0)	480 100 (2)	62 800 (0)	23 300 (0)	19 700 (2)
HCV-infected population characteristics						
Total HCV-infected population in 2001, 3.4 million	237 400 (-27)	194 100 (-26)	347 800 (-26)	47 600 (-24)	17 800 (-23)	14 500 (-25)
Total HCV-infected population in 2001, 4.9 million	407 500 (25)	325 800 (24)	579 100 (23)	75 900 (21)	28 300 (22)	23 300 (21)
Chronic-infection ratio, 70.4%	275 200 (-15)	224 100 (-15)	400 800 (-15)	54 200 (-13)	20 300 (-12)	16 700 (-13)
Chronic-infection ratio, 86.6%	383 800 (18)	308 600 (17)	548 400 (17)	71 600 (14)	26 800 (15)	21 900 (13)
Percentage of patients unaware of their HCV infection, 50%	326 200 (0)	262 100 (0)	469 000 (0)	62 700 (0)	23 200 (0)	19 100 (-1)
Percentage of patients unaware of their HCV infection, 75%	326 100 (0)	263 600 (0)	469 800 (0)	62 400 (0)	23 300 (0)	19 100 (-1)
Chronic contraindication, 31.14%	325 600 (0)	262 900 (0)	468 900 (0)	62 600 (0)	23 400 (1)	19 100 (-1)
Chronic contraindication, 38.06%	326 100 (0)	263 700 (0)	469 800 (0)	63 000 (1)	23 200 (0)	19 100 (-1)
Other						
Percentage of patients who pursue treatment, 72%	325 200 (0)	263 700 (0)	470 300 (0)	62 600 (0)	23 400 (1)	19 100 (-1)
Percentage of patients who pursue treatment, 88%	326 200 (0)	262 400 (0)	469 000 (0)	62 500 (0)	23 100 (0)	19 200 (0)
Percentage of patients who accept screening and receive correct results, 73.71%	325 300 (0)	263 300 (0)	469 100 (0)	62 300 (-1)	23 300 (0)	19 200 (-1)
Percentage of patients who accept screening and receive correct results, 90.09%	325 900 (0)	263 200 (0)	469 300 (0)	62 400 (-1)	23 400 (1)	19 100 (-1)

HCV = hepatitis C virus; F0 = METAVIR stage for no fibrosis; F1 = METAVIR stage for portal fibrosis without septa; F2 = METAVIR stage for portal fibrosis with few septa; F3 = METAVIR stage for numerous septa without cirrhosis; F4 = METAVIR stage for cirrhosis; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; LRD = liver-related deaths; SVR = sustained virologic response.

Supplement Table 13. **Results of 1-Way Sensitivity Analyses for Group Parameters***

	Cumulative incidence in 2014–2050 (Percent difference from base-case)			Peak annual incidence in 2014–2050 (Percent difference from base-case)		
Parameter	**DC**	**HCC**	**LRD**	**Peak annual DC incidence**	**Peak annual HCC incidence**	**Peak annual LRD**
Base-case results	325 500	262 800	469 700	62 700	23 200	19 300
HCV-infected population characteristics						
Sex (%)						
Male 58.03%, Female 41.97%	329 000 (1)	264 000 (0)	473 200 (1)	63 300 (1)	23 200 (0)	19 100 (-1)
Male 67.90%, Female 32.10%	324 600 (0)	261 200 (-1)	466 700 (-1)	62 300 (-1)	23 300 (0)	19 100 (-1)
HCV genotype (%)						
1, 65%	322 100 (-1)	260 500 (-1)	465 800 (-1)	62 100 (-1)	23 200 (0)	18 900 (-2)
1, 83%	329 700 (1)	265 500 (1)	474 100 (1)	63 500 (1)	23 300 (1)	19 200 (-1)
2, 12.6%	326 200 (0)	263 500 (0)	469 700 (0)	62 800 (0)	23 300 (0)	19 100 (-1)
2, 15.4%	324 600 (0)	261 800 (0)	468 200 (0)	62 500 (0)	23 300 (0)	19 100 (-1)
3, 7.2%	324 900 (0)	263 200 (0)	468 500 (0)	62 400 (0)	23 200 (0)	19 200 (-1)
3, 8.8%	325 300 (0)	262 400 (0)	468 600 (0)	62 400 (0)	23 400 (1)	19 000 (-1)
Other, 4.5%	325 700 (0)	262 900 (0)	469 900 (0)	62 700 (0)	23 100 (0)	19 100 (-1)
Other, 5.5%	326 200 (0)	263 300 (0)	470 000 (0)	63 000 (1)	23 300 (1)	19 200 (-1)
Stage distribution of HCV-infected population in 2001 (%)						
F0, 24.48%	360 300 (11)	295 500 (12)	541 400 (15)	77 500 (24)	28 600 (23)	23 700 (23)
F0, 29.92%	350 500 (8)	286 600 (9)	521 900 (11)	73 600 (17)	27 100 (17)	22 300 (16)
F1, 30.05%	357 100 (10)	293 100 (12)	536 900 (14)	77 100 (23)	28 600 (23)	23 500 (22)
F1, 36.73%	354 200 (9)	290 600 (11)	528 000 (12)	73 900 (18)	27 700 (19)	22 500 (17)
F2, 15.40%	353 200 (9)	289 400 (10)	528 700 (13)	75 100 (20)	27 500 (19)	22 600 (17)
F2, 18.82%	358 900 (10)	295 400 (12)	537 600 (14)	76 300 (22)	28 400 (22)	23 100 (20)
F3, 9.97%	354 600 (9)	289 000 (10)	527 800 (12)	74 200 (18)	27 400 (18)	22 600 (17)
F3, 12.19%	357 100 (10)	293 800 (12)	536 000 (14)	76 200 (21)	28 300 (22)	23 200 (20)
F4, 8.65%	354 100 (9)	290 600 (11)	529 100 (13)	74 200 (18)	27 700 (19)	22 700 (17)
F4, 10.57%	354 900 (9)	292 800 (11)	534 200 (14)	76 300 (22)	28 100 (21)	23 000 (19)
DC, 1.29%	357 100 (10)	291 800 (11)	533 000 (13)	75 500 (20)	28 000 (20)	23 000 (19)
DC, 1.57%	354 600 (9)	291 500 (11)	531 600 (13)	75 600 (21)	27 800 (20)	22 900 (19)
HCC, 0.20%	355 000 (9)	291 200 (11)	531 400 (13)	75 100 (20)	27 800 (20)	22 900 (19)
HCC, 0.16%	355 700 (9)	292 000 (11)	532 200 (13)	75 400 (20)	27 900 (20)	23 000 (19)
Age distribution for HCV-infected population in 2001 (%)						
18–19, 1.60%	325 000 (0)	261 600 (0)	467 900 (0)	62 500 (0)	23 200 (0)	19 200 (-1)

18–19, 1.96%	326 200 (0)	264 100 (0)	470 500 (0)	62 500 (0)	23 600 (2)	19 100 (-1)
20–29, 9.60%	323 200 (-1)	260 100 (-1)	465 200 (-1)	62 500 (0)	23 400 (1)	19 200 (0)
20–29, 11.74%	327 800 (1)	264 800 (1)	472 400 (1)	62 600 (0)	23 300 (1)	19 200 (-1)
30–39, 20.40%	322 100 (-1)	259 300 (-1)	463 500 (-1)	62 100 (-1)	23 300 (0)	18 900 (-2)
30–39, 24.94%	330 500 (2)	266 300 (1)	476 100 (1)	63 000 (0)	23 300 (0)	19 200 (-1)
40–49, 26.00%	324 000 (0)	261 900 (0)	467 200 (-1)	62 400 (0)	23 200 (0)	19 000 (-2)
40–49, 31.78%	328 000 (1)	264 200 (1)	471 700 (0)	63 500 (1)	23 400 (1)	19 200 (0)
50–59, 18.40%	328 200 (1)	264 800 (1)	472 800 (1)	63 000 (0)	23 300 (1)	19 000 (-1)
50–59, 22.48%	323 300 (-1)	261 000 (-1)	465 300 (-1)	62 800 (0)	23 300 (0)	18 900 (-2)
60–69, 8.40%	329 300 (1)	265 500 (1)	474 000 (1)	63 000 (0)	23 400 (1)	19 300 (0)
60–69, 10.26%	322 900 (-1)	260 700 (-1)	466 100 (-1)	62 700 (0)	23 600 (2)	19 200 (-1)
70–100, 5.60%	328 600 (1)	265 200 (1)	472 900 (1)	63 300 (1)	23 600 (2)	19 400 (0)
70–100, 6.84%	322 600 (-1)	260 800 (-1)	465 300 (-1)	62 100 (-1)	23 200 (0)	19 200 (-1)
Age distribution of the new HCV infections (%)						
18–19, 2.88%	325 600 (0)	262 200 (0)	468 600 (0)	62 700 (0)	23 300 (0)	19 100 (-1)
18–19, 3.52%	325 400 (0)	263 400 (0)	469 300 (0)	62 400 (0)	23 200 (0)	19 100 (-1)
20–29, 23.67%	325 800 (0)	263 500 (0)	468 700 (0)	62 800 (0)	23 400 (1)	19 200 (-1)
20–29, 28.93%	325 300 (0)	262 500 (0)	469 100 (0)	62 300 (-1)	23 300 (0)	19 200 (-1)
30–39, 24.93%	325 200 (0)	262 700 (0)	468 800 (0)	62 400 (0)	23 300 (0)	19 100 (-1)
30–39, 30.47%	325 900 (0)	262 400 (0)	468 900 (0)	62 800 (0)	23 400 (1)	19 200 (-1)
40–49, 22.41%	325 400 (0)	262 400 (0)	468 900 (0)	62 900 (0)	23 200 (0)	19 100 (-1)
40–49, 27.39%	325 700 (0)	262 700 (0)	468 600 (0)	62 700 (0)	23 300 (1)	19 200 (-1)
50–59, 12.06%	325 300 (0)	263 600 (0)	469 400 (0)	62 400 (-1)	23 400 (1)	19 100 (-1)
50–59, 14.74%	325 800 (0)	262 600 (0)	469 100 (0)	62 300 (-1)	23 300 (1)	19 000 (-1)
60–69, 3.96%	325 700 (0)	263 400 (0)	469 800 (0)	62 800 (0)	23 200 (0)	19 100 (-1)
60–69, 4.84%	325 000 (0)	262 700 (0)	468 600 (0)	62 900 (0)	23 300 (0)	19 100 (-1)
70–100, 0.09%	325 200 (0)	261 600 (0)	467 600 (0)	62 600 (0)	23 100 (0)	19 000 (-2)
70–100, 0.11%	326 000 (0)	262 800 (0)	469 800 (0)	62 600 (0)	23 200 (0)	19 300 (0)
Distribution of treatment-experienced patients (%)						
Genotype 1						
Relapses, 42.93%	325 800 (0)	263 100 (0)	469 200 (0)	62 900 (0)	23 200 (0)	19 100 (-1)
Relapses, 58.30%	325 200 (0)	262 600 (0)	468 900 (0)	62 600 (0)	23 100 (0)	19 100 (-1)
Partial responses, 17.10%	324 900 (0)	263 700 (0)	469 400 (0)	63 000 (0)	23 600 (2)	19 200 (0)
Partial responses, 20.90%	325 400 (0)	262 800 (0)	469 000 (0)	62 900 (0)	23 400 (1)	19 300 (0)
Null responses, 25.20%	325 000 (0)	263 400 (0)	468 900 (0)	62 800 (0)	23 300 (0)	19 100 (-1)
Null responses, 30.80%	326 600 (0)	262 700 (0)	469 700 (0)	62 800 (0)	23 400 (1)	19 100 (-1)
Genotype 2–6						

Relapses, 42.30%	325 900 (0)	263 000 (0)	469 600 (0)	62 700 (0)	23 500 (1)	19 100 (-1)
Relapses, 51.70%	326 300 (0)	263 000 (0)	469 700 (0)	62 900 (0)	23 300 (0)	19 300 (0)
Partial responses, 14.40%	325 900 (0)	263 200 (0)	469 100 (0)	62 800 (0)	23 500 (1)	19 100 (-1)
Partial responses, 17.60%	324 900 (0)	262 700 (0)	468 700 (0)	62 400 (0)	23 300 (0)	19 200 (-1)
Null responses, 33.30%	325 600 (0)	262 700 (0)	468 500 (0)	62 700 (0)	23 500 (1)	19 200 (0)
Null responses, 40.70%	325 800 (0)	263 000 (0)	469 100 (0)	62 400 (0)	23 700 (2)	19 000 (-2)

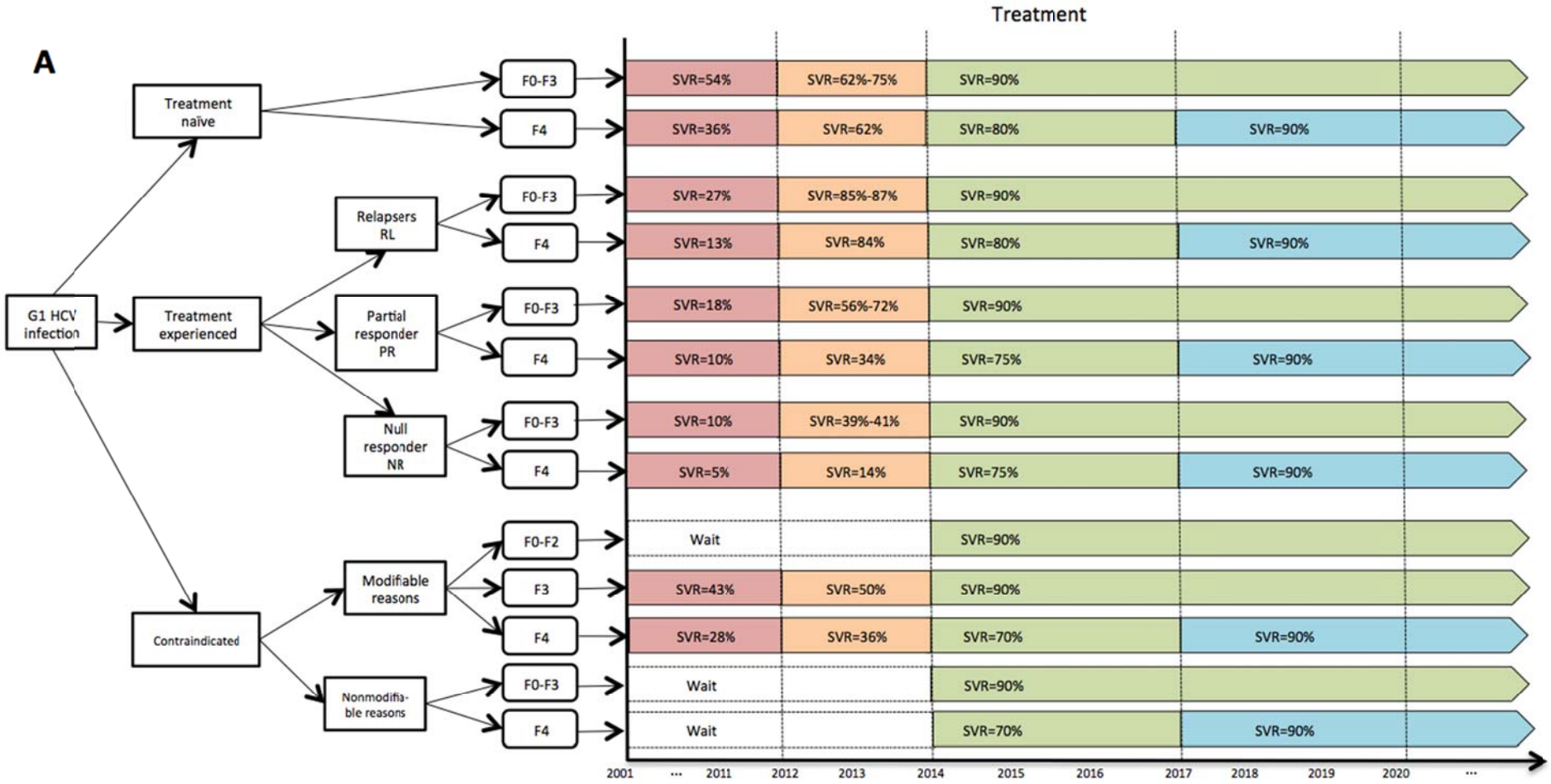
*The value of each parameter in a group affects the values of the other parameters in the same group, since the total percentage of patients in each group should sum to 100%. These groups of parameters are related to patients' sex, genotype, age groups and treatment history. In each 1-way sensitivity analysis, we adjusted the values of the other parameters in the same group, proportionate to the base-case settings.

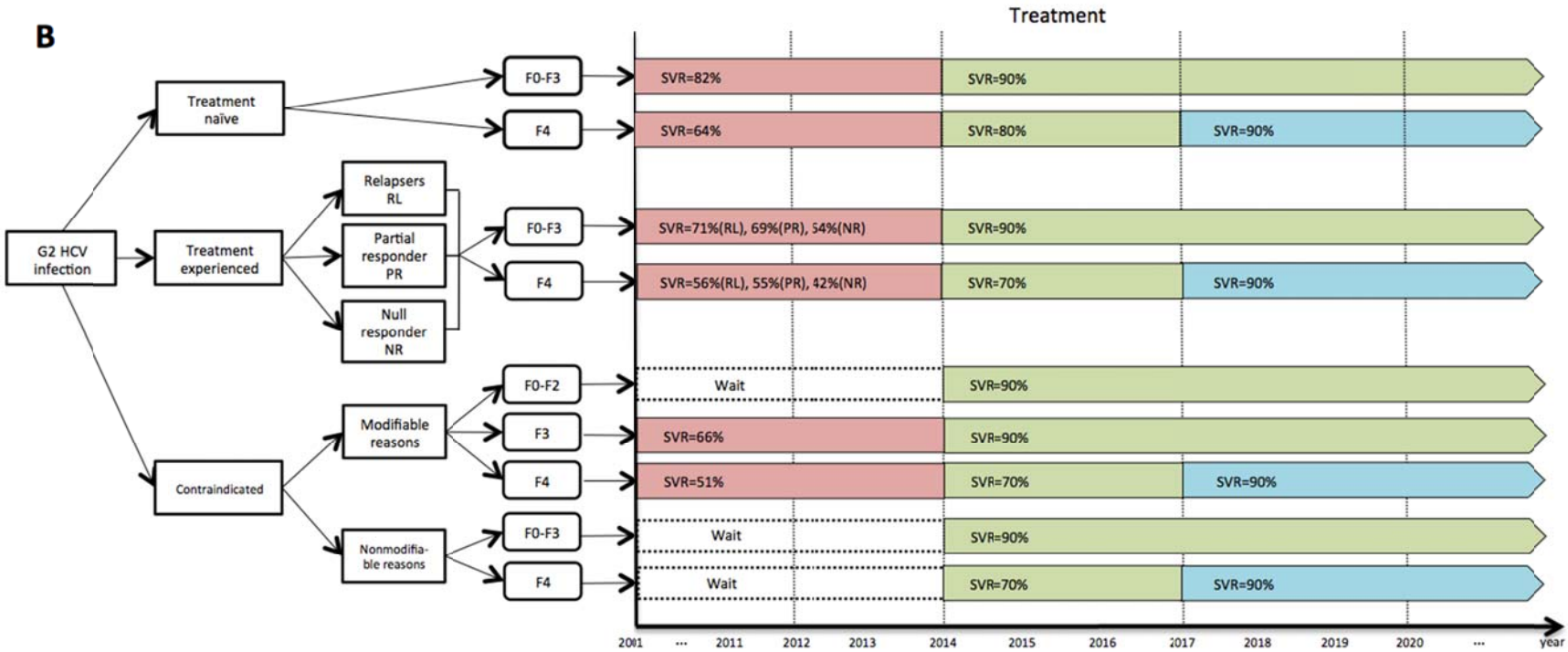
HCV = hepatitis C virus; F0 = METAVIR stage for no fibrosis; F1 = METAVIR stage for portal fibrosis without septa; F2 = METAVIR stage for portal fibrosis with few septa; F3 = METAVIR stage for numerous septa without cirrhosis; F4 = METAVIR stage for cirrhosis; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; LRD = liver-related deaths.

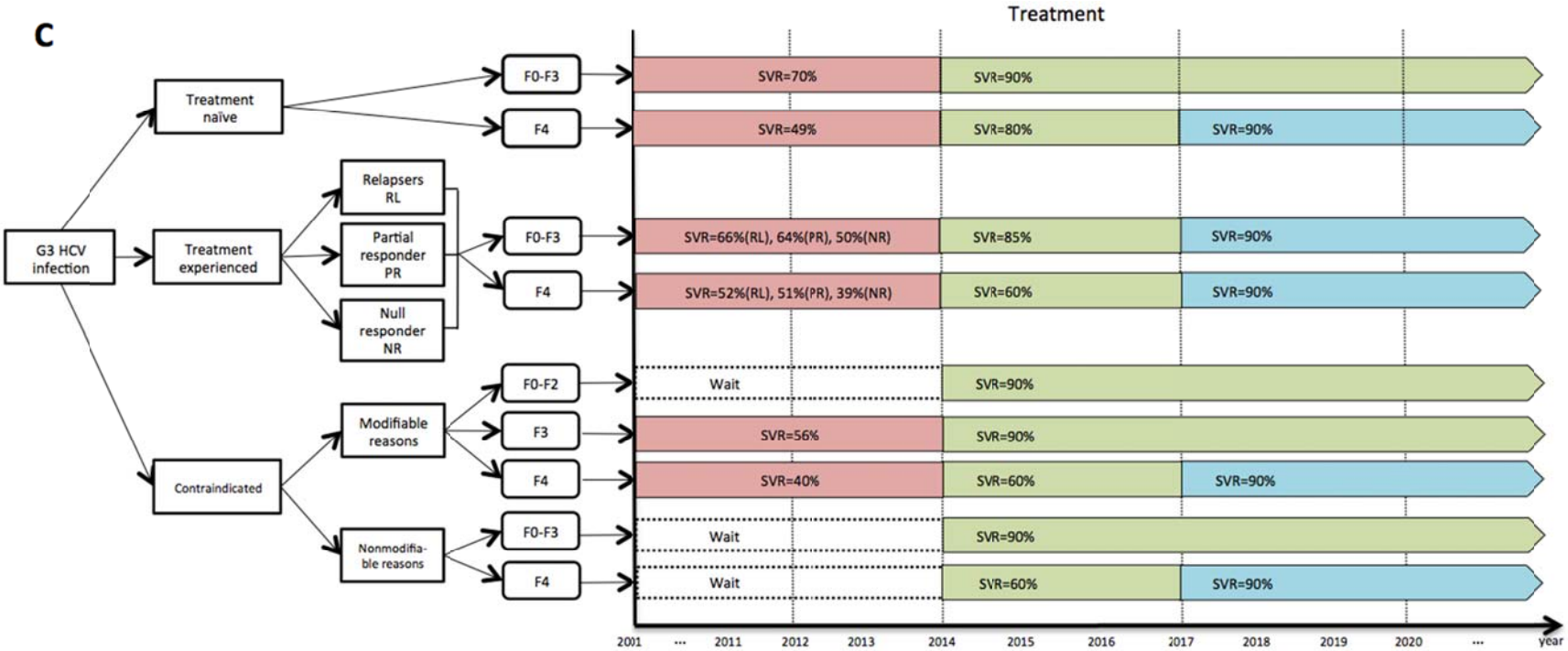
Supplement Table 14. **The Effect of Changing Annual Incidence on Advanced-Stage Hepatitis C Outcomes**

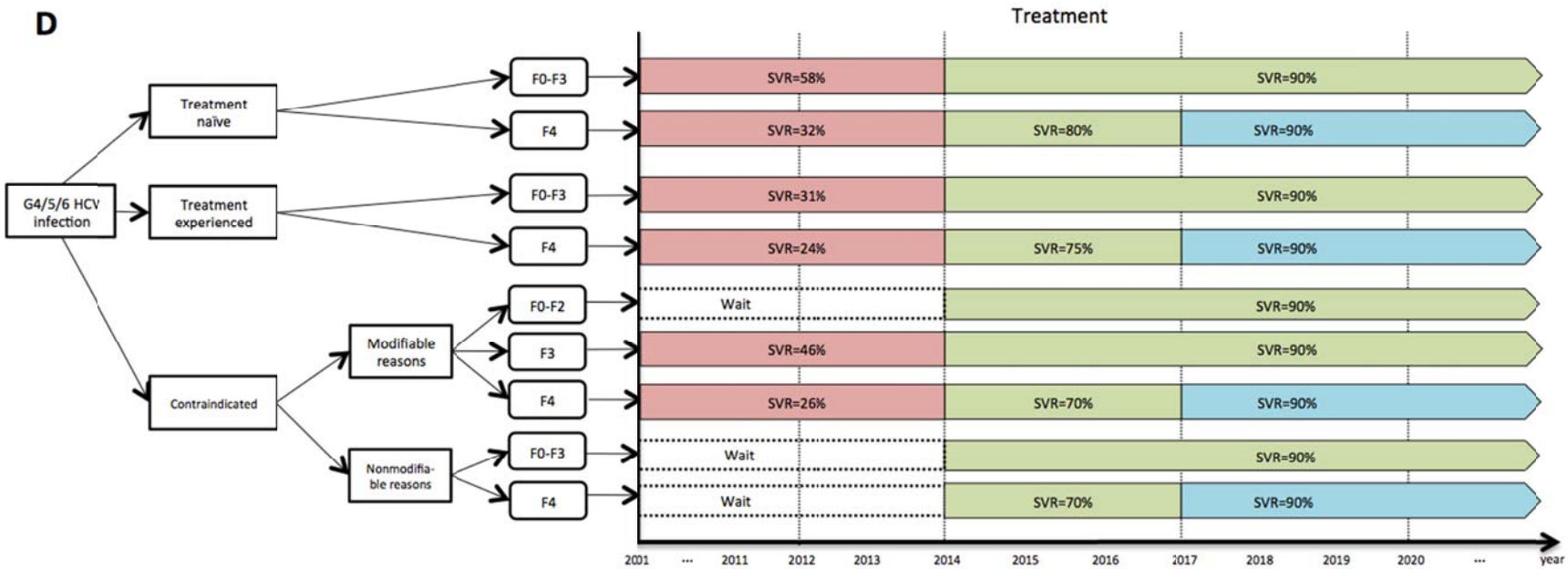
Advanced-stage disease outcomes	Scenario		
	Base case*	Decreasing incidence†	Increasing incidence‡
Decompensated cirrhosis			
Cumulative incidence (2014–2050)	293 900	292 100	297 000
Peak annual prevalence	62 700	62 800	62 400
Year of peak annual prevalence	2019	2019	2019
Peak annual incidence	15 300	15 300	15 400
Year of peak annual incidence	2014	2015	2018
Hepatocellular carcinoma			
Cumulative incidence (2014–2050)	240 200	238 800	241 900
Peak annual prevalence	23 200	23 300	23 200
Year of peak annual prevalence	2019	2018	2020
Peak annual incidence	11 400	11 500	11 300
Year of peak annual incidence	2019	2017	2017
Liver-related deaths			
Total deaths (2014–2050)	433 600	431 100	435 700
Peak annual deaths	19 300	19 100	18 900
Year of peak annual deaths	2020	2019	2018
Liver transplants			
Total transplants (2014–2050)	37 900	38 100	38 300
Peak annual liver transplants	2 100	2 100	2 000
Year of peak annual liver transplants	2016	2018	2017

*Base case scenario = simulation scenario with risk-based and birth-cohort screening, treatment with peginterferon and ribavirin and/or DAAs before 2014, and newly approved and future therapies starting in 2014, and limited treatment capacity. Hepatitis C annual incidence was assumed to be constant starting in 2011 (Supplement Table 2).
†3.24% relative decrease in hepatitis C incidence during each year
‡3.24% relative increase in hepatitis C incidence during each year
Note: 3.24% relative decrease represented the decreasing rate of annual HCV incidence during 2001–2010 reported by CDC in Supplement Table 2. For consistency, we used the same rate for increase in HCV incidence.

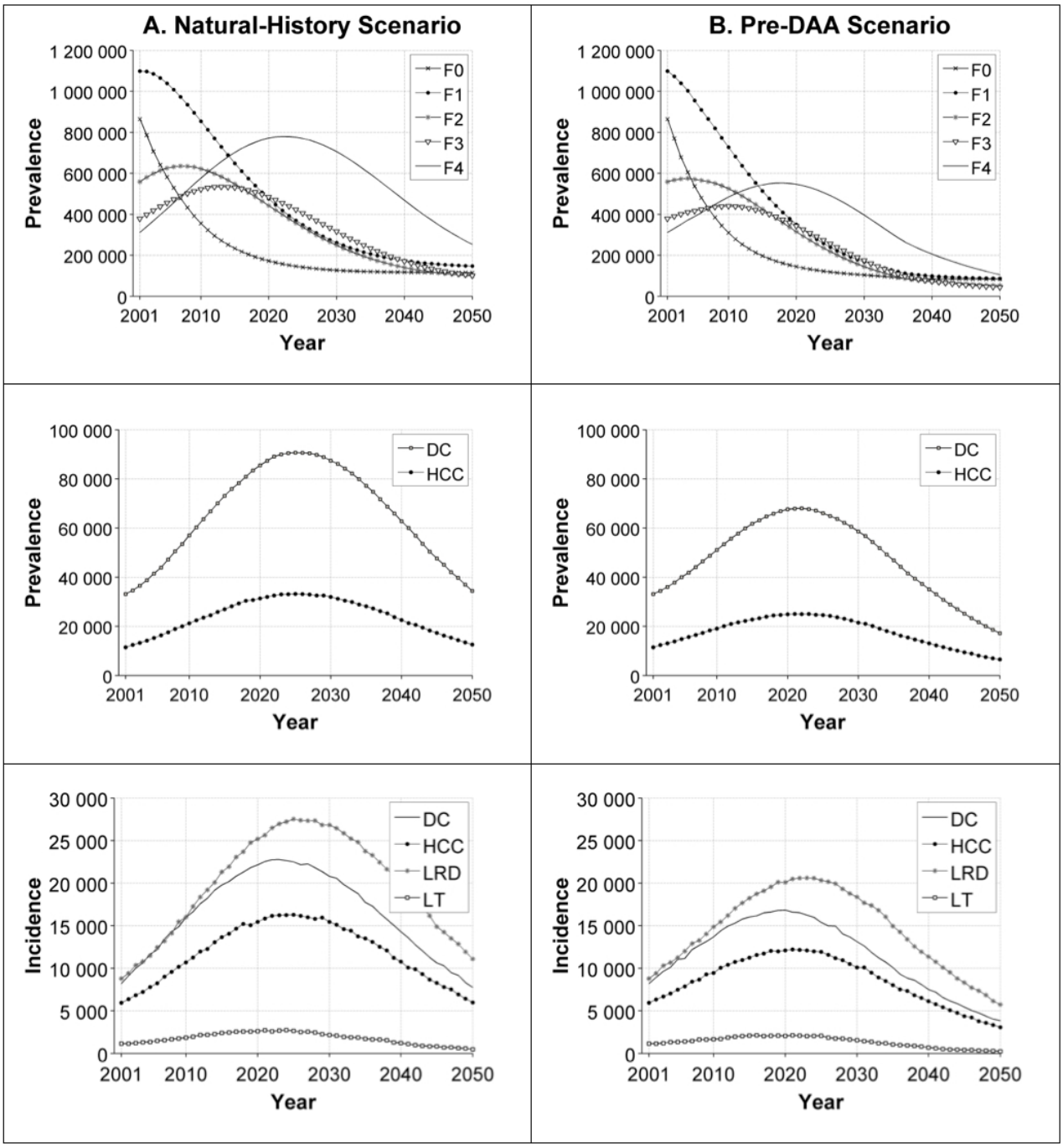








Supplement Figure 1. **Treatment options with the existing and future drugs for patients with (A): HCV genotype 1; (B): HCV genotype 2; (C): HCV genotype 3; (D): HCV genotypes 4–6.** HCV = hepatitis C virus; F0 = METAVIR stage for no fibrosis; F1 = METAVIR stage for portal fibrosis without septa; F2 = METAVIR stage for portal fibrosis with few septa; F3 = METAVIR stage for numerous septa without cirrhosis; F4 = METAVIR stage for cirrhosis; SVR = sustained virologic response; PEG-RBV = peginterferon and ribavirin; BOC/TEL+PR = boceprevir or telaprevir plus peginterferon and ribavirin; G1 = genotype 1; G2 = genotype 2; G3 = genotype 3; G4/5/6 = genotypes 4–6; Wave 1 = new therapies launched in 2014 for all patients that increased treatment response rates to 90% in non-cirrhotic patients and 60%–80% in cirrhotic patients; Wave 2 = future therapies that we assumed would be launched in 2017 and increase treatment response rates to 90% in cirrhotic patients.



Supplement Figure 2. **Model results according to the natural-history (column A) and the pre-DAA (column B) scenarios from 2001 to 2050.** Row 1: the prevalence of fibrosis stages; Row 2: the prevalence of DC and HCC; Row 3: the incidence of DC, DCC, LRD, and LT. Note: The results of the natural-history and pre-DAA scenarios are presented in Supplement Figure 2. Natural history = simulation scenario with no screening and no treatment; Pre-DAA = simulation scenario with risk-based screening and peginterferon and ribavirin treatment; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; LRD = liver-related deaths; LT = liver transplants; DAA = direct-acting antiviral agent.

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