CADTH Health Technology Assessment

Screening for Hepatitis C Virus: A Systematic Review and Meta-analysis — Project Protocol

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RATIONALE AND POLICY ISSUES

Worldwide, it is estimated that 130 to 150 million individuals live with a chronic hepatitis C virus (HCV) infection and 350,000 to 500,000 deaths occur each year as a result of hepatitis C–related liver diseases.[1] In 2011, an estimated 220,697 Canadians were living with chronic HCV infection.[2] The rate of reported HCV cases in 2009 was 33.7 per 100,000 and ranged from 15.5 per 100,000 in Nunavut to 107.0 per 100,000 in the Yukon Territory.[3] The majority of cases (76%) were reported in Ontario, British Columbia, and Quebec.[3] Of those living with HCV, an estimated 21% to 70% are unaware of their condition.[2-6]

HCV is a single-stranded *Flaviviridae* ribonucleic acid (RNA) virus that is transmitted primarily through injected or infused contaminated serum.[4,7] There are six major genotypes, labelled 1 through 6, with genotype 1 being the most common in Canada.[6,7] Certain demographics, such as illicit drug users, prisoners, and persons with HIV, are associated with a higher than average transmission risk.[8] There is a high risk of transmission through contaminated drug paraphernalia, unregulated drug transfusion, and unregulated tattooing and piercing. In pregnant women, risk of transmission from mother to fetus is generally low, except in the presence of HIV.[8] Similarly, risk of transmission during sexual activity is low, except when there are existing sexually transmitted infections or tissue abrasions.[8]

Treatment

Treatment for HCV infection has evolved with time. Previously, interferon-alfa (IFN-alfa) was the sole means of treating HCV infection. By 2000, it was understood that the addition of ribavirin increased the rate of sustained virologic response (SVR) and the addition of inert polyethylene glycol increased the half-life of IFN-alfa (pegylated IFN-alfa [pegIFN-alfa]). A combination of pegIFN-alfa and ribavirin became the standard of treatment, given over a 24-week period to patients with HCV genotypes 2 or 3 or 48 weeks to patients with genotypes 1, 4, 5, or 6.[6] The effect of polyethylene glycol on SVR is genotype-specific.[6,9] Since 2011, antiviral therapy has included direct-acting antiviral (DAA) agents in combination with pegIFN and ribavirin.[9,10] The introduction of DAAs such as boceprevir and telaprevir are associated with SVR rates of 65% to 75% relative to dual therapy.[9] However, increased toxicity and adverse drug interactions are among side effects linked to triple therapy.[6]

Screening and Diagnosis

Early HCV infection is often asymptomatic, which adds a level of complexity to its detection. Clinicians may use enzyme immunoassay tests to detect HCV antibodies in serum; however, the production of antibodies may be delayed by up to 12 weeks following infection (leading to false negatives in patients with early acute stage infection or in immunosuppressed patients). Infection may spontaneously clear or not be present at all.[2,3,9,11] Enzyme immunoassay tests therefore require confirmation by a test with higher sensitivity. In some cases, clinicians may have to rely on testing for elevated levels (> 10 times the upper limit of normal levels) of alanine aminotransferase (ALT) associated with inflammation of the liver, as a surrogate marker for HCV infection.[9] Irrespective of the initial method for detecting signs of positive HCV infection, confirmation of the presence of the virus' RNA with a sensitive molecular method (with lower limit of detection < 15 international units per millilitre), such as the polymerase chain reaction (PCR) test, is necessary.[11] Diagnosis with the PCR test is definitive.

In an average of 25% to 33% of patients, HCV spontaneously clears without treatment, whereas in the remainder of patients, the infection can become chronic and lead to liver damage (cirrhosis), liver cancer, liver failure, and death.[4,11,12] Detecting early signs of HCV may lead to

treatment before patients develop serious and life-threatening conditions.[13] The importance of screening for HCV infection in Canada is apparent, given that up to 70% of the Canadian population who are living with HCV are unaware of their condition.[6] However, evidence on the benefits, harms, costs, and associated patient perspectives of screening with currently available tests in the Canadian population remains to be explored.

Objectives

This project will involve a systematic review of published research evidence on the clinical effectiveness, harms, cost-effectiveness, and associated patient preferences and values of screening for HCV infection in asymptomatic non-pregnant adults; as well as of the diagnostic test accuracy of one screening test available in Canada, the enzyme-linked immunosorbent assay (ELISA) version 3.0 test, compared with the reference standard PCR test, for detecting HCV infection in the same population.

RESEARCH QUESTIONS

The systematic review will address the following questions:

Hepatitis C Virus Screening

Q1. What is the clinical effectiveness of screening for HCV infection in asymptomatic, non-pregnant, treatment-naive adults with unknown liver enzyme values?
Q2. What is the frequency of harms associated with screening for HCV infection in asymptomatic, non-pregnant, treatment-naive adults with unknown liver enzyme values?
Q3. What is the cost-effectiveness of screening for HCV infection in asymptomatic, non-pregnant, treatment-naive adults with unknown liver enzyme values in Canada?
Q4. 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?

Enzyme-Linked Immunosorbent Assay Version 3.0 Test

Q5. 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?

METHODS

Search Strategy

The search strategy described here applies to all research questions. The literature search will be performed by an information specialist using a peer-reviewed search strategy according to the PRESS checklist. Published literature will be identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; The Cochrane Library via Wiley; and PubMed. The search strategy will consist of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Grey literature (literature that is not commercially published) will be identified by searching the *Grey Matters* checklist,[14] which includes the websites of regulatory agencies, health technology assessment agencies, clinical guideline repositories, and professional associations. Google and other Internet search engines will be used to search for additional Web-based materials.

Methodological filters will not be applied to limit retrieval by study design. Publication year will be limited to January 2000 to present. Where possible, retrieval will be limited to the human population and to the English and French languages. Conference abstracts, dissertations, editorials, and guidelines will be excluded from the search results. Bi-weekly alerts will be established to update the searches until the publication of the final report. Regular search updates will be performed on databases that do not provide alert services. The searches will be supplemented by reviewing the bibliographies of key papers (including relevant systematic reviews) and through contacts with appropriate content experts and industry. See APPENDIX 1 for the detailed literature search strategy.

Eligibility Criteria

Table 1 and Table 2 present the eligibility criteria for included studies. Studies will be considered for inclusion if results are reported for asymptomatic, treatment-naive, non-pregnant adults who are at least 18 years old and have unknown liver enzyme values. Studies enrolling mixed categories of participants will be included if they report results for asymptomatic patients separately. Studies that do not specify pregnancy status of adults will also be included. For clinical effectiveness (Q1), harms (Q2), cost-effectiveness (Q3), and patient preferences (Q4), the intervention of interest is any screening method, and the comparator is no screening. For DTA (Q5), the index test is the ELISA version 3.0 test and the reference standard is the dichotomous PCR test.

Outcomes of interest were selected and ranked for clinical importance by members of the Canadian Task Force on Preventive Health Care's HCV working group and by a sample of 19 adults who represent a cross-section of the general population (including people with and without HCV infection).[15] The input from these 19 adults was gathered by an independent research group with expertise in knowledge translation at St. Michael's Hospital, Toronto, Ontario. All outcomes ranked as critical (scores 7 to 9) or important (scores 4 to 6) by at least one of the groups are included. Outcomes of interest for clinical effectiveness (Q1) are mortality due to HCV infection, morbidity including cirrhosis (compensated or decompensated) due to HCV infection, hepatocellular carcinoma, liver transplantation, quality of life, HCV transmission, virologic response, behavioural changes to improve health outcomes, and histological changes. For harms (Q2), the outcomes are overdiagnosis, overtreatment, false positives, false negatives, harms of follow-up tests (including biopsy), abuse or violence, and anxiety. Other outcomes, such as change in insurance premiums, labelling, and partner discord, will also be included if relevant data are located within the planned search strategy. Cost-effectiveness

analysis outcomes are relevant to cost-effectiveness (Q3); for example, the incremental cost-effectiveness ratio (ICER) and willingness to be screened and factors considered in decisions to be screened are relevant to patient preferences (Q4). For DTA (Q5), all diagnostic test accuracy outcomes are considered. Table 1 outlines the inclusion criteria.

Studies will be included if they are done within primary care or other settings generalizable to primary care, and settings in which screening is commonly performed (for example, emergency department and urgent care units). The question on cost-effectiveness (Q3) applies only to Canada, and therefore only data generated in Canada will be included. For all other questions, studies from any country will be included.

To be included as part of the body of evidence for clinical effectiveness (Q1), studies must be randomized controlled trials (RCTs), non-randomized studies with a comparator group, or disease-progression modelling studies. If no comparative studies are found, the project team may decide to expand the study selection to include non-comparative studies (i.e., single-arm studies). For harms (Q2), studies will include RCTs, non-randomized studies with or without a comparator group, and disease-progression modelling studies. RCTs, economic evaluations, and economic modelling studies will apply to cost-effectiveness (Q3), and qualitative studies, surveys, and mixed-methods studies will apply to patient preferences (Q4). Cross-sectional studies (sometimes known as cohort type accuracy studies) designed to evaluate diagnostic test accuracy will apply to DTA (Q5). If no cross-sectional studies are found, two-gate or case-control type accuracy studies will be considered. Studies designed with the intent to evaluate DTA, with any time interval between the index and reference tests, will be included. Prognostic or predictive accuracy studies will not be included.

Screening and Selecting Studies for Inclusion

Two reviewers will independently screen titles and abstracts relevant to the research questions and compare their results. Full texts of potentially relevant articles identified through the initial screen will be retrieved and independently assessed for possible inclusion based on the pre-determined selection criteria outlined in Table 1 and Table 2. See APPENDIX 2 for the full-text screening checklist. The two reviewers will then compare their chosen included and excluded studies. Disagreements will be resolved through discussion or third-party consultation until consensus is reached. The study selection process will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.[16] Based on the search strategy, multiple flow charts may be created. APPENDIX 3 reports the PRISMA flow chart.

Exclusion Criteria

Studies will be excluded if they do not meet the selection criteria. Duplicate publications, narrative reviews, case series, case reports, conference abstracts, and editorials will be excluded from the assessment. Multiple publications, such as companion reports of the same study, will be excluded unless they provide additional information of interest and fulfill the remaining eligibility criteria listed in Table 1 and Table 2. When data are extracted from companion reports, they will be used for supplementary material only. Studies will be excluded if they report on screening for HCV infection in pregnant women, post-transplant patients, patients with HIV, hemodialysis patients, or patients with occupational exposure without separately reporting results for asymptomatic, non-pregnant, treatment-naive adults. A list of excluded studies, with reasons for exclusion, will be provided for each research question.

TABLE 1: STUDY ELIGIBILITY CRITERIA FOR CLINICAL EFFECTIVENESS (Q1), HARMS (Q2), COST-EFFECTIVENESS (Q3), AND PATIENT PREFERENCES (Q4)

<table>
<tr><th>Clinical Effectiveness (Q1)</th><th>Harms (Q2)</th><th>Cost-effectiveness (Q3)</th><th>Patient Preferences (Q4)</th></tr>
<tr><td colspan="4">Population: Asymptomatic, non-pregnant, treatment-naive adults ≥ 18 years with unknown liver enzyme values
Exclusions: Post-transplant patients, patients with HIV, hemodialysis patients, patients with occupational exposure</td></tr>
<tr><td colspan="4">Intervention: Any screening method for HCV infection</td></tr>
<tr><td colspan="4">Comparator: No screening</td></tr>
<tr><td>Outcomes: Long-term outcomes: Mortality due to HCV infection, morbidity (including compensated or decompensated cirrhosis) due to HCV infection, HCC, liver transplantation, or quality of life.

Intermediate outcomes: HCV transmission, virologic response, behavioural changes to improve health outcomes, or histological changes.</td><td>Outcomes[a]: Overdiagnosis, overtreatment, false positives, false negatives, harms of follow-up tests (including biopsy), abuse or violence, or anxiety.</td><td>Outcomes: Cost-effectiveness analysis outcomes (e.g., ICER, ICUR, CBR) or budget impact analysis outcomes.</td><td>Outcomes: Willingness to be screened and factors considered in decisions to be screened.</td></tr>
<tr><td colspan="4">Settings: Care settings: Primary care or other settings generalizable to primary care; other settings in which screening is commonly performed (e.g., emergency department, urgent care units)

Country setting (Q3 [cost-effectiveness]): Canada</td></tr>
<tr><td>Study Designs[b]: RCTs, non-randomized studies with a comparator group, or disease-progression modelling studies</td><td>Study Designs[b]: RCTs, non-randomized studies with or without a comparator group, or disease-progression modelling studies</td><td>Study Designs[b]: RCTs, economic evaluations, and economic modelling studies</td><td>Study Designs[b]: Descriptive studies (surveys, qualitative) and mixed-methods studies</td></tr>
</table>

Clinical Effectiveness (Q1)	Harms (Q2)	Cost-effectiveness (Q3)	Patient Preferences (Q4)
Languages: English and French			
Search Time Frame: As of January 1, 2000			

CBR = cost-benefit ratio; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; RCT = randomized controlled trial.
[a] If data relevant to change in insurance premiums, labelling, or partner discord are located within the planned search, it will be included in this review. It is possible that research into the impact of HCV screening on these outcomes is published in databases, not included in our planned search strategy.
[b] Duplicate publications, narrative reviews, case series, case reports, and editorials will be excluded from the assessment. Multiple publications (such as companion reports) of the same trial are also excluded, unless they provide additional information of interest and fulfill the remaining study eligibility criteria.

TABLE 2: STUDY ELIGIBILITY CRITERIA FOR DTA

DTA (Q5)
Population: Asymptomatic, non-pregnant, treatment-naive adults ≥ 18 years with unknown liver enzyme values *Exclusions:* Post-transplant patients, patients with HIV, hemodialysis patients, patients with occupational exposure
Index Test: ELISA version 3.0 test
Reference Standard: Qualitative dichotomous (positive-negative) PCR test
Outcomes: DTA outcomes (e.g., sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio, diagnostic odds ratio, or AUC), detection rate, number needed to screen to detect 1 case
Settings: *Care settings:* Primary care or other settings generalizable to primary care; other settings in which screening is commonly performed (for example, emergency department, urgent care units)
Study Designs[a]: Cross-sectional[b]
Languages: English and French
Search Time Frame: As of January 1, 2000

AUC = area under the receiver-operating characteristic curve; DTA = diagnostic test accuracy; ELISA = enzyme-linked immunosorbent assay; PCR = polymerase chain reaction; RCT = randomized controlled trial.
[a] Duplicate publications, narrative reviews, case series, case reports, and editorials will be excluded from the assessment. Multiple publications (such as companion reports) of the same trial are also excluded, unless they provide additional information of interest and fulfill the remaining study eligibility criteria.
[b] Cross-sectional studies may be referred to as cohort type accuracy studies. If no cross-sectional studies are found, two-gate or case-control accuracy studies will be included. Prognostic or predictive accuracy studies will not be included.

Data Collection and Extraction

Two reviewers will independently extract data from each selected study report and enter the information into an Excel spreadsheet. Disagreements will be resolved through discussion or third-party consultation until a consensus is reached. Data from figures will not be used if the data points are not explicitly stated. If necessary, the reviewers will attempt to contact authors of included studies to provide any missing information, clarify any issues, or verify extracted data. Samples of data extraction forms have been designed and can be found in APPENDIX 4, APPENDIX 5, and APPENDIX 6. The forms are intended to document characteristics of studies, included patients (including demographic information), interventions, comparators, settings, countries where research took place, when the study was conducted, outcomes of interest, and author's conclusions.

Before beginning data extraction, in a pilot test, each reviewer will independently extract data from two studies for each form. Both reviewers will compare their results. If necessary, amendments to the data extraction forms will be made and data from another two studies will be extracted, until sufficient agreement is reached.

Outcomes and Prioritization

There are currently multiple outcomes of interest for all questions. All outcomes listed are considered important or critical and will therefore be included in the review.

Critical Appraisal and Risk of Bias Assessment

Following data extraction, two reviewers will independently assess the quality of each included study using the assessment tool that is most appropriate, as described below.

RCTs will be appraised with the Cochrane Risk of Bias tool,[17] and observational studies will be appraised using A Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI).[18] For non-comparative studies, a formal critical appraisal will not be done; however, comments will be made on the overall quality of the studies. Economic analyses and economic modelling studies will be evaluated using the Drummond Checklist.[19] The critical appraisal of qualitative studies will follow criteria outlined in the Critical Appraisal Skills Program (CASP) checklist.[20] In the absence of a validated, English critical appraisal tool for cross-sectional surveys, we will assess the quality of any included surveys based on the clarity and appropriateness of study methods, with particular attention to sampling decisions, the validity and reliability in data collection methods, and the comprehensive reporting of results. The criteria are outlined in a tool shown in APPENDIX 7. Studies relevant to DTA will be assessed with the QUADAS-2 tool.[21] A modified version of the Drummond Checklist will be used to assess disease-progression modelling studies.[22] Disagreements within study appraisal between the two reviewers will be resolved through discussion or third-party consultation if consensus cannot be reached.

SUMMARY OF EVIDENCE AND DATA SYNTHESIS

Description of Study Characteristics

For each question, a narrative summary will be undertaken to report on the quantity of studies by design, country of origin, size, population, intervention, comparator, settings, and outcome measures, where applicable. Tables will accompany the narrative summary, to ensure the consistency of the presented information across all studies and facilitate study comparisons by the reader.

Summary of Critical Appraisal

A narrative summary of the results of the critical appraisals will be presented separately for each research question, including an overall impression of the quality of included studies. Tables outlining the strengths and limitations of each study will accompany the narrative summary, to ensure consistency of presented information across all studies and facilitate study comparisons by the reader. Separate tables will be created for each study design, or tabulated data will be separated within the same table by the use of subheadings.

Data Synthesis

Tables will be created to summarize quantitative findings for each outcome listed in Table 1. Data will be synthesized separately for each question, by outcome.

Clinical Effectiveness (Q1)

Where possible, meta-analyses will be carried out to derive pooled estimates of effect for each outcome of interest reported by two or more studies. Dichotomous outcomes will be summarized using relative risks and 95% confidence intervals (CIs), and analyses of continuous outcomes will be summarized using differences in means and 95% CIs. When different scales are used, analyses of continuous outcomes will be summarized as standardized mean differences with 95% CIs. Outcomes of interest are:

- Mortality rate due to HCV infection
- Morbidity rate due to HCV infection
- Hepatocellular carcinoma rate
- Liver transplantation rate
- Quality of life measures
- HCV transmission
- Virologic response
- Behavioural changes to improve health outcomes
- Histological changes.

Evaluation of Heterogeneity

The decision on whether to meta-analyze outcome data will be based on assessments of clinical, methodological, and statistical heterogeneity across studies. Results will not be meta-analyzed in the presence of substantial heterogeneity, as described below. Clinical heterogeneity refers to variation in clinical parameters between studies — for example, timing or setting of screening — and will be evaluated in consultation with content experts. Methodological heterogeneity refers to differences in the design of studies reporting on the same outcome. Methodological heterogeneity will be minimized by combining data from similarly designed studies. For example, data from RCTs will be combined separately from non-randomized studies. Statistical heterogeneity between studies will be assessed using the I^2 test of heterogeneity. I^2 is commonly defined as the percentage of the total variation in estimated

effects that is due to heterogeneity across studies rather than to chance. An I^2 value lower than 25% is associated with low heterogeneity, with $I^2 \geq 70\%$ indicating considerable heterogeneity across studies.[17]

If sufficiently low heterogeneity ($I^2 < 25\%$) is found across studies, such that it is reasonable to assume that all studies are estimating an identical effect, the meta-analyses performed will consider a fixed effects model. For studies with I^2 between 25% and 70%, we will attempt to pool the individual study results using a random effects model. Findings will be reported as "not statistically significant" if the 95% CI of the overall estimate includes unity for dichotomous data or includes 0 for continuous data. Forest plots will be presented for all evidence syntheses to supplement reported estimates.

In the situation that outcome data cannot be quantitatively synthesized due to significant clinical, methodological, or statistical ($I^2 \geq 70\%$) heterogeneity, a narrative synthesis of the results will be performed. Point estimates and their variance (for example, means and standard deviations, or median values and ranges) will be reported for each outcome of interest in tables alongside clinical and methodological characteristics that appear to contribute to the observed heterogeneity. Patterns within and between studies will be assessed in order to describe the direction and size of observed effects, and consistency in effect across included studies.

Subgroup Analyses

Subgroup analyses will be completed when possible to evaluate the following:

- The clinical effectiveness of HCV screening based on screening method; for example, risk-based screening versus prevalence-based HCV screening versus other screening methods
- The clinical effectiveness of ELISA version 3.0 test for HCV screening versus other screening tests.

Frequency of Harms (Q2)

Where possible, meta-analyses will be carried out to derive pooled estimates of effect for each of the following outcomes of interest reported by two or more studies:

- Overdiagnosis (mean difference)
- Overtreatment (mean difference)
- False positives (relative risk)
- False negatives (relative risk)
- Harms of follow-up tests (including biopsy) (relative risk)
- Abuse or violence
- Anxiety.

Data on change in insurance premiums, labelling, or partner discord will be analyzed, if they are available.

If meta-analyses are not possible, a narrative synthesis will be conducted as described above for clinical effectiveness (Q1). Subgroup analyses by screening method (for example, risk-based versus prevalence-based) and screening test (e.g., ELISA version 3.0 test versus other tests) will be conducted if there are sufficient included studies.

Cost-effectiveness (Q3)

A narrative synthesis of the evidence on cost-effectiveness will be conducted. Data will be grouped in tables by study design, patient characteristics, or screening method. Modelling analyses will not be performed. Outcomes of interest are:

- ICER
- ICUR
- Cost-benefit ratio
- Change in budget values.

Patients' Preferences and Values (Q4)
A content analysis will be conducted, which will involve first inductively coding data line by line for both meaning and content in order to develop a coding template that represents all extracted data. The coded data will then be organized into descriptive themes that remain close to the original results, with minimal interpretation. Data within each thematic area will be summarized descriptively, noting differences across study contexts or populations, where apparent, in order to comprehensively describe patient preferences and values with regard to HCV infection screening. The analysis will not provide an interpretation of themes nor proceed to theory development.

Diagnostic Test Accuracy (Q5)
The accuracy of the ELISA version 3.0 test in detecting HCV will be evaluated relative to the qualitative dichotomous PCR test reference standard. If a sufficient number of studies is available, a summary receiver-operating characteristic curve will be used to demonstrate the relationship between sensitivity and specificity and to characterize heterogeneity across the studies.[17] Coupled forest plots depicting sensitivity and specificity values for multiple studies will be useful for visually assessing heterogeneity across studies. Outcomes of interest are:

- Diagnostic accuracy outcomes (for example, sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratios, diagnostic odds ratio, or area under the curve [AUC])
- Detection rate
- Number needed to screen to detect one case.

Sensitivity analysis will be conducted across studies to evaluate the impact of time intervals between tests on the outcomes.

All meta-analyses will be conducted using Cochrane Review Manager (RevMan) software version 5.3.

Assessment of the Overall Quality of the Evidence Using GRADE

After the evidence has been synthesized (quantitatively or descriptively) for each of the outcomes, two reviewers will independently assess the quality of the body of evidence or confidence in the effect for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[23] Disagreements will be resolved through discussion or third-party consultation until consensus is reached. All data will be processed with the GRADEpro software package and presented in tables.

Clinical Effectiveness (Q1), Frequency of Harms (Q2), and Cost-Effectiveness (Q3)
The reviewers will use relevant GRADE criteria, including overall risk of bias, inconsistency, indirectness, imprecision, publication bias, magnitude of the effect, dose-response gradient, influence of residual plausible confounding, and bias, to assess the evidence.[23]

We will describe the results using the magnitude or importance of the effect and the quality of the evidence. We will interpret the quality of evidence as:

- High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate quality: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low quality: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low quality: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Patients' Preferences and Values (Q4)

The GRADE methodology toolbox contains the Confidence in the Evidence from Reviews of Qualitative Research (CERQual) approach, which addresses the evaluation of reviews of qualitative research studies.[24] The tool will be used to evaluate the methodological limitations, relevance, adequacy of data, and coherence of the review.

Diagnostic Test Accuracy (Q5)

The reviewers will use GRADE criteria specific to DTA studies to evaluate the evidence.[25] These criteria are study design, risk of bias, indirectness, inconsistency, imprecision, and publication bias. When there is serious or very serious concern with a criterion, the evidence will be downgraded accordingly by a level or two. Upgrading for dose effect will not be performed, as questions remain about the impact of this criterion on the quality of evidence in DTA studies.

SUMMARY OF THE FINDINGS

The main findings of the review will be presented in table format, as recommended by GRADE.[23] The generalizability of findings, key limitations, and overarching conclusions will be included. The effects (including relative and absolute effects) and the quality of evidence (including reasons for the level of evidence) also will be presented.

PEER REVIEW

The protocol has been registered in the PROSPERO database and will be posted on the CADTH website. CADTH has an in-depth review process for reports, which incorporates an internal review by CADTH staff, an external review by expert peer reviewers (two clinical experts and one methodological expert), and other identified stakeholders, and the protocol is posted to the CADTH website for feedback.

AREAS FOR POTENTIAL AMENDMENTS

If amendments are required at any time during the study, reasons for changes will be recorded in a study file and subsequently reported within the final study report. If necessary, a rescreening of the previous literature search or an updated literature search will be performed to capture additional data according to the amendments.

STUDY TEAM

Dinsie Williams, CADTH (Clinical Research Officer/Project Lead/Co-author)
Elizabeth Pitre (Clinical Research Officer/Co-author)
Jordan Feld, University Health Network (Content Expert/Co-author)
Caitlyn Ford, CADTH (Information Specialist/Co-author)
Laura Weeks, CADTH (Scientific Advisor)
Sarah Jennings (Knowledge Mobilization Officer)
Adina Gottardi, CADTH (Project Manager)
Julie Polisena, CADTH (Research Manager)

CONFLICT OF INTEREST STATEMENT

None of the study team members have any known actual or perceived conflicts of interest related to this review.

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APPENDIX 1: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Ovid MEDLINE In-Process & Other Non-Indexed Citations Embase 1974 to 2015 November 12
Date of Search:	November 13, 2015
Alerts:	Bi-weekly search alerts will be run
Study Types:	Study design filters per unique question, as per protocol. See below strategy for exact applications
Limits:	Publication years 2000 to 2015 English and French language

SYNTAX GUIDE	
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.pt	Publication type
.kf	Author-provided keyword

MULTI-DATABASE STRATEGY	
Research Question 1 (Clinical Effectiveness):	
1	Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C Antibodies/ or exp Hepatitis C Antigens/
2	(hepatitis C or hepC or hep C or hepacivirus* or HCV).ti,ab,kf.
3	1 or 2
4	exp Mass screening/
5	(detect or detection or screen or screens or screened or screening).ti,ab,kf.
6	4 or 5
7	3 and 6
8	meta-analysis.pt.
9	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
10	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.

MULTI-DATABASE STRATEGY	
11	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
12	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
13	(data synthes* or data extraction* or data abstraction*).ti,ab.
14	(handsearch* or hand search*).ti,ab.
15	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
16	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab.
17	(meta regression* or metaregression*).ti,ab.
18	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
19	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
20	(cochrane or (health adj2 technology assessment) or evidence report).jw.
21	(meta-analysis or systematic review).md.
22	(comparative adj3 (efficacy or effectiveness)).ti,ab.
23	(outcomes research or relative effectiveness).ti,ab.
24	((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab.
25	or/8-24
26	(Randomized Controlled Trial or Controlled Clinical Trial).pt.
27	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
28	Multicenter Study.pt.
29	Randomized Controlled Trial/
30	Randomized Controlled Trials as Topic/
31	"Randomized Controlled Trial (topic)"/
32	Controlled Clinical Trial/
33	Controlled Clinical Trials as Topic/
34	"Controlled Clinical Trial (topic)"/
35	Clinical Trial/ or Phase 2 Clinical Trial/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/
36	Clinical Trials as Topic/ or Clinical Trials, Phase II as Topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/
37	"Clinical Trial (topic)"/ or "Phase 2 Clinical Trial (topic)"/ or "Phase 3 Clinical Trial (topic)"/ or "Phase 4 Clinical Trial (topic)"/
38	Multicenter Study/ or Multicenter Study as Topic/ or "Multicenter Study (topic)"/
39	Randomization/
40	Random Allocation/
41	Double-Blind Method/
42	Double Blind Procedure/
43	Double-Blind Studies/
44	Single-Blind Method/
45	Single Blind Procedure/

MULTI-DATABASE STRATEGY	
46	Single-Blind Studies/
47	Placebos/
48	Placebo/
49	Control Groups/
50	Control Group/
51	Cross-Over Studies/ or Crossover Procedure/
52	(random* or sham or placebo*).ti,ab,hw.
53	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
54	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
55	(control* adj3 (study or studies or trial*)).ti,ab,hw.
56	(clinical adj3 (study or studies or trial*)).ti,ab,hw.
57	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.
58	(phase adj3 (study or studies or trial*)).ti,ab,hw.
59	((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw.
60	((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw.
61	allocated.ti,ab,hw.
62	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.
63	trial.ti.
64	or/26-63
65	exp animals/
66	exp animal experimentation/
67	exp models animal/
68	exp animal experiment/
69	nonhuman/
70	exp vertebrate/
71	animal.po.
72	or/65-71
73	exp humans/
74	exp human experiment/
75	human.po.
76	or/73-75
77	72 not 76
78	64 not 77
79	epidemiologic methods.sh.
80	epidemiologic studies.sh.
81	cohort studies/
82	cohort analysis/
83	longitudinal studies/
84	longitudinal study/
85	prospective studies/
86	prospective study/
87	follow-up studies/

MULTI-DATABASE STRATEGY	
88	follow up/
89	followup studies/
90	retrospective studies/
91	retrospective study/
92	case-control studies/
93	exp case control study/
94	cross-sectional study/
95	observational study/
96	quasi experimental methods/
97	quasi experimental study/
98	validation studies.pt.
99	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab.
100	cohort*.ti,ab.
101	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti,ab.
102	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab.
103	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti,ab.
104	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti,ab.
105	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab.
106	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab.
107	(population adj3 (study or studies or analysis or analyses)).ti,ab.
108	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab.
109	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab.
110	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab.
111	((natural adj experiment) or (natural adj experiments)).ti,ab.
112	(quasi adj (experiment or experiments or experimental)).ti,ab.
113	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab.
114	(prevalence adj3 (study or studies or analysis or analyses)).ti,ab.
115	case series.ti,ab.
116	case reports.pt.
117	case report/
118	case study/
119	(case adj3 (report or reports or study or studies or histories)).ti,ab.
120	organizational case studies.sh.
121	or/79-120
122	(disease adj2 (progress* or predict* or prognosis) adj2 (Outcome* or Risk* or Model*)).ti,ab,kf.
123	(Predict* adj2 (Outcome* or Risk* or Model*)).ti,ab,kf.
124	((History or Variable* or Criteria or Scor* or Characteristic* or Finding* or Factor*) adj2 (Predict* or Model* or Decision* or Identif* or Prognos*)).ti,ab,kf.

MULTI-DATABASE STRATEGY	
125	((Prognostic or prognostic) adj2 (History or Variable* or Criteria or Scor* or Characteristic* or Finding* or Factor* or Model*)).ti,ab,kf.
126	Disease model*.ti,ab,kf.
127	Decision*.ti,ab,kf. and *Logistic Models/
128	122 or 123 or 124 or 125 or 126 or 127
129	7 and 25
130	7 and 78
131	7 and 121
132	7 and 128
133	129 or 130 or 131 or 132
134	limit 133 to english language
135	limit 133 to french
136	134 or 135
137	limit 136 to yr="2000 -Current"
138	137 use pmez
139	exp hepatitis C/ or exp Hepatitis C virus/ or exp hepatitis C antibody/ or exp hepatitis C antigen/
140	2 or 139
141	exp antibody screening/ or exp mass screening/ or exp screening/ or exp screening test/
142	5 or 141
143	140 and 142
144	25 and 143
145	78 and 143
146	121 and 143
147	128 and 143
148	144 use oemezd
149	145 use oemezd
150	146 use oemezd
151	147 use oemezd
152	148 or 149 or 150 or 151
153	152 not conference abstract.pt.
154	limit 153 to english language
155	limit 153 to french
156	154 or 155
157	limit 156 to yr="2000 -Current"
158	138 or 157
159	limit 158 to yr="2000 - 2010"
160	remove duplicates from 159
161	limit 158 to yr="2011 -Current"
162	remove duplicates from 161
163	160 or 162

MULTI-DATABASE STRATEGY	
Research Question 1 (Clinical Effectiveness; Focused on: Risk-Based Screening, Prevalence-Based Screening):	
1	Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C Antibodies/ or exp Hepatitis C Antigens/
2	(hepatitis C or hepC or hep C or hepacivirus* or HCV).ti,ab,kf.
3	1 or 2
4	(opportunistic adj2 (screen* or detect or detection or test or testing or tests)).ti,ab,kf.
5	(universal adj2 (screen* or detect or detection or test or testing or tests)).ti,ab,kf.
6	((individual or group or public or formal or informal or ongoing exposure or active or spontaneous or proactive* or preemptiv* or community or communities or open or widespread or organised or organized or target* or population focused or specific population or population based or group specific or group based or first line) adj2 (screen* or detect or detection or test or tests or testing) adj2 (program* or service or services or pathway* or path way or path ways)).ti,ab,kf.
7	((behaviour* or behavior* or risk or risks or riskbased* or prevalence) adj2 (screen*or detect or detection or test or testing or tests)).ti,ab,kf.
8	((primary care or point of care or POC or ER or ED or emergency department or emergency room) adj2 (screen*or detect or detection or test or testing or tests)).ti,ab,kf.
9	(screen* adj3 (test or testing) adj3 (antibody or antibodies)).ti,ab,kf.
10	4 or 5 or 6 or 7 or 8 or 9
11	3 and 10
12	exp hepatitis C/ or exp Hepatitis C virus/ or exp hepatitis C antibody/ or exp hepatitis C antigen/
13	2 or 12
14	10 and 13
15	11 use pmez
16	14 use oemezd
17	15 or 16
18	limit 17 to yr="2000 -Current"
19	limit 18 to english language
20	limit 19 to french
21	19 or 20
22	remove duplicates from 21
23	22 not conference abstract.pt
Research Question 1 (Clinical Effectiveness; Focused on: Enzyme Immunoassay Screening):	
1	Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C Antibodies/ or exp Hepatitis C Antigens/
2	(hepatitis C or hepC or hep C or hepacivirus* or HCV).ti,ab,kf.
3	1 or 2
4	exp Mass screening/
5	(detect or detection or screen or screens or screened or screening).ti,ab,kf.
6	4 or 5

MULTI-DATABASE STRATEGY	
7	3 and 6
8	meta-analysis.pt.
9	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
10	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
11	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
12	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
13	(data synthes* or data extraction* or data abstraction*).ti,ab.
14	(handsearch* or hand search*).ti,ab.
15	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
16	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab.
17	(meta regression* or metaregression*).ti,ab.
18	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
19	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
20	(cochrane or (health adj2 technology assessment) or evidence report).jw.
21	(meta-analysis or systematic review).md.
22	(comparative adj3 (efficacy or effectiveness)).ti,ab.
23	(outcomes research or relative effectiveness).ti,ab.
24	((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab.
25	or/8-24
26	(Randomized Controlled Trial or Controlled Clinical Trial).pt.
27	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
28	Multicenter Study.pt.
29	Randomized Controlled Trial/
30	Randomized Controlled Trials as Topic/
31	"Randomized Controlled Trial (topic)"/
32	Controlled Clinical Trial/
33	Controlled Clinical Trials as Topic/
34	"Controlled Clinical Trial (topic)"/
35	Clinical Trial/ or Phase 2 Clinical Trial/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/
36	Clinical Trials as Topic/ or Clinical Trials, Phase II as Topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/
37	"Clinical Trial (topic)"/ or "Phase 2 Clinical Trial (topic)"/ or "Phase 3 Clinical Trial (topic)"/ or "Phase 4 Clinical Trial (topic)"/
38	Multicenter Study/ or Multicenter Study as Topic/ or "Multicenter Study (topic)"/
39	Randomization/

MULTI-DATABASE STRATEGY	
40	Random Allocation/
41	Double-Blind Method/
42	Double Blind Procedure/
43	Double-Blind Studies/
44	Single-Blind Method/
45	Single Blind Procedure/
46	Single-Blind Studies/
47	Placebos/
48	Placebo/
49	Control Groups/
50	Control Group/
51	Cross-Over Studies/ or Crossover Procedure/
52	(random* or sham or placebo*).ti,ab,hw.
53	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
54	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
55	(control* adj3 (study or studies or trial*)).ti,ab,hw.
56	(clinical adj3 (study or studies or trial*)).ti,ab,hw.
57	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.
58	(phase adj3 (study or studies or trial*)).ti,ab,hw.
59	((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw.
60	((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw.
61	allocated.ti,ab,hw.
62	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.
63	trial.ti.
64	or/26-63
65	exp animals/
66	exp animal experimentation/
67	exp models animal/
68	exp animal experiment/
69	nonhuman/
70	exp vertebrate/
71	animal.po.
72	or/65-71
73	exp humans/
74	exp human experiment/
75	human.po.
76	or/73-75
77	72 not 76
78	64 not 77
79	epidemiologic methods.sh.
80	epidemiologic studies.sh.
81	cohort studies/

MULTI-DATABASE STRATEGY	
82	cohort analysis/
83	longitudinal studies/
84	longitudinal study/
85	prospective studies/
86	prospective study/
87	follow-up studies/
88	follow up/
89	followup studies/
90	retrospective studies/
91	retrospective study/
92	case-control studies/
93	exp case control study/
94	cross-sectional study/
95	observational study/
96	quasi experimental methods/
97	quasi experimental study/
98	validation studies.pt.
99	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab.
100	cohort*.ti,ab.
101	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti,ab.
102	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab.
103	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti,ab.
104	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti,ab.
105	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab.
106	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab.
107	(population adj3 (study or studies or analysis or analyses)).ti,ab.
108	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab.
109	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab.
110	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab.
111	((natural adj experiment) or (natural adj experiments)).ti,ab.
112	(quasi adj (experiment or experiments or experimental)).ti,ab.
113	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab.
114	(prevalence adj3 (study or studies or analysis or analyses)).ti,ab.
115	case series.ti,ab.
116	case reports.pt.
117	case report/
118	case study/
119	(case adj3 (report or reports or study or studies or histories)).ti,ab.

MULTI-DATABASE STRATEGY	
120	organizational case studies.sh.
121	or/79-120
122	(disease adj2 (progress* or predict* or prognosis) adj2 (Outcome* or Risk* or Model*)).ti,ab,kf.
123	(Predict* adj2 (Outcome* or Risk* or Model*)).ti,ab,kf.
124	((History or Variable* or Criteria or Scor* or Characteristic* or Finding* or Factor*) adj2 (Predict* or Model* or Decision* or Identif* or Prognos*)).ti,ab,kf.
125	Decision*.ti,ab,kf. and *Logistic Models/
126	((Prognostic or prognostic) adj2 (History or Variable* or Criteria or Scor* or Characteristic* or Finding* or Factor* or Model*)).ti,ab,kf.
127	Disease model*.ti,ab,kf.
128	122 or 123 or 124 or 125 or 126 or 127
129	exp Enzyme-Linked Immunosorbent Assay/
130	(ELISA or EIA or enzyme immunoassa* or enzyme linked immunosorben* or enzyme linked immunoassa* or enzyme linked immuno-sorben* or enzyme linked immunoblot*).ti,ab,kf.
131	((immunosorb* or immuno-sorb*) adj2 enzyme* adj2 (assay or assays)).ti,ab,kf.
132	(Index test or index tests or index standard).ti,ab,kf.
133	129 or 130 or 131 or 132
134	7 and 133
135	134 and 25
136	134 and 78
137	134 and 121
138	134 and 128
139	135 or 136 or 137 or 138
140	exp hepatitis C/ or exp Hepatitis C virus/ or exp hepatitis C antibody/ or exp hepatitis C antigen/
141	2 or 140
142	exp antibody screening/ or exp mass screening/ or exp screening/ or exp screening test/
143	5 or 142
144	141 and 143
145	exp enzyme linked immunosorbent assay/
146	130 or 131 or 132 or 145
147	144 and 146
148	147 use oemezd
149	147 and 25
150	147 and 78
151	147 and 121
152	147 and 128
153	149 or 150 or 151 or 152
154	139 use pmez
155	153 or 154
156	limit 155 to yr="2000 -Current"

MULTI-DATABASE STRATEGY	
157	limit 156 to english language
158	limit 156 to french
159	157 or 158
160	remove duplicates from 159
161	160 not conference abstract.pt
Research Question 2 (Harms):	
1	*Hepatitis C/ or *Hepatitis C, Chronic/ or *Hepacivirus/ or *Hepatitis C Antibodies/ or exp *Hepatitis C Antigens/
2	(hepatitis C or hepC or hep C or hepacivirus* or HCV).ti,kf.
3	1 or 2
4	exp *Mass screening/
5	(detect or detection or screen or screens or screened or screening).ti,kf.
6	4 or 5
7	3 and 6
8	exp safety/
9	equipment safety/
10	exp equipment failure/
11	consumer product safety/
12	"product recalls and withdrawals"/
13	medical device recalls/
14	"safety-based medical device withdrawals"/
15	product surveillance, postmarketing/
16	postmarketing surveillance/
17	clinical trial, phase iv.pt.
18	phase 4 clinical trial/
19	clinical trials, phase iv as topic/
20	"phase 4 clinical trial (topic)"/
21	exp postoperative complications/
22	exp postoperative complication/
23	exp intraoperative complications/
24	peroperative complication/
25	exp side effect/
26	"side effects (treatment)"/
27	(hazard* or defect* or misuse* or failure* or malfunction* or error*).ti.
28	(safe* or adverse* or undesirable or harm* or injurious or risk or risks or reaction* or complication* or poison*).ti.
29	(side effect* or safety or unsafe).ti,ab.
30	((adverse or undesirable or harm* or toxic or injurious or serious or fatal) adj3 (effect* or reaction* or event* or outcome* or incident*)).ab.
31	(toxic or toxicit* or toxologic* or intoxication or noxious or tolerability or teratogen*).ti,ab.
32	(warning* or recall* or withdrawn* or withdrawal*).ti.
33	(death or deaths or fatal or fatality or fatalities).ti.

MULTI-DATABASE STRATEGY	
34	or/8-33
35	exp Enzyme-Linked Immunosorbent Assay/ae, px [Adverse Effects, Psychology]
36	exp Disclosure/ or exp Self Disclosure/ or exp Ethics/ or social support/ or *privacy/ or exp *Sociology/ or exp Psychology, Social/
37	(overdiagnos* or over diagnos* or overtreat* or misdiagnose*).ti,ab,kf.
38	((over or unnecessar* or execess*) adj2 (treat* or test* or procedure*)).ti,ab,kf.
39	(stress or stressor* or anxious or anxiety or descriminat* or stigma* or violence or violent or social or harm or harms or anxiety or anxieties or threat or threatening or threatened).ti,ab,kf.
40	(psychological or psycholog* or psychosocial or preference* or motivation* or intention* or behaviour* or behavior* or attitude* or moral or morals or morality or ethics or ethical or bioethic* or genethic* or confidential* or disclosure* or communication or acceptance or accepting or adjustment or ethic* or moral* or privacy).ti.
41	((care or treatment or presumed) adj2 (duty or obligat* or consent)).ti.
42	(inform* adj (choice* or decision* or consent)).ti.
43	(social adj (responsib* or obligat*)).ti.
44	(legal* or liabilit* or litigation* or constitutional or justice or law or laws or jurisprudence or complicit*).ti.
45	human right*.ti,ab,kf.
46	civil right*.ti,ab,kf.
47	(prejudice* or inequalit* or fairness).ti,ab,kf.
48	((care or treatment) adj2 (duty or obligat*)).ti,ab,kf.
49	(social* adj (responsibl* or obligat*)).ti,ab,kf.
50	(communitarian* or beneficence or nonmaleficence or non-maleficence or accountability).ti,ab,kf.
51	or/35-50
52	7 and 34
53	7 and 35
54	7 and 51
55	52 or 53 or 54
56	55 use pmez
57	exp hepatitis C/ or exp Hepatitis C virus/ or exp hepatitis C antibody/ or exp hepatitis C antigen/
58	2 or 57
59	exp antibody screening/ or exp mass screening/ or exp screening/ or exp screening test/
60	5 or 59
61	58 and 60
62	enzyme linked immunosorbent assay/ae [Adverse Drug Reaction]
63	34 or 51 or 62
64	61 and 63
65	64 use oemezd
66	56 or 65

MULTI-DATABASE STRATEGY	
67	66 not conference abstract.pt.
68	limit 67 to english language
69	limit 67 to french
70	68 or 69
71	limit 70 to yr="2000 -Current"
72	remove duplicates from 71
Research Question 3 (Cost-effectiveness):	
1	Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C Antibodies/ or exp Hepatitis C Antigens/
2	(hepatitis C or hepC or hep C or hepacivirus* or HCV).ti,ab,kf.
3	1 or 2
4	exp Mass screening/
5	(detect or detection or screen or screens or screened or screening).ti,ab,kf.
6	4 or 5
7	3 and 6
8	Economics/
9	exp "Costs and Cost Analysis"/
10	Economics, Nursing/
11	Economics, Medical/
12	Economics, Pharmaceutical/
13	exp Economics, Hospital/
14	Economics, Dental/
15	exp "Fees and Charges"/
16	exp Budgets/
17	budget*.ti,ab.
18	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti.
19	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2
20	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab.
21	(value adj2 (money or monetary)).ti,ab.
22	exp models, economic/
23	economic model*.ti,ab.
24	markov chains/
25	markov.ti,ab.
26	monte carlo method/
27	monte carlo.ti,ab.
28	exp Decision Theory/
29	(decision* adj2 (tree* or analy* or model*)).ti,ab.
30	or/8-29
31	"Value of Life"/

MULTI-DATABASE STRATEGY	
32	Quality of Life/
33	quality of life.ti.
34	((instrument or instruments) adj3 quality of life).ab.
35	Quality-Adjusted Life Years/
36	quality adjusted life.ti,ab.
37	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab.
38	disability adjusted life.ti,ab.
39	daly*.ti,ab.
40	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
41	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab.
42	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab.
43	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab.
44	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab.
45	(hql or hqol or h qol or hrqol or hr qol).ti,ab.
46	(hye or hyes).ti,ab.
47	(health* adj2 year* adj2 equivalent*).ti,ab.
48	(pqol or qls).ti,ab.
49	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab.
50	nottingham health profile*.ti,ab.
51	sickness impact profile.ti,ab.
52	exp health status indicators/
53	(health adj3 (utilit* or status)).ti,ab.
54	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab.
55	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab.
56	disutilit*.ti,ab.
57	rosser.ti,ab.
58	willingness to pay.ti,ab.
59	standard gamble*.ti,ab.
60	(time trade off or time tradeoff).ti,ab.
61	tto.ti,ab.
62	(hui or hui1 or hui2 or hui3).ti,ab.
63	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab.
64	duke health profile.ti,ab.
65	functional status questionnaire.ti,ab.
66	dartmouth coop functional health assessment*.ti,ab.

MULTI-DATABASE STRATEGY	
67	or/31-66
68	exp Canada/
69	(canadian* or canada* or british columbia* or alberta* or saskatchewan* or manitoba* or ontario* or quebec* or new brunswick* or prince edward island* or nova scotia* or labrador* or newfoundland* or nunavut* or northwest territor* or yukon* or toronto* or montreal* or vancouver* or ottawa* or calgary* or edmonton* or winnipeg* or first nation* or metis).ti,ab,hw.
70	(canadian* or canada* or british columbia* or alberta* or saskatchewan* or manitoba* or ontario* or quebec* or new brunswick* or prince edward island* or nova scotia* or labrador* or newfoundland* or nunavut* or northwest territor* or yukon* or toronto* or montreal* or vancouver* or ottawa* or calgary* or edmonton* or winnipeg* or first nation* or metis).jw,jx.
71	canada.lo.
72	(canadian* or canada* or british columbia* or alberta* or saskatchewan* or manitoba* or ontario* or quebec* or new brunswick* or prince edward island* or nova scotia* or labrador* or newfoundland* or nunavut* or northwest territor* or yukon* or toronto* or montreal* or vancouver* or ottawa* or calgary* or edmonton* or winnipeg* or first nation* or metis).sd,ss,if,cr.
73	or/68-72
74	7 and 73
75	30 and 74
76	67 and 74
77	75 or 76
78	limit 77 to english language
79	limit 77 to french
80	78 or 79
81	80 use pmez
82	exp hepatitis C/ or exp Hepatitis C virus/ or exp hepatitis C antibody/ or exp hepatitis C antigen/
83	82 or 2
84	exp antibody screening/ or exp mass screening/ or exp screening/ or exp screening test/
85	84 or 5
86	83 and 85
87	socioeconomics/
88	exp Quality of Life/
89	quality of life.ti.
90	((instrument or instruments) adj3 quality of life).ab.
91	Quality-Adjusted Life Year/
92	quality adjusted life.ti,ab.
93	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab.
94	disability adjusted life.ti,ab.
95	daly*.ti,ab.
96	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short

MULTI-DATABASE STRATEGY	
	form thirty six).ti,ab.
97	(sf6 or sf 6 or short form 6 or shortform 6 or sf6d or sf 6d or short form 6d or shortform 6d or sf six or sfsix or shortform six or short form six).ti,ab.
98	(sf8 or sf 8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab.
99	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab.
100	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab.
101	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab.
102	(hql or hqol or h qol or hrqol or hr qol).ti,ab.
103	(hye or hyes).ti,ab.
104	(health* adj2 year* adj2 equivalent*).ti,ab.
105	(pqol or qls).ti,ab.
106	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab.
107	nottingham health profile*.ti,ab.
108	nottingham health profile/
109	sickness impact profile.ti,ab.
110	sickness impact profile/
111	health status indicator/
112	(health adj3 (utilit* or status)).ti,ab.
113	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab.
114	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab.
115	disutilit*.ti,ab.
116	rosser.ti,ab.
117	willingness to pay.ti,ab.
118	standard gamble*.ti,ab.
119	(time trade off or time tradeoff).ti,ab.
120	tto.ti,ab.
121	(hui or hui1 or hui2 or hui3).ti,ab.
122	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab.
123	duke health profile.ti,ab.
124	functional status questionnaire.ti,ab.
125	dartmouth coop functional health assessment*.ti,ab.
126	or/87-125
127	socioeconomics/
128	exp Quality of Life/
129	quality of life.ti.
130	((instrument or instruments) adj3 quality of life).ab.
131	Quality-Adjusted Life Year/

MULTI-DATABASE STRATEGY	
132	quality adjusted life.ti,ab.
133	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab.
134	disability adjusted life.ti,ab.
135	daly*.ti,ab.
136	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
137	(sf6 or sf 6 or short form 6 or shortform 6 or sf6d or sf 6d or short form 6d or shortform 6d or sf six or sfsix or shortform six or short form six).ti,ab.
138	(sf8 or sf 8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab.
139	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab.
140	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab.
141	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab.
142	(hql or hqol or h qol or hrqol or hr qol).ti,ab.
143	(hye or hyes).ti,ab.
144	(health* adj2 year* adj2 equivalent*).ti,ab.
145	(pqol or qls).ti,ab.
146	or/127-145
147	86 and 126
148	86 and 146
149	147 or 148
150	73 and 149
151	150 use oemezd
152	81 or 151
153	limit 152 to yr="2000 - 2015"
154	limit 153 to english language
155	limit 153 to french
156	154 or 155
157	156 not conference abstract.pt.
158	remove duplicates from 167
Research Question 4 (Patient Preferences):	
1	Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C Antibodies/ or exp Hepatitis C Antigens/
2	(hepatitis C or hepC or hep C or hepacivirus* or HCV).ti,ab,kf.
3	1 or 2
4	exp Mass screening/
5	(detect or detection or screen or screens or screened or screening).ti,ab,kf.
6	4 or 5
7	3 and 6
8	meta-analysis.pt.

MULTI-DATABASE STRATEGY	
9	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
10	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
11	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
12	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
13	(data synthes* or data extraction* or data abstraction*).ti,ab.
14	(handsearch* or hand search*).ti,ab.
15	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
16	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab.
17	(meta regression* or metaregression*).ti,ab.
18	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
19	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
20	(cochrane or (health adj2 technology assessment) or evidence report).jw.
21	(meta-analysis or systematic review).md.
22	(comparative adj3 (efficacy or effectiveness)).ti,ab.
23	(outcomes research or relative effectiveness).ti,ab.
24	((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab.
25	or/8-24
26	(Randomized Controlled Trial or Controlled Clinical Trial).pt.
27	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
28	Multicenter Study.pt.
29	Randomized Controlled Trial/
30	Randomized Controlled Trials as Topic/
31	"Randomized Controlled Trial (topic)"/
32	Controlled Clinical Trial/
33	Controlled Clinical Trials as Topic/
34	"Controlled Clinical Trial (topic)"/
35	Clinical Trial/ or Phase 2 Clinical Trial/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/
36	Clinical Trials as Topic/ or Clinical Trials, Phase II as Topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/
37	"Clinical Trial (topic)"/ or "Phase 2 Clinical Trial (topic)"/ or "Phase 3 Clinical Trial (topic)"/ or "Phase 4 Clinical Trial (topic)"/
38	Multicenter Study/ or Multicenter Study as Topic/ or "Multicenter Study (topic)"/
39	Randomization/
40	Random Allocation/
41	Double-Blind Method/

MULTI-DATABASE STRATEGY	
42	Double Blind Procedure/
43	Double-Blind Studies/
44	Single-Blind Method/
45	Single Blind Procedure/
46	Single-Blind Studies/
47	Placebos/
48	Placebo/
49	Control Groups/
50	Control Group/
51	Cross-Over Studies/ or Crossover Procedure/
52	(random* or sham or placebo*).ti,ab,hw.
53	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
54	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
55	(control* adj3 (study or studies or trial*)).ti,ab,hw.
56	(clinical adj3 (study or studies or trial*)).ti,ab,hw.
57	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.
58	(phase adj3 (study or studies or trial*)).ti,ab,hw.
59	((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw.
60	((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw.
61	allocated.ti,ab,hw.
62	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.
63	trial.ti.
64	or/26-63
65	exp animals/
66	exp animal experimentation/
67	exp models animal/
68	exp animal experiment/
69	nonhuman/
70	exp vertebrate/
71	animal.po.
72	or/65-71
73	exp humans/
74	exp human experiment/
75	human.po.
76	or/73-75
77	72 not 76
78	64 not 77
79	epidemiologic methods.sh.
80	epidemiologic studies.sh.
81	cohort studies/
82	cohort analysis/
83	longitudinal studies/

MULTI-DATABASE STRATEGY	
84	longitudinal study/
85	prospective studies/
86	prospective study/
87	follow-up studies/
88	follow up/
89	followup studies/
90	retrospective studies/
91	retrospective study/
92	case-control studies/
93	exp case control study/
94	cross-sectional study/
95	observational study/
96	quasi experimental methods/
97	quasi experimental study/
98	validation studies.pt.
99	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab.
100	cohort*.ti,ab.
101	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti,ab.
102	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab.
103	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti,ab.
104	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti,ab.
105	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab.
106	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab.
107	(population adj3 (study or studies or analysis or analyses)).ti,ab.
108	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab.
109	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab.
110	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab.
111	((natural adj experiment) or (natural adj experiments)).ti,ab.
112	(quasi adj (experiment or experiments or experimental)).ti,ab.
113	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab.
114	(prevalence adj3 (study or studies or analysis or analyses)).ti,ab.
115	case series.ti,ab.
116	case reports.pt.
117	case report/
118	case study/
119	(case adj3 (report or reports or study or studies or histories)).ti,ab.
120	organizational case studies.sh.
121	or/79-120

MULTI-DATABASE STRATEGY	
122	exp patient acceptance of health care/ or exp Attitude to Health/ or exp Attitude/ or exp Attitude to Death/ or Health Behavior/ or exp Illness Behavior/
123	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) and (attitude or attitudes or preference* or input or experience or experiences or value or values or perspective* or expectation* or choice* or choose* or choosing or "day-to-day" or participat* or acceptance or symptom or symptoms or limitations or survey* or focus group* or lives or interview* or quality of life or satisfaction or burden or attitude* or knowledge or lessons or reaction* or motivation* or intention* or involv* or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding)).ti,ab,kf.
124	(heuristic* or attitude or attitudes preference* or input or experience or experiences or value or values or perspective* or expectation* or choice* or choose* or choosing or "day-to-day" or participat* or acceptance or limitations or survey* or focus group* or lives or interview* or quality of life or satisfaction or burden or attitude* or knowledge or lessons or reaction* or motivation* or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding).ab. /freq=2
125	patient*.jw.
126	122 or 123 or 124 or 125
127	7 and 126
128	121 and 127
129	25 and 127
130	78 and 127
131	128 or 129 or 130
132	131 use pmez
133	exp hepatitis C/ or exp Hepatitis C virus/ or exp hepatitis C antibody/ or exp hepatitis C antigen/
134	133 or 2
135	exp antibody screening/ or exp mass screening/ or exp screening/ or exp screening test/
136	135 or 5
137	134 and 136
138	exp attitude to health/ or attitude/ or attitude to illness/ or exp attitude to death/ or exp health behavior/ or exp illness behavior/
139	123 or 124 or 125 or 138
140	137 and 139
141	140 and 25
142	140 and 78
143	140 and 121
144	141 or 142 or 143
145	144 use oemezd
146	132 or 145
147	limit 146 to yr="2000 -Current"
148	limit 147 to english language

MULTI-DATABASE STRATEGY	
149	limit 147 to french
150	148 or 149
151	150 not conference abstract.pt.
152	remove duplicates from 151
Research Question 5 (Diagnostic Test Accuracy):	
1	Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C Antibodies/ or exp Hepatitis C Antigens/
2	(hepatitis C or hepC or hep C or hepacivirus* or HCV).ti,ab,kf.
3	1 or 2
4	exp Mass screening/
5	(detect or detection or screen or screens or screened or screening).ti,ab,kf.
6	4 or 5
7	3 and 6
8	exp Enzyme-Linked Immunosorbent Assay/
9	(ELISA or EIA or enzyme immunoassa* or enzyme linked immunosorben* or enzyme linked immunoassa* or enzyme linked immuno-sorben* or enzyme linked immunoblot*).ti,ab,kf.
10	((immunosorb* or immuno-sorb*) adj2 enzyme* adj2 (assay or assays)).ti,ab,kf.
11	8 or 9 or 10
12	exp "Sensitivity and Specificity"/ or Limit of Detection/ or ROC Curve/ or Diagnostic errors/ or exp False Positive Reactions/ or exp "Predictive Value of Tests"/
13	(false adj2 (positive* or negative*)).ti,ab,kf.
14	(Sensitivity or specificity).ti,ab,kf.
15	(predictive valu* or validity).ti,ab,kf.
16	((test* or diagnostic* or diagnosis) adj2 (performance or accurac*)).ti,ab,kf.
17	(ROC or AUROCC or DTA).ti,ab,kf.
18	diagnostic test accuracy.ti,ab,kf.
19	12 or 13 or 14 or 15 or 16 or 17 or 18
20	11 and 19
21	7 and 20
22	exp hepatitis C/ or exp Hepatitis C virus/ or exp hepatitis C antibody/ or exp hepatitis C antigen/
23	22 or 2
24	exp antibody screening/ or exp mass screening/ or exp screening/ or exp screening test/
25	5 or 24
26	23 and 25
27	exp enzyme linked immunosorbent assay/
28	9 or 10 or 27
29	26 and 28
30	exp diagnostic accuracy/ or exp "sensitivity and specificity"/ or exp "limit of detection"/ or exp roc curve/ or exp receiver operating characteristic/ or exp diagnostic error/ or exp false positive result/ or exp false negative result/ or exp predictive value/
31	13 or 14 or 15 or 16 or 17 or 18 or 30

MULTI-DATABASE STRATEGY	
32	29 and 31
33	21 use pmez
34	32 use oemezd
35	33 or 34
36	35 not conference abstract.pt.
37	limit 36 to english language
38	limit 36 to french
39	37 or 38
40	limit 39 to yr="2000 -Current"
41	remove duplicates from 40

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

Grey Literature

Dates for Search:	November 2015
Keywords:	Included terms for hepatitis, hepatitis screening, screening methods, screening tests (e.g., ELISA)
Limits:	Publication years 2000 onward

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching,"[14] were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Databases (free)
- Internet Search.

APPENDIX 2: FULL-TEXT SCREENING CHECKLIST

Reviewer: _____ Date: _____

Ref ID: **Author:** **Publication Year:**			
Did the study include:	**Yes (Include)**	**Unclear (Include)[a]**	**No (Exclude)**
1) Non-pregnant, treatment-naive adults with unknown liver enzyme values?	☐	☐	☐
2) Q1 (clinical effectiveness) to Q4 (patient preferences): Any screening program for HCV infection? Q5 (DTA): ELISA version 3.0?	☐	☐	☐
3) Q1 (clinical effectiveness) to Q4 (patient preferences): A comparison with no screening? Q5 (DTA): PCR reference standard?	☐	☐	☐
4) Any of the following as the study outcomes? **Q1 (clinical effectiveness)** • Mortality due to HCV infection • Morbidity due to HCV infection (e.g., cirrhosis [compensated or decompensated] and HCC) • Rate of liver transplantation • Quality of life • Reduced HCV transmission • Sustained or improved virologic response • Behavioural changes to improve health outcomes • Histological improvements. **Q2 (harms)** • Overdiagnosis • Overtreatment • False positives • False negatives • Harms of follow-up tests (including biopsy) • Insurance premiums • Labelling	☐	☐	☐

Ref ID: **Author:** **Publication Year:**			
Did the study include:	**Yes (Include)**	**Unclear (Include)[a]**	**No (Exclude)**
• Abuse or violence • Anxiety • Partner discord **Q3 (cost-effectiveness)** • CEA outcomes (e.g., ICER, ICUR, CBR) • Budget impact analysis outcomes **Q4 (patient preferences)** Patient preferences and values regarding HCV screening; for example: • Willingness to be screened • Factors considered in decisions to be screened **Q5 (DTA)** • Diagnostic test accuracy (e.g., sensitivity, specificity, PPV, NPV, LR, diagnostic OR, AUC) • Detection rate • Number needed to screen to detect one case			
5) Any of the following study designs? **Q1 (clinical effectiveness), Q2 (harms)** • RCT • Non-randomized study with a comparator group • Non-randomized study without a comparator group • Disease-progression modelling study **Q3 (cost effectiveness)** • RCT • Economic evaluation • Modelling study **Q4 (patient preferences)** • Qualitative study • Survey	☐	☐	☐

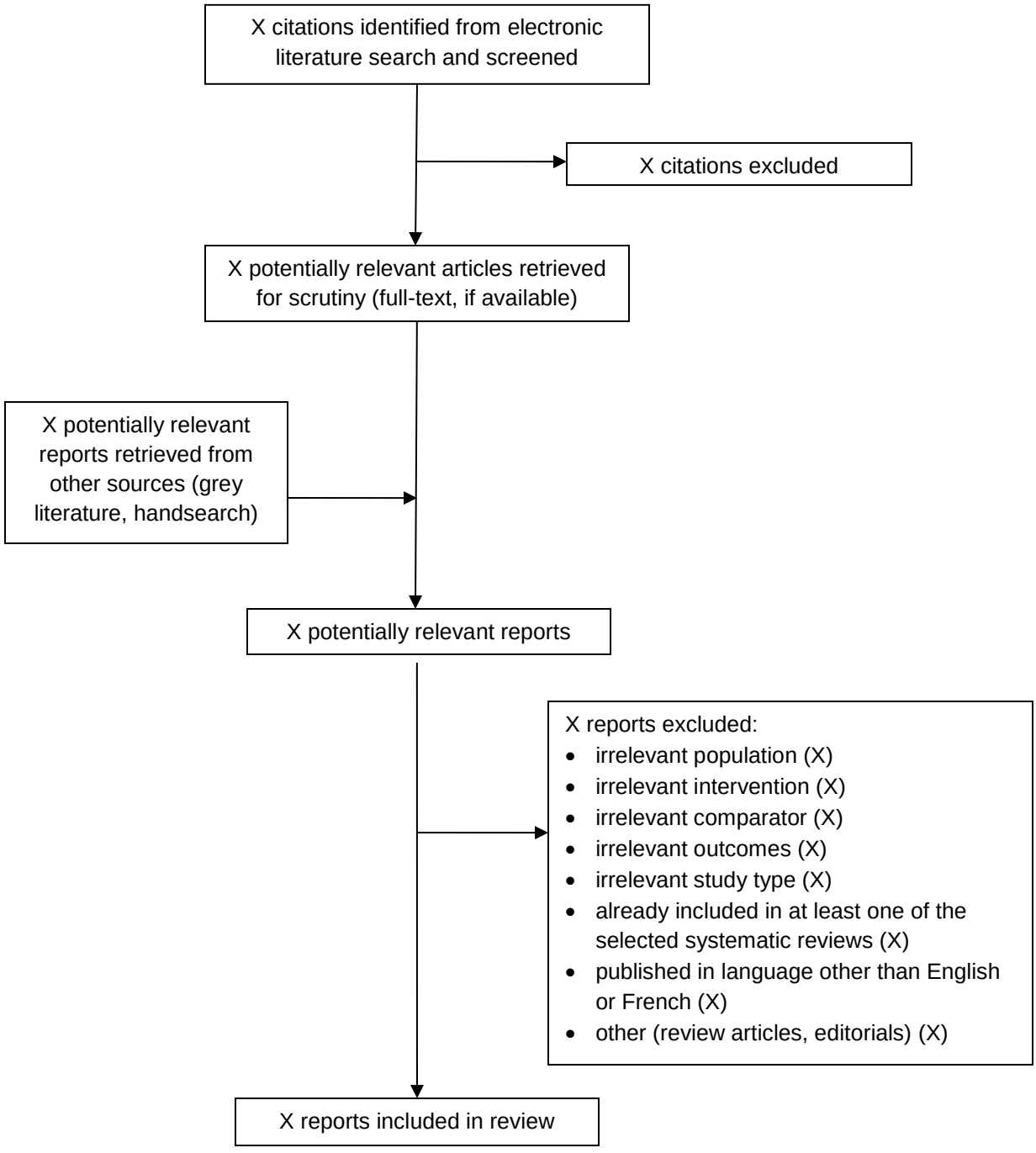
Ref ID: **Author:** **Publication Year:**			
Did the study include:	**Yes (Include)**	**Unclear (Include)[a]**	**No (Exclude)**
• Mixed-methods study **Q5 (DTA)** • RCT • Cross-sectional study • Case-control study			
6) Conducted in a primary care setting, setting generalizable to primary care, or other setting in which screening is commonly performed (e.g., emergency department, urgent care unit)?	☐	☐	☐
7) Conducted in Canada? **Q3 (cost-effectiveness)**	☐	☐	☐
8) Published in English or French?	☐	☐	☐
Decision to include the study in the review:	**Yes**☐		**No**☐
Reason(s) for exclusion:	☐ Inappropriate study population ☐ No intervention of interest ☐ No/inappropriate comparator ☐ No relevant outcomes ☐ Irrelevant study type ☐ Irrelevant language of publication ☐ Not primary report of study ☐ Study description only ☐ Other:_____		

AUC = area under the receiver-operating characteristic curve; CBR = cost-benefit ratio; CEA = cost-effectiveness analysis; DTA = diagnostic test accuracy; ELISA = enzyme-linked immunosorbent assay; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; LR = likelihood ratios; NPV = negative predictive value; OR = odds ratio; PCR = polymerase chain reaction; PPV = positive predictive value; RCT = randomized controlled trial.

Note: If all items are answered "yes" or "unclear", then the study is included.

[a] Discuss with a second reviewer.

APPENDIX 3: PRISMA FLOW CHART TEMPLATE



APPENDIX 4: DATA ABSTRACTION FORM — CLINICAL EFFECTIVENESS, HARMS, DIAGNOSTIC TEST ACCURACY

DATA ABSTRACTION FORM: Clinical Effectiveness (Q1), Frequency of Harms (Q2), DTA (Q5)		
Reviewer		
RefID		
Author, date		
Study Characteristics		
Country setting		
Care setting		
Study design		
Study duration		
Inclusion and exclusion criteria		
Description of study population (e.g., HCV high-risk group)		
Q1 (clinical effectiveness), Q2 (harms): description of intervention; Q5 (DTA): description of index test		
Q1 (clinical effectiveness), Q2 (harms): description of comparator; Q5 (DTA): description of reference standard		
Q5 (DTA): timing of or interval between index test and reference standard administration		
Conflicts of interest (yes, no, none declared, not mentioned)		
Funding status		
Other		
Patient Characteristics		
	Intervention	**Comparator**
Number enrolled		
Number completing study		
Age (mean, SD)		
Female, n (%)		
Male, n (%)		
Other		
Clinical Effectiveness Outcomes (Q1)		
	Intervention	**Comparator**
Long-term outcomes: • Mortality due to HCV infection • Morbidity due to HCV infection • Compensated cirrhosis		

DATA ABSTRACTION FORM: Clinical Effectiveness (Q1), Frequency of Harms (Q2), DTA (Q5)		
• Decompensated cirrhosis • Hepatocellular carcinoma • Rate of liver transplantation • Quality of life		
Intermediate outcomes: • HCV transmission • Virologic response rates (RVR, eRVR, EVR, SVR12, SVR24) • Behavioural changes to improve health outcomes • Histological improvements		
Comments		
Frequency of Harms Outcomes (Q2)		
	Intervention	**Comparator**
• Overdiagnosis • Overtreatment • False positives • False negatives • Harms of follow-up tests (including biopsy) • Effect on insurance premiums • Labelling • Abuse or violence • Anxiety • Partner discord		
Comments		
DTA Outcomes (Q5)		
	Index Test	**Reference Standard**
• Sensitivity • Specificity • Positive predictive value • Negative predictive value • Positive likelihood ratio • Negative likelihood ratio • Diagnostic odds ratio • AUC • Detection rate		

DATA ABSTRACTION FORM: Clinical Effectiveness (Q1), Frequency of Harms (Q2), DTA (Q5)		
• Number needed to screen to detect 1 case		
Comments		

AUC = area under the receiver-operating characteristic curve; DTA = diagnostic test accuracy; eRVR = extended rapid virologic response; EVR = early virologic response; HCV = hepatitis C virus; n = number; PCR = polymerase chain reaction; RVR = rapid virologic response; SD = standard deviation; SVR12 = sustained virologic response at 12 weeks after treatment; SVR24 = sustained virologic response at 24 weeks after treatment.

APPENDIX 5: DATA ABSTRACTION FORM — COST-EFFECTIVENESS

DATA ABSTRACTION FORM: Cost-Effectiveness (Q3)		
Reviewer		
RefID		
Author, date		
Study Characteristics		
Country setting	Canada	
Care setting		
Type of analysis		
Analysis perspective		
Description of study population (e.g., HCV high-risk group)		
Description of intervention		
Description of comparator		
Time horizon		
Model inputs		
Source of utilities		
Main assumptions		
Conflicts of interest (yes, no, none declared, not mentioned)		
Funding status		
Other		
Patient Characteristics		
	Intervention	**Comparator**
Number enrolled		
Number completing study		
Age (mean, SD or median, range)		
Female, n (%)		
Male, n (%)		
Other		
Outcomes		
	Intervention	**Comparator**
• ICER • ICUR • Cost-benefit ratio • Budget impact analysis outcomes		
Comments		

HCV = hepatitis C virus; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; n = number; SD = standard deviation.

APPENDIX 6: DATA ABSTRACTION FORM — PATIENT PREFERENCES

DATA ABSTRACTION FORM: Patient Preferences (Q4)	
Reviewer	
RefID	
Author, date	
Study Characteristics	
Country setting	
Study setting	
Funding sources	
Ethics approval	□ Yes □ No Comments:
Study design	□ Descriptive survey □ Ethnography □ Phenomenology □ Grounded theory □ Qualitative description □ Other (specify):
Study objectives	
Inclusion and exclusion criteria	
Recruitment method	
Data collection methods	□ Questionnaire □ Interview □ Focus group □ Observation □ Document review □ Other (specify):
Data analysis methods	
Other	
Patient Characteristics	
Sample size	
Age	
Female, n (%)	
Male, n (%)	
Income	
Education	

DATA ABSTRACTION FORM: Patient Preferences (Q4)	
Relationship status	
Other	
Study Results	
In the following table, extract verbatim results statements. Results statements will typically, but not always, be presented within the “results” section of a report. Results statements do not include raw data, study methods, external data, and researchers’ conclusions and implications.	
Results statements	

APPENDIX 7: QUALITY APPRAISAL CRITERIA — SURVEYS

Reviewer: _____ Date: _____

STUDY CHARACTERISTICS	
Ref ID:	
First Author:	
Publication Year:	
1. Was ethics approval obtained?	□ Yes □ No □ Unclear Comments:
RESEARCH QUESTION AND STUDY DESIGN	
2. Are the research questions and/or objectives clearly stated?	□ Yes □ No □ Unclear Comments:
3. Are the research questions suitable for a survey design?	□ Yes □ No □ Unclear Comments:
PARTICIPANTS AND SAMPLING	
4. Is the sampling strategy clearly described?	□ Yes □ No □ Unclear Comments:
5. Is the sampling strategy congruent with the research questions and/or objectives?	□ Yes □ No □ Unclear Comments:
6. Is the sample of participants representative of the target sample or the population to which the findings will be generalized?	□ Yes □ No □ Unclear Comments:
7. Could the way the sample was obtained introduce selection bias?	□ Yes □ No □ Unclear Comments:

8. Was a sufficient sample size calculation provided?	□ Yes □ No □ Unclear Comments:
DATA COLLECTION	
9. Was a pilot test of survey methods conducted?	□ Yes □ No □ Unclear Comments:
10. Was the study questionnaire valid?	□ Yes □ No □ Unclear Comments:
11. Was the study questionnaire reliable?	□ Yes □ No □ Unclear Comments:
DATA ANALYSIS	
12. Were the data analysis strategies appropriate for the type of data collected?	□ Yes □ No □ Unclear Comments:
13. Were all analyses planned a priori?	□ Yes □ No □ Unclear Comments:
RESULTS	
14. Was a satisfactory response rate achieved?	□ Yes □ No □ Unclear Comments:
15. Were all significant and non-significant quantitative results reported?	□ Yes □ No □ Unclear Comments:
16. Were all qualitative results, resulting from open-ended questions, summarized and reported?	□ Yes □ No □ Unclear Comments:

DISCUSSION AND CONCLUSIONS	
17. Have the researchers drawn an appropriate link between the data and their conclusions?	□ Yes □ No □ Unclear Comments:
18. Have all potential biases been identified and discussed?	□ Yes □ No □ Unclear Comments: