

Appendix 1 (as supplied by the authors): Detailed Methodology

We used the previously developed state-transition model and followed the same approach¹ to examine the health and economic effects of two general screening strategies: 1) “No screening”; and 2) “Screen-and-treat with direct-acting antiviral agents (DAA).

Cohort

We examined four different cohorts that are under consideration by CTFPHC: 1) Asymptomatic individuals not at high risk for HCV; 2) Immigrant populations with high prevalence; 3) Birth cohort aged 25 to 64 years of age; and 4) Birth cohort aged 45-64 years of age. Detailed cohort definitions are provided in Table 1.

Strategies

In our baseline analysis, for each cohort, we consider the following screening strategies.

1. “*No Screening, treat with DAA*” if diagnosed: Depending on different scenarios, we assume that certain proportions of HCV-infected patients are initially unaware of their infection and do not receive antiviral treatment. Each year, we assume that 0.68% of the unaware infected individuals will discover that they are infected with CHC², and may undergo treatment. If HCV infection remains undetected, we assume that liver disease is detected when they develop cirrhosis with liver failure and/or hepatocellular carcinoma (HCC).
2. “*Screen and Treat with DAA*”: Individuals are offered one-time screening for HCV infection through their primary care physician at a visit scheduled for another purpose. This represents a “case finding” strategy. Screening involves a blood test for HCV antibody. All positive antibody tests will be followed by an HCV RNA test to confirm infection. Our analysis assumes that all individuals who are tested positive for both tests

will be referred to a hepatologist /gastroenterologist/ infectious disease specialist and may be offered treatment with DAA according to the Canadian guidelines³.

Treatment Considered

We assumed that patients with genotype 1 infection would be treated either with 12 weeks of Hologic Pak (dasabuvir + ombitasvir/paritaprevir/ritonavir) or Harvoni (ledipasvir + sofosbuvir); genotype 2 patients would be treated with 12 weeks of sofosbuvir plus ribavirin; genotype 3 patients would be treated with 24 weeks of sofosbuvir plus ribavirin; while all the other genotypes would receive PR. Additionally, in an exploratory analysis, we assumed patients with genotype 4/5/6 infections would receive 12 weeks of Epclusa (sofosbuvir+velpatasvir). We also assumed that treatment reimbursement restrictions⁴ were imposed for F0 and F1 patients in our base case analysis, where diagnosed F0 and F1 patients were not treated by the interferon-free DAA immediately, but were followed-up and offered treatment when they progressed to F2 or above⁴.

Decision Model

In our analysis, we developed a cohort-based, state transition model using TreeAge Pro 2016 software⁵. In our simulations, cohort members move between predefined health states in weekly cycles until all members die. Health states related to treatment, fibrosis stages (F0 to F4), presence or absence of a clinical diagnosis, and clinical states (e.g., Cirrhosis, HCC). Detailed health states and allowed transitions among health states are shown in Figure 1.

When simulation was initiated, a cohort member might be in any of the following health states: undiagnosed CHC (further subdivided into health states according to different levels of fibrosis); diagnosed CHC (also subdivided into health states according to different levels of fibrosis) or no evidence of previous exposure to HCV.

The diagnosed CHC cohort members may receive one of the treatment regimens depending on genotype and the uptake of treatment, which takes into account loss to follow-up prior to treatment initiation, Table 2. After treatment, treated cohort members were classified into SVR group or non-SVR group depending on the probability of achieving SVR based on the efficacy of the treatment regimens, Table 2. The model assumed that non-cirrhotic (F0, F1, F2, and F3) patients who achieved SVR would not further progress into advanced liver disease, while patients with cirrhosis (F4) who achieved SVR will progress into advanced liver disease in a lowered rate. For those patients who are undiagnosed or did not achieve SVR, the model assumed that they will progress over time to different clinical states of CHC infection and/or cirrhosis based on the natural history progression.

Model Parameters

We parameterized the existing model with values suggested by CTFPHC and validated by clinical experts. Specifically, the important parameters included: 1) Prevalence^{6,7}; 2) Uptake of screening; 3) Distribution of the disease stages at diagnosis (fibrosis stages); and 4) Uptake of treatment, which takes into account loss to follow-up prior to treatment initiation. Table 2 represents the key parameter values for each scenario.

Fibrosis progression parameters were obtained from a systematic review conducted by Thein et al. in 2008⁸. Transition probabilities to advanced liver disease were obtained from a published study that provided separate estimates for both SVR and non-SVR among CHC infected patients⁹. Transition probabilities to liver transplant were also obtained from a published study¹⁰. The baseline probability of achieving SVR were updated based on the findings of the current CADTH therapeutic review^{11,12} (Table 2). The annual mortality risks associated with

advanced liver diseases were obtained from a US study based on cancer registries¹³, as well as a systematic review¹⁴. All-cause mortality was obtained from Statistics Canada¹⁵ (Appendix 1).

The CHC infection-related costs were collected from a large Canadian costing study using administrative data. The model assumed that when an individual achieved SVR, annual costs for non-CHC individuals would be applied. The liver transplant-related costs were collected from a Canadian costing study based on patient medical records obtained from hospitals¹⁶. The costs of antiviral therapies (Table 3) were collected from CADTH therapeutic review^{11,12}.

Utility information for health states were obtained from the most recent and valid Canadian utility study available using Health Utilities Index Mark 2 (HUI2)¹⁷. The study included 700 patients across different CHC infection health states.

Economic Assumptions

All the analyses were carried out from the payer perspective were structured as a cost-utility analysis, with primary outcomes expressed in expected quality-adjusted-life-years (QALYs) and costs. Health events such as the number of cases of decompensated cirrhosis, number of cases of hepatocellular carcinoma (HCC), number of HCV-related liver deaths and the number of HCV-deaths prevented were reported. Future costs and health benefits were discounted at 5% annually. All cost data were inflated to 2015 using the Statistics Canada Consumer Price Index for healthcare and personal items. Supplementary Table 2 summarizes all the assumptions.

Model Validation

For validation purposes, we ran our model using the baseline parameter values. We compared the predicted outcomes of our model against published studies^{10,18,19}. These outcomes

included: probability of progression to cirrhosis and probability of liver-death at 20 years and/or at 30 years. Our model results closely matched the results of the published studies^{10,18,19}.

Analytic Strategy

In our analysis, we first conducted a base-case analysis to estimate the expected value using deterministic calculations. We then ran deterministic one-way sensitivity analysis on all model parameters over the plausible ranges using the reported 95% confidence interval (CI) ranges if available or using $\pm 25\%$ of the reference value as indicated in tables. Finally, we ran probabilistic sensitivity analyses (PSA) using the Monte Carlo simulation for 1,000 iterations for each sub-group analysis. All probabilistic parameters and utilities used in the model are represented by beta distributions formed by the corresponding ranges as indicated in tables; all the cost parameters are represented by gamma distributions formed by the corresponding ranges as indicated in tables.

Supplementary Table 1: All Parameters used in the model

<u>Costs</u>	<u>Baseline</u>	<u>Low</u>	<u>High</u>	<u>Source</u>
Cost				
Cost of transplant	\$120,593	\$90,445	\$150,741	²⁰
Cost of post-transplant	\$19,400	\$14,550	\$24,250	²⁰
Cost of adverse events				
Anemia (Cost per week)	\$107	\$80	\$134	²¹
Depression (Cost per week)	\$73	\$55	\$91	²¹
Rash (Cost per week)	\$12	\$9	\$15	²¹
Cost of Anti-HCV test	\$14.48	\$10.86	\$18.1	²²
Cost of HCV RNA test	\$100	\$75	\$125	²²

<u>Utilities</u>	<u>Baseline</u>	<u>Low</u>	<u>High</u>	<u>Source</u>
Utilities				
Canadian population average				
Age 25 – 34	0.90	0.89	0.92	^{23,24}
Age 35 – 44	0.88	0.86	0.91	^{23,24}
Age 45 – 54	0.86	0.83	0.88	^{23,24}
Age 55 – 64	0.83	0.80	0.87	^{23,24}
Utility for CHC related health states				

Non-cirrhosis (F0 – F3)	0.73	0.69	0.77	¹⁷
Compensated cirrhosis (F4)	0.69	0.65	0.73	¹⁷
HCC	0.72	0.68	0.75	¹⁷
Decompensated cirrhosis	0.65	0.65	0.73	^{17,25}
Post-transplant	0.75	0.70	0.79	¹⁷
Viral clearance	0.80	0.76	0.84	¹⁷
On-treatment	0.71	0.67	0.75	¹⁷

Other Variables	Baseline	Low	High	Source
Population				
Proportion known infected CHC	0.305	0.157	0.507	⁶
Proportion of spontaneous clearance	0.28	0.16	0.30	²⁶
Annual diagnosis rate (no screening)	0.0068	0.0034	0.0085	²
Genotype distribution				
G1	0.67	0.50	0.84	²⁷
G2	0.09	0.07	0.11	²⁷
G3	0.22	0.17	0.28	²⁷
G4	0.01	0.00	0.02	²⁷
G5/6	0.01	0.00	0.02	²⁷
Natural history of CHC				
Annual probability for fibrosis progression				
F0 → F1	0.117	0.104	0.13	⁸
F1 → F2	0.085	0.075	0.096	⁸
F2 → F3	0.12	0.109	0.133	⁸
F3 → F4	0.116	0.104	0.129	⁸
Annual probability for cirrhosis progression				
F4 → decompensated (Non-SVR)	0.035	0.027	0.043	⁹
F4 → decompensated (SVR)	0.002	0.0001	0.005	⁹
F4 → HCC (Non-SVR)	0.024	0.018	0.031	⁹
F4 → HCC (SVR)	0.005	0.001	0.030	^{9,28}
Annual CHC related mortality				
HCC	0.411	0.31*	0.51*	¹³
Decompensated Cirrhosis	0.216	0.162*	0.27*	¹⁴
Liver transplant (1 st year)	0.142	0.124	0.159	²⁹
Liver transplant (> 1 year)	0.034	0.024	0.043	²⁹
Annual probability for liver transplantation				
From Decompensated Cirrhosis	0.033	0.017	0.049	¹⁰
From HCC	0.033	0.017	0.049	¹⁰
Discount Rate	5%	3%	5%	³⁰

Costs	Baseline	Low*	High*	Source
Cost⁺				
Annual cost CHC early phase				
Age 15 – 24	\$4,179	\$4,016	\$4,350	¹⁶
Age 25 – 34	\$4,069	\$3,988	\$4,151	¹⁶
Age 35 – 44	\$3,888	\$3,812	\$3,967	¹⁶

Age 45 – 54	\$4,589	\$4,498	\$4,682	¹⁶
Age 55 – 64	\$5,541	\$5,377	\$5,710	¹⁶
Age 65 – 74	\$7,325	\$7,038	\$7,624	¹⁶
Age 75+	\$7,736	\$6,930	\$8,635	¹⁶
Annual cost CHC late phase				
Age 15 – 24	\$5,103	\$4,054	\$6,422	¹⁶
Age 25 – 34	\$10,344	\$8,640	\$12,384	¹⁶
Age 35 – 44	\$12,054	\$11,582	\$12,546	¹⁶
Age 45 – 54	\$14,597	\$13,475	\$15,813	¹⁶
Age 55 – 64	\$12,337	\$11,619	\$13,100	¹⁶
Age 65 – 74	\$11,558	\$10,670	\$12,520	¹⁶
Age 75+	\$9,885	\$8,855	\$11,034	¹⁶
Annual cost CHC pre-death phase				
Age 15 – 24	\$23,970	\$19,822	\$28,985	¹⁶
Age 25 – 34	\$42,955	\$36,603	\$50,408	¹⁶
Age 35 – 44	\$35,544	\$32,811	\$38,504	¹⁶
Age 45 – 54	\$41,823	\$39,388	\$44,410	¹⁶
Age 55 – 64	\$52,102	\$49,561	\$54,773	¹⁶
Age 65 – 74	\$44,649	\$43,765	\$45,551	¹⁶
Age 75+	\$40,424	\$38,453	\$42,497	¹⁶
Annual cost non-CHC before pre-death phase				
Age 15 – 24	\$1,665	\$1,616	\$1,716	¹⁶
Age 25 – 34	\$1,633	\$1,600	\$1,665	¹⁶
Age 35 – 44	\$1,813	\$1,777	\$1,850	¹⁶
Age 45 – 54	\$2,362	\$2,338	\$2,387	¹⁶
Age 55 – 64	\$3,925	\$3,809	\$4,044	¹⁶
Age 65 – 74	\$6,083	\$5,962	\$6,205	¹⁶
Age 75+	\$7,440	\$7,148	\$7,743	¹⁶
Annual cost non-CHC pre-death phase				
Age 15 – 24	\$60,850	\$49,324	\$75,069	¹⁶
Age 25 – 34	\$39,226	\$34,791	\$44,228	¹⁶
Age 35 – 44	\$42,291	\$40,229	\$44,459	¹⁶
Age 45 – 54	\$45,207	\$44,312	\$46,120	¹⁶
Age 55 – 64	\$44,542	\$43,660	\$45,442	¹⁶
Age 65 – 74	\$44,854	\$43,966	\$45,761	¹⁶
Age 75+	\$36,548	\$35,825	\$37,287	¹⁶

Supplementary Table 2 – Summary of Assumptions

<ul style="list-style-type: none">• Treatment restriction were assumed for patients with F0 and F1 CHC patients.
<ul style="list-style-type: none">• HCC and decompensated cirrhosis were assumed to occur only at F4.
<ul style="list-style-type: none">• One-time treatment was assumed for all patients.
<ul style="list-style-type: none">• Model assumed no other pre-existing conditions; e.g., HIV.
<ul style="list-style-type: none">• Model assumed no spontaneous remission.
<ul style="list-style-type: none">• Patients who discontinued treatment were assumed not to have achieved SVR.
<ul style="list-style-type: none">• For non-cirrhotic (F0, F1, F2, and F3) patients who achieved SVR, the model assumed that they would not further progress into advanced liver disease, while those with cirrhosis (F4) who achieved SVR would progress into advanced liver disease at a lower rate.
<ul style="list-style-type: none">• For patients who are undiagnosed or who did not achieved SVR, the model assumed that they will progress over time to different clinical states of CHC and/or cirrhosis based on the natural history of CHC.
<ul style="list-style-type: none">• Model did not consider negotiated drug prices.
<ul style="list-style-type: none">• Analyses were carried out from the payer perspective.
<ul style="list-style-type: none">• Future costs and health benefits were discounted at 5% annually.

Supplementary Table 3 – Undiscounted Life Years Results

Undiscounted Life Years Results for Scenario 1

<u>Age range</u>	<u>Strategy</u>	<u>LY*</u>	<u>Δ LY*</u>
15-79	No screening, treat with Interferon-free DAA if diagnosed	41.8691	
	Screen & treat with Interferon-free DAA*	41.8778	0.0087

Undiscounted Life Years Results for Scenario 2

<u>Age range</u>	<u>Strategy</u>	<u>LY*</u>	<u>Δ LY*</u>
15-79	No screening, treat with Interferon-free DAA if diagnosed	39.5067	
	Screen & treat with Interferon-free DAA*	39.5859	0.0791-0.0792

Undiscounted Life Years Results for Scenario 3

<u>Age range</u>	<u>Strategy</u>	<u>LY*</u>	<u>Δ LY*</u>
25-64	No screening, treat with Interferon-free DAA if diagnosed	40.2555	
	Screen & treat with Interferon-free DAA*	40.2808-40.2809	0.02534-0.02539

Undiscounted Life Years Results for Scenario 4

<u>Age range</u>	<u>Strategy</u>	<u>LY*</u>	<u>Δ LY*</u>
45-64	No screening, treat with Interferon-free DAA if diagnosed	31.9540	
	Screen & treat with Interferon-free DAA*	31.9796-31.9797	0.02561-0.02566

*Range indicate the different between which DAA was used for treating genotype 1 patients
Abbreviations: LY: life-years; DAA; Direct acting agents

Supplementary Table 4 - Net Life Year and QALY Life Year Gained for Screening Scenarios 1 to 4

	Maximum Estimated Affected population screening size ⁺³¹	Per person LY gained (undiscounted)*	Per person QALY gained (5% discounted)*	Net LY gained (undiscounted)*	Net QALY gained (5% discounted)*
Scenario 1	27,370,909	0.008740551	0.002011377	239,237	55,053
Scenario 2	5,801,856	0.079163108	0.019654945	459,293	114,035
Scenario 3	19,171,503	0.025339886	0.007979182	485,804	152,973
Scenario 4	9,814,702	0.025614459	0.008779324	251,398	86,166
+Maximum estimated affected population screening size according to the data source. *compare between “Screen & treat with Interferon-free DAA” with “No screening, treat with Interferon-free DAA”					

Supplementary Table 5 – Exploratory Analysis (Epclusa (sofosbuvir+velpatasvir)) Details and Results

Treatment Efficacy (Sustained Virologic Response)				
Description	Base Estimate	Lower Limit (95% CrI)	Upper Limit (95% CrI)	Source
Genotype 4-6				
SOF12 + VEL12	0.98	0.85	1	32,33

Adverse Events				
Description	Base Estimate	Lower Limit (95% CrI)	Upper Limit (95% CrI)	Source
Treatment-Naive				
Depression				
SOF12 + VEL12	0.0026	0.0003	0.0137	Assumed same as SOF12 + LDV12
Anemia				
SOF12 + VEL12	0.0119	0.0047	0.0282	Assumed same as SOF12 + LDV12
Rash				
SOF12 + VEL12	0.0480	0.0259	0.0878	Assumed same as SOF12 + LDV12

Treatment Discontinuation Rate				
Description	Base Estimate	Lower Limit (95% CI)	Upper Limit (95% CI)	Source
SOF12 + VEL12	0.005	0.002	0.007	32,33

Drug Cost				
Description	Base Estimate	Lower Limit (95% CI)	Upper Limit (95% CI)	Source
SOF12 + VEL12	\$60,000	\$45,000	\$75,000	32,33

Exploratory Analysis - Cost-Effectiveness Results

Scenario 1

<u>Age range</u>	<u>Strategy</u>	<u>Cost</u>	<u>QALYs</u>	<u>ΔCost</u>	<u>ΔQALYs</u>	<u>ICER</u>
15-79	No screening, treat with Interferon-free DAA if diagnosed	\$69,770	14.0644			
	Screen & treat with Interferon-free DAA*	\$69,872- \$69,878	14.0664	\$102 - \$108	0.0020	\$50,752- \$53,313

Scenario 2

<u>Age range</u>	<u>Strategy</u>	<u>Cost</u>	<u>QALYs</u>	<u>ΔCost</u>	<u>ΔQALYs</u>	<u>ICER</u>
15-79	No screening, treat with Interferon-free DAA if diagnosed	\$72,775	13.7297			
	Screen & treat with Interferon-free DAA*	\$73,393- \$73,455	13.7479- 13.7480	\$618- \$680	0.0183	\$33,841- \$37,192

Scenario 3

<u>Age range</u>	<u>Strategy</u>	<u>Cost</u>	<u>QALYs</u>	<u>ΔCost</u>	<u>ΔQALYs</u>	<u>ICER</u>
25-64	No screening, treat with Interferon-free DAA if diagnosed	\$72,507	14.2536			
	Screen & treat with Interferon-free DAA*	\$72,770 \$72,792	14.2616	\$263- \$286	0.0080	\$32,968- \$35,787

Scenario 4

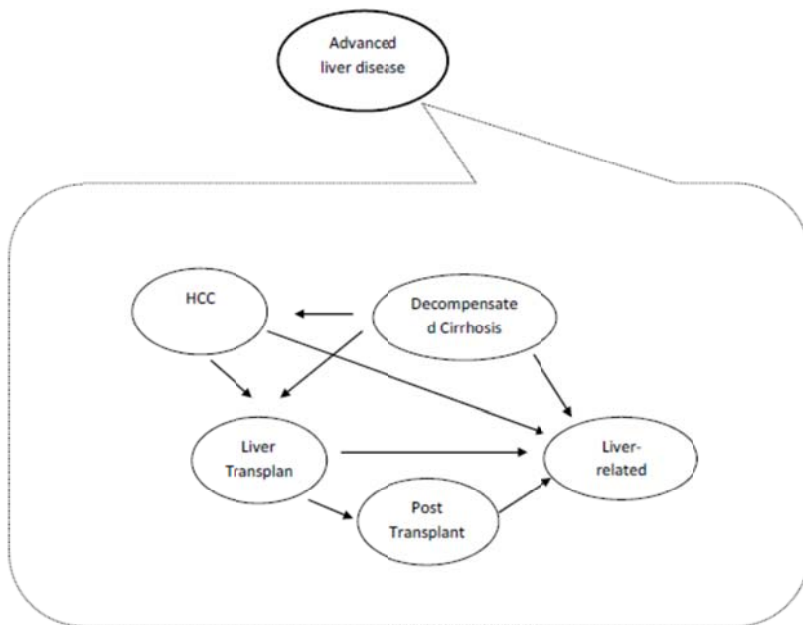
<u>Age range</u>	<u>Strategy</u>	<u>Cost</u>	<u>QALYs</u>	<u>ΔCost</u>	<u>ΔQALYs</u>	<u>ICER</u>
45-64	No screening, treat with Interferon-free DAA if diagnosed	\$84,611	12.7980			
	Screen & treat with Interferon-free DAA*	\$84,918- \$84,942	12.8068	\$306- \$331	0.0088	\$34,678- \$37,442

*Range indicate the different between which DAA was used for treating genotype 1 patients
 Abbreviations: QALYs: Quality-adjusted-life-years; ICER: incremental cost-effectiveness ratio;
 DAA; Direct acting agents

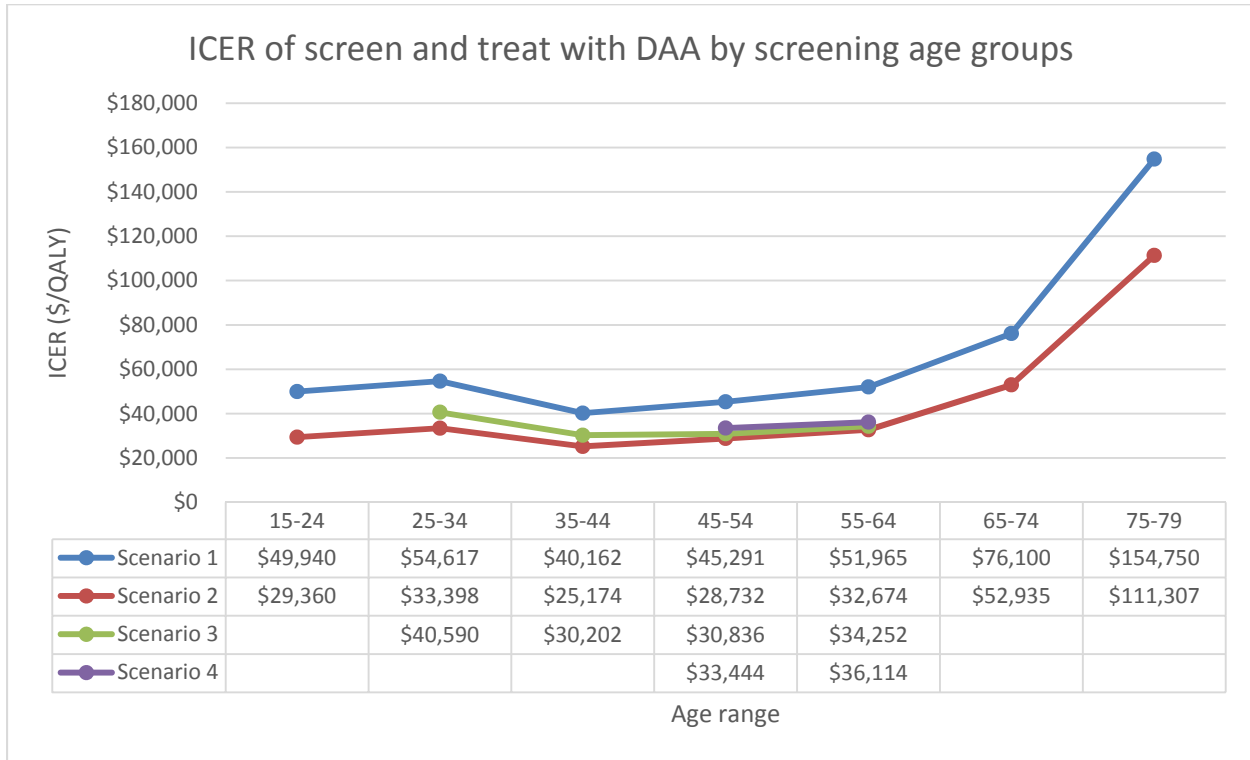
Supplementary Table 6 – Exploratory Analysis (new discount rate and no treatment restriction) Results

	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Per person cost increased	\$120-\$128	\$763-\$847	\$317-\$346	\$359-\$388
Per person QALY gained	0.0052	0.0482	0.0178	0.0173
ICER (compare with no screening)	\$23,123-\$24,736	\$15,821-\$17,579	\$17,780-\$19,418	\$20,754-\$22,424
PSA Results % of cost-effectiveness (WTP:\$50,000)	63.3%	71.7%	74.2%	72.2%

Supplementary Figure 1: Detailed Markov model of Chronic HCV infection and progression



Supplementary Figure 2: Sensitivity Analyses Results – Cost-Effectiveness results by screening age groups and tornado Diagrams



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