COMPUTER SIMULATIONS IN HEALTH POLICY: METHODOLOGY AND APPLICATIONS IN THE MANAGEMENT OF CHRONIC DISEASES

by

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ABSTRACT

Among the main challenges of public-health policy makers is reducing gaps in the delivery of care, given limited human and monetary resources. In a public health setting, decision-analysis tools such as simulation models can be used to inform decision-makers in answering what-if policy questions in order to improve public health and clinical practice, optimize resource allocation, or guide funding and reimbursement decisions. Of the main public-health challenges in the United States is the burden of chronic infectious diseases. The prevalence and associated cost of chronic infectious diseases, such as hepatitis C virus (HCV) and sexually transmitted diseases (STDs) has increased in the United States due to rising life expectancy and social changes. Many of these diseases have effective therapies, but there are gaps in research on effective mitigation strategies. The public health significance of this dissertation was to apply rigorous decision-sciences methods using computer simulations in health services research and to expand the application of existing methods to answer real-world questions in health policy of chronic infectious diseases.

In the first section of this dissertation, I quantified the effects of new HCV therapies and updated screening guidelines on the burden of HCV and associated disease outcomes in the United States using an individual-level state-transition microsimulation model. The second section of this dissertation, estimated the status of HCV disease burden and the potential budget impact of various

treatment strategies in the Pennsylvania Medicaid population using the HCV microsimulation model that was calibrated to Pennsylvania Medicaid according to the claims data from 2007–2012. The last section of this dissertation, included the development and maintenance of sexual partnership networks using an agent-based simulation modeling approach, according to serial cross-sectional data obtained from the 2007–2014 National Health and Nutrition Examination Survey. This study provides a tool for understanding the dynamics of sexual partnership networks which is critical to improve the impacts of STD mitigation strategies that focus on the sexual behaviors of individuals. In conclusion, this dissertation provided the details of two computer-simulation applications in health-related multi-disciplinary policy research, and delivers insights on how to use computer simulation in medical decision-sciences and policy problems.

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PREFACE

I dedicate my dissertation work to my parents, Ali and Minoo, for their unconditional love and words of encouragement, and to my beloved husband, Kai, for his endless support, kindness, and patience. You have been my best cheerleader! I also dedicate this dissertation to my many friends who have supported me throughout this journey.

1.0 INTRODUCTION

Among the main challenges of public-health policy makers is reducing gaps in the delivery of care, given limited human and monetary resources. In a public health setting, decision-analysis tools such as simulation models can be used to inform decision-makers in answering what-if policy questions in order to improve public health and clinical practice, optimize resource allocation, or guide funding and reimbursement decisions. The objectives of this research were to apply rigorous decision-sciences methods in health services research and to expand the application of existing methods to answer real-world questions in health policy.

Of the main public-health challenges in all countries including the United States is the burden of chronic infectious diseases. The prevalence and associated cost of chronic infectious diseases has increased in the United States due to rising life expectancy and social changes. Many of these diseases such as hepatitis C virus (HCV) and sexually transmitted diseases (STDs) have effective therapies, but there are gaps in research on effective mitigation strategies. In my dissertation, I chose to focus on two simulation-modeling approaches in order to discuss policy decisions around HCV-infected population and the study of sexual networks for STDs.

The first dissertation paper, titled “The Changing Burden of Hepatitis C Virus Infection in the United States: Model-Based Predictions [1],” focused on the effects of new HCV therapies and updated screening guidelines on the burden of HCV and associated disease outcomes in the United States. This individual-level state-transition microsimulation models HCV disease progression,

treatment and screening of the infected population starting in 2001 and was validated with several published studies. The results of this paper showed that HCV currently affects around 2.3 million individuals. With existing treatment rates, HCV could become a rare disease in the next 22 years. New therapies for HCV infection and widespread implementation of screening and treatment will play an important role in reducing the burden of HCV disease. More aggressive screening recommendations are also needed to identify a large pool of infected patients.

In the second dissertation paper, "Estimating the Prevalence and Economic Burden of Hepatitis C in Pennsylvania Medicaid Using Simulation Model [2]," I estimated the number of people infected with HCV, the prevalence of HCV genotypes, the distribution of disease severity, and the potential budget impact of various treatment strategies for HCV in the Pennsylvania Medicaid population using Pennsylvania Medicaid claims data from 2007–2012 and a microsimulation model. In this research, I used the results of claims data analysis to calibrate and validate the HCV microsimulation model developed in Paper 1. This model was then used to project the future prevalence and economic burden of HCV in Pennsylvania Medicaid.

The objective of the third dissertation paper, titled "Creating a Sexual Partnership Network in an Agent-Based Modeling Platform Using Survey Data" was to develop an agent-based simulation model to construct a sexual partnership network of individuals, as a tool to investigate future mitigation strategies targeting STDs. The main innovative component of this model was the development of a social network through which the disease transmits, according to serial cross-sectional survey data of sexual behaviors. In this research, I instantiate and maintained a heterosexual partnership network according to data obtained from the National Health and Nutrition Examination Survey (NHANES) and by defining the characteristics of sexual behaviors

for agents (individuals) in the agent-based simulation model. The results of this model were then validated against NHANES sexual partnership data.

These works would be valuable in providing insights to HCV- and STD-related policy decisions. The results of HCV research would identify the gaps in national management of HCV screening and treatment, and identify key points to make HCV a rare disease earlier. The results of modeling HCV in Pennsylvania Medicaid would focus on improving the commonwealth to better provide individuals with HCV care, and inform coverage decisions. In the third paper, creating a practical basis to model the transmission of STDs in an agent-based model through sexual networks not only provides us with a tool to test STD mitigation strategies, but also a basis for the simulation of other infectious-disease transmission that depend on social interactions.

2.0 THE CHANGING BURDEN OF HEPATITIS C INFECTION IN THE UNITED STATES: MODEL-BASED PREDICTIONS

2.1 BACKGROUND

Chronic hepatitis C virus (HCV) infection is a major health problem in the United States (US) affecting 3.2 million people [3]. HCV is the leading cause of chronic liver disease and hepatocellular carcinoma (HCC) and is the leading indication for liver transplantation in the US [4]. The number of deaths from HCV in the US surpassed those from human immunodeficiency virus infection in 2007 [5]. In 2011, the economic burden associated with chronic HCV infection in the US was estimated at $6.5 billion [6].

HCV treatment has rapidly evolved over the past 2 decades. The launch of direct-acting antivirals (DAAs) in 2011 and recent availability of first all-oral HCV regimens, represent a significant shift in HCV treatment paradigm [7]. The sustained virologic response (SVR) rates for certain patients increased to 97% [8]. New treatments currently under investigation have shown potential to further increase response rates, decrease treatment duration, and improve side effect profiles. These therapies are being studied as combinations of DAAs, with and without ribavirin and interferon [9, 10].

In addition to advances in treatment, key changes in HCV screening recommendation have taken place. The Centers for Disease Control and Prevention (CDC) and the US Preventive Services Task Force (USPSTF) expanded their HCV screening recommendation to include 1-time screening for anyone born between 1945 and 1965 [11, 12]. Modeling studies have shown that this screening strategy can be cost-effective and can reduce the burden of HCV disease [13-15].

Finally, the Patient Protection and Affordable Care Act might facilitate the implementation of recommended HCV screening strategies and the link to care and treatment [16].

The launch of DAAs along with the combination of the new screening recommendations are collectively expected to substantially reduce the burden of HCV in the US; however, the effect of these changes has not yet been quantified. Previous studies did not project the burden of HCV infection under these changing dynamics but instead limited the studies' analyses to the old standard of care (SOC)—peginterferon and ribavirin (PEG-RBV) without HCV screening [6, 17]—or evaluated only the cost-effectiveness of HCV screening without projecting the changing burden of HCV [13, 18, 19]. Finally, the effect of limited treatment capacity on the burden of HCV disease also has not been studied. Our objective was thus to project the burden of HCV disease in the US by considering recent therapeutic advances, treatment capacity, and the implementation of a 1-time birth-cohort or universal screening.

2.2 METHODS

2.2.1 HCV-Infected Population Characterization

We developed an individual-level state-transition model [20] that simulated the HCV-infected population of the US from 2001 to 2050. We used a nationally representative distribution of patients' age, gender, HCV awareness status, HCV genotype, stage of disease, and treatment history, using data from the National Health and Nutrition Examination Survey (NHANES, 1999–2002) and published clinical studies (**Table A. 1**) [13, 17, 21-24]. We added new HCV infections in the model based on the annual new HCV infections reported by the CDC (**Table A. 2**) [25].

Each newly infected patient was added as an acute case that could progress to the chronic phase [21]. Patients could become aware of their HCV status in the course of disease progression (**Table A. 3**). At any given time, patients occupied one of the health states (**Figure 2.1**), and could transition to another state with a predefined probability depending on their current state (**Table A. 4**).

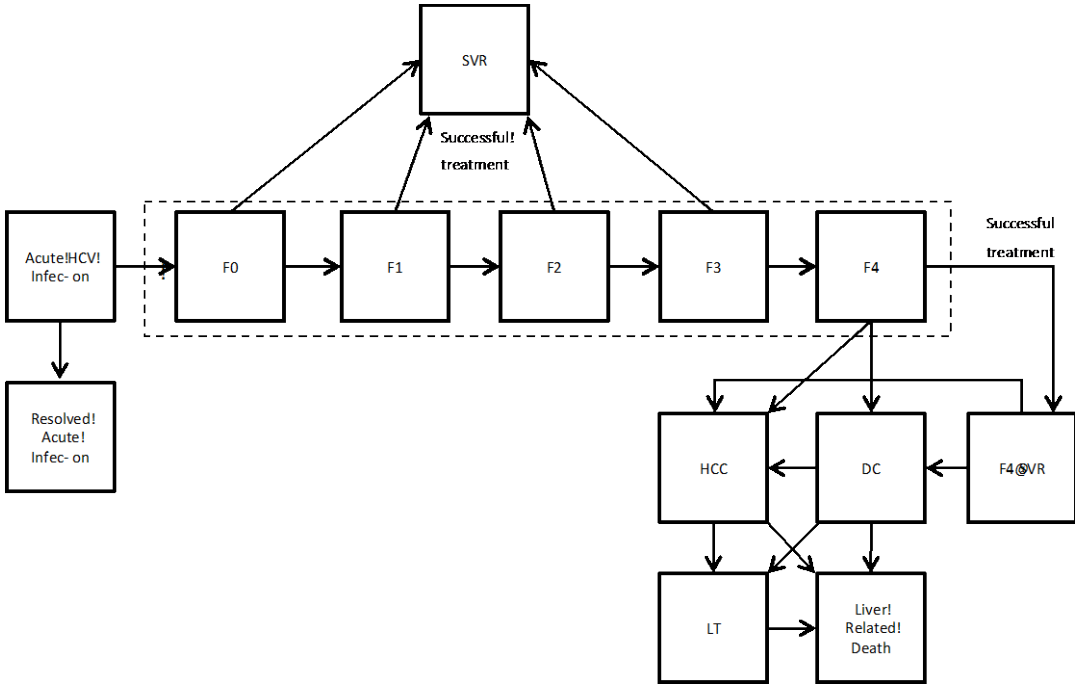


Figure 2.1. State-transition diagram showing states of the hepatitis C disease-burden model.

At any given time, a patient is represented by one of the health states, which are shown by squares. Arrows between states represent possible transitions based on annual probabilities (**Table A. 1**). Patients who are successfully treated transition to the "SVR" state. Patients who achieve SVR from F0–F3 states are assumed to be cured; however, F4 patients after a successful treatment transition to "F4-SVR" state and they could develop further complications. Patients in HCC, DC, and LT have a higher mortality than the general population, therefore can transition to "Liver-Related Death" state. All other patients have the same mortality risk as the general population.
Abbreviations: HCV = hepatitis C virus; F0 = METAVIR stage for no liver 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; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; LT = liver transplant. Note: the probability of death from other causes exists in every state, but deaths from other causes are not shown in this figure.

2.2.2 Natural History of HCV

The chronic phase of the infection was defined using the METAVIR scoring system: no fibrosis of the liver (F0), portal fibrosis without septa (F1), portal fibrosis with few septa (F2), numerous septa without cirrhosis (F3), and cirrhosis (F4). Patients could further progress to decompensated cirrhosis (DC) or to HCC, receive a liver transplant, or die from liver-related complications (**Figure 2.1**). The model assumed a liver-transplantation age limit of 75 years [26]. All disease progression probabilities are presented in **Table A. 1**. Patients who achieved SVR in F0–F3 states were assumed to be cured of HCV; however, those who achieved SVR in F4 state could further progress to DC and/or HCC, though at a slower rate than HCV-infected patients.

2.2.3 Simulation Scenario: Current Clinical Practice

We simulated the current clinical practice as our base case, i.e., 1-time birth-cohort HCV screening starting in 2013 and treatment with PEG-RBV or PI-based triple therapy before 2014, sofosbuvir- and simeprevir-based therapies starting in 2014, and future drugs as they become available.

We implemented 1-time birth-cohort HCV screening of people born between 1945 and 1965 that detected unaware prevalent cases. We also included risk-based screening under this scenario. We assumed that 91% of these patients would accept screening and 90% of those who tested positive would receive those results [13]. We assigned the uptake of screening such that the majority of these patients would receive screening gradually during 5 years beginning in 2013.

We estimated that 80% of the patients aware of their HCV status would initiate HCV treatment [13, 27-30]. Treatment regimens were assigned based on patients' prior treatment

history, HCV genotype, contraindication to interferon, and the standard-of-care at the time of treatment.

For genotype 1 patients, we assigned PEG-RBV during 2001–2011, followed by a combination of a first-generation protease inhibitor (PI)—boceprevir or telaprevir, and PEG-RBV in 2012–2013. For non-genotype 1 patients, we assigned PEG-RBV during the entire period of 2001–2013. We assumed that the patients who failed PEG-RBV treatment could be retreated at most once with PEG-RBV or PI-based therapy. We also assumed that patients who failed PI-based therapy were not eligible for retreatment with the same drug class.

On the basis of recently published evidence, we expect higher treatment response rates in all patients after 2013 owing to the availability of new therapies, albeit at different intervals [31-43]. Therefore, we assumed that these therapies could be divided into 2 major waves on the basis of therapy availability, cure rates and target populations (**Table 2.1**). We assumed that during 2011–2013, 75% of the eligible patients with mild fibrosis (F0–F2) and 25% of the eligible patients with bridging fibrosis (F3) waited for newer therapies [44].

Table 2.1. Estimated Effectiveness of Treatment for Hepatitis C in the United States from 2001 to 2050.

Treatment history / Genotype	HCV state	PEG-RBV	BOC/TEL+PR	Wave 1 (2014)	Wave 2 (2017)	Reference
Naïve						
Genotype 1						[32, 37-39, 43, 45-52]
	F0–F2	0.54	0.75	0.90	--	
	F3	0.54	0.62	0.90	--	
	F4	0.36	0.62	0.80	0.90	
Genotype 2						[46, 53-55]
	F0–F3	0.82	--	0.90	--	
	F4	0.64	--	0.80	0.90	
Genotype 3						[46, 53, 54, 56]
	F0–F3	0.70	--	0.90	--	
	F4	0.49	--	0.80	0.90	
Genotype 4/5/6						[46, 50, 57]
	F0–F3	0.58	--	0.90	--	
	F4	0.32	--	0.80	0.90	
Relapser						
Genotype 1						[22, 31, 34, 38, 39, 49, 52, 55, 58, 59]
	F0–F2	0.27	0.87	0.90	--	
	F3	0.27	0.85	0.90	--	
	F4	0.13	0.84	0.80	0.90	
Genotype 2						[23, 55, 60, 61]
	F0–F3	0.71	--	0.90	--	
	F4	0.56	--	0.70	0.90	
Genotype 3						[23, 56, 60, 61]
	F0–F3	0.66	--	0.85	--	
	F4	0.52	--	0.60	0.90	
Genotype 4/5/6						[23, 46, 50, 57]
	F0–F3	0.31	--	0.90	--	
	F4	0.24	--	0.75	0.90	
Partial responder						
Genotype 1						[22, 31, 34, 38, 39, 49, 52, 55, 58, 59]
	F0–F2	0.18	0.72	0.90	--	
	F3	0.18	0.56	0.90	--	
	F4	0.10	0.34	0.75	0.90	
Genotype 2						[23, 55, 60, 61]
	F0–F3	0.69	--	0.90	--	
	F4	0.55	--	0.70	0.90	
Genotype 3						[23, 56, 60, 61]
	F0–F3	0.64	--	0.85	--	
	F4	0.51	--	0.60	0.90	
Genotype 4/5/6						[23, 46, 50, 57]
	F0–F3	0.31	--	0.90	--	
	F4	0.24	--	0.75	0.90	
Null responder						
Genotype 1						[22, 31, 34, 38, 39, 49, 52, 55, 58, 59]
	F0–F2	0.10	0.41	0.90	--	
	F3	0.10	0.39	0.90	--	
	F4	0.05	0.14	0.75	0.90	

Table 2.1 continued

Treatment history / Genotype	HCV state	PEG-RBV	BOC/TEL+PR	Wave 1 (2014)	Wave 2 (2017)	Reference
Genotype 2						[23, 55, 60, 61]
	F0–F3	0.54	--	0.90	--	
	F4	0.42	--	0.70	0.90	
Genotype 3						[23, 56, 60, 61]
	F0–F3	0.50	--	0.85	--	
	F4	0.39	--	0.60	0.90	
Genotype 4/5/6						[23, 46, 50, 57]
	F0–F3	0.31	--	0.90	--	
	F4	0.24	--	0.75	0.90	
Contraindicated with modifiable reasons						
Genotype 1						[22, 32, 38, 49, 55] - expert opinion
	F0–F2	--	--	0.90	--	
	F3	0.43	0.50	0.90	--	
	F4	0.28	0.36	0.70	0.90	
Genotype 2						[55, 60] - expert opinion
	F0–F3	0.66	--	0.90	--	
	F4	0.51	--	0.70	0.90	
Genotype 3						[56, 60, 61] - expert opinion
	F0–F3	0.56	--	0.90	--	
	F4	0.40	--	0.60	0.90	
Genotype 4/5/6						[57] - expert opinion
	F0–F3	0.46	--	0.90	--	
	F4	0.26	--	0.70	0.90	
Contraindicated with non-modifiable reasons						
Genotype 1/2/4/5/6						[32, 38, 55, 60] - expert opinion
	F0–F3	--	--	0.90	--	
	F4	--	--	0.70	0.90	
Genotype 3						[56, 60, 61] - expert opinion
	F0–F3	--	--	0.90	--	
	F4	--	--	0.60	0.90	
Failed triple therapy						
Genotype 1						[49] - expert opinion
	F0–F3	--	--	0.95	--	
	F4	--	--	0.75	0.90	

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; Relapser = a patient whose HCV RNA became undetectable during treatment with PEG-RBV, but reappeared after the end of treatment; Partial responder = a patient whose HCV RNA level decreased by 2 log IU/mL or more at week 12 of treatment with PEG-RBV, but was detectable at week 24; Null responder = a patient whose HCV RNA level decreased less than 2 log IU/mL at week 12 of treatment with PEG-RBV; Contraindicated with modifiable reasons = a patient who had contraindications to regiments that included pegylated interferon and ribavirin such as anemia, depression, and substance abuse, that were modifiable by medical or psychiatric interventions; Contraindicated with non-modifiable reasons = a patient who had contraindications to regiments that include pegylated interferon and ribavirin such as autoimmune disease, coronary artery disease, retinopathy, etc., that were not modifiable by medical or psychiatric interventions; Failed triple therapy = a patient whose HCV RNA level detectable after the treatment with boceprevir or telaprevir combined with a first-generation protease inhibitor.

* The SVR rates were either derived directly from the references or were indirectly inferred on the basis of the mentioned references.

Table 2.1 continued

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; PEG-RBV = peginterferon and ribavirin; BOC/TEL+PR = boceprevir or telaprevir plus peginterferon and ribavirin.

Wave 1 of new treatments was assumed to start in 2014; we also assumed that with Wave 1 the SVR rates would increase up to 90% in the groups of genotype 1–6 non-cirrhotic patients (**Table 2.1**). Though the reported SVR rates were as high as 97% in some patients, we used a conservative estimate of 90% in some patients to account for lower SVR rates in real-life [62]. The first wave included therapies for genotype 1–6 cirrhotic patients as well, but we assumed that the response rates among these would still remain suboptimal (**Figure A. 1**) [60]. We assumed that Wave 2 of treatment would begin in 2017 and increase the response rates up to 90% in all patients. We included the retreatment of patients who failed PEG-RBV or PI-based therapy before 2014 with Wave 1 or Wave 2 therapies. The SVR rates by treatment history, genotype, fibrosis stage, and interferon contraindication are presented in **Table 2.1** and Appendix. **Figure A. 1** illustrates the treatment used for each category of patients at different time intervals.

Since it is impracticable to treat all HCV-infected patients within a year, we introduced an annual constraint on the number of people who could access HCV treatment. Our rationale was to model the effect of limited treatment uptake as well as limited resources (budget, physicians, etc.) available to treat all eligible patients. For our base case, we used historic data to determine the national treatment uptake [63] and performed sensitivity analyses.

2.2.4 Simulation Scenario: Ideal Case

We simulated the effect of a hypothetically ideal scenario that represented an upper limit of the benefits that could be achieved by ongoing advancements in therapies and policy-level changes. We simulated best possible combination of 1-time universal screening in all adults, adoption of new drugs as they become available and unlimited treatment capacity. We distributed the uptake of screening proportionally over the period of 5 years beginning 2013.

2.2.5 Simulation Scenario: Pre-DAA and Natural-History

For the purpose of estimating the incremental benefits of therapeutic advancements and policy-level changes, we simulated two comparator scenarios: Pre-DAA scenario and natural-history scenario. The Pre-DAA scenario represented screening and treatment practice until the launch of DAAs. It simulated HCV treatment with PEG-RBV only, from 2001 onwards, with risk-based screening only. The natural-history scenario simulated the HCV disease burden under no screening and no treatment. The characteristics of each simulation scenario are presented in **Table 2.2**.

Table 2.2. Default Characteristics of the Scenarios in Our Model of Hepatitis C Disease Burden in the United States, from 2001 to 2050.

Scenario	Characteristics		
	HCV treatment (time period)	**Screening**	**Treatment capacity**
Natural history	No treatment	No screening	N/A
Pre-DAA	PEG-RBV (2001–2050)	Risk-based	Variant based on historic data (2001–2007) Constant at 83 270 (2008–2050)
Base case	PEG-RBV (2001–2011) BOC/TEL+PR (2012–2013) Wave 1 (2014–2016) Wave 2 (2017–2050)	Risk-based and Birth-cohort	Variant based on historic data (2001–2007) Constant at 83 270 (2008–2050)
Ideal	PEG-RBV (2001–2011) BOC/TEL+PR (2012–2013) Wave 1 (2014–2016) Wave 2 (2017–2050)	Universal	Unlimited treatment capacity

Natural history = simulation scenario with no screening and no treatment; 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.
HCV = hepatitis C virus; PEG-RBV = peginterferon and ribavirin; BOC/TEL+PR = boceprevir or telaprevir plus peginterferon and ribavirin; DAA = direct-acting antiviral agent; 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.

2.2.6 Model Outcomes

We projected the prevalence of HCV from 2001 to 2050. In addition, we projected the prevalence and incidence of early stages of HCV—fibrosis scores F0–F4, advanced stages of disease—DC, HCC, and the number of liver-transplants and liver-related deaths.

2.2.7 Model Validation

Using the model outcomes from 2001 to 2013, we validated our model with several published studies. First, we compared the predicted prevalence of HCV with a recently published

NHANES 2003–2010 study [64]. Second, we compared the predicted incidence and prevalence by stages of HCV disease with published studies and CDC reports [17, 22, 65-67]. Third, we compared our model's natural history of HCV with the results of a multicenter follow-up study of patients with advanced fibrosis [68]. Finally, we cross-validated our model with earlier modeling studies [6, 17] by comparing the results of the natural-history and pre-DAA scenarios.

2.2.8 Sensitivity Analyses

We tested the effect of the SVR rates, the timing of the availability of future therapies, treatment capacity, patients' decision to wait for new drugs, and changing annual HCV incidence on the burden of HCV disease. We performed deterministic sensitivity analyses on the natural history parameters of HCV and patient characteristics (**Table A. 4–5**).

We also evaluated the effect of treatment capacity on HCV disease burden by simulating 4 scenarios: (1) increased treatment capacity by 10% after the launch of DAAs in 2012 and additional increased capacity by 50% after the launch of new therapies in 2014; (2) increased capacity by 10% in 2012 but decreased by 20% after the launch of new therapies in 2014 due to high drug cost; and (3) unlimited treatment capacity (**Table A. 6**).

2.3 RESULTS

2.3.1 Validation

Our model projected that the average number of chronic HCV cases in 2003–2010 were 2.7 million, which is equal to the reported values in NHANES 2003–2010 study [64] (**Table A. 7**). The projected average prevalence of HCC in 2001–2004 was within 3% of the reported values [65]. The incidence of HCC and liver-related deaths in 2005 were within 1–15% of the reported values [22]. The projected distribution of different stages of chronic HCV closely matched that of another modeling study [17]. Finally, our model's 10-year cumulative incidence rates of DC, HCC, and combined liver-related mortality and liver transplants closely matched the results of a recently published multicenter follow-up study (**Table A. 8**) [68].

2.3.2 HCV Disease Burden

Our model projected that the chronic HCV cases in the US decreased from 3.2 million in 2001 to 2.3 million in 2013 (**Figure 2.2**). From 2001 to 2013, 157 300 HCV-infected people died because of liver-related complications, 415 000 died because of other reasons, and 589 100 achieved SVR. During the same period 251 000 new people got chronically infected with HCV. Considering the population growth in the US [69], we projected that HCV would become a rare disease by 2036, i.e. affecting about 1 in 1500 people [70]. Under the ideal scenario, HCV could become a rare disease by 2026.

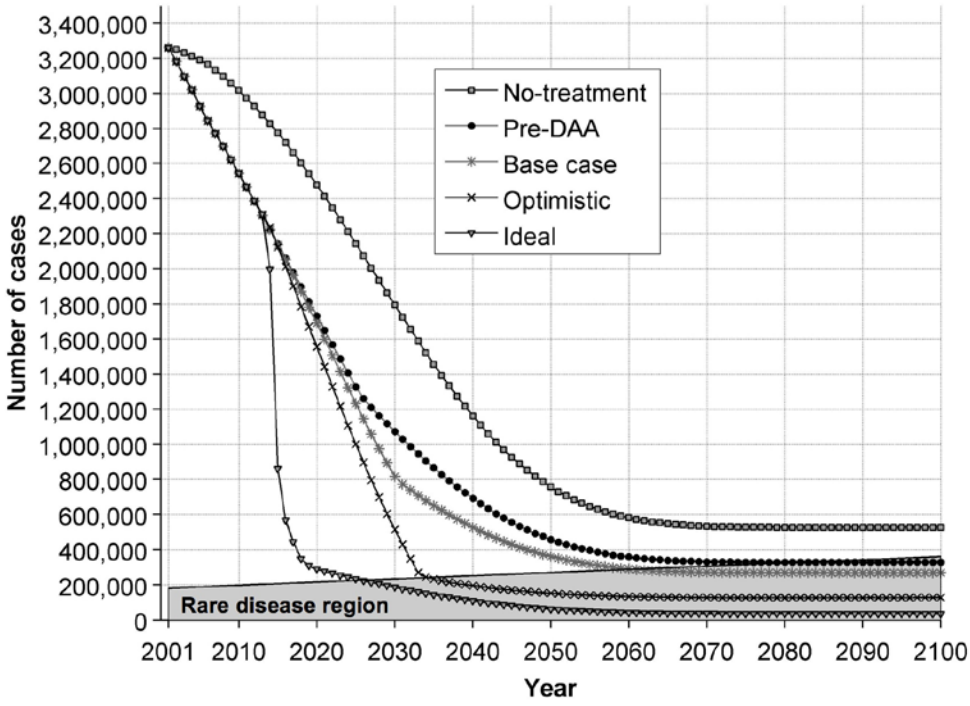


Figure 2.2. The estimated prevalence of chronic hepatitis C virus cases in the United States from 2001 to 2050 under different simulation scenarios.

The rare-disease region is calculated based on the definition of a rare disease, and adjusted to the United States population. Based on the Rare Disease Act of 2002 [68], a rare disease affects about 1 in 1500 people. The rare-disease region is increasing with time because of population growth. Natural history = simulation scenario with no screening and no treatment; 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 1-time 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.

In 2001, 682 400 people were chronically infected with HCV who were born between 1945 and 1965 and unaware of their disease. However, by 2013, only 531 200 HCV infected patients (24% of the total HCV infection in the US) were eligible for birth-cohort screening, i.e., unaware of their disease status and still between fibrosis scores F0–F4. The implementation of 1-time birth-cohort screening beginning 2013 is expected to identify 487 000 additional HCV cases in this cohort in the next 10 years.

Under the base-case scenario, our model projected that the prevalence of DC and HCC, and liver-related deaths will reach their peak values during 2019–2020 and start declining afterwards (**Figure 2.3**).

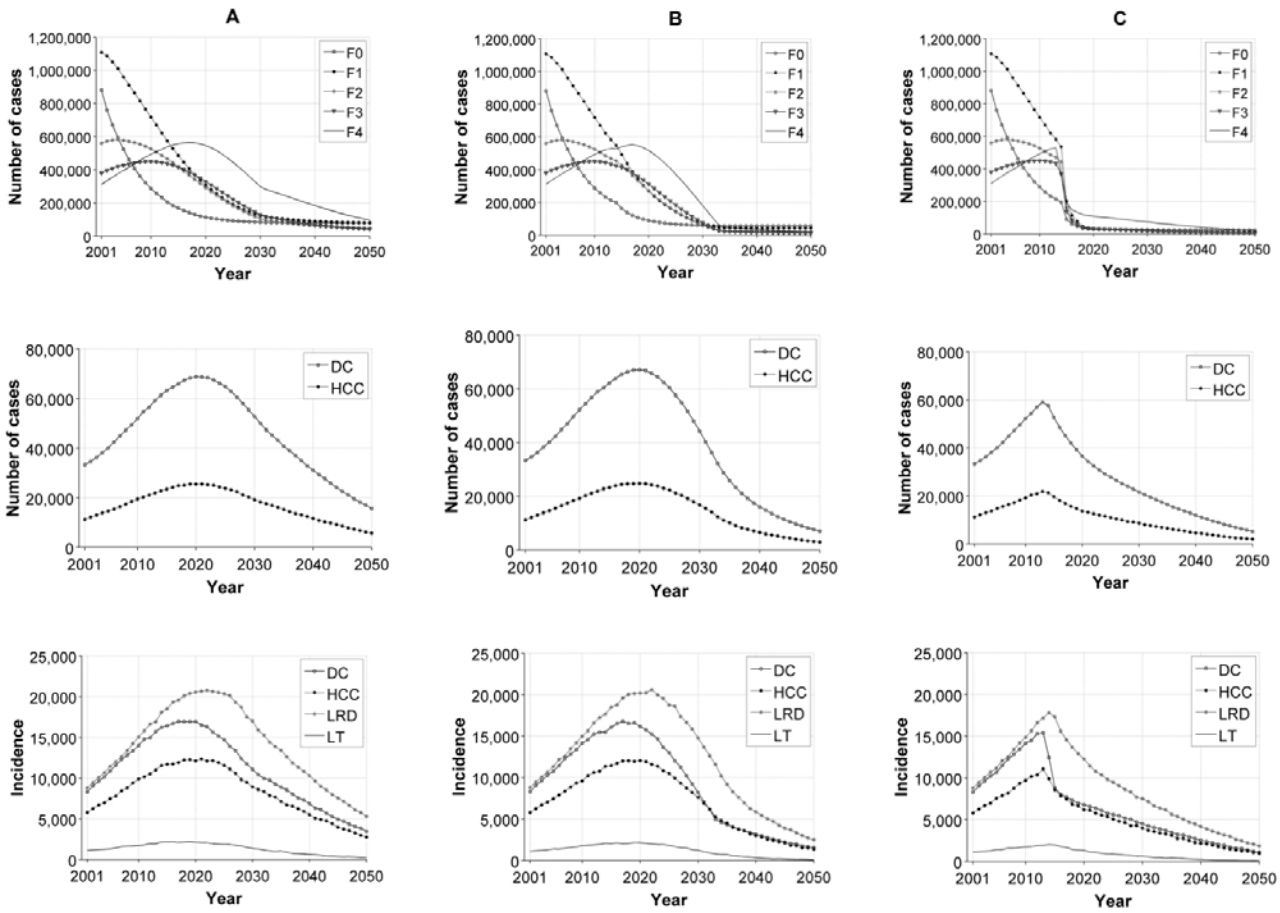


Figure 2.3. Model results according to the base-case scenario (column A) and the ideal scenario (column B) of hepatitis C disease burden in the United States from 2001 to 2050.

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 **Figure A. 2**. Natural history = simulation scenario with no screening and no treatment; 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. Abbreviations: DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; LRD = liver-related deaths; LT = liver transplants; DAA = direct-acting antiviral agent.

2.3.3 Ideal Scenario

Under the ideal scenario, HCV can become a rare disease by 2026, i.e. 10 years earlier than that with the base case (**Figure 2.2**). The implementation of 1-time universal screening could identify 933 700 HCV cases in the next 10 years. Compared with the base case (current clinical practice), ideal scenario could reduce the total number of DC cases, HCC cases, liver-related deaths, and liver-transplants by 135 800 (46%), 96 300 (40%), 161 500 (37%), and 13 900 (37%), respectively during 2014–2050 (**Table 2.3**).

2.3.4 Pre-DAA Scenario

Under the Pre-DAA scenario, HCV did not become a rare disease. Compared with the base-case, Pre-DAA scenario would have increased the number of DC cases, HCC cases, liver-related deaths, and liver-transplants by 124 200 (30%), 78 700 (25%), 126 500 (23%), and 9900 (21%), respectively, during 2014–2050 (**Table 2.3**).

Table 2.3. Estimated Effect of Each Scenario on the Outcomes of Advanced-Stage Hepatitis C Outcomes According to Our Model of Hepatitis C Disease Burden in the United States from 2014 to 2050.

		Scenario		
Advanced-stage disease outcomes	**Natural history**	**Pre-DAA**	**Base case**	**Ideal**
Decompensated cirrhosis				
Cumulative incidence (2014–2050)	647 000	418 100	293 900	158 100
Peak annual prevalence	90 700	68 000	62 700	56 000
Year of peak annual prevalence	2025	2022	2019	2014
Peak annual incidence	22 800	16 800	15 300	12 000
Year of peak annual incidence	2023	2020	2014	2014
Hepatocellular carcinoma				
Cumulative incidence (2014–2050)	473 000	318 900	240 200	143 900
Peak annual prevalence	33 200	25 000	23 200	20 800
Year of peak annual prevalence	2025	2021	2019	2014
Peak annual incidence	16 300	12 200	11 400	9 500
Year of peak annual incidence	2025	2021	2019	2014
Liver-related deaths				
Total deaths (2014–2050)	811 600	560 100	433 600	272 100
Peak annual deaths	27 500	20 600	19 300	17 500
Year of peak annual deaths	2025	2023	2020	2014
Liver transplants				
Total transplants (2014–2050)	67 100	47 800	37 900	24 000
Peak annual liver transplants	2700	2100	2100	2000
Year of peak annual liver transplants	2024	2021	2016	2014

Natural history = simulation scenario with no screening and no treatment; 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.

2.3.5 Sensitivity analyses

We evaluated the effect of increased treatment capacity on the burden of disease (**Table A. 6**). Compared to the base case, 10% increase in treatment capacity in 2012 and 50% increase beyond 2014 (Scenario 1) would reduce the number of DC, HCC, liver-related deaths and liver transplants by 9–14%. Whereas, 20% decrease in treatment capacity beyond 2014 (Scenario 2) would increase the corresponding adverse outcomes by 16–22%. Compared to the base case,

unlimited treatment capacity from 2014 onwards (Scenario 3) would prevent 128 800 DC, 91 000 HCC, and 153 200 liver-related deaths and 13 400 liver transplants.

When the SVR rates of the available and future drugs were reduced by 10%, the cumulative incidence of DC and HCC, and liver-related deaths and liver transplants increased by 4% to 23%, depending on the simulation scenario (**Table A. 9**). Delayed or early launch of Wave 2 of HCV therapies did not substantially change the disease burden (**Table A. 10**). In addition, we found that the results were not sensitive to the percentages of patients in F0–F3 who might choose to wait for future therapies instead of initiating treatment with PI-based therapies (**Table A. 11**). Among the natural-history parameters, we found that the probability of developing DC and HCC in cirrhotic patients had the greatest effect on the disease burden.

We also performed a sensitivity analysis on the prevalence of HCV. Assuming 4.9 million people were infected with HCV in 2001 which was the 95% CI upper limit NHANES 1999–2002 estimate [21], the cumulative incidence of DC, HCC, and liver-related mortality increased by 23–25% in comparison with the base-case scenario (**Table A. 12–13**). Finally, we evaluated the impact of decreasing and increasing annual HCV incidence and found no substantial effect on the outcomes (**Table A. 14**).

2.4 DISCUSSION

Our model estimated that 2.3 million people were chronically infected in the beginning of 2013, as compared with 3.2 million people in 2001. With the implementation of birth-cohort screening and the availability of highly effective new therapies, HCV could become a rare disease

by 2036. In addition, these changes could substantially decrease the overall clinical burden associated with HCV in the US.

Our study also identified trends in the HCV disease burden that have not been previously reported. As corroborated by recently published NHANES 2003–2010 data [64], we estimated that the current number of chronic HCV cases in the US is actually lower than the commonly reported 3.2 million estimate. The HCV prevalence decreased mainly because of deaths and successful treatments in this cohort. Also, our model projected that fewer patients are eligible for birth-cohort screening than estimated in a previously published study [13]. Our results differed because we accounted for the possibility that birth-cohort patients progressed beyond cirrhosis or became aware of their disease before the implementation of screening in 2013.

Our study underscores the need for more aggressive screening strategies and higher treatment capacity to further reduce the burden of HCV. Birth-cohort screening, though impactful, would fail to identify a large pool of existing HCV patients who could advance to severe disease stages without treatment. In addition, the number of patients who are able to receive treatment greatly affects the potential disease burden. This number is dependent on the treatment capacity, availability of new drugs, treatment cost, and insurance coverage. With the launch of all-oral drugs that can simplify treatment, primary care physicians or infectious disease specialists also may take on the role of treating HCV patients, thus alleviating the burden on specialists [71]. In addition, programs like the Extension for Community Healthcare Outcomes can further help to increase the treatment capacity by improving access to care for underserved populations [72]. However, the high price of new therapies could become a barrier to timely HCV treatment, thus inhibit the full potential of therapeutic advances and screening recommendations [73].

Our study has several limitations. The historic number of HCV cases in the model is based on NHANES 1999–2002 data that underestimate the prevalence of HCV in the US by excluding the institutionalized population. However, we tested its effect on the future HCV burden in a sensitivity analysis. Second, we estimated the total patients who received treatment from drug prescription data reported by insurance companies [63], which may underestimate the number of patients who got treated. Third, our model does not account for co-infections and other risk factors, such as alcohol consumption, that affect disease progression [74, 75]. These limitations may have resulted in an underestimation of the projected burden of HCV disease. Fourth, we do not consider the potential effect of treatment on disease transmission. Although improved treatment would be expected to decrease HCV transmission, new cases are a very small proportion of the existing HCV cases.

Information about SVR rates and the launch time of new therapies is limited. Our SVR rates were based on results from several phase 2 and 3 clinical studies, but the real-life SVR rates may be different. Our assumptions about the launch time of new therapies were based on the end dates of clinical trials. Finally, due to the lack of knowledge in the retreatment of patients who will fail recently approved and future therapies, the analysis of the retreatment of these patients is beyond the scope of our analysis.

In conclusion, we evaluated the effect of the launch of DAAs, recently approved and other potential future therapies, and changes in HCV-screening recommendations on the future burden of HCV disease in the US. We found that with ongoing therapeutic advancements and screening policy changes, HCV could become a rare disease within the next 22 years. We also found that the current screening recommendations are helpful in decreasing the future burden of HCV, but more

aggressive recommendations should be proposed in conjunction with an increase in HCV treatment capacity.

3.0 LONG-TERM DISEASE AND ECONOMIC OUTCOMES OF PRIOR AUTHORIZATION CRITERIA FOR HEPATITIS C TREATMENT IN PENNSYLVANIA MEDICAID

3.1 BACKGROUND

Chronic hepatitis C virus (HCV) infection is a major, and costly, health problem in the United States, affecting 2.7–3.2 million people [64] with the majority unaware of their disease [6]. Beginning in 2014, interferon-free HCV therapies, such as sofosbuvir, simeprevir, ledipasvir [76], were introduced, leading to substantially improved sustained virologic response (SVR) rates – a surrogate for cure – as high as 98% [77], with shorter treatment duration and few adverse effects. However, their high prices ($40,000–$94,500 for 12-week therapy) in combination with a large number of treatment candidates translates into substantial budgetary impact for health-care payers.

The prevalence of HCV is higher among low-income populations, who are often enrolled in Medicaid [78]. Although state Medicaid programs are eligible to receive at least a 23.1% rebate off average manufacturer prices, they spent $1.1 billion on treating HCV-infected individuals in 2014 [79-81]. Pennsylvania Medicaid, which is the 5th largest Medicaid program by health expenditures and the 6th largest by enrollment in the United States [82, 83], spent about 4% of its 2014 prescription drug expenditures on sofosbuvir alone [84].

Facing high costs of treatment and operating within budgetary constraints, 36 state Medicaid programs have developed treatment authorization guidelines [85] to prioritize HCV treatment to patients with more advanced disease. These decisions have been criticized by patient advocacy groups and the Centers for Medicare and Medicaid Services [86, 87]. Nevertheless, only

seven out of these 36 states had expanded treatment to patients with mild fibrosis scores as of February 2015 [88]. Pennsylvania expanded treatment to patients with F2 fibrosis score in July of 2015 [89] and is currently considering further expansions.

State Medicaid coverage decisions are complicated by the absence of reasonable estimates of HCV prevalence. Such estimates are difficult to generate given that roughly half of patients are unaware of infection [13]. Medicaid programs also lack fibrosis scores and genotype information in their administrative data, which are required for treatment planning [83]. Additionally, the impact of Medicaid treatment strategies on long-term disease and cost outcomes is difficult to measure. Since chronic HCV is a slowly progressive disease, Medicaid's decisions could impact downstream HCV spending in Medicare once individuals reach age 65 or become dually enrolled due to disability.

Many of these challenges can be addressed with the use of simulation modeling. The objective of our study was twofold: (I) To use a well-validated national HCV simulation model to estimate the number of people currently infected with HCV in Pennsylvania Medicaid along with their disease characteristics; and (II) to use the model to project the economic and disease impact of different prior authorization criteria for treatment in Pennsylvania Medicaid.

3.2 METHODS

We used a three-step approach to address the above objectives. First, we estimated the *observed* HCV burden in Pennsylvania Medicaid using claims data from 2007–2012. Second, we adapted our previously developed and validated HCV disease burden model (HEP-SIM) [1, 90] to Pennsylvania Medicaid using claims data and other published studies. Finally, we used HEP-SIM

to estimate the disease burden (both observed and unobserved) of HCV and evaluated the long-term disease and economic impact of different prior authorization guidelines for treatment in Pennsylvania Medicaid.

3.2.1 Analysis of Pennsylvania Medicaid Claims Data

We obtained data from the Pennsylvania Medicaid program for paid claims and encounters covering services rendered in 2007–2012 for enrollees both in fee-for-service Medicaid and in Medicaid managed-care-organizations. We identified individuals diagnosed with HCV for the purposes of model validation, defined by the presence of at least one paid inpatient, outpatient or professional claim with an ICD-9 diagnosis code for HCV (**Table B. 1**). Among HCV-diagnosed individuals, we identified those with potential treatment contraindications, HCV-related complications, liver transplants and rates of HCV treatment, for use as inputs in the microsimulation model (**Appendix B.1**).

3.2.2 Microsimulation Model for Pennsylvania Medicaid

HEP-SIM has been extensively validated with the National Health and Nutrition Examination Surveys and several published data sources [1, 21, 64, 68]. The natural history of HCV in the model was defined using the Metavir scoring system for fibrosis stages: F0 for no fibrosis, F1 for portal fibrosis without septa, F2 for portal fibrosis with few septa, F3 for numerous septa without cirrhosis, and F4 for compensated cirrhosis (**Figure B. 1** and **Table B. 2** of **Appendix B.2**). Patients in the F4 stage could further progress to decompensated cirrhosis or hepatocellular carcinoma, receive a liver transplant, or die from liver-related complications.

We incorporated Pennsylvania Medicaid's population characteristics into the HEP-SIM model, including demographics, HCV incidence, new enrollments in Medicaid, HCV screening (both risk-based and birth-cohort) rate, and historic HCV treatment rate. **Appendix B.2** and **Table B. 3–4** provide detailed descriptions of model parameters and how the model was adapted to fit Pennsylvania, using a combination of prior literature, publically available data sources, and the Medicaid claims data.

3.2.2.1 Coverage Scenarios

We simulated three coverage scenarios according to different treatment authorization guidelines starting in 2014: (I) Our base-case scenario, in which HCV treatment is available to patients with a fibrosis score of F2–F4, consistent with the recent Pennsylvania Medicaid HCV treatment authorization criteria[89]; (II) the scenario to expand treatment to all diagnosed HCV patients; and (III) the scenario to limit treatment to F3–F4 patients only, consistent with the treatment authorization criteria in Pennsylvania Medicaid prior to July 2015, and in several other states.

In each scenario, we assumed that 40% of diagnosed HCV-infected individuals *who are treatment candidates* received treatment each year after 2014 - defined in our model as 'treatment penetration rate' - in order to account for limitations in provider availability and patient's preference (**Table B. 5**). Using a 40% treatment penetration rate across scenarios, we assumed that a larger number of individuals could be treated annually under F0–F4 coverage (8,200 patients) than with F3–F4 (2,500 patients). We address this assumption in more detail in the sensitivity analyses. Note that a treatment penetration rate of 40% is greater than the actual treatment rate in Pennsylvania Medicaid in 2014.

3.2.2.2 Cost

We set the weekly costs of older HCV therapies, peginterferon, ribavirin, boceprevir, and telaprevir, at $587, $309, $1100, and $4100, respectively [91]. We set the weekly costs of sofosbuvir at $7000, ledipasvir/sofosbuvir at $7875, and paritaprevir, ritonavir, ombitasvir, and dasabuvir at $6,943 [91, 92]. We applied 23% and 46% discounts to the available average wholesale drug costs in 2014 and in 2015 and beyond, respectively, according to the average reported discounts and rebates provided to health-care payers [93] (**Table B. 6**). We also included the cost of managing early and advanced stages of HCV including hepatocellular carcinoma and liver transplantation, which were obtained from prior literature (**Table B. 7**) [94, 95].

3.2.2.3 Model Outputs

We projected the temporal trends in the prevalence of HCV, number of people *aware* and *unaware* of their infection, and distribution of fibrosis scores. Since HCV is a slow-progressive disease and the benefits of HCV treatment will accrue years later, we simulated our model for a long time horizon, from 2015 to 2050. Under each coverage scenario described above, we projected the incidence of advanced liver disease, number of liver transplants, and liver-related deaths in 2015–2050. We also estimated the long-term cost of chronic HCV management until 2050. Because of variable HCV treatment costs in the future, we also estimated the short-term budget impact on Medicaid from 2015–2025.

3.2.2.4 Medicare Outputs for Transitions between Medicaid and Medicare

Since several benefits of HCV treatment will accrue after some patients have transitioned from Medicaid-only coverage to Medicare-only or dual coverage, we estimated the impact of Medicaid's coverage decisions on the disease and cost outcomes in Medicare. In all scenarios, we

assumed that patients who did not receive or failed to respond to HCV treatment in Medicaid would transition to Medicare at the age of 61, a transition age calculated according to our claims-based analyses and a published study [96]. We assumed that all patients who transitioned to Medicare, who were aware of their infection, and eligible for treatment, would receive treatment irrespective of their fibrosis score once in Medicare.

3.2.2.5 Sensitivity analyses

Using one-way deterministic sensitivity analysis, we analyzed the effect of model parameters on the incidence of advanced-stage liver diseases and budget needed for disease management and treatment costs (**Appendix B.3**). We examined the impact of expanded treatment coverage scenarios on model outcomes assuming there is a fixed maximum number of patients who can be treated in a given year (because of the number of liver specialists, availability of appointments, etc.), instead of a variable treatment penetration rate. We assessed the effect of alternative treatment penetration rates on model outcomes in the base case (F2–F4 treatment), and also added scenarios in which the expansion of treatment to F2 patients might be delayed until 2017 or 2020, instead of 2015 in the base case.

3.3 RESULTS

3.3.1 Diagnosed HCV Population in Claims Data

The number of enrollees who had a claim with one or more HCV diagnosis codes increased steadily from 18,955 (882 per 100,000) in 2007 to 26,432 (1,023 per 100,000) in 2012 (**Table 3.1**

and **Appendix B.4**). The number of enrollees who initiated medication therapy increased from 797 in 2007 to 1,025 in 2012; however, the proportion of individuals who initiated treatment during this period remained nearly constant (4%). Pennsylvania Medicaid covered twelve liver transplants performed on enrollees with HCV on average each year in 2007–2012.

3.3.2 Model Validation

The model-based estimates of the number of patients who were aware of their HCV infection in 2007–2012 matched closely the number of HCV-diagnosed enrollees in claims data (**Table 3.2**). The model predicted in 2012 a total of 49,500 patients with HCV (including those unaware/undiagnosed), with 14 liver transplants. The projected trend in the number of liver transplants from the model was comparable to the trend observed in claims data (**Figure B. 2** in **Appendix B.5**). In addition, the projected percentage of individuals with cirrhosis who were aware of their disease during 2007–2012 was within 5% of the number of enrollees diagnosed with cirrhosis in the analyses of claims data. These findings indicate that the model was appropriately calibrated to approximate the characteristics of the Pennsylvania Medicaid population.

Table 3.1. HCV-diagnosed population in the Pennsylvania Medicaid claims, 2007–2012, excluding Medicare dual eligibles.

Parameter	2007	2008	2009	2010	2011	2012
Number of hepatitis C-infected individuals	18,955	20,242	23,234	24,352	26,061	26,432
Mean age	44.7	44.9	45.0	45.4	45.8	46.3
Sex (%)						
Female	46.7	46.5	46.2	46.0	45.8	46.1
Male	53.3	53.5	53.8	54.0	54.2	53.9
Age distribution (%)						
<18	1.0	1.1	1.1	1.1	1.0	0.9
18–29	14.6	14.8	15.0	14.6	13.4	12.4
30–39	13.1	13.4	13.8	14.1	15.5	17.0
40–49	30.4	28.3	26.0	23.9	21.8	19.7
50–60	35.3	36.0	37.1	38.5	39.2	39.7
61–64	4.2	4.9	5.5	6.2	7.0	8.0
65+	1.5	1.5	1.5	1.7	2.1	2.4
Number of months enrolled in Medicaid (%)*						
<2	3.3	2.9	2.7	2.2	2.7	2.6
2-6	11.5	10.2	10.2	9.4	9.0	8.6
6+	85.2	86.9	87.1	88.5	88.3	88.7
Eligibility type (%)						
General assistance	42.5	41.7	42.0	40.9	40.0	36.8
Supplemental Security Income	43.3	44.3	44.4	45.2	47.0	49.7
Temporary assistance for needy families	14.2	14.0	13.6	13.9	13.1	13.4
Waiver	0.0	0.0	0.1	0.1	0.0	0.1
Number (%) of individuals with any interferon contraindication (substance abuse/depression)	7,302 (39%)	7,999 (40%)	9,956 (43%)	10,693 (44%)	11,771 (45%)	12,337 (47%)
Number (%) of people who initiated treatment	797 (4.2%)	863 (4.3%)	977 (4.2%)	855 (3.5%)	807 (3.1%)	1,025 (3.9%)

Source: Authors' analysis of Pennsylvania Medicaid claims data of 2007–2012.
* Enrolled during the calendar year, not the total number of months ever enrolled.

Table 3.2. Estimated prevalence of HCV infected patients in Pennsylvania Medicaid in 2007–2015 and the number of new episodes of decompensated cirrhosis, hepatocellular carcinoma, and liver transplant.

Year	HCV cases in Claims data*	Model-based HCV-infected population in Medicaid†				
	Total with diagnoses	Total aware	Total	DC incidence	HCC incidence	Liver transplants
2001	-	19,700	50,000	50	57	12
2002	-	19,600	50,000	40	43	14
2003	-	19,600	50,000	56	51	11
2004	-	19,500	49,800	70	59	9
2005	-	19,700	50,200	81	49	10
2006	-	19,900	50,000	94	57	11
2007	18,955	20,400	49,500	101	60	12
2008	20,242	21,800	50,800	111	65	11
2009	23,234	22,800	50,400	120	66	12
2010	24,352	24,000	50,200	129	70	13
2011	26,061	25,400	49,900	141	79	14
2012	26,432	26,700	49,500	149	83	14
2013	-	28,500	48,400	143	84	15
2014	-	30,100	47,700	139	86	15
2015		31,200	46,700	108	78	16

Source: Simulation model results
* The numbers of HCV cases identified from claims data are included for comparison in the highlighted column.
† The model-based results for each year indicate values at the end of the calendar year.
Abbreviations: HCV = hepatitis C virus; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma.

3.3.3 HCV Burden in Pennsylvania Medicaid - Model Predictions

The model projected the HCV-infected population at the end of 2015 at 46,700, with 31,200 (67%) aware of their diagnosis (**Table 3.2**). In the base case (treatment for F2–F4), the overall burden of HCV in Pennsylvania Medicaid and the prevalence of undiagnosed cases are projected to decrease by 23% and 50% from 2015 to 2025, respectively (**Figure 3.1**).

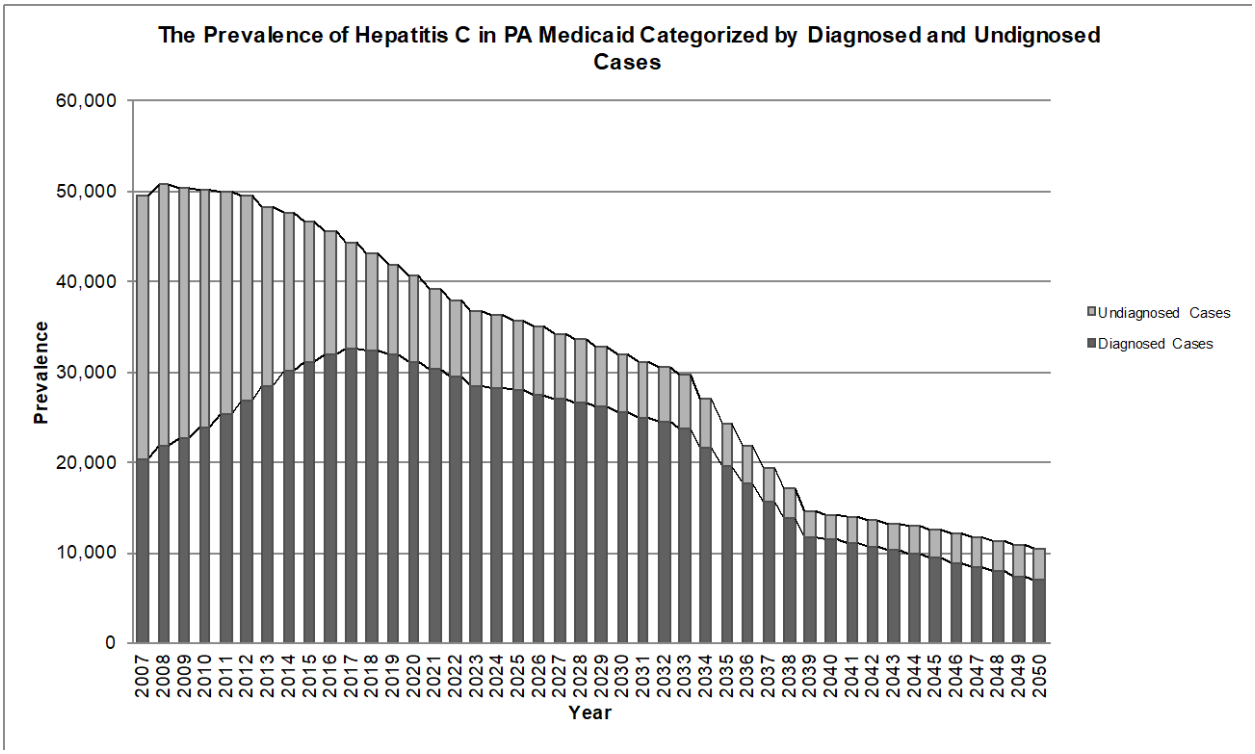


Figure 3.1. The projected prevalence of hepatitis C in Pennsylvania Medicaid categorized by diagnosed and undiagnosed cases in 2007–2050.

Note: After 2014, the projection of HCV prevalence was calculated under the coverage scenario of treating patients with F2–F4 fibrosis levels.

Table 3.3 shows the projected cumulative incidence of advance liver diseases, liver-related mortality, chronic disease cost in 2015–2050, and cumulative antiviral treatment cost in 2015–2025 under each scenario. With a base-case treatment penetration rate of 40%, up to 4,300 HCV-infected individuals were treated annually in 2015 and beyond (**Table B. 8**). Compared to the base case, limiting treatment coverage to F3–F4 with a 40% treatment penetration rate (treating up to 2,500 HCV-infected individuals annually) would reduce cumulative treatment cost from $955 million to $682 million ($274 million reduction) during the next decade (**Table 3.3**, **Panel A**), incur 15% ($60 million) increase in downstream cumulative chronic disease cost from 2015–2050, but minimally affect the cumulative incidence of liver complications and liver-related mortality in

Pennsylvania Medicaid through 2050. Compared to the base-case coverage scenario (F2–F4 treatment), the further coverage expansion to F0 and F1 fibrosis scores (treating up to 8,200 HCV-infected individuals annually) would increase the cumulative cost of treatment by an additional $693 million by 2025, reduce the long-term cost incurred by chronic HCV cases by 35% ($116 million), but not substantially decrease the overall burden of liver complications in Medicaid through 2050. The majority of the 10-year cumulative cost of treatment among these coverage scenarios occurred in the first 5 years, a period when the majority of HCV patients received treatment (**Figure B. 3, Panel A**).

Table 3.3. Cumulative incidence of HCV outcomes and costs in 2015–2050 under each coverage scenario (Panel A) and with different treatment penetration rates under base-case coverage (Panel B).

	Cumulative results in Pennsylvania Medicaid						Cumulative results incurred to Medicare					
	Incidence 2015–2050				Cost ($million)		Incidence 2015–2050				Cost ($million)	
	DC	HCC	LT	LRD	Chronic disease 2015–2050*	Treatment 2015–2025†	DC	HCC	LT	LRD	Chronic disease 2015–2050*	Treatment 2015–2025†
Panel A. Coverage Scenarios												
F3–F4	708	645	138	1,360	392	682	840	721	106	1,440	175	702
F2–F4 (base case)	696	636	136	1,351	331	955	830	714	104	1,482	173	619
F0–F4	688	633	136	1,340	215	1,648	823	703	102	1,452	170	475
Panel B. Treatment Penetration Rate in PA Medicaid‡												
20%	950	783	161	1,595	387	838	1,025	859	123	1,796	219	613
40%	696	636	136	1,351	331	955	830	714	104	1,482	173	619
60%	625	588	126	1,261	311	975	786	681	98	1,505	163	616
80%	595	576	125	1,241	305	986	779	681	98	1,449	162	610
100%	570	560	121	1,212	299	995	775	673	95	1,432	161	605

* Chronic disease cost is the cost incurred by chronic stages of hepatitis C virus and the cost of managing associated liver complications.

† Cost of HCV treatment with new oral antiviral therapies.

‡ Panel B presents the results of different annual penetration rates, assuming treatment of F2–F4 after 2015. Treatment penetration rate is the annual percentage of treatment-eligible Medicaid enrollees who receive treatment. This parameter could be affected by the number of physicians to provide HCV treatment, and individuals' care-seeking behavior.

Abbreviations: F0 = Metavir stage for no liver 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; LT = liver transplant; LRD = liver-related death.

3.3.4 HCV Burden in Transitions from Medicaid to Medicare

Under Medicaid's F2–F4 treatment coverage and 40% treatment penetration rate (base-case), HCV-infected individuals who failed treatment in Medicaid or transitioned to Medicare at 61 years old without receiving treatment would incur an economic disease burden of $173 million in 2015–2050 and treatment cost burden of $619 million in 2015–2025 (**Table 3.3, Panel A)**. Expanding treatment to include F0 and F1 fibrosis scores in Pennsylvania Medicaid reduced the

costs for treatment in Medicare by 23%, or $144 million (from $619 million to $475 million) through 2025 and reduced the number of individuals receiving treatment in Medicare from 2015–2050 by 46%, from 6,600 to 3,500. Changes in treatment coverage in Medicaid, however, did not substantially impact the burden of new cases of decompensated cirrhosis, hepatocellular carcinoma or liver transplant in Medicare.

3.3.5 Sensitivity Analyses

Variations in treatment penetration rate in Pennsylvania Medicaid would have a substantial impact on the annual HCV treatment costs (**Figure B. 3**, **Panel B**) and the incidence of advanced liver disease (**Table 3.3**, **Panel B**, and **Figure B. 4**). For example, if all treatment-eligible patients (100%) were to receive treatment under F2–F4 coverage, costs of therapy would increase by $40 million (4%) in the next decade when compared to a 40% treatment penetration rate (i.e. 955 million to 995 million) (**Table 3.3**, **Panel B**). However, the incidence of liver transplant would drop by 11% (15 fewer liver transplants) through 2050 and liver-related death decrease by 10% (139 deaths).

Setting a maximum number of individuals who could be treated annually in 2015 and beyond (instead of setting a treatment penetration rate) substantially altered model outputs in different coverage scenarios (**Table 3.4**). Compared to F2–F4 coverage, expanding treatment to F0 and F1 fibrosis when only 2,200 patients can be treated annually *increased* the cumulative incidence of advanced liver diseases and liver-related deaths by 30%. It was only in a scenario of unlimited treatment capacity that expansion to F0–F4 did not increase the incidence of liver complications and death.

The impact of delaying the inclusion of F2 fibrosis levels in treatment coverage depended on the treatment penetration rate. Waiting until 2017 or 2020 to expand treatment to F2 (compared to expanding in 2015) would have beneficial effects on liver-related outcomes if treatment penetration is limited, while it would have a modest negative impact if treatment penetration is 100% (**Table B. 9**). Overall, model projections were robust to changes in other model parameters (**Table B. 10**).

Table 3.4. Cumulative incidence of HCV outcomes and costs in 2015–2050 under various coverage scenarios, altering the maximum number of individuals treated annually in 2015 and beyond.

Maximum individuals treated annually in 2015 and beyond	Coverage Scenario	Cumulative results in Pennsylvania Medicaid						Cumulative results incurred to Medicare					
		Incidence 2015–2050				Cost ($million)		Incidence 2015–2050				Cost ($million)	
		DC	HCC	LT	LRD	Chronic disease 2015–2050*	Treatment 2015–2025**	DC	HCC	LT	LRD	Chronic disease 2015–2050*	Treatment 2015–2025**
2,200	**Panel A.**												
	F3–F4	744	659	140	1,382	396	660	873	750	108	1,631	184	696
	F2–F4 (base case)	957	784	163	1,600	386	838	1,020	855	125	1,839	219	611
	F0–F4	1,424	1,050	212	2,061	399	1,004	1,409	1,117	159	2,443	296	425
4,300	**Panel B.**												
	F3–F4	614	585	125	1,257	369	702	782	688	98	1,470	163	704
	F2–F4 (base case)	696	636	136	1,351	331	955	830	714	104	1,482	173	619
	F0–F4	896	742	155	1,531	269	1,489	972	818	119	1,795	207	503
6,400	**Panel C.**												
	F3–F4	572	563	121	1,214	361	712	782	682	97	1,487	161	699
	F2–F4 (base case)	623	587	129	1,259	311	975	784	687	98	1,487	164	616
	F0–F4	742	660	141	1,381	229	1,592	859	741	108	1,603	181	486
8,500	**Panel D.**												
	F3–F4	576	560	120	1,214	361	712	774	677	97	1,415	162	699
	F2–F4 (base case)	595	575	124	1,240	305	985	782	675	99	1,456	162	610
	F0–F4	672	621	132	1,310	208	1,642	816	704	102	1,519	170	475
Unlimited	**Panel E.**												
	F3–F4	584	567	121	1,224	362	712	781	677	97	1,398	162	698
	F2–F4 (base case)	575	559	121	1,214	300	996	771	673	97	1,403	161	604
	F0–F4	574	556	122	1,210	180	1,718	775	673	96	1,465	160	447

* Chronic disease cost is the cost incurred by chronic stages of hepatitis C virus and the cost of managing associated liver complications.
** Cost of HCV treatment with new antiviral therapies.
Abbreviations: F0 = Metavir stage for no liver 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; LT = liver transplant; LRD = liver-related death.

3.4 DISCUSSION

Our study applied microsimulation modeling to estimate the prevalence of HCV in Pennsylvania Medicaid and analyze the cost and disease burden impact of broadening treatment coverage. We projected that including F2 fibrosis patients in treatment coverage - something only seven states had done as of February 2016 - compared to limiting treatment to F3–F4 patients only, would increase the cumulative treatment cost by $274 million in 2015–2025, decrease long-term chronic HCV cost by $60 million in 2015–2050, but would not substantially decrease the incidence of advanced liver diseases or liver-related death in the Medicaid population in Pennsylvania. Expanding treatment in Medicaid would decrease treatment costs in Medicare – an impact that is not fully considered in policy discussions or prior literature [97]. Furthermore, our findings highlight the critical importance of treatment penetration rate in estimating the impact of coverage scenarios; in settings of limited treatment penetration or capacity, expansion of eligibility could potentially worsen liver related outcomes.

Our study uses a novel approach of combining claims-based analyses and validated microsimulation modeling to estimate the impact of treatment coverage scenarios on HCV disease and cost burden in the future. Importantly, our analyses do not measure cost-effectiveness, as in prior studies [98], but focus on treatment costs and liver-related outcomes for one payer (Pennsylvania Medicaid), uniquely accounting for treatment capacity and for the transition in insurance between Medicaid and Medicare.

Treatment penetration rate is an especially important variable in Pennsylvania, where Medicaid guidelines stipulate that HCV therapies should be prescribed by physicians specialized

in infectious disease, gastroenterology, hepatology, or transplantation [89]. The limited availability of these specialists in some areas could limit the number of enrollees who are able to pursue treatment and result in low treatment penetration rate [99], although opportunities exist to expand access to specialists through telemedicine. Our findings suggest that within the base-case scenario (treatment of F2–F4), expanding the treatment penetration rate improved liver-related outcomes while increasing cost. However, with a fixed treatment rate and limits on the maximum number of annually treated individuals, expanding treatment to lower fibrosis levels may potentially lead to F0–F2 patients being treated before F3–F4 patients and worse outcomes. In fact, with a low treatment penetration rate among enrollees, the state could potentially benefit by delaying the expansion of treatment, thus ensuring that more severe cases are treated before less severe ones. The expanded treatment coverage in 2015 would be beneficial only if the treatment penetration rate were 80% or higher – a rate that may potentially exceed provider capacity - highlighting the policy significance of ensuring adequate system capacity for treating all HCV patients before eligibility criteria are expanded.

Our results show that expanded HCV treatment policies in Medicaid may not substantially decrease the incidence of liver complications and death in this population. Patients may be successfully treated as they progress to more advanced fibrosis levels while in Medicaid, and others still in early fibrosis stages (F0 or F1) may transition out of Medicaid into Medicare, which offers treatment to all eligible patients in our model regardless of fibrosis levels. Our analysis highlights the potential tradeoffs between Medicaid and Medicare - expanded treatment coverage and the rates of treatment penetration in Medicaid would impact the future disease burden and costs incurred to Medicare when patients transition in coverage. While important, these results can be considered estimates only, given the limitations of the model in precisely defining the moment

of transition from Medicaid to Medicare. Nonetheless, our analyses document the importance of expanding the discussion about costs and impacts of treatment beyond Medicaid only for conditions with slow rates of progression like HCV.

One final consideration in evaluating the potential impact of HCV treatment coverage decisions is the expected future drop in drug prices [100]. For example, the Department of Veterans Affairs was able to end treatment prioritization and expand HCV treatment to all Veterans regardless of disease severity in February 2016 [101], due to their ability to lower prices and due to an infusion of funds from Congress. Our model is based on current pricing data and will overestimate costs if HCV drug prices for Medicaid fall substantially in the future. Costs, however, will not change the impact of a given coverage decision for HCV on future liver-related health outcomes.

Our study has several limitations. First, our model cannot fully account for transitions from Medicaid coverage only to dual eligibility for Medicare, a transition potentially related to the onset of advanced liver disease. However, our claims-based analyses and a published study [96] suggests that most individuals with HCV transition to Medicare by age 61; thus we assumed Medicare became the primary payer after that age. We also assumed that all patients are treated in Medicare once leaving Medicaid regardless of fibrosis level. Second, we did not analyze the potential effect of treatment on the transmission of HCV in the Medicaid population. However, since the magnitude of HCV incidence did not affect the projected prevalence of HCV according to our sensitivity analyses, we do not expect this omission to substantially change the findings. Third, the costs of chronic disease management were not drawn from Medicaid or Medicare data due to limited data availability. As a result, we mainly focused on the relative (rather than absolute) differences in projected disease management costs between different coverage scenarios. Fourth,

our analysis did not incorporate potential benefits of treatment on improved quality of life and increased economic productivity [86]. Finally, we did not consider the impact of Medicaid expansion, which was implemented in Pennsylvania in 2015, for which there was no available information on changes in population clinical characteristics at the time of our study.

In conclusion, the expansion of treatment prior authorization criteria would significantly increase the economic burden of HCV treatment and somewhat reduce the cost of chronic HCV in Pennsylvania, but would not substantially decrease HCV-related complications among infected Medicaid enrollees. Concurrent with patient prioritization policies, the issue of treatment accessibility and treatment penetration rate among eligible patients should also be a focus of policy efforts. Expanding eligibility for hepatitis C treatment could potentially be counterproductive if patients with less severe liver disease are treated before those whose disease is more advanced.

4.0 CREATING A SEXUAL PARTNERSHIP NETWORK IN AN AGENT-BASED MODELING PLATFORM USING SURVEY DATA

4.1 BACKGROUND

Sexually transmitted diseases (STDs) have a large human and economic burden in the United States. Using the National Health and Nutrition Examination Survey (NHANES), the Centers for Disease Control and Prevention (CDC) estimated about 20 million new STD infections and an overall 110 million prevalent STD cases in the United States in 2008 with an estimated $16 billion in direct medical costs annually [102]. Sexual transmissions account for the majority of new chronic disease infections with various routs of transmission, such as human immunodeficiency virus (HIV) [103]. For example, men who have sex with men, heterosexuals, and injection drug users accounted for 63%, 25%, and 8% of new HIV infections [104]. More than half of these new infections are due to transmission by the individuals who are unaware of their disease [105].

Improving public health programs to tackle the burden of STDs is challenging due to large health disparities among various risk groups, mainly driven by social and behavioral factors. The structure of sexual networks and including socioeconomic factors of individuals in the formation of social and sexual networks at a population level directly impacts the transmission of sexually transmitted diseases [106, 107]. The studies of social networks have been evolving since 1970s [108], though surveys and questionnaires have remained as the main sources of obtaining sexual network data. Researchers have published several studies about STD's transmission and care management using evidence-based approaches with limited datasets of social networks [109-120].

These studies mostly targeted specific healthcare settings, or a certain infected sub-population with static network contacts, and lacked the dynamics of sexual interactions. Computer simulations have also been recently used to study social network structures and sexual transmission [121-123], though an analysis of a generic sexual transmission network with a sexual-network design using public survey data has not been presented yet.

In this study, we aimed to create a mechanism to instantiate and maintain a sexual partnership network according to publicly available survey data in an agent-based simulation model. Agent-based computer simulation modeling is a relatively new tool in public health decision analysis and policy. An agent-based model is an informative flexible tool to simulate the dynamics of a complex system with discrete micro-entities known as agents. Using an agent-based model, we can model the interactions of agents and their environment, as well as the interactions among agents. The characteristics of agents and environment in an agent-based model could be designed to represent realistic information such as geographic and socio-economic factors with a capacity of including necessary sources of heterogeneity [124]. The objective of this study is to add the development and maintenance of sexual networks in the Framework for Reconstruction of Epidemiological Diseases (FRED), an agent-based modeling platform. Our study focused on the heterosexual network of individuals and serves as a first developmental step to simulate the transmission of STDs through a dynamic sexual transmission network.

4.2 METHODS

4.2.1 NHANES Data

In order to instantiate a sexual partnership network, we analyzed the individual-level data entries of NHANES 2007–2014 data files [79]. We obtained age and sex records from the demographics files and the number of sexual partners over an individual's lifetime and in the past 12 months from the sexual behavior files, using the variable codes shown in **Table 4.1**. Entries with missing values and response codes of "refused" and "don't know" were excluded from the analysis. We defined the categories of number of partners as 0, 1, 2, 3 or more, and divided the 3-or-more partner category to three subcategories of 3–6, 7–14, and 15 or more partners. We calculated the distribution of individuals for these categories by age group and sex. **Figure C. 1** includes the distribution of the number of partners in lifetime for the analyzed NHANES data files.

Table 4.1. Variable Names and Questions used from the sexual behavior NHANES data files.

Variable Codes and Question*	Target Age
Females respondents	
SXQ700 - Ever had vaginal sex with a man	18–69 years
SXQ706 - Ever had anal sex with a man	18–69 years
SXD101 - Number of male sex partners/lifetime	18–69 years
SXD450 - Number of male sex partners/year (past 12 months)	18–59 years
Male respondents	
SXQ800 - Ever had vaginal sex with a woman	18–69 years
SXQ806 - Ever had anal sex with a woman	18–69 years
SXD171 - Number of female sex partners/lifetime	18–69 years
SXD510 - Number of female sex partners/year (past 12 months)	18–59 years

* Variable codes are shown for NHANES 2009–2010. Some variable codes differed in different years of NHANES data. The target age in NAHENS 2001–2002 and 2005–2006 was chosen as 20–59 years.

The analysis of four serial cross-sectional NHANES data in 2007–2014 indicated that the distribution of the total number of partners in individuals' lifetime differed considerably by sex, whereas in theory, these distributions should be similar. This data discrepancy indicated the known systematic and egocentric bias in behavior-related survey data and the over-perception of the number of sexual partners by males [108, 125-127]. Specifically, Brown and colleagues reported that men's estimates of the number of sexual partners in lifetime are two to four times greater that the estimates reported by women since estimation strategies vary by sex [126]. As a result, we used the average of the distributions for the number of partners in lifetime and per year among males and females by age group in our study. We chose NHANES 2009–2010 results (**Table 4.2**) as the basis of implementing sexual partnership status in our model, since it provided enough follow-up time from the initiation of the model to the present year, and also included individuals younger than 20 years, as opposed to NHANES data prior to 2008.

Table 4.2. The percentage of individuals with different number of partners in lifetime and in the past 12 months by age according to NHANES 2009–2010 data, on average among males and females.

	Number of opposite-sex partners in lifetime						
Age	**0**	**1**	**2**	**3 or more**	**3–6**	**7–14**	**15 or more**
15–19	22.3	19.7	10.3	47.7	62.0	26.3	11.8
20–24	11.7	12.0	8.7	67.6	46.5	31.9	21.6
25–29	6.3	11.7	10.0	72.0	38.5	32.4	29.1
30–34	1.2	13.5	9.8	75.5	39.6	31.2	29.1
35–39	2.6	12.8	6.3	78.3	36.0	34.0	30.0
40–44	2.4	12.6	7.0	78.0	41.2	28.3	30.6
45–49	2.8	13.4	5.1	78.7	41.7	21.2	37.1
50–54	3.9	11.8	8.3	76.0	44.0	26.4	29.6
55–59	5.8	12.4	10.2	71.6	46.3	24.7	29.1
	Number of opposite-sex partners in the past 12 months						
Age	**0**	**1**	**2**	**3 or more**	**3–6**	**7–14**	**15 or more**
15–19	28.0	36.9	15.4	19.7	83.3	9.5	7.2
20–24	17.4	49.2	13.0	20.4	86.3	7.4	6.3
25–29	11.8	66.1	13.5	8.6	67.5	30.0	2.5
30–34	9.0	72.8	9.5	8.7	82.1	12.5	5.4
35–39	9.1	78.7	4.6	7.7	90.0	10.0	0.0
40–44	10.9	76.3	6.0	6.8	83.1	14.6	2.3
45–49	15.7	71.9	6.8	5.6	75.0	17.5	7.5
50–54	26.7	61.4	6.5	5.3	85.7	7.1	7.1
55–59	33.1	59.0	4.9	2.9	52.8	22.2	25.0

4.2.2 Initiation of Sexual Partnership Network

We used the Framework for Reconstruction of Epidemiological Diseases (FRED), an open-source large-scale agent-based simulation model developed by the Public Health Dynamics Laboratory of University of Pittsburgh, as our agent-based modeling platform to create a heterosexual partnership network. FRED uses a census-based synthetic population that includes sociodemographic information of the population and specific geographical locations, household, workplace and school information [128]. We chose the United States synthetic population of Allegheny County, Pennsylvania [129, 130] aged between 15–75 years available in FRED, as the baseline population in the simulation. We excluded the individuals who were labeled as unattended

minors or were in households defined as same-sex couples or families (**Appendix C.2**). The population aged between 15–59 years were the focus of our analysis due to availability of NHANES data for this age range, but we included the individuals in 60–75 age range to allow for the continuation of established partnerships as adults aged in our simulation.

We initiated the sexual partnerships for males and females of different age groups in two main steps: first, we labeled individuals according to the number of partners during a year according to their sex and age group, and matched male and females according to their labeled number of partners and age-mixing patterns observed in data. Second, we assigned the duration of partnerships and the probability of sexual contact. The details of each step are described in the following sections.

4.2.2.1 Partnerships formation

We assigned the initial number of desired partners to individuals according to the cross-sectional distribution of partners in a year observed in NHANES 2009–2010 data (**Table 4.2**) [79, 131]. We then matched males and females according to their desired number of partners and age-mixing patterns presented in **Table 4.3** [132]. The details of partnership matching process are available in **Appendix C. 3**.

Table 4.3. Age-mixing patterns among heterosexual adults based on sex.

	Partner, %					
Age (years)	**<19**		**20–29**		**30 or older**	
	Women	**Men**	**Women**	**Men**	**Women**	**Men**
<19	48.1	83.3	50.3	16.1	1.6	0.5
20–29	5.8	22.7	72.3	64.5	21.9	12.8
30 or older	1.9	2.9	26.2	44.3	71.8	52.9

4.2.2.2 Partnership duration, concurrency, and sexual acts

We categorized sexual partnerships into two types of long term and short term, and assumed that short-term partnerships lasted less than three years. We calculated partnership type and duration for adult males, and assigned the same duration and type to their female partners. Using the probability of first marriage among adult males by age, derived from a survival analysis based on 2006–2010 National Survey of Family Growth (**Table 4.4**) [84], we calculated the hazard rate of entering a long-term relationship for males over all ages (**Figure C. 2**) in the simulation model in order to select the duration type of partnership. We assumed that each individual could have at most one long-term partnership at each point in time.

Table 4.4. Probability of first marriage among men aged 18–44 years, by specified age and selected characteristics: United States, 2006–2010.

By age	Probability of first marriage	
	Value	**Standard Error**
20	0.05	0.004
25	0.31	0.011
30	0.56	0.013
35	0.71	0.013
40	0.78	0.013

We used the data provided by How Couples Meet and Stay Together (HCMST) study [133] to categorize the short-term partnership durations to two groups of less than one year and one to three years, (**Table C. 1**). We assigned individuals to these short-term partnership categories according to the data, and then calculated the duration using the uniform distribution.

The duration of long-term partnerships were calculated according to another survival analysis in the 2006–2010 National Survey of Family Growth [84]. In this study, individuals were categorized into three 'age at first marriage' categories: under 20 years, 20–24 years, and 25 years

and older. This study also provided the probability of first marriages remaining intact for 5, 10, 15 and 20 years, for each age at first marriage categories (**Table C. 2**). Using these probabilities, we fitted exponential probability distributions of marriage duration, for each category of age at first marriage (**Figure C. 3**) and used them to calculate the duration of long-term partnerships, in an individual were assigned to start one in a given year. **Appendix C. 4** includes detailed information on calculating the duration of partnerships in the model.

We included partnership concurrency for individuals with two or more partners, defined as the overlapping duration of partnerships, according to the number of partners and duration of each partnership **(Appendix C. 5**). We used the estimated number of sexual acts for American males from a published study [134] (**Appendix C. 6**) to calculate the daily probability of having a sexual act for males with partners. We randomly picked a partner if a male had more than two partners on the day that a sexual act was scheduled.

4.2.3 Dynamics of Sexual Partnership Network

Subsequent to network initiation, the dynamics of sexual partnership network were used to simulate individuals and their partnerships through their lifetime. We constructed the dynamics of the sexual partnership network based on two main components: 1) the overall population dynamics as individuals entered and exited the simulation model due to births and deaths, and 2) the evolution of individuals' partnerships over time.

For the first component, we included FRED's capabilities for creating the incoming cohorts of individuals using birth rates and allowed individuals to enter the sexual partnership network on their 15th birthday. We also simulated the outgoing population if they aged past 75 years, or in case of death using all-cause mortality rates in the synthetic population.

The second component of network dynamics involved setting rules for updating sexual partnerships and calibrating the model to produce network characteristics similar to that in the NHAHES data. On each day, the simulation updated the duration left in partnerships, removed the partnerships that had no duration left, updated the number of partnerships for individuals whose birthdays were on the same day, matched individuals who needed new partners after the update, and removed the individuals from the network according to their age or mortality rates (**Figure 4.1**).

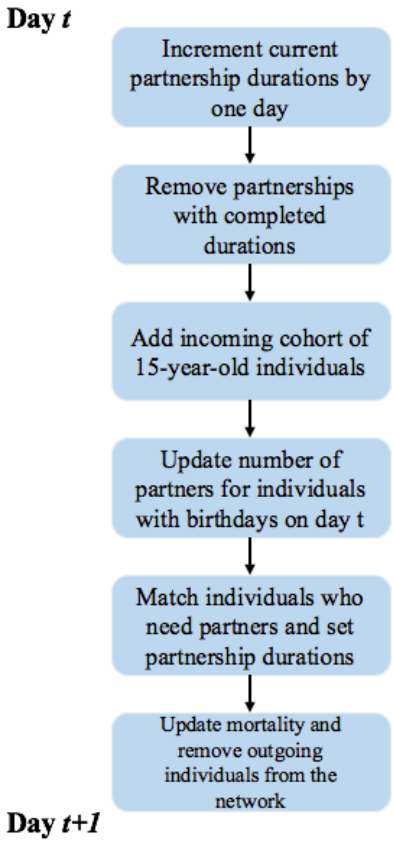


Figure 4.1. Steps for updating the sexual partnership network on each day in the simulation.

The mechanism of updating an individual's number of partnerships in each year was according to the individual's partnership history. For this purpose, we defined the probabilities of starting new partnerships so that an individual could go from one category of number of partners in lifetime, to another category, given the individual's age, current number of partners, and the total number of partners in his/her lifetime. These probabilities were defined for each age group and the category of the number of partners. For example, five probabilities were defined for 15–20 year-old individuals with one partners in their lifetime: the probability of having no new partners (staying in the category of one partner in lifetime), the probability of having one new partners (moving to the category of two partners in lifetime), probability of having 2–5 new partners (moving to the category of 3–6 partners in lifetime), probability of having 6–13 new partners (moving to the category of 7–14 partners in lifetime), and probability of having 14 or more new partners (moving to the category of 15 or more partners in lifetime). **Figure 4.2** illustrates these probabilities for age groups 15–19 and 20–24. Note that the probabilities of moving to ≥ 3 partner categories are not all shown for simplicity.

We aimed to calibrate our model by distributing preference characteristics across our synthetic population in such a way to reproduce and maintain population network characteristics of number partners in lifetime and per year in NHANES data. Our model calibration included adjusting the probabilities used for updating the number of partnerships in each age group as described above.

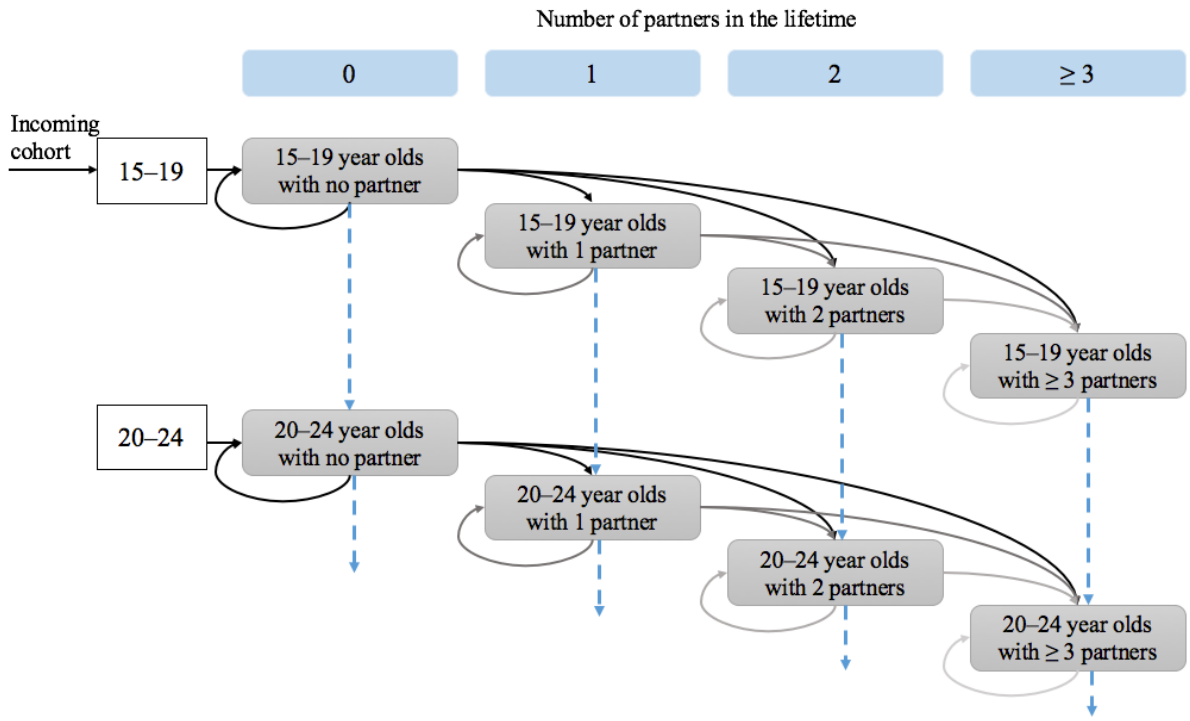


Figure 4.2. Mechanism of updating the number of partners in each year for 15–19 age group.

Note: The black and grey arrows indicate the transition probabilities between partner categories within the same age group. The blue dashed arrows indicate the movement of individuals between age groups on their birthday. For example, a 19-year-old individual with one partner in his lifetime, would transition to a 20-year-old individual with one partner in lifetime on his birthday.

4.2.4 Model Outputs and Sensitivity Analyses

We projected the distribution of number of partners in lifetime and per year for adults aged 15–59 years in the sexual partnership network at the end of each simulated year in FRED over 10 years. We also studied the impact of changes (± 0.05) in the probabilities of having new partners for individuals based on the history of their partnerships, on the overall distribution of number of partners in lifetime among adults. These probabilities were defined as: p1: probability of moving from no partner in lifetime to one partner in lifetime in a year; p2: probability of moving from one partner in lifetime to two partners in lifetime in a year; p3: probability of moving from two partners

in lifetime to ≥ 3 partners in lifetime in a year; p4: probability of moving from 3–6 partners in lifetime to 7–14 partners in lifetime in a year; and p5: probability of moving from 7–14 partners in lifetime to ≥ 15 partners in lifetime in a year.

4.3 RESULTS

Our mechanism for instantiating and maintaining a heterosexual partnership network, generated the distribution of number of partners in a lifetime and per year by age group over 10 years. During our model calibration process for adjusting the probability of new partnerships, we recreated the distribution of number of partners similar to our target values, the observed distribution found in NHANES 2009–2010 data. **Table C. 5** present the cross-sectional distribution of the individuals with different number of partners in their lifetime, at the end of each year in the simulation. Ninety-three percent of the projected values for the percentage of individuals in categories of 0, 1, 2 or ≥ 3 partners in lifetime were within five percentage points of the values in NAHNES 2009–2010 on average over 10 simulation years. **Table C. 6** presents the difference in the percentages of people in each partner category, between model results over 10 years and NHANES 2009–2010. Our model results were the most different from NHANES 2009–2010 values for the projected values for the sub-categories of ≥ 3 partners, i.e. 3–6, 7–14 and ≥ 15 partners in lifetime, for 45–49, 50–54 and 55–59 age groups.

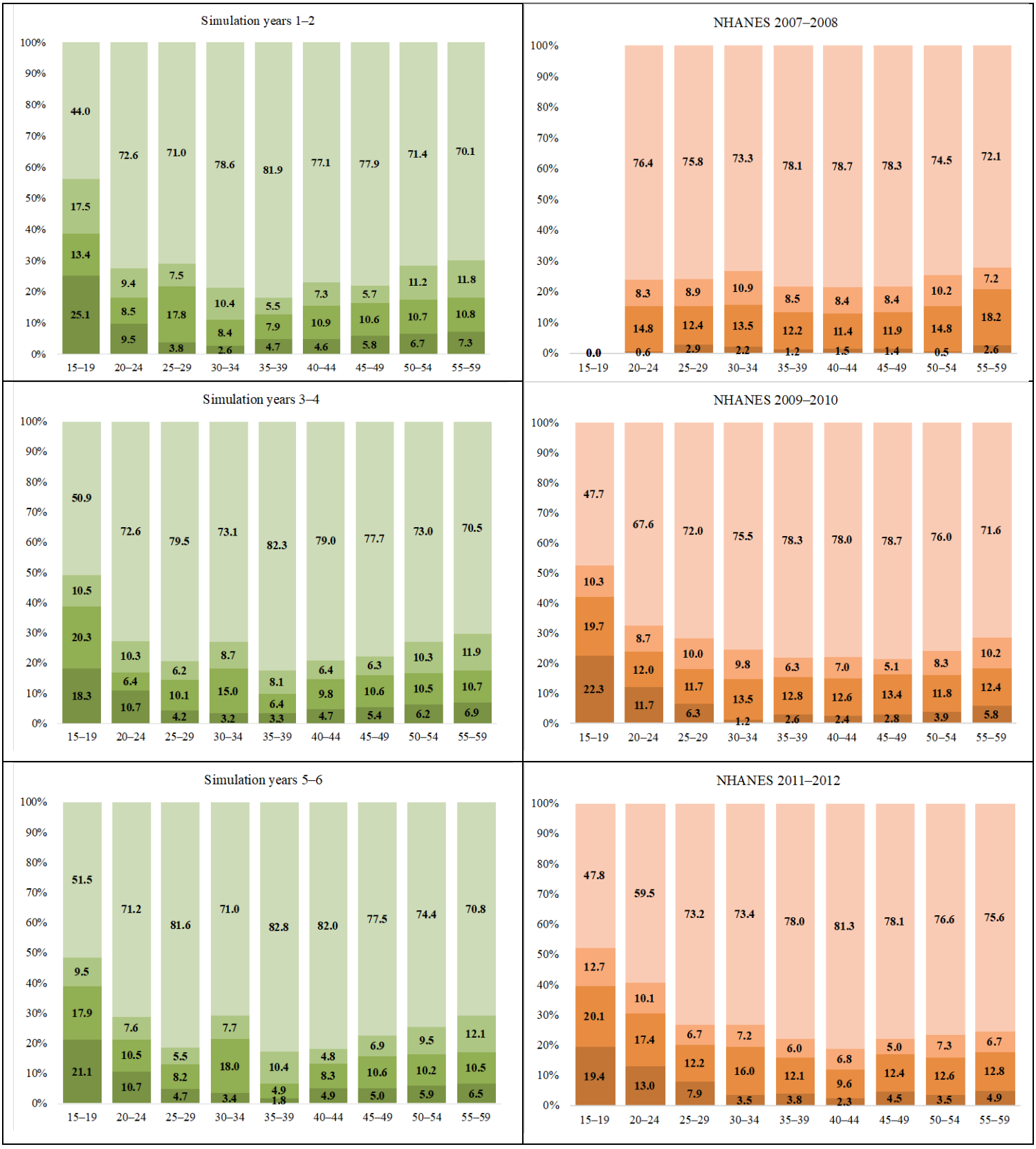
The percentages of individuals for partner in lifetime categories of 0, 1, 2, and ≥ 3 obtained from model results over eight years, and NHANES 2007–2014 are presented in **Figure 4.3**. Each graph in the left column of this figure represents a cross-sectional image of the network characteristics in FRED at the end of two years, and each graph in the right column represents the

results of data analysis of the number of partners in lifetime for four NHANES datasets. In this figure, we observe that the FRED's overall projected patterns of partnership network characteristics in the synthetic population were similar to the network characteristics found in this series of cross-sectional NHANES data.

Our model also projected the distribution of the number of partners per year among heterosexual adults (**Table C. 7**). **Table C. 8** presents the difference in the percentages of people in each partner-in-year category, between model results over 10 years and NHANES 2009–2010. Our model projected the percentages of individuals with two or ≥ 3 partners in year, similar to the observed values in NHANES 2009–2010. However, the simulation projected consistently higher number of single individuals, and lower number of individuals in monogamous partnerships compared to the values obtained in the NHANES 2009–2010 data. In addition, our model produced a similar proportion of individuals who had ≥ 15 partners in a given year, but produced lower percentages of individuals with 3–6 and higher percentages of individuals with 7–14 partners in a year compared to NHANES data.

4.3.1 Sensitivity analyses

Table C. 9 presents the results of our sensitivity analyses on changing five probabilities of individuals moving from one partner-in-lifetime category to the next partner-in-lifetime category on the percentage of individuals in different partner categories in the model, at the end of 10 years. The distribution of the number of individuals in with different categories partners in lifetime were the most sensitive to changes in parameters used in 15–19, 20–24, and 25–29 age groups. Specifically, changing the parameters used in these age groups modified the distribution in the same age groups (15–19, 20–24, and 25–29) rather than those in older age groups.


Simulation years 1–2
NHANES 2007–2008
Simulation years 3–4
NHANES 2009–2010
Simulation years 5–6
NHANES 2011–2012
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
15–19
20–24
25–29
30–34
35–39
40–44
45–49
50–54
55–59
44.0
17.5
13.4
25.1
72.6
9.4
8.5
9.5
71.0
7.5
17.8
3.8
78.6
10.4
8.4
2.6
81.9
5.5
7.9
4.7
77.1
7.3
10.9
4.6
77.9
5.7
10.6
5.8
71.4
11.2
10.7
6.7
70.1
11.8
10.8
7.3
0.0
76.4
8.3
14.8
0.6
75.8
8.9
12.4
2.9
73.3
10.9
13.5
2.2
78.1
8.5
12.2
1.2
78.7
8.4
11.4
1.5
78.3
8.4
11.9
1.4
74.5
10.2
14.8
0.5
72.1
7.2
18.2
2.6
50.9
10.5
20.3
18.3
72.6
10.3
6.4
10.7
79.5
6.2
10.1
4.2
73.1
8.7
15.0
3.2
82.3
8.1
6.4
3.3
79.0
6.4
9.8
4.7
77.7
6.3
10.6
5.4
73.0
10.3
10.5
6.2
70.5
11.9
10.7
6.9
47.7
10.3
19.7
22.3
67.6
8.7
12.0
11.7
72.0
10.0
11.7
6.3
75.5
9.8
13.5
1.2
78.3
6.3
12.8
2.6
78.0
7.0
12.6
2.4
78.7
5.1
13.4
2.8
76.0
8.3
11.8
3.9
71.6
10.2
12.4
5.8
51.5
9.5
17.9
21.1
71.2
7.6
10.5
10.7
81.6
5.5
8.2
4.7
71.0
7.7
18.0
3.4
82.8
10.4
4.9
1.8
82.0
4.8
8.3
4.9
77.5
6.9
10.6
5.0
74.4
9.5
10.2
5.9
70.8
12.1
10.5
6.5
47.8
12.7
20.1
19.4
59.5
10.1
17.4
13.0
73.2
6.7
12.2
7.9
73.4
7.2
16.0
3.5
78.0
6.0
12.1
3.8
81.3
6.8
9.6
2.3
78.1
5.0
12.4
4.5
76.6
7.3
12.6
3.5
75.6
6.7
12.8
4.9

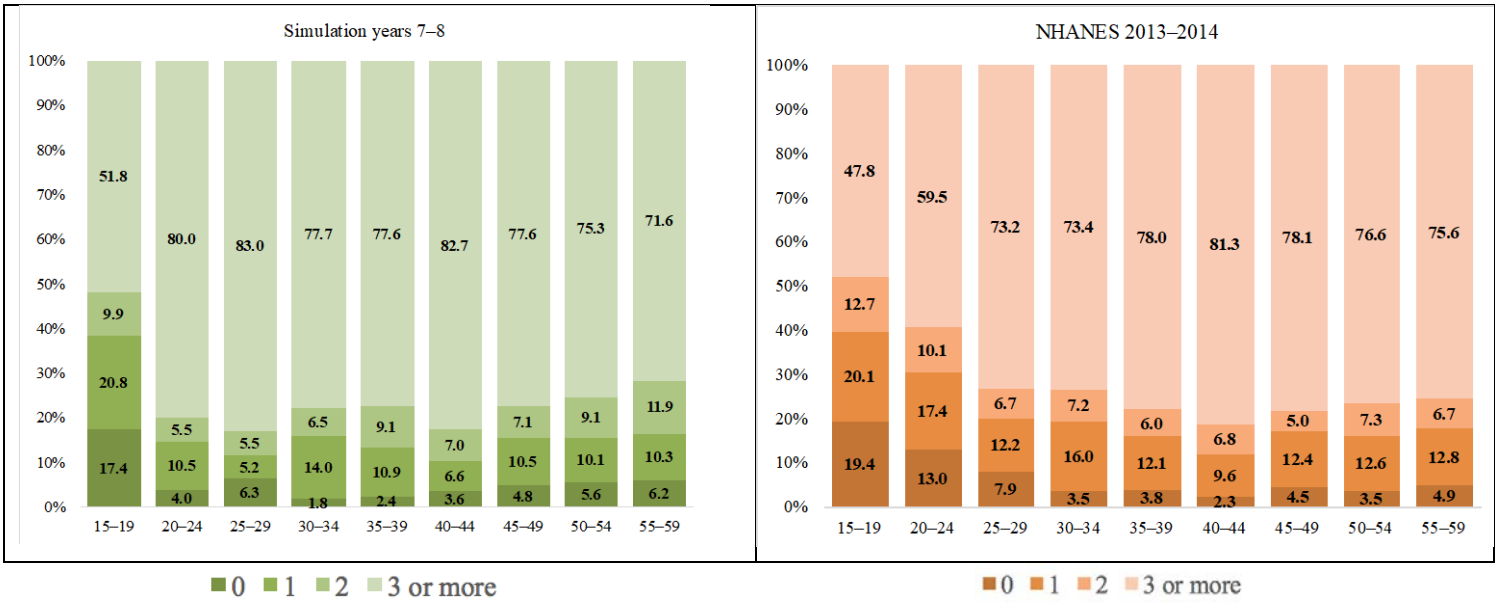


Figure 4.3. Model results and the 2007–2014 NHANES data for the distribution of number of partners in lifetime by age group.

4.4 DISCUSSION

The objective of our study was to develop a mechanism to use a serial cross-sectional survey of sexual behavior to instantiate and maintain a network of sexual partnerships. We designed the principal methods by which we go from serial survey result data by setting the behaviors of adults in an agent-based modeling platform, FRED, to produce the observed cross-sectional network characteristics. Our methods incorporate important components to represent an individual's sexual behavior, such as the individual's history of sexual partnerships, sexual mixing patterns based on age, concurrent partners with different partnership durations, and the frequency of sexual acts.

Our mechanism for structuring a sexual partnership network resulted in distribution of number of partners in lifetime and in a year by age, similar to those reported in NHANES 2009–2010 survey data. The NHANES surveys include serial cross-sectional data on nationally representative samples of individuals in two-year intervals, although the individuals in these samples differ in each survey. However, the design of our simulation model is inherently different. Our model includes a synthetic population of individuals, with incoming and outgoing cohorts based on birth and death rates, respectively. Our model updates this dynamic synthetic population as they age through the simulation, and our results represent the cross-sectional status of the same population at the end of each year. In other words, our results represent serial cross-sectional data of a longitudinally simulated synthetic population. Therefore, we could interpret our results as to how the actual network characteristics would be if the NHANES included the same sample of individuals over time, and its participants responded accurately and without bias.

We faced two main challenges in developing the methods to instantiate and maintain the partnership network. First, due to data discrepancies in the number of partners in a lifetime and a year for males and females in the 2009–2010 NHANES survey of sexual behaviors, we used the average values of the percentage of individuals with different number of partners in a lifetime as calibration targets in our model over a 10-year period. Second, the serial cross-sectional surveys from NHANES data presented an over-identification problem. We could not choose both distributions of partners in lifetime and partners in a year from NHANES data as calibration targets, since matching our results to either of these distributions resulted in large differences between NHAHES data and our model results for the other distribution. Focusing on matching the distribution of partners in a year resulted in significant differences in the other distribution, leaving more than 90% of the individuals in ≥ 15 partners-in-lifetime category. Therefore, we focused on maintaining the distribution of the number of partners in lifetime in the model calibration process.

Our current simulation model uses a synthetic population that represents the population of our target geographical location, Allegheny county, Pennsylvania. However, our model calibration process of adjusting a matrix of probabilities of having different numbers of new partners given an individual's age and previous number of partners in lifetime, could accommodate the adjustments to represent other populations with different network partnership characteristics. The structures needed to simulate other partnership networks would be the distributions of partners in lifetime and in a year by age and sex. Other useful inputs that would make the model calibration process easier are more granulated age-mixing patterns and duration of partnerships, and individual's preferences on starting new partnerships after their first long-term partnership ends due to divorce or partner's death.

Reducing the number of STD transmissions through prevention interventions has been a focus of health policy strategies for decades [135]. Understanding the dynamics of sexual partnership networks is critical to improve the impacts of interventions that focus on individual behaviors, since these dynamics are representative of individual behaviors and the leading factors of STD transmissions. Most large-scale microsimulation models developed for the analysis of STDs' health interventions and policy, however, lack integrated models for sexual transmission through partnership networks. In these models, the estimated number of transmissions are usually obtained from the literature, or calculated in a separate compartmental model of differential equations[1] and fed into the microsimulation. Both of these approaches exclude the dynamics of sexual partnerships with respect to duration and concurrency of partnerships. Moreover, the compartmental models have limited flexibility in incorporating the details of individual characteristics, behavior, and interventions. Our simulation model, however, incorporated a detailed mechanism for developing a sexual partnerships networks in a flexible stochastic agent-based modeling platform, which has the capacity of simulating every individual through his lifetime, incorporating infectious diseases natural history and treatments at patient level, and accounting for sexual transmission simultaneously.

Our agent-based modeling platform offers several research applications in the study of STD epidemics. Given that the agent-modeling platform can accommodate the details of multiple infectious diseases, our simulation can be used to test the impact of various biological or behavioral interventions on STD epidemics by instantiating, maintaining, and projecting the evolution of STD epidemics in the future using the sexual partnership network. We focused on generating a generic

[1] Compartmental models usually estimate the number of people in susceptible, exposed, infected, and recovered states of an infection given an initial number of patients in each state

sexual network structure with age mixing patterns, partnership status and durations as the key determinants for sexual partnership formations and dissolutions. As a result, our model has the potential of representing other sexual networks such as a network of homosexual partnerships.

Our study has several limitations. First, limited data on the sexual behaviors and number of partners for heterosexual population was our main challenge in developing this tool. Data sources that provide detailed information on the structure of a sexual partnership network are related to studies of cross-sectional STD outbreaks with a small sample size. As a result, we chose NHANES sexual behavior survey data for model calibration since it is a nationally representative, longitudinal survey that includes larger sample sizes compared to other cross-sectional studies, and made several assumptions due to the survey data discrepancy issues. Moreover, the unavailability of a detailed large-scale dataset of sexual contacts makes the simulation model susceptible to over- or under-estimating the status of STD prevalence and transmission in the population. We speculate that a number of undiagnosed people are not included in STD-related statistics, which also contributes to estimation biases. Second, the topography of a sexual network depends on geographical location and the characteristics of the people involved in big network components. However, due to unavailability of large-scale real-world data, we cannot verify the topography of sexual networks in the model. Third, our simulation does not include race, an important factor in sexual and social mixing patterns, due to limited time and resources for this project. Though given the availability of data and resources, our flexible modeling mechanism has the capability of adjusting sexual partnership networks by race.

In conclusion, we developed the principal methods of using cross-sectional sexual behavior survey data to instantiate and maintain a sexual partnership network in an agent-based modeling platform. Given the flexibility of agent-based models in individual-level simulations of biological

and behavioral features, our study is a significant developmental step to have a comprehensive tool to study the interventions aimed at reducing the burden of sexually transmitted infections.

APPENDIX A: THE CHANGING BURDEN OF HEPATITIS C INFECTION IN THE UNITED STATES: MODEL-BASED PREDICTIONS

This appendix provides data and supporting results, including validation, sensitivity analyses, and additional clinical scenarios for the first section.

A.1 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).

A.2 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 [13], 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.

A.3 MODEL INPUTS

Several model input parameters values and their descriptions are as following:

Table A. 1. Model Parameter Values.

Variable	Value	References
Natural history transition probabilities*		
F0 to F1	0.117	[136]
F1 to F2	0.085	[136]
F2 to F3	0.120	[136]
F3 to F4	0.116	[136]
F4 to DC	0.029	[137]
F4 to HCC	0.014	[137]
SVR F4 to DC	0.008	[138]
SVR F4 to HCC	0.005	[138]
DC to HCC	0.068	[139]
DC to liver transplantation	0.023	[17, 140]
DC (first year) to liver-related death	0.182	[139]
DC (>1 year) to liver-related death	0.112	[139]
HCC to liver transplantation	0.040	[67, 141]
HCC to liver-related death	0.427	[137]
Liver transplantation (first year) to liver-related death	0.116	[142]
HCV-infected population characteristics		
Total active HCV-infected population in 2001 (million)	3.2	[21]
Chronic-infection ratio (%)†	75	[13]
Percentage of patients unaware of their HCV infection	60	[13, 15, 143-147]
Chronic contraindication (%)‡	34.6	[13]
Sex (%)		[21]
Male	64.22	
Female	35.78	
HCV genotype (%)		[25]
1	73	
2	14	
3	8	
Other	5	
Stage distribution of HCV-infected population in 2001 (%)		[17]
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 (%)		[21]
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	

Table A. 1 continued

Variable	Value	References
Age distribution of the new HCV infections (%)		[22]
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	[22]
Partial responders	19	[22]
Null responders	28	[22]
Genotype 2–6		
Relapsers	47	[23]
Partial responders	16	[23]
Null responders	37	[23]

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.

Table A. 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 [112], and we assumed the annual HCV incidence to be constant beyond 2011 at 18 000 cases in all clinical scenarios.

Table A. 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.

Table A. 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	[136]
F1 to F2	0.085	0.075	0.096	[136]
F2 to F3	0.120	0.109	0.133	[136]
F3 to F4	0.116	0.104	0.129	[136]
F4 to DC	0.029	0.010	0.039	[137]
F4 to HCC	0.013	0.010	0.079	[137]
SVR F4 to DC	0.008	0.002	0.036	[138]
SVR F4 to HCC	0.005	0.002	0.013	[138]
DC to HCC	0.068	0.030	0.083	[139]
DC to liver transplantation	0.023	0.010	0.062	[17, 140]
DC (first year) to liver-related death	0.182	0.065	0.190	[139]
DC (>1 year) to liver-related death	0.112	0.065	0.190	[139]
HCC to liver transplantation	0.040	0.000	0.140	[67, 141]
HCC to liver-related death	0.427	0.330	0.860	[137]
Liver transplantation (first year) to liver-related death	0.116	0.060	0.420	[142]
Liver transplantation (>1 year) to liver-related death	0.044	0.024	0.110	[142]
HCV-infected population characteristics				
Total HCV-infected population in 2001 (million)	4.2	3.4	4.9	[21]
Chronic infection ratio (%)†	78	70.4	86.6	[21]
Percentage of patients unaware of their HCV infection	60	50	75	[13]
Chronic contraindication (%)‡	34.6	31.14	38.06	[13]
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.

Table A. 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	[21]
Female	35.78	41.97	32.10	
HCV genotype (%)*				[25, 148]
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%	[17]
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	[22]
Partial responders	19	17.1	20.9	[22]
Null responders	28	25.2	30.8	[22]
Genotype 2–6				
Relapsers	47	42.3	51.7	[23]
Partial responders	16	14.4	17.6	[23]
Null responders	37	33.3	40.7	[23]

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%.

Table A. 5 continued

[‡]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%.

A.4 MODEL OUTPUTS

Table A. 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 [63]
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

Table A. 6 continued

Advance-stage disease outcomes	Treatment capacity scenarios			
	Baseline*	**Scenario 1**	**Scenario 2†**	**Scenario 3**
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.

Table A. 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)	[64]
Hepatocellular carcinoma prevalence	12 700 (average in 2001–2004)	12 300 (average in 2001–2004)	[65]
Hepatocellular carcinoma incidence	7500 (2005)	6500 (2005)	[66, 67]
Liver-related deaths	11 900 (2005)	11 850 (2005)	[22]
Comparison with other modeling study – 2001 projections	**Model estimation (% of total chronic HCV cases in 2001)**	**Previously published modeling study estimation (% of total chronic HCV cases in 2001)**	
Chronic HCV cases	3.2 million	3.5 million	[17]
F0 cases	864 700 (26.92)	970 000 (27.66)	[17]
F1 cases	1 098 600 (34.20)	1 190 000 (33.93)	[17]
F2 cases	558 800 (17.40)	610 000 (17.39)	[17]
F3 cases	378 600 (11.79)	395 000 (11.26)	[17]
F4 cases	311 400 (9.69)	342 500 (9.76)	[17]
Decompensated cirrhosis cases	33 100 (-)	47 000 (-)	[17]
Liver transplants	2100 (-)	1800 (-)	[17]

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.

Table A. 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. [68]	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.

Table A. 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

Table A. 9 continued

Scenario	Advance-stage disease outcomes	Baseline	10% relative decrease* (% change)	5% relative increase† (% change)
	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.

Table A. 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.

Table A. 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.

Table A. 12. Results of 1-Way Sensitivity Analyses.

Parameter	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**
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)

Table A. 12 continued

Parameter	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**
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.

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

Parameter	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
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)

Table A. 13 continued

Parameter	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
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)

Table A. 13 continued

Parameter	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
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)

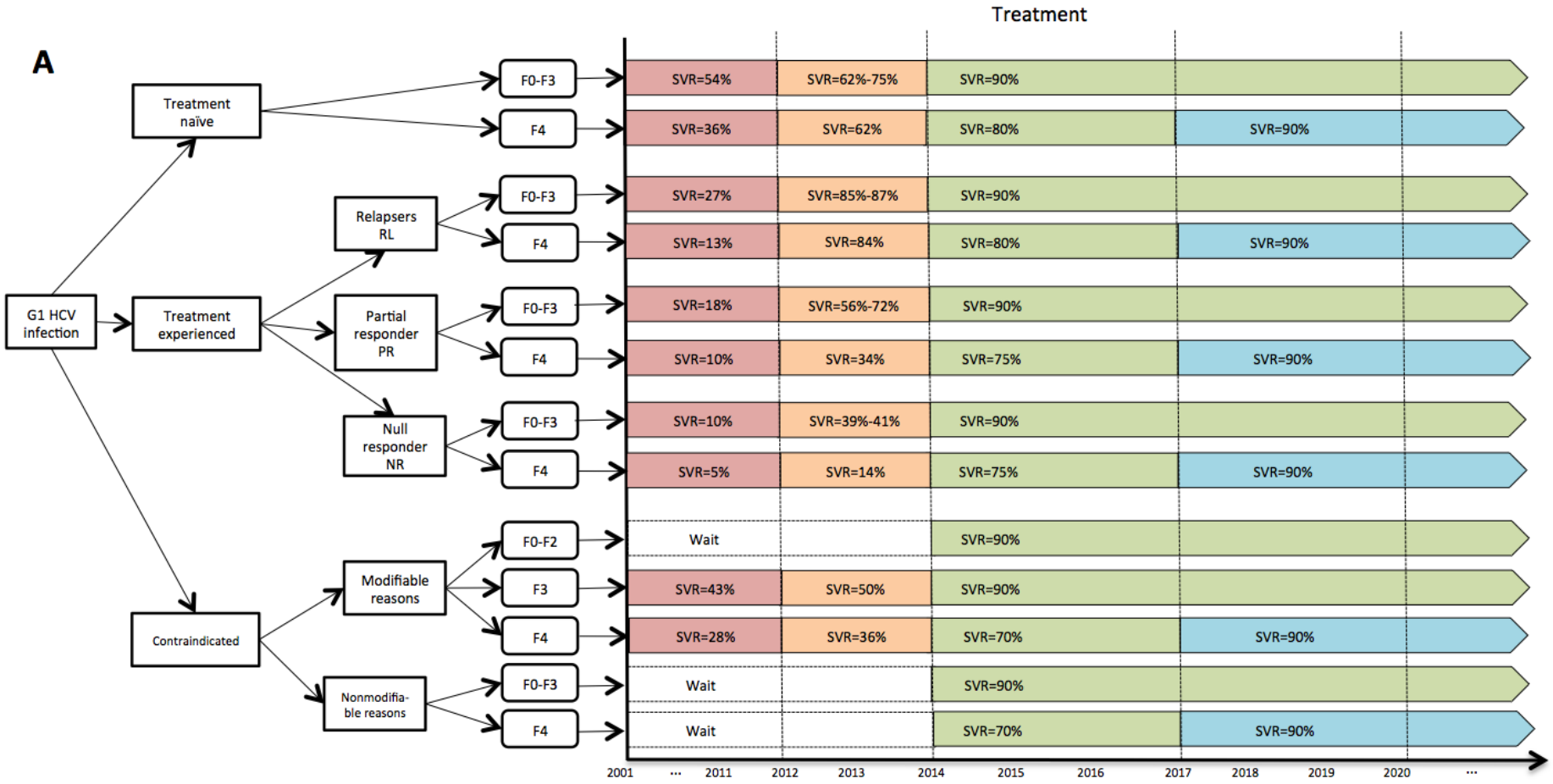
*The value of each parameter in a group affects the values of the other parameters in the same group, since the total percentage of patients in each group should sum to 100%. These groups of parameters are related to patients' sex, genotype, age groups and treatment history. In each 1-way sensitivity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

Table A. 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.
†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 **Table A. 2**. For consistency, we used the same rate for increase in HCV incidence.


A
Treatment
G1 HCV infection
Treatment naïve
Treatment experienced
Contraindicated
Relapsers RL
Partial responder PR
Null responder NR
Modifiable reasons
Nonmodifia-ble reasons
F0-F3
F4
F0-F2
F3
SVR=54%
SVR=62%-75%
SVR=90%
SVR=36%
SVR=62%
SVR=80%
SVR=27%
SVR=85%-87%
SVR=13%
SVR=84%
SVR=18%
SVR=56%-72%
SVR=10%
SVR=34%
SVR=75%
SVR=39%-41%
SVR=5%
SVR=14%
Wait
SVR=43%
SVR=50%
SVR=28%
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2001
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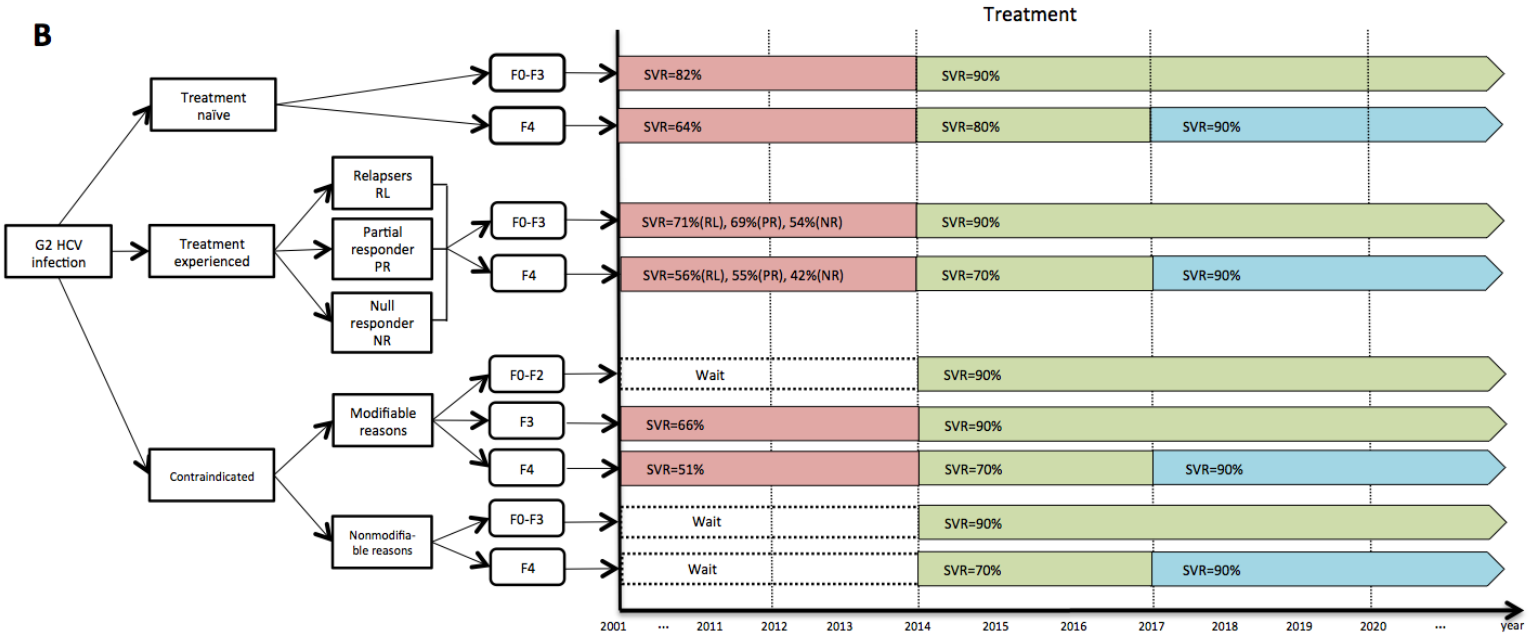
2019
2020


B
Treatment
G2 HCV infection
Treatment naïve
Treatment experienced
Contraindicated
Relapsers RL
Partial responder PR
Null responder NR
Modifiable reasons
Nonmodifia-ble reasons
F0-F3
F4
F0-F2
F3
SVR=82%
SVR=90%
SVR=64%
SVR=80%
SVR=90%
SVR=71%(RL), 69%(PR), 54%(NR)
SVR=90%
SVR=56%(RL), 55%(PR), 42%(NR)
SVR=70%
SVR=90%
Wait
SVR=90%
SVR=66%
SVR=90%
SVR=51%
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SVR=90%
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SVR=90%
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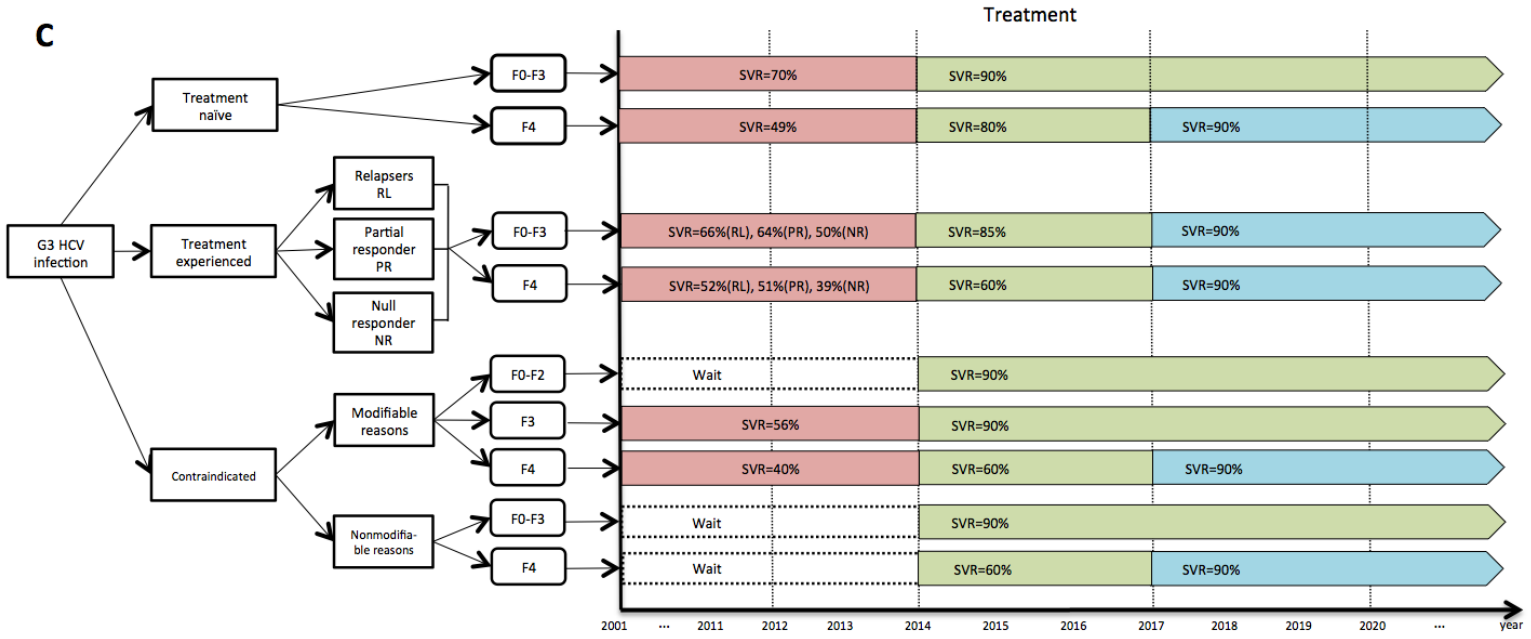
C
Treatment
G3 HCV infection
Treatment naïve
Treatment experienced
Contraindicated
Relapsers RL
Partial responder PR
Null responder NR
Modifiable reasons
Nonmodifia-ble reasons
F0-F3
F4
F0-F2
F3
SVR=70%
SVR=90%
SVR=49%
SVR=80%
SVR=90%
SVR=66%(RL), 64%(PR), 50%(NR)
SVR=85%
SVR=90%
SVR=52%(RL), 51%(PR), 39%(NR)
SVR=60%
SVR=90%
Wait
SVR=90%
SVR=56%
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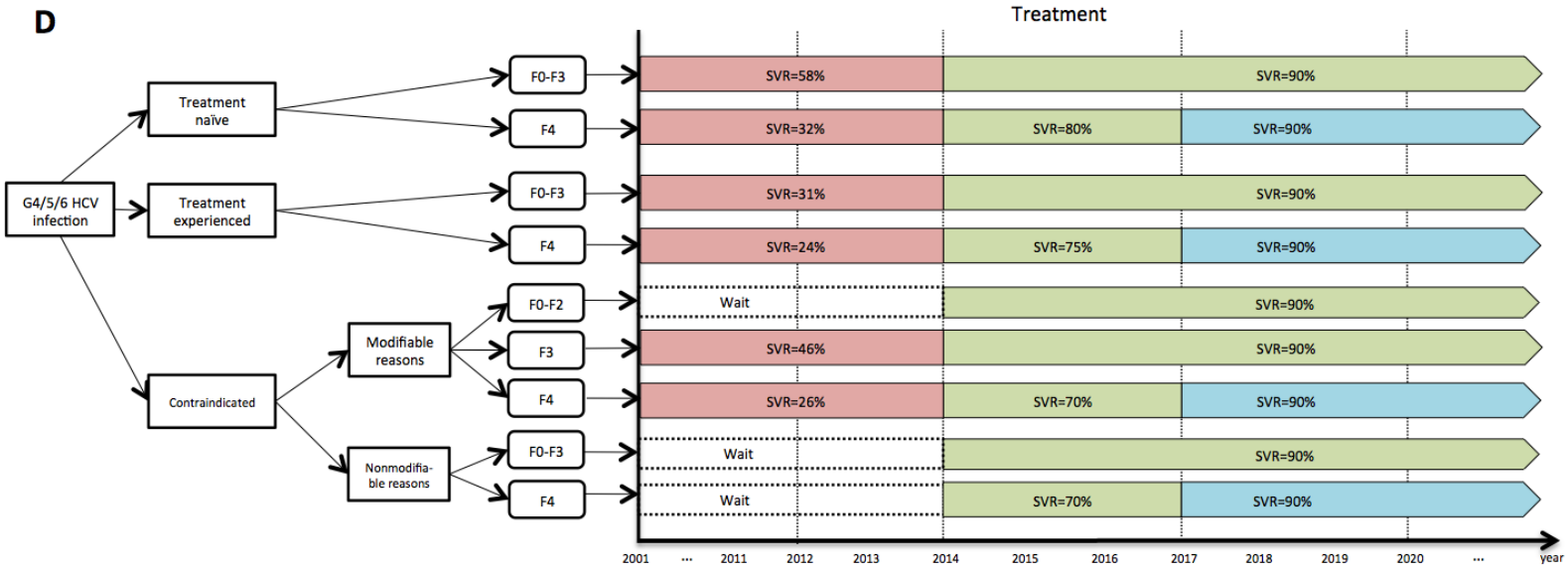


Figure A. 1. Treatment options with the existing and future drugs for patients with (A): HCV genotype 1; (B): HCV genotype 2; (C): HCV genotype 3; (D): HCV genotypes 4–6.

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.

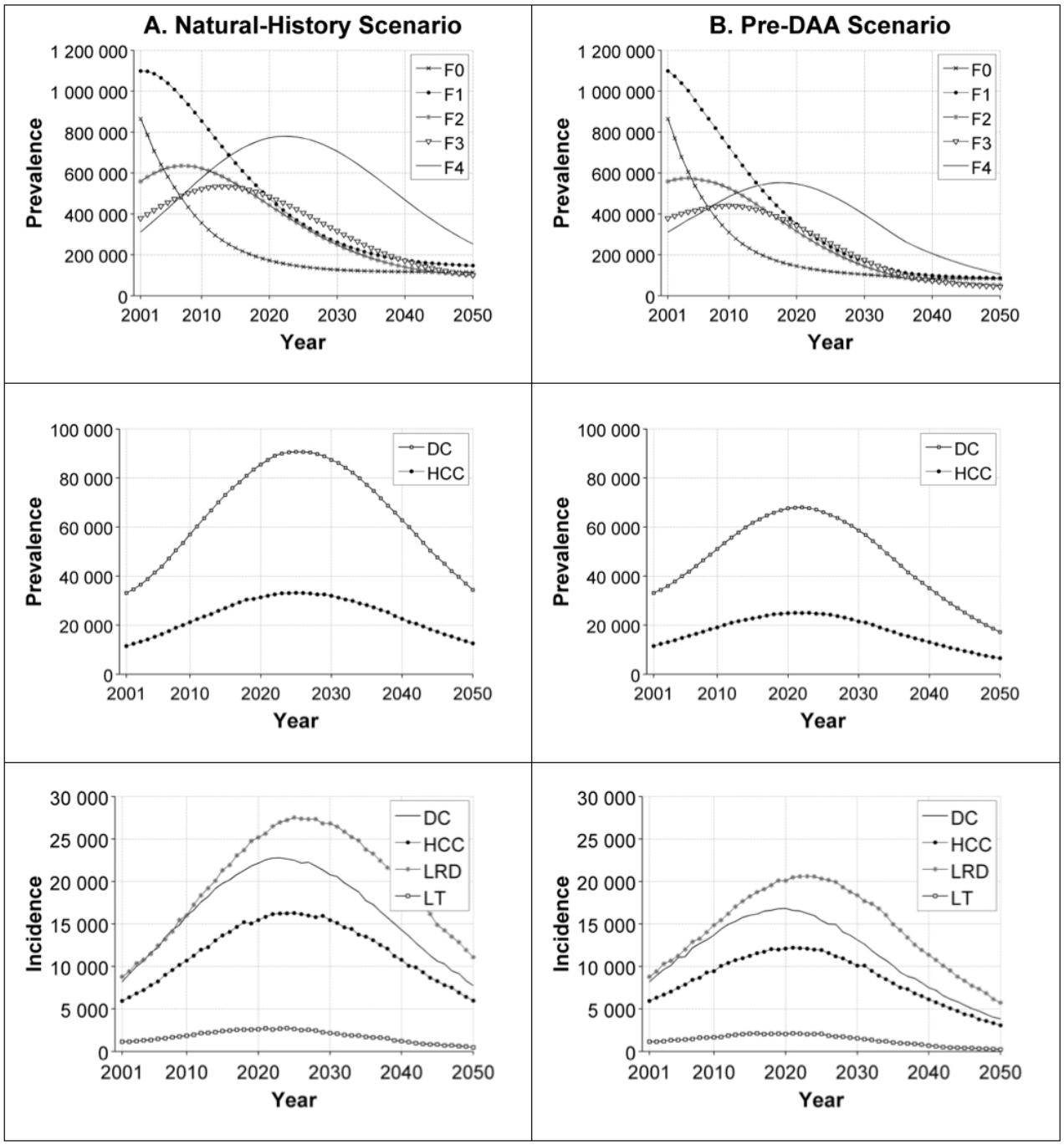


Figure A. 2. Model results according to the natural-history (column A) and the pre-DAA (column B) scenarios from 2001 to 2050.

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. 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.

APPENDIX B: LONG-TERM DISEASE AND ECONOMIC OUTCOMES OF PRIOR AUTHORIZATION CRITERIA FOR HEPATITIS C TREATMENT IN PENNSYLVANIA MEDICAID

This appendix accompanies the third chapter entitled, "Long-term Disease and Economic Outcomes of Prior Authorization Criteria for Hepatitis C Treatment in Pennsylvania Medicaid: A Microsimulation Model" and provides additional data and supporting results.

B.1 CLAIMS-BASED ANALYSES

We included Medicaid beneficiaries in both fee-for-service and managed care plans in our analysis. We searched inpatient, outpatient, and professional claims to identify individuals diagnosed with HCV using HCV ICD-9 codes (**Table B. 1**). Patients dually eligible for Medicare were excluded from the analysis because Medicare would be the primary payer for these enrollees and we lacked access to Medicare paid claims. Using all ICD-9 codes for individuals diagnosed with HCV, we created indicators for potential treatment contraindication (for interferon-based therapies), including substance abuse and depression. In addition, we identified individuals with HCV complications including cirrhosis and liver cancer. In each year, we identified new episodes of decompensated cirrhosis and hepatocellular carcinoma among individuals enrolled in Pennsylvania Medicaid for two consecutive years (in order to identify new diagnoses among those without a diagnosis in the first year). We used CPT codes 47135 and 47136 to identify new liver transplants each year and used this information for model calibration.

In order to inform our simulation model of the estimated number of HCV patients who could receive treatment in Medicaid, we used rates of treatment found in the Pennsylvania Medicaid pharmacy claims for 2007–2012. Specifically, we identified the number of individuals who received HCV peginterferon and ribavirin (PEG-RBV) therapy, and PEG-RBV combined with a first-generation direct acting antiviral –boceprevir or telaprevir. We defined treatment initiation as concurrently filling prescriptions for PEG-RBV with or without boceprevir and telaprevir, given no use of HCV medication in the preceding year. Given that our data extends only through 2012, we could not measure the number of patients receiving newer all-oral HCV therapies, although we received information on the overall number of patients treated with oral HCV therapy in 2014 directly from the Department of Human Services.

Table B. 1. ICD-9 codes, including Hepatitis C and related conditions.

Condition	ICD-9 codes
Hepatitis C virus	07041,07044,07051,07054, V0262, 0707, 07070, 07071
Substance abuse, non-ETOH* codes	292, 2920, 2921, 29211, 29212, 2922, 2928, 29281, 29282, 29283, 29284, 29285, 29289, 2929, 304, 3040, 30400, 30401, 30402, 30403, 3041, 30410, 30411, 30412, 30413, 3042, 30420, 30421, 30422, 30423, 3043, 30430, 30431, 30432, 30433, 3044, 30440, 30441, 30442, 30443, 3045, 30450, 30451, 30452, 30453, 3046, 30460, 30461, 30462, 30463, 3047, 30470, 30471, 30472 , 30473, 3048, 30480, 30481, 30482 , 30483, 3049, 30490 , 30491, 30492 , 30493, 3052, 30520 , 30521, 30522, 30523, 3053, 30530, 30531, 30532, 30533, 3054, 30540 , 30541, 30542, 30543, 3055, 30550, 30551 , 30552 , 30553 , 3056, 30560, 30561 , 30562 , 30563, 3057, 30570, 30571, 30572, 30573, 3058, 30580, 30581, 30582 , 30583 , 3059, 30590, 30591 , 30592 , 30593 , 3576, 76072 , 76073, 76075 , 7795, 965, 9650, 96500, 96501, 96502, 96509, 967, 9670, 9671, 9672, 9673, 9674, 9675, 9676, 9678, 9679, 9680, 9690, 96900, 96901, 96902, 96903, 96904, 96905, 96909, 9691, 9692, 9693, 9694, 9695, 9696, 9697, 96970, 96971, 96972, 96973, 96979, 9698 , 9699 , 9700 , 9701 , 9708 , 9709
Substance abuse, ETOH codes	2910, 2911, 2912, 2913, 2914, 2915, 2918, 29181, 29182, 29189, 2919, 303, 3030, 30300, 30301, 30302, 30303, 3039, 30390, 30391, 30392, 30393, 3050, 30500, 30501, 30502, 30503, 3575, 4255, 5353, 5710, 5711 , 5712 , 5713 , 76071, 7903, 9800, E8600, E8601
Depression	29620, 29621, 29622, 29623, 29624, 29625, 29626, 29630, 29631, 29632, 29633, 29634, 29635, 29636, 29651, 29652, 29653, 29654, 29655, 29656, 29660, 29661, 29662, 29663, 29664, 29665, 29666, 29689, 2980, 3004, 3091, 311
Cirrhosis	5712, 5715, 5716
Decompensated cirrhosis	4560, 4561, 45620, 45621, 78951, 78959, 5722, 5723, 5724, 3483
Hepatocellular carcinoma	1550

*ETOH = Ethanol

B.2 MODEL INPUTS

Figure B. 1 illustrates the progression of hepatitis C disease according to Metavir scoring system. At any given time, a patient is in one of these health states indicated in oval shapes. A patient could transition according to arrows between these health states based on annual probabilities (**Table B. 2**). We defined a health state for patients who achieved SVR in F0–F3 assuming complete clearance of infection, and separated the patients who achieved SVR in F4 since these patients could further progress to the advanced stages of liver disease. Patients in HCC, DC, and LT have a higher mortality than the general population and can transition to "Liver-Related Death" state. All other patients have the same mortality risk as the general population. Our natural history model was previously validated based on a published multi-center study [68]. The model assumed a liver-transplantation upper age limit of 75 years [149].

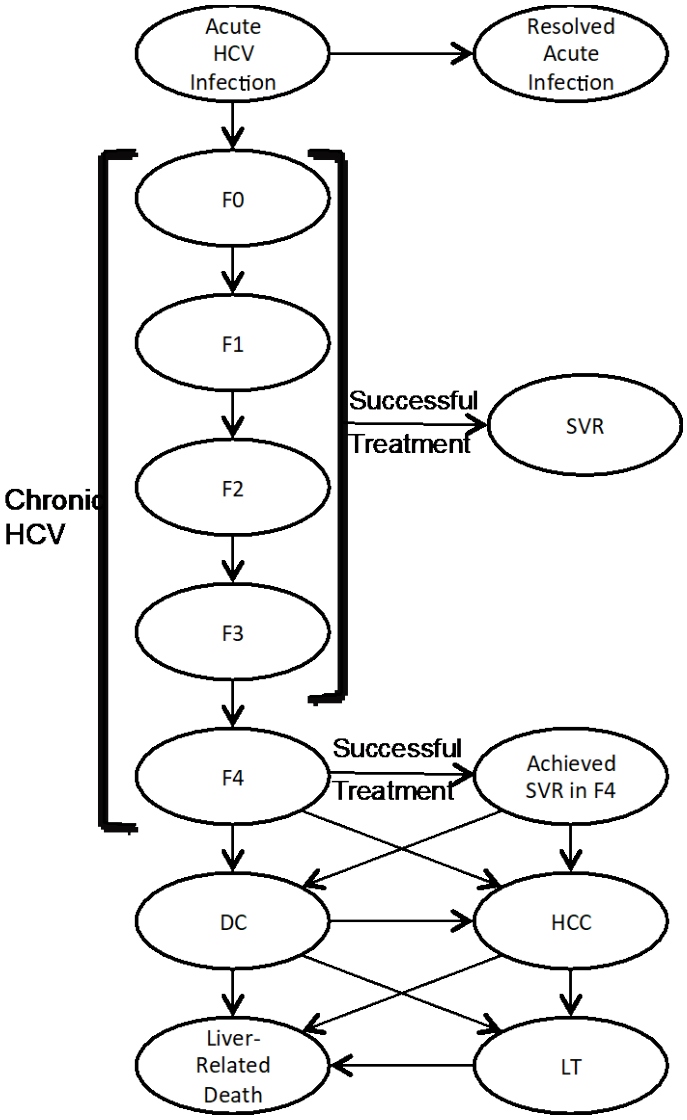


Figure B. 1. The progression of hepatitis C disease according to Metavir scoring system.

Abbreviations: HCV = hepatitis C virus; F0 = Metavir stage for no liver 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; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; LT = liver transplant.

Table B. 2. Annual transition probabilities between health states.

Variable	Transition probabilities	References
F0 to F1	0.117	[136]
F1 to F2	0.085	[136]
F2 to F3	0.120	[136]
F3 to F4	0.116	[136]
F4 to DC	0.029	[137]
F4 to HCC	0.014	[137]
SVR F4 to DC	0.008	[138]
SVR F4 to HCC	0.005	[138]
DC to HCC	0.068	[139]
DC to liver transplantation	0.021	[17, 140]
DC (first year) to liver-related death	0.182	[139]
DC (>1 year) to liver-related death	0.112	[139]
HCC to liver transplantation	0.026	[67, 141]
HCC to liver-related death	0.427	[137]
Liver transplantation (first year) to liver-related death	0.116	[142]

Abbreviations: HCV = hepatitis C virus; F0 = Metavir stage for no liver 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; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; LT = liver transplant. Note: the probability of death from other causes exists in every state according to mortality rates of general population.

We included the demographic characteristics (**Table B. 3**) and rate of contraindication to HCV therapy (pre all-oral therapy) based on claims analyses, and HCV genotypes and HCV awareness status based on national estimates (**Table B. 3**). We accounted for annual HCV incidence according to the Centers for Disease Control and Prevention (CDC) estimates of annual HCV incidence in Pennsylvania during 2006–2012 [150] and assumed that approximately 19% of new cases are in Medicaid [151] (**Table B. 4**). We also accounted for annual Medicaid enrollment fluctuations by adding new enrollees with chronic HCV infection in our model proportional to the enrollment changes in Medicaid during the period of study, adjusting for the decreasing trend in the overall national HCV prevalence over time. In addition to risk-based screening, we included the screening recommendations approved by the CDC and the U.S. Preventative Task Force of one-time screening for individuals born between 1945 and 1965 at a steadily increasing rate

starting in 2012 [46, 56, 57, 60, 120, 152-155]. HCV treatment in our model was based on HCV treatment guidelines since 2001 similar to that in our previously published model [1] and included the recent updates of HCV treatment guidelines in August 2015 published by the American Association for the Study of Liver Diseases and Infectious Disease Society of America [46, 56, 57, 60, 120, 152-155]. Until 2015, we assumed that 80% of individuals eligible for treatment would seek therapy based on published literature [13, 27, 30]. In 2015 and later, we defined annual treatment penetration rate as the annual number of people who were treated in Pennsylvania Medicaid. We chose a penetration rate of 40% as our base case to match what we knew about actual rates of treatment in 2014 and provide for additional treatment capacity over time and performed sensitivity analysis to study the impact of different treatment penetration rates on model outcomes.

Table B. 3. Model input parameters for the HCV-infected population characteristics, distribution of hepatitis C genotype, treatment history in interferon-based treatment era, and the sustained virologic response rates of new therapies according to genotype and treatment history.

Model Input Parameters	Value	Reference
Total HCV-infected population in 2001*	49,900	Based on model validation
Chronic-infection ratio (%)	75	[13]
Percentage of patients unaware of their HCV infection in 2001*	60	[13, 15, 144, 145, 147, 156, 157]
Interferon contraindication (%)	42.77	Medicaid claims data
HCV genotype (%)		[25]
1	73	
2	14	
3	8	
Other	5	
Stage distribution of HCV-infected population in 2001 (%)**		[17]
F0	53.2	
F1	32.0	
F2	7.2	
F3	1.7	
F4	1.5	
Decompensated cirrhosis	1.7	
Hepatocellular carcinoma	0	
Age distribution of HCV-infected population in 2001 (%)		Calibrated based on Medicaid claims data
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	
Age distribution of the new HCV infections (%)		Calibrated based on Medicaid claims data
18–19	3.3	
20–29	26.4	
30–39	27.7	
40–49	24.9	
50–59	13.4	
60–69	4.4	
70–100	0	
Distribution of treatment-experienced patients with peginterferon-ribavirin treatment before 2014 (%)		
Genotype 1		
Relapsers***	53	[158]
Partial responders†	19	[158]
Null responders§	28	[158]
Genotype 2–6		
Relapsers	47	[23]
Partial responders	16	[23]
Null responders	37	[23]

Table B. 3 continued

Model Input Parameters	Value	Reference
SVR rates of the new therapies (%)		
Treatment Naïve		[46, 56, 57, 60, 120, 152-155]
Genotype 1–6 (fibrosis)	90	
Genotype 1–6 (cirrhosis)	80	
Relapser		
Genotype 1/2/4/5/6 (fibrosis)	90	
Genotype 3 (fibrosis)	85	
Genotype 1 (cirrhosis)	80	
Genotype 2 (cirrhosis)	70	
Genotype 3 (cirrhosis)	60	
Genotype 4/5/6 (cirrhosis)	75	
Partial and null responder		
Genotype 1/2/4/5/6 (fibrosis)	90	
Genotype 3 (fibrosis)	85	
Genotype 1 (cirrhosis)	75	
Genotype 2 (cirrhosis)	70	
Genotype 3 (cirrhosis)	60	
Genotype 4/5/6 (cirrhosis)	75	

* The total number of infected population and percentage of individuals who are unaware of their infection was used at the initiation of the simulation, which was chosen as 2001. These values changed in the microsimulation model over time based on screening rates, HCV treatments, and the incidence of HCV in Pennsylvania Medicaid.

** The percentages of individuals in each fibrosis score was used at the initiation of the simulation, which was chosen as 2001. These percentages changed in the microsimulation model over time based on screening rates, HCV treatments, and the incidence of HCV in Pennsylvania Medicaid.

*** Relapser = a patient whose HCV RNA became undetectable during treatment with peginterferon-ribavirin, but reappeared after the end of treatment.

† Partial responder = a patient whose HCV RNA level decreased by 2 log IU/mL or more at week 12 of treatment with peginterferon-ribavirin, but was detectable at week 24.

§ Null responder = a patient whose HCV RNA level decreased less than 2 log IU/mL at week 12 of treatment with peginterferon-ribavirin.

Abbreviations: HCV = hepatitis C virus; F0 = Metavir stage for no liver 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.

Table B. 4. Annual hepatitis C virus infection incidence in Pennsylvania Medicaid.

Year	Incidence in Pennsylvania	Reference	HCV Incidence in Pennsylvania Medicaid
2001	900	Assumption	318
2002	900	Assumption	281
2003	900	Assumption	248
2004	900	Assumption	219
2005	900	Assumption	194
2006	900	CDC	171
2007	680	CDC	129
2008	540	CDC	103
2009	780	CDC	148
2010	520	CDC	99
2011	700	CDC	133
2012	1,320	CDC	251
2013	-	Assumption*	251
2014	-	Assumption	251

* We assumed that hepatitis C incidence in Pennsylvania Medicaid beyond 2013 was similar to that in 2012.

We used the Medicaid prescription claims data to determine the maximum number treated during 2007–2012 (**Table B. 5)**. In previous years, we assumed the number treated was similar to 2007, given no additional data. We obtained the number of patients treated in 2014 from the Pennsylvania Department of Health Services. After 2014, we assumed that 40% of diagnosed HCV-infected individuals who are eligible for treatment would receive it. This rate is higher than the actual treatment rate in Pennsylvania Medicaid in 2014 under the base case (F2–F4 treatment), to account for limitations in provider availability and capacity, besides increased treatment demand due to the availability of highly effective treatments.

Table B. 5. Maximum number of HCV-infected individuals treated annually in Medicaid.

Year	Value	Source
2001	797	Assumption
2002	797	Assumption
2003	797	Assumption
2004	797	Assumption
2005	797	Assumption
2006	797	Assumption
2007	797	Medicaid claims data
2008	863	Medicaid claims data
2009	977	Medicaid claims data
2010	855	Medicaid claims data
2011	807	Medicaid claims data
2012	1,025	Medicaid claims data
2013	1,025	Assumption
2014	1,350	Medicaid data

We calculated the price of combined therapies based on disease stage and the recommended duration of treatment for each new all-oral therapy (**Table B. 6**). We assumed that drug manufacturers would offer wholesale discounts and rebates to Pennsylvania Medicaid program to remain in the competitive drug market, hence we used the average cost of therapy among different therapies in our cost analyses.

Table B. 6. Weekly and 12-week cost of HCV therapies.

Treatment	Treatment Cost						Reference
Regimens developed before 2014	**Weekly**	**12-week therapy**					
Peginterferon	$587	$7,044					[122, 159]
Ribavirin	$309	$3,708					[122, 159]
Boceprevir	$1,100	$13,200					[122, 159]
Telaprevir	$4,100	$49,200					[122, 159]
Regimens developed in 2014 and beyond	**Base price**		**Price in 2014**		**Price in 2015 and beyond**		
	Weekly	**12-week therapy**	**Weekly**	**12-week therapy**	**Weekly**	**12-week therapy**	
Sofosbuvir	$7,000	$84,000	$5,320	$63,840	$3,780	$45,360	[91, 160]
Sofosbuvir-Ledipasvir	$7,875	$94,500	$5,985	$71,820	$4,253	$51,036	[91, 160]
Paritaprevir, ritonavir, ombitasvir, and dasabuvir	$6,943	$83,316	$5,277	$63,324	$3,749	$44,988	[124]

Table B. 7. Annual health state cost in chronic hepatitis C infection.

Health State	Annual Cost	Reference
F0, F1	$728	[94, 95]
F2	$737	[94, 95]
F3	$1,496	[94, 95]
F4	$1,745	[95]
Decompensated cirrhosis	$19,389	[95]
Hepatocellular carcinoma	$35,655	[95]
Liver transplant (first year)	$103,102	[95]
Post Liver transplant	$27,057	[95]

Abbreviations: F0 = Metavir stage for no liver 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.

B.3 SENSITIVITY ANALYSES

We undertook a number of sensitivity analyses: 1) We varied HCV treatment penetrance from 20% to 100% and projected the number of prevented cases of decompensated cirrhosis, hepatocellular carcinoma and liver transplants. We varied HCV treatment penetration based on the assumption that the available number of providers able to treat HCV, and the acceptance of therapy, would not allow 100% of eligible individuals to be treated each year. 2) We varied the percentage of new cases of HCV in Pennsylvania that would be found in Medicaid to 14% and 24% (from our base case of 19%). 3) To account for potential differences in the distribution of genotypes among HCV patient, we modified the proportion of each genotype by ±5%. 4) We repeated the analysis for fibrosis scores and age distributions by changing the percentage of each category by ±10%. 5) Finally, treatment efficacies of regimens were varied by ±10%.

B.4 RESULTS OF CLAIMS-BASED ANALYSES

The proportion of individuals under the age of 30 decreased in 2007–2012, as did the proportion between 40 and 49 (**Table 3.1** of main text). However, the proportions of 30–39 and over 50 age groups increased over time. During 2007–2012, more than 85% of the individuals were enrolled in Medicaid more than 6 months per year, and the percentage of male patients consistently stayed around 53%. The proportion of HCV-diagnosed patients enrolled through Supplemental Security Income (SSI) increased over time, representing almost 50% of the diagnosed HCV population in 2012. The proportion of enrollees with substance use disorder, diabetes or depression—major causes of treatment contraindication in the interferon era—increased from 38.5% in 2007 to almost half (46.7%) of the HCV-diagnosed population in 2012.

B.5 MODEL RESULTS

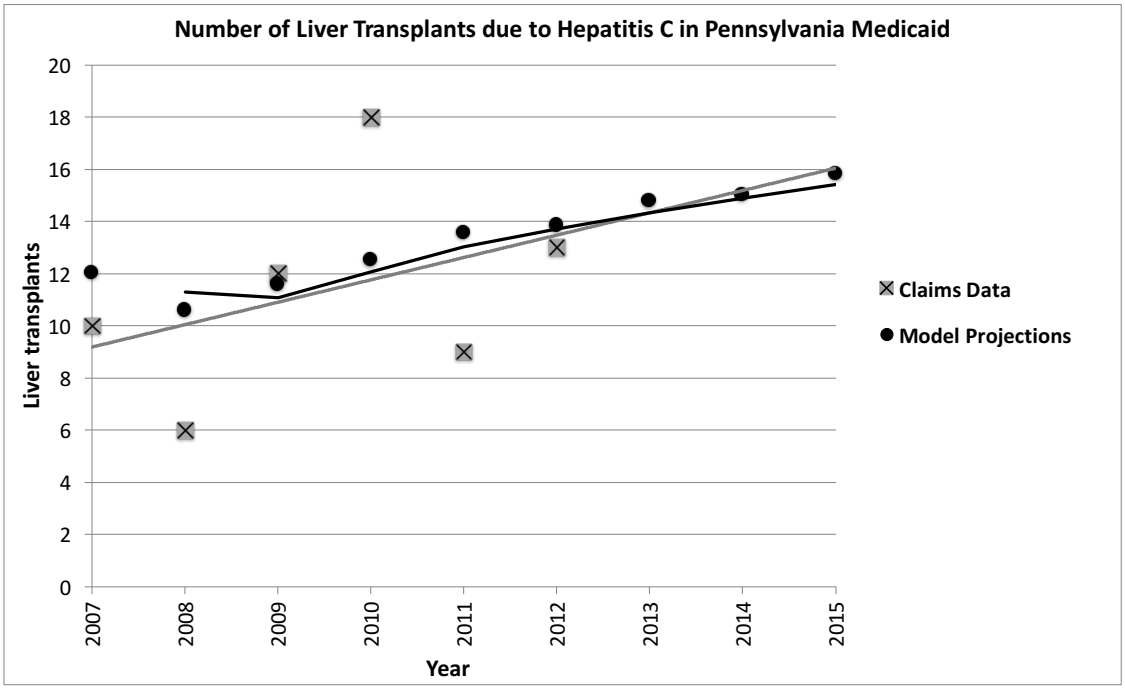


Figure B. 2. Number of liver transplants in Pennsylvania Medicaid based on analyses of claims data and model projections

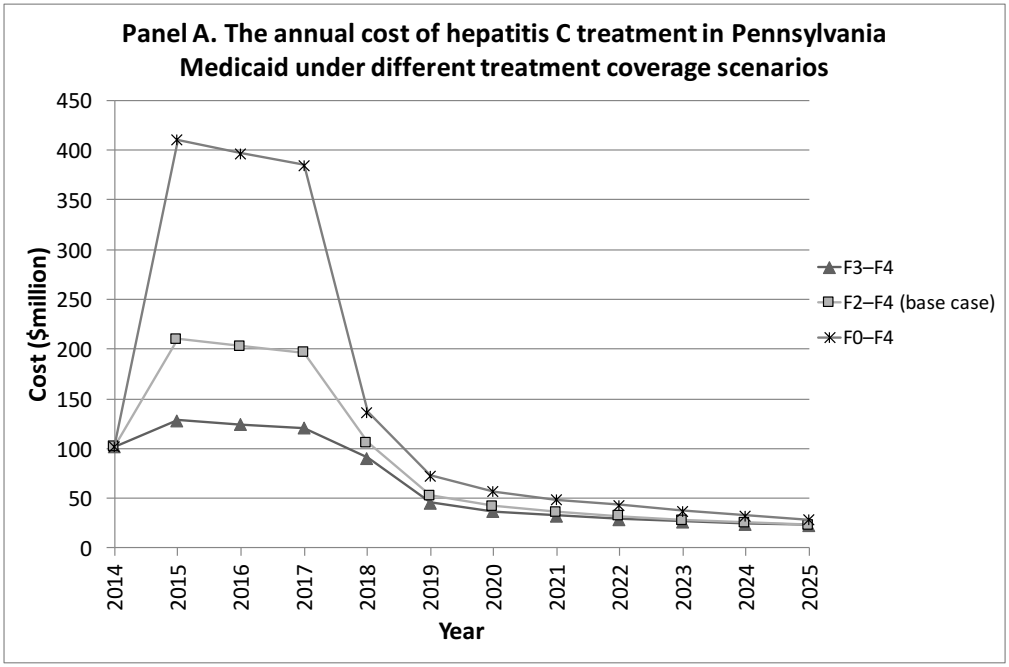
Table B. 8. The number of individuals eligible to receive hepatitis C treatment, and the individuals who received hepatitis C treatment in each fibrosis score in the base-case treatment scenario (coverage for F2–F4 fibrosis), during each year under various treatment penetration rates.

	Number of treatment-eligible patients in fibrosis stage					Number of treated patients in fibrosis stage				
20% treatment penetration rate										
Year	**F0**	**F1**	**F2**	**F3**	**F4**	**F0**	**F1**	**F2**	**F3**	**F4**
2015	3,894	5,913	4,404	3,009	3,177	0	0	878	597	636
2016	3,996	6,091	3,912	2,815	2,861	0	0	860	618	634
2017	4,047	6,243	3,495	2,552	2,496	0	0	863	630	618
2018	4,035	6,253	3,091	2,225	2,098	0	0	884	627	600
2019	3,985	6,215	2,672	1,848	1,663	0	0	911	630	571
2020	3,929	6,141	2,267	1,439	1,230	0	0	972	608	530
2021	3,866	6,041	1,849	1,025	819	0	0	1,057	578	475
2022	3,782	5,937	1,398	616	442	0	0	1,195	511	382
2023	3,678	5,825	864	226	125	0	0	839	207	125
2024	3,590	5,758	668	84	28	0	0	651	74	28
2025	3,490	5,669	620	55	14	0	0	608	50	14
40% treatment penetration rate										
Year	**F0**	**F1**	**F2**	**F3**	**F4**	**F0**	**F1**	**F2**	**F3**	**F4**
2015	3,905	5,974	4,445	3,023	3,220	0	0	1,769	1,208	1,286
2016	4,017	6,161	3,299	2,278	2,323	0	0	1,780	1,222	1,261
2017	4,065	6,307	2,314	1,489	1,381	0	0	1,903	1,214	1,147
2018	4,057	6,326	1,328	648	482	0	0	1,293	616	482
2019	4,025	6,272	894	277	125	0	0	868	257	125
2020	3,956	6,184	808	185	66	0	0	793	176	66
2021	3,867	6,068	749	147	48	0	0	737	141	48
2022	3,800	5,962	712	113	35	0	0	700	107	35
2023	3,720	5,848	671	86	26	0	0	659	82	26
2024	3,619	5,792	652	69	18	0	0	641	66	18
2025	3,501	5,704	623	54	15	0	0	613	51	15
60% treatment penetration rate										
Year	**F0**	**F1**	**F2**	**F3**	**F4**	**F0**	**F1**	**F2**	**F3**	**F4**
2015	3,892	5,916	4,398	3,011	3,181	0	0	2,633	1,801	1,903
2016	3,990	6,090	2,602	1,739	1,716	0	0	2,579	1,716	1,716
2017	4,038	6,246	1,105	499	349	0	0	1,066	464	349
2018	4,034	6,251	922	312	158	0	0	897	292	158

Table B. 8 continued

	Number of treatment-eligible patients in fibrosis stage					Number of treated patients in fibrosis stage				
	F0	**F1**	**F2**	**F3**	**F4**	**F0**	**F1**	**F2**	**F3**	**F4**
2019	3,992	6,213	848	237	90	0	0	834	229	90
2020	3,941	6,142	793	180	63	0	0	780	174	63
2021	3,878	6,052	749	144	48	0	0	736	139	48
2022	3,795	5,946	710	115	34	0	0	697	109	34
2023	3,696	5,835	663	88	24	0	0	651	83	24
2024	3,597	5,764	650	69	18	0	0	639	65	18
2025	3,497	5,677	619	53	13	0	0	608	50	13
80% treatment penetration rate										
Year	**F0**	**F1**	**F2**	**F3**	**F4**	**F0**	**F1**	**F2**	**F3**	**F4**
2015	3,883	5,920	4,392	3,012	3,178	0	0	3,513	2,404	2,541
2016	3,983	6,090	1,940	1,194	1,143	0	0	1,910	1,165	1,143
2017	4,029	6,241	1,063	445	291	0	0	1,025	412	291
2018	4,025	6,249	916	303	151	0	0	896	289	151
2019	3,983	6,212	846	235	90	0	0	832	227	90
2020	3,935	6,134	795	182	63	0	0	781	175	63
2021	3,868	6,045	750	146	49	0	0	737	140	49
2022	3,784	5,940	710	113	35	0	0	698	108	35
2023	3,686	5,825	670	88	26	0	0	658	84	26
2024	3,587	5,754	649	69	18	0	0	639	65	18
2025	3,488	5,665	620	55	13	0	0	610	52	13
100% treatment penetration rate										
Year	**F0**	**F1**	**F2**	**F3**	**F4**	**F0**	**F1**	**F2**	**F3**	**F4**
2015	3,896	5,909	4,399	3,017	3,173	0	0	4,399	3,011	3,173
2016	3,992	6,092	1,275	654	560	0	0	1,238	619	560
2017	4,036	6,237	1,011	396	231	0	0	973	364	231
2018	4,028	6,247	907	294	142	0	0	891	285	142
2019	3,989	6,207	847	237	91	0	0	833	229	91
2020	3,938	6,131	795	180	64	0	0	782	173	64
2021	3,878	6,032	752	143	48	0	0	740	138	48
2022	3,793	5,928	711	111	34	0	0	698	106	34
2023	3,696	5,815	669	85	27	0	0	656	81	27
2024	3,597	5,752	649	70	18	0	0	637	66	18
2025	3,496	5,663	620	56	13	0	0	610	52	13

Abbreviations: F0 = Metavir stage for no liver 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.



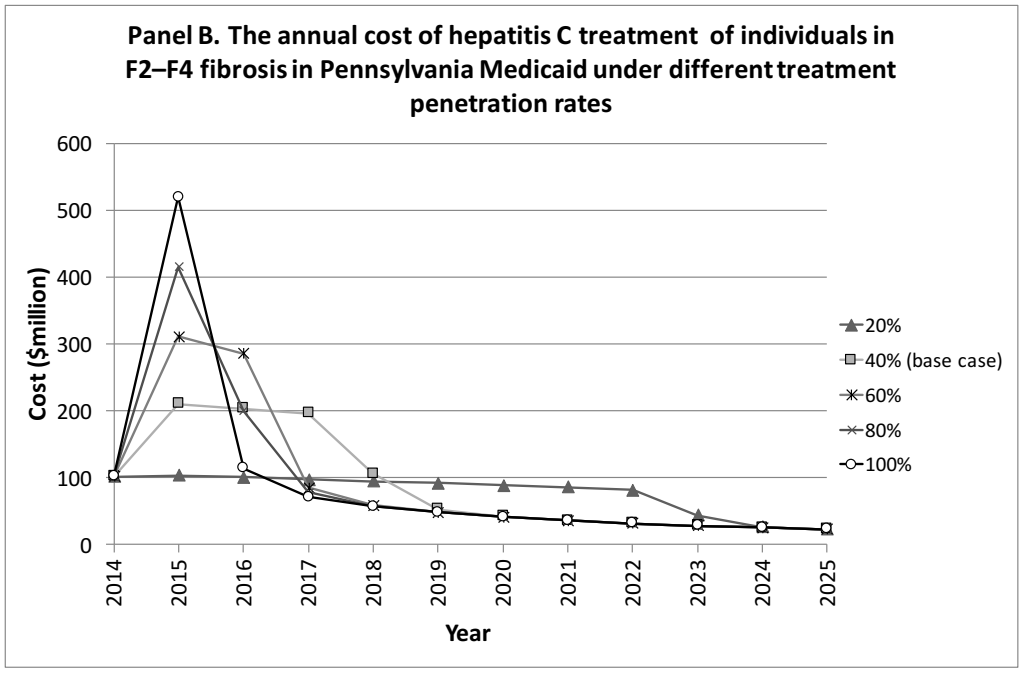
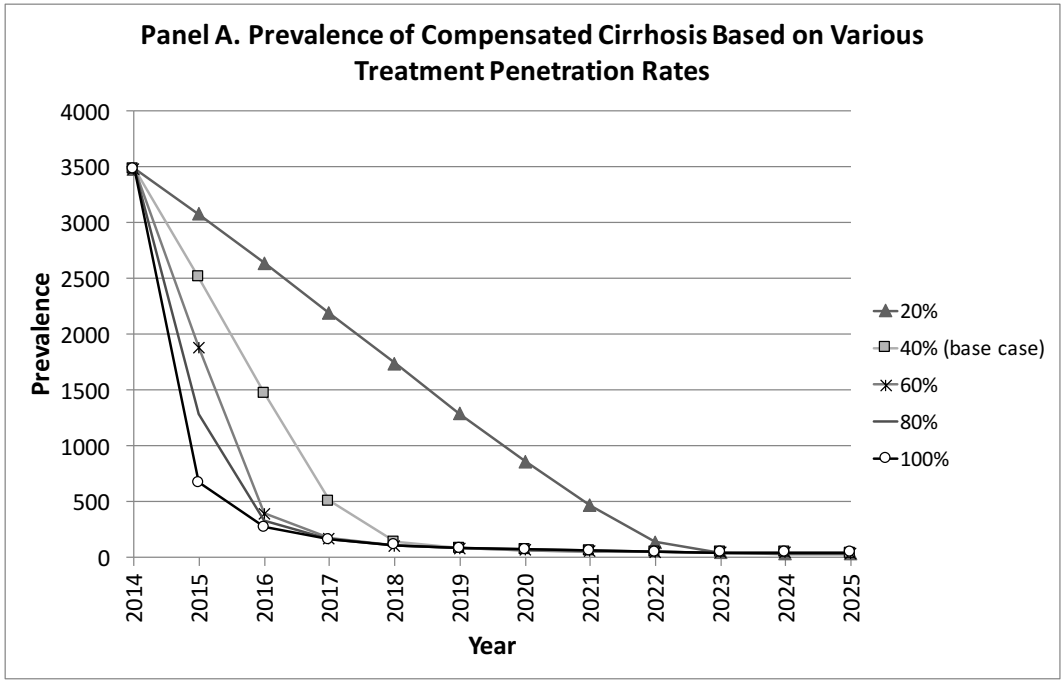
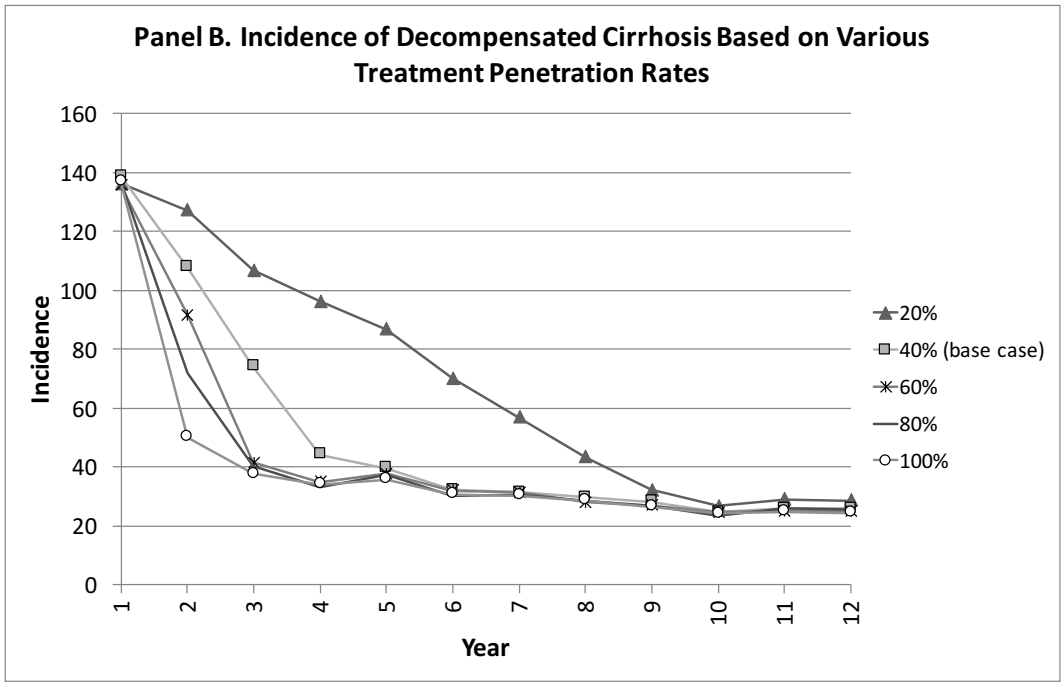


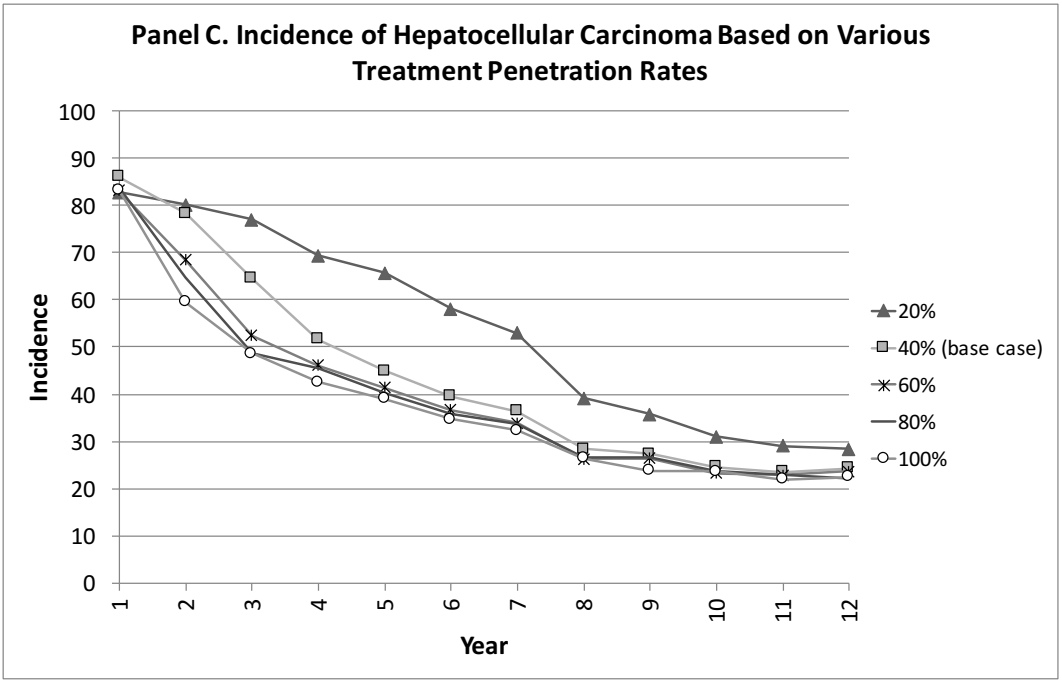
Figure B. 3. The annual cost of hepatitis C treatment in Pennsylvania Medicaid under different treatment cove rage scenarios (Panel A), and various treatment penetration rates in the base-case treatment scenario (coverage for F2–F4 fibrosis) (Panel B).

Abbreviations: F0 = Metavir stage for no liver 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.

Each panel of **Figure B. 4** illustrates the prevalence of compensated cirrhosis, incidence of decompensated cirrhosis, incidence of hepatocellular carcinoma, and number of liver transplants are illustrated at the end of each year in the base-case scenario under different rates of treatment penetration rates. Hence the number of people eligible for treatment in compensated cirrhosis (in **Table B. 8**) is different from the number of people in compensated cirrhosis stage in Panel A of this exhibit.


Panel A. Prevalence of Compensated Cirrhosis Based on Various Treatment Penetration Rates
Prevalence
4000
3500
3000
2500
2000
1500
1000
500
0
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
2025
Year
20%
40% (base case)
60%
80%
100%


Panel B. Incidence of Decompensated Cirrhosis Based on Various Treatment Penetration Rates
Incidence
160
140
120
100
80
60
40
20
0
1
2
3
4
5
6
7
8
9
10
11
12
Year
20%
40% (base case)
60%
80%
100%



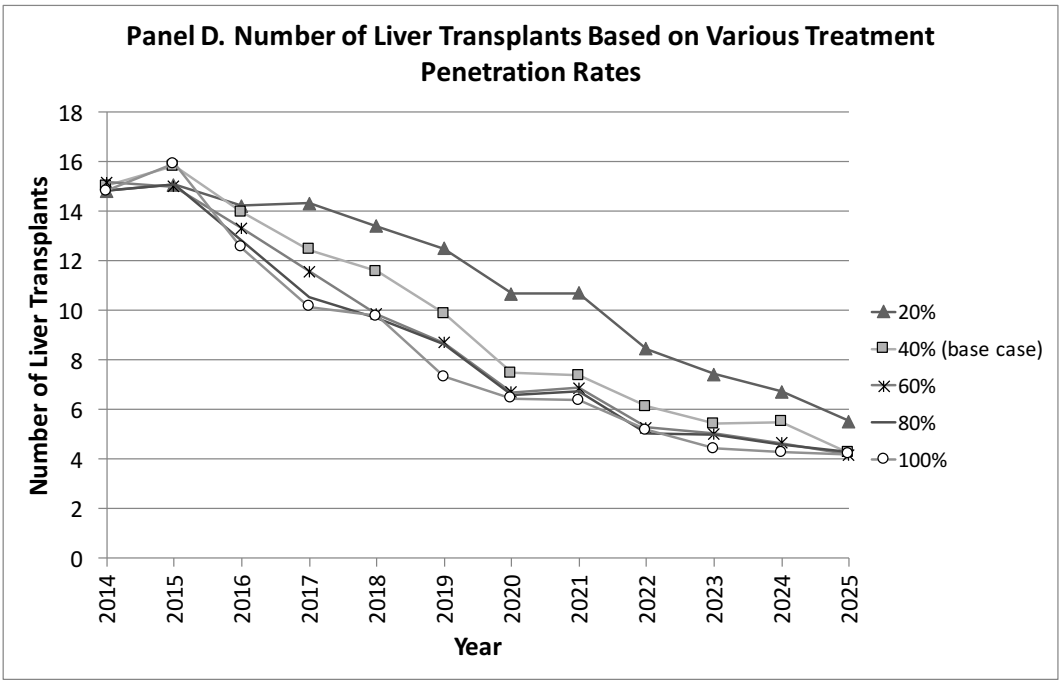


Figure B. 4. Prevalence of compensated cirrhosis (F4) (panel A), incidence of decompensated cirrhosis (panel B), incidence of hepatocellular carcinoma (panel C), and number of liver transplants (panel D) in the base-case scenario under different rates of treatment penetration rates.

Delaying the inclusion of F2 fibrosis level until 2017 or 2020 would have limited impact on the incidence of decompensated cirrhosis, hepatocellular carcinoma, liver transplants and liver-related deaths, and may have beneficial effects if the treatment penetration rate is constrained. For example, delaying the expansion to F2 treatment from 2015 until 2020 under 20% treatment penetration rate would increase chronic disease cost by 16%, but respectively decrease treatment cost and the total incidence of end-stage liver disease by 8% and 30% in Medicaid since some patients with F2 fibrosis would receive treatment instead of patients with F3 fibrosis. However, delaying F2 treatment from 2015 to 2020 under a high treatment penetration rate of 80% would increase chronic disease cost by 7%, and respectively decrease treatment cost and the total incidence of liver complications by 8% and 3%.

Table B. 9. Cumulative incidence of HCV outcomes and costs in 2015–2050 under various scenarios, altering the timing of expanding treatment to F2 fibrosis levels and treatment penetration rates.

Year of F2 treatment availability (treatment penetration rate)***	Cumulative results in Pennsylvania Medicaid						Cumulative results incurred to Medicare					
	Incidence 2015–2050				Cost ($million)		Incidence 2015–2050				Cost ($million)	
	DC	HCC	LT	LRD	Chronic disease 2015–2050*	Treatment 2015–2025 **	DC	HCC	LT	LRD	Chronic disease 2015–2050*	Treatment 2015–2025 **
2015 (20%)	947	778	160	1,591	385	839	1,025	854	123	1,798	218	613
2017 (20%)	616	587	126	1,253	317	948	782	684	101	1,438	164	636
2020 (20%)	616	585	126	1,250	316	950	783	684	97	1,388	163	669
2015 (40%)	696	636	136	1,351	331	955	830	714	104	1,482	173	619
2017 (40%)	620	583	127	1,253	317	948	792	686	99	1,397	164	636
2020 (40%)	616	583	126	1,250	314	906	786	685	99	1,325	163	669
2015 (60%)	618	586	128	1,264	311	974	781	682	98	1,363	163	615
2017 (60%)	617	586	128	1,252	317	947	789	687	99	1,439	164	636
2020 (60%)	617	588	126	1,253	327	906	789	687	100	1,473	164	668
2015 (80%)	598	576	124	1,239	306	984	778	682	97	1,417	162	610
2017 (80%)	615	587	125	1,257	316	947	783	684	98	1,469	163	636
2020 (80%)	615	589	127	1,259	326	906	783	684	98	1,554	163	669
2015 (100%)	569	561	120	1,205	299	996	771	674	98	1,407	161	605
2017 (100%)	615	584	125	1,257	316	948	782	681	100	1,420	163	636
2020 (100%)	616	585	126	1,259	326	906	786	683	99	1,473	163	669

* Chronic disease cost is the cost incurred by chronic stages of hepatitis C virus and the cost of managing associated liver complications.
** Cost of HCV treatment with new antiviral therapies.
*** The base-case scenario was including F2 fibrosis level, besides F3 and F4, in the treatment coverage in 2015, with 40% treatment penetration among patients. Treatment penetration rate is the annual percentage of treatment-eligible Medicaid enrollees who receive treatment. This parameter could be affected by the number of physicians to provide HCV treatment, and individuals' care-seeking behavior.
Abbreviations: F0 = Metavir stage for no liver 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; LT = liver transplant; LRD = liver-related death.

Table B. 10. Impact of input parameter on model results through sensitivity analyses.

		Model outcomes (% difference from base case)							
Sensitivity analysis	**Parameter**	**Total chronic aware in 2015**	**Total chronic in 2015**	**DC cumulative incidence in 2015–2050**	**HCC cumulative incidence in 2015–2050**	**Cumulative LT in 2015–2050**	**Cumulative LRD in 2015–2050**	**Cumulative cost of disease in 2015–2050**	**Cumulative cost of treatment in 2015–2025**
	Base case	31,200	46,700	696	636	136	1,351	331	955
Incidence	**14% of PA incidence**	30,300 (-3)	45,300 (-3)	684 (-2)	626 (-2)	133 (-2)	1,321 (-2)	316 (-5)	920 (-4)
	24% of PA incidence	31,700 (2)	47,700 (2)	694 (-0)	631 (-1)	135 (-1)	1,338 (-1)	337 (2)	967 (1)
Genotype distribution									
	Genotype 1, -5%	31,000 (-1)	46,500 (-0)	688 (-1)	615 (-3)	134 (-2)	1,316 (-3)	327 (-1)	959 (0)
	Genotype 1, +5%	31,000 (-1)	46,500 (-0)	692 (-1)	641 (1)	135 (-1)	1,345 (-0)	328 (-1)	934 (-2)
	Genotype 2, -5%	31,000 (-1)	46,500 (-0)	690 (-1)	636 (0)	135 (-1)	1,333 (-1)	328 (-1)	952 (-0)
	Genotype 2, +5%	31,000 (-1)	46,500 (-0)	686 (-1)	616 (-3)	131 (-4)	1,313 (-3)	325 (-2)	943 (-1)
	Genotype 3, -5%	31,000 (-1)	46,500 (-0)	700 (1)	641 (1)	136 (-0)	1,346 (-0)	328 (-1)	905 (-5)
	Genotype 3, +5%	31,000 (-1)	46,500 (-0)	680 (-2)	611 (-4)	131 (-4)	1,304 (-3)	326 (-2)	988 (3)
	Genotype 4/5/6, -5%	31,000 (-1)	46,500 (-0)	689 (-1)	634 (-0)	135 (-1)	1,339 (-1)	328 (-1)	947 (-1)
	Genotype 4/5/6, +5%	31,000 (-1)	46,500 (-0)	692 (-1)	617 (-3)	131 (-4)	1,317 (-3)	327 (-1)	945 (-1)
Fibrosis distribution of initial population (-10% and +10% for each stage)									
	F0, 47.9%	31,000 (-1)	46,300 (-1)	711 (2)	645 (1)	139 (2)	1,380 (2)	334 (1)	946 (-1)
	F0, 58.5%	31,100 (-0)	46,800 (0)	667 (-4)	602 (-5)	129 (-5)	1,267 (-6)	320 (-4)	944 (-1)
	F1, 28.8%	31,000 (-1)	46,500 (-0)	681 (-2)	621 (-2)	132 (-3)	1,311 (-3)	326 (-2)	940 (-2)
	F1, 35.2%	31,100 (-0)	46,600 (-0)	699 (0)	641 (1)	136 (-0)	1,346 (-0)	328 (-1)	953 (-0)
	F2, 6.5%	31,000 (-1)	46,600 (-0)	683 (-2)	622 (-2)	133 (-2)	1,321 (-2)	326 (-2)	946 (-1)
	F2, 7.9%	31,000 (-1)	46,500 (-0)	697 (0)	631 (-1)	136 (-0)	1,343 (-1)	329 (-1)	948 (-1)
	F3, 1.6%	31,000 (-1)	46,500 (-0)	686 (-1)	627 (-1)	135 (-1)	1,327 (-2)	327 (-1)	946 (-1)
	F3, 1.8%	31,000 (-1)	46,500 (-0)	690 (-1)	628 (-1)	135 (-1)	1,332 (-1)	328 (-1)	947 (-1)
	F4, 1.4%	31,000 (-1)	46,600 (-0)	685 (-2)	626 (-2)	134 (-2)	1,321 (-2)	326 (-2)	947 (-1)
	F4, 1.7%	31,000 (-1)	46,500 (-0)	689 (-1)	629 (-1)	136 (-0)	1,331 (-1)	328 (-1)	946 (-1)
	DC, 4.0%	31,100 (-0)	46,600 (-0)	695 (-0)	634 (-0)	137 (1)	1,332 (-1)	327 (-1)	951 (-0)
	DC, 4.9%	30,900 (-1)	46,400 (-1)	686 (-1)	624 (-2)	132 (-3)	1,322 (-2)	327 (-1)	941 (-2)
Age distribution of initial population (-10% and +10% for each age group)									
	20–29, 28.80%	30,900 (-1)	45,700 (-2)	649 (-7)	585 (-8)	127 (-7)	1,247 (-8)	315 (-5)	919 (-4)
	20–29, 35.20%	31,100 (-0)	47,400 (2)	727 (4)	666 (5)	139 (2)	1,400 (4)	338 (2)	973 (2)
	30–39, 9.00%	30,900 (-1)	46,300 (-1)	684 (-2)	622 (-2)	133 (-2)	1,319 (-2)	326 (-2)	940 (-2)
	30–39, 11.00%	31,200 (0)	46,700 (0)	694 (-0)	630 (-1)	135 (-1)	1,340 (-1)	329 (-1)	953 (-0)
	40–49, 27.00%	30,400 (-3)	46,200 (-1)	709 (2)	641 (1)	135 (-1)	1,352 (0)	328 (-1)	943 (-1)
	40–49, 33.00%	31,600 (1)	46,800 (0)	671 (-4)	613 (-4)	130 (-5)	1,300 (-4)	324 (-2)	950 (-1)
	50–59, 16.14%	31,500 (1)	47,200 (1)	700 (1)	642 (1)	135 (-1)	1,353 (0)	332 (0)	966 (1)
	50–59, 19.72%	30,600 (-2)	45,800 (-2)	679 (-2)	608 (-4)	130 (-5)	1,299 (-4)	321 (-3)	926 (-3)
	60–69, 9.06%	31,300 (0)	47,000 (1)	698 (0)	637 (0)	135 (-1)	1,343 (-1)	331 (-0)	958 (0)
	60–69, 11.08%	30,700 (-2)	46,100 (-1)	681 (-2)	622 (-2)	134 (-1)	1,314 (-3)	324 (-2)	934 (-2)

Abbreviations: F0 = Metavir stage for no liver 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; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; LT = liver transplant; LRD = liver-related death; PA = Pennsylvania.

APPENDIX C: CREATING A SEXUAL PARTNERSHIP NETWORK IN AN AGENT-BASED MODELING PLATFORM USING SURVEY DATA

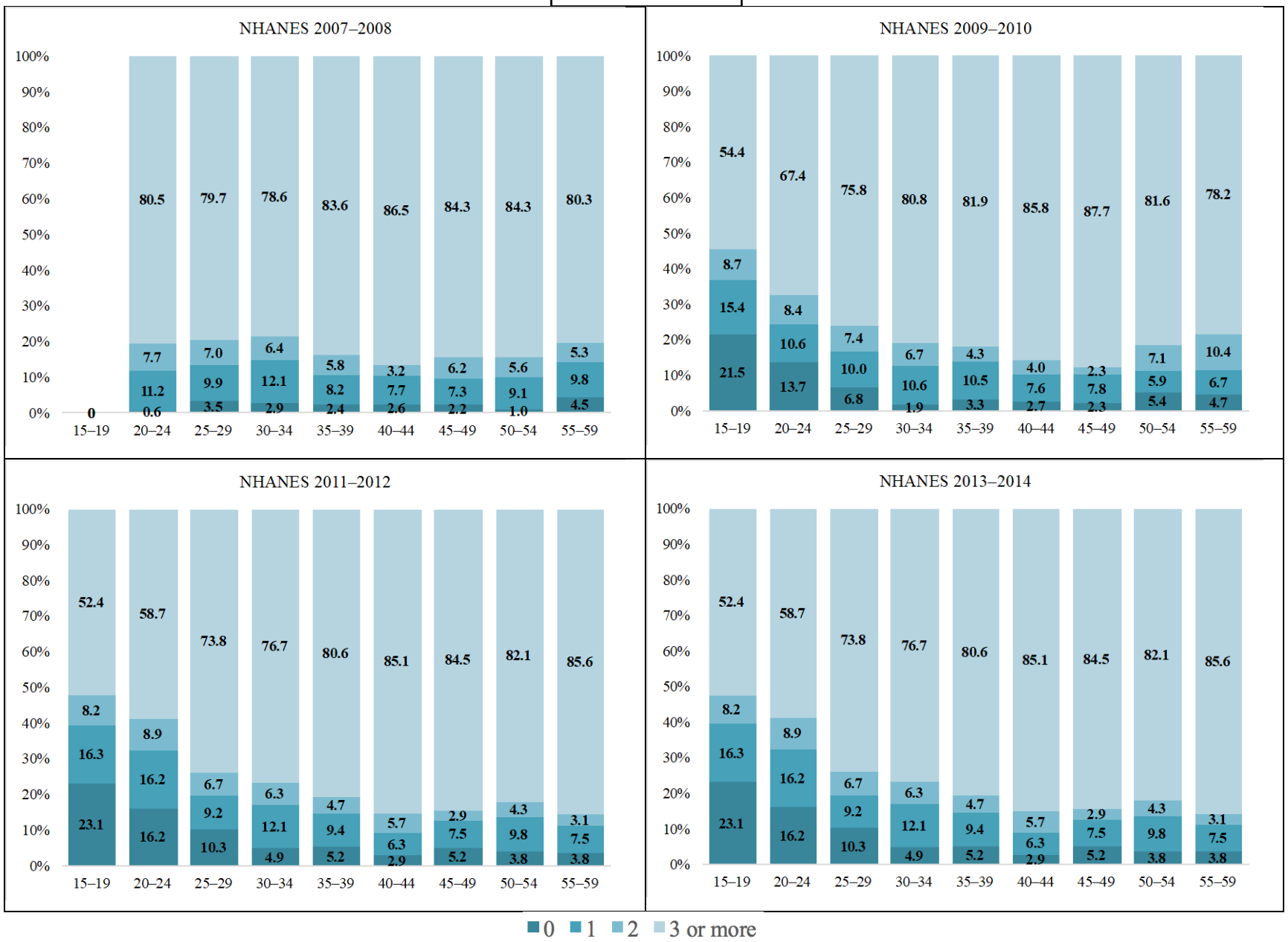
This appendix accompanies the fourth chapter entitled “Creating a Sexual Partnership Network in an Agent-Based Modeling Platform Using Survey Data”, providing additional data and supporting results.

C.1 NUMBER OF SEXUAL PARTNERS

We examined the individual-level demographics and sexual behavior data of multiple NHANES data files [79], in order to identify the number of sexual partners in lifetime by age and sex, using R software.

Figure C. 1 summarizes the data on the number of sexual partners in lifetime for adults by sex and age for selected years of NHANES data. **Table 4.2** of the main text summarizes the data for NHANES 2009–2010.

Panel A: Males



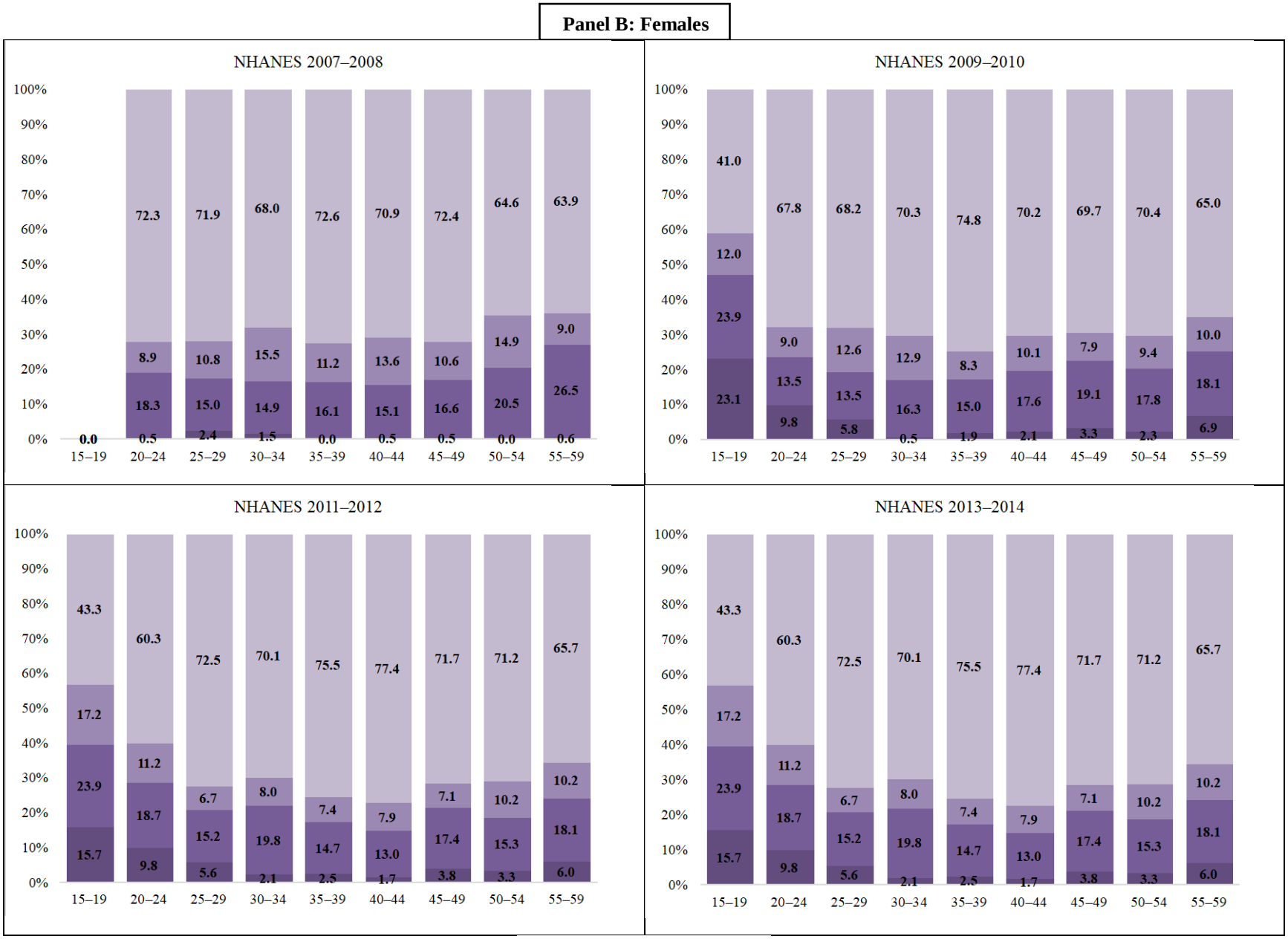


Figure C. 1. The percentage of individuals with different number of partners in lifetime by sex and age.

C.2 SYNTHETIC POPULATION HOUSEHOLDS

We included the information provided by the FRED's synthetic population data on individual's household types in labeling the individuals for their number of desired partners. The household types defined in FRED were as following:

1. single-female
2. single-male
3. opp-sex-sim-age-pair
4. opp-sex-dif-age-pair
5. opp-sex-two-parent-family
6. single-parent-family
7. single-parent-multigen-family
8. two-parent-multigen-family
9. unattended_minors (Excluded)
10. other-family
11. young-roomies
12. older-roomies
13. mixed-roomies
14. same-sex-sim-age-pair (Excluded)
15. same-sex-dif-age-pair (Excluded)
16. same-sex-two-parent-family (Excluded)

Since our objective was to create a heterosexual transmission network, we excluded individuals in 'same-sex-sim-age-pair', 'same-sex-dif-age-pair', 'same-sex-two-parent-family' household types and 'unattended minors'. We assumed that 90% of the individuals in family-type households (categories 3, 5, and 8) were monogamous, i.e. were assigned partnerships labels equal to one). The individuals in other household types were assigned labels so that the overall population included in the simulation had desired partnership labels according to the results of NHANES analysis.

C.3 PARTNERSHIP FORMATION

We matched individuals of opposite sex with respect to their desired number of partners (partnership labels) and age-mixing patterns following these steps:

Step 1. Monogamous relationships: if a male and a female were in one household and both labeled as monogamous in household types 3, 5 and 8, we matched them in a monogamous relationship. Males and females in other household types who were labeled as monogamous, were assigned to a partner based on search algorithm according to sexual mixing patterns by age in **Table 4.3** of the main text.

Step 2. Non-monogamous relationships: We grouped all males and females, who were labeled to have 1, 2, and 3 or more partners who did not have enough matched partner yet, according to their age group. We randomly picked a male from the group of available males, chose the age group of a partner according to age-mixing patterns, and randomly matched him to a female(s) who were “available” in the corresponding age group. We continued this process until every male had enough matched partners according to their desired partnerships label.

C.4 PARTNERSHIP DURATION

Using the probability of first marriage among adult males by age, derived from a survival analysis based on 2006–2010 National Survey of Family Growth (**Table 4.4** of the main text) [84], we calculated the hazard rate of entering a long-term relationship for males over all ages. The probability of entering a long-term relationship was calculated according to this formula:

Probability of entering a long-term relationship = 1- [-ln(age)/0.07 + ln(3.357)]

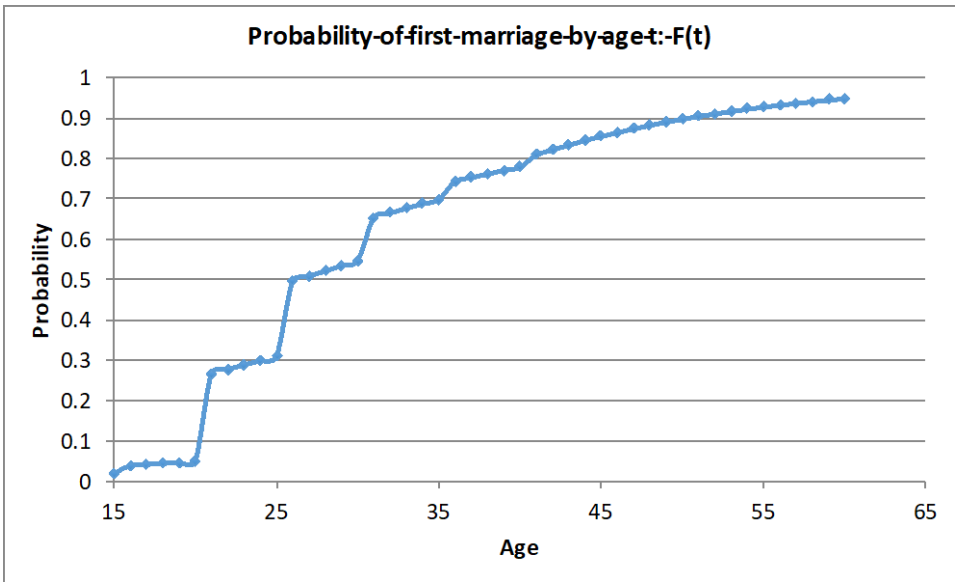


Figure C. 2. The probability of starting a long-term relationship for adult males by age.

We assigned the durations on short-term and long-term partnership durations after defining the partnership duration type, according to the following:

Short-term partnership duration

Table C. 1. The percentage of males categorized by the duration of partnerships in each age group (204 males).

Partnership Duration (%)	Age Category					
	15–19	20–24	25–29	30–34	35–39	40–50
<= 1 year	88.89	47.83	32.14	37.50	43.75	40.00
More than 1 year and less than 3 years	11.11	43.48	50.00	50.00	43.75	45.00
3 years or more	0.00	8.70	17.86	12.50	12.50	15.00

Data source: How Couples Meet and Stay Together (HCMST) [133]

Long-term partnership duration

If an individual started a long-term relationship in a year, we used the probability of first marriages remaining intact for specified durations, according to age at first marriage (**Table C. 2**) calculated based on a survival analysis in the 2006–2010 National Survey of Family Growth [84].

Table C. 2. Probability that a first marriage will remain intact (survive) at specified durations among men aged 15–44 years, age at first marriage: United State, 2006–2010.

	Duration of marriage survival (years)			
Age at first marriage	**5**	**10**	**15**	**20**
Under 20 years	0.66	0.48	0.46	0.41
20–24 years	0.81	0.7	0.6	0.54
25 years and over	0.84	0.76	0.68	N/A

Using this data, we assigned the duration of long-term relationships, by fitting exponential probability distributions to the data for each category of age at first marriage (**Figure C. 3**). The formula for the duration of the long-term relationship in each category of ‘age at first marriage’, based on a random number drawn in the simulation (defined as x):

Age at first marriage: under 20 years

Duration = -ln(x)/0.037 + ln(0.824)

Age at first marriage: 20-24 years

Duration = -ln(x)/0.027 + ln(0.9222)

Age at first marriage: 25 years and older

Duration = -ln(x)/0.021 + ln(0.9353)

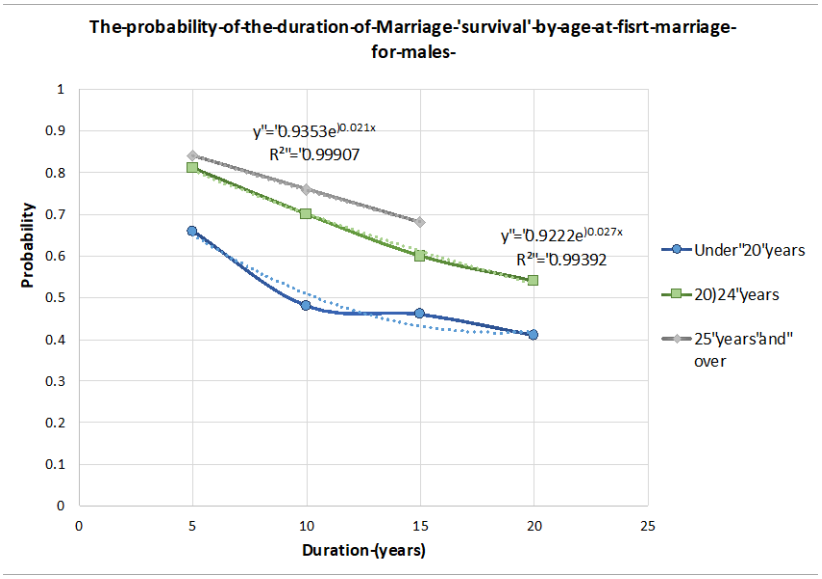


Figure C. 3. Fitted exponential probability distributions of marriage duration by age at first marriage.

C.5 PARTNERSHIP CONCURRENCY

We assumed the following in assigning partnership concurrencies:

- Adults with 2 or more partners could have concurrent partnerships according to the duration of partnerships assigned to each of their partners.
- If a new partner is assigned to an individual in a year, the start and end dates of the new partnership are assigned according to the concurrency duration with the individual's other partners (if any).
- At the beginning of each year, we identified the partner with the longest duration left in partnership, and calculated the concurrency duration for that partner with each of the other partners according to **Table C. 3**.
- If a person had one or more matched partners, having a long-term partner was determined first.
- If the person had a long-term partner, a partner was randomly picked for a long-term relationship from the matched partners. The duration of this partnership is calculated according to the long-term partnership distribution described in **Appendix C. 3**.
- A person with multiple partners could have a long-term partnership only with one partner. i.e. maximum one long-term partnership at each point in time.

Table C. 3. Duration of concurrent partnership according to number of partners and their corresponding duration.

Partner of an individual	**Duration of partnership left (in days)**	**Number of concurrent days during the year**
Partner 1* Partner 2	≥ 365 ≥ 365	Concurrent days equal 365 days
Partner 1 Partner 2	≥ 365 < 365	Concurrent days equal the number of days left in Partner 2's partnership this year. The partnership starts and ends days of partner 2 are randomly determined in the year.
Partner 1 Partner 2	< 365 < 365	If the sum of Partner 1 and partner 2's days left in partnerships is greater than 365 days: The minimum number of concurrent days = number of days left in partner 1's partnership + number of days left in partner 2's partnership - 365 The maximum number of concurrent days = minimum of the number of days left in partner 1's partnership and number of days left in partner 2's partnership Concurrent days = uniform distribution with minimum and maximum limits described above Pick a partner randomly to start the partnership first, and assign her start and end partnership days randomly, given that both Partner 1 and Partner 2's relationships should fit in the same year. Calculate the start and end days of the other partner, given the number of concurrent days and duration left. If the sum of partner 1 and partner 2's days left in partnerships is less than 365 days, there MIGHT be no overlap between their partnerships. The probability of having a concurrent relationship among adult males was calculated at 15.2% [122]. First a random number was drawn and compared to 0.152. If the random number is less than 0.152 (to have overlapping days) The minimum number of concurrent days = 1 The maximum number of concurrent days = minimum of the number of days left in partner 1's partnership and number of days left in partner 2's partnership Concurrent days = uniform distribution with minimum and maximum limits described above Pick a partner randomly to start the partnership first, and assign her start and end partnership days randomly, given that both Partner 1 and Partner 2's relationships should fit in the same year. Calculate the start and end days of the other partner, given the number of concurrent days and duration left. If the random number is greater than 0.152, concurrent days equal zero. Pick a partner randomly to start the partnership first, and assign her start and end partnership days randomly, given that both Partner 1 and Partner 2's relationships should fit in the same year. Calculate the start and end days of the other partner, given the duration left, and zero overlapping days.

* Assumption in table: Partner 1 has the longest duration of partnership left.

C.6 PROBABILITY OF SEXUAL ACT

The number of sexual acts for American males and females were obtained from a study published by Smith [134]. Among American males aged 18–29, sexual acts frequency averages about 84 times per year. This then falls off steadily to 63.5 times per year for those in their 40s to 10 times per year for those 70 and older. **Table C. 4** presents the average number of sexual acts per year per gender and age category. The process of assigning a sexual act to a partnership on a given day was as following:

1. Calculated the probability of a sexual act occurring on a day which equaled: the average number of sexual acts per year divided by 365 days
2. Drew a random number each day for a person who had matched partners.
3. If the random number was less than the probability of a sexual act, we assigned a sexual act to this person.
4. Picked randomly among the matched partners of this person for the sexual act.

Table C. 4. Average number of sexual acts for adult males and females based on age category.

Age	Mean number of sexual acts per year	
	Males	**Females**
18–29	84.4	83.6
30–39	82.4	78.0
40–49	68.1	59.7
50–59	55.1	37.9
60–69	36.1	19.6
70+	17.3	5.5

C.7 SEXUAL PARTNERSHIP NETWORK RESULTS

Table C. 5. Model results for the the cross-sectional distribution of the individuals with different number of partners in lifetime by age group over 10 simulation years.

Year 1							
Age	0	1	2	3 or more	3–6	7–14	15 or more
15–19	25.1	13.4	17.5	44.0	45.0	19.7	35.3
20–24	9.5	8.5	9.4	72.6	47.0	29.0	24.0
25–29	3.8	17.8	7.5	71.0	47.5	29.4	23.1
30–34	2.6	8.4	10.4	78.6	43.2	28.3	28.6
35–39	4.7	7.9	5.5	81.9	34.1	33.0	33.0
40–44	4.6	10.9	7.3	77.1	31.6	34.4	34.0
45–49	5.8	10.6	5.7	77.9	80.1	16.9	3.1
50–54	6.7	10.7	11.2	71.4	85.7	14.3	0.0
55–59	7.3	10.8	11.8	70.1	86.5	13.5	0.0
Year 2							
15–19	21.1	19.4	13.0	46.6	59.7	14.5	25.7
20–24	9.0	7.5	10.5	73.0	47.5	25.5	27.1
25–29	2.5	14.3	6.9	76.2	46.8	28.9	24.3
30–34	3.0	11.6	9.4	76.1	43.8	26.4	29.9
35–39	4.0	7.1	6.8	82.1	35.9	29.9	34.1
40–44	4.7	10.4	6.9	78.0	29.7	34.1	36.2
45–49	5.6	10.6	6.1	77.8	71.8	21.6	6.5
50–54	6.4	10.6	10.7	72.2	80.4	19.4	0.2
55–59	7.1	10.8	11.9	70.3	80.9	18.9	0.2
Year 3							
15–19	18.3	20.3	10.5	50.9	67.1	12.0	20.9
20–24	10.7	6.4	10.3	72.6	49.5	23.7	26.8
25–29	4.2	10.1	6.2	79.5	46.5	27.8	25.7
30–34	3.2	15.0	8.7	73.1	44.6	25.4	30.0
35–39	3.3	6.4	8.1	82.3	37.8	28.3	34.0
40–44	4.7	9.8	6.4	79.0	28.5	33.8	37.7
45–49	5.4	10.6	6.3	77.7	65.1	24.7	10.2
50–54	6.2	10.5	10.3	73.0	76.0	23.3	0.7
55–59	6.9	10.7	11.9	70.5	76.2	23.0	0.8
Year 4							
15–19	25.4	16.5	8.6	49.6	72.9	16.6	10.5
20–24	10.8	8.5	8.7	72.0	48.6	18.2	33.2
25–29	3.8	11.3	5.4	79.5	46.5	26.5	27.0
30–34	3.3	16.5	8.0	72.1	45.7	24.4	29.9
35–39	2.5	5.6	9.4	82.5	39.5	26.6	33.9
40–44	4.8	9.1	5.7	80.3	27.1	33.8	39.1
45–49	5.2	10.6	6.6	77.6	59.5	26.7	13.8
50–54	6.0	10.3	9.9	73.7	72.2	26.4	1.4
55–59	6.7	10.6	12.0	70.7	72.2	26.3	1.5
Year 5							
15–19	21.1	17.9	9.5	51.5	74.1	16.9	9.0
20–24	10.7	10.5	7.6	71.2	51.1	16.2	32.7
25–29	4.7	8.2	5.5	81.6	47.2	24.8	28.0
30–34	3.4	18.0	7.7	71.0	47.5	23.8	28.7
35–39	1.8	4.9	10.4	82.8	41.3	25.0	33.7
40–44	4.9	8.3	4.8	82.0	26.3	33.7	40.1
45–49	5.0	10.6	6.9	77.5	54.5	28.0	17.5
50–54	5.9	10.2	9.5	74.4	68.9	29.0	2.2
55–59	6.5	10.5	12.1	70.8	68.9	28.8	2.3

Year 6							
Age	0	1	2	3 or more	3–6	7–14	15 or more
15–19	18.5	20.3	9.8	51.5	74.9	16.4	8.7
20–24	5.6	10.7	6.3	77.3	54.1	15.7	30.1
25–29	4.9	3.1	4.9	87.1	49.2	21.8	29.0
30–34	2.5	17.9	7.2	72.4	46.1	25.4	28.5
35–39	2.2	8.1	9.6	80.1	41.5	24.4	34.1
40–44	4.3	7.5	5.9	82.4	28.4	32.3	39.3
45–49	4.9	10.6	7.0	77.5	50.7	29.0	20.3
50–54	5.7	10.1	9.2	74.9	65.4	30.7	3.8
55–59	6.3	10.4	12.1	71.2	65.9	31.0	3.1
Year 7							
15–19	17.4	20.8	9.9	51.8	76.5	15.7	7.8
20–24	4.0	10.5	5.5	80.0	56.7	15.4	27.9
25–29	6.3	5.2	5.5	83.0	50.2	19.6	30.2
30–34	1.8	14.0	6.5	77.7	45.4	25.5	29.1
35–39	2.4	10.9	9.1	77.6	42.0	24.1	34.0
40–44	3.6	6.6	7.0	82.7	30.4	31.1	38.5
45–49	4.8	10.5	7.1	77.6	47.6	29.7	22.7
50–54	5.6	10.1	9.1	75.3	62.2	31.9	6.0
55–59	6.2	10.3	11.9	71.6	63.2	32.7	4.1
Year 8							
15–19	26.5	16.8	8.7	48.0	76.7	16.1	7.2
20–24	5.5	9.7	4.7	80.1	58.5	14.5	27.0
25–29	7.2	8.6	6.2	78.0	52.0	18.2	29.8
30–34	1.1	15.2	5.6	78.1	44.7	25.1	30.3
35–39	2.6	13.8	8.9	74.7	42.9	23.8	33.3
40–44	3.0	5.9	8.1	82.9	32.2	29.9	37.9
45–49	4.8	10.4	7.1	77.7	45.0	30.3	24.6
50–54	5.4	10.1	9.0	75.5	59.2	32.6	8.3
55–59	6.0	10.2	11.7	72.1	60.8	34.1	5.2
Year 9							
15–19	22.2	17.8	9.5	50.5	75.8	15.7	8.6
20–24	5.0	10.2	4.9	79.9	63.5	15.7	20.7
25–29	7.0	10.8	6.3	75.9	50.3	14.7	35.0
30–34	0.5	13.1	4.8	81.6	44.2	24.6	31.2
35–39	2.7	16.5	8.7	72.1	44.3	23.2	32.5
40–44	2.3	5.1	9.3	83.3	34.0	28.9	37.1
45–49	4.7	10.2	7.0	78.0	42.9	30.8	26.3
50–54	5.3	10.1	8.9	75.7	56.4	33.0	10.6
55–59	5.9	10.1	11.4	72.6	58.6	35.1	6.3
Year 10							
15–19	18.3	19.8	9.8	52.1	75.0	16.6	8.4
20–24	6.5	9.8	4.7	79.0	64.2	16.0	19.8
25–29	6.6	12.8	6.4	74.2	52.2	13.5	34.3
30–34	0.0	13.0	5.7	81.3	44.1	23.6	32.3
35–39	2.8	15.6	8.7	72.9	46.0	22.9	31.1
40–44	1.7	4.5	10.2	83.6	35.8	27.6	36.6
45–49	4.7	10.1	6.9	78.3	41.1	31.2	27.7
50–54	5.2	10.1	8.9	75.8	53.7	33.2	13.1
55–59	5.7	10.0	11.1	73.1	56.7	35.8	7.6

Table C. 6. The difference in the percentages of people in each partner in lifetime category, between model results over 10 years and NHANES 2009–2010.

Age	0	1	2	3 or more	3–6	7–14	15 or more
15–19	0.9	1.3	-0.4	-1.7	-7.3	10.3	-3.0
20–24	4.3	2.9	1.4	-8.7	-7.9	12.6	-4.7
25–29	1.2	1.3	3.8	-6.3	-10.5	10.1	0.4
30–34	-0.8	-0.4	2.4	-1.2	-5.0	5.8	-0.8
35–39	-0.4	2.6	-2.0	-0.1	-4.4	7.8	-3.4
40–44	-1.4	4.8	-0.4	-3.1	10.3	-3.5	-6.8
45–49	-2.3	3.0	-1.6	0.9	-14.3	-5.6	19.8
50–54	-1.9	1.6	-1.5	1.8	-23.9	-0.8	24.7
55–59	-0.7	2.0	-1.6	0.3	-22.7	-3.1	25.9

Note: Each value presents the average of differences (the value in NAHNES 2009–2010 minus the value in model results) over 10 years.

Table C. 7. Model results for the the cross-sectional distribution of the individuals with different number of partners in a year by age group over 10 simulation years.

Year 1							
Age	**0**	**1**	**2**	**3 or more**	**3–6**	**7–14**	**15 or more**
15–19	30.3	28.0	7.2	34.4	72.7	11.0	16.3
20–24	14.3	42.3	5.6	37.8	59.9	32.9	7.2
25–29	9.8	53.6	8.1	28.5	62.5	32.0	5.5
30–34	22.1	56.0	4.7	17.2	68.5	31.0	0.5
35–39	23.6	55.6	3.8	17.1	72.7	27.3	0.0
40–44	20.8	62.4	4.0	12.8	73.0	27.0	0.0
45–49	49.8	43.0	2.7	4.5	95.7	4.3	0.0
50–54	58.7	34.3	2.6	4.4	97.9	2.2	0.0
55–59	63.3	29.9	2.6	4.3	98.5	1.5	0.0
Year 2							
15–19	27.8	34.9	10.9	26.4	71.1	13.1	15.8
20–24	24.4	47.6	5.9	22.1	53.7	36.5	9.8
25–29	17.8	58.6	6.2	17.4	54.9	36.6	8.5
30–34	25.2	59.8	3.9	11.2	63.7	35.2	1.1
35–39	26.1	61.5	2.5	9.9	62.3	37.7	0.0
40–44	22.6	66.1	2.2	9.1	61.8	38.2	0.0
45–49	44.0	47.4	2.8	5.9	91.2	8.8	0.0
50–54	53.0	38.3	2.8	5.9	94.8	5.2	0.0
55–59	57.6	33.6	2.7	6.0	95.1	4.9	0.0
Year 3							
15–19	26.3	36.1	11.2	26.4	69.8	15.3	14.8
20–24	30.4	45.4	4.9	19.4	48.3	40.8	10.9
25–29	20.8	57.3	5.5	16.4	43.9	45.8	10.3
30–34	26.5	59.1	3.5	10.8	58.7	40.2	1.1
35–39	27.1	61.7	2.2	9.1	54.4	45.6	0.0
40–44	23.2	65.5	2.1	9.2	55.6	44.4	0.0
45–49	40.4	50.5	2.7	6.4	88.4	11.6	0.0
50–54	49.7	40.6	2.9	6.8	93.9	6.1	0.0
55–59	54.4	35.8	2.8	7.0	94.3	5.7	0.0
Year 4							
15–19	33.8	34.3	10.4	21.5	69.3	22.8	7.9
20–24	34.6	39.9	4.0	21.5	43.1	40.0	17.0
25–29	24.4	54.5	4.3	16.8	38.3	50.9	10.7
30–34	30.4	55.5	3.1	11.0	57.9	40.9	1.2
35–39	28.5	59.1	2.1	10.3	57.0	42.9	0.1
40–44	24.2	62.5	2.2	11.2	56.9	43.0	0.1
45–49	38.3	52.5	2.7	6.5	85.8	14.2	0.0
50–54	48.3	41.7	3.0	7.1	93.9	6.1	0.0
55–59	53.3	36.5	3.0	7.3	94.3	5.7	0.0
Year 5							
15–19	29.1	35.2	11.7	24.1	74.3	19.8	5.9
20–24	36.7	38.3	3.8	21.1	39.6	46.9	13.5
25–29	23.4	56.0	3.6	16.9	30.3	58.9	10.7
30–34	30.9	56.5	2.7	9.8	46.4	52.5	1.1
35–39	29.1	59.9	1.6	9.4	46.2	53.7	0.1
40–44	24.4	63.2	1.7	10.8	46.0	53.8	0.2
45–49	36.4	54.5	2.6	6.5	83.1	16.8	0.1
50–54	47.4	42.3	3.0	7.2	93.9	6.1	0.0
55–59	52.9	36.8	3.0	7.4	94.4	5.6	0.0

Year 6							
Age	**0**	**1**	**2**	**3 or more**	**3–6**	**7–14**	**15 or more**
15–19	25.5	37.9	11.0	25.6	75.0	18.7	6.2
20–24	34.6	40.1	4.1	21.2	39.0	49.5	11.5
25–29	28.7	53.1	2.9	15.2	25.1	63.3	11.5
30–34	30.0	57.2	2.5	10.3	42.4	55.7	1.9
35–39	29.3	59.9	1.6	9.2	42.3	57.5	0.2
40–44	25.1	63.1	1.5	10.3	43.9	55.8	0.2
45–49	35.0	56.1	2.5	6.5	81.1	18.8	0.1
50–54	46.5	43.1	3.1	7.3	92.9	7.1	0.0
55–59	52.4	37.0	3.0	7.6	94.4	5.6	0.0
Year 7							
15–19	25.6	38.0	11.8	24.6	75.3	19.5	5.3
20–24	35.0	40.3	4.3	20.4	39.9	49.5	10.6
25–29	31.9	50.4	2.5	15.2	24.5	64.7	10.9
30–34	29.1	57.4	2.3	11.3	40.8	57.3	2.0
35–39	29.7	59.5	1.7	9.0	42.3	57.3	0.4
40–44	25.6	62.9	1.4	10.1	43.0	56.9	0.1
45–49	33.9	57.2	2.5	6.4	79.8	20.2	0.1
50–54	45.4	44.2	3.0	7.3	91.3	8.7	0.1
55–59	51.8	37.4	3.1	7.7	94.5	5.5	0.0
Year 8							
15–19	34.9	34.3	10.5	20.3	72.8	23.1	4.2
20–24	34.6	40.6	4.1	20.8	40.6	49.4	10.0
25–29	37.0	46.7	2.2	14.1	24.6	66.1	9.3
30–34	28.2	57.0	2.3	12.6	40.0	58.2	1.8
35–39	29.9	59.2	1.8	9.1	42.7	57.1	0.2
40–44	25.9	62.5	1.4	10.2	44.2	55.7	0.2
45–49	33.1	58.1	2.4	6.4	78.9	21.0	0.1
50–54	44.4	45.5	3.0	7.2	89.8	10.1	0.1
55–59	51.3	37.9	3.1	7.7	94.5	5.5	0.0
Year 9							
15–19	29.9	34.9	11.6	23.7	75.6	18.6	5.8
20–24	37.2	41.2	4.4	17.2	45.3	46.6	8.1
25–29	38.2	43.9	1.7	16.3	22.5	68.7	8.7
30–34	27.0	56.6	2.3	14.1	38.9	59.7	1.4
35–39	30.2	58.8	1.9	9.0	41.6	58.0	0.4
40–44	26.2	62.4	1.3	10.1	44.4	55.4	0.2
45–49	32.5	58.9	2.3	6.3	78.0	21.9	0.1
50–54	43.2	46.7	2.9	7.1	88.4	11.6	0.1
55–59	50.7	38.4	3.2	7.8	94.6	5.4	0.0
Year 10							
15–19	25.4	37.5	11.0	26.1	75.8	18.0	6.2
20–24	37.7	41.1	4.5	16.8	45.8	45.4	8.8
25–29	40.9	41.9	1.4	15.8	20.4	71.2	8.4
30–34	26.0	56.4	2.2	15.4	38.2	60.4	1.4
35–39	30.3	58.7	2.0	9.1	42.2	57.4	0.5
40–44	26.6	62.0	1.3	10.2	44.1	55.8	0.2
45–49	31.9	59.5	2.3	6.3	77.1	22.8	0.1
50–54	42.0	48.1	2.8	7.0	86.8	13.1	0.1
55–59	50.0	38.9	3.2	7.9	94.4	5.6	0.0

Table C. 8. The difference in the percentages of people in each partner per year category, between model results over 10 years and NHANES 2009–2010.

Age	0	1	2	3 or more	3–6	7–14	15 or more
15–19	-0.8	1.8	4.8	-5.8	10.3	-8.3	-1.9
20–24	-14.0	7.1	8.4	-1.5	40.2	-36.0	-4.1
25–29	-15.9	15.0	9.6	-8.7	32.3	-25.5	-6.8
30–34	-18.2	15.6	6.5	-3.9	32.2	-36.2	4.0
35–39	-19.2	19.3	2.4	-2.5	39.2	-39.0	-0.2
40–44	-13.5	13.0	4.1	-3.6	31.2	-33.4	2.2
45–49	-21.9	18.2	4.2	-0.6	-9.0	1.5	7.5
50–54	-21.2	18.9	3.6	-1.3	-6.5	-0.6	7.1
55–59	-20.7	22.8	2.0	-4.1	-42.2	17.2	25.0

Note: Each value presents the average of differences (the value in NAHNES 2009–2010 minus the value in model results) over 10 years.

Table C. 9. The percentage points differences by changing the probabilities of individuals moving from one partner-in-lifetime category to the next partner-in-lifetime category on the percentage of individuals in different partner categories at the end of 10 years.

		Modified parameter and their impact on network characteristics at the end of 10 years in the model.									
			p1*		**p2***		**p3***		**p4***		**p5***
Parameter change in age category:	**Impact on values by age category**	**p1-0.05**	**p1+0.05**	**p2-0.05**	**p2+0.05**	**p3-0.05**	**p3+0.05**	**p4-0.05**	**p4+0.05**	**p5-0.05**	**p5+0.05**
15–19	**15–19**	8.8	9.1	16.3	3.3	34.6	22.5	20.2	47.5	49.7	43.7
	20–24	20.5	32.4	33.5	7.6	47.1	36.4	76.1	20.6	48.7	51.1
	25–29	3.8	7.0	8.4	4.8	2.6	3.3	2.4	2.5	4.7	3.0
	30–34	1.2	2.5	2.2	3.6	3.0	3.4	2.6	4.3	2.9	2.9
	35–39	6.0	8.7	3.3	6.5	3.8	9.6	6.5	5.4	6.2	5.3
	40–44	3.7	3.3	3.2	3.7	3.1	3.3	3.1	4.6	4.4	3.9
	45–49	1.1	1.3	1.5	1.8	1.8	2.0	1.5	1.4	0.8	0.6
	50–54	1.7	1.6	2.5	1.9	2.4	1.8	1.5	1.4	3.1	2.7
	55–59	2.0	1.4	2.3	1.9	4.8	2.4	1.6	2.4	6.2	3.1
20–24	**15–19**	15.5	15.5	15.5	22.4	9.6	33.3	18.1	22.4	9.1	8.8
	20–24	1.6	2.4	3.4	1.5	1.6	3.2	1.4	1.9	20.8	32.6
	25–29	11.5	11.5	11.5	16.8	5.9	23.3	13.7	17.1	5.1	5.7
	30–34	2.4	5.6	2.9	3.0	3.6	3.6	4.4	2.2	3.5	3.3
	35–39	9.2	9.2	10.5	10.1	8.3	7.1	10.3	9.1	7.6	4.9
	40–44	2.5	2.5	2.9	2.5	3.3	3.3	2.9	2.3	2.9	3.5
	45–49	1.0	1.0	1.5	1.3	2.2	0.9	1.2	0.8	1.0	1.2
	50–54	1.6	1.6	2.4	3.4	1.5	1.6	2.5	3.5	2.0	2.1
	55–59	8.2	8.2	10.8	15.0	1.7	1.6	11.3	16.6	2.2	2.2
25–29	**15–19**	10.3	15.5	15.6	22.3	15.6	22.5	18.0	22.4	15.5	15.5
	20–24	63.2	11.3	11.3	18.8	11.3	18.7	13.8	18.7	11.3	11.3
	25–29	7.6	11.3	11.5	16.9	11.6	16.9	13.4	17.0	11.8	11.8
	30–34	4.5	2.1	2.8	1.5	2.4	2.2	3.9	1.8	2.6	2.3
	35–39	8.9	9.6	4.5	9.8	7.8	12.3	9.8	9.2	5.8	5.8
	40–44	2.1	2.9	3.2	2.7	3.4	3.0	3.0	2.2	2.8	2.8
	45–49	1.7	1.5	1.1	1.2	1.0	0.8	1.3	1.0	1.3	1.3
	50–54	1.2	2.6	2.2	3.9	3.0	3.4	2.6	4.3	2.9	2.9
	55–59	6.9	11.6	9.8	15.7	11.3	15.2	11.4	15.8	10.4	10.4
30–34	**15–19**	1.0	1.6	1.5	2.2	1.0	1.6	1.3	1.9	42.5	33.2
	20–24	6.2	11.2	11.3	18.7	6.5	11.2	8.5	14.7	47.1	46.2
	25–29	15.7	13.1	2.7	2.8	2.3	3.2	52.2	13.6	22.4	17.1
	30–34	1.8	1.8	2.0	2.9	2.6	1.6	2.4	3.4	3.4	1.6
	35–39	6.7	9.1	6.7	10.7	8.5	6.9	6.2	12.1	9.6	5.6
	40–44	3.0	3.0	2.7	2.5	3.3	3.5	2.4	2.5	4.7	3.0
	45–49	1.1	0.9	1.5	1.8	1.7	1.1	1.5	1.0	1.1	0.7
	50–54	1.3	2.7	2.2	3.6	1.6	2.7	1.6	3.1	2.1	2.6
	55–59	5.8	12.4	10.8	15.8	6.7	10.4	7.8	13.1	2.7	5.5
35–39	**15–19**	1.3	1.9	1.0	1.0	1.0	1.6	1.3	1.9	43.0	34.2
	20–24	8.6	14.6	6.3	6.3	6.2	11.2	8.4	14.6	48.7	45.8
	25–29	1.0	1.4	0.8	0.8	0.7	1.1	1.0	1.4	21.1	18.3
	30–34	1.0	4.0	3.2	3.0	1.6	2.4	3.4	1.5	1.6	3.2
	35–39	7.6	9.8	6.3	6.3	10.5	9.1	7.6	6.5	5.4	8.3
	40–44	2.9	3.0	3.6	3.6	4.4	2.2	3.5	3.3	3.5	3.8
	45–49	0.6	1.3	1.3	1.3	1.1	1.4	1.3	1.3	1.5	1.8
	50–54	2.6	3.3	1.3	1.3	1.3	2.4	2.0	3.1	1.9	2.0
	55–59	9.4	12.5	6.7	6.7	6.0	10.3	9.0	11.1	3.1	3.9

Table C. 9 continued

		Modified parameter and their impact on network characteristics at the end of 10 years in the model.									
		p1*		p2*		p3*		p4*		p5*	
Parameter change in age category:	**Impact on values by age category**	**p1-0.05**	**p1+0.05**	**p2-0.05**	**p2+0.05**	**p3-0.05**	**p3+0.05**	**p4-0.05**	**p4+0.05**	**p5-0.05**	**p5+0.05**
40–44	**15–19**	1.3	1.9	1.0	1.6	1.6	2.2	4.5	20.2	44.0	34.4
	20–24	8.4	14.5	6.3	11.2	11.3	18.7	5.0	71.0	47.3	45.8
	25–29	0.9	1.4	0.8	1.2	1.1	1.7	3.6	14.7	19.4	16.3
	30–34	1.6	2.4	3.4	1.5	1.6	1.1	1.7	1.4	1.0	4.0
	35–39	1.1	0.5	1.4	10.7	8.0	10.3	3.4	5.8	6.9	5.6
	40–44	3.2	2.9	4.2	4.2	2.4	3.1	2.9	4.7	3.4	2.4
	45–49	0.7	1.5	1.1	0.5	1.2	1.2	1.1	0.5	1.4	1.5
	50–54	2.1	2.8	1.5	2.4	2.2	3.9	1.8	2.6	2.3	2.4
	55–59	8.4	13.5	5.7	10.0	11.4	15.5	2.3	1.7	3.8	3.5
45–49	**15–19**	1.3	1.9	1.0	1.6	1.6	2.2	4.0	21.0	42.1	33.9
	20–24	8.5	14.6	6.3	11.2	11.2	18.8	5.2	73.0	45.8	49.8
	25–29	1.0	1.4	0.7	1.2	1.2	1.7	3.8	15.1	19.5	18.8
	30–34	4.2	4.0	1.0	4.0	3.2	2.9	4.2	4.2	2.4	3.1
	35–39	8.5	10.9	6.5	9.8	8.9	12.1	6.5	5.1	7.8	9.2
	40–44	3.3	2.7	2.9	3.2	3.7	2.8	3.9	3.2	3.0	2.4
	45–49	1.0	1.3	1.5	1.6	0.9	1.1	1.6	1.6	1.3	1.2
	50–54	2.1	2.8	1.3	2.6	2.3	3.1	1.3	2.4	2.1	2.4
	55–59	7.5	11.5	7.7	10.4	9.8	14.4	1.3	2.1	3.5	3.9
50–54	**15–19**	1.3	1.9	1.0	1.5	1.5	2.2	3.3	20.9	41.9	33.9
	20–24	8.5	14.6	6.2	11.2	11.3	18.8	0.1	0.7	0.5	0.5
	25–29	0.9	1.4	0.7	1.1	1.2	1.7	0.0	0.1	0.2	0.2
	30–34	8.6	8.5	9.9	15.0	1.5	1.5	4.2	4.0	1.7	1.1
	35–39	8.3	10.9	5.3	9.8	8.5	9.2	7.6	8.9	5.8	5.4
	40–44	4.1	3.5	2.5	2.9	2.6	2.4	3.4	4.2	3.4	3.0
	45–49	2.0	0.8	1.1	1.1	1.4	1.3	0.6	1.4	1.1	1.3
	50–54	1.5	2.7	1.7	2.8	2.5	4.4	1.5	0.8	1.9	2.0
	55–59	7.5	12.0	6.5	11.0	11.1	16.4	1.7	1.1	4.1	2.8
55–59	**15–19**	1.3	1.9	1.3	1.9	1.6	2.2	3.3	3.3	41.6	33.9
	20–24	8.4	14.6	8.6	14.6	2.4	3.7	5.3	5.3	45.8	47.8
	25–29	0.9	1.4	1.0	1.4	1.1	1.7	4.1	4.1	19.0	15.7
	30–34	2.8	3.9	3.2	3.0	2.4	4.7	3.4	0.5	1.2	1.2
	35–39	8.5	9.6	7.2	7.8	1.1	0.5	1.4	6.5	9.2	6.0
	40–44	2.1	3.2	2.3	2.8	3.0	2.8	2.7	2.7	2.4	3.7
	45–49	1.3	1.4	1.7	1.4	1.0	1.1	0.7	0.7	1.6	1.8
	50–54	1.6	3.0	1.6	2.8	2.3	3.2	2.0	2.0	2.8	2.3
	55–59	7.1	12.5	8.6	12.2	9.9	15.0	1.5	1.5	4.2	4.0

* p1 = probability of moving from no partner in lifetime to one partner in lifetime in a year; p2 = probability of moving from one partner in lifetime to two partners in lifetime in a year; p3 = probability of moving from two partners in lifetime to ≥ 3 partners in lifetime in a year; p4 = probability of moving from 3–6 partners in lifetime to 7–14 partners in lifetime in a year; p5 = probability of moving from 7–14 partners in lifetime to ≥ 15 partners in lifetime in a year.

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