Recommendations on Screening for Hepatitis C

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1. Background and Objective

The Hepatitis C virus (HCV) is a virus that attacks the liver and can cause liver disease.\(^1\) It is estimated that 3% of the world’s population has a chronic hepatitis C virus infection.\(^2\) In 2011, it was estimated that 0.64% of Canadians, or approximately 220,000 persons, had chronic HCV infection, but that 44% of cases were not diagnosed.\(^3\) Individuals living with undiagnosed HCV infection remain infectious and can potentially transmit the virus to others through blood-to-blood contact.\(^1\)

The Canadian Task Force on Preventive Health Care (CTFPHC) aims to develop recommendations on screening for hepatitis C informed by two systematic reviews of published literature:

1. A systematic review of published research evidence on the clinical effectiveness (i.e. impact on patient important outcomes), harms, cost-effectiveness, and associated patient preferences and values of screening for HCV infection in asymptomatic non-pregnant adults. This review will also examine the diagnostic test accuracy of enzyme-linked immunoassay (ELISA) version 3.0 compared with a reference standard PCR test for detecting HCV infection in this population. This report will be prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH).

2. A systematic review of published research evidence on the effectiveness and harms of treatment in non-pregnant, treatment-naive adults. This report will be prepared by scientific staff at the Public Health Agency of Canada (PHAC), Centre for Chronic Disease Prevention, Prevention Guidelines Division.

If direct studies evaluating the effectiveness of screening for HCV are not available, the CTFPHC will build a model to link screening test accuracy data to evidence about downstream consequences (i.e. patient important outcomes). These data will be used as indirect evidence to inform recommendations on screening for hepatitis C.

2. Previous CTFPHC Recommendations and Other Guidelines

The CTFPHC has not yet published recommendations on screening for HCV infection. Other groups with recommendations from the past 5 years are listed in Table 1 below.

<table>
<thead>
<tr>
<th>Group (Guideline name, year of publication)</th>
<th>Recommendations</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO (Guidelines for the Screening, Care and Treatment of Persons with)</td>
<td>It is recommended that HCV serology testing be offered to individuals who are part of a population with high HCV seroprevalence or who have a history of HCV risk exposure/behaviour.</td>
<td>Strong recommendation, moderate quality evidence</td>
</tr>
</tbody>
</table>
The USPSTF recommends screening for hepatitis C virus (HCV) infection in persons at high risk for infection. Persons who are at risk because of potential exposure before universal blood screening and are not otherwise at increased risk need only be screened once. Persons with continued risk for HCV infection (injection drug users) should be screened periodically. The USPSTF also recommends offering 1-time screening for HCV infection to adults born between 1945 and 1965.

B grade: The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.

### 3. Current Clinical Practice

An initial screening test is conducted to detect HCV antibodies in the blood. If the screening test is positive, an additional blood test is conducted to detect HCV RNA in the blood to confirm current infection with HCV. Currently, there are no national or provincial screening programs in Canada for HCV infection. In 2009, the College of Family Physicians of Canada and PHAC recommended that anyone with risk behaviours or potential exposures to HCV and those with clinical clues that raise suspicion of possible HCV infection receive testing. However, evidence suggested that risk-factor based testing have failed to identify a large proportion of infected people, possibly due to inaccurate reporting of risk-status by patients or lack of time and expertise necessary to conduct a proper risk assessment by health providers. So in 2012, the Canadian Liver Foundation issued a statement recommending that all adults born between 1945 and 1975 be tested once for HCV infection.

Treatment of HCV infection is through antiviral therapy and effectiveness is often evaluated by sustained virological response (SVR), or undetectable serum levels of HCV RNA, after a defined period post-treatment. Until 2011, the standard of care for treatment of chronic HCV infection was pegylated interferon alpha + ribavirin (PR) administered for 48 weeks, resulting in SVR rates between 40%-80%, depending on the HCV genotype of the patient. Since then, the standard of care has changed due to regulatory approvals for use of direct-acting antivirals (DAAs) such as boceprevir, telaprevir, simeprevir and sofosbuvir, which, in combination with PR, offer substantial improvement in SVR rates compared to PR alone. Besides improvements in SVR rates, some newer treatments are interferon-free, resulting in fewer side effects, or are all-oral treatments that reduce the burden on patients compared to injection-based treatments.
4. Research Questions, Ranking of Outcomes, Eligibility Criteria, and Analytical Framework

4.1 Research Questions
The research questions and analytical framework have been developed by members of the CTFPHC HCV working group and focus on the impact that screening and treatment for HCV infection would have on patient important outcomes. The findings from these research questions will be used to inform the CTFPHC recommendations on screening for hepatitis C and are as follows:

4.1.1 Research Questions: Hepatitis C virus (HCV) Screening (CADTH review)

KQ1. What is the clinical effectiveness of screening for HCV infection in asymptomatic, non-pregnant, treatment-naive adults with unknown liver enzyme values?
KQ2. What is the frequency of harms associated with screening for HCV infection in asymptomatic, non-pregnant, treatment-naive adults with unknown liver enzyme values?
KQ3. What is the cost-effectiveness of screening for HCV infection in asymptomatic, non-pregnant, treatment-naive adults with unknown liver enzyme values in Canada? The CTFPHC ranked this outcome as important (6) and, thus, will be considered for guideline decision making. See section 4.2 for a description of the process that was followed to rank outcomes.
KQ4. What are the patients’ preferences and values regarding HCV infection screening of asymptomatic, non-pregnant, treatment-naive adults with unknown liver enzyme values?

Enzyme-Linked Immunosorbent Assay (ELISA) Version 3.0 Test
KQ5. What is the diagnostic test accuracy of ELISA version 3.0 test, as compared with the reference standard of PCR testing, for detecting HCV infection in asymptomatic, non-pregnant, treatment-naive adults with unknown liver enzyme values?

4.1.2 Research Questions: Hepatitis C virus (HCV) Treatment (PHAC review)

KQ6. What is the comparative clinical benefit of treatment regimens for patients diagnosed with chronic hepatitis C (CHC) infection (genotype 1 to 6) who are treatment naive?
KQ7. What are the harms associated with treatment regimens for patients diagnosed with chronic hepatitis C (CHC) infection (genotype 1 to 6) who are treatment naive?

4.2 Outcomes Rankings
Outcomes of interest have been selected and ranked for clinical importance by members of the CTFPHC HCV working group and by a sample of 19 adults belonging to hepatitis C screening and treatment populations in Canada (i.e. patients). The input from patients were gathered and summarized by an
independent research group with expertise in knowledge translation from St. Michael’s Hospital, Toronto, Ontario.\textsuperscript{15}

Lay language outcomes definitions are provided in Appendix A.

The numbers in Tables 2 to 5 indicate the Grading of Recommendations Assessment, Development and Evaluation (GRADE) rankings for each outcome (i.e., 7-9 indicate critical outcomes; 4-6 indicate important outcomes; and 1-3 indicate outcomes that are not important and therefore not included here).\textsuperscript{16}

**Table 2: Outcomes Rankings for Clinical Utility of Screening for HCV Infection**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CTFPHC HEP C working group</th>
<th>Patient Preferences Part 3 Survey\textsuperscript{15}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality due to HCV infection</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Morbidity due to HCV infection</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Hepato-cellular carcinoma</td>
<td>8</td>
<td>8.5</td>
</tr>
<tr>
<td>Rate of liver transplant</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Quality of life</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Reduced HCV transmission</td>
<td>7</td>
<td>8.5</td>
</tr>
<tr>
<td>Sustained or improved virological response rates</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Behavioural changes to improve health outcomes</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Histological improvements</td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>

**Table 3: Outcomes Rankings for Harms of Screening for HCV Infection**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CTFPHC HEP C working group</th>
<th>Patient Preferences Part 3 Survey\textsuperscript{15}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overdiagnosis/overtreatment</td>
<td>7</td>
<td>6.5</td>
</tr>
<tr>
<td>False Positives</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>False Negatives</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Harms of biopsy</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Effects in insurance premiums</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Labeling</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Abuse or violence</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Partner Discord</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
Table 4: Outcomes Rankings for Treatment benefits

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CTFPHC Hep C working group</th>
<th>Patient Preference Part 3 Survey\textsuperscript{15}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (hepatic)</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Reduced HCV transmission</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Hepatic decompensation</td>
<td>8</td>
<td>8.5</td>
</tr>
<tr>
<td>Need for liver transplantation</td>
<td>8</td>
<td>8.5</td>
</tr>
<tr>
<td>Sustained virological response</td>
<td>6</td>
<td>8.5</td>
</tr>
<tr>
<td>Quality of life</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Improvement in liver histology</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Mortality (all cause)</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 5: Outcomes Rankings for Treatment harms

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CTFPHC Hep C working group</th>
<th>Patient preference Part 3 Survey\textsuperscript{15}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal due to adverse events</td>
<td>6</td>
<td>6.5</td>
</tr>
<tr>
<td>Psychological adverse events</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5</td>
<td>6.5</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Anemia</td>
<td>5</td>
<td>6.5</td>
</tr>
<tr>
<td>Rash</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

The CTFPHC also ranked “resource use” as an important outcome (ranking of 6) and, thus, will be considered for guideline decision making.
4.3 Eligibility Criteria
The inclusion and exclusion criteria that will be used to select studies to answer the research questions are summarized in the respective protocols.

4.3.1 Eligibility Criteria: Hepatitis C virus (HCV) Screening (CADTH review)

The inclusion/exclusion criteria for research questions 1 through 5 related to the effectiveness of screening can be found in Tables 1 and 2 in the protocol developed by CADTH http://www.cadth.ca/screening-hepatitis-c-systematic-review-and-meta-analysis..

4.3.2 Eligibility Criteria Hepatitis C virus (HCV) Treatment (PHAC review)

The inclusion/exclusion criteria for research questions 6 and 7 related to the effectiveness of treatment can be found in Table 1 in the protocol developed by PHAC http://www.canadiantaskforce.ca/ctfphc-guidelines/2015-hepatitis-c/protocol.
4.4 Figure 1: Analytic Framework

The analytic framework that will be used to develop the CTFPHC recommendations on screening for hepatitis C is shown below. The framework includes the population, the intervention and the patient-related outcomes of interest.

- **KQ1**: Screening for HCV infection
  - Non-pregnant adults
  - Treatment for HCV

- **KQ2**: Asymptomatic non-pregnant adults with unknown liver enzyme values
  - Overdiagnosis and overtreatment; harms of biopsy; effect on insurance premium; abuse or violence; labeling; anxiety; partner discord
  - Screening test accuracy: (e.g., sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio, diagnostic odds ratio, or area under the ROC curve [AUC]); Prevalence of HCV in screen positive and negative in relevant populations

- **KQ3**: Willingness to be screened and factors considered in decisions to be screened
  - Incremental cost-effective ratio [ICER]; incremental cost utility ratio [ICUR]; cost-benefit ratio [CBR]; budget impact

- **KQ4**: Withdrawals due to adverse events; psychological adverse events; neutropenia; flu-like symptoms; anemia; rash

- **KQ5**: For screening & treatment
  - Surrogate outcomes: HCV transmission; For screening only: sustained virological response; behavioural changes to improve health outcomes; histological improvements
  - For treatment only: sustained virological response; improvement in liver histology

- **KQ6**: For screening & treatment patient important outcomes
  - Hepato-cellular carcinoma; quality of life
  - Mortality & morbidity due to HCV infection; liver transplant
  - Mortality (hepatic & all cause); cirrhosis; hepatic decompensation; need for liver transplantation

- **KQ7**: Incremental cost-effective ratio [ICER]; incremental cost utility ratio [ICUR]; cost-benefit ratio [CBR]; budget impact
5. Methods

The recommendations on screening for hepatitis C will be developed and graded according to the Grading of Recommendations Assessment, Development and Evaluation system (GRADE). After the evidence has been synthesised (quantitatively or descriptively) for each of the outcomes, CADTH and PHAC will also follow the GRADE methods to rate the quality of the evidence and to summarize and present the findings. All data will be processed with the GRADEPro software package and presented in tables. More information about the CTFPHC’s methods can be found elsewhere and on the CTFPHC website (http://canadiantaskforce.ca/methods/methods-manual).

5.1 Methods: Hepatitis C virus (HCV) Screening (CADTH review)

After the evidence has been synthesised (quantitatively or descriptively) for each of the outcomes, CADTH will assess the quality of the body of evidence using the GRADE approach. All data will be processed with the GRADEPro software package and presented in tables. The detailed methods that will be applied to address research questions 1 through 5 related to the effectiveness of screening can be found in the protocol developed by CADTH http://www.cadth.ca/screening-hepatitis-c-systematic-review-and-meta-analysis.

5.2 Methods: Hepatitis C virus (HCV) Treatment (PHAC review)

To evaluate the effectiveness of treatment the scientific staff at PHAC will use a CADTH review on the effectiveness of treatment for HCV (in progress; to be released Dec 2015) (Ref). The CTFPHC decided not to conduct its own review as the CADTH comparative effectiveness review was already underway. Once completed, the CADTH review will be assessed using AMSTAR to ensure it meets CTFPHC standards of quality. After the evidence has been synthesised (quantitatively or descriptively) for each of the outcomes, PHAC will assess the quality of the body of evidence for each outcome using the GRADE approach. All data will be processed with the GRADEPro software package and presented in tables. The detailed methods that will be applied to address research questions 6 and 7 related to the effectiveness of treatment can be found in the protocol developed by PHAC http://www.canadiantaskforce.ca/ctfphc-guidelines/2015-hepatitis-c/protocol.

5.3 Methods to link accuracy data to patient important outcomes

If direct studies evaluating the effectiveness of screening are not available, following the GRADE methods, the CTFPHC will use information drawn from test accuracy data to inform the recommendations on screening for hepatitis C. This will be done by developing a model that will link accuracy data to evidence about downstream consequences (i.e. long-term patient important outcomes). This model will incorporate data from the treatment review to be conducted by the PHAC. If no direct evidence on the effect of treatment is available, we will also model this component. The Analytical Framework below (Figure 1) describes the approach that the CTFPHC will apply to move from screening test accuracy data to patient important outcomes and summarizes the actions that follow from applying the screening test to an asymptomatic population. Where needed, prognostic studies
will be used to model patient-important outcomes. The quality of the evidence will be assessed using GRADE and will be done at each layer of evidence: accuracy data (layer 1), linked evidence (layer 2), patient important outcomes (layer 3). Following the GRADE methods, members of the CTFPHC HCV working group will assess how directly the accuracy of the screening test relates to the final patient important outcomes (Figure 2).

5.3.1 Question details (analytical PICO framework)

**Population:** Asymptomatic, treatment-naïve non-pregnant adults with unknown liver enzyme values

**Purpose:** Develop recommendations on screening for hepatitis C

**Intervention:** Screening and treatment for hepatitis C

**Comparison:** No screening

**Type of test:** ELISA version 3.0

**Linked treatments:** Treatment is typically provided to individuals if Hepatitis C virus is confirmed by PCR. Two principle treatment options will be considered: usual care and emerging direct acting anti-viral for all genotypes (1-6)

**Anticipated outcomes**

**Surrogate outcomes:** HCV transmission; sustained virological response; behavioural changes to improve health outcomes; histological improvements;

**Patient-important outcomes:** hepato-cellular carcinoma (HCC); quality of life; mortality (hepatic and all cause); morbidity due to HCV infection; liver transplant; cirrhosis; hepatic decompensation; need for liver transplant.

**Setting:** Primary care or other settings generalizable to primary care, other settings in which screening is commonly performed (e.g., blood banks, emergency department or urgent care units)

**Perspective:** Population perspective

**Subgroups:** High risk and high-prevalence groups; low risk and low-prevalence groups.
Figure 2: Analytical Framework – from screening test accuracy to patient important outcomes

The elements presented in this analytical framework represent the core items but there are other elements, such as the uptake of follow-up testing and treatment, which will also be estimated when evaluating the impact of the accuracy of the screening tools on patient outcomes.

** The results of the systematic reviews to be conducted by PHAC and by CADTH will be used as input in the model for the items highlighted in yellow.
Figure 3: GRADE methods to move from diagnostic test accuracy to patient important outcomes

**Step 1**

**Diagnostic Test Accuracy Synthesis**

STUDIES

Sensitivity, Specificity

Apply GRADE for Diagnostic Test Accuracy studies

- TP +
- FP -
- TN -
- FN +

5 factors to downgrade (factors to upgrade?)

High ★★★★★
Moderate ★★★★
Low ★★★
Very low ★★

**Step 2**

**Assess linked evidence**

Directness of the outcome

- Very uncertain
- Uncertain
- Moderate certain
- Certain
- Very certain

Lower our confidence

Mortality

- High ★★★★★
- Moderate ★★★★
- Low ★★★
- Very low ★★

Morbidity

QoL

Harms

Resources

Other

E.g. Natural History
Patients will suffer from disease without being detected or suffer from symptoms and undergo repeat testing or testing for other disease that will happen at certain rate.

SR required, full framework always needs to be developed.
1. Planned Schedule and Timeline

- Draft recommendations: April 2016
- Journal submission: June 2016
- Final published recommendations: October 2016

2. Amendments
If amendments to this document are required at any time during the development of the recommendations, reasons for changes will be recorded and reported in an appendix to this document.

3. Conflict of interest statement
None of the working group members have any known actual or perceived conflicts of interest related to these recommendations.
References


# Appendix A: Lay Language Outcomes Definitions

<table>
<thead>
<tr>
<th>Original wording</th>
<th>Lay wording</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Effectiveness</td>
<td>Impact of screening or treatment on patient important outcomes.</td>
</tr>
<tr>
<td>Anemia</td>
<td>feeling weak and tired, because people have low levels of red blood cells. Red blood cells carry oxygen to cells in the body</td>
</tr>
<tr>
<td>Anxiety</td>
<td>feeling anxious about getting a positive test result (i.e., a test result that says that a person has hepatitis C)</td>
</tr>
<tr>
<td>Behavioral changes to improve health outcomes</td>
<td>changing behaviour in ways that can improve health (e.g., be less likely to drink alcohol and use recreational injection drugs, which can cause liver damage)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>developing cirrhosis (permanent liver scarring)</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>experiencing flu-like symptoms</td>
</tr>
<tr>
<td>Hepatic decompensation</td>
<td>developing liver damage that is so severe that people will not survive without a liver transplant</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>developing liver cancer</td>
</tr>
<tr>
<td>Histological improvements</td>
<td>improvement in the health of the liver</td>
</tr>
<tr>
<td>Labelling</td>
<td>being viewed negatively by others if people end up getting diagnosed with hepatitis C. This is because people may believe that only those individuals who lead unhealthy lifestyles or use recreational drugs get hepatitis C. People may also avoid contact with someone who has hepatitis C because they may be worried that they will easily catch the virus from this individual</td>
</tr>
<tr>
<td>Morbidity due to HCV infection including hepatic cirrhosis</td>
<td>becoming seriously ill from the virus and developing cirrhosis (permanent liver scarring)</td>
</tr>
<tr>
<td>Mortality (all cause)</td>
<td>dying from causes other than liver disease</td>
</tr>
<tr>
<td>Mortality (hepatic)</td>
<td>dying from liver disease</td>
</tr>
<tr>
<td>Mortality due to HCV infection</td>
<td>dying from hepatitis C</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>being more vulnerable to infections because people have low levels of neutrophils in their body. Neutrophils are cells that help to fight infections.</td>
</tr>
<tr>
<td>Overdiagnosis</td>
<td>being diagnosed with a disease that may never cause any health problems. Because most people with hepatitis C will never develop end-stage liver disease, people may receive unnecessary treatments for hepatitis C that can harm them (see below for more information about these harms)</td>
</tr>
<tr>
<td>Partner discord, abuse, or violence</td>
<td>having problems in relationships with romantic partners if people end up getting</td>
</tr>
</tbody>
</table>
diagnosed with hepatitis C. These problems can range from having minor disagreements to being a victim of violence or abuse.

<table>
<thead>
<tr>
<th>Psychological adverse events</th>
<th>experiencing unpleasant psychological side effects (e.g., depression)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of life</td>
<td>quality of life</td>
</tr>
<tr>
<td>Rash</td>
<td>developing skin rashes</td>
</tr>
<tr>
<td>Rate of liver transplantation</td>
<td>needing a liver transplant</td>
</tr>
<tr>
<td>Reduced HCV transmission</td>
<td>being less likely to infect another person with hepatitis C</td>
</tr>
<tr>
<td>Sustained virological response rates</td>
<td>getting successfully treated for the virus so that the virus is cleared from the body. Although this isn’t a “cure”, people are less likely to develop liver cancer or die when the virus has been cleared from their body.</td>
</tr>
<tr>
<td>Withdrawals due to adverse events</td>
<td>experiencing unpleasant side effects that lead people to stop taking their medication. This can reduce the chance that the treatment will work.</td>
</tr>
</tbody>
</table>