Appendix 2 (as supplied by the authors): Detailed methodology section

METHODS

We developed a state-transition model of HCV to assess the cost-effectiveness of alternative screening strategies for patients with chronic HCV mono-infection in Canada.

Cohort

We included individuals who are currently living in Canada. Our baseline analysis considered screening both 25-64 year-old and 45-64 year-old individuals.

Strategies

In our baseline analysis, we consider four different screening strategies for the cost-effectiveness analysis.

(1) "No Screening" (Status Quo): We assume that 69.5% of HCV-infected patients are initially unaware of their infection and do not receive antiviral treatment (20% - 70% in sensitivity analysis).[1] Each year, we assume that 0.68% of the unaware infected individuals will discover that they are infected with CHC.[2] 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 pegylated interferon plus ribavirin (PR)*"*: 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 PR according to the Canadian guidelines.[3]

(3) "*Screen and Treat* with PR-based direct-acting antiviral agents (DAA)*":* We used the assumptions as in strategy (2). However in this strategy, we assume that the patients with genotype 1 infection will be offered simeprevir-based combination therapy;[4,5] patients with genotype 2 or 3 will be offered sofosbuvir-based combination therapy will be offered;[6,7] and patients with remaining genotype will be offered PR.[3]

(4) "*Screen and Treat* with interferon-free (IFN-Free) antiviral agents": Same assumptions as in strategy (3); however in this strategy, we assume that the patients with genotype 1 infection will be offered interferon-free therapy (ABT-450 combination therapy).[8,9]

Decision Model

In our analysis, we developed a cohort-based, state transition model using TreeAge Pro 2013 software.[10] Our model includes 42 Health states related to treatment and adverse events, fibrosis stages (F0 to F4), presence or absence of a clinical diagnosis, and clinical states (e.g., Cirrhosis, HCC).

In our simulations, cohort members move between predefined health states in weekly cycles until all members die. At the time of screening, 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. Health states and allowed transitions among health states are shown in Figure 1 and Appendix 1, respectively.

Appendix to: Wong WWL, Tu HA, Feld JJ, et al. Cost-effectiveness of screening for hepatitis C in Canada. *CMAJ* 2015. DOI:10.1503/cmaj.140711. Copyright © 2015 The Author(s) or their employer(s).
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In this model, CHC-infected individuals with fibrosis F0 to F3 are initially assumed to have no cirrhosis but progress over time to different clinical states of CHC, and/or cirrhosis. Those developing cirrhosis may develop decompensated liver disease and/or HCC and may die from the complications of liver disease or require a liver transplant.

Model Probabilities

Disease progression parameters were obtained from a systematic review conducted by our group, which estimated the annual transition probabilities between fibrosis stages from 111 prognostic studies including 33,121 patients.[11] Transition probabilities to advanced liver disease were obtained from a published study,[12] which provided separate estimates for both SVR and non-SVR CHC patients. Mortality rates for advanced liver disease were obtained from a US study[13] based on cancer registries and a systematic review.[14]

Treatment for CHC

We assume that patients who are offered an antiviral therapy would be treated with PR, simeprevir-based combination therapy, sofosbuvir-based combination therapy or ABT-450-based interferon-free combination therapy according to the Canadian guidelines or phase III clinical trials.[3–9,15]

In the "Screen and treat with PR" strategies, patient with genotype 1, 4, 5 and 6 CHC will receive 48 weeks of PR, while patient with genotype 2 and 3 CHC will receive 24 weeks of PR treatment.[3] In the "Screen and treat with PR-based DAA" strategies, genotype 1 CHC patients will receive simeprevir-based combination therapy according to the phase III clinical trials.[4,5] Patient with genotype 2 will receive 12 weeks of sofosbuvir in combination with ribavirin (SOF/RBV), while patient with genotype 3 CHC will receive 24 weeks of SOF/RBV.[6,7] Patient with genotype 4, 5 and 6 CHC will receive 48 weeks of PR. In the "Screen and treat with IFN-free DAA" strategies, genotype 1 CHC patients will receive ABT-450-based combination therapy according to the phase III clinical trials.[8,9] Patient with genotype 2 will receive 12 weeks of sofosbuvir in combination with ribavirin (SOF/RBV), while patient with genotype 3 CHC will receive 24 weeks of SOF/RBV.[4,5] Patient with genotype 4, 5 and 6 CHC will receive 48 weeks of PR.[3]

Stopping rules for treatment algorithms are also implemented according to the guidelines or clinical trials,[3–9] respectively. Currently, we assume that adherence to antiviral therapy has been reflected in the overall discontinuation rate (patients who do not complete treatment) according to each treatment.

Table 1 (main article) summarizes the treatment efficacy data for PR, simeprevir-based combination therapy, sofosbuvir-based combination therapy or ABT-450-based interferon-free combination therapy. We obtained data on treatment efficacy by conducting our own meta-analysis, combining data from individual studies using a random-effect model.[16] The odds of treatment success and 95% confidence intervals (CI) were used as measures of effect and uncertainty. We mainly used data from phase III randomized control trials for PR,[17–30] simeprevir-based combination therapy,[4,5] sofosbuvir-based combination therapy[6,7] and ABT-450-based interferon-free combination therapy.[8,9]

The probability of being treated by genotypes was estimated using the medical records of patients with CHC who attend the liver clinic at Toronto Western Hospital.

Epidemiologic Variables

In order to estimate the distribution of age-specific fibrosis states (See Appendix Table 1, below) among patients with CHC, we reviewed the medical records of patients with CHC who attended the tertiary referral liver clinic at Toronto Western Hospital. We extracted date of birth, date of first visit, CHC genotype, alanine transaminase (ALT) level, aspartate aminotransferase (AST) level, platelet test from the clinic database to estimate the distribution of fibrosis states in patients stratified by seven age groups (0-24, 25-34, 35-44, 45-54, 55-64, 65-74, and 75 years and above) using FIB-4.[37] A total of 2,529 medical records were retrieved.

Appendix Table 1: Population-related model variables				
Variables	**Baseline**	**Low**	**High**	**Source**
Population				
Prevalence				
Age 25 – 34	0.004	0.002	0.007	[1]
Age 35 – 44	0.004	0.002	0.007	[1]
Age 45 – 54	0.008	0.004	0.015	[1]
Age 55 – 64	0.008	0.004	0.015	[1]
Proportion known infected CHC	0.305	0.157	0.507	[1]
Proportion of spontaneous clearance	0.28	0.16	0.30	[31]
Acceptance rate when screening offered	0.91	0.172	1	[32]
Annual screening rate (no screening)	0.0068	0.0034	0.0085	[2]
Genotype distribution				
G1	0.67	0.50	0.84	[33]
G2	0.09	0.07	0.11	[33]
G3	0.22	0.17	0.28	[33]
G4	0.01	0.00	0.02	[33]
G5/6	0.01	0.00	0.02	[33]
Distribution of fibrosis stages by age				
Age 25 – 34				
F0	0.2	0.15	0.25	TWH medical records
F1	0.36	0.27	0.45	TWH medical records
F2	0.36	0.27	0.45	TWH medical records
F3	0.05	0.04	0.06	TWH medical records
F4	0.04	0.03	0.05	TWH medical records
Age 35 – 44				
F0	0.07	0.05	0.09	TWH medical records
F1	0.365	0.27	0.46	TWH medical records
F2	0.365	0.27	0.46	TWH medical records
F3	0.14	0.11	0.18	TWH medical records
F4	0.07	0.05	0.09	TWH medical records
Age 45 – 54				
F0	0.01	0.00	0.01	TWH medical records
F1	0.25	0.19	0.31	TWH medical records
F2	0.25	0.19	0.31	TWH medical records
F3	0.27	0.20	0.34	TWH medical records
F4	0.22	0.17	0.28	TWH medical records
Age 55 – 64				
F0	0	0.00	0.00	TWH medical records
F1	0.15	0.11	0.19	TWH medical records
F2	0.15	0.11	0.19	TWH medical records
F3	0.34	0.26	0.43	TWH medical records
F4	0.36	0.27	0.45	TWH medical records
Natural history of CHC				
Annual probability for fibrosis progression				
F0 → F1	0.117	0.104	0.13	[11]
F1 → F2	0.085	0.075	0.096	[11]
F2 → F3	0.12	0.109	0.133	[11]
F3 → F4	0.116	0.104	0.129	[11]
Annual probability for cirrhosis progression				

F4 → decompensated (Non-SVR)	0.035	0.027	0.043	[12]
F4 → decompensated (SVR)	0.002	0.0001	0.005	[12]
F4 → HCC (Non-SVR)	0.024	0.018	0.031	[12]
F4 → HCC (SVR)	0.005	0.001	0.009	[12]
CHC related mortality				
HCC	0.411	0.31*	0.51*	[13]
Decompensated Cirrhosis	0.216	0.162*	0.27*	[14]
Liver transplant (1st year)	0.142	0.124	0.159	[34]
Liver transplant (> 1 year)	0.034	0.024	0.043	[34]
Annual probability for liver transplantation				
From Decompensated Cirrhosis	0.033	0.017	0.049	[35]
From HCC	0.033	0.017	0.049	[35]
Discount Rate	5%	3%	5%	[36]

The prevalence used in the model is 0.5%[1] (0.3% - 0.9% in sensitivity analysis). The proportion known infected with CHC is assumed to be around 30%.[1] The spontaneous clearance is assumed to be around 28%.[31] The acceptance rate when screening is offered is assumed to be 91%.[32] The genotype distributions of the general Canadian population used in the model are G1: 67%; G2: 9% G3: 22%; G4/5/6:2%.[33] The general population distribution were obtained from 2011 Census profile.[38]

The annual screening rate under "no screening" strategy (0.68%) was derived from the total number of ordered hepatitis C antibody tests reported in 2004 in Ontario.[2]

Direct Medical Costs and Utilities

CHC-related costs were collected from a large Canadian costing study using administrative data.[39] These costs include hospitalization, ambulatory care, long-term care, physician services, and diagnostic tests costs for 22,179 patients with CHC. The costs of antiviral therapies were collected from common drug review reports.[40] The cost of screening was based on the Ontario Health Insurance (OHIP) Schedule of Benefits and Fees.[41] Table 2 (main article) summarizes the cost data used in the model.

We obtained utility data from a published study conducted by our group of over 700 patients with CHC across different CHC health states (Table 2 of main article).[42] The utilities used in the analysis were based on the published Health Utilities Index Mark 2 (HUI2) scores.[42]

Economic Assumptions

The analysis was conducted from the payer perspective and was structured as a cost-utility analysis, with outcomes expressed in quality-adjusted life-years (QALYs) and costs. Future costs and health benefits were discounted at 5% annually.[36] Non-Canadian cost data were converted to Canadian dollars at the purchasing power parity conversion rate.[43] All cost data were inflated to 2012 using the Statistics Canada Consumer Price Index for health care and personal items.[44]

Analytic Strategy

In our analysis, we first conducted a base-case analysis to estimate the expected value using deterministic calculations. We then ran a full deterministic one-way sensitivity analysis on all model parameters over the plausible ranges using the reported 95% confidence interval (CI) ranges (Tables 1, and 2 of main article). Finally we ran probabilistic sensitivity analyses (PSA) using the Monte Carlo simulation for 5,000 iterations for all three screening strategies. All probabilistic parameters and utilities used in the model are represented by beta distributions formed by the corresponding ranges as indicated in table 1 and Appendix table 1 (above); all the cost parameters are represented by gamma distributions formed by the corresponding ranges as indicated in Table 2 (main article) and Appendix Table 2 (below).

Appendix Table 2: Additional Costs used in the model				
Costs	**Baseline**	**Low***	**High***	**Source**
Cost+				
Annual cost CHC early phase				
Age 25 – 34	$4,086	$4,005	$4,168	39
Age 35 – 44	$3,904	$2,928	$4,880	39
Age 45 – 54	$4,608	$3,456	$5,760	39
Age 55 – 64	$5,564	$4,173	$6,955	39
Annual cost CHC late phase				
Age 25 – 34	$10,387	$8,676	$12,436	39
Age 35 – 44	$12,105	$9,079	$15,131	39
Age 45 – 54	$14,658	$10,994	$18,323	39
Age 55 – 64	$12,389	$9,292	$15,486	39
Annual cost CHC pre-death phase				
Age 25 – 34	$43,136	$36,757	$50,620	39
Age 35 – 44	$35,693	$26,770	$44,616	39
Age 45 – 54	$41,999	$31,499	$52,499	39
Age 55 – 64	$52,320	$39,240	$65,400	39
Annual cost non-CHC before pre-death phase				
Age 25 – 34	$1,640	$1,607	$1,672	39
Age 35 – 44	$1,820	$1,365	$2,275	39
Age 45 – 54	$2,372	$1,779	$2,965	39
Age 55 – 64	$3,942	$2,957	$4,928	39
Annual cost non-CHC pre-death phase				
Age 25 – 34	$39,391	$34,937	$44,414	39
Age 35 – 44	$42,468	$31,851	$53,085	39
Age 45 – 54	$45,396	$34,047	$56,745	39
Age 55 – 64	$44,730	$33,548	$55,913	39
***Note:** 2012 Canadian dollars				

Model Validation

For validation purposes, we ran our model using the baseline parameter values. In Appendix 3, we compared the predicted outcomes of our model against external studies.[35,45,46] These outcomes included: probability of progression to cirrhosis and probability of liver-death. Our model results closely matched results of the external studies.[35,45,46]

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