EVALUATING TREATMENT OF CHRONIC LIVER DISEASE & HEPATOCELLULAR CARCINOMA

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Submitted to the Graduate Faculty of

the School of Medicine in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2015

UNIVERSITY OF PITTSBURGH

SCHOOL OF MEDICINE

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Alexis-Pluscherie Chidi, PhD

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Chronic liver disease is a major cause of morbidity and mortality worldwide. More than 3 million patients are infected with chronic hepatitis C which, when left untreated, can result in liver cirrhosis, liver transplantation, hepatocellular carcinoma, and early mortality. Successful treatment of hepatitis C can dramatically reduce these risks, however the high cost of treatment may limit its use. Similarly, surgical intervention can be curative for patients with hepatocellular carcinoma, however nonclinical barriers may limit access to surgical intervention for medically eligible patients. The papers in this dissertation evaluated methods of improving access to and equitable utilization of available treatment options to interrupt the continuum of chronic liver disease. First, we compared the cost-effectiveness of two novel drug regimens for US Veterans with genotype 1 hepatitis C using various strategies to prioritize patients for treatment in light of resource constraints. While both drug regimens were cost-effective, we found that treating any eligible patient was less costly and more effective than prioritizing treatment of patients with advanced disease. Next, we determined the degree to which the current Medicaid policy restricting hepatitis C treatment to patients with advanced disease would lead to increased long-term costs and worse health outcomes for Medicare and the Centers for Medicare and Medicaid Services. We found that full access to hepatitis C treatment was cost saving and more effective compared to restricting treatment to patients with advanced disease from both perspectives. A full access strategy could also avert numerous future liver transplants, cases of hepatocellular

carcinoma, and deaths. Finally, we evaluated geographic disparities in surgical intervention for hepatocellular carcinoma and determined the influence of physician recommendations on the type of treatment a patient ultimately receives. Interestingly, we found that urban patients who live closer to high volume centers are *less* likely to undergo surgical intervention. Furthermore, disparities tend to exist in referral for surgical intervention; once referred, most patients receive the recommended surgical procedure. These studies reveal opportunities to improve treatment of patients with hepatitis C and hepatocellular carcinoma, which could ultimately interrupt the continuum of chronic liver disease and improve health outcomes.

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PREFACE

Research reported in this publication was supported by the National Center For Advancing Translational Sciences of the National Institutes of Health under Award Number TL1TR000145. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The article included in Chapter 4 was published in *Annals of Surgery* and the publisher retains the copyright for this material (1).

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1.0 INTRODUCTION

Chronic liver disease is a major cause of morbidity and mortality worldwide (2, 3). In contrast to many other forms of disease, chronic liver disease often occurs along a lifelong continuum, which presents unique challenges and opportunities for intervention **(**Figure 1.1). In the United States, 3 to 5 million patients are currently infected with hepatitis C virus and develop chronic infection, which can be asymptomatic for decades (4, 5). Left untreated, chronic hepatitis C can lead to liver cirrhosis, decompensated cirrhosis, and liver transplantation (6-8). Patients with cirrhosis are also at an increased risk of developing hepatocellular carcinoma, the most common form of primary liver cancer and the second leading cause of cancer death worldwide (9).

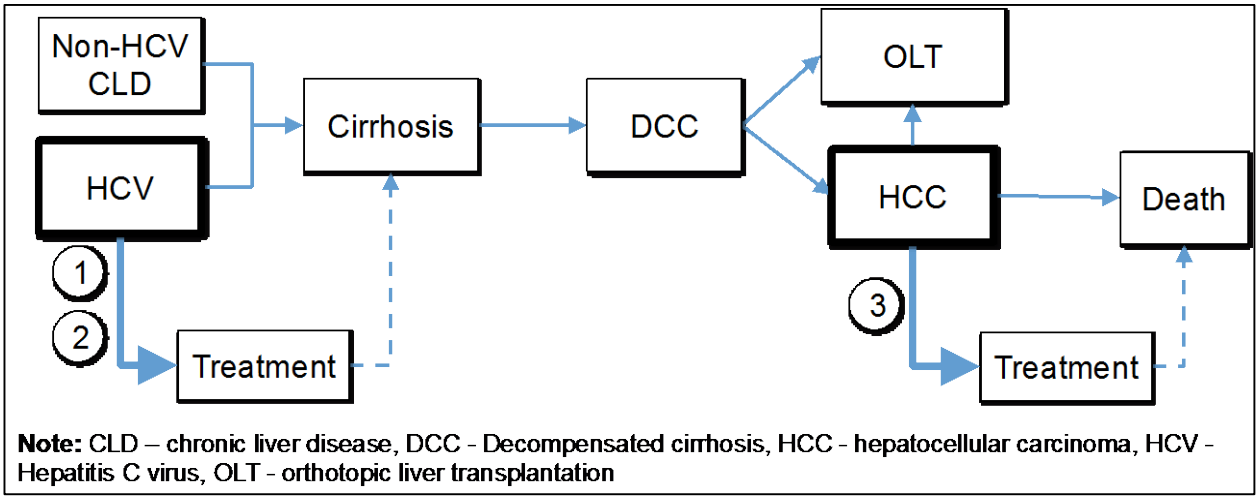

Figure 1.1. The Continuum of Chronic Liver Disease

There are a number of opportunities to improve treatment and interrupt the continuum of chronic liver disease (Figure 1.1). For patients with hepatitis C, successful treatment can reduce or eliminate the risk of future complications, but historic regimens have been ineffective and poorly tolerated (5). Newly approved interferon-free medication regimens are highly effective, but extremely high costs threaten their widespread use (6-8). For patients with hepatocellular carcinoma, there has been little progress in improving treatment over the past 40 years, so it is essential to maximize the effectiveness and reach of existing treatment options (9). Although surgical intervention can be curative for patients with hepatocellular carcinoma, surgical care has been inequitably distributed (10-12).

The projects in this dissertation address each of these issues. In Project 1, we evaluate the cost-effectiveness of strategies to treat US Veterans with highly effective but extremely costly novel therapeutic regimens for hepatitis C. In Project 2, we estimate the effects of restrictive treatment policies on Medicare and government payer costs and health outcomes, and then evaluate the cost-effectiveness of expanding access to treatment. Finally, in Project 3, we determine whether geographic factors, such as proximity to a surgical center and urban/rural residence, are associated with variations in referral for and receipt of surgical intervention for hepatocellular carcinoma.

2.0 COST-EFFECTIVENESS OF NOVEL TREATMENT STRATEGIES FOR HEPATITIS C

2.1 BACKGROUND

Hepatitis C (HCV) affects over 174 million people worldwide and up to 5 million people in the US (10, 11). Although patients often remain asymptomatic for years, chronic HCV infection is a leading cause of liver cirrhosis and hepatocellular carcinoma and the most common indication for liver transplantation in the US (6, 7, 12). Patients with HCV experience substantially higher mortality than the general population (8, 13, 14). Although there are 6 HCV genotypes, approximately 75% of US patients are infected with genotype 1 (15, 16). Successful HCV treatment leads to sustained virologic response, improving quality of life and reducing morbidity and mortality (8, 17-20). However, due in part to the poor efficacy and eligibility restrictions for prior therapeutic options, many HCV patients remain untreated (5, 21-23).

Recently approved HCV drug regimens have dramatically improved treatment efficacy, but high drug prices have necessitated novel strategies for determining which patients would benefit most from treatment. Historically, HCV treatment regimens have included pegylated interferon, ribavirin and direct acting antiviral drugs (telaprevir or boceprevir). These regimens required up to 48 weeks of therapy, were only modestly efficacious, and caused significant dose-limiting morbidity (24-27). In 2013, the FDA approved two new drugs, sofosbuvir and

simeprevir, which improved treatment efficacy to over 90% in many patient subgroups (28-34). These regimens still included poorly tolerated interferon for most patients and cost up to $1800 per dose. With these high treatment costs, two studies evaluating restricting treatment to patients with advanced liver disease concluded that treating all patients was more cost-effective (30, 35). One of these studies found that it was cost-effective to prioritize those with advanced disease in select patient subgroups (35). Since these analyses, a new wave of interferon-free regimens received FDA approval, including sofosbuvir/ledipasvir (SOF/LDV) and a multidrug regimen of ombitasvir, ritonavir, paritaprevir and dasabuvir (3D), with or without ribavirin. Both of these regimens result in nearly universal cure rates with lower costs than sofosbuvir/simeprevir and without the adverse effects or eligibility restrictions of interferon-based regimens. 3D is more effective and less expensive per dose than SOF/LDV, but requires multiple daily pills for 12-24 weeks, compared to 8-12 weeks of a single daily dose of SOF/LDV (36-40). In addition, 3D includes ritonavir, which has drug interactions precluding its use in some patients, and may require ribavirin, which can cause dose-limiting anemia (37, 38, 41). Both regimens are more costly than sofosbuvir/ribavirin/interferon, with wholesale prices of up to $1125 per dose.

The Veterans Health Administration (VA) is a leading provider of HCV care in the US and a useful model for evaluating changes in treatment policy. HCV prevalence is two-fold greater in Veterans than the general US population with more than 170,000 HCV positive Veterans currently receiving VA healthcare (42, 43). VA's unified national electronic medical record system and its national Hepatitis C Clinical Case Registry provide extensive data about the natural history of hepatitis C and associated treatment costs, distinguishing VA as an excellent system in which to model changes in treatment policy (22).

With the advent of interferon-free therapy, optimal treatment for genotype 1 HCV remains unclear. Because of differences in drug pricing, treatment duration, efficacy, and quality of life associated with SOF/LDV and 3D, it is unclear which drug regimen is most cost-effective. Because newer regimens are so costly, it is important to determine how they compare to previously used sofosbuvir regimens and to assess whether alternative strategies, such as prioritizing patients with advanced disease, may now be cost-effective. Thus, we compared the cost-effectiveness of managing a cohort of treatment-naïve genotype 1 HCV patients using SOF/LDV versus 3D, and sought to determine whether certain patients should be prioritized for treatment.

2.2 METHODS

2.2.1 Model Structure and Perspective

We created a Markov state-transition model with one-year cycle length to compare the cost-effectiveness of treatment strategies for a cohort of previously untreated, 60-year-old US Veterans with genotype 1 HCV mono-infection. The cohort did not include patients with decompensated cirrhosis or HIV co-infection at baseline. We used a lifetime time horizon and took a VA perspective, including drug and medical costs. We conducted sensitivity analyses including relative prices (i.e., differences in cost between regimens) for each treatment regimen to make our results generalizable to systems with alternative price structures. Future costs and utilities were discounted 3% per year (44). Costs were adjusted to 2014 US dollars using the Consumer Price Index.

2.2.2 Model Cohort

We examined a hypothetical cohort of untreated HCV patients seeking treatment in VA in a given year, with an average age and distribution of fibrosis similar to that of VA HCV patients in 2013 (22). We defined chronic HCV severity using the Meta-analysis of Histologic Data in Viral Hepatitis (METAVIR) histologic scoring system: F0, no hepatic fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, many septa without cirrhosis; F4, cirrhosis (45). After treatment, patients could experience sustained virologic response, remain infected and progress through stages of fibrosis, develop cirrhosis or hepatocellular carcinoma, undergo liver transplantation, or die (Figure 2.1). Age-specific, annual all-cause mortality was estimated using US life tables (46). Excess mortality associated with HCV infection was estimated using METAVIR stage and treatment status. For Veterans with F0-F2 fibrosis, we assumed that after sustained virologic response, annual treatment costs, QALYs, morbidity and mortality would be similar to uninfected Veterans. For those with F3 or F4 disease, we assumed that morbidity and mortality were significantly reduced after sustained virologic response (Table 2.1). Each year, patients accrued the costs and QALYs associated with their current Markov state. Only one state transition was possible during each model cycle, and progression occurred according to previously established transition probabilities (Table 2.1).

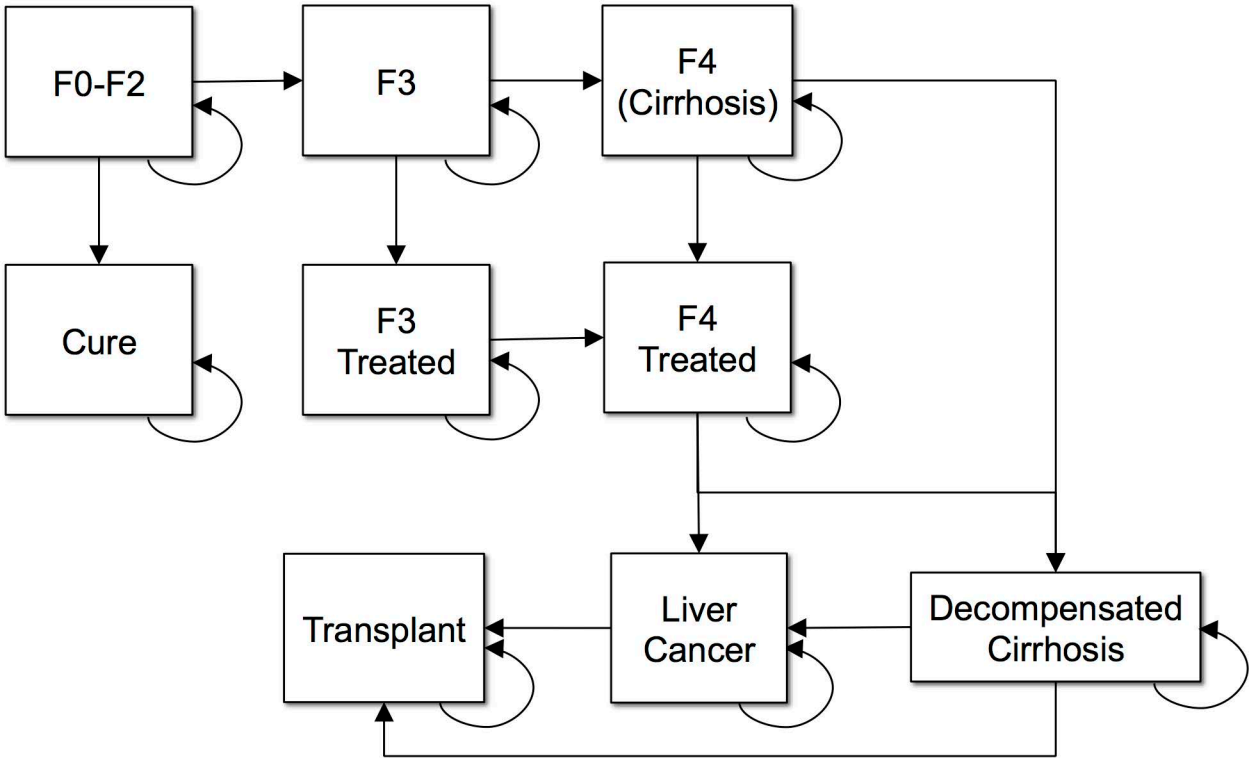

Figure 2.1 Markov State Transition Model Simulating the Natural History of Hepatitis C
Note: Transition probabilities derived from recent population-based studies. F0-2, F3 and F4 represent METAVIR stages of hepatic fibrosis. F3 and F4 treated states involve reduced risks of liver-related morbidity and mortality compared to untreated states.

Table 2.1 Hepatitis C Cohort Characteristics, Natural History, Costs, and Utilities

Description	Base Case	Low	High	Distribution	Source
Cohort Characteristics					
Age (years)	60	50	70	Gamma	VA CCR
F0-2 (%)	0.76	0.56	0.85	Dirichlet	(5, 47)
F3 (%)	0.12	0.11	0.44	Dirichlet	(5, 47)
Interferon-Ineligible (%)	0.37	0.20	0.57	Beta	(48)
Genotype 1a (%)	0.65	0.50	0.75	Beta	(15, 49)
<6 million HCV RNA	0.59	0.10	0.99	Beta	(40)
Risk of Disease Progression (%)					
F0-2 to F3	0.12	0.11	0.13	Beta	(50)
F3 to F4	0.12	0.09	0.14	Beta	(50)
F3 to HCC	0.01	0	0.03	Beta	(51)
F4 to DC	0.04	0.01	0.04	Beta	(51, 52)
F4 to HCC	0.03	0.01	0.08	Beta	(51, 53)
DC to HCC	0.07	0.03	0.08	Beta	(12)
DC to Transplant	0.03	0.02	0.06	Beta	(47, 54)
HCC to Transplant	0.04	0	0.14	Beta	(55, 56)
Progression After SVR (%)					
F3 to HCC	0.007	0.006	0.008	Beta	(8)
F4 to DC	0.005	0.002	0.096	Beta	(19)
F4 to HCC	0.005	0	0.019	Beta	(19)
Mortality Rates					
Hepatitis C*	2.37	1.28	4.38	Lognormal	(14)
Cirrhosis (RR)†	2.50	1.23	5.08	Lognormal	(17)
SVR*	1.00				
SVR after F4 (RR)‡	0.39	0.14	0.65	Lognormal	(8, 17, 18)
DC (%)	0.10	0.04	0.21	Beta	(12)
HCC (%)	0.43	0.34	0.51	Beta	(52)
Transplant Year 1 (%)	0.14	0.06	0.42	Beta	(57, 58)
Transplant Year 2+ (%)	0.03	0.02	0.11	Beta	(58)
Annual Follow-Up Costs (2014 $US)					
F0-3	$190	$90	$555	Gamma	(19)
F4	$1,264	$740	$1,789	Gamma	(19)
DC	$16,214	$12,971	$40,076	Gamma	(19)
HCC Treatment	$50,754	$26,124	$75,384	Gamma	(19)
Transplant Year 1	$310,023	$248,019	$372,028	Gamma	(19)
Transplant Year 2+	$46,985	$37,588	$56,382	Gamma	(19)
SVR (F0-2)	$0				

Note: DC - compensated cirrhosis, F0-2, F3, F4 - METAVIR stages of hepatic fibrosis, G1a - genotype 1a, HCC - hepatocellular carcinoma, HCV – hepatitis C virus, RR - relative risk, SVR – sustained virologic response, VA CCR – VA Clinical Case Registry 2013, * - compared to all-cause mortality, † - compared to F0-2, ‡ - compared to pre-treatment state

Table 2.1 Hepatitis C Cohort Characteristics, Natural History, Costs and Utilities (Continued)

Description	Base Case	Low	High	Distribution	Source
Utilities before SVR					
F0-2	0.85	0.83	0.87	Beta	(57, 59)
F3	0.79	0.77	0.81	Beta	(57, 59)
F4	0.76	0.67	0.79	Beta	(57, 59)
DC	0.69	0.44	0.69	Beta	(19)
HCC	0.67	0.6	0.72	Beta	(19)
Transplant Year 1	0.5	0.3	0.8	Beta	(19)
Transplant Year 2+	0.77	0.57	0.77	Beta	(19)
Utilities After SVR					
F0-2	0.92	0.9	0.94	Beta	(19)
F3	0.86	0.84	0.88	Beta	(19)
F4	0.83	0.81	0.85	Beta	(19)

Note: DC - compensated cirrhosis, F0-2, F3, F4 - METAVIR stages of hepatic fibrosis, G1a - genotype 1a, HCC - hepatocellular carcinoma, HCV – hepatitis C virus, RR - relative risk, SVR – sustained virologic response, VA CCR – VA Clinical Case Registry 2013, * - compared to all-cause mortality, † - compared to F0-2, ‡ - compared to pre-treatment state

2.2.3 Model Assumptions

To model HCV natural history, we made a number of assumptions. The METAVIR score has been used more widely in the literature than the FIB-4 scoring system used in VA. Because FIB-4 scores of 3.25 or above correlate with biopsy results demonstrating advanced liver disease, we estimated that 50% of patients with FIB-4 scores above 3.25 had METAVIR F3 disease, while the others had METAVIR F4 disease (60). We also assumed that liver transplantation would not occur after age 75 (61). Finally, we assumed no additional costs for HCV sub-genotyping because this is routinely performed for HCV patients in the VA.

2.2.4 Costs and Effectiveness

We obtained VA drug costs from VA Pharmacy Benefits Management and varied them by ±25% in sensitivity analyses. Because VA prices for SOF/LDV and 3D were not determined at the time of the study and are not publicly available, we assumed that both drugs were discounted at the Federal Supply Schedule price, reflecting the 24% minimum discount from average wholesale prices required for federal contracts. We varied the absolute and relative prices of these regimens in sensitivity analyses. We also estimated medical monitoring costs based on estimates from recent literature reviews (19, 30). These costs included a single pre-treatment office visit, complete blood count, complete metabolic panel, and viral load measurement; monthly office visits and metabolic panels during treatment; quarterly on-treatment viral load measurements; and a post-treatment office visit, viral load measurement, and metabolic panel.

Treatment regimen efficacy data were obtained from recent clinical trials (Table 2.2). Because treatment duration with SOF/LDV for non-cirrhotic patients depends on the viral load at treatment initiation, we assumed that the proportion of patients eligible for 8-week therapy was similar to that found in the ION-3 study (40, 62). Because some clinicians are using 12 weeks of 3D for genotype 1a cirrhotic patients, we included this regimen in sensitivity analyses. The utility of each treatment regimen was estimated based on patient reports of treatment-related quality-of-life from sofosbuvir clinical trials (32, 33, 63). In the base case, we assumed that the utility of using SOF/LDV or 3D was similar to that of sofosbuvir/simeprevir, while 3D/ribavirin was similar to that of sofosbuvir/ribavirin.

Table 2.2 Hepatitis C Treatment Parameters

Parameters	Base Case	Low	High	Distribution	Source
Treatment Efficacy					
Sofosbuvir/Interferon/RBV	0.92	0.80	0.99	Beta	(28, 64)
Sofosbuvir/Interferon/RBV (F4)	0.80	0.66	0.89	Beta	(28)
Sofosbuvir/Simeprevir	0.95	0.79	1.00	Beta	(29)
Sofosbuvir/Simeprevir (F4)	0.94	0.73	1.00	Beta	(29)
SOF/LDV (8 weeks)	0.94	0.90	0.97	Beta	(40)
SOF/LDV (12 weeks)	0.96	0.92	1.00	Beta	(39, 40)
SOF/LDV (F4)	0.97	0.84	1.00	Beta	(39)
3D/RBV Genotype 1a	0.96	0.93	0.98	Beta	(36, 37)
3D/RBV Genotype 1a (F4)	0.94	0.90	0.98	Beta	(38)
3D Genotype 1b	0.99	0.98	1.00	Beta	(37)
3D/RBV Genotype 1b (F4)	0.99	0.96	1.00	Beta	(38)
Treatment Disutilities					
Sofosbuvir/RBV	-0.04	-0.05	-0.03	Beta	(32, 33)
Sofosbuvir/Interferon/RBV	-0.11	-0.12	-0.09	Beta	(32, 33)
Sofosbuvir/Simeprevir	0	-0.04	0	Beta	(57)
Drug Costs (weekly, ±25%)					
Interferon	$178	$134	$223	Gamma	VA PBM
Ribavirin	$42	$32	$53	Gamma	VA PBM
Simeprevir	$2,641	$1,981	$3,301	Gamma	VA PBM
Sofosbuvir	$3,796	$2,847	$4,745	Gamma	VA PBM
SOF/LDV	$5,985	$4,489	$7,481	Gamma	Estimated
3D	$5,277	$3,958	$6,596	Gamma	Estimated
Medical Monitoring Costs (each, ±25%)					
Office visits	$76.19	$57.14	$95.24	Gamma	(19, 30)
Complete blood count	$10.32	$7.74	$12.90	Gamma	(19, 30)
Complete metabolic panel	$15.27	$11.45	$19.09	Gamma	(19, 30)
Quantitative HCV PCR	$61.89	$46.42	$77.36	Gamma	(19, 30)

Note: HCV – hepatitis C, 3D – ombitasvir, ritonavir, paritaprevir, dasabuvir, PCR – polymerase chain reaction test, SOF/LDV – sofosbuvir/ledipasvir, VA PBM - VA Pharmacy Benefits Management

2.2.5 Treatment Strategies

We compared seven treatment strategies for both SOF/LDV and 3D (Figure 2.2). Five compared using SOF/LDV or 3D to treat: (1) any patient seeking treatment, (2) only patients with cirrhosis, (3) only patients with F3-F4 disease, (4) patients with cirrhosis first and then patients with F0-3 disease the following year, or (5) patients with F3-4 disease in the first year, and those with F0-2 disease one year later. In addition to a no treatment strategy, we also included the previous recommendation of the American Association for the Study of Liver Diseases to use sofosbuvir/interferon/ribavirin for all eligible patients and sofosbuvir/simeprevir for interferon-ineligible patients. Treating only F0-2 patients was considered ethically unjustifiable and was not included in the analysis.

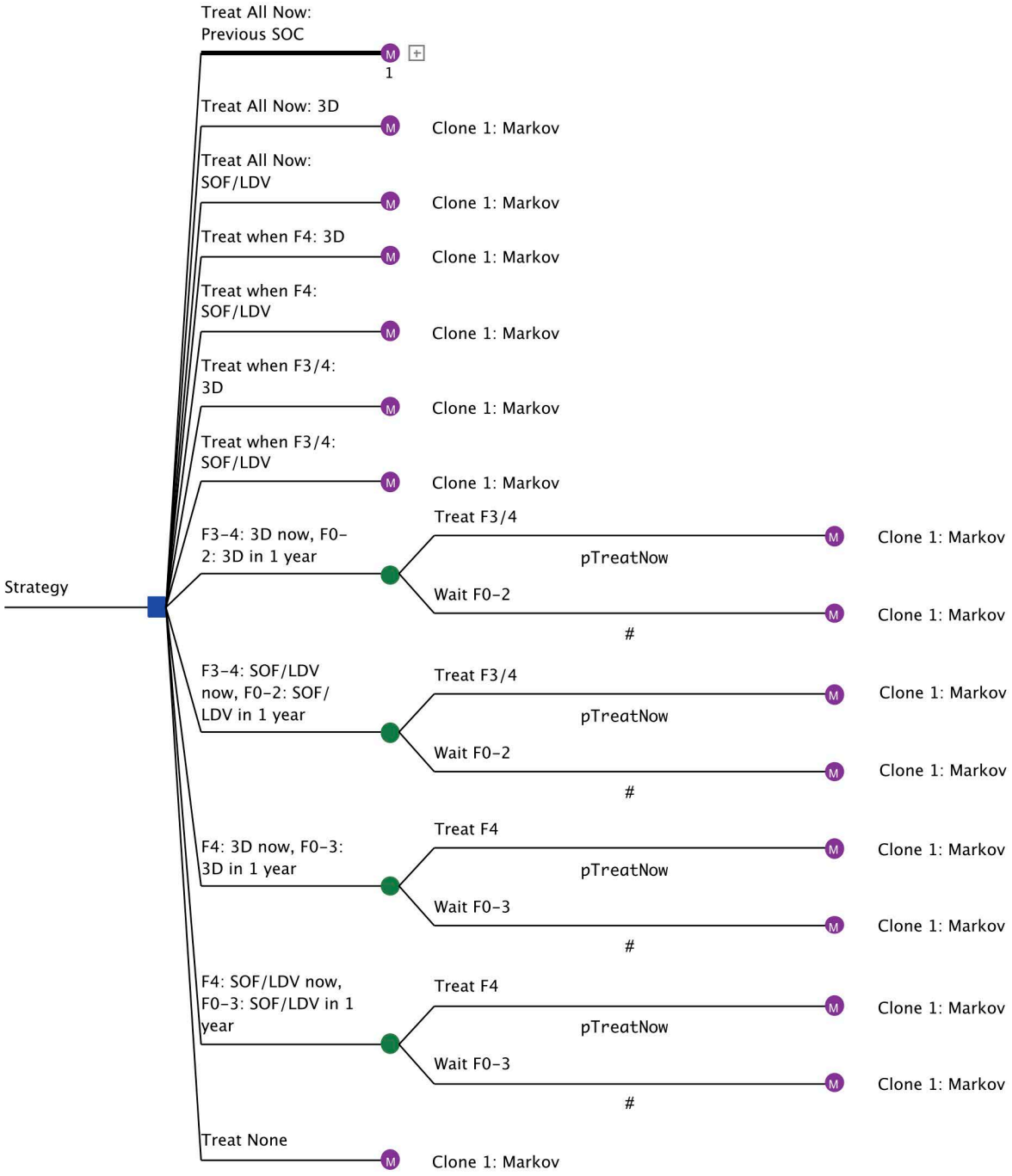

Figure 2.2 Decision Tree with Strategies for Managing Hepatitis C in US Veterans
Note: 3D - ombitasvir, ritonavir, paritaprevir, dasabuvir ± ribavirin, F0-F4 – METAVIR stages of hepatic fibrosis, Previous SOC - sofosbuvir/pegylated interferon/ribavirin or sofosbuvir/simeprevir as appropriate, SOF/LDV – sofosbuvir/ledipasvir.

2.2.6 Analyses

In our base case analysis, we calculated the incremental cost-effectiveness ratio (ICER), the additional cost required to derive additional QALYs for a given treatment strategy compared to a less costly and less effective strategy. Strategies that were more costly and less effective or had higher ICERs than more effective strategies were considered dominated (65). Although the VA does not use cost-effectiveness thresholds to make treatment decisions, $100,000 per QALY is often considered a reasonable threshold for cost-effectiveness in contemporary studies (66, 67). We conducted one-way sensitivity analyses to determine whether varying any single model input changed the preferred strategy and included estimates for the general population in all ranges. Finally, we conducted Monte Carlo probabilistic sensitivity analyses in which all model inputs were simultaneously varied. Values were sampled from each variable's probability distribution over 5,000 iterations to determine the likelihood that a given strategy would be cost-effective (68). Distributions were chosen based on parameter characteristics: beta distributions were used for transition probabilities, treatment efficacy, annual mortality rates, utilities, and cohort characteristics; gamma distributions were used for model costs; Dirichlet distributions were used for fibrosis staging; and log-normal distributions were used for relative risks of mortality (Table 2.1**,** Table 2.2). Analyses were performed using TreeAge Pro 2014 (TreeAge Software, Inc., Williamstown, MA).

2.3 RESULTS

2.3.1 Validation

We validated the model using the no treatment strategy ($38,246, 9.0 QALYs). Our results are similar to those in recent cost-effectiveness analyses (69, 70). To further validate the model, we created survival and state probability curves for the no treatment strategy, which were compared to recent estimates of the changing natural history of HCV (5). Our estimates of the magnitude and timing of the peak annual prevalence for decompensated cirrhosis, hepatocellular carcinoma, and overall survival were similar to reported values (±15% relative to previous estimates).

2.3.2 Base Case Analysis

Compared to no treatment, we found that treating any patient with SOF/LDV cost an additional $29,436 and yielded an additional 4.88 QALYs (or $6,027/QALY gained). Treating any patient with 3D cost an additional $8,683 and yielded 0.04 additional QALYs compared to SOF/LDV ($197,782/QALY). Strategies treating only patients with F3 fibrosis and/or cirrhosis and those treating patients with F3 fibrosis or cirrhosis first were dominated (Table 2.3). The previous standard of care, sofosbuvir with interferon and ribavirin or sofosbuvir with simeprevir, was also dominated (Table 2.3).

Table 2.3 Cost-Effectiveness of Treating Hepatitis C Among US Veterans: Base Case Results

Strategy	Costs	QALYs	ICER ($/QALY)
No Treatment	$38,426	9.0	--
Treat Any: SOF/LDV	$67,682	13.9	$6,027
Treat Any: 3D	$76,365	14.0	$197,782
Treat When F4: SOF/LDV	$51,908	10.5	Dominated
Treat When F3/F4: SOF/LDV	$61,233	12.2	Dominated
Staged F4 First: SOF/LDV	$67,146	13.6	Dominated
Staged F3/F4 First: SOF/LDV	$67,196	13.6	Dominated
Treat When F4: 3D	$67,731	10.5	Dominated
Treat When F3/F4: 3D	$68,573	12.3	Dominated
Treat Any: Previous SOC	$68,620	13.7	Dominated
Staged F3/4 First: 3D	$75,699	13.7	Dominated
Staged F4 First: 3D	$75,980	13.6	Dominated

Note: F3, F4 – METAVIR stages of fibrosis, ICER – incremental cost-effectiveness ratio, 3D – ombitasvir, ritonavir, paritaprevir with dasabuvir, Previous SOC – sofosbuvir with pegylated interferon/ribavirin or simeprevir, QALY – quality adjusted life-year, SOF/LDV – sofosbuvir/ledipasvir

2.3.3 One-Way Sensitivity Analysis

In one-way sensitivity analysis, cost-effectiveness ratios were impacted by changes in several key variables, including 3D and SOF/LDV efficacy and the relative costs of each drug regimen. 3D was cost-effective at a $100,000/QALY threshold if <29% of patients were eligible for the 8-week SOF/LDV regimen, or if SOF/LDV was <92% effective. In addition, SOF/LDV was no longer preferred if the 12-week SOF/LDV regimen was <93% effective for non-cirrhotic patients or <90% effective for cirrhotic patients, if 3D was >97% effective for patients with genotype 1a or if <50% of patients had genotype 1a disease. Finally, when the unit cost of 3D was at least 18% less than that of SOF/LDV, treating any patient with 3D became cost-effective at $100,000/QALY. The ICER was robust to variations in all other model parameters, including

cohort age. When we included a 12-week regimen of 3D for genotype 1a cirrhotic patients, treating any with 3D became the preferred strategy ($91,720/QALY).

2.3.4 Probabilistic Sensitivity Analysis

In our probabilistic sensitivity analysis, treating any patient with SOF/LDV was preferred in 60% of iterations at a willingness-to-pay threshold of $50,000/QALY and 58% of iterations at a willingness-to-pay threshold of $100,000 per QALY (Figure 2.3). Treating any patient with 3D became the most cost-effective treatment option at a willingness-to-pay threshold of ≥$215,000/QALY gained.

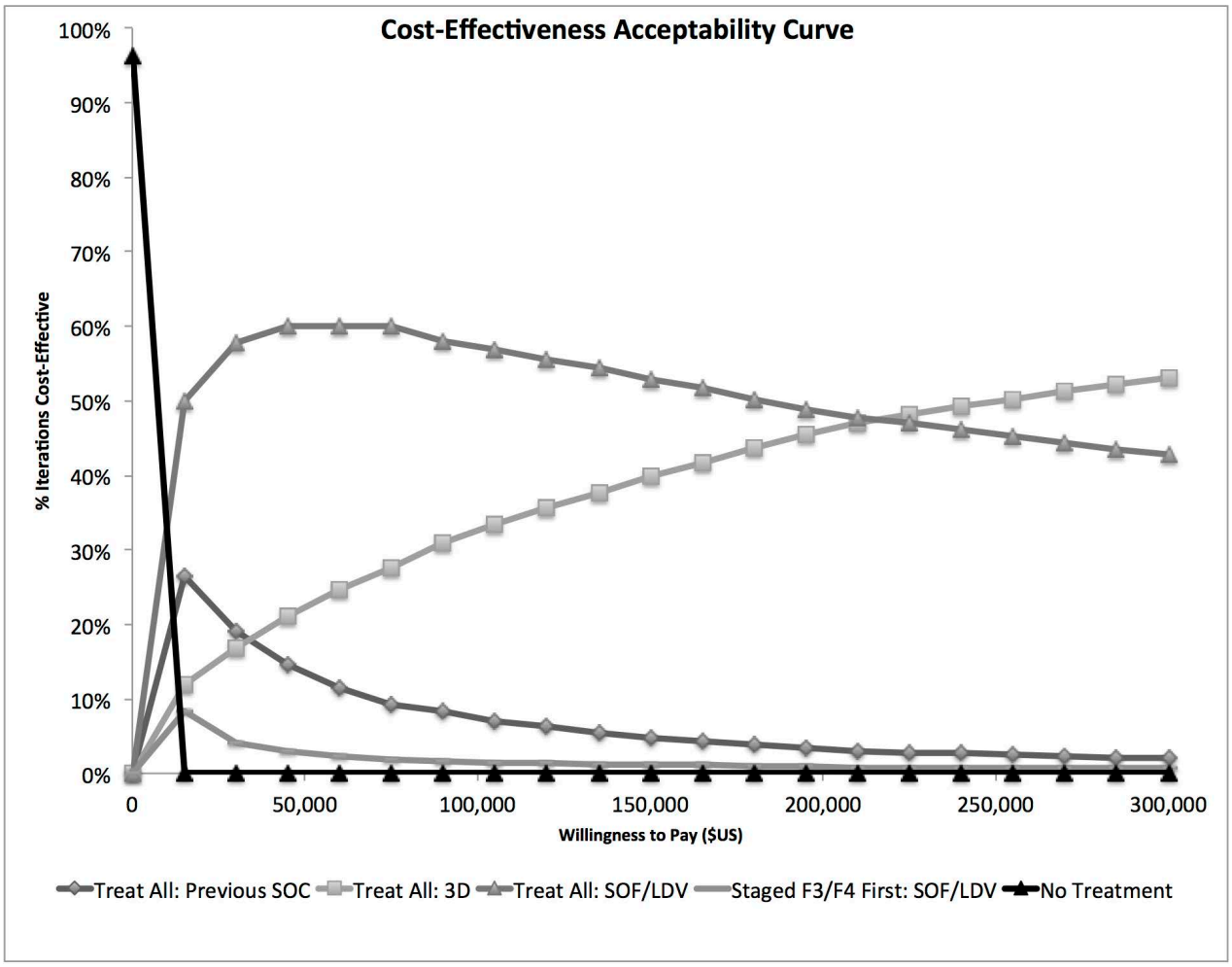

Figure 2.3 Probabilistic Sensitivity Analysis of Hepatitis C Treatment Strategies for US Veterans
Note: F3 and F4 – METAVIR stages of hepatic fibrosis, 3D – ombitasvir, ritonavir, paritaprevir, dasabuvir ± ribavirin, Previous SOC – sofosbuvir/pegylated interferon/ribavirin or sofosbuvir/simeprevir as appropriate, SOF/LDV – sofosbuvir/ledipasvir. Treating when F3/F4 and Treating F3/F4 first with 3D and SOF/LDV, and Treating F4 first with 3D were cost-effective in <5% of iterations and are not depicted.

2.4 DISCUSSION

In this cost-effectiveness analysis, we found that, for a cohort of treatment-naïve genotype 1 HCV-infected Veterans, managing patients with SOF/LDV regardless of disease status was the most economically reasonable strategy. Treating patients with 3D was marginally more effective, but considerably more expensive unless the price was substantially reduced relative to SOF/LDV. We found it economically unfavorable to restrict treatment to patients with METAVIR F3-F4 disease or prioritize treatment of these patients in early years. The cost-effectiveness of 3D versus SOF/LDV depended on the efficacy and price of each drug regimen and the proportion of patients with genotype 1a.

We demonstrated that regimens using 3D were more costly and more effective than those based on SOF/LDV. SOF/LDV was more cost-effective at a threshold of $100,000 per QALY, but ICERs of up to $300,000 per QALY have been considered cost-effective in contemporary studies (66, 67). Though the unit price of 3D is less than that of SOF/LDV, 3D strategies were more costly due to differences in cost and efficacy for patients with genotype 1a disease, who comprised 65% of the study population. For example, some patients would be eligible for 8 weeks of therapy with SOF/LDV, which was less expensive than the 12 weeks required for 3D/ribavirin, under our assumptions. Similarly, cirrhotic patients may require up to 24 weeks of treatment with 3D/ribavirin, which is almost twice as costly as the 12 weeks of SOF/LDV they would otherwise receive. Varying the price, efficacy, or duration of these treatments could change the preferred strategy, so price negotiations and real-world effectiveness data will inform the true cost-effectiveness of each regimen.

In addition, we found that restricting treatment or prioritizing advanced disease was not cost-effective at $100,000/QALY. This was because these strategies had higher ICERs than

treating any eligible patient and were eliminated from further consideration based on current guidelines (65). This is likely because patients with advanced disease require longer, more costly treatment and have a higher risk of morbidity and mortality after sustained virologic response than healthier patients (65). These findings are similar to those of previous studies, in which staging-guided therapy was not favorable compared to treating all patients (30). In one study, staging-guided therapy was cost-effective for patients with cirrhosis, but only when compared to waiting one year for treatment with future regimens (35). These results suggest that treating healthier patients is more cost-effective than treating sicker ones. However, strategies favoring treatment of healthier patients are clinically and ethically unfavorable; treating the sickest patients first is ethically ideal. In practice, it is unlikely that all cirrhotic patients can be quickly identified and prepared for treatment, so there may be opportunities for healthy patients to be treated as well. Thus it may be preferable to implement a triage policy similar to that employed in emergency rooms, in which efforts are made to identify and treat the sickest patients, but healthier patients are also treated whenever possible.

We also found that interferon-free treatment regimens were preferred to the previous standard of care. This is likely because new interferon-free regimens are more efficacious, have improved quality of life compared to interferon-containing regimens, and are less costly than sofosbuvir/simeprevir. Our findings are consistent with prior studies, in which interferon-free regimens were cost-effective at a $50,000/QALY threshold compared to previous therapeutic options (30, 70).

While we demonstrate that treating any patient is cost-effective compared to restricted strategies, practical limitations influence the application of these findings. VA policy allows for HCV treatment in all patient populations, however clinical capabilities and financial limitations

dictate that it will take several years to treat the hundreds of thousands of VA HCV patients. Even without clinical capacity limitations, treating only 70,000 untreated VA HCV patients at a discounted price of $50,000 per treatment course would require $3.5 billion in pharmacy costs for HCV alone. By comparison, in 2014, HCV treatment accounted for $520 million of the $4.8 billion in total pharmacy purchasing through the VA Pharmaceutical Prime Vendor (Vincent Calabrese, VA Pharmacy Benefits Management, Hines, IL, written communication, 2/10/15). Due to limited resources, clinicians will ultimately determine when to treat individual patients.

Our results have important policy implications for the VA and may be more broadly applicable to state Medicaid and national Medicare systems, which assume both the costs and benefits of treatment. Though resource constraints clearly limit treatment capabilities, our analyses suggest that short-term efforts to improve treatment capacity could ultimately lead to significant long-term improvements in health outcomes and reduced costs for patients with HCV. To improve throughput, VA is considering a number of potential strategies, including using primary care and telehealth providers in uncomplicated cases. Similar strategies could be employed by other healthcare systems to improve the public health impact of HCV treatment.

Our study has some limitations. First, instead of modeling fibrosis regression, we used stage-specific progression rates to account for slower disease progression after sustained virologic response. Second, we did not stratify our analyses by gender or race/ethnicity because neither parameter has been demonstrated to impact sustained virologic response in recent trials. Third, our analyses do not consider aggregate cost, clinic availability or differing models of care. Fourth, we derived treatment efficacy data from clinical trials, however success rates may be lower in real-world clinical practice. Finally, our analyses are conducted from the VA perspective, including VA-specific drug pricing. To improve the generalizability of our results,

we included general population data in ranges used for sensitivity analyses and used relative drug prices, making our results relevant to systems with other price structures.

In conclusion, we determined that it is economically reasonable to manage treatment naïve US Veterans with genotype 1 HCV using novel interferon-free regimens regardless of fibrosis status. Still, we demonstrate that treatment efficacy is an important aspect of cost-effectiveness. In addition to monitoring the real world effectiveness of both drugs, it will become important to identify predictors of adherence, sustained virologic response, and reinfection after successful treatment. Interferon-free regimens for genotype 1 HCV can confer long-term health benefits for US Veterans and are cost-effective regardless of fibrosis status.

3.0 ECONOMIC AND PUBLIC HEALTH IMPACTS OF POLICIES RESTRICTING ACCESS TO HEPATITIS C TREATMENT FOR MEDICAID PATIENTS

3.1 BACKGROUND

Hepatitis C affects over 3.2 million patients in the United States and is a common cause of chronic liver disease worldwide (10, 11). Most infected patients develop chronic disease that can remain asymptomatic for decades. However, left untreated, chronic hepatitis causes progressive hepatic fibrosis, which can result in severe complications. After developing cirrhosis, patients are at risk for hepatocellular carcinoma, may require liver transplantation, and have a markedly increased risk of early mortality (6-8). Successful treatment can drastically reduce the morbidity associated with chronic hepatitis C infection and improve patients' quality of life (8, 17, 18). In fact, if recent advances in drug regimens are widely implemented, hepatitis C could become a rare disease as early as 2036 (5).

Whereas new hepatitis C treatments are highly effective and have few side effects, their high costs could limit access to these medications. The preceding generation of interferon-based treatment regimens were poorly tolerated by patients and required lengthy treatment durations, so many patients have remained untreated (21). With the recent introduction of interferon-free drug regimens, treatment courses are more than 94% effective in as few as 8 weeks for many patient sub-groups, but can cost up to $190,000 per patient (71-73).

Resource-constrained government health insurance programs, including Medicaid and Medicare, cover a substantial proportion of US patients with hepatitis C and are heavily impacted by the high prices of these drugs. In fact, most state Medicaid programs restrict treatment of hepatitis C to patients with advanced liver disease, due to medication costs (74). Because hepatitis C is most prevalent in patients aged 45 and older, many Medicaid patients with early-stage disease may not develop advanced disease or complications until years later, after becoming eligible for Medicare (75, 76).

Though restrictive hepatitis C treatment policies are likely to reduce short-term costs to state Medicaid programs, it remains unclear to what degree they shift the financial burden of hepatitis C treatment and follow-up to the Medicare program and/or increase overall costs to the Centers for Medicare and Medicaid Services (CMS). In addition, the public health impact of delaying treatment for early-stage patients until disease progression occurs remains unknown. Thus, the aim of this study was to evaluate the cost-effectiveness of current Medicaid policies restricting hepatitis C treatment to patients with advanced disease compared to a strategy that provides unrestricted access to hepatitis C treatment. Our analyses also assess the budget and public health impact of each strategy to estimate the feasibility and long-term effects of increasing access to treatment for patients with hepatitis C.

3.2 METHODS

3.2.1 Model Structure and Perspective

We created a Markov state-transition model to simulate the epidemiology and natural history of hepatitis C infection. We conducted cost-effectiveness, budget and public health impact analyses from the perspectives of: (1) CMS, which incorporated costs and effects accrued during the entire study period; and (2) the Medicare program, which included costs and effects accrued after patients became eligible for Medicare benefits. We considered lifetime costs and outcomes, adjusted all prices to 2015 US dollars using the Consumer Price Index, and discounted all future costs and utilities by 3% per year. The discount rate is used in cost-benefit analyses to reflect the lower value placed on future outcomes compared to current outcomes. Empirical evidence suggests that an annual discount rate of 3% may account for true time preferences for costs and health outcomes, especially from a governmental perspective (44). We varied the discount rate from 0-7% in sensitivity analyses.

3.2.2 Model Cohort

We modeled hypothetical cohorts of 45-, 50-, and 55-year-old Medicaid patients diagnosed with genotype 1 hepatitis C who had no prior history of treatment with interferon-based regimens (treatment-naïve) or who had failed therapy with previous regimens (treatment-experienced). Based on data from the 2011-2012 National Health and Nutrition Examination Survey (NHANES), the average Medicaid patient with hepatitis C is 51 years old, so our selected age groups comprise approximately 95% of Medicaid patients with hepatitis C (77). Our cohorts

excluded patients with any prior history of decompensated cirrhosis, liver transplantation, or HIV co-infection. Chronic hepatitis C disease severity is measured using the Meta-analysis of Histologic Data in Viral Hepatitis (METAVIR) score, which describes five stages of liver fibrosis: F0, no hepatic fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, many septa without cirrhosis; F4, cirrhosis (45). In this analysis, we estimated the baseline distribution of METAVIR scores using model-based predictions of the HCV-infected population in 2014 (Table 3.1) (5, 78).

3.2.3 Natural History Model

We created a Markov model to simulate the natural history of hepatitis C infection (Figure 3.1**)**. Patients accrued liver-related treatment and follow-up costs as well as quality-adjusted life years (QALYs) for their Markov state at the end of each one-year cycle. Patients could make one state transition each year. Mortality was possible during each model stage; we estimated age-specific, annual all-cause mortality rates using US life tables (46). Disease progression and excess liver-related mortality occurred according to stage-specific transition probabilities and relative risks of mortality established in previously published studies (Table 3.1).

Table 3.1 Hepatitis C Cohort Characteristics, Natural History, Costs and Utilities

Description	Base Case	Low	High	Distribution	Source
Cohort Characteristics (%)					
F0-2	0.51	0.38	0.64	Dirichlet	(5, 78)
F3	0.21	0.16	0.26	Dirichlet	(5, 78)
F4	0.28	0.21	0.35	Dirichlet	(5, 78)
Treatment-Naive	0.61	0.46	0.76	Beta	(5, 78)
Risk of Disease Progression (%)					
F0-2 to F3	0.12	0.11	0.13	Beta	(50)
F3 to F4	0.12	0.09	0.14	Beta	(50)
F3 to HCC	0.01	0	0.03	Beta	(51)
F4 to DC	0.04	0.01	0.04	Beta	(51, 52)
F4 to HCC	0.03	0.01	0.08	Beta	(51, 53)
DC to HCC	0.07	0.03	0.08	Beta	(12)
DC to Transplant	0.03	0.02	0.06	Beta	(47, 54)
HCC to Transplant	0.04	0	0.14	Beta	(55, 56)
Progression After SVR (%)					
F3 to HCC	0.007	0.006	0.008	Beta	(8)
F4 to DC	0.005	0.002	0.096	Beta	(19)
F4 to HCC	0.005	0	0.019	Beta	(19)
Mortality Rates					
Hepatitis C*	2.37	1.28	4.38	Lognormal	(14)
Cirrhosis (RR)†	2.50	1.23	5.08	Lognormal	(17)
SVR*	1.00	--	--	--	Estimate
SVR after F4 (RR)‡	0.39	0.14	0.65	Lognormal	(8, 17, 18)
DC (%)	0.10	0.04	0.21	Beta	(12)
HCC (%)	0.43	0.34	0.51	Beta	(52, 79)
Transplant Year 1 (%)	0.14	0.06	0.42	Beta	(57, 58)
Transplant Year 2+ (%)	0.03	0.02	0.11	Beta	(58)
Annual Follow-Up Costs (2015 $US)					
F0-3	1,357	89	4,072	Gamma	(19, 30, 80)
F4	1,409	729	3,342	Gamma	(19, 30, 80)
DC	22,338	12,768	39,446	Gamma	(19, 80)
HCC	47,885	25,713	74,200	Gamma	(19, 80)
Transplant Year 1	228,090	165,537	366,183	Gamma	(19, 80, 81)
Transplant Year 2+	38,662	36,998	55,497	Gamma	(19, 80)
SVR (F0-2)	0	--	--	--	Estimate

Note: DC - decompensated cirrhosis, F0-2, F3, F4 - METAVIR stages of hepatic fibrosis, HCC - hepatocellular carcinoma, RR - relative risk, SVR - sustained virologic response, * - compared to all-cause mortality, † - compared to F0-2, ‡ - compared to pre-treatment state.

Table 3.1 Hepatitis C Cohort Characteristics, Natural History, Costs and Utilities (Continued)

Description	Base Case	Low	High	Distribution	Source
Utilities before SVR					
F0-2	0.85	0.83	0.87	Beta	(57, 59)
F3	0.79	0.77	0.81	Beta	(57, 59)
F4	0.76	0.67	0.79	Beta	(57, 59)
DC	0.69	0.44	0.69	Beta	(19)
HCC	0.67	0.6	0.72	Beta	(19)
Transplant Year 1	0.50	0.30	0.80	Beta	(19)
Transplant Year 2+	0.77	0.57	0.77	Beta	(19)
Utilities After SVR					
F0-2	0.92	0.90	0.94	Beta	(19)
F3	0.86	0.84	0.88	Beta	(19)
F4	0.83	0.81	0.85	Beta	(19)

Note: DC - decompensated cirrhosis, F0-2, F3, F4 - METAVIR stages of hepatic fibrosis, HCC - hepatocellular carcinoma, RR - relative risk, SVR - sustained virologic response, * - compared to all-cause mortality, † - compared to F0-2, ‡ - compared to pre-treatment state.

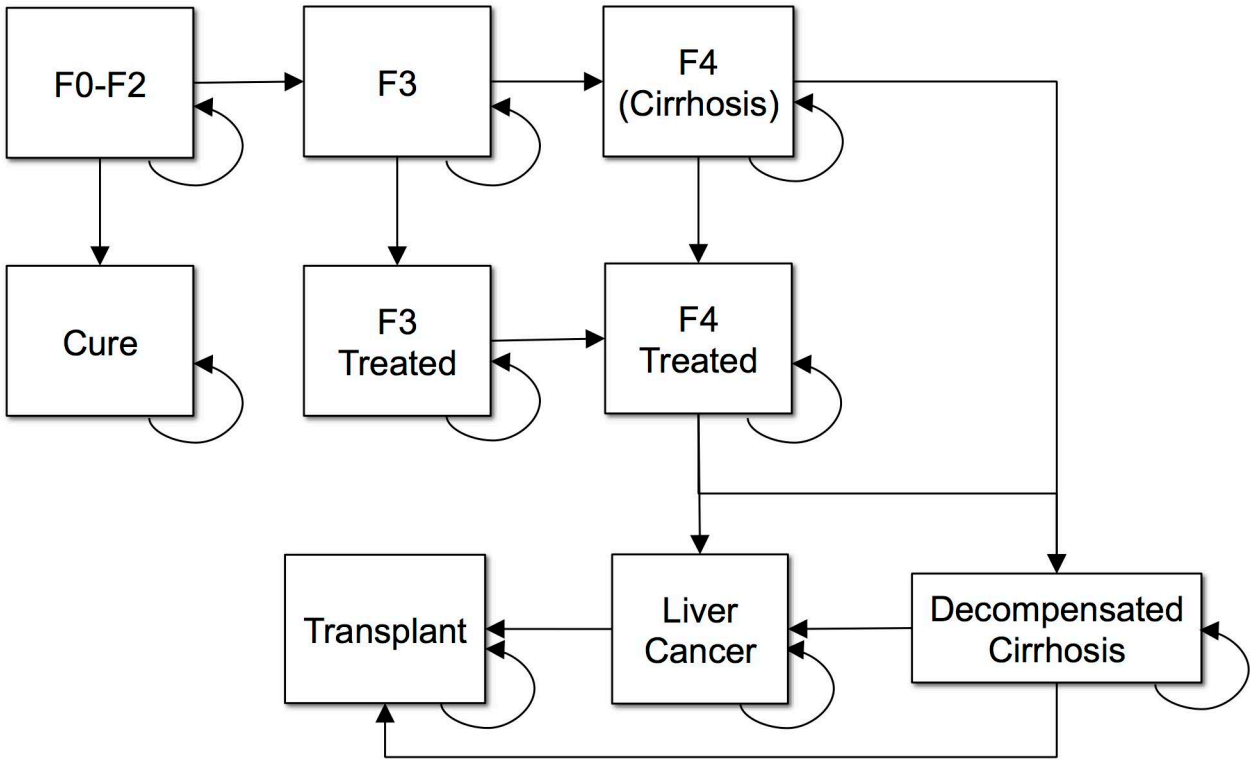

Figure 3.1 Markov State Transition Model Simulating the Natural History of Hepatitis C
Note: Transition probabilities derived from recent population-based studies. F0-2, F3 and F4 represent METAVIR stages of hepatic fibrosis. F3 and F4 treated states involve reduced risks of liver-related morbidity and mortality compared to untreated states.

At baseline, we grouped patients into three stages of baseline disease severity: early-stage disease (METAVIR F0-F2), advanced fibrosis (METAVIR F3), and compensated cirrhosis (METAVIR F4). Patients with compensated cirrhosis could later develop complications including decompensated cirrhosis, liver transplantation, and hepatocellular carcinoma. Patients with early-stage disease, advanced fibrosis, or compensated cirrhosis could receive hepatitis C treatment. We assumed that after successful treatment, patients with F0-F2 disease would return to full health and accrue no further hepatitis C infection-related costs. In contrast, patients with advanced fibrosis or cirrhosis would have markedly reduced risks of disease progression, complications, and mortality, but no reduction in follow-up costs after successful treatment (Table 3.1).

3.2.4 Treatment

We assumed that all patients would be treated with one of two currently available interferon-free hepatitis C drug regimens: a single dose two-drug combination of sofosbuvir/ledipasvir (SOF/LDV) or a multi-dose three-drug combination of ombitasvir, paritaprevir, and ritonavir with dasabuvir (3D). The American Association for the Study of Liver Diseases currently recommends both of these treatments for patients with genotype 1 hepatitis C (Table 3.2). Because utility data were not available for the 3D regimen at the time of our analysis, we performed our primary analysis using data for SOF/LDV (Table 3.3) and used estimates for 3D in sensitivity analyses. We estimated the efficacy of each treatment regimen using data from recently published clinical trials (36-40, 82-85). In patient subgroups for which several alternative treatment options have demonstrated similar effectiveness, we chose the least costly drug regimen. For example, we assumed that treatment-naïve patients with fewer than 6 million

copies of hepatitis C viral RNA at baseline would receive treatment with SOF/LDV for 8 weeks instead of 12 weeks. Similarly, we assumed that treatment-experienced cirrhotic patients would receive 12 weeks of SOF/LDV combined with ribavirin instead of 24 weeks without ribavirin.

We determined SOF/LDV treatment disutility using data from a quality-of-life study conducted as part of a recent clinical trials (86). Because utility data for the 3D and 3D with ribavirin regimens were not available, we used treatment disutility data for the SOF/LDV and SOF/LDV with ribavirin regimens, respectively, in our sensitivity analysis (Table 3.3).

Table 3.2 Recommended Treatment Regimens for Genotype 1 Hepatitis C

	Sofosbuvir/Ledipasvir	**Three-Drug**
Treatment Naïve		
No Cirrhosis		
	<6 million HCV RNA: 8 weeks, >6 million HCV RNA: 12 weeks	1a: 12 weeks + RBV 1b: 12 weeks
Cirrhosis		
	12 weeks	1a: 24 weeks + RBV 1b: 12 weeks + RBV
Treatment-Experienced		
No Cirrhosis		
Genotype 1a Genotype 1b	12 weeks	1a: 12 weeks + RBV 1b: 12 weeks
Cirrhosis		
Genotype 1a Genotype 1b	24 weeks *or* 12 weeks + RBV	1a: 24 weeks + RBV 1b: 12 weeks + RBV

Note: RBV: ribavirin, Three Drug: Ombitasvir, paritaprevir/ritonavir plus dasabuvir**.**
Source: American Association for the Study of Liver Diseases (hcvguidelines.org), Accessed 5/1/2015.

Table 3.3 Hepatitis C Treatment Parameters

Parameters	Base Case	Low	High	Distribution	Source
Treatment Efficacy					
SOF/LDV x 8 weeks	0.94	0.90	0.97	Beta	(40)
SOF/LDV x 12 weeks (Naïve)	0.96	0.92	1.00	Beta	(39, 40)
SOF/LDV x 12 weeks (Naïve F4)	0.97	0.84	1.00	Beta	(39)
SOF/LDV x 12 weeks (Experienced)	0.95	0.89	0.99	Beta	(82)
SOF/LDV/RBV x 12 weeks (F4)	0.88	0.72	0.92	Beta	(82, 83)
Treatment Disutilities					
SOF/LDV x 8 weeks	0.03	-0.19	0.25	Normal	(86)
SOF/LDV x 12 weeks	0.04	-0.20	0.28	Normal	(86)
SOF/LDV/RBV x 12 weeks	-0.02	-0.30	0.26	Normal	(86)
Drug Costs (weekly)					
SOF/LDV	$5,874	$2,500	$7,875	Gamma	NADAC
Ribavirin	$152.78	$114.59	$190.98	Gamma	(19)
Medical Monitoring Costs (each, ±25%)					
Office visits (CPT 99213)	$72.94	51.13	$79.69	Gamma	MPFS
Complete blood count	$10.58	$8.81	$14.30	Gamma	MPFS
Complete metabolic panel	$14.37	$11.51	$19.43	Gamma	MPFS
Quantitative HCV PCR	$58.29	$38.61	$78.77	Gamma	MPFS

Note: AWP – Average wholesale price, HCV – hepatitis C, 3D – ombitasvir, ritonavir, and paritaprevir with dasabuvir, MPFS – Medicare Physician Fee Schedule 2015, NADAC – National Average Drug Acquisition Cost, PCR – polymerase chain reaction test, SOF/LDV – sofosbuvir/ledipasvir

3.2.5 Costs and Effectiveness

We used a variety of sources to estimate treatment and follow-up costs for patients with hepatitis C (Table 3.1). In the base case, we discounted the national average drug acquisition price for each drug regimen by 23.1%, which is required as part of the Medicaid drug rebate program. Although the discount rate accounted for likely reductions in future hepatitis C drug prices, we also varied drug prices in sensitivity analysis. We used the Medicare physician fee schedule to calculate the costs of on-treatment medical monitoring (87). Expected costs included a single pre-treatment office visit, complete blood count, complete metabolic panel, and viral load measurement; monthly office visits, viral load measurements and metabolic panels during treatment; and a single post-treatment office visit, viral load measurement, and metabolic panel. We assumed that patients using ribavirin-containing regimens were monitored more frequently, with twice-monthly office visits and complete blood counts (Table 3.3).

From the Medicare perspective, costs and QALYs began to accrue upon Medicare eligibility at age 65. From the CMS perspective, costs and QALYs accrued throughout the study period. Because Medicare Part D can involve substantial cost-sharing for seniors not receiving Medicaid benefits, we subtracted expected patient out-of-pocket costs estimated using current Part D coverage rules (88). Because the prescription drug coverage gap (i.e. “donut hole”) is scheduled to be eliminated in 2020, we assumed that this would not be in place by the time the oldest cohort becomes eligible for Medicare benefits.

We determined annual follow-up costs for each health state using recent estimates for cohorts of Medicare and managed care patients (19, 30, 80, 81), and used age-specific median utility values for healthy patients (89). We estimated utility weights for each hepatitis C-related

health state based on recent comprehensive reviews of the literature (19, 57, 59). Finally, we varied all parameters over feasible ranges in sensitivity analyses (Table 3.1).

3.2.6 Strategies

We compared two strategies for managing hepatitis C infection in cohorts of current Medicaid beneficiaries: **(1) *Current Practice*** – only patients with advanced fibrosis or cirrhosis are treated for hepatitis C before becoming eligible for Medicare, treatment for patients with early-stage disease is deferred until disease progression or Medicare eligibility; and **(2) *Full Access*** – patients with early-stage disease, advanced fibrosis, and cirrhosis are treated before becoming eligible for Medicare benefits (Figure 3.2**).** Because some Medicare Advantage plans are adopting more restrictive treatment strategies, we assumed in the base case that 50% of patients with early stage disease would be treated upon Medicare eligibility and varied this assumption from 0-100% in sensitivity analysis.

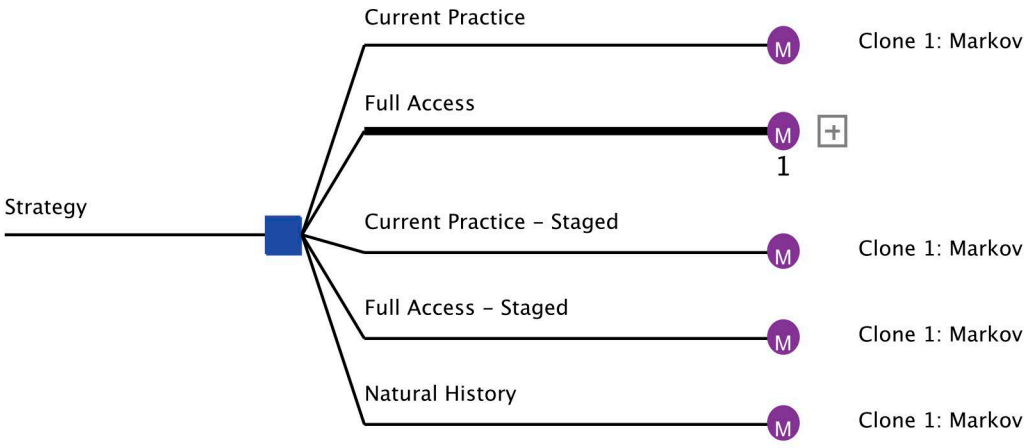

Figure 3.2 Decision Tree with Strategies for Treating Hepatitis C in Medicaid Beneficiaries

3.2.7 Assumptions

To perform this analysis, we made a number of simplifying assumptions to systematically bias the model against the "Full Access" strategy. We assumed that: (1) patients who failed treatment with sofosbuvir- or ombitasvir-based regimens would not be retreated because guidelines have not yet been developed for retreatment after treatment failure with novel regimens; (2) only patients 75 years of age or younger would undergo liver transplantation (61); (3) the costs of follow-up and treatment would be similar for the Medicaid and Medicare programs; (4) patients would become eligible for full Medicare benefits at age 65, however to accounted for Medicare-Medicaid dual eligibility, we estimated that 14% of Medicaid recipients under age 65 would receive Medicare disability benefits while 14% of Medicare beneficiaries over 65 received Medicaid benefits (90, 91); and (5) the size of the Medicaid hepatitis C population would remain static over time. We accounted for increased prevalence of hepatitis C in the Medicaid population in a sensitivity analysis.

3.2.8 Cost-Effectiveness Analyses

We completed the analysis separately for cohorts of 45-, 50-, 55-year-old Medicaid beneficiaries with hepatitis C. In the base-case analyses, we calculated the incremental cost-effectiveness ratio (ICER), which reflects the additional investment required to gain an additional QALY. In recent studies, ICER thresholds of $50,000-$300,000/QALY have been considered cost-effective (66, 67).

We also conducted sensitivity analyses to determine whether variations in model inputs would change the preferred strategy. First, we varied model inputs individually over a range of

plausible values in one-way sensitivity analyses (Table 3.1). Then, we used Monte Carlo probabilistic sensitivity analyses, in which values are randomly sampled from each variable's probability distribution and repeated over 5,000 iterations to determine the likelihood that each strategy is cost-effective (68). We performed all analyses using TreeAge Pro 2015 (TreeAge Software, Williamstown, MA).

3.2.9 Structural Sensitivity Analyses

Because it is not feasible to treat all Medicaid patients with HCV in a single year, we also conducted structural sensitivity analyses using staged treatment strategies, in which patients would be treated over time. Using data from the 2011-2012 NHANES survey and recently published studies, we estimated that approximately 450,000 patients with genotype 1 hepatitis C are currently receiving Medicaid benefits (75, 77, 92). Because the Affordable Care Act expanded Medicaid eligibility in many states, more low-income patients will have access to Medicaid insurance, some of whom may have chronic hepatitis C. The prevalence of hepatitis C in this population is unknown, but in a sensitivity analysis we determined the effects of a 33% increase in the size of the Medicaid hepatitis C population. This is likely to be an overestimation based on expected enrollment if Medicaid expansion is adopted in all 50 states (93, 94).

We also estimated treatment capacity for each strategy. Based on total Medicaid hepatitis C drug expenditures in 2014 and previous reports of treatment capacity, we estimated that approximately 30,000 Medicaid patients with hepatitis C could be treated in a given year (95, 96). Because more patients are likely to be treated each year under the Full Access strategy, we also modeled an expanded Full Access strategy with an annual treatment capacity of 40,000 patients. Recent developments suggest that increased treatment capacity is likely to be feasible

because new drug regimens are now 24-36 weeks shorter in duration than interferon-based regimens, allowing more patients to be treated by the same number of physicians in any given year. In addition, a recent study demonstrated that primary care providers can effectively administer hepatitis C treatment in uncomplicated cases (97). If this practice is widely adopted in the U.S., then a much larger physician workforce would be available to treat early-stage patients with hepatitis C. To derive approximate annual treatment probabilities, we estimated that 13% of early-stage patients die or progress each year, while the number of patients with advanced-stage disease is reduced by approximately 1% each year, accounting for entry, progression, and death, based on data from our natural history model (Table 3.4). In the Current Practice strategy, treatment would be offered to early-stage patients only after all patients with advanced fibrosis or cirrhosis have been treated. In the Full Access strategies, treatment would be equally allocated across fibrosis stages each year.

3.2.10 Budget & Public Health Impact Analyses

Finally, we compared the budget and public health impact of each treatment strategy. We used a Markov cohort analysis, which describes the costs and utilities associated with each Markov state during each model year. Using these data, it is possible to estimate and compare cost estimates as well as adverse health outcomes for each strategy. We first compared the annual and cumulative costs for both treatment strategies in our base case analysis. Next, we used the model to estimate the annual and cumulative number of cases of adverse health outcomes such as hepatocellular carcinoma, liver transplantation, and mortality, per hundred thousand Medicaid recipients.

Table 3.4 Annual Treatment Probabilities for Staged Hepatitis C Treatment Strategies

Current Practice								
Year	F3-F4 At Risk	F0-F2 At Risk	F3-F4 #Tx	F0-F2 # Tx	F3-F4 % Tx	F0-F2 % Tx	F3-F4 Not Tx	F0-F2 Not Tx
1	220,500	229,500	30,000	0	13.6%	0.0%	190,500	229,500
2	188,595	199,665	30,000	0	15.9%	0.0%	158,595	199,665
3	157,009	173,709	30,000	0	19.1%	0.0%	127,009	173,709
4	125,739	151,127	30,000	0	23.9%	0.0%	95,739	151,127
5	94,782	131,480	30,000	0	31.7%	0.0%	64,782	131,480
6	64,134	114,388	30,000	0	46.8%	0.0%	34,134	114,388
7	33,793	99,518	30,000	0	88.8%	0.0%	3,793	99,518
8	3,755	86,581	3,755	26,245	100.0%	30.3%	0	60,336
9	0	52,492	0	30,000	100.0%	57.2%	0	22,492
10	0	19,568	0	19,568	100.0%	100.0%	0	0
11	–	–	–	–	–	–	–	–
Full Access								
Year	F3-F4 At Risk	F0-F2 At Risk	F3-F4 #Tx	F0-F2 # Tx	F3-F4 % Tx	F0-F2 % Tx	F3-F4 Not Tx	F0-F2 Not Tx
1	220,500	229,500	14,700	15,300	6.7%	6.7%	205,800	214,200
2	203,742	186,354	15,669	14,331	7.7%	7.7%	188,073	172,023
3	186,192	149,660	16,632	13,368	8.9%	8.9%	169,560	136,292
4	167,864	118,574	17,581	12,419	10.5%	10.5%	150,283	106,155
5	148,780	92,355	18,510	11,490	12.4%	12.4%	130,270	80,865
6	128,967	70,353	19,411	10,589	15.1%	15.1%	109,556	59,764
7	108,460	51,995	20,279	9,721	18.7%	18.7%	88,181	42,274
8	87,299	36,778	21,108	8,892	24.2%	24.2%	66,191	27,886
9	65,529	24,261	21,894	8,106	33.4%	33.4%	43,635	16,155
10	43,199	14,055	15,945	14,055	36.9%	100.0%	27,254	0
11	26,981	0	26,981	0	100.0%	100.0%	0	0
Expanded Full Access								
Year	F3-F4 At Risk	F0-F2 At Risk	F3-F4 #Tx	F0-F2 # Tx	F3-F4 % Tx	F0-F2 % Tx	F3-F4 Not Tx	F0-F2 Not Tx
1	220,500	229,500	19,600	20,400	8.9%	8.9%	200,900	209,100
2	198,891	181,917	20,891	19,109	10.5%	10.5%	178,000	162,808
3	176,220	141,643	22,176	17,824	12.6%	12.6%	154,044	123,819
4	152,504	107,723	23,442	16,558	15.4%	15.4%	129,062	91,165
5	127,771	79,314	24,680	15,320	19.3%	19.3%	103,091	63,994
6	102,060	55,675	25,881	14,119	25.4%	25.4%	76,179	41,556
7	75,417	36,154	27,038	12,962	35.9%	35.9%	48,379	23,192
8	47,895	20,177	19,823	20,177	41.4%	100.0%	28,072	0
9	27,791	0	27,791	0	100.0%	100.0%	0	0
10	–	–	–	–	–	–	–	–
11	–	–	–	–	–	–	–	–

***Note:** Based on starting population of 450,000 Medicaid patients with genotype 1 hepatitis C. Assumes 13% net annual risk of progression or death for patients with F0-F2 disease and 1% net annual risk of progression or death for those with F3-F4 disease. F0-F4: METAVIR stages of hepatic fibrosis, Tx: treated

3.3 RESULTS

3.3.1 Base Case Analyses

In the base case, the Full Access strategy was cost saving compared to the Current Practice strategy for all age cohorts from the Medicare perspective (Table 3.5). For the 50-year-old cohort, which represented the average Medicaid patient with hepatitis C, the Current Practice strategy ($30,306, 5.51 QALYs) cost an additional $9,199 per patient and yielded 0.85 fewer QALYs compared to the Full Access strategy ($21,107, 6.36 QALYs). Cost savings for the Full Access strategy increased with cohort age.

From the CMS perspective, the Full Access strategy was also cost saving for each age cohort, but to a lesser degree. Compared to the Full Access strategy ($89,825, 15.85 QALYs), the Current Practice strategy cost an additional $8,148 per patient and yielded 2.74 fewer QALYs ($97,829, 13.11 QALYS) for the 50-year-old cohort (Table 3.5). The Full Access strategy was more cost saving for younger cohorts from the CMS perspective.

3.3.2 Sensitivity Analyses

In one-way sensitivity analyses from the Medicare perspective, the Full Access strategy was cost saving for all age cohorts regardless of variations in any individual model input. From the CMS perspective, variations in the cost of follow-up for patients with early-stage disease and in the discount rate impacted the ICER differently in each age cohort. The Full Access strategy remained cost saving as long as the cost of follow-up for early-stage patients was more than approximately $200 per year in the 45-year-old cohort, $350 per year in the 50-year-old cohort,

and $600 per year in the 55-year-old cohort. In addition, the Full Access strategy was cost saving for discount rates below 5-6%, depending on the age of the cohort. The Full Access strategy was cost saving over the range of plausible values for all other model inputs.

Table 3.5 Cost-Effectiveness of Restricted Access to Hepatitis C Treatment: Base Case Results

Strategy	Medicare Perspective			CMS Perspective		
	Costs	QALYs	ICER ($/QALY)	Costs	QALYs	ICER ($/QALY)
45-year-old cohort						
Full Access	$19,947	5.36		$92,411	17.20	
Current Practice	$27,458	4.54	Dominated	$102,686	14.19	Dominated
50-year-old cohort						
Full Access	$21,107	6.36		$89,825	15.85	
Current Practice	$30,306	5.51	Dominated	$97,829	13.11	Dominated
55-year-old cohort						
Full Access	$22,404	7.61		$86,900	14.40	
Current Practice	$34,363	6.80	Dominated	$92,268	12.09	Dominated

Note: ICER - incremental cost-effectiveness ratio, QALY - quality-adjusted life-year

In probabilistic sensitivity analysis, the Full Access strategy was cost-effective in 100% of iterations from the Medicare perspective at all willingness-to-pay thresholds. From the CMS perspective, the Full Access strategy was cost-effective in 93% of iterations at the cost saving threshold of $0/QALY and in 100% of iterations at $4,500/QALY. Including 3D regimens instead of SOF/LDV did not change the preferred strategy from either perspective. In our structural sensitivity analysis, the staged Full Access strategy was cost saving compared to the staged Current Practice strategy for all age cohorts, regardless of annual treatment capacity or the size of the Medicaid hepatitis C population (Table 3.6).

Table 3.6 Cost-Effectiveness of Staged Treatment Strategies for Medicaid Patients with Hepatitis C

	450,000 Patients		600,000 Patients	
Strategy	**Costs**	**QALYs**	**Costs**	**QALYs**
45-year-old cohort				
Expanded Full Access	$96,453	14.79	$96,800	14.26
Full Access	$96,800	14.26	$96,915	13.68
Current Practice	$99,881	14.14	$100,111	13.60
50-year-old cohort				
Full Access	$92,067	13.02	$91,672	12.48
Expanded Full Access	$92,156	13.52	$92,067	13.02
Current Practice	$95,196	12.90	$94,949	12.40
55-year-old cohort				
Full Access	$86,339	11.71	$85,087	11.21
Expanded Full Access	$87,241	12.18	$86,339	11.71
Current Practice	$89,757	11.60	$88,626	11.13

Note: Current Practice & Full Access – 30,000 patients treated per year, Expanded Full Access – 40,00 patients treated per year, QALYs- quality-adjusted life years

3.3.3 Budget and Public Health Impact Analyses

Our budget impact analyses revealed that, from the CMS perspective, the Full Access strategy became cost saving compared to the Current Practice strategy after 16 years for the 45-year-old cohort, after 15 years for the 50-year-old cohort, and after 13 years for the 55-year-old cohort. By the end of the study period, the Full Access strategy saved $10,340 per patient for the 45-year-old cohort, $8,148 for 50-year-olds, and $5,695 for 55-year-old patients. With staged treatment strategies, Full Access became cost saving after 9 years for each age cohort. In the worst-case scenario, with 600,000 hepatitis C patients and 30,000 treated per year, the Full Access strategy saved $3,197-$3,568 per patient by the end of the study period, depending on the age of the cohort. The public health impact analysis demonstrated that for every 100,000 50-year-old Medicaid beneficiaries, the Full Access strategy could avert approximately 5,994 cases

of hepatocellular carcinoma and 121 liver transplants compared to the Current Practice strategy. The number of cases averted varied over time for each age cohort (Figure 3.3).

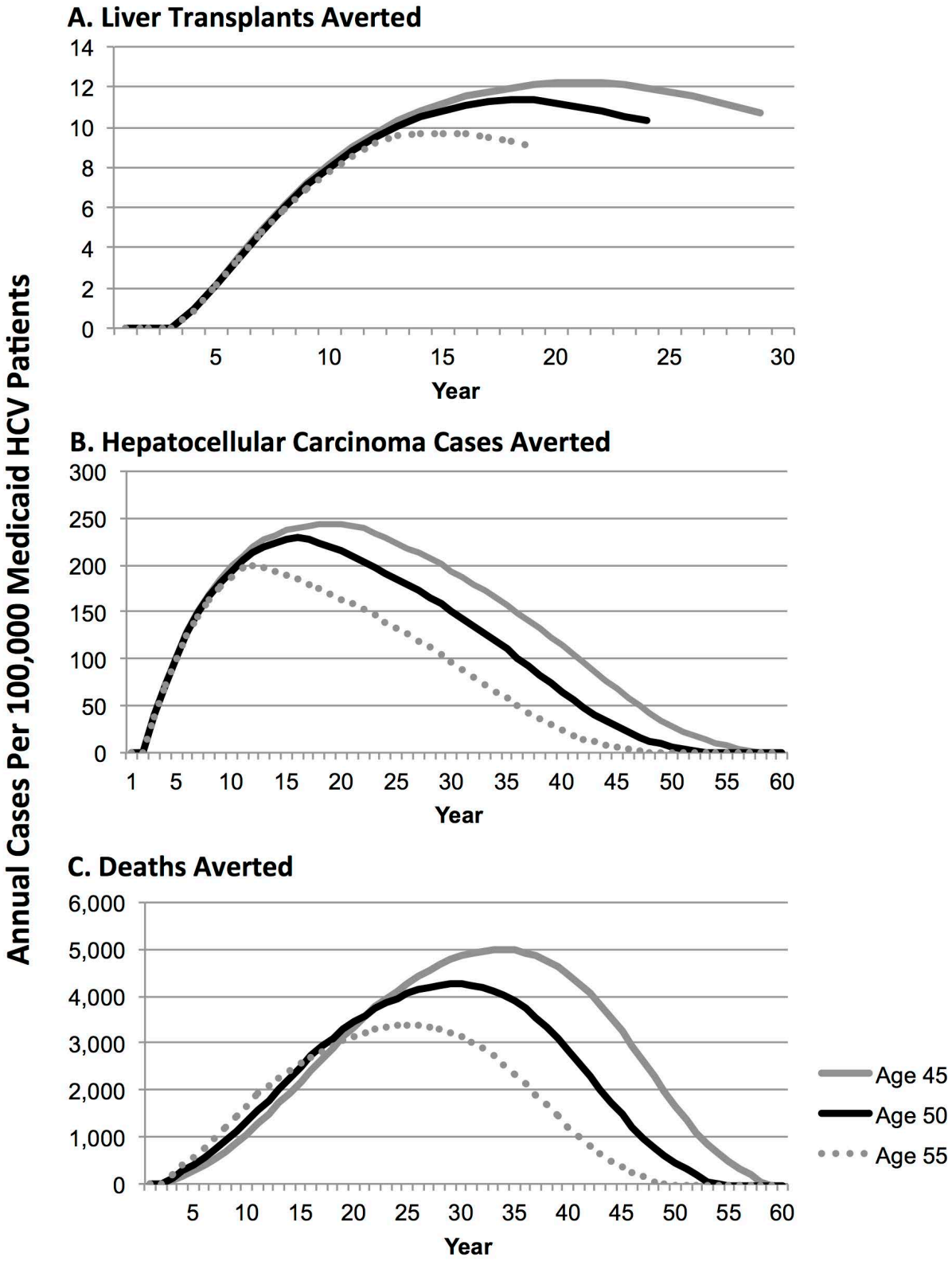

Figure 3.3 Annual Public Health Impact of Unrestricted vs. Restricted Access to Hepatitis C Treatment Among Medicaid Beneficiaries

3.4 DISCUSSION

This cost-effectiveness analysis revealed that for current Medicaid beneficiaries, full access to hepatitis C treatment is cost saving compared to the current practice of restricting treatment to only patients with advanced liver disease. The increased short-term costs of increasing access to care can be recouped in savings from reduced complications in 9-16 years, depending on the treatment strategy and age of the cohort. Furthermore, increased access to treatment could avert numerous future cases of hepatocellular carcinoma, reduce the need for liver transplantation and prevent early mortality.

We demonstrated that Full Access to hepatitis C treatment was actually cost saving compared to the more restrictive Current Practice strategy in the long run. In fact, under ideal circumstances, the total savings could exceed $3.5 billion for the 450,000 Medicaid beneficiaries with hepatitis C. There are two likely explanations for this phenomenon. First, open access would lead to earlier treatment and substantially reduced annual follow-up costs for patients with early-stage disease. This interpretation is supported by the results of our sensitivity analysis, which demonstrated that the full access strategy is only cost saving if annual follow-up costs for early-stage patients exceed $600, meaning that it is economically advantageous to avert these costs. Second, open access to treatment would reduce the number of early-stage patients who progress to advanced fibrosis or cirrhosis before being treated. This is important because even after successful treatment, patients with advanced disease still have high follow-up costs and a small risk of developing costly complications, while successfully treated early-stage patients have similar outcomes to their uninfected age-matched peers.

Our results were robust to variations in most model inputs. In sensitivity analyses, the Full Access strategy was no longer cost saving for very high discount rates (≥5%) or very low

follow-up costs for early-stage patients (<$600), both of which are unlikely. Cost-effectiveness guidelines suggest that a 3% discount rate is likely to be appropriate as the Office of Management and Budget recently suggested that a 3.4% nominal 30-year interest rate should be used for cost-effectiveness analyses (65, 98). Similarly, most studies suggest that costs of follow-up for early-stage patients with hepatitis C are much higher than $600. Recently, the rate of hospitalizations for patients with early-stage and advanced hepatitis C has increased, which suggests that the costs of managing these patients are likely to be increasing as well (99).

Because the assumptions made were generally biased against the Full Access strategy, our estimates are likely to be conservative. Our structural sensitivity analysis showed that the Full Access strategy was still cost saving if the size of the Medicaid population with hepatitis C increased by one-third. However, Medicaid expansion is only expected to increase the program's enrollment by approximately 25% and many new enrollees will likely be children (94). Furthermore, the Full Access strategy was cost saving even if there was no associated increase in treatment capacity. In reality, doubling the pool of eligible patients is likely to increase the absolute number of patients seeking treatment, bounded only by physician availability, patients' knowledge of their disease status, and medical eligibility for treatment. Finally, we assumed that drug prices would be similar for Medicare and Medicaid. However, many state Medicaid programs are negotiating dramatic price discounts for hepatitis C treatment regimens, which could reduce the total cost of the Full Access strategy (100). Meanwhile, because the Medicare program cannot negotiate drug prices, the costs of waiting to treat patients after Medicare eligibility are likely to be higher than our estimates, which were based on Medicaid prices.

Our results are consistent with those of recent studies evaluating the impact of novel interferon-free treatment regimens. Recent reports have demonstrated that novel interferon-free

drug regimens are cost-effective for many patient subgroups (78, 101). One study in particular demonstrated that the SOF/LDV regimen could be cost saving compared to the previous standard of care if treatment was substantially discounted, but did not evaluate the effects of restrictive vs. inclusive treatment strategies (101). In addition, the results of our public health impact analysis are consistent with findings from Kabiri et al (5), who also demonstrated that increased access to hepatitis C treatment could result in substantial long-term reductions in morbidity and mortality.

This study addresses the dilemma of determining which patients with hepatitis C should be treated first, which has been highlighted in numerous recent editorials (74, 102, 103). Briefly, from one perspective, patients with advanced disease should be treated first because they may benefit most in the short-term from treatment, as they have the highest immediate risk of morbidity and mortality. From a different perspective, it may not be ethical to require patients with early-stage disease to develop advanced fibrosis or cirrhosis before offering them access to potentially curative treatments, especially because early-stage patients require shorter, less expensive drug regimens. Here, we offer empiric evidence to inform this debate and demonstrate that, from a government payer perspective, allowing access to treatment for early-stage patients may be the less costly and more effective long-term strategy.

Our analysis is quite interesting in light of current events in public health. For example, the US Preventive Services Task Force recently recommended birth cohort screening for hepatitis C for adults born between 1945 and 1965 (104). A recent study determined that screening is cost-effective, but assumed that patients would be treated after disease was identified, albeit with older regimens (105). It is important to determine whether birth cohort screening is still cost-effective if diagnosis with hepatitis C is not paired with treatment initiation. Moreover, the epidemiology of hepatitis C in the United States is changing. Although

the prevalence is highest among patients aged 45 and older, the incidence of hepatitis C has recently been rising at an alarming rate among younger injection drug users (106). Although our analysis focused on older cohorts, we demonstrate that Full Access is increasingly cost saving for younger patients. Because these younger patients will live with the disease for a longer period of time, treating them while they have early-stage disease will avoid the high costs of disease management and potential complications that would accrue if these patients were treated after disease progression. Treating younger patients may also curb the spread of the disease and reduce the duration of the epidemic.

This study has some limitations that must be acknowledged. First, Markov models do not take into account resource constraints, such as treatment capacity, which extend the time required to treat all untreated patients with hepatitis C. To approximate the effects of treating patients over time, we estimated annual treatment probabilities for patients at each stage of the disease. Other analytic methods, such as discrete event simulation, may provide more precise estimates, but because our assumptions tended to bias the model against the full access strategy, the conclusions are likely to be similar. Second, our estimation of the Medicaid hepatitis C population size and treatment capacity are approximations based on the most recent published data from the Centers for Disease Control. To account for measurement error, we used an overestimate of the Medicaid hepatitis C population to derive conservative estimates in our sensitivity analyses. Third, our analysis does not include patient premiums or state financial contributions to the Medicaid program. This is unlikely to significantly impact our results; patient premiums would be constant for both treatment strategies and the federal government contributes up to 90% of the costs of state Medicaid programs, depending on their participation in Medicaid expansion (107). Fourth, because real-world effectiveness data were not available

for either medication regimen, we used efficacy data from recent clinical trials, which may overestimate treatment success rates. Finally, our model only included long-term costs related to liver disease. In fact, reducing early mortality may allow patients to live long enough to develop diseases of older age and paradoxically increase overall costs to the Medicare program. This concern is beyond the scope of this analysis but is an interesting topic for future study.

In conclusion, using cost-effectiveness analyses, we found that the current Medicaid policy of restricting hepatitis C treatment to patients with advanced disease is more costly and less effective than providing open access to treatment for patients with early-stage disease as well. Although our results provide empiric support for providing open access to treatment for hepatitis C, additional factors, including the size of the physician workforce and budgetary limitations, must also be considered. Our results suggest that collaborative efforts between state and federal payers may be needed to achieve the maximum possible public health impact of novel hepatitis C medications.

4.0 DIFFERENCES IN PHYSICIAN REFERRAL DRIVE DISPARITIES IN SURGICAL INTERVENTION FOR HEPATOCELLULAR CARCINOMA

4.1 BACKGROUND

Hepatocellular carcinoma (HCC) is the second most common cause of cancer death worldwide (9). Although its incidence in the United States has more than tripled over the last 40 years, only modest improvements in survival have been made during that period (108). Currently, only 15% of patients live for five years or longer (109) and surgical interventions (radiofrequency ablation, resection or transplantation) are the only potentially curative treatment options (110-112). These interventions offer dramatic survival advantages over palliative therapies, but only 30-40% of patients with HCC actually receive such surgery (110, 113-115).

Though sociodemographic factors are associated with use of surgical interventions for HCC (114-120), referral for surgery may be the most significant barrier. Referral for surgical intervention is a key step in the process between diagnosis with HCC and receipt of surgical intervention but has not been well studied. One recent study considered referral for surgery as a secondary outcome but did not identify factors independently associated with this outcome (121). Others have tried to understand referral for surgery by studying referral to a specialist. While patients referred to specialists are more likely to receive some form of treatment for HCC,

being seen by a specialist does not guarantee that an eligible patient will be offered a potentially curative surgery (122, 123).

There is also evidence that geographic location may impact referral for and use of surgical intervention for HCC. Use of surgical intervention can vary based on rural location (rurality) and region of residence (114, 118). Regional differences could be attributed to differences in proximity to specialized cancer care, which affects the use of specialized treatment approaches for other types of cancer (124-130). The relationship between geographic location and referral for surgery has not been explored, but there are significant regional differences in specialist consultation for HCC, which may partially influence referral for surgery (123).

In summary, the literature points to some important gaps in our understanding of surgical intervention for HCC. Even though referral is a prerequisite for receipt of surgery, few studies distinguish between factors affecting referral for surgery and factors affecting receipt of a recommended surgical intervention. Similarly, geographic factors, including rural residence or proximity to specialized care, may contribute to variations in surgical intervention for HCC but have not yet been explored. Our study aims were to determine whether sociodemographic and geographic factors, including proximity to a surgical center and rurality, are associated with referral for surgery and receipt of a recommended surgical intervention for HCC.

4.2 METHODS

4.2.1 Design and Data Sources

We conducted a retrospective cohort study using secondary data from the Pennsylvania Cancer Registry, Pennsylvania Health Care Cost Containment Council, and US Census Bureau. Pennsylvania Cancer Registry collects standardized information on all patients diagnosed with or treated for cancer in Pennsylvania and includes more than 95% of all new cancer cases. The Pennsylvania Health Care Cost Containment Council Database includes records from inpatient hospital visits at general acute care hospitals statewide and can be used to calculate hospital procedure volume. The US Census Bureau's 2011 American Community Survey includes information about educational attainment and median household income. The 2010 Census includes information about rurality, defined as the percent of the population in a ZIP Code Tabulation Area (ZCTA) that resides in a rural area.[1] The University of Pittsburgh Institutional Review Board approved this as an exempt study.

4.2.2 Participants

We included patients ages 18 and older who were diagnosed with HCC between January 1, 2006 and December 31, 2011. During this period, there were no substantial changes to HCC treatment guidelines. At diagnosis, patients were residents of Pennsylvania or a geographically contiguous state. We excluded patients who were diagnosed with HCC at autopsy or using death certificates,

[1] Because ZIP codes refer to United States Postal Service mailing routes, the US Census Bureau created a geographic representation called the ZCTA, which identifies the areas in which a given ZIP code is most prevalent.

had unknown treatment type or stage, or had contraindications for surgery in their Pennsylvania Cancer Registry record (e.g. based on age or comorbid conditions).

4.2.3 Study Outcomes

We used the Pennsylvania Cancer Registry to identify two outcomes: (1) referral for surgery for HCC and (2) receipt of surgical intervention. Surgical intervention was defined as liver resection, ablation, or transplantation. Because referral is a prerequisite for receiving surgery, patients in the latter analysis are a subset of those who were referred for surgery.

4.2.4 Variables

Our primary independent variables of interest were (1) proximity to a surgical center and (2) rurality. We defined proximity as residence within 30 minutes of a center that performed at least 30 liver cancer-directed procedures annually (top quintile of hospital procedure volume) (131-134). Hospitals where 30 or more hepatic resections are performed have significantly less morbidity and mortality than lower volume hospitals (131). Liver cancer-directed procedures were identified using Pennsylvania Health Care Cost Containment Council data and *International Classification of Diseases, Ninth Revision, Clinical Modification* procedure codes for liver resection, liver ablation, and liver transplantation. The twenty-six hospitals in Pennsylvania designated as surgical centers perform over 90% of liver cancer-directed procedures. These hospitals serve 19,000 to 326,000 patients each year and most are teaching hospitals located in large metropolitan areas. We then used ArcGIS 10 (ESRI, Redlands, CA) to map the location of surgical centers and the residence of patients with HCC at time of diagnosis.

Finally, we calculated travel time between the centroid of each patient's home ZIP code and the nearest surgical center. We defined rurality as a continuous measure describing the proportion of rural (versus urban) residential housing within a specified geographic area. In the current analysis, it is expressed as the proportion of residents in the patient's ZCTA living in rural areas according to 2010 Census data.

We also abstracted patient demographic data (including age, race, sex, and primary medical insurance at diagnosis) and National Cancer Institute Statistics, Epidemiology and End Results Program (SEER) summary stage at diagnosis for all patients with HCC. We used 5-year estimates from the 2011 American Community Survey to identify median household income and educational attainment for each patient's ZCTA.

4.2.5 Primary Analyses

We compared baseline patient characteristics for each outcome using the Wilcoxon rank sum test for continuous variables and chi-square or Fisher's exact tests for categorical variables. We used logistic regression to assess the univariable associations between all independent and control variables and referral for and receipt of surgical intervention for HCC. We used multivariable logistic regression models to determine whether sociodemographic and geographic factors, including rurality and proximity, were associated with referral for surgical intervention or receipt of surgical intervention. We decided *a priori* to adjust multivariable models for known confounders, including patient age, race, sex, tumor stage, insurance type, income and educational attainment. To address potential collinearity in our multivariable models, we used Pearson correlation coefficients to evaluate pairwise relationships between predictor variables. For pairs of highly correlated variables ($r > |0.5|$), we included in the multivariable model the

predictor that was most strongly associated with the outcome variable. We derived odds ratios (ORs) and 95% confidence intervals (CIs) from univariable and multivariable logistic regression models, calculated variance inflation factors to identify further collinearity and evaluated all potential interactions between variables. We defined statistical significance as a two-tailed p-value of less than 0.05. All statistical analyses were performed using Stata 13 (StataCorp, College Station, TX).

4.2.6 Secondary Analyses

We conducted sensitivity analyses for variables that were excluded from multivariable models due to collinearity. We identified significant collinearity between proximity to a surgical center and rurality (r=-0.51) and between income and educational attainment (r=0.67), so we included proximity and income in our multivariable models. We then conducted sensitivity analyses testing the effects of building the multivariable models using rurality instead of proximity to a surgical center or using educational attainment instead of income.

We also identified determinants of proximity to a surgical center and rurality. We compared characteristics of patients living within 30 minutes of a surgical center with those living further away using the Wilcoxon rank sum test for continuous variables and chi-square test for categorical variables. Similarly, we identified factors associated with rurality using Pearson's correlations for continuous variables, Wilcoxon rank-sum tests for binary variables, and Kruskal-Wallis tests for other categorical variables.

4.3 RESULTS

After identifying 4,560 case records for adults living in Pennsylvania or a contiguous state with a diagnosis of HCC in calendar years 2006 through 2011, we excluded patients with duplicate records (n=11), tumors of unknown stage (n=382), documented contraindications for surgery (n=360), or an uncertain course of treatment (n=230). The study cohort consisted of 3,576 unique patients with HCC. The mean patient age was 63.4 years (SD 11.5), 77.3% were male, and 71.7% were non-Hispanic Caucasian (**Table 4.1**).

A total of 1,466 (40.6%) patients were referred for surgery, of which 1,276 (87.0%) received a surgical intervention. The 190 patients who were referred but did not receive surgery either died before surgery could be performed (n=24), refused surgery (n=40), or did not undergo surgical intervention for unknown reasons (n=128).

4.3.1 Referral for Surgery

Patients referred (vs. not referred) for surgery were more often younger, Caucasian or Asian, and privately insured; they also had higher median income, educational attainment, and a greater frequency of localized disease (**Table 4.2**). In univariable analyses, patients living within 30 minutes of a surgical center were significantly less likely to be referred for surgical intervention than those living farther away (OR: 0.76, 95% CI: 0.66-0.87) (**Table 4.3**).

Table 4.1 Demographic Characteristics of Patients Undergoing Surgical Intervention

Characteristics	All Patients (N=3,576)
Demographic Characteristics	
Age in years *Mean (SD)*	63.5 (11.5)
Male sex *N (%)*	2,765 (77.3)
Race *N (%)*	
White	2,565 (71.7)
African-American	653 (18.3)
Hispanic	120 (3.4)
Asian	163 (4.6)
Other/Unknown	75 (2.1)
Insurance Type *N (%)*	
Private	1,282 (35.9)
Medicare	1,522 (42.6)
Medicaid	470 (13.1)
Other	302 (8.5)
Income, $1000s *Median (IQR)*	48.5 (27.0)
Percent high school graduates *Median (IQR)*	88.2 (9.0)
Other Characteristics	
SEER summary stage *N (%)*	
Localized	1,979 (55.3)
Regional	1,055 (29.5)
Distant	542 (15.2)
Proximity to high volume surgical center (<30 minutes) *N (%)*	2,230 (62.4)
Rural residence *Median (IQR)*	0.4 (18.7)

Abbreviations: IQR: interquartile range; N: number of patients; SD: standard deviation; SEER: National Cancer Institute Surveillance, Epidemiology and End Results program.

Table 4.2 Univariable Analyses of Factors Associated with Referral for Surgery for Hepatocellular Carcinoma

Characteristics	Referred (N=1,466)	Not Referred (N=2,110)	OR (95% CI)	P-Value*
Demographic Characteristics				
Age in years *Mean (SD)*	62.6 (11.2)	64.1 (11.6)	0.99 (0.98, 0.99)	<.001
Male sex *N (%)*	1,093 (74.6)	1,672 (79.2)	0.77 (0.66, 0.90)	.001
Race *N (%)*				<.001
White	1064 (72.6)	1501 (71.1)	1.00	--
African-American	234 (15.9)	419 (19.9)	0.79 (0.66, 0.94)	.009
Hispanic	40 (2.7)	80 (3.8)	0.71 (0.48, 1.04)	.078
Asian	88 (6.0)	75 (3.6)	1.66 (1.20, 2.27)	.002
Other/Unknown	40 (2.7)	35 (1.7)	1.61 (1.02, 2.55)	.042
Insurance type *N (%)*				<.001
Private	611 (41.7)	671 (31.8)	1.00	--
Medicare	597 (40.7)	925 (43.8)	0.71 (0.61, 0.82)	<.001
Medicaid	157 (10.7)	313 (14.8)	0.55 (0.44, 0.69)	<.001
Other	101 (6.9)	201 (9.5)	0.55 (0.42, 0.72)	<.001
Income, $1000s *Median (IQR)*	50.3 (26.4)	46.8 (25.8)	1.01 (1.00, 1.01)	<.001
Percent high school graduates *Median (IQR)*	88.7 (8.3)	87.7 (9.1)	1.02 (1.01, 1.02)	.001
Other Characteristics				
SEER summary stage *N (%)*				<.001
Localized	1110 (75.7)	869 (41.2)	1.00	--
Regional	304 (20.7)	751 (35.6)	0.32 (0.27, 0.37)	<.001
Distant	52 (3.6)	490 (23.2)	0.08 (0.06, 0.11)	<.001
Proximity to high volume surgical center (<30 minutes) *N (%)*	858 (58.5)	1,372 (65.0)	0.76 (0.66, 0.87)	<.001
Rural residence *Median (IQR)*	0.8 (20.3)	0.6 (17.5)	1.23 (0.97, 1.57)	.087

Abbreviations: CI: confidence interval; IQR: Interquartile range; N: number of patients; OR: odds ratio; SD: standard deviation; SEER: National Cancer Institute Surveillance, Epidemiology and End Results program. *P-values were calculated using univariable logistic regression analyses.

Table 4.3 Univariable Analyses of Factors Associated with Receipt of Surgery for Hepatocellular Carcinoma

Characteristics	Receipt of Surgery (N=1,276)	No Receipt of Surgery (N=190)	OR (95% CI)	P-Value*
Demographic Characteristics				
Age in years *Mean (SD)*	62.5 (11.2)	63.3 (11.2)	0.99 (0.98, 1.01)	.363
Male sex *N (%)*	943 (73.9)	150 (79.0)	0.76 (0.52, 1.09)	.137
Race *N (%)*				.052
White	927 (72.7)	137 (72.1)	1.00	—
African-American	203 (15.9)	31 (16.3)	0.97 (0.64, 1.47)	.878
Hispanic	33 (2.6)	7 (3.7)	0.70 (0.64, 1.47)	.396
Asian	83 (6.50)	5 (2.6)	2.45 (0.98, 6.16)	.056
Other/Unknown	30 (2.4)	10 (5.3)	0.44 (0.21, 0.93)	.031
Insurance type *N (%)*				.630
Private	531 (41.6)	80 (42.1)	1.00	—
Medicare	522 (40.9)	75 (39.5)	1.05 (0.75, 1.47)	.783
Medicaid	139 (10.9)	18 (9.5)	1.16 (0.68, 2.01)	.586
Other	84 (6.6)	17 (9.0)	0.74 (0.42, 1.32)	.312
Income, $1000s *Median (IQR)*	50.3 (26.9)	50.1 (25.4)	1.00 (0.99, 1.01)	.677
Percent high school graduates *Median (IQR)*	89.0 (8.3)	88.1 (9.7)	1.01 (0.99, 1.03)	.393
Other Characteristics				
SEER summary stage *N (%)*				<.001
Localized	976 (76.5)	134 (70.5)	1.00	—
Regional	265 (20.8)	39 (20.5)	0.93 (0.64, 1.37)	.721
Distant	35 (2.7)	17 (9.0)	0.28 (0.15, 0.52)	<.001
Proximity to high volume surgical center (<30 minutes) *N (%)*	740 (58.0)	118 (62.1)	0.84 (0.62, 1.15)	.281
Rural residence *Median (IQR)*	0.9 (21.5)	0.3 (8.4)	1.82 (0.98, 3.36)	.058

Abbreviations: CI: confidence interval; IQR: Interquartile range; N: number of patients; OR: odds ratio; SD: standard deviation; SEER: National Cancer Institute Surveillance, Epidemiology and End Results program. *P-values were calculated using univariable logistic regression analyses.

In our multivariable logistic regression model, proximity to a surgical center was independently associated with 21% lower odds of referral for surgery (adjusted OR: 0.79, 95% CI: 0.68-0.92) (**Table 4.4**). Older age, male sex, Medicaid or other insurance, and regional or distant tumor stage at diagnosis were associated with a decreased frequency of surgical referral. Asian race was positively associated with referral for surgery. There were no significant differences in referral based on African-American, Hispanic, or "Other/Unknown" race, Medicare insurance, or median household income. There were no significant interactions between predictor variables and referral for surgery, including interactions between race and proximity to a surgical center ($p>0.05$ for all potential interactions).

4.3.2 Receipt of Surgical Intervention

Patients who received surgical intervention (vs. not receiving surgery) were less likely to have an "Other/Unknown" race/ethnicity and to have distant involvement of HCC (**Table 4.3**). Our univariable logistic regression model revealed no significant differences in receipt of surgery based on proximity to a surgical center (OR: 0.84, 95% CI: 0.62-1.15). In our multivariable logistic regression model (**Table 4.4**), proximity to a surgical center was not significantly associated with receipt of surgical intervention (adjusted OR: 0.84, 95% CI: 0.60, 1.15). Distant stage at diagnosis was negatively associated with receipt of surgical intervention. There were no significant differences in receipt of surgery based on age, sex, African-American, Hispanic or Asian race/ethnicity, insurance type, or median household income. In this analysis, there were no significant interactions between predictor variables and receipt of surgical intervention; potential interactions between race and proximity to a surgical center were non-significant ($p>0.05$ for all potential interactions).

Table 4.4 Multivariable Analyses of Factors Associated with Referral for & Receipt of Surgical Intervention

Characteristics	Referral for Surgical Intervention		Receipt of Surgical Intervention	
	AOR (95% CI)	P-Value*	AOR (95% CI)	P-Value*
Demographic Characteristics				
Age in years	0.98 (0.98, 0.99)	<.001	0.99 (0.97, 1.00)	.127
Male sex	0.75 (0.63, 0.90)	.001	0.73 (0.50, 1.07)	.104
Race		.025		.038
White (Reference)	1.00	–	1.00	–
African-American	0.89 (0.73, 1.10)	.291	1.02 (0.64, 1.61)	.941
Hispanic	0.72 (0.47, 1.09)	.123	0.64 (0.27, 1.50)	.304
Asian	1.48 (1.05, 2.11)	.027	2.29 (0.90, 5.79)	.081
Other/Unknown	1.44 (0.87, 2.37)	.154	0.41 (0.19, 0.86)	.018
Insurance type		<.001		.508
Private (Reference)	1.00	–	1.00	–
Medicare	0.83 (0.69, 1.00)	.053	1.23 (0.84, 1.80)	.295
Medicaid	0.58 (0.46, 0.75)	<.001	1.29 (0.67, 2.11)	.538
Other	0.62 (0.46, 0.82)	.001	0.81 (0.45, 1.45)	.312
Income, $1000s	1.00 (0.99, 1.01)	.125	1.00 (0.99, 1.01)	.708
Other Characteristics				
SEER summary stage		<.001		<.001
Localized (Reference)	1.00	–	1.00	–
Regional	0.32 (0.27, 0.38)	<.001	0.94 (0.64, 1.38)	.721
Distant	0.09 (0.06, 0.12)	<.001	0.27 (0.15, 0.50)	<.001
Proximity to high volume surgical center (<30 minutes)	0.79 (0.68, 0.92)	.002	0.83 (0.60, 1.15)	.273

Abbreviations: CI: confidence interval; AOR: adjusted odds ratio; SEER: National Cancer Institute Surveillance, Epidemiology and End Results program. *P-values were calculated using multivariable logistic regression analyses. Educational attainment and rurality were not included due to multi-collinearity.

4.3.3 Additional Analyses

Our sensitivity analyses were conducted to determine the effects of replacing proximity to a surgical center with rurality or replacing income with educational attainment in our multivariable models. There were no substantial changes to the multivariable model for referral for surgery after either substitution or to the multivariable model for receipt of surgery after substituting educational attainment for income. However, while we found no significant association between proximity to a surgical center and receipt of surgery, rurality was associated with a significantly increased likelihood of receipt of surgery (OR: 2.10, 95% CI: 1.10, 4.00).

Based on the results of our primary analyses, we identified factors associated with proximity to a surgical center and rurality. Patients who lived close to a surgical center were more often African-American or insured by Medicaid, and lived in ZCTAs with higher median incomes, lower educational attainment and decreased rurality (**Table 4.5**). There were no significant differences in proximity to a surgical center based on age, sex, or tumor stage. Rurality was negatively associated with African-American, Hispanic, or Asian race/ethnicity ($p<.001$), Medicaid insurance ($p<.001$), median household income ($p=.03$), and proximity to a surgical center ($p<.001$). There were no significant differences in rurality based on age ($p=.61$), sex ($p=.59$), tumor stage ($p=.11$), or educational attainment ($p=.31$).

Table 4.5 Characteristics of Patients with Hepatocellular Carcinoma, By Proximity to a High Volume Center

Characteristics	<30 Minutes (N=2,230)	≥ 30 Minutes (N=1,346)	P-Value*
Demographic Characteristics			
Age in years *Mean (SD)*	63.5 (11.4)	63.5 (11.5)	.523
Male sex *N (%)*	1,726 (77.4)	1,039 (77.1)	.886
Race *N (%)*			<.001
White	1,431 (64.1)	1,134 (84.3)	
African-American	545 (24.4)	108 (8.0)	
Hispanic	89 (4.0)	31 (2.3)	
Asian	119 (5.3)	44 (3.3)	
Other/Unknown	46 (2.1)	29 (2.2)	
Insurance Type *N (%)*			<.001
Private	775 (34.8)	507 (37.7)	
Medicare	925 (41.5)	597 (44.4)	
Medicaid	345 (15.5)	125 (9.3)	
Other	185 (8.3)	117 (8.7)	
Income, $1000s *Median (IQR)*	48.6 (29.9)	48.0 (21.3)	.002
Percent high school graduates *Median (IQR)*	88.0 (10.6)	88.3 (6.4)	.006
Other Characteristics			
SEER summary stage *N (%)*			.342
Localized	1,213 (54.4)	766 (56.9)	
Regional	672 (30.1)	383 (28.5)	
Distant	345 (15.5)	197 (14.6)	
Rural residence *Median (IQR)*	0 (1.1)	21.2 (47.2)	<.001

Abbreviations: 95% CI: 95% confidence interval; IQR: Interquartile range; N: number of patients; SD: standard deviation; SEER: National Cancer Institute Surveillance, Epidemiology and End Results program. *P-values were calculated using Wilcoxon-Mann-Whitney and χ^2 tests.

4.4 DISCUSSION

In this retrospective cohort study of patients with hepatocellular carcinoma, we found that a number of non-clinical factors are associated with referral for surgery but that the vast majority of patients who were referred ultimately underwent surgical intervention. We also found that proximity to a surgical center was independently associated with decreased odds of referral for surgical intervention.

Our results suggest that socioeconomic and geographic disparities in surgical intervention tend to occur when patients are evaluated for treatment. The published literature offers weak explanations for this phenomenon. A few studies have identified disparities in referral to a specialist (defined as an oncologist or surgeon) after diagnosis with HCC (122, 123), but specialist referral only partially accounted for variations in treatment type; specialist referral is neither necessary nor sufficient for a patient to be referred for surgery. We demonstrate that almost every patient who is referred for surgery ultimately undergoes surgical intervention, which suggests that referral to a specialist is not the only underlying factor. Some suggest that comorbidities and age may influence a physician's choice of initial therapy for HCC, but our analysis excluded patients for whom documented contraindications to surgery existed. Referral for surgery is a result of both the physician's decision to recommend and the patient's decision to consider a potentially curative treatment. While racial and psychosocial disparities exist in refusal of HCC-directed surgery (121), we considered a patient to have been referred whether or not they declined to undergo surgical intervention. Unfortunately, few studies have specifically evaluated referral for surgery, so much remains unknown about the barriers and facilitators of the referral process. Further studies are required to understand referral for surgery. It is conceivable that urban patients may be more likely to experience certain psychosocial issues such as

healthcare mistrust and poor health literacy. This could impact their likelihood of having an established relationship with a physician and of being referred for surgical intervention. These psychosocial issues could be identified and addressed in order to improve surgical referral and ultimately patient outcomes.

Furthermore, our results suggest that geographic proximity to a surgical center may not translate into improved access to care. We could not control for rurality in our multivariable model (due to collinearity), but our post-hoc analysis revealed that proximity to a surgical center was a uniquely urban phenomenon. Urban residence has long been associated with low socioeconomic status and poor access to care, but we attempted to control for some of these factors using proxy measures of socioeconomic status. The fact that proximity to care is still independently associated with lower odds of referral for surgery suggests that there may be some unmeasured characteristics of urban patients that impede access to care. This idea is supported in part by the literature. For example, African-American patients tend to live in urban areas close to sources of healthcare, but report longer travel times than patients of other races (130, 134). This suggests that mode of transportation may be an important aspect of access to care for some urban patients, but not for their rural counterparts.

The findings in our study are consistent with the published literature in certain ways. For example, we identified many of the same socioeconomic disparities in referral for surgery as have previously been identified for overall utilization of surgery and found similar rates of surgery (114-120). However, when we excluded patients who were not referred for surgery from the analysis, we no longer identified socioeconomic disparities. The few studies that have separately considered referral for and receipt of surgery have focused on refusal of surgical intervention, which is associated with older age, African-American race, advanced tumor stage,

and marital status (121). While our results differ, the previous study did not consider other reasons for which patients might not undergo surgery (e.g., patient preferences) and used data from 1985-2004, when different treatment options were available.

Other aspects of our results differ significantly from those found in the published literature. For example, disparities in surgery for African-American patients have been uniformly identified (114-120), but African-American race was not significantly associated with referral for or receipt of surgery in our study. We found significant racial variations in referral for surgery in our univariable analysis, but these differences were no longer apparent in the adjusted model. However, our secondary analysis revealed that African-American patients were more likely to live close to surgical centers than to live further away. This suggests that racial disparities in surgery might be better explained by geographic factors such as proximity to a surgical center. Still, the population of patients near surgical centers was still predominantly White and tended to have higher median incomes, so it is unlikely that proximity is solely a function of race or socioeconomic status.

We recognize that our study has some limitations. First, most patients who were referred for surgery went on to undergo surgical intervention, so our analysis may not have had sufficient power to identify significant differences in receipt of surgery. Second, income and educational attainment data were aggregated at the ZCTA level, which could obscure systematic differences from the population mean. However, it is common practice to abstract these data from the US Census when individual-level data are unavailable. Third, because we used an administrative database, we could not identify patient-level factors, including detailed comorbidity information or laboratory or radiographic data to quantify the severity of a patient's underlying liver disease, which could impact the decision to refer a patient for surgery. Instead, we had to rely on a

variable that indicated that a patient had documented contraindications to surgical intervention, which we hoped would include patients whose background liver disease precluded possible surgical intervention. Fourth, we also could not identify delays in referral, which could affect patient outcomes. Finally, this analysis was conducted using data from patients in Pennsylvania and may not be generalizable to other geographic areas in the United States or to healthcare systems outside the US.

Our study builds on previous health disparities research in treatment for hepatocellular carcinoma. A commonly used conceptual framework defines three stages of health disparities research: (1) detection, (2) understanding, and (3) reducing disparities (135). Our study addressed stage 2; we built upon the previous foundation of disparities research in HCC and aimed to further understand the underlying processes. Our findings suggest that future efforts to investigate disparities in HCC treatment may need to qualitatively assess barriers to surgical referral for urban populations and among physicians. Currently, surgical intervention offers patients with HCC the best chance at long-term survival, so it is important to identify barriers and design interventions to ensure broad, equitable access to potentially curative treatment for *all* eligible patients with HCC.

5.0 CONCLUSION

The projects included in this dissertation aimed to evaluate current practices in the treatment of chronic liver diseases and hepatocellular carcinoma. We demonstrated that for two populations of patients with hepatitis C, including military Veterans and Medicaid beneficiaries, it is cost-effective to treat patients with both early- and advanced-stage fibrosis with recently approved interferon-free regimens. By comparison, we found that relaxing restrictions on hepatitis C treatment in the Medicaid program can result in substantial reductions in morbidity, mortality, and long-term costs for both the Medicare program and the Centers for Medicare and Medicaid Services overall. Finally, we determined that, for patients who have developed hepatocellular carcinoma, socioeconomic and geographic disparities in the use of potentially curative surgical intervention are driven by differences in physician treatment recommendations.

Our work makes strides toward the goal of interrupting the continuum of chronic liver disease (Figure 1.1). The first two studies evaluated strategies for improving access to hepatitis C treatment, which would reduce the incidence of diseases further on the continuum, including cirrhosis and hepatocellular carcinoma, and ultimately reduce mortality. The third study revealed previously unidentified barriers to surgical intervention for patients with hepatocellular carcinoma. Because surgical intervention is the only potentially curative treatment option for these patients, effectively addressing nonclinical barriers to surgery may be an ideal method of improving survival.

The studies included in this dissertation highlight important issues for future study. For patients with hepatitis C, it will become important to maximize the impact of investments in new medication regimens. This can be accomplished by continued evaluation of strategies to expand the physician workforce available to treat hepatitis C, ensure adherence to medication regimens, and reduce the risk of reinfection. Furthermore, the framework we have used to consider these highly effective but extremely costly medications will become increasingly important as payers are faced with more and more exorbitant prices for breakthrough medications (136). For patients with hepatocellular carcinoma, it will be important to understand why physician recommendations vary based on nonclinical factors and evaluate barriers that may adversely impact access to care for urban patients despite their relative proximity to high volume centers. Perhaps more importantly, it is essential that efforts to document and understand healthcare disparities ultimately give rise to effective interventions to equitably distribute quality care and improve public health (137).

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