Recommendations on Hepatitis C Screening for Adults (2017):

Guideline Presentation Speaker deck

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HEPATITIS C WORKING GROUP

The Hepatitis C Working Group included members from the Canadian Task Force on Preventive Health Care (CTFPHC) and the Public Health Agency of Canada (PHAC). Systematic reviews were conducted by the Canadian Agency for Drugs and Technologies in Health (CADTH) and PHAC. The Toronto Health Economics and Technology Assessment Collaborative conducted a modelling study, led by Dr. William Wong.

CTFPHC members of the working group include:

- Roland Grad (Chair)
- Brett Thombs
- Scott Klarenbach
- Harminder Singh
- Maria Bacchus
- Richard Birtwhistle

Public Health Agency of Canada (PHAC) members of the working group (non-voting members) include:

- Alejandra Jaramillo Garcia (Co-Chair)
- Véronique Dorais

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OVERVIEW OF WEBINAR

We will review the following:

1. Background on Hepatitis C Screening
2. Methods of the CTFPHC
3. Key Findings
4. Recommendation
5. Implementation Considerations
6. Conclusions

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SCREENING FOR HEPATITIS C: BACKGROUND

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BACKGROUND

Approximately, 0.65%-0.71% of Canadians have chronic hepatitis C virus (HCV) infection and 44% of this group may be undiagnosed. Not all people with chronic HCV infection will develop cirrhosis or signs indicative of liver disease.

Those at higher risk for HCV include individuals who inject drugs; have been incarcerated; have received a blood transfusion or organ transplant prior to 1992 in Canada; or have travelled or resided in endemic regions.

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BACKGROUND & PURPOSE OF HEPATITIS C SCREENING GUIDLINE 2017

The Public Health Agency of Canada (PHAC) and the College of Family Physicians of Canada (CFPC) recommend testing for hepatitis C in people at increased risk. There is no organized general population screening for adults who are not otherwise at increased risk for HCV in Canada.

This recommendation was developed as there are new treatments for chronic HCV infection and to help clarify conflicting messages with guideline producers from the United States.

This recommendation is intended to provide clinicians and policy-makers with guidance on screening asymptomatic Canadian adults for HCV.

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SCREENING FOR HEPATITIS C: METHODS

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METHODS OF THE CTFPHC

The CTFPHC is an independent panel of clinicians and methodologists with expertise in prevention, primary care, literature synthesis, and critical appraisal. The mandate of the CTFPHC is to apply the latest evidence in preventive health care research to primary care practice and policy across Canada.

The Hepatitis C Working Group is composed of 6 CTFPHC members who are supported by PHAC science officers and clinical experts in Hepatitis C to establish key research questions, an analytical framework, and clinical and patient outcomes.

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CTFPHC REVIEW PROCESS

The CTFPHC conducts both an (i) internal review and (ii) external review of all its guidelines. The internal review process involves the guideline working group, the full CTFPHC, and PHAC science officers.

The external review process involves the review of the protocol, systematic review, and guideline by key stakeholders including: generalist and disease specific organizations; academic peer reviewers; and Federal, Provincial and Territorial stakeholder groups. The Canadian Medical Association Journal (CMAJ), where most of the CTFPHC guidelines are published, undertakes its own independent peer review journal process.

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WHAT 'EVIDENCE' DOES THE CTFPHC CONSIDER?

The CTFPHC considered four types of evidence for the HCV guideline: direct evidence, indirect evidence, patient focus groups, and stakeholder survey results.

Direct evidence was examined through a screening review conducted by CADTH. This review examined the benefits and harms of screening, cost-effectiveness, patient preferences and values, and screening test clinical validity.

Indirect evidence was examined through a treatment review by PHAC and a modelling study completed by Dr. Wong at the Toronto Health Economics and Technology Assessment Collaborative. The treatment review focused on the benefits and harms of treatment and the modelling study considered the long term benefits of screening.

Patient preferences and values related to key outcomes were collected through patient focus groups conducted by the St. Michael's Hospital (SMH) Knowledge Translation (KT) Program.

The Feasibility, Acceptability, Cost, and Health Equity (FACE) tool was used with organizational stakeholders to gain their perspective (via survey) on the priority, feasibility, acceptability, cost, and equity of the recommendation.

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ELIGIBILITY CRITERIA: SCREENING REVIEW

In total, seven key questions were addressed by the screening and treatment reviews.

The population of interest for the Hepatitis C screening review was asymptomatic, non-pregnant, HCV treatment-naive adults 18 years or older with unknown liver enzyme values. Post-transplant patients, patients with HIV, hemodialysis patients and patients with occupational exposure were excluded from the review.

All studies in English and French were included in the review.

The CADTH screening review answered five key research questions.

(KQ1): What is the clinical effectiveness of screening for HCV infection in asymptomatic, nonpregnant, treatment-naive adults with unknown liver enzyme values?

Key Question 1 asked about clinical effectiveness of screening for HCV infection. Long-term outcomes of interest included mortality due to HCV infection, morbidity due to HCV infection, hepatocellular carcinoma (HCC), liver transplantation, or quality of life. Intermediate outcomes of interest included HCV transmission, virologic response, behavioural changes to improve health outcomes, or histological changes. Randomized control trials (RCTs), nonrandomized studies with a comparator group, or disease progression modelling studies were eligible for review.

(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?

Key question two looked at the frequency of harms associated with HCV infection. Outcomes of interest included overdiagnosis, overtreatment, false positives, false negatives, harms of follow-up tests (including biopsy), abuse or violence, or anxiety. RCTs, nonrandomized studies with or without a comparator group, or disease-progression modelling studies were eligible for review.

(KQ3): What is the cost-effectiveness of screening for HCV infection in asymptomatic, nonpregnant, treatment-naive adults with unknown liver enzyme values in Canada?

Key question three looked at cost-effectiveness of screening for HCV infection. Outcomes of interest included cost-effectiveness analysis outcomes or budget impact

analysis outcomes. RCTs, economic evaluations, and economic modelling studies were eligible for review.

(KQ4): What are patient preferences and values regarding the decision to be screened for HCV infection in asymptomatic, non-pregnant, treatment-naive adults with unknown liver enzyme values?

Key question four looked into patient preferences and values regarding the decision to be screened for HCV infection. Outcomes of interest included willingness to be screened and factors considered in decisions to be screened. Descriptive studies (i.e., surveys and qualitative studies) and mixed-methods studies were eligible for review.

(KQ5): What is the diagnostic test accuracy (DTA) of the ELISA version 3.0 test, as compared with the reference standard PCR test, for detecting HCV infection in asymptomatic, non-pregnant, treatment-naive adults with unknown liver enzyme values?

Key question five looked at the DTA of the ELISA version 3.0 test. Outcomes of interest included DTA outcomes (e.g., sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio, diagnostic odds ratio, or area under the receiver-operating characteristic curve (AUC)), detection rate, and the number needed to screen to detect one case. Cross-sectional studies were eligible for review.

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ELIGIBILITY CRITERIA: Treatment Review

The PHAC treatment review explored two key questions: comparative clinical benefit of treatments and harms associated with treatment.

The population of interest of the screening review was asymptomatic, non-pregnant, HCV treatment-naive adults 18 years or older with unknown liver enzyme values. Post-transplant patients, patients with HIV, hemodialysis patients and patients with occupational exposure were excluded from the review. All studies in English and French were included in the review. Randomized or non-randomized, controlled or uncontrolled, and intervention studies were eligible for 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 naïve?

Key question six looked at the comparative clinical benefits of treatment for HCV. Long-term outcomes of interest included mortality (hepatic & all cause), cirrhosis, hepatocellular carcinoma, hepatic decompensation, need for liver transplantation,

quality of life (all scales reported). Intermediate outcomes of interest included reduced HCV transmission, sustained virological response, and improvement in liver histology.

KQ7): What are the frequency of harms associated with treatment regimens for patients diagnosed with chronic hepatitis C (CHC) infection (genotype 1 to 6) who are treatment naïve?

Key question seven looked at the harms associated with treatment for HCV. Outcomes of interest included withdrawal due to adverse events, psychological adverse events, neutropenia, flu-like symptoms, anemia, rash.

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HOW DOES THE CTFPHC GRADE EVIDENCE?

The CTFPHC utilizes the GRADE system for providing clinical practice guideline recommendations based on a systematic review of the available evidence. The **GRADE** acronym stands for: **G**rading of **R**ecommendations, **A**ssessment, **D**evelopment and **E**valuation.

The GRADE system is composed of two main components:

1. **The quality of the evidence**: The quality of the evidence measures the degree of confidence that the available evidence correctly reflects the theoretical true effect of the intervention or service. It is graded as high, moderate, low or very low based on how likely further research is to change our confidence in the estimate of effect.
2. **The strength of recommendation:** The strength of the recommendation (strong/weak) is based on the quality of supporting evidence, the degree of uncertainty about the balance between desirable and undesirable effects, the degree of uncertainty or variability in values and preferences, and the degree of uncertainty about whether an intervention represents a wide use of resources.

How is the Strength of Recommendations Determined?

The strength of the recommendations (strong or weak) is based on four factors:

1. The quality of the supporting evidence
2. The certainty about the balance between desirable and undesirable effects
3. The certainty or variability in the values and preferences of individuals
4. The certainty about whether the intervention represents a wise use of resources

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SCREENING FOR HEPATITIS C: KEY FINDINGS

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KEY FINDINGS: SCREENING

CADTH's systematic review found no studies of the clinical effectiveness of HCV screening in the general population or in any other higher risk or higher prevalence subgroup (e.g., those born from 1950 to 1975).

The Toronto Health Economics and Technology Assessment Collaborative modelling study led by Dr. Wong modelling found that one-time screening of 100,000 individuals not at elevated risk of HCV (0.2% prevalence) prevented 20 cases of hepatocellular carcinoma over a lifetime horizon. This resulted in 40 lives saved over a lifetime horizon.

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KEY FINDINGS: TREATMENT

The PHAC review on treatment found moderate quality evidence that treatment with new direct-acting antiviral (DAA)-based regimens achieved higher sustained virologic response SVR rate than traditional regimens (Pegylated interferon) and reduced the frequency of harms. The review also found very low quality evidence that there was no difference in quality of life or all cause mortality at 36-72 weeks post-treatment.

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PATIENT VALUES AND PREFERENCES

The CADTH review of 12 observational studies examining patients' decision to be screened for HCV found: 1) patient preference findings were highly variable; and 2) stigma and access to care were importance decision making concerns.

The CTFPHC commissioned the SMH KT Program to conduct surveys and focus groups with 15 patients. The commissioned investigation found: 1) patients' placed equal value on the benefits and harms of screening; 2) reduced mortality was perceived as a very important benefit; and 3) concerns were noted about stigma and psychological adverse events from positive screening test results. These study findings reinforced those found in the CADTH review.

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RESOURCE USE

Estimated costs to screen the Canadian population for HCV would be $844 million.

If we assumed 50% off the current Canadian HCV drug list price for DAA-based regimens, it would cost approximately $1.5 billion to screen and provide treatment.

The CTFPHC places a relatively higher value on the very large impact that screening would have on healthcare budgets and the limit on funding for health care interventions supported by better evidence.

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FEASIBILITY, ACCEPTABILITY, AND EQUITY

The majority of individuals identified as having HCV by screening would not qualify for treatment in Canada because they would be asymptomatic, be in the early stages of fibrosis, and have no comorbidities.

A recommendation in favour of screening would increase the number of people with known HCV who cannot access treatment.

It is unlikely that funders would find a population-wide screening program acceptable due to the lack of health system resources for treating all those with HCV.

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RECOMMENDATION

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HEPATITIS C 2017 GUIDELINE: RECOMMENDATION

For practitioners on preventive health screening in a primary care setting we recommend against screening for HCV in adults who are not at elevated risk. This is a strong recommendation, with very low quality evidence.

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OVERALL QUALITY OF EVIDENCE

The overall quality of evidence supporting this recommendation is considered very low (i.e., highly uncertain), given the lack of direct evidence on screening for HCV in all groups of the population and that many assumptions were required by the modelling study (i.e., several model parameters were based on expert opinion).

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RATIONALE FOR DIRECTION OF RECOMMENDATION AGAINST SCREENING

There remains substantial uncertainty about the effectiveness of screening, including benefits and harms, among adults not at elevated risk for HCV in Canada.

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CTFPHC RATIONALE

This CTFPHC HCV screening recommendation places a relatively lower value on the:

1. Very low quality indirect evidence suggesting a potentially small benefit from screening;
2. Low risk of household and sexual transmission of HCV among individuals not at elevated risk;
3. Low risk of transmission through blood products given routine screening of blood and organs; and
4. Potential risk of developing end-stage liver disease and transmitting the infection despite being asymptomatic.

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On the other hand, this CTFPHC HCV screening recommendation places a relatively higher value on the:

1. Anticipated increase in harm resulting from diagnosing and treating individuals who screen positive but would have never developed HCV related disease during their lifetime;
2. False positives and false negatives, which could lead to unnecessary anxiety and/or false reassurance;
3. Very large impact that screening and treatment would have on health care budgets and associated opportunity costs;
4. Potential for screening to increase inequity, given that among those who do not meet current eligibility criteria (e.g., specific comorbidities), only wealthier individuals or those with private insurance would obtain earlier access to treatment not currently funded by government; and
5. Unknown magnitude of benefit of treatment on reducing risk of transmission.

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RATIONALE FOR STRENGTH OF RECOMMENDATION AGAINST SCREENING

We are confident of the potential for harm resulting from screening and treatment for HCV. A recommendation to screen for HCV would result in screening and treating people who would have never develop HCV related disease during their lifetime, thereby causing unnecessary anxiety and stigma.

We are confident that a recommendation to screen and therefore treat those identified as HCV positive would require substantial resources to address access to care and treatment restrictions.

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CONSIDERATIONS FOR RE-EVALUATING THE CTFPHC 2017 HEP C SCREENING GUIDELINE

This guideline may be re-evaluated as evidence on the benefit and/or harm of screening emergences (i.e., evidence on rates of transmission or evidence examining real-life consequences of screening and treating those who would have otherwise never developed complications or died from liver disease) or as other factors influencing the recommendation change (i.e., improved access to care and treatment through a significant reduction in drug prices and a successful roll out of a health system-wide treatment strategy, thereby permitting all individuals with HCV to be treated). Newer drugs will not trigger an update as higher rates of sustained virologic response (SVR) are already assumed resulting from DAA treatment regimens.

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CTFPHC GUIDELINE VS. OTHER RECOMMENDATIONS

The CTFPHC HCV guideline recommendation aligns with guidelines from the World Health Organization (WHO); the National Institute for Health and Care Excellence (NICE); Immigration, Refugees and Citizenship Canada; Scottish Intercollegiate Guidelines Network (SIGN); United Kingdom National Screening Committee (NSC); and the Gastroenterological Society of Australia (GESA).

The recommendation partly aligns with guidelines from the Centres for Disease Control and Prevention (CDC) and the U.S. Preventive Services Task Force (USPSTF). These guidelines recommend birth cohort screening based on indirect evidence and a 4 times higher HCV prevalence (3.25%) in U.S. ‘baby boomers’ than Canadian ‘baby boomers’ (0.8%).

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KNOWLEDGE GAPS

Identified knowledge gaps include:

1) Lack of high quality, population-based prevalence data on chronic hepatitis C in Canada among the general population and in key sub-groups;
2) Unavailable trial data on the benefits and harms of screening in asymptomatic populations;
3) Unavailable trial data on the benefits of earlier versus later treatment (F0-F1 treatment versus F2, F3, or F4);
4) Lacking evidence on the progression of chronic HCV to cirrhosis and to end-stage liver disease; and
5) Inadequate evidence on the progression of disease despite sustained virologic response(SVR).

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SCREENING FOR HEPATITIS C: IMPLEMENTATION CONSIDERATIONS

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The CTFPHC has included important implementation considerations within its HCV guideline. More persons in subgroups such as the Indigenous population (3% prevalence) and the cohort born from 1950 to 1975 (0.8% prevalence) are diagnosed with chronic HCV. These populations have a higher proportion of individuals at higher risk for HCV because of identifiable risk factors. If we account for the subgroups of individuals who are at an elevated risk for HCV transmission due to risk behaviours, prevalence in these groups would be similar to the lower risk population. For example, removing from the Indigenous population people who inject drugs would reduce the HCV prevalence from 3% to 0.5%. Individuals from the Indigenous population who are not otherwise at increased risk are, therefore, included in the present task force guidance, which recommends against screening adults who are not at elevated risk. In the judgment of the task force, neither Indigenous people nor members of the 1950–1975 birth cohort should be screened for HCV in the absence of other characteristics that would place them at increased risk for HCV. More evidence would be needed before making a recommendation about birth cohort testing, separate from adults in the general population.

IMPLEMENTATION CONSIDERATIONS

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A joint 2009 recommendation from CFPC and PHAC addressed those individuals who are at increased risk. Populations targeted in the CFPC/PHAC guideline include people who inject drugs (currently or in the past); individuals who have been incarcerated; individuals who may have been exposed to contaminated blood, blood products or medical equipment; and those who have travelled or resided in endemic regions. The CFPC/PHAC guidance suggests testing for HCV in "anyone with risk behaviours for HCV, with potential exposure to HCV, and/or with clinical clues suspicious for HCV." The CTFPHC supports this recommendation.

Some immigrants are at increased risk for HCV due to iatrogenic exposure in their country of origin (e.g., lack of standard precautions, or as a result of medical or dental procedures with contaminated equipment) and not necessarily from injection drug use or other higher-risk behaviours. The CTFPHC-supported CFPC/PHAC guidance recommends testing for HCV in individuals who were "born, traveled or resided in a region in which HCV infection is more common." A list of endemic countries and a related map are provided in Appendix 6 of the published guideline.

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KT TOOLS

The CTFPHC creates KT tools to support the implementation of guidelines into clinical practice. A KT tool has been developed to help clinicians understand and implement the hepatitis C screening guideline. This tool will be freely available for download in both French and English on the CTFPHC website at www.canadiantaskforce.ca

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SCREENING FOR HEPATITIS C: CONCLUSIONS

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CONCLUSIONS

The CTFPHC recommends against screening adults not at elevated risk for HCV.

In Canada, the prevalence of HCV is less than 1% and the direct evidence of the benefits and harms of screening adults for HCV is not available.

Not screening for HCV will focus our limited health care resources to test (and treat) individuals at elevated risk for HCV and to provide other medical interventions that are proven to be of benefit.

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More Information

For more information on the details of this guideline or to access the KT tool, please refer to the CTFPHC website at www.canadiantaskforce.ca**.**

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Questions and Answers

Thank you