Title: Model-based Projection of Health and Economic Effects of Screening for Hepatitis C Canada: Informing National Screening Recommendations

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All authors contributed in the revision of the manuscript and gave final approval for the version to be published

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ABSTRACT

Background: Recent development of direct-acting antiviral agents (DAAs) has transformed hepatitis C virus (HCV) treatment. While cost-effective, the high cost of DAAs seriously restrict treatment access. Since the majority of infections are asymptomatic and often unrecognized, screening for hepatitis C has been proposed as a plausible strategy. In order to assist the Canadian Task Force on Preventive Health Care in making screening recommendations, the objective of this study is to examine the health and economic consequences of a selective one-time hepatitis C screening program.

Methods: We used a state-transition model to evaluate two strategies: (1) "No screening"; and (2) "Screen-and-treat". We considered four populations/scenarios: 1) Asymptomatic individuals not at high-risk for HCV; 2) Immigrant populations with high prevalence; 3) 25-64 years of age birth-cohort; and 4) 45-64 years of age birth-cohort. Data were obtained from the published literature and expert opinions. We used a payer perspective, a lifetime time horizon and a 5% discount rate.

Results: The "Screen and Treat" is more costly but also more effective under all scenarios. For every 100,000 people screened, screening prevented 41, 420, 153 and 169 HCV-related deaths over the lifetime for scenarios 1-4, respectively. For cost-effectiveness, screening produced incremental-cost-effectiveness-ratios (ICER) between $31,468/QALY-$50,490/QALY under all the scenarios.

Interpretation: Our analyses suggest that a one-time hepatitis C screening and treatment program in Canada is likely to be cost-effective for scenario 2-4. The screening programs will identify the asymptomatic yet chronically infected individuals and offer medical treatment if needed before advanced liver disease is present.

INTRODUCTION

The growing burden of chronic hepatitis C (CHC) infection poses a significant public health concern. A recent study from Ontario ranked hepatitis C first among all infectious diseases in health-related burden of illness (1). Since the majority of CHC infections are asymptomatic, many infections remain undiagnosed until later stages of disease. Canadian estimates suggest that between 45% and 70% of chronically infected individuals remain undiagnosed (2, 3). Early diagnosis and treatment may reduce complications associated with late stage disease (4). Therefore, targeted HCV screening would seem to be a plausible strategy (5).

In 2014, the Public Health Agency of Canada (PHAC) commissioned the development of a state transition model to examine the cost-effectiveness of various screening strategies (5). The analyses suggested that a selective one-time hepatitis C screening program for 25–64 year-old, and 45–64 year-old individuals in Canada would likely be cost-effective (5).

Since 2014, the availability of interferon-free direct-acting antivirals (DAA) has transformed HCV treatment, offering high cure rates (defined by sustained virologic response (SVR) typically at 12 or 24 weeks) with markedly improved tolerability. While shown to be cost-effective in selected populations (6), the high cost of DAAs together with the high but decreasing prevalence of CHC and low incidence creates a unique situation where price inflexibility and budget constraints may necessitate limits on access to treatment (7). Most Canadian reimbursement programs restrict eligibility to patients with moderate to advanced liver fibrosis (7). This would be further complicated, if HCV is diagnosed earlier and more comprehensively through population screening. Thus, the benefit of the hepatitis C screening program becomes uncertain. To improve the efficiency of screening, some countries have adopted targeted

screening in populations with higher prevalence, such as immigrants from HCV-endemic regions or birth-cohorts with higher prevalence, such as those born from 1945-1965 (Baby Boomers).

In anticipation of the need for supporting evidence on the health and economic consequences of hepatitis C screening, and to assist the Canadian Task Force on Preventive Health Care (CTFPHC) in making up-to-date recommendations, we updated the state transition model with new parameters and ran new scenario analyses to re-examine the health and economic consequences of a selective one-time hepatitis C screening program for specific populations.

METHODS

We used the previously developed state-transition model and followed the same approach (5) 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 CHC (8), 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 guidelines (9).

Treatment Considered

We assumed that patients with genotype 1 infection would be treated either with 12 weeks of Holkira 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 restrictions (7) 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 above (7).

Decision Model

In our analysis, we developed a cohort-based, state transition model using TreeAge Pro 2016 software (10). In our simulations, cohort members move between predefined health states in weekly cycles until all members die. Health states and allowed transitions among health states are shown in Figure 1.

Model Parameters

We parameterized the existing model with values suggested by CTFPHC and validated by clinical experts. Specifically, the important parameters included: 1) Prevalence (2, 3); 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. All efficacy and adverse effect data were updated based on the findings of the current CADTH therapeutic review (11, 12) (Table 2). All other parameters were collected from the literature (13) (Appendix 1).

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.

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 (14-16). 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 (14-16).

RESULTS

Base Case

Scenario 1 – Screening asymptomatic individuals not at high risk for HCV

In our baseline estimate for 15-79 year-old individuals (Table 3), the "Screen and Treat" strategy is more costly but also more effective than "No screening". For every 100,000 people screened, around 199 HCV cases will be identified. Identifying these HCV cases by screening will prevent 40 HCV-related deaths if we used DAAs for treatment over the lifetime of the cohort. Thus, 2,500 individuals would need to be screened to prevent one HCV-related death if DAAs were used for treatment. Figure 2 summarizes the trends of the liver-related health events per 100,000 screened accumulated overtime. In terms of cost-effectiveness, if we use an IFN-Free DAA for treatment (e.g. Holkira Pak), the "Screen and Treat" strategy would result in a net cost increment of approximately $102 and 0.0020 QALYs gained per person (or 0.0087 undiscounted life years (Appendix 2)), translating to an ICER of $50,490/QALY gained compared with "No screening". Table 2 summarizes the cost-effectiveness results.

Scenario 2 – Screening high prevalence immigrant populations

For every 100,000 people screened, around 1,661 HCV cases will be identified. Identifying these HCV cases by screening will prevent at least 414 HCV-related deaths if we used DAAs for

treatment over the lifetime of the cohort. Thus, 242 individuals would need to be screened to prevent one HCV-related death if DAAs were used for treatment. For cost-effectiveness, the "Screen and Treat" strategy would result in a net cost increment of approximately $619 and 0.0197 QALYs gained per person (or 0.0792 undiscounted life year (Appendix 2)), translating in an ICER of $31,468/QALY gained compared with "No screening".

Scenario 3 and 4 – Screening specific birth cohorts

If the screening program targeted a 25-64 years old cohort, for every 100,000 people screened, around 582 HCV cases will be identified. Identifying these HCV cases by screening will prevent at least 148 HCV-related deaths if we used DAAs for treatment over the lifetime of the cohort. Thus, 676 individuals would need to be screened to prevent one HCV-related death if DAAs were used for treatment. Alternatively, if the screening program targets 45-64 years old cohort, in which the prevalence of HCV is increased, for every 100,000 people screened, around 769 HCV cases will be identified. Identifying these HCV cases by screening will prevent at least 163 HCV-related deaths if we used DAAs for treatment over the lifetime of the cohort. Thus, 613 individuals would need to be screened to prevent one HCV-related death if DAAs were used for treatment. For cost-effectiveness, the "Screen and Treat" strategy would result in a net cost increment of approximately $261 and 0.0080 QALYs gained per person for 25-64 years old cohort (or $304 and 0.0088 QALYs for 45-64 years old cohort), translating to an ICER of $32,712/QALY gained compared with "No screening" for 25-64 years old cohort (or $34,614/QALY for 45-64 years old cohort).

Appendix 3 summarize the total estimated net health gain for each scenario. Among all scenarios, Scenarios 2 and 3 will produce the largest net health gain.

Sensitivity Analyses

We performed both one-way deterministic sensitivity analyses and probabilistic sensitivity analyses (PSA) to explore the impact of the model's parameter uncertainty.

Deterministic Sensitivity Analyses:

Tornado diagrams in Appendix Figure 2 summarize the results of the deterministic sensitivity analyses for all scenarios.

Consistent with our previously published model, in general, varying CHC utilities had the largest effect on the main results. When we varied CHC utilities, the ICER for scenario 1 ranged from $51,816/QALY to $73,430/QALY ($31,886/QALY to $71,185/QALY for scenario 2; $31,710/QALY to $44,812/QALY for scenario 3; and $32,671/QALY to $46,294/QALY for scenario 4).

When we varied screening-related parameters such as prevalence, screening acceptance rate, known HCV infection rate and the cost of screening, the ICER for scenario 1 ranged from $48,233/QALY to $76,061/QALY. With the exception of scenario 1, for which we assumed that the general population has a very low prevalence, the sensitivity analysis results for all other scenarios indicated that our main conclusion will not change as long as the prevalence remains greater than 0.2%.

We also conducted additional sensitivity analyses regarding: 1) SVR progression/re-infection assumption, where we assumed 8.6% (17) will continue to progress even after achieving SVR; and 2) the assumption of relaxing the restriction on treatment for F0/F1 patients. Sensitivity analyses for both of these assumptions indicated that the main conclusions will not change significantly if these new assumptions were applied.

Probabilistic Sensitivity Analyses:

Our probabilistic sensitivity analyses for scenario 1 to 4 indicated that the chance that screen and treat would be cost-effective at $50,000 cost effectiveness threshold were 39.5%, 63.2%, 58.4% and 58.1% respectively. At a $100,000 cost effectiveness threshold, the chances of being cost-effective were 62.2%, 74.1%, 72.4% and 70.6% for scenario 1 to 4 respectively.

Exploratory Analysis

Note that Epclusa (sofosbuvir+velpatasvir) is not yet approved for reimbursement in most Canadian programs. However, when we assumed treatment with 12 weeks of Epclusa (sofosbuvir+velpatasvir) for genotype 4/5/6 patients, the main results did not change significantly for any of the scenarios considered and the main conclusions remained unaffected. Refer to Appendix 4 for the detail of the exploratory analysis.

INTERPRETATION

Main Findings

Our analyses suggest that, compared to the current situation in Canada (i.e. "No screening, treat with IFN-Free if diagnosed with treatment restriction for F2 and above"), a one-time hepatitis C screening and treatment program for scenarios 2 to 4 is likely to save lives and be cost-effective at $31,468/QALY to $34,614/QALY gained over the lifetime of the cohort. The screening strategies that are most likely to be cost-effective are those focusing on: immigrant populations with high prevalence (Scenario 2); a birth cohort aged 25 to 64 years (Scenario 3); and a birth cohort aged 45-64 years (Scenario 4). On the other hand, screening and treatment programs targeting very low risk populations (e.g. prevalence at 0.2%), will only be marginally cost-effective at $50,490/QALY gained over the lifetime of the cohort. The conventional upper limit of cost-effectiveness thresholds varies among countries from CAD$50,000/QALY to

CAD$120,000/QALY (18-20). In terms of screening efficiency, Scenario 2 would be the most attractive option, where 242 individuals would need to be screened to prevent one HCV-related death, compared with 2,500 individuals / 676 individuals / 613 individuals needed to be screened to prevent one HCV-related death for scenarios 1, 3 and 4 respectively. In terms of overall impact of screening program based on estimated affected screening population (21) (Appendix 3), Scenarios 2 and 3 will produce the largest net health gain.

Comparison with other studies

A recent systematic review (22) identified seven cost-utility analyses on hepatitis C birth-cohort screening, and five for the general population from various countries. The results for screening birth-cohorts ranged from CAD$5,400 to CAD$65,749 per QALY gained, while the results for screening the general population ranged from CAD$7,900 to CAD$91,000 per QALY gained. However, most of the studies were conducted before 2014, before the interferon-free DAAs were available, and did not reflect the current treatment restriction situation. Instead, we believe our study, based largely on Canadian data, better reflects the current treatment and restricted reimbursement situation, and thus offers more accurate projections for Canada.

Limitations

Our analysis also has limitations. The current analysis is based on a case-finding screening programme (i.e. individuals are offered one-time screening for HCV infection through their primary care physician at a visit scheduled for another purpose) rather than a universal screening of the population. In addition, the utilities used in the model of CHC patients who have decompensated cirrhosis and HCC were based on very small sample sizes and may not cover the full spectrum of disease severity. Lastly, our analyses did not consider co-infected patients and subsequent treatment of re-infected individuals.

Policy Implications

Implementing wide-scale screening requires a high burden of proof before asymptomatic people are exposed to the effects of medical interventions, in order to avoid doing harm (23), and producing unnecessary stigma(24).

For hepatitis C screening, we have a large subclinical burden of a serious disease that is now the leading cause of liver transplant and liver death in Canada (25, 26). We also have a simple screen, and very well tolerated and safe treatment that, at high cost, can cure HCV in most cases. The best available evidence, integrated into our model, suggests that some form of screening would likely be cost-effective. Although we did not evaluate budget impact, the implementation of a national screening program will almost certainly drive up the drug plan budgets, as it will identify individuals who require treatment.

Given the uncertainty of the long-term benefits of screening, we believe that modeling is the most reliable way, at present, to weigh the risks and benefits of screening. Rational health policy regarding HCV screening does need to consider the potential harm of overdiagnosis. But we also have an obligation to give the appropriate weight to the many Canadians who have a curable disease that may shorten their lives.

Other countries have "grasped the nettle" of HCV control. Australia has plans to "eradicate the deadly and debilitating disease within a generation" (27). In the United States, the US Centers for Disease Control and Prevention (CDC) and the US Preventive Services Task Force (28) recommends birth cohort screening (1945 – 1965, aged 50-69 years in 2014) for hepatitis C on top of risk-based screening. WHO's Strategy on Viral Hepatitis, to which Canada is a signatory, calls for a 90% reduction in new chronic hepatitis C cases, a 65% reduction in HCV-related deaths, and treatment of 80% of eligible cases (29).

Conclusion

Our model suggests that some form of screening may be a rational health policy for Canada. Screening policy will also need to consider the aggregate health gains and budget impact of screening strategies, as well as the effects of screening on stigma, and health equity.

Table 1: Scenario Definitions

	Scenario	Definition
1	Asymptomatic individuals not at high risk for HCV	Non-Aboriginal, non-immigrant asymptomatic individuals (not suspected of having HCV) living in Canada age 15-79 years
2	Immigrant populations with high prevalence	Individuals age 15-79 granted the right to live in Canada permanently (including all landed immigrants, permanent residents, refugees and granted Canadian citizens. Excludes persons born outside of Canada who are Canadian citizens by birth
3	Specific birth cohort (25 to 64 years of age)	Individuals living in Canada age 25-64
4	Specific birth cohort (45-64 years of age)	Individuals living in Canada age 45-64

Table 2: New parameters and treatment-related parameters used in the model

Key Parameters Used				
Description	**Scenario 1**	**Scenario 2**	**Scenario 3**	**Scenario 4**
Cost of Holkira Pak(11)	$55,860	$55,860	$55,860	$55,860
Cost of Harvoni (11)	$67,000	$67,000	$67,000	$67,000
Cost of PR (11)	$19,075	$19,075	$19,075	$19,075
Prevalence	0.20 (0.10-0.30)(3)	1.90 (1.30-2.60)(3)	14-49:0.4 (0.2-0.7) 50-79:0.8 (0.4-1.5)(2)	14-49:0.4 (0.2-0.7) 50-79:0.8 (0.4-1.5)(2)
Uptake of screening*	89.5 (70-100)	76.6 (60 – 100)	89.5 (60 – 100)	90 (76-100)
Uptake of treatment*	80 (80-100)	95 (80-100)	95 (80-100)	80(80-100)
Known CHC (2)	0.305	0.305	0.305	0.305
Age Distribution (30)	15-24: 0.17 25-34:0.17 35-44:0.17 45-54:0.20 55-64:0.16 65-74:010 75-79:0.03	15-24: 0.10 25-34:0.15 35-44:0.21 45-54:0.22 55-64:0.19 65-74:0.10 75-79:0.03	25-34:0.20 35-44:0.27 45-54:0.29 55-64:0.24	45-54:0.54 55-64:0.46
	Scenario 1 - 4			
Fibrosis Distribution*	**Age 15-34**	**Age 35-44**	**Age 45-54**	**Age 55-79**
F0	45 (30-35)	10 (5-15)	5(0-10)	5(0-10)
F1	45 (30-55)	43 (30-60)	25(15-30)	10(5-15)
F2	8 (5-20)	13 (13-60)	25(25-45)	15(10-20)
F3	1(0-5)	19 (5-20)	25(20-30)	45(40-60)
F4	1 (0-5)	15(0-20)	20 (5-35)	25(15-40)

***clinical experts' opinion**

Treatment Efficacy (Sustained Virologic Response)				
Description	**Baseline[a]/ RR**	**Lower Limit (95% CrI)**	**Upper Limit (95% CrI)**	**Source**
Genotype 1				
Non-cirrhosis				
Reference baseline PR48	0.4913[a]	0.4359	0.5456	(11, 12)
SOF12 + LDV12	1.978	1.78	2.225	(11, 12)
PAR/RIT12 + OMB12 + DAS12	1.932	1.337	2.211	(11, 12)
Cirrhosis				
Reference baseline PR48	0.3898 [a]	0.3099	0.475	(11, 12)
SOF12 + LDV12	2.442	1.956	3.091	(11, 12)
PAR/RIT12 + OMB12 + DAS12+ RBV12	2.416	1.942	3.057	(11, 12)
Genotype 2				
Non-cirrhosis				
SOF12 + RBV12	1.16	1.083	1.244	(11, 12)
Reference baseline PR24	0.8191[a]	0.7687	0.8619	(11, 12)

Treatment Efficacy (Sustained Virologic Response)				
Description	**Baseline[a]/ RR**	**Lower Limit (95% CrI)**	**Upper Limit (95% CrI)**	**Source**
Cirrhosis				
SOF12 + RBV12	1.375	1.026	1.791	(11, 12)
Reference baseline PR24	0.6209[a]	0.4966	0.7344	(11, 12)
Genotype 3				
Non-cirrhosis				
Reference baseline PR48	0.7051[a]	0.6393	0.765	(11, 12)
SOF24 + RBV24	1.318	1.177	1.47	(11, 12)
DCV12 + SOF12	1.375	1.233	1.525	(11, 12)
Cirrhosis				
Reference baseline PR48	0.6021[a]	0.5584	0.6441	(11, 12)
SOF24 + RBV24	1.509	1.142	1.702	(11, 12)
Genotype 4-6				
PR48	0.65	0.57	0.71	(31-33)

Adverse Events				
Description	**Baseline[a]/ RR**	**Lower Limit (95% CrI)**	**Upper Limit (95% CrI)**	**Source**
Treatment-Naive				
Depression				
Reference baseline PR48	0.1381[a]	0.11	0.1683	(11, 12)
SOF12 + RBV12	0.2861	0.07992	0.958	(11, 12)
SOF24 + RBV24	0.7751	0.165	3.181	(11, 12)
SOF12 + LDV12	0.01888	0.002205	0.09946	(11, 12)
PAR/RIT12 + OMB12 + DAS12 + RBV12	0.4174	0.08099	1.534	(11, 12)
PR24	0.756	0.1592	2.831	(11, 12)
Anemia				
Reference baseline PR48	0.2136[a]	0.1838	0.2459	(11, 12)
SOF12 + RBV12	0.6949	0.3601	1.309	(11, 12)
SOF24 + RBV24	1.263	0.4806	2.528	(11, 12)
SOF12 + LDV12	0.05568	0.02193	0.1322	(11, 12)
PAR/RIT12 + OMB12 + DAS12	0.3454	0.1431	0.7469	(11, 12)
PAR/RIT12 + OMB12 + DAS12 + RBV12	0.3826	0.1549	0.8366	(11, 12)
PR24	0.9708	0.4121	2.065	(11, 12)
Rash				
Reference baseline PR48	0.1828[a]	0.1465	0.2186	(11, 12)
SOF12 + RBV12	0.5244	0.167	1.598	(11, 12)
SOF24 + RBV24	0.7655	0.07902	2.721	(11, 12)

Adverse Events				
Description	**Baseline[a]/ RR**	**Lower Limit (95% CrI)**	**Upper Limit (95% CrI)**	**Source**
SOF12 + LDV12	0.2626	0.1415	0.4803	(11, 12)
PAR/RIT12 + OMB12 + DAS12	0.2194	0.08837	0.525	(11, 12)
PAR/RIT12 + OMB12 + DAS12 + RBV12	0.7214	0.3777	1.301	(11, 12)
PR24	1.03	0.3068	2.839	(11, 12)

Treatment Discontinuation Rate				
Description	**Base Estimate**	**Lower Limit (95% CI)**	**Upper Limit (95% CI)**	**Soruce**
PR48	0.173	0.096	0.292	(11, 12)
SOF12 + RBV12	0.089	0.038	0.194	(11, 12)
SOF24 + RBV24	0.054	0.015	0.180	(11, 12)
SOF12 + LDV12	0.044	0.023	0.083	(11, 12)
PAR/RIT12 + OMB12 + DAS12	0.005	0.001	0.033	(11, 12)
PAR/RIT12 + OMB12 + DAS12 + RBV12	0.015	0.003	0.071	(11, 12)

Table 3: Base case Cost-Effectiveness Results

Scenario 1

Age range	Strategy	Cost	QALYs	ΔCost	ΔQALYs	ICER
15-79	No screening, treat with Interferon-free DAA if diagnosed	$69,769	14.0644			
	Screen & treat with Interferon-free DAA*	$69,871-$69,877	14.0664	$102-$108	0.0020	$50,490-$53,938

Scenario 2

Age range	Strategy	Cost	QALYs	ΔCost	ΔQALYs	ICER
15-79	No screening, treat with Interferon-free DAA if diagnosed	$72,765	13.7281			
	Screen & treat with Interferon-free DAA*	$73,384-$73,446	13.7478	$619-$681	0.0197	$31,468-$34,600

Scenario 3

Age range	Strategy	Cost	QALYs	ΔCost	ΔQALYs	ICER
25-64	No screening, treat with Interferon-free DAA if diagnosed	$72,506	14.2536			
	Screen & treat with Interferon-free DAA*	$72,767-$72,789	14.2615-14.2616	$261-$284	0.0080	$32,712-$35,619

Scenario 4

Age range	Strategy	Cost	QALYs	ΔCost	ΔQALYs	ICER
45-64	No screening, treat with Interferon-free DAA if diagnosed	$84,610	12.7979			
	Screen & treat with Interferon-free DAA*	$84,914-$84,938	12.8067	$304-$328	0.0088	$34,614-$37,167

*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

Figure 1: State-Transition Model of Hepatitis C Screening Program

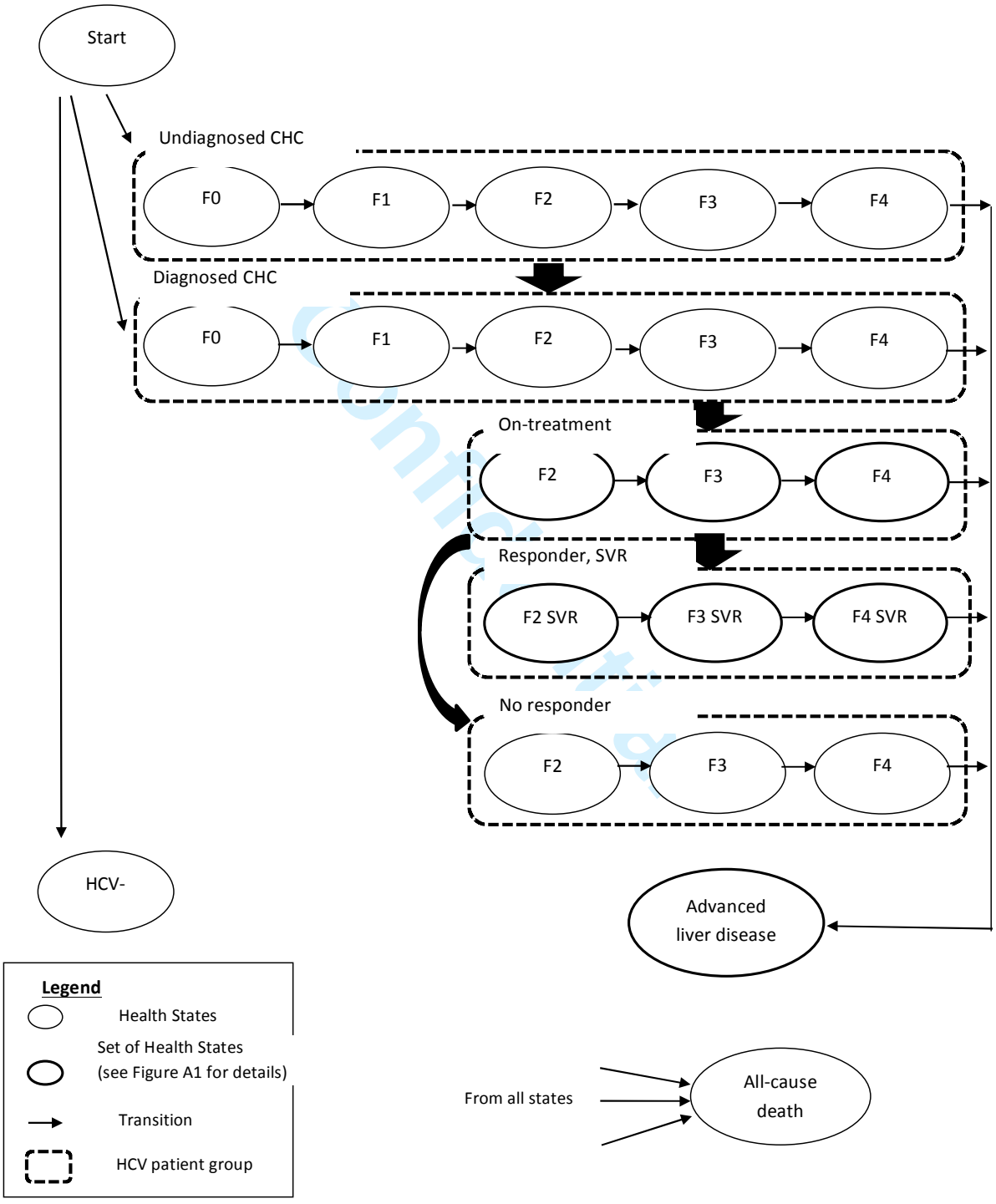
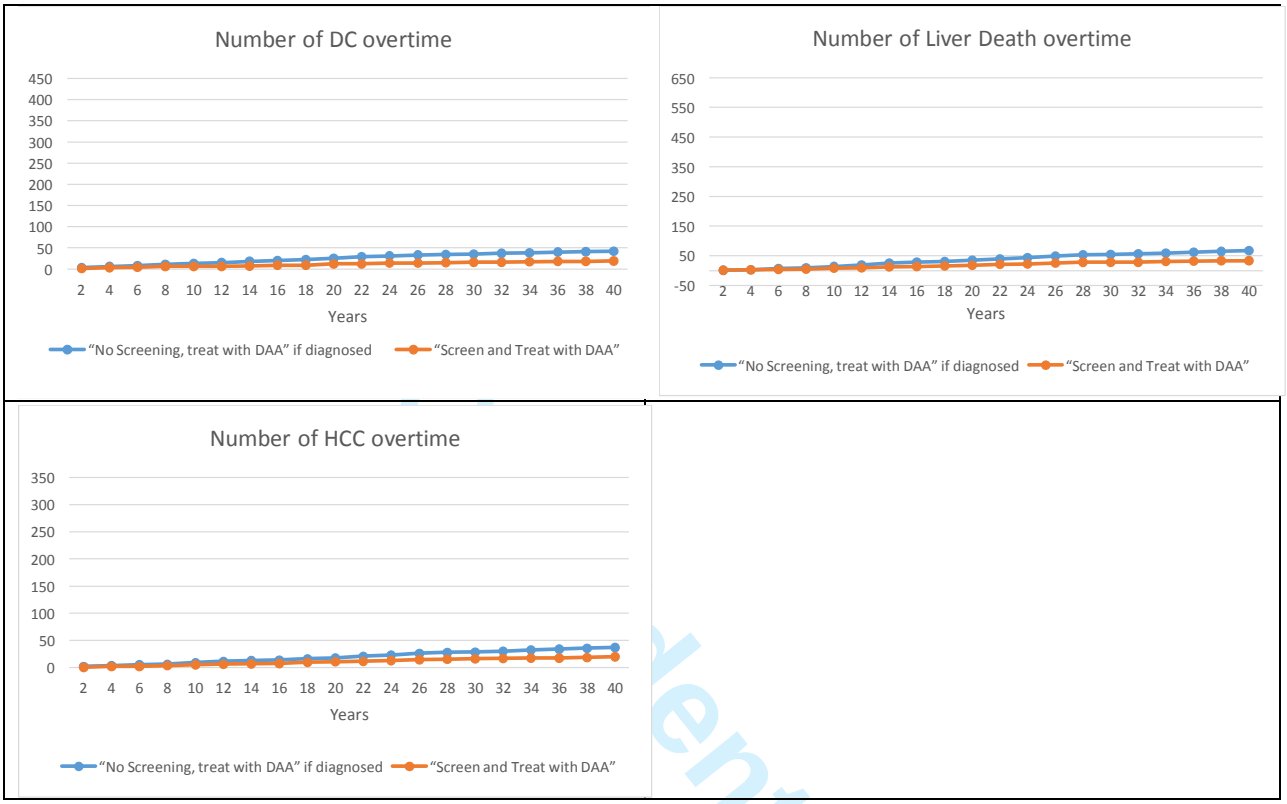


Figure 2: Population Outcomes Accumulated Over Time- Health Events per 100,000

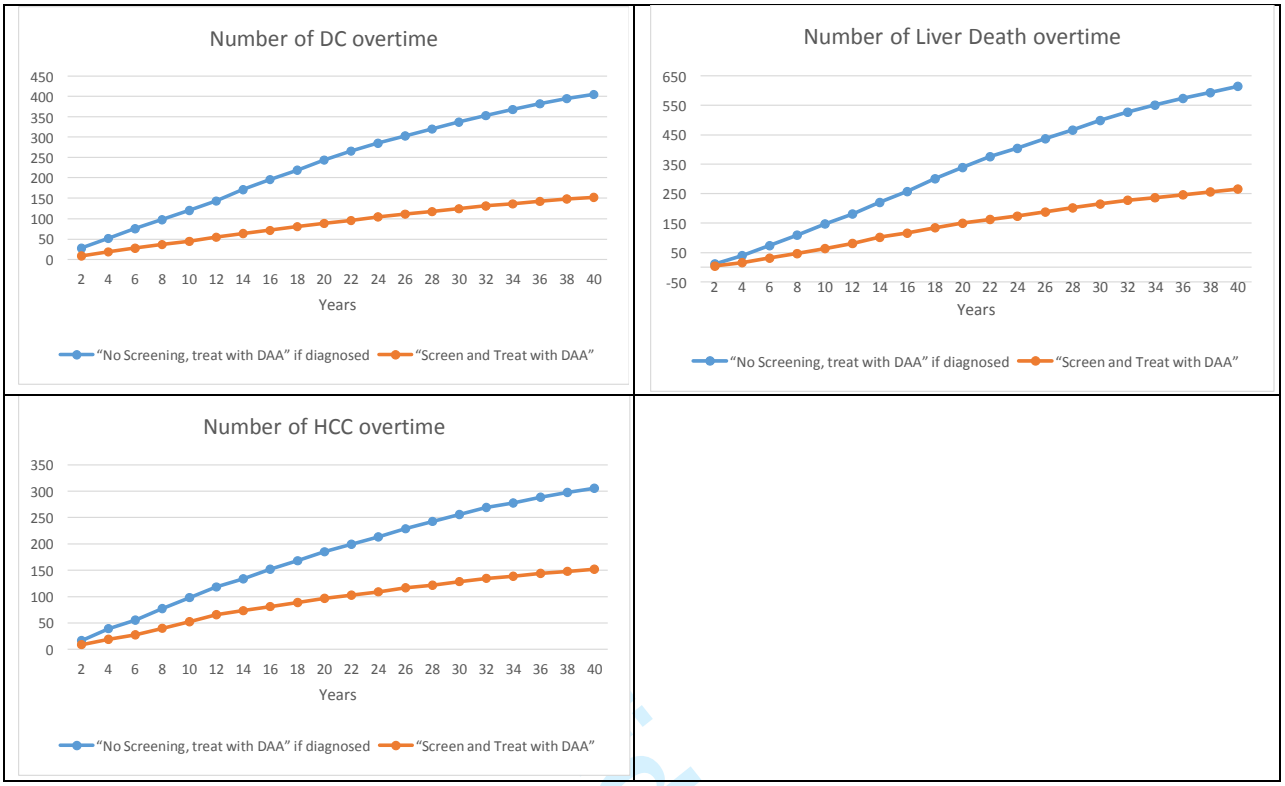
Scenario 1 - Asymptomatic individuals not at high risk for HCV



Strategy	Time	Number of DC	Number of HCC	Number of HCV-related liver death	Number of HCV-related deaths prevented
"No Screening, treat with DAA" if diagnosed	5 yr	7.1	4.8	6.0	-
	10 yr	13.1	9.5	13.9	-
	20 yr	25.1	17.9	35.1	-
	LT	49.1	42.2	80.9	-
"Screen and Treat with DAA"	5 yr	3.8	2.0	2.6	3.4
	10 yr	6.3	5.1	8.4	5.5
	20 yr	11.9	10.3	18.0	17.1
	LT	23.1	22.4	40.8	40.2

Abbreviations: LT: Lifetime; DC decompensated cirrhosis; HCC: Hepatocellular carcinoma

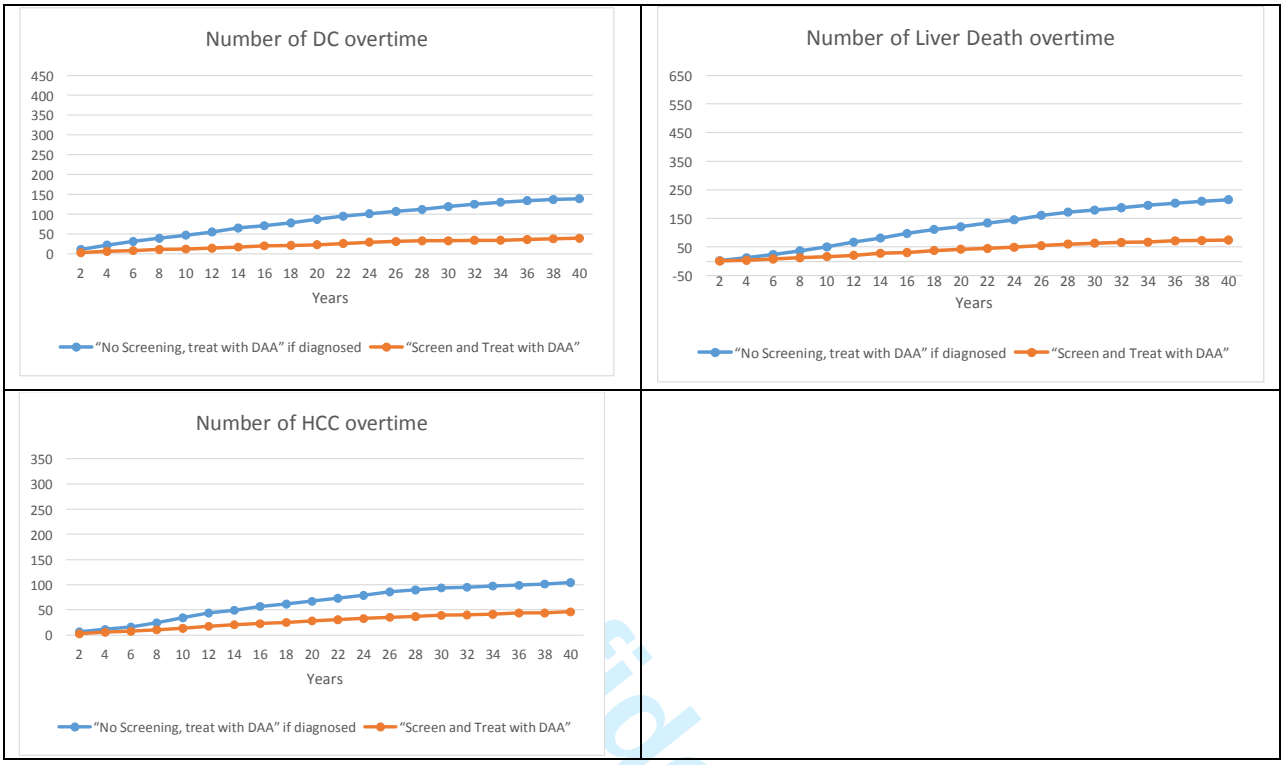
Scenario 2 - Immigrant populations with high prevalence



Strategy	Time	Number of DC	Number of HCC	Number of HCV-related liver death	Number of HCV-related deaths prevented
"No Screening, treat with DAA" if diagnosed	5 yr	64.5	47.4	55.1	-
	10 yr	120.8	98.1	147.4	-
	20 yr	245.6	186.0	339.8	-
	LT	465.9	343.9	731.7	-
"Screen and Treat with DAA"	5 yr	25.1	23.7	22.2	32.9
	10 yr	44.2	52.5	63.3	84.1
	20 yr	88.4	96.9	150.5	189.3
	LT	174.8	169.9	312.0	419.7

Abbreviations: LT: Lifetime; DC decompensated cirrhosis; HCC: Hepatocellular carcinoma

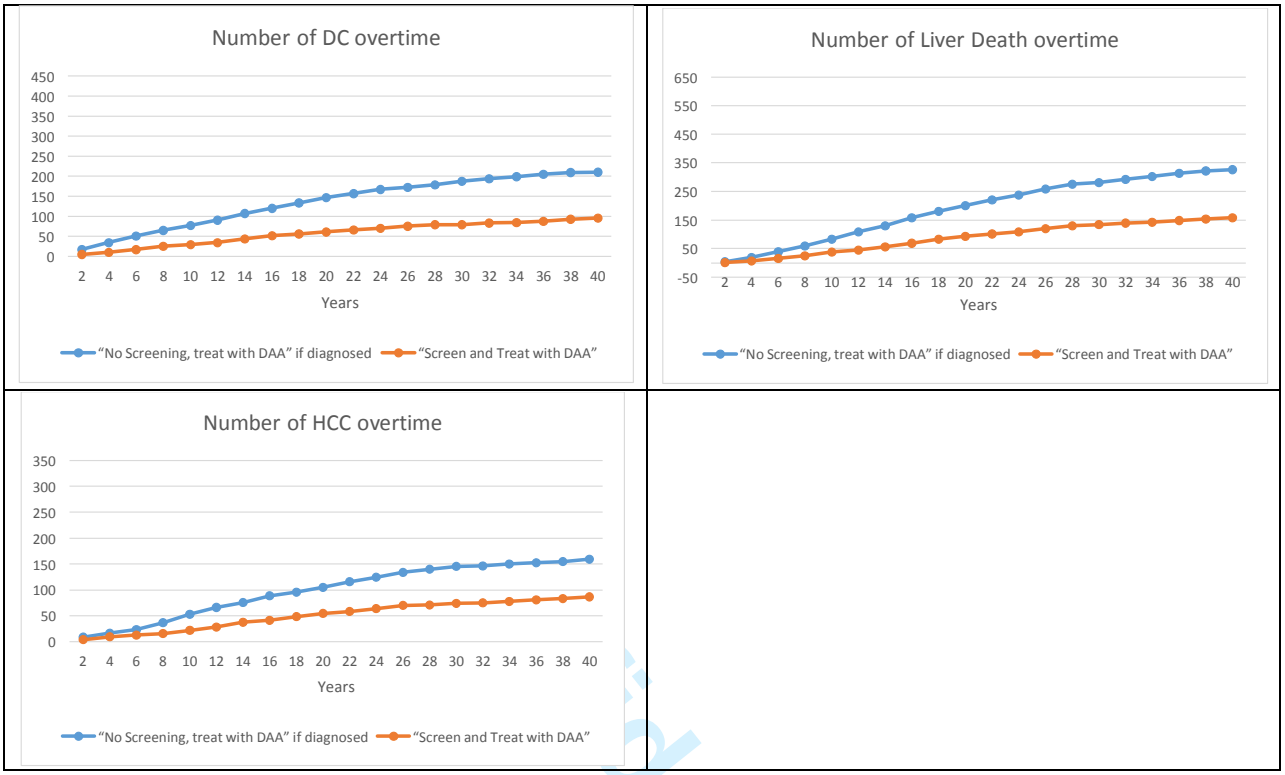
Scenario 3 - Specific birth cohort (25 to 64 years of age)



Strategy	Time	Number of DC	Number of HCC	Number of HCV-related liver death	Number of HCV-related deaths prevented
"No Screening, treat with DAA" if diagnosed	5 yr	25.9	12.3	17.6	-
	10 yr	46.9	34.7	49.9	-
	20 yr	87.6	67.7	121.5	-
	LT	150.9	112.2	237.7	-
"Screen and Treat with DAA"	5 yr	7.6	6.5	5.4	12.2
	10 yr	12.2	13.6	16.2	33.7
	20 yr	23.7	28.8	41.2	80.3
	LT	43.7	49.2	85.4	152.3

Abbreviations: LT: Lifetime; DC decompensated cirrhosis; HCC: Hepatocellular carcinoma

Scenario 4 - Specific birth cohort (45-64 years of age)



Strategy	Time	Number of DC	Number of HCC	Number of HCV-related liver death	Number of HCV-related deaths prevented
"No Screening, treat with DAA" if diagnosed	5 yr	40.9	18.0	27.6	-
	10 yr	77.5	53.2	82.9	-
	20 yr	148.7	105.1	200.8	-
	LT	214.8	160.9	338.6	-
"Screen and Treat with DAA"	5 yr	14.7	10.7	9.8	17.7
	10 yr	30.1	22.3	38.2	44.7
	20 yr	63.0	54.8	92.4	108.5
	LT	97.9	88.6	170.5	168.1

Abbreviations: LT: Lifetime; DC decompensated cirrhosis; HCC: Hepatocellular carcinoma

Appendix 1 All Parameters used in the model

Costs	Baseline	Low	High	Source
Cost				
Cost of transplant	$120,593	$90,445	$150,741	(34)
Cost of post-transplant	$19,400	$14,550	$24,250	(34)
Cost of adverse events				
Anemia (Cost per week)	$107	$80	$134	(35)
Depression (Cost per week)	$73	$55	$91	(35)
Rash (Cost per week)	$12	$9	$15	(35)
Cost of Anti-HCV test	$14.48	$10.86	$18.1	(36)
Cost of HCV RNA test	$100	$75	$125	(36)

Utilities	Baseline	Low	High	Source
Utilities				
Canadian population average				
Age 25 – 34	0.90	0.89	0.92	(37, 38)
Age 35 – 44	0.88	0.86	0.91	(37, 38)
Age 45 – 54	0.86	0.83	0.88	(37, 38)
Age 55 – 64	0.83	0.80	0.87	(37, 38)
Utility for CHC related health states				
Non-cirrhosis (F0 – F3)	0.73	0.69	0.77	(39)
Compensated cirrhosis (F4)	0.69	0.65	0.73	(39)
HCC	0.72	0.68	0.75	(39)
Decompensated cirrhosis	0.65	0.65	0.73	(39, 40)
Post-transplant	0.75	0.70	0.79	(39)
Viral clearance	0.80	0.76	0.84	(39)
On-treatment	0.71	0.67	0.75	(39)

Other Variables	Baseline	Low	High	Source
Population				
Proportion known infected CHC	0.305	0.157	0.507	(2)
Proportion of spontaneous clearance	0.28	0.16	0.30	(41)
Annual diagnosis rate (no screening)	0.0068	0.0034	0.0085	(8)
Genotype distribution				
G1	0.67	0.50	0.84	(42)
G2	0.09	0.07	0.11	(42)
G3	0.22	0.17	0.28	(42)
G4	0.01	0.00	0.02	(42)
G5/6	0.01	0.00	0.02	(42)
Natural history of CHC				
Annual probability for fibrosis progression				
F0 → F1	0.117	0.104	0.13	(43)
F1 → F2	0.085	0.075	0.096	(43)
F2 → F3	0.12	0.109	0.133	(43)
F3 → F4	0.116	0.104	0.129	(43)

Annual probability for cirrhosis progression				
F4 → decompensated (Non-SVR)	0.035	0.027	0.043	(44)
F4 → decompensated (SVR)	0.002	0.0001	0.005	(44)
F4 → HCC (Non-SVR)	0.024	0.018	0.031	(44)
F4 → HCC (SVR)	0.005	0.001	0.009	(44)
Annual CHC related mortality				
HCC	0.411	0.31*	0.51*	(45)
Decompensated Cirrhosis	0.216	0.162*	0.27*	(46)
Liver transplant (1st year)	0.142	0.124	0.159	(47)
Liver transplant (> 1 year)	0.034	0.024	0.043	(47)
Annual probability for liver transplantation				
From Decompensated Cirrhosis	0.033	0.017	0.049	(14)
From HCC	0.033	0.017	0.049	(14)
Discount Rate	5%	3%	5%	(48)

Costs	**Baseline**	**Low***	**High***	**Source**
Cost+				
Annual cost CHC early phase				
Age 15 – 24	$4,179	$4,016	$4,350	(49)
Age 25 – 34	$4,069	$3,988	$4,151	(49)
Age 35 – 44	$3,888	$3,812	$3,967	(49)
Age 45 – 54	$4,589	$4,498	$4,682	(49)
Age 55 – 64	$5,541	$5,377	$5,710	(49)
Age 65 – 74	$7,325	$7,038	$7,624	(49)
Age 75+	$7,736	$6,930	$8,635	(49)
Annual cost CHC late phase				
Age 15 – 24	$5,103	$4,054	$6,422	(49)
Age 25 – 34	$10,344	$8,640	$12,384	(49)
Age 35 – 44	$12,054	$11,582	$12,546	(49)
Age 45 – 54	$14,597	$13,475	$15,813	(49)
Age 55 – 64	$12,337	$11,619	$13,100	(49)
Age 65 – 74	$11,558	$10,670	$12,520	(49)
Age 75+	$9,885	$8,855	$11,034	(49)
Annual cost CHC pre-death phase				
Age 15 – 24	$23,970	$19,822	$28,985	(49)
Age 25 – 34	$42,955	$36,603	$50,408	(49)
Age 35 – 44	$35,544	$32,811	$38,504	(49)
Age 45 – 54	$41,823	$39,388	$44,410	(49)
Age 55 – 64	$52,102	$49,561	$54,773	(49)
Age 65 – 74	$44,649	$43,765	$45,551	(49)
Age 75+	$40,424	$38,453	$42,497	(49)
Annual cost non-CHC before pre-death phase				
Age 15 – 24	$1,665	$1,616	$1,716	(49)
Age 25 – 34	$1,633	$1,600	$1,665	(49)
Age 35 – 44	$1,813	$1,777	$1,850	(49)
Age 45 – 54	$2,362	$2,338	$2,387	(49)
Age 55 – 64	$3,925	$3,809	$4,044	(49)
Age 65 – 74	$6,083	$5,962	$6,205	(49)
Age 75+	$7,440	$7,148	$7,743	(49)
Annual cost non-CHC pre-death phase				

Age 15 – 24	$60,850	$49,324	$75,069	(49)
Age 25 – 34	$39,226	$34,791	$44,228	(49)
Age 35 – 44	$42,291	$40,229	$44,459	(49)
Age 45 – 54	$45,207	$44,312	$46,120	(49)
Age 55 – 64	$44,542	$43,660	$45,442	(49)
Age 65 – 74	$44,854	$43,966	$45,761	(49)
Age 75+	$36,548	$35,825	$37,287	(49)

APPENDIX 2 – Undiscounted Life Years Results

Undiscounted Life Years Results for Scenario 1

Age range	Strategy	LY*	Δ LY*
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

Age range	Strategy	LY*	Δ LY*
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

Age range	Strategy	LY*	Δ LY*
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

Age range	Strategy	LY*	Δ LY*
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

Appendix 3 - Net Life Year and QALY Life Year Gained for Screening Scenarios 1 to 4

	Maximum Estimated Affected population screening size+(21)	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

+Maxmium estimated affected population screening size according to the data source.

*compare between "Screen & treat with Inferferon-free DAA" with "No screening, treat with Interferon-free DAA"

APPENDIX 4 – Exploratory Analysis 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	(50, 51)

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)**	**Soruce**
SOF12 + VEL12	0.005	0.002	0.007	(50, 51)

Drug Cost				
Description	**Base Estimate**	**Lower Limit (95% CI)**	**Upper Limit (95% CI)**	**Soruce**
SOF12 + VEL12	$60,000	$45,000	$75,000	(50, 51)

Exploratory Analysis - Cost-Effectiveness Results

Scenario 1

Age range	Strategy	Cost	QALYs	ΔCost	ΔQALYs	ICER
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

Age range	Strategy	Cost	QALYs	ΔCost	ΔQALYs	ICER
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

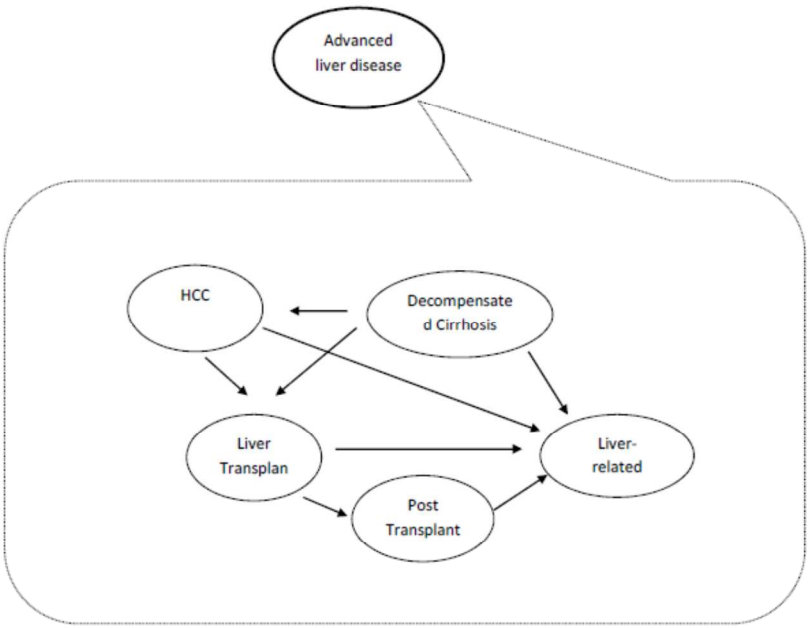
Age range	Strategy	Cost	QALYs	ΔCost	ΔQALYs	ICER
25-64	No screening, treat with Interferon-free DAA if diagnosed	$72,507	14.2536			
	Screen & treat with Interferon-free DAA*	$72,770 $72,792	14.2616	$263-$286	0.0080	$32,968-$35,787

Scenario 4

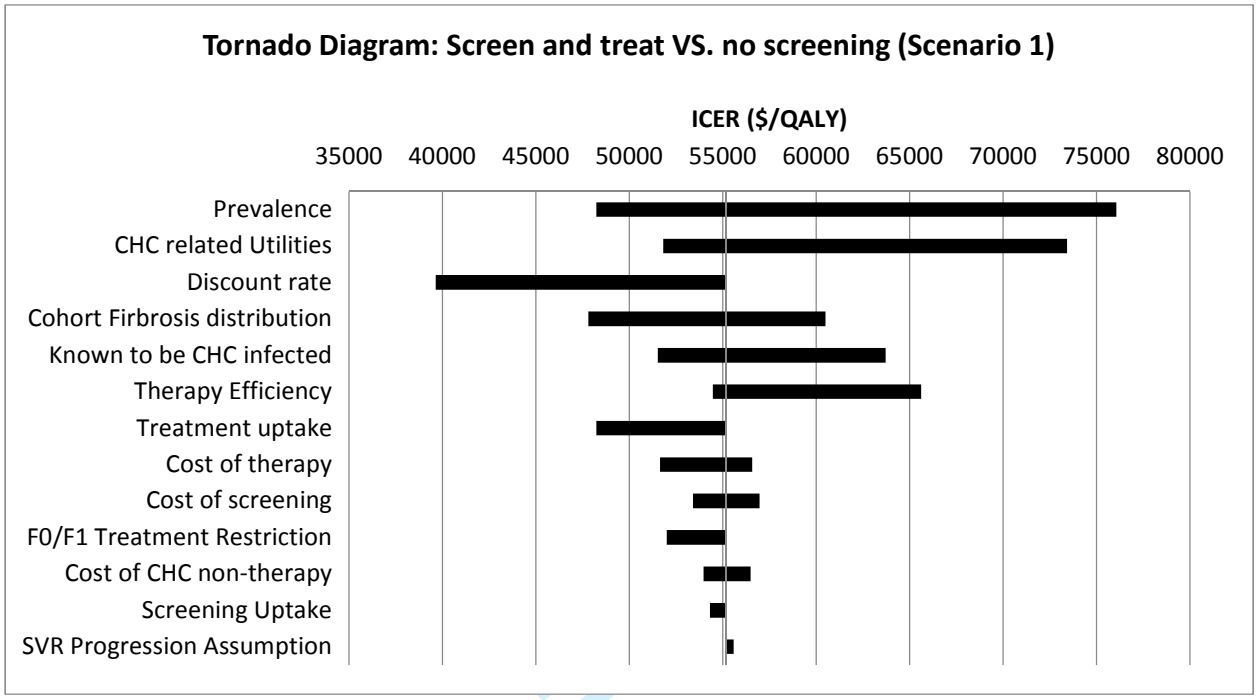
Age range	Strategy	Cost	QALYs	ΔCost	ΔQALYs	ICER
45-64	No screening, treat with Interferon-free DAA if diagnosed	$84,611	12.7980			
	Screen & treat with Interferon-free DAA*	$84,918-$84,942	12.8068	$306-$331	0.0088	$34,678-$37,442

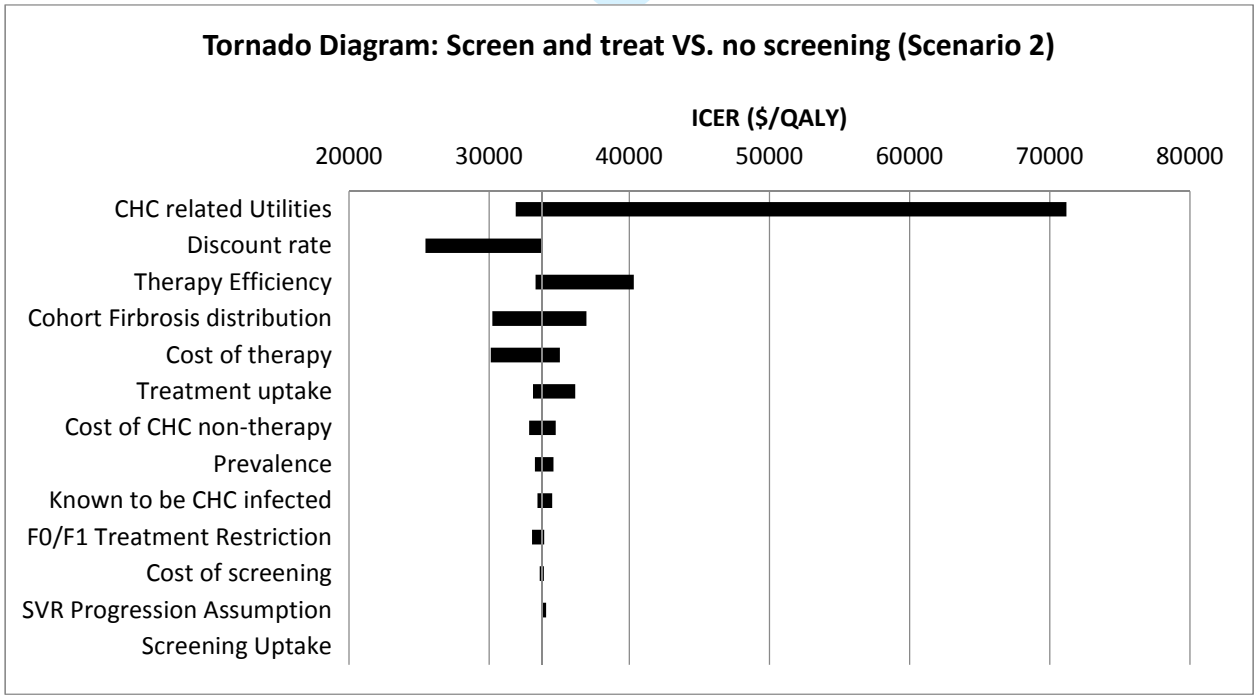
*Range indicate the different between which DAA was used for treating genotype 1 patients
Abbreviations: QALYs: Quality-adjusted-life-years; ICER: incremental cost-effectiveness ratio; DAA; Direct acting agents

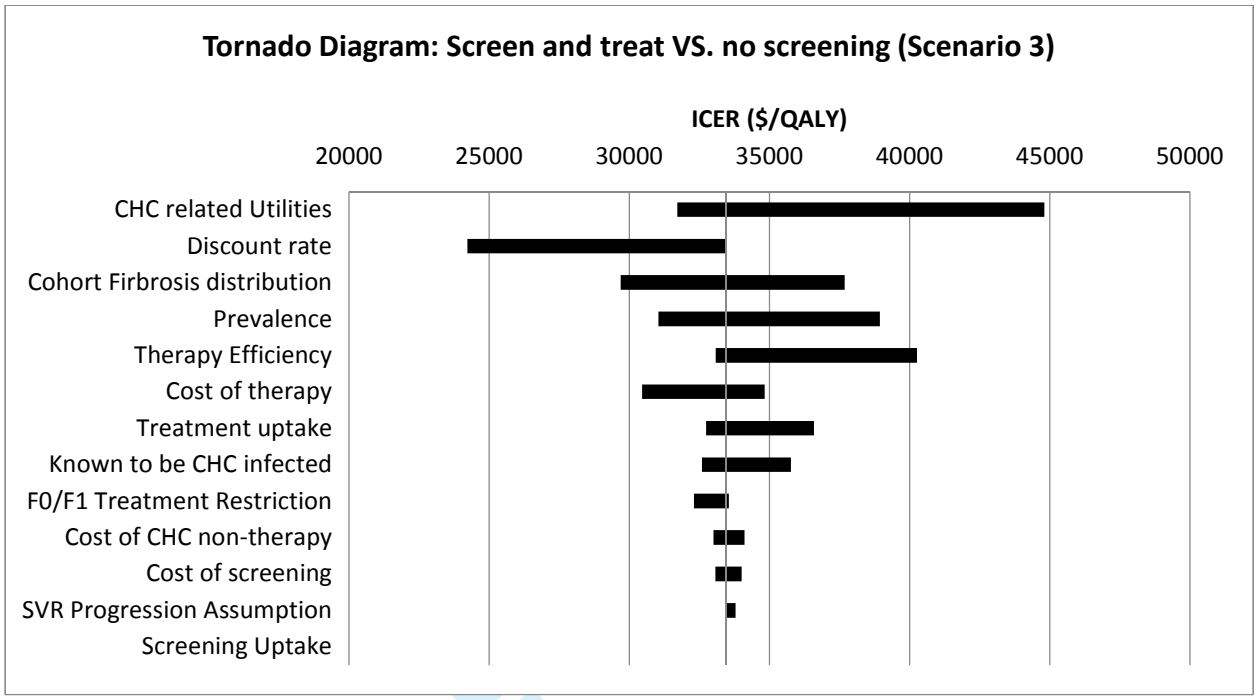
Appendix Figure 1: Detailed Markov model of Chronic HCV infection and progression

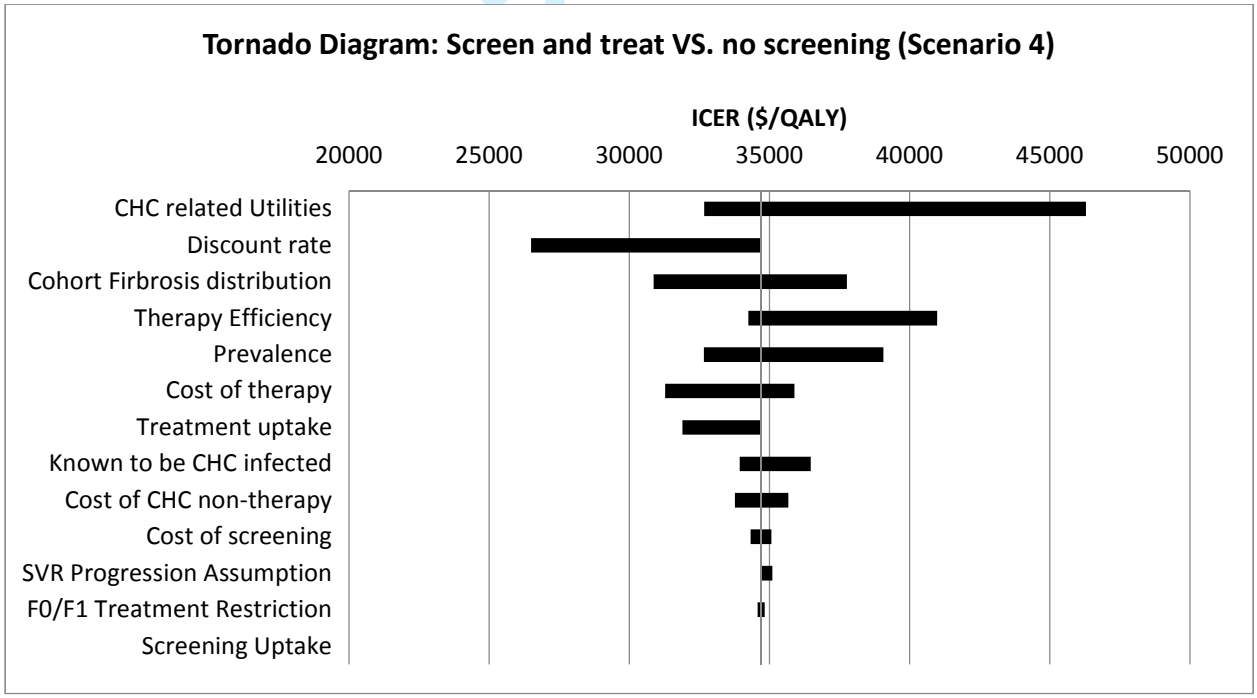


Appendix Figure 2: Sensitivity Analyses Results - Tornado Diagrams









1. Kwong JC, Crowcroft NS, Campitelli MS, Ratnasingham S, Daneman N, Deeks SL, et al. Ontario Burden of Infectious Disease Study. Toronto, Ontario, Canada: Institute for Clinical Evaluative Sciences (ICES), 2010.

2. Rotermann M, Langlois K, Andonov A, Trubnikov M. Seroprevalence of hepatitis B and C virus infections: Results from the 2007 to 2009 and 2009 to 2011 Canadian Health Measures Survey. Health Reports: Health Analysis Division of Statistics Canada; 2013.
3. Trubnikov M, Yan P, Archibald C. Estimated prevalence of Hepatitis C virus infection in Canada, 2011. Canada Communicable Disease Report. 2014;40(19):429-37.
4. Shah HA, Heathcote J, Feld JJ. A Canadian screening program for hepatitis C: is now the time? CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2013;185(15):1325-8.
5. Wong WW, Tu HA, Feld JJ, Wong T, Krahn M. Cost-effectiveness of screening for hepatitis C in Canada. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2015.
6. Wong WW, Lee KM, Singh S, Wells G, Feld JJ, Krahn M. Cost-Effectiveness Analysis of Drugs for Chronic Hepatitis C Infection: Informing on Listing Decisions in Canada. CMAJ Open. 2017;in press.
7. Marshall AD, Saeed S, Barrett L, Cooper CL, Treloar C, Bruneau J, et al. Restrictions for reimbursement of direct-acting antiviral treatment for hepatitis C virus infection in Canada: a descriptive study. CMAJ Open. 2016;4(4):E605-E14.
8. Ontario's use of funding provided by the federal hepatitis c undertaking agreement. Toronto, Ontario: Government of Ontario; 2007.
9. Myers RP, Shah H, Burak KW, Cooper C, Feld JJ. An update on the management of chronic hepatitis C: 2015 Consensus guidelines from the Canadian Association for the Study of the Liver. Canadian journal of gastroenterology & hepatology. 2015;29(1):19-34.
10. TreeAge 2013 Professional. Williamstown, MA, USA.: TreeAge Software; 2013.
11. Wong WWL, Krahn M, Lee K, Singh S. CADTH THERAPEUTIC REVIEW 8: Drugs for Chronic Hepatitis C Infection: Cost-Effectiveness Analysis. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health; 2016.
12. CADTH Therapeutic Review: Drugs for Chronic Hepatitis C Infection: Clinical Report. Ottawa, Ontario, Canada: 2015.
13. Wong WWL, Tu HA, Feld J, Wong T, Krahn M. Cost-Effectiveness of Screening for Hepatitis C in Canada. Canadian Medical Association Journal. 2015;187(3):E110.
14. Krahn M, Wong JB, Heathcote J, Scully L, Seeff L. Estimating the prognosis of hepatitis C patients infected by transfusion in Canada between 1986 and 1990. Med Decis Making. 2004;24(1):20-9.
15. Salomon JA, Weinstein MC, Hammitt JK, Goldie SJ. Cost-effectiveness of treatment for chronic hepatitis C infection in an evolving patient population. JAMA. 2003;290(2):228-37.
16. Wong JB, Bennett WG, Koff RS, Pauker SG. Pretreatment evaluation of chronic hepatitis C: risks, benefits, and costs. JAMA. 1998;280(24):2088-93.
17. Chahal HS, Marseille EA, Tice JA, Pearson SD, Ollendorf DA, Fox RK, et al. Cost-effectiveness of Early Treatment of Hepatitis C Virus Genotype 1 by Stage of Liver Fibrosis in a US Treatment-Naive Population. JAMA Intern Med. 2016;176(1):65-73.
18. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. CMAJ. 1992;146(4):473-81.
19. McCabe C, Claxton K, Culyer AJ. The NICE cost-effectiveness threshold: what it is and what that means. Pharmacoeconomics. 2008;26(9):733-44.

20. WHO. Choosing Interventions that are Cost Effective (WHO-CHOICE). Geneva: WHO, 2005.
21. Statistics Canada. Table 051-0001 - Estimates of population, by age group and sex for July 1, Canada, provinces and territories, annual (persons unless otherwise noted) [Internet]. 2011.
22. Coward S, Leggett L, Kaplan GG, Clement F. Cost-effectiveness of screening for hepatitis C virus: a systematic review of economic evaluations. BMJ Open. 2016;6(9).
23. Gray JA, Patnick J, Blanks RG. Maximising benefit and minimising harm of screening. Bmj. 2008;336(7642):480-3.
24. Batchelder AW, Peyser D, Nahvi S, Arnsten JH, Litwin AH. "Hepatitis C treatment turned me around:" Psychological and behavioral transformation related to hepatitis C treatment. Drug Alcohol Depend. 2015;153:66-71.
25. de Oliveria Andrade LJ, D'Oliveira A, Melo RC, De Souza EC, Costa Silva CA, Parana R. Association between hepatitis C and hepatocellular carcinoma. J Glob Infect Dis. 2009;1(1):33-7.
26. Myers RP, Krajden M, Bilodeau M, Kaita K, Marotta P, Peltekian K, et al. Burden of disease and cost of chronic hepatitis C infection in Canada. Canadian journal of gastroenterology & hepatology. 2014;28(5):243-50.
27. Turnbull Government Invests over $1 billion to Cure HEP C [press release]. Australia: Minister of Health, Commonwealth of Australia2015.
28. Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945 - 1965. Morbidity and Mortality Weekly Report. Atlanta, GA: Centers for Disease Control and Prevention; 2012.
29. World Hepatitis Summit harnesses global momentum to eliminate viral hepatitis [press release]. Glasgow, UK: World Health Organization2015.
30. Census Profile. 2011 Census. Statistics Canada Catalogue no. 98-316-XWE. Ottawa, Ontario: Statistics Canada; 2012.
31. Hasan F, Asker H, Al-Khaldi J, Siddique I, Al-Ajmi M, Owaid S, et al. Peginterferon alfa-2b plus ribavirin for the treatment of chronic hepatitis C genotype 4. The American journal of gastroenterology. 2004;99(9):1733-7.
32. Alfaleh FZ, Hadad Q, Khuroo MS, Aljumah A, Algamedi A, Alashgar H, et al. Peginterferon alpha-2b plus ribavirin compared with interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C in Saudi patients commonly infected with genotype 4. Liver Int. 2004;24(6):568-74.
33. Kamal SM, El Tawil AA, Nakano T, He Q, Rasenack J, Hakam SA, et al. Peginterferon {alpha}-2b and ribavirin therapy in chronic hepatitis C genotype 4: impact of treatment duration and viral kinetics on sustained virological response. Gut. 2005;54(6):858-66.
34. Sullivan P. New price tag put on liver transplants. Canadian Medical Association Journal 2003;168(2):206.
35. Gao X, Stephens JM, Carter JA, Haider S, Rustgi VK. Impact of adverse events on costs and quality of life in protease inhibitor-based combination therapy for hepatitis C. Expert Rev Pharmacoecon Outcomes Res. 2012;12(3):335-43.
36. Schedule of Laboratory Fees [Internet]. Ontario Ministry of Health and Long-term Care. 2008. Available from: http://www.health.gov.on.ca/english/providers/program/ohip/sob/lab/labfimmu.html.

37. Chen W. Chronic Hepatitis C among Immigrants Living in Canada: Natural History, Disease Burden, and Cost-Effectiveness of Screening. Toronto: University of Toronto; 2010.
38. Maddigan SL, Feeny DH, Johnson JA. Health-related quality of life deficits associated with diabetes and comorbidities in a Canadian National Population Health Survey. Qual Life Res. 2005;14(5):1311-20.
39. Hsu PC, Federico CA, Krajden M, Yoshida EM, Bremner KE, Anderson FH, et al. Health utilities and psychometric quality of life in patients with early- and late-stage hepatitis C virus infection. J Gastroenterol Hepatol. 2012;27(1):149-57.
40. McLernon DJ, Dillon J, Donnan PT. Health-state utilities in liver disease: a systematic review. Medical decision making : an international journal of the Society for Medical Decision Making. 2008;28(4):582-92.
41. Yeung LT, To T, King SM, Roberts EA. Spontaneous clearance of childhood hepatitis C virus infection. Journal of viral hepatitis. 2007;14(11):797-805.
42. Chaudhary R, Tepper M, Eisaadany S, Gully PR. Distribution of hepatitis C virus genotypes in Canada: Results from the LCDC Sentinel Health Unit Surveillance System. Can J Infect Dis. 1999;10(1):53-6.
43. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008;48(2):418-31.
44. van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012;308(24):2584-93.
45. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol. 2009;27(9):1485-91.
46. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol. 2006;44(1):217-31.
47. Charlton M, Seaberg E, Wiesner R, Everhart J, Zetterman R, Lake J, et al. Predictors of patient and graft survival following liver transplantation for hepatitis C. Hepatology. 1998;28(3):823-30.
48. Guidelines for the Economic Evaluation of Health Technologies: Canada2006. Available from: www.cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf.
49. Krajden M, Kuo M, Zagorski B, Alvarez M, Yu A, Krahn M. Health care costs associated with hepatitis C: a longitudinal cohort study. Can J Gastroenterol. 2010;24(12):717-26.
50. Feld JJ, Jacobson IM, Hezode C, Asselah T, Ruane PJ, Gruener N, et al. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. N Engl J Med. 2015;373(27):2599-607.
51. Common Drug Review - Sofosbuvir/Velpatasvir Final Recommendation. Canadian Agency for Drugs and Technologies in Health, Ottawa2016.