

# Real-World Value of Direct-Acting Antivirals for Hepatitis C at Kaiser Permanente Southern California

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**H**epatitis C virus (HCV) infection is the most common blood-borne infectious disease in the United States, with more than 2 million Americans currently infected.<sup>1</sup> Although nonalcoholic fatty liver disease is a rapidly growing cause of chronic liver disease resulting in an increase in advanced liver disease,<sup>2,3</sup> HCV remains a leading cause of liver-related morbidity and mortality in the United States and may cause numerous extrahepatic manifestations.<sup>4,5</sup> Persons born between 1945 and 1965 have been identified as the population cohort with the highest prevalence of HCV.<sup>1,6,7</sup> Consequently, the prevalence of advanced liver disease is expected to increase in the coming years, which is anticipated to lead to an increase in costly liver-related events.<sup>4</sup>

HCV treatment has evolved with the introduction of interferon (IFN)-free direct-acting antivirals (DAAs),<sup>8</sup> which have higher efficacy (ie, sustained virologic response [SVR] rates) and good safety profiles and thus can be used in patients with IFN contraindications and IFN intolerance.<sup>9</sup> Further, achievement of SVR, defined as cure from HCV, prevents the risk of liver disease progression and is associated with a decrease in advanced liver disease events,<sup>10</sup> increased life expectancy, and a substantial reduction in overall mortality.<sup>10,11</sup>

DAAs result in initial cure rates of more than 95%<sup>12,13</sup>; however, the high cost of DAAs leads to a high budget impact in the short term. Due to the short-term high cost of DAAs, payers have previously limited access to these lifesaving drugs.<sup>14,15</sup> However, DAAs may bring value to health systems over the long term, given the reduction in costly liver-related events<sup>10</sup> with SVR and the ability to treat more patients effectively. Previous studies have demonstrated that even when using the earliest interferon-containing triple-therapy DAA regimens (containing boceprevir or telaprevir), the cost for patients achieving SVR was lower than the cost of uncured patients; however, SVR rates were low. Price et al examined the experience of all Kaiser Permanente Northern California patients initiating telaprevir or boceprevir triple therapy from June 2011 to March 2012.<sup>16</sup> This real-world study demonstrated that most (69%) patients completed a full treatment course and SVR was achieved in 55% of patients.<sup>16</sup> Nyberg et al evaluated costs associated with HCV treatment at Kaiser Permanente Southern California (KPSC)

## ABSTRACT

**OBJECTIVES:** Direct-acting antivirals (DAAs) for chronic hepatitis C virus (HCV) lead to cure in more than 95% of recipients; however, payers may limit access to these lifesaving drugs due to high initial cost. Here, the cost-effectiveness of treating HCV with DAAs vs no treatment over a lifetime horizon is evaluated from the perspective of Kaiser Permanente Southern California (KPSC).

**STUDY DESIGN:** A hybrid decision-tree Markov model.

**METHODS:** The model simulated the health and economic outcomes for a real cohort of patients with HCV treated with either ledipasvir-sofosbuvir or sofosbuvir-velpatasvir between November 1, 2014, and October 31, 2019, at KPSC. Patients entered the model at different stages of liver disease and received either active treatment with DAAs or no treatment. Patients who did not achieve sustained virological response experienced disease progression; those who achieved sustained virological response experienced either significantly slower or no disease progression depending on the stage of fibrosis at model start. Demographics, treatment experience, genotype, baseline fibrosis stage, treatment rates, and treatment efficacy were sourced from KPSC real-world data. Costs and utilities were sourced from published literature.

**RESULTS:** A total of 7255 patients with a mean age of 59 years were treated during the study period. Over a lifetime horizon, DAAs resulted in significant reduction in advanced liver disease events and a total cost savings of \$1 billion compared with no treatment based on a hybrid decision-tree Markov state-transition model. Cost savings were achieved after only 3 years. DAA intervention dominated no treatment on a per-patient and cohort basis.

**CONCLUSIONS:** DAA treatment at KPSC is predicted to significantly reduce HCV-related morbidity and mortality, providing an anticipated return on investment in drug costs after 3 years of treatment.

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TAKEAWAY POINTS

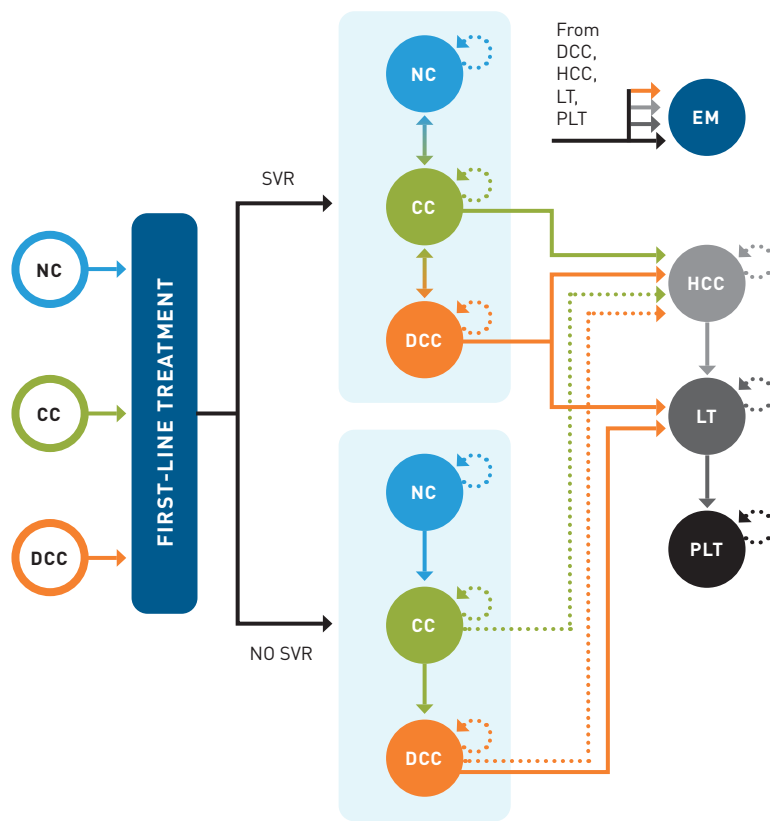
Use of direct-acting antivirals (DAAs) in patients with hepatitis C virus (HCV) in the Kaiser Permanente Southern California health care system can provide value by reducing long-term HCV-related morbidity and mortality while quickly providing a net monetary benefit.

- ▶ Over a lifetime horizon, DAAs are predicted to result in a significant reduction in advanced liver disease events compared with no treatment.
- ▶ DAA intervention dominated (ie, was more effective and less costly than) no treatment.
- ▶ DAAs are anticipated to result in a total cost savings of \$1 billion over a lifetime horizon compared with no treatment based on a hybrid decision-tree Markov state-transition model. Cost savings are anticipated to be achieved quickly post treatment, with DAAs being less costly than the untreated scenario after 3 years.

that SVR rates with ledipasvir and sofosbuvir (LDV/SOF; Harvoni) were high (96% to 100%) and the cost per SVR was approximately one-third lower than that of interferon-based regimens.<sup>18</sup>

However, there is a lack of studies evaluating the costs and benefits of DAAs from a long-term perspective using real-world efficacy data in the integrated health care delivery system at KPSC. Therefore, the objective of this study was to evaluate the cost-effectiveness of treating patients with HCV at KPSC with DAAs compared with no treatment over a lifetime horizon.

FIGURE 1. Model Diagram<sup>a</sup>



METHODS

Model Overview

A previously developed lifetime Markov cohort model was adapted to project the impact of treatment with DAA regimens or no treatment on health and economic outcomes from the perspective of the KPSC health care delivery system.<sup>19</sup> A time horizon of 50 years was modeled assuming patients who enter the model will reach death based on the life tables of the US population.<sup>20</sup> Health and economic outcomes were discounted at an annual rate of 3.0%.<sup>21</sup>

Model Structure

A previously developed hybrid decision-tree Markov state-transition model<sup>19</sup> was utilized for this study (Figure 1). A real-world cohort of patients with chronic hepatitis C at KPSC entered the model at different stages of liver disease (noncirrhosis [NC], compensated cirrhosis [CC], or decompensated cirrhosis [DCC]) and either received active treatment with DAA therapy or did not receive any treatment. Patients who did not achieve SVR within the model experienced disease progression, including end-stage liver disease; those who achieved SVR experienced either significantly slower or no further disease progression depending on the stage of liver disease at model start. Advanced liver disease was defined as disease progression to higher disease severity states, including CC, DCC, hepatocellular carcinoma (HCC), and liver transplantation

CC, compensated cirrhosis; DCC, decompensated cirrhosis; EM, excess mortality; HCC, hepatocellular carcinoma; LT, liver transplantation; NC, noncirrhosis; PLT, post liver transplantation; SVR, sustained virological response.

<sup>a</sup>Schematic representation of state-transition Markov cohort model. For each simulation, patients transit from left to right in the model. Health states modeled are represented by circles. Solid arrows indicate a transition between health states permitted in the model, and dotted arrows indicate staying in the same health states over subsequent cycles. EM was the absorbing health state in the model.

from January 1, 2002, to December 31, 2012.<sup>17</sup> This study reported costs per SVR of \$147,274 and \$172,158 for boceprevir- and telaprevir-based triple therapy, respectively.<sup>17</sup> Another study by Nyberg et al evaluating costs associated with HCV treatment at KPSC reported

(LT).<sup>3</sup> For each 1-year cycle length, patients either stayed in or transitioned between the following health states: NC, CC, DCC, HCC, LT, post LT, and excess mortality. Death was the absorbing health state in the model. Costs and utilities are associated with

each state. Background general mortality was considered in every state of the model; HCV-related mortality was associated with only advanced liver disease (CC, DCC, HCC, and LT).

## Patient Population

The study population was derived from a real-world cohort of patients 18 years and older with HCV treated with either LDV/SOF or sofosbuvir and velpatasvir (SOF/VEL; Epclusa) between November 1, 2014, and October 31, 2019, at KPSC (eAppendix Figure 1 [eAppendix available at [ajmc.com](http://ajmc.com)]). Additional inclusion criteria were known genotype and at least 12 months of continuous membership in the KPSC health plan, allowing for a gap of, at most, 2 consecutive months in membership during the preindex date baseline period and a minimum of 12 weeks before prescription index date and 24 weeks after prescription index date. Data used to establish HCV diagnosis and to determine stage of disease were obtained from October 1, 2009, to December 31, 2019. Laboratory studies to determine genotype and SVR were obtained from January 1, 2000, to April 30, 2021. Among the eligible population, SVR4 (ie, SVR at 4 weeks) was identified based on the first SVR and first dispense date of either LDV/SOF or SOF/VEL. Cirrhosis was identified 0 to 6 months and 7 to 12 months before first dispense date of either LDV/SOF or SOF/VEL using previously described criteria published by our group.<sup>3</sup> Cirrhosis was defined as a diagnosis of hepatic encephalopathy and no diagnosis of constipation or more than 3 dispenses of lactulose and at least 1 of the following: (1) platelet count of less than 100,000 and (2) total bilirubin level of 2.5 mg/dL or greater. In addition, more than 400 charts were manually reviewed to validate the eligible study population, and approximately 200 charts were manually reviewed to determine missing genotype and validate SVR results for the population included in the model. The definitions of cirrhosis and of DCC are described in detail in work published by Nyberg et al.<sup>3</sup> This electronic algorithm was validated, and the methods were described in detail by Nyberg et al.<sup>3</sup> Although the algorithm was developed and validated in a population of patients with nonalcoholic fatty liver disease, the variables are universal for cirrhosis irrespective of etiology. Using Child-Pugh scores is not feasible for this population because all variables for the laboratory and/or clinical data were not available within the standard time frame of 6 months.

Manual chart review for validation of the algorithm for cirrhosis showed a sensitivity of 88% for true cirrhosis, as evidenced by imaging (liver nodularity with or without evidence of portal hypertension) and/or having a diagnosis of cirrhosis made by a specialist in gastroenterology/hepatology. Most also had other abnormalities such as elevated liver enzyme tests and transient elastography values consistent with cirrhosis. The electronic algorithm used to define DCC includes laboratory values, procedure codes, imaging, pharmacy records, and *International Classification of Diseases, Ninth Revision* and *International Statistical Classification of Diseases, Tenth Revision* codes. Patients with a paracentesis code were also required to have a diagnosis code for either ascites or spontaneous bacterial peritonitis

and to have a current or subsequent diagnosis of cirrhosis. Charts flagged with a procedure code for esophagogastroduodenoscopy were considered decompensated only if they also had a code for upper gastrointestinal bleeding. A procedure code for transjugular intrahepatic portosystemic shunt any time during the study period qualified as a decompensating event. In addition to diagnosis codes, hepatic encephalopathy was identified by pharmacy dispenses and laboratory data. An associated diagnosis of hepatic encephalopathy required a lactulose or rifaximin prescription and no diagnosis of constipation or more than 3 dispenses (lactulose and/or rifaximin) and at least 1 of the following: (1) platelet count of less than 100,000, (2) bilirubin level greater than 2.5 mg/dL, (3) propranolol or nadolol dispense, (4) ammonia test result, and (5) prescription by a gastrointestinal specialist. Manual chart review performed to validate the electronic algorithm for DCC showed a sensitivity of 83% for true decompensation by imaging (ascites: 76% of chart-review population) and/or other clinical criteria, including endoscopy with variceal bleeding and/or hepatic encephalopathy diagnosed and treated by a gastroenterologist/hepatologist.

After applying the inclusion and exclusion criteria, the total sample size was 7255. The mean age was 59 years. The baseline patient distribution by HCV genotype was 82.5%, 6.6%, 7.1%, 2.5%, and 1.3% across genotypes 1, 2, 3, 4, and 5/6, respectively. At baseline, the distribution of liver fibrosis was 66%, 22%, and 12% across NC, CC, and DCC, respectively. Distribution by prior treatment experience was 87% treatment-naïve patients and 13% treatment-experienced patients. Treatment-naïve patients included those whose first treatment dispensed for HCV was either LDV/SOF or SOF/VEL. Treatment-experienced patients included those with any prior treatment use for HCV. Prior treatments for patients included in the analysis included IFN plus ribavirin (LDV/SOF group: 54% of patients; SOF/VEL group, 31% of patients), first-line DAAs (44% and 12% of patients, respectively), and IFN-free DAAs (2% and 57% of patients, respectively).

## Treatment Strategies

The model evaluated 2 scenarios. First, for the DAA strategy, the model evaluated 2 DAA treatment regimens: SOF/VEL and LDV/SOF. The FDA prescribing information was used for each treatment to determine dosing and duration of therapy. Second, a scenario for no treatment was included in the model.

## Transition Probabilities

Annual transition probabilities between health states are summarized in [Table 1](#).<sup>4,22-31</sup> These probabilities were sourced from the literature.<sup>4,22-31</sup> It was assumed that patients would not experience disease progression during the initial first year of treatment. Achieving SVR was assumed to reduce disease progression in patients with NC, CC, and DCC.<sup>27</sup> In addition, patients with fibrosis stages F3 and F4 achieving SVR were assumed to experience fibrosis regression. Although patients can transition to death from every health state in the model, mortality was considered both via background mortality

**TABLE 1.** Annual Health State Transition Probabilities<sup>4,22-31</sup>

Parameters	Base case value	Source
NC to CC	0.057	Nyberg et al (2015) <sup>22</sup>
NC to EM	0.000	Assumption
NC SVR to CC SVR	0.000	Assumption
NC SVR to EM	0.000	Assumption
CC to DCC	0.099	Nyberg et al (2015) <sup>22</sup>
CC to HCC	0.005	Nyberg et al (2015) <sup>22</sup>
CC to EM	0.000	Assumption
CC SVR to NC SVR	0.076	D'Ambrosio et al (2012) <sup>23</sup>
CC SVR to DCC SVR	0.003	Dienstag et al (2011) <sup>27</sup> ; Morgan et al (2013) <sup>28</sup>
CC SVR to EM	0.000	Assumption
CC SVR to HCC	0.006	Morgan et al (2013) <sup>28</sup>
DCC to HCC	0.033	Nyberg et al (2015) <sup>22</sup>
DCC to LT	0.023	Chhatwal et al (2015) <sup>25</sup> ; Chhatwal et al (2013) <sup>24</sup>
DCC to EM	0.129	Fattovich et al (1997) <sup>26</sup>
DCC SVR to CC SVR	0.076	D'Ambrosio et al (2012) <sup>23</sup>
DCC SVR to HCC	0.003	Morgan et al (2013) <sup>28</sup>
DCC SVR to LT	0.007	Assume RR of 0.296 for DCC to LT (RR from Saab et al [2010] <sup>31</sup> )
DCC SVR to EM	0.042	Assume RR of 0.381 for DCC to EM (RR from Saab et al [2010] <sup>31</sup> )
HCC to LT	0.040	Chhatwal et al (2015) <sup>25</sup> ; Lang et al (2010) <sup>29</sup>
HCC to EM	0.485	Liu et al (2012) <sup>30</sup>
LT to EM	0.107	Razavi et al (2013) <sup>4</sup>
Post LT to EM	0.049	Razavi et al (2013) <sup>4</sup>

CC, compensated cirrhosis; DCC, decompensated cirrhosis; EM, excess mortality; HCC, hepatocellular carcinoma; LT, liver transplantation; NC, noncirrhosis; RR, relative risk; SVR, sustained virological response.

(sourced from the life tables)<sup>32</sup> and via excess mortality (incorporated into transition probabilities) for mortality that was due to HCV.<sup>33</sup>

**Treatment Efficacy**

SVR rates for the treated cohort (N=7255) were derived from real-world data after treatment at KPSC from both the pharmacy database and the manual patient medical chart review. SVR rates were stratified by genotype, treatment experience, fibrosis stage, and type of DAA treatment (eAppendix Table 1). SVR rates are presented for the per-protocol population.

When necessary, SVR rates were adjusted by relative risk to impute missing data, as done in a previously published cost-utility analysis of chronic HCV.<sup>34</sup> For example, if a study only reported SVR rates by genotype and by cirrhosis status separately (ie, 1 rate for patients with genotype 2, 1 rate for patients with genotype 3, 1 rate for all patients with NC in the study, 1 rate for all patients with CC in the study) instead of for patients with cirrhosis and a specific genotype (ie, patients with genotype 2 and cirrhosis), the genotype

**TABLE 2.** Model Inputs: Costs and Utilities<sup>35-43</sup>

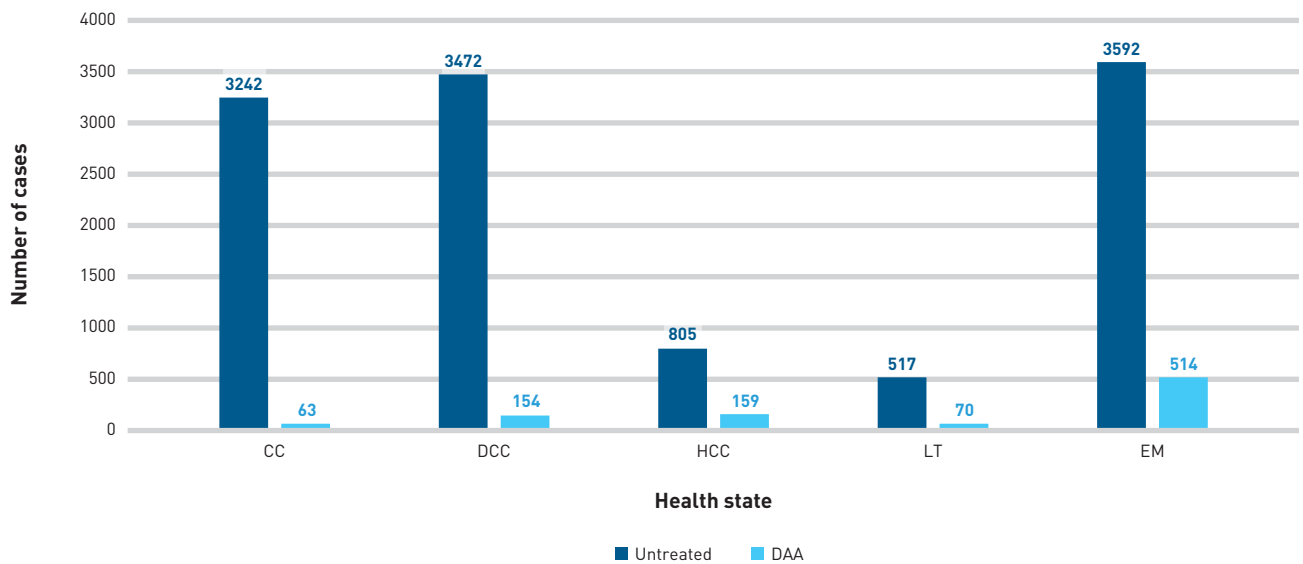
Parameters	Base case value	Source
<b>Annual health state costs, US\$</b>		
NC	\$6,305	Mean of McAdam-Marx et al (2011), <sup>38</sup> Gordon et al (2012), <sup>37</sup> and Baran et al (2015) <sup>36</sup>
NC SVR	\$0	Assumption
CC	\$7,658	Mean of McAdam-Marx et al (2011), <sup>38</sup> Gordon et al (2012), <sup>37</sup> and Baran et al (2015) <sup>36</sup>
CC SVR	\$639	Mean of McAdam-Marx et al (2011), <sup>38</sup> Gordon et al (2012), <sup>37</sup> and Baran et al (2015) <sup>36</sup>
DCC	\$45,801	Mean of McAdam-Marx et al (2011), <sup>38</sup> Gordon et al (2012), <sup>37</sup> and Baran et al (2015) <sup>36</sup>
DCC SVR	\$45,801	Assumption
HCC	\$113,639	Mean of McAdam-Marx et al (2011), <sup>38</sup> Gordon et al (2012), <sup>37</sup> and Baran et al (2015) <sup>36</sup>
LT	\$207,748	Mean of McAdam-Marx et al (2011), <sup>38</sup> Gordon et al (2012), <sup>37</sup> and Baran et al (2015) <sup>36</sup>
Post LT	\$51,950	McAdam-Marx et al (2011) <sup>38</sup>
<b>Total treatment costs, US\$</b>		
Sofosbuvir-velpatasvir	\$24,000.00	RED BOOK <sup>35</sup>
Sofosbuvir-velpatasvir + ribavirin	\$24,112.00	RED BOOK <sup>35</sup>
Ledipasvir-sofosbuvir	\$27,727.10	RED BOOK <sup>35</sup>
Ledipasvir-sofosbuvir + ribavirin	\$36,112.00	RED BOOK <sup>35</sup>
<b>Utilities</b>		
NC	0.790	McLernon et al (2008), <sup>40</sup> Wright et al (2006), <sup>41</sup> Thein et al (2005), <sup>42</sup> Chong et al (2003), <sup>43</sup> and Hsu et al (2012) <sup>39</sup>
NC SVR	0.840	
CC	0.748	
CC SVR	0.798	
DCC	0.672	
DCC SVR	0.722	
HCC	0.610	
LT	0.650	
Post LT	0.709	

CC, compensated cirrhosis; DCC, decompensated cirrhosis; EM, excess mortality; HCC, hepatocellular carcinoma; LT, liver transplantation; NC, noncirrhosis; SVR, sustained virological response.

SVR was multiplied by the relative risk for the cirrhosis SVR rate relative to the overall population. If the SVR rate was 100% for the genotype or subpopulation, no adjustment was made.

**Cost Inputs**

The model accounted for direct costs such as treatment costs and health state costs (Table 2<sup>35-43</sup>). Treatment costs comprised drug costs that were sourced from the IBM Micromedex RED BOOK

**FIGURE 2.** Number of Advanced Liver Disease Events

CC, compensated cirrhosis; DAA, direct-acting antiviral; DCC, decompensated cirrhosis; EM, excess mortality; HCC, hepatocellular carcinoma; LT, liver transplantation.

database.<sup>35</sup> The DAAs used for treatment were derived from the KPSC data; 22% of patients were treated with SOF/VEL and 78% with LDV/SOF. Health state costs included inpatient, outpatient, emergency department, ambulatory, and pharmacy costs. These health state costs, including utilization costs, were sourced from the published literature.<sup>36-38</sup> All costs were adjusted to 2021 US\$, inflated using the consumer price index<sup>44</sup> where required.

### Utility Values

Health utilities were sourced from the published literature.<sup>39-43</sup> A utility value was assigned to each health state modeled that ranged between 1 (perfect health) and 0 (death), representing the quality of life for patients in that health state (Table 2). It was assumed that there were no utility differences between treatment-naïve and treatment-experienced patients. Health state utility was higher for patients who achieved SVR for NC, CC, and DCC states.

### Model Outcomes

Model outcomes included the number of advanced liver disease events over a lifetime horizon for each scenario (eg, number of CC, DCC, HCC, LT, and liver-related mortality events), total costs on both a patient level and a population level, and cost-effectiveness outcomes including total life-years (LYs) and quality-adjusted LYs (QALYs).

### Sensitivity Analyses

To account for the uncertainty around model parameters and to test the robustness of the model, both deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis were conducted. One-way

DSA was conducted by varying 1 parameter at a time. Parameters were varied by  $\pm 10\%$  of their base case values. A multivariate probabilistic sensitivity analysis randomly sampled parameters from within chosen distributions over 5000 iterations. A willingness-to-pay threshold of \$100,000 was considered cost-effective.

### Scenario Analysis

Two scenarios were examined. The first scenario used data from the intent-to-treat population. The second scenario assumed that there was no benefit to patients who achieved SVR with DCC in terms of impact on disease progression or even on regression of cirrhosis.

## RESULTS

### Lifetime Health Outcomes

Over a lifetime horizon, the use of DAAs is predicted to result in a significant reduction in advanced liver disease events and liver-related deaths compared with no treatment. The predicted reductions in advanced liver disease cases in the untreated cohort compared with the DAA cohort were as follows: 98% reduction in CC (3242 vs 63, respectively), 96% reduction in DCC (3472 vs 154), 80% reduction in HCC (805 vs 159), 86% reduction in LT (517 vs 70), and 86% reduction in HCV-related deaths (3592 vs 514) (Figure 2).

### Cost Outcomes

The DAA treatment strategy is anticipated to incur higher initial costs due to higher drug acquisition costs (eAppendix Figure 2).

**TABLE 3.** Cost-Effectiveness Outcomes

Treatment arm	Total costs	Total QALYs	Total LYs	Incremental costs	Incremental QALYs	ICER (\$/QALY)
<b>Per-patient level</b>						
DAA	\$56,479	13.20	16.03		Reference	
Untreated	\$201,072	9.67	12.82	-\$144,592	3.53	DAA dominates <sup>a</sup>
<b>Cohort level</b>						
DAA	\$409,757,417	95,746	116,332		Reference	
Untreated	\$1,458,774,194	70,150	92,980	-\$1,049,016,777	25,597	DAA dominates <sup>a</sup>

DAA, direct-acting antiviral; ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted LY.

<sup>a</sup>Dominates: less costly and more effective.

However, this strategy is anticipated to result in cost savings over a lifetime horizon due to a reduction in advanced liver disease events and corresponding costs. DAA treatment led to a total cost savings of \$1 billion (72% reduction in total costs) over a lifetime horizon compared with those who were untreated (eAppendix Table 2). Furthermore, cost savings were anticipated to be achieved quickly after treatment, with the DAA scenario being less costly than the untreated scenario after 3 years (eAppendix Figure 2).

### Cost-Effectiveness Outcomes

DAA regimens are predicted to confer more LYs and QALYs compared with no treatment—3.21 and 3.53 per patient, respectively (Table 3). These gains in LYs and QALYs conferred by DAA regimens were reflected at the cohort level (Table 3). The DAA intervention is anticipated to dominate (ie, be more effective and less costly than) no treatment on both a per-patient and a cohort basis.

### Sensitivity Analyses

Sensitivity analyses showed that the results were robust when model parameters were varied. In the DAA vs the untreated DSA, the net monetary benefit was most sensitive to the proportion of treatment-naïve patients on DAA, the proportion of patients treated with LDV/SOF, and the proportion of patients with genotype 1a on DAA (eAppendix Figure 3). The cost-effectiveness scatter plot shows that the DAA scenario is dominant; the scenario always results in an incremental gain in QALYs and an incremental reduction in costs (eAppendix Figure 4). Thus, the base case results are robust in sensitivity analyses.

### Scenario Analysis

Results from the scenario analysis using the intent-to-treat population were consistent with those from the per-protocol analysis, finding that use of all-oral DAAs was a dominant treatment strategy compared with no treatment (eAppendix Table 3). Scenario analysis assuming that there is no benefit to patients who achieve SVR with DCC in terms of impact on disease progression or even on regression of cirrhosis resulted in an incremental QALY gain of 2.91 QALYs for patients treated with DAAs vs untreated patients at a cost savings of \$145,197, suggesting that DAAs still dominate no treatment.

## DISCUSSION

This analysis quantifies the economic benefits of treating chronic hepatitis C with DAAs over a lifetime from the perspective of a large, integrated health care delivery system (KPSC). The data on demographics, SVR, and the proportions treated with LDV/SOF and SOF/VEL were derived from KPSC to develop a model that accurately represents a real-world population. We show that treating patients with HCV with DAAs over their lifetime is anticipated to result in substantial cost savings and is predicted to improve health outcomes compared with untreated patients based on a hybrid decision-tree Markov state-transition model. Despite high initial treatment costs and a greater number of patients being treated with DAAs, the use of DAAs is anticipated to result in substantial cost savings and to be a cost-effective strategy compared with no treatment due to cost offsets stemming from a reduction in advanced liver disease events. A recent study in another large health care setting, the US Department of Veterans Affairs health system, demonstrated a decrease in HCC due to HCV infection following the use of DAAs.<sup>45</sup> Further, our results regarding the total number of and reduction in advanced liver disease events for no treatment and treatment with DAAs are similar to those observed in other prior economic analyses.<sup>46</sup> This finding lends support to our study results, suggesting that the use of DAAs reduces the risk of advanced liver disease events.<sup>47</sup> In addition, another study in the Veterans Affairs system reported that patients with cirrhosis had lower short-term costs after achieving cure vs those who were not cured.<sup>48</sup>

Other analyses similar to our study have found an increase in the number of patients treated with DAAs due to higher efficacy, better safety profile, and tolerability,<sup>49</sup> which in turn led to reductions in HCV-related morbidity and mortality.<sup>46</sup> Additional analyses have also shown DAAs to result in cost savings. Following the introduction of DAA regimens, cost savings of \$15,907 per year were estimated for each Medicaid beneficiary across 16 states in the United States, and total cost savings to Medicaid were estimated at \$12 billion by 2022.<sup>50</sup> Numerous other publications demonstrate either cost-effectiveness or cost savings associated with the use of DAAs.<sup>51,52</sup> To the best of our knowledge, this is the first cost-effectiveness study of treatment with DAAs considering a large community-based integrated health care delivery system perspective that highlights the cost savings

and improvement in health outcomes achieved by DAA regimens compared with no treatment for patients with HCV in the United States. Although we did not analyze the value of DAAs at varying levels of disease severity in our analysis, we believe that we would observe greater benefits when treating patients with earlier-stage disease consistent with prior analyses.<sup>34,53</sup>

## Limitations

Limitations to this study include the fact that drug costs were calculated based on published wholesale acquisition costs,<sup>35</sup> which may not reflect the actual cost of drugs paid in the Kaiser Permanente health care system. The incorporation of net pricing would likely reduce the up-front financial impact of DAAs and the time to break even on investment. In addition, health care utilization costs were sourced from the literature, which may not reflect the actual health care costs paid in the Kaiser Permanente health care system because Kaiser Permanente is a large closed system. Further, the impact of a higher proportion of patients achieving cure was not reflected in terms of possible downstream impacts on HCV incidence and prevalence. We would also expect greater gains in HCV-related morbidity and mortality in terms of the economic impact if the curative impact of DAA therapy on disease transmission was also accounted for in the model. We also note that we did not consider a societal impact (eg, inclusive of impact of treatment on indirect costs, such as work productivity) in our analysis. We would expect that inclusion of indirect costs would improve the cost-effectiveness of DAAs further, in line with other analyses that have compared results of DAAs for HCV using direct vs both direct and indirect costs.<sup>54-56</sup> Another limitation of our analysis is the use of a Markov cohort approach. Although this is in line with numerous prior studies, it may not fully reflect the variability in natural history that may occur across patients with HCV. Lastly, the count of real-world treated patients is likely higher, as the modeled sample size was restricted by study eligibility criteria. These combined effects suggest that the true clinical and economic benefits realized by KPSC may be higher than reported here.

## CONCLUSIONS

The use of DAA-based treatments in patients with HCV in the KPSC health care delivery system is predicted to significantly reduce long-term HCV-related morbidity and mortality and anticipated to provide a quick return on investment in drug costs via cost savings after 3 years of treatment based on a hybrid decision-tree Markov state-transition model. ■

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**eAppendix Table 1.** SVR Rates by Genotype, Cirrhosis Stage, and Treatment Experience for DAA-Treated Patients

Genotype and treatment	Treatment-naïve			Treatment-experienced			Source
	NC	CC	DCC	NC	CC	DCC	
<b>Genotype 1</b>							
SOF/VEL	98.4%	96.3%	95.3%	95.3%	93.2%	92.3%	Kaiser
LDV/SOF	98.2%	96.0%	96.2%	98.5%	96.3%	96.5%	Permanente
<b>Genotype 1a</b>							
SOF/VEL	98.0%	95.9%	94.9%	94.9%	92.9%	92.0%	Kaiser
LDV/SOF	97.9%	95.7%	95.9%	98.1%	95.9%	96.2%	Permanente
<b>Genotype 1b</b>							
SOF/VEL	99.3%	97.2%	96.2%	96.2%	94.1%	93.2%	Kaiser
LDV/SOF	99.1%	96.8%	97.1%	99.4%	97.1%	97.3%	Permanente
<b>Genotype 2</b>							
SOF/VEL	100.0%	98.2%	97.2%	97.1%	95.1%	94.1%	Kaiser
LDV/SOF	100.0%	98.4%	98.7%	100.0%	98.7%	98.9%	Permanente
<b>Genotype 3</b>							
SOF/VEL	98.6%	96.5%	95.5%	95.5%	93.4%	92.5%	Kaiser
LDV/SOF	96.4%	94.2%	94.5%	96.7%	94.5%	94.7%	Permanente
<b>Genotype 4</b>							
SOF/VEL	100.0%	99.0%	98.1%	98.0%	95.9%	95.0%	Kaiser
LDV/SOF	95.8%	93.7%	93.9%	96.1%	93.9%	94.2%	Permanente
<b>Genotype 5-6</b>							
SOF/VEL	100.0%	99.0%	98.1%	98.0%	95.9%	95.0%	Kaiser
LDV/SOF	92.5%	90.4%	90.6%	92.7%	90.6%	90.8%	Permanente

**Abbreviations:** CC, compensated cirrhosis; DAA, direct-acting antivirals; DCC, decompensated cirrhosis; LDV, ledipasvir; NC, non-cirrhosis; SOF, sofosbuvir; SVR, sustained virological response; VEL, velpatasvir

**eAppendix Table 2.** Lifetime Cost Outcomes (Per Patient)

Cost components	Total Costs	
	DAA	Untreated
Drug costs	\$97,427,439	--
Health state costs	\$312,329,978	\$1,458,774,194

**Abbreviation:** DAA, direct-acting antivirals

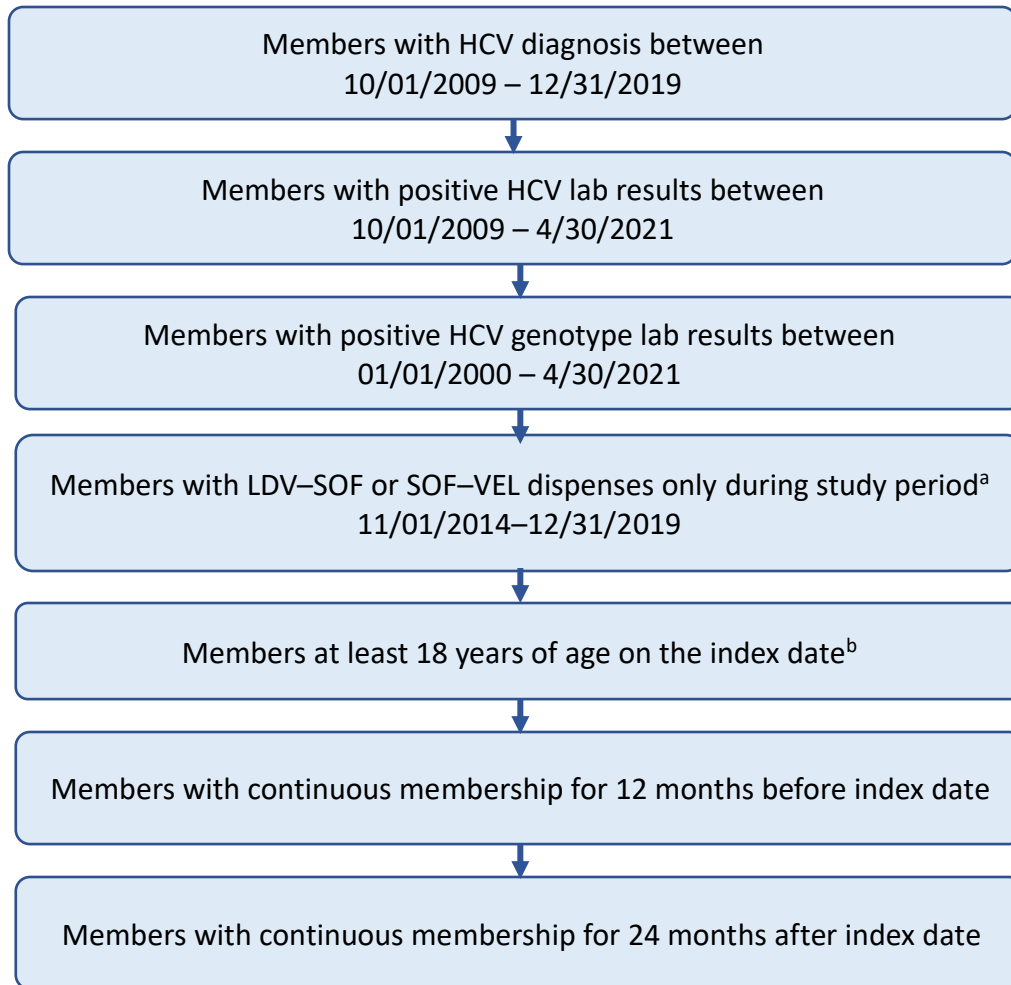
**eAppendix Table 3.** Cost-Effectiveness Outcomes in Intent-to-Treat Population

Treatment arm	Total costs	Total QALYs	Total LYs	Incremental costs	Incremental QALYs	ICER (\$/QALY)
<b>Per Patient Level</b>						
DAA	\$67,124	12.94	15.80	<i>Reference</i>		
Untreated	\$201,072	9.67	12.82	\$(133,948)	3.27	DAA Dominates <sup>a</sup>
<b>Cohort Level</b>						
DAA	\$486,983,071	93,884	114,624	<i>Reference</i>		
Untreated	\$1,458,774,194	70,150	92,980	\$(971,791,123)	23,734	DAA Dominates <sup>a</sup>

**Abbreviations:** DAA, direct-acting antivirals; QALYs, quality-adjusted-life-years; LYs, life years; ICER, incremental cost-effectiveness ratio

<sup>a</sup> Dominates, less costly and more effective

**eAppendix Figure 1.** Selection Criteria for Model Population

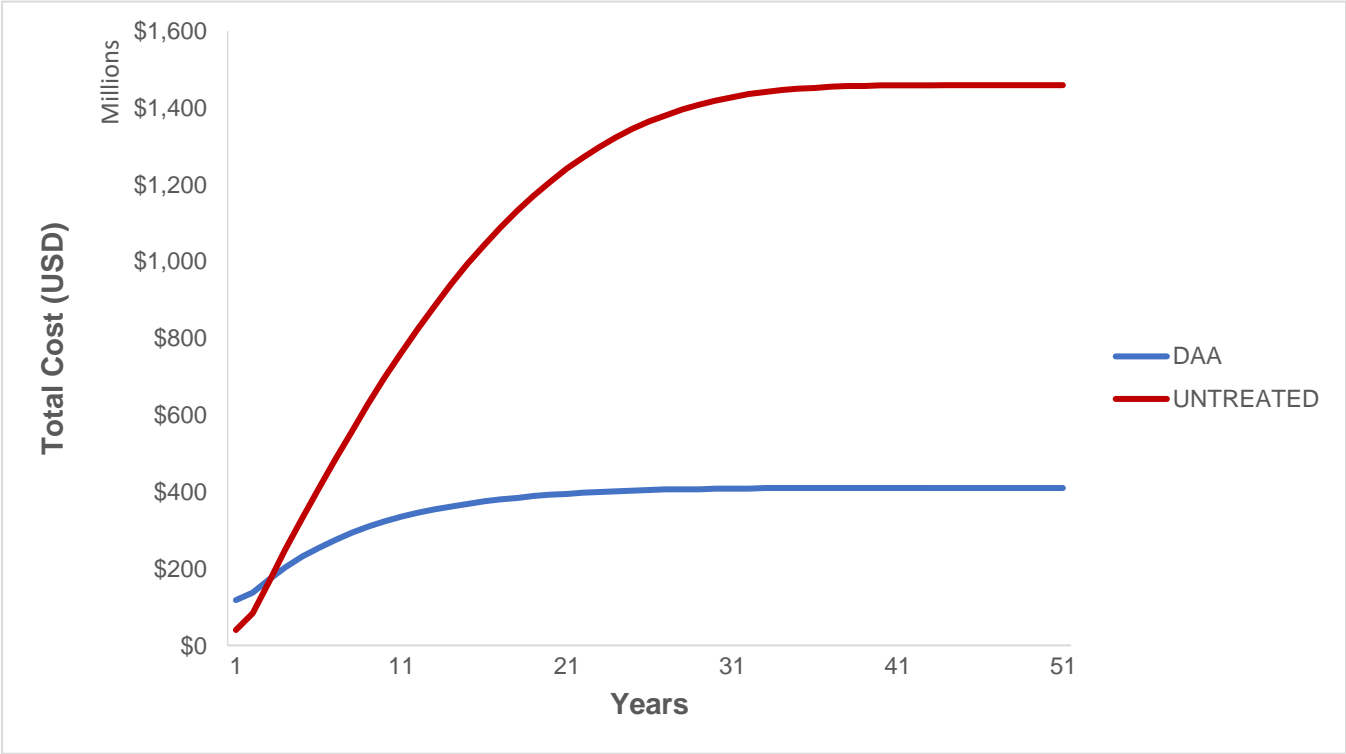


<sup>a</sup>Treatment naïve defined as those with either LDV–SOF or SOF–VEL as the first-ever HCV prescription dispensed. Treatment experienced is defined as those with either LDV–SOF or SOF–VEL not the first-ever HCV prescription dispensed. For members with both LDV–SOF and SOF–VEL dispensed, only the latter drug will be included.

<sup>b</sup>Index date was defined as the earliest date of HCV diagnosis or positive HCV RNA

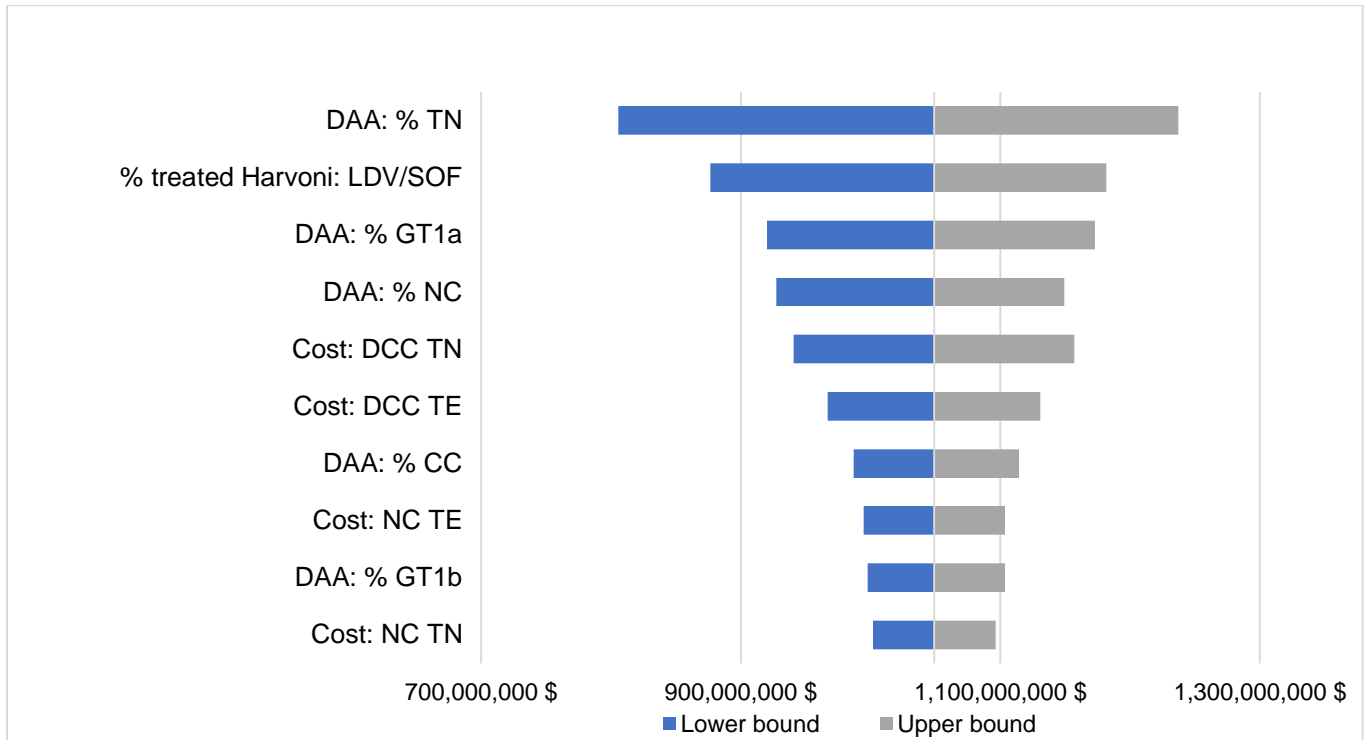
**Abbreviations:** HCV, hepatitis C virus; lab, laboratory; LDV, ledipasvir; RNA, ribonucleic acid; SOF, sofosbuvir; VEL, velpatasvir

**eAppendix Figure 2.** Lifetime Cost Outcomes by Scenario



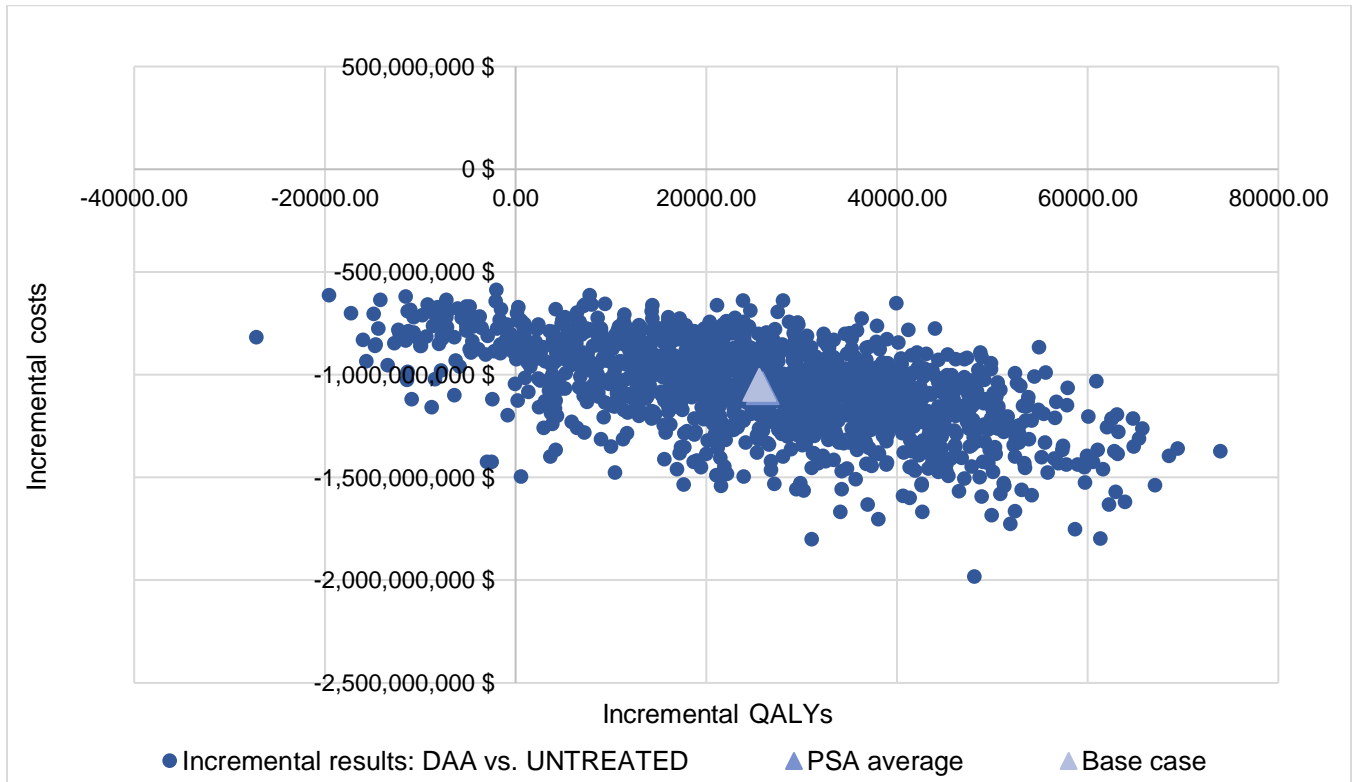
**Abbreviations:** DAA, direct-acting antiviral; USD, United States Dollar

**eAppendix Figure 3. One-Way Deterministic Sensitivity Analysis**



**Abbreviations:** CC, compensated cirrhosis; DAA, direct-acting antiviral; DCC, decompensated cirrhosis; GT, genotype; LDV/SOF, ledipasvir and sofosbuvir, NC, non-cirrhosis; TE, treatment-experienced; TN, treatment-naïve

**eAppendix Figure 4.** Probabilistic Sensitivity Analysis Scatterplot: Incremental Outcomes



**Abbreviations:** DAA, direct-acting antiviral; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life years