Hepatitis C Screening in Alberta

A Health Technology Assessment

The Health Technology Assessment Unit, University of Calgary

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Abbreviations

AASLD American Association for the Study of Liver Disease
AHRQ Agency for Healthcare Research and Quality
ALT Alanine Aminotransferase
CADTH Canadian Agency for Drugs and Technologies in Health
CDC Centers for Disease Control and Prevention
CHEERS Consolidated Health Economic Evaluation Reporting Standards
CNDSS Canadian Notifiable Diseases Surveillance System
CUPS Calgary Urban Project Society
DAA Direct-acting antiviral
EIA Enzyme Immunoassays
ELISA Enzyme-linked Immunosorbent Assay
G Genotype
GP general practitioner
HCV Hepatitis C Virus
HCC Hepatocellular Carcinoma
HIV Human Immunodeficiency Virus
HPV human papillomavirus
HTAi Health Technology Assessment International
ICER Incremental Cost-effectiveness Ratio
IDU Injection Drug Users
NANB non-A, non-B hepatitis
NHS National Health Service
NICE National Institute for Health and Care Excellence
PCR Polymerase Chain Reaction
peg-IFN pegylated interferon
PHAC Public Health Agency of Canada
PHN Pan-Canadian Public Health Network
PHN Council Pan-Canadian Public Health Network Council
ProvLab Provincial Laboratory for Public Health
QALY Quality Adjusted Life Year
RN Registered nurse
RNA Ribonucleic acid
RCT Randomized Controlled Trial
STD Sexually Transmitted Disease
STI Sexually Transmitted Infection
UK United Kingdom
US United States
USPSTF United States Preventive Services Task Force
WTP Willingness-to-pay
Executive Summary

This report presents the findings and conclusions of a provincial health technology assessment on Hepatitis C Virus (HCV) screening. The primary policy question for this report was:

1. What is the optimal strategy for HCV screening in Alberta?
   A. What is the appropriate population for targeted HCV screening in Alberta?
      i. Are there any relevant non age-based sub-populations at particular risk for HCV for whom targeted HCV screening would be appropriate?
      ii. Is it appropriate to introduce age-based targeted HCV screening in Alberta?

Introduction:

- HCV is a single stranded ribonucleic acid virus that is transmitted through exposure to infected blood.
- HCV is a slow-progressing disease; many individuals remain undiagnosed due to either non-specific symptoms or asymptomatic disease presentation, particularly in early stages of infection.
- In 2007, 0.8% of the Canadian population was estimated to be infected with HCV; of the individuals infected with HCV, approximately 21% are not aware that they have the infection.
- As the disease progresses treatment becomes less effective, and costly, making early diagnosis potentially advantageous for both the patient and the health care system.
- Population screening may be one strategy to identify HCV infections earlier in their disease course and may lead to more successful HCV treatment, prevent long-term liver damage and, if behaviour is modified, decrease HCV transmission.

Approach

I. An environmental scan of published HTAs, websites of HTA agencies, and emails to public health contacts in all Canadian provinces and territories
II. Key informant interviews with members of the Expert Advisory Group and other HCV experts
III. A systematic review of the published literature on patient perspectives of living with HCV and HCV screening
IV. A systematic review of the published literature on the effectiveness/efficacy of opportunistic and organized screening programs
V. A systematic review of published economic evaluations of HCV screening programs
VII. Projected budget impact analysis for Alberta

Key Findings

Organized Screening Programs and Guidelines in other Jurisdictions

- Internationally, five countries with organized screening programs were identified (Canada [Ontario, PEI], US, UK, Australia, Saudi Arabia).
• The United States is the only country with guidelines recommending screening by birth cohort (those born between 1945 and 1965); the policy response to this recommendation has been limited (i.e. three states).
• There is limited activity across Canada to address HCV.
• In Canada, and internationally, HCV screening is typically integrated into health and social service centres and agencies, rather than in stand-alone screening programs.

**Alberta Context and Program Feasibility: Key Informant Interviews**
• In Alberta, assessment and treatment of HCV is provided primarily by specialist physicians with considerable nursing support.
• Some capacity is available to support implementation of provincial screening, as well as the increased assessment and treatment of those diagnosed with HCV; additional resources, and some significant changes to current assessment and treatment models, would be required. Some gaps may exist in the capacity of a new care pathway if more patients were to require care.
• Perspectives on implementation of screening were varied; if birth cohort screening were to be adopted, key informants recommended a phased-in approach.
• The decision to screen was reported by key informants as being inextricably linked to the decision to publicly fund direct acting antiviral agents (DAAs); the belief was that you should not screen if you cannot treat.

**Patient Perspective: A Systematic Review of the Literature**
• Six studies on screening for HCV indicate that personal barriers (i.e. time, transportation), stigma, and poor relationships with health care providers prevent individuals from seeking HCV screening.
• Forty-six studies on experiences living with HCV indicate that those with HCV often feel stigmatized, and unsupported in their care, relationships, and work environment while coping with physical and psychological symptoms.

**Effectiveness of Organized Screening Programs: A Systematic Review of the Literature**
• Ten studies were included: three RCTs which compared various methods of organized screening, and seven studies of other designs.
• No studies compared population screening for HCV using an opportunistic or organized model.
• All three RCTs and five of the seven non-RCT studies found that screening uptake was higher for organized programs, than opportunistic screening.

**Cost-effectiveness Analysis: A Systematic Review of the Literature**
• Screening injection drug users, “high risk” (as defined by authors of included studies), birth cohort (those born between 1950 and 1970), and general populations would generally be considered good value for money using a threshold of $50,000 per quality-adjusted life year (QALY) gained.
• Screening pregnant women, prisoners, individuals who have had surgery and those who attend genito-urinary clinics would generally be considered poor value for money.
• No evidence was found on the cost-effectiveness of screening immigrant populations, aboriginal populations, or other risk groups.
• Uncertainty in the prevalence, screening uptake and treatment uptake affect the estimate of the cost per QALY.

**Cost-effectiveness of a Birth Cohort Screening Program in Alberta**

• Birth cohort screening (those born between 1950 and 1970) in Alberta incurs additional cost ($207-$544 depending on the selected treatment pathway) and results in additional clinical benefit (0.0059-0.0147 QALYs gained).
• The cost per QALY gained compared to no screening ranges from $34,751 - $44,614 depending on the treatment strategy; all could be considered reasonable value for money.
• All treatment strategies considered resulted in fewer decompensated cirrhosis, hepatocellular carcinoma, liver transplants, and liver-related deaths.

**Projected Budget Impact**

• Ranging from $253 million to $5.5 million, the order of most to least expensive populations in Alberta to screen and treat are: general population, birth cohort, followed by high-risk populations including aboriginal, immigrants, intravenous drug users (IDU), prisoners, and pregnant individuals.
• The cost to screen the birth cohort (those born between 1950 and 1970) would be approximately $47 million, and the cost to both screen and treat this population would be approximately $134 million, assuming a 20% treatment uptake.
• Costs increase as the number screened, proportion of positive tests, and uptake of screening and treatment increase; the main factors that could greatly affect the estimated budget impact are uptake of screening and treatment.
1 Introduction

1.1 Hepatitis C Virus Overview
Hepatitis C Virus is a growing public health concern in Alberta. Previously known as non-A, non-B hepatitis (NANB), the Hepatitis C Virus (HCV) is a single stranded ribonucleic acid (RNA) virus of the Flaviviridae family. Six HCV genotypes have been identified whose prevalence varies by geographic region. In North America the most prevalent genotype is genotype 1, which comprises over 70% of all HCV infections in Canada\(^1\). Genotypes are further categorized into subtypes, of which there are approximately 100\(^2\).

Initial symptoms of acute HCV appear within 2-24 weeks of exposure, and may include: fatigue, poor appetite, weight loss, abdominal discomfort (including nausea), and jaundice (yellowing of the skin and eye whites)\(^3\). However, many individuals infected with acute HCV go undiagnosed, as 90% of cases are asymptomatic\(^2\). Of those infected with acute HCV, 50 - 80% of individuals will develop chronic HCV\(^2\). Due to non-specific symptoms or asymptomatic disease progression, chronic HCV cases may continue to remain undiagnosed\(^2\).

Asymptomatic infections may be detected early in the disease progression by chance, through blood donor screening, or detection of high alanine aminotransferase (ALT) levels during routine blood work\(^3,4\). However, many HCV cases are diagnosed at a late stage in the disease, when liver damage is extensive. Approximately half of the cases of chronic HCV will progress to either cirrhosis or hepatocellular carcinoma (HCC)\(^5\); in 2007, approximately 802 individuals in Canada developed HCV- related cirrhosis, 292 were diagnosed with HCV- related hepatocellular carcinoma and 473 developed HCV-related decompensated liver failure\(^1\).

As the disease progresses, treatment becomes less effective\(^5\), and costly\(^5\), making early diagnosis advantageous for both the patient and the health care system. Although HCV prevalence is decreasing in Canada (with prevalence peaking in 1998)\(^6\) the costs associated with HCV have continued to rise primarily due to the high cost of caring for
advanced liver disease; 56% of HCV associated costs in 2013 were due to advanced liver disease\(^6\). Population screening programs may be one approach for identifying HCV infections earlier in their disease course.

### 1.2 Prevalence and Incidence

Prevalence and incidence vary across country, birthplace, and population. In 2007, 0.8% (242,500) of the Canadian population was estimated to be infected with HCV\(^7\). Using mathematical modeling, it was estimated that in 2007, 79% of those infected with HCV had been diagnosed\(^7\). The Public Health Agency of Canada (PHAC) reports that approximately 21% of individuals infected with HCV, are unaware that they have the disease\(^8\).

Based on data from the Canadian Notifiable Diseases Surveillance System (CNDSS), the number of cases diagnosed in Canada is declining, with a diagnosis rate of 40.4 per 100,000 in 2005, and 33.7 per 100,000 in 2009\(^1\). The majority of HCV cases diagnosed in Canada are among males over 30 years old; however, there are increasing rates of HCV diagnoses in young females\(^1\). Of the Canadian incident cases reported in 2007, 6,607 were IDUs, one was a transfused patient, and 1,337 were classified as “other”\(^1\). In 2009, the rate of HCV case diagnoses was highest in the Yukon Territory (107 cases per 100,000) and British Columbia (54.9 per 100,000)\(^1\). Rates were lowest in Nunavut (15.5 per 100,000) and Newfoundland (17.7 per 100,000)\(^1\).

Similar to Canada-wide data, Alberta based data suggests that the number of new HCV cases has been declining in recent decades. In Alberta, the rate of HCV diagnosis was approximately 41.7 per 100,000 in 2005, while in 2009 the rate of HCV diagnosis was 30.6 per 100,000\(^1\). A January 2013 report published by Alberta Health reports that in Alberta, men are twice as likely to be diagnosed with HCV than women; in 2006, 911 men were diagnosed with HCV and 464 women were diagnosed \(^2\). For men, the highest rate of new diagnoses is within those who are 40-59 years old, while for women, those age 30-39 have the highest rate of diagnoses\(^2\). First Nations represent a large proportion of the HCV cases diagnosed within Alberta, accounting for 13.6% of the diagnoses between 1998 and 2006\(^2\). It is important to note that diagnosed cases do not represent the
complete burden of disease as many cases remain undiagnosed with people unaware they are carriers.

For comparison, the prevalence of HCV in the United States has been estimated at 1.3% (95% Confidence Interval 0.9%-1.8%), or 3.5 million non-incarcerated individuals infected\(^9\), higher than the estimated prevalence of 0.8% in Canada. Globally, genotype 1 is the most prevalent (83.4 million cases or 46.2% of all HCV cases), followed by genotype 3 (54.3 million cases, or 30.1% of all HCV cases)\(^{10}\).

Prevalence and incidence of HCV vary by population, with some populations being more at risk of infection than others. This is primarily due to behaviours and actions that could result in blood to blood contact with other individuals. Estimated prevalence and incidence of HCV within sub-groups of the general population have been presented below in Table 1. When possible, these estimates are based on Canadian data; however, in some cases data from other countries has been included if Canadian data was unavailable.

Incidence estimates were not available for birth cohort (those born 1950-1970), pregnant women, and immigrants. As the birth cohort would have predominately been at high risk of HCV exposure decades prior due to high risk behaviour, incidence estimates would likely now reflect the incidence rates of the general population. Women who are pregnant likely would have obtained the HCV infection prior to pregnancy, so it is anticipated that incidence estimates for this population would be small.
Table 1: Estimated Prevalence and Incidence, by Population

<table>
<thead>
<tr>
<th>Population</th>
<th>Prevalence</th>
<th>Year and Source of Prevalence Estimate</th>
<th>Incidence</th>
<th>Year and Source of Incidence Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Population</td>
<td>0.69% (Alberta-based prevalence)</td>
<td>2007</td>
<td>1 per 3,900 (0.026%)</td>
<td>2007</td>
</tr>
<tr>
<td>Birth Cohort</td>
<td>1.5%</td>
<td>2011</td>
<td>No estimate available</td>
<td></td>
</tr>
<tr>
<td>Current or former injection drug user</td>
<td>88%</td>
<td>1997</td>
<td>1 per 4.83 (20.7%) for current intravenous drug users, 0% for former</td>
<td>2007</td>
</tr>
<tr>
<td>Prisoners</td>
<td>12-35%</td>
<td>2014</td>
<td>1.1 infections per 100 person-years of incarceration among males in Maryland, US</td>
<td>1993</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>0.8%</td>
<td>1999</td>
<td>No estimate available</td>
<td></td>
</tr>
<tr>
<td>Immigrants (persons born outside of Canada)</td>
<td>1.9%</td>
<td>2011</td>
<td>No estimate available</td>
<td></td>
</tr>
<tr>
<td>Aboriginals</td>
<td>3.24%</td>
<td>2008</td>
<td>17 per 100,000 (0.017%)</td>
<td>2008</td>
</tr>
</tbody>
</table>

1.3 Transmission Patterns

HCV is transmitted through exposure to infected blood and cannot be spread through intact skin or mucous membranes\textsuperscript{17}. In Canada, injection drug users (IDU) have the highest prevalence of HCV, and account for approximately 58% of all documented HCV infections\textsuperscript{4}. HCV can also be transmitted through drug snorting or any other method where membrane integrity is compromised and blood transfer can occur\textsuperscript{18}.
As testing blood products for HCV in Canada was initiated in 1990, with more sensitive tests introduced in 1992\textsuperscript{17}, those who received blood products or organ transplants prior to 1992 are at increased risk for HCV infection. While in 2007, blood transfusion accounted for approximately 11\% of the current HCV infections in Canada\textsuperscript{4}, a residual risk of acquiring HCV through blood transfusions is estimated to be 0.43\% per transfusion\textsuperscript{19}.

Vertical transmission of HCV (either in utero or intrapartum) has been reported, however the risk of perinatal transmission is low. While the risk is thought to be higher with increased maternal viral loads, cases of perinatal transmission have been reported from mothers with undetectable viral loads\textsuperscript{18,20}. Other risk factors for HCV transmission include: improperly sterilized tattoo or piercing equipment, dental or medical equipment, or acupuncture equipment. Other less frequent methods of transmission include sexual activity where compromised mucus membranes come into contact with blood from an HCV infected individual, and transmission through sharing personal items with an HCV infected individual (e.g. razor, tweezers, nail clippers)\textsuperscript{20}.

1.4 Screening and Diagnosis of Hepatitis C Virus
Screening algorithms for HCV employ Enzyme Immunoassays (EIA) to detect the presence of HCV specific antibodies in serum. In Alberta, a PCR test used to confirm the HCV diagnosis.

Not all individuals who are offered screening consent to receive screening. In a recent Canadian study, 90\% of participants indicated that they would consent to being tested for HCV\textsuperscript{21}. In two United Kingdom (UK) studies examining a primary care setting and a general population, the proportion accepting the test was 28\%\textsuperscript{22} and 56\%\textsuperscript{23}. In drug services clinics, acceptability was found in one study in the United States (US) to be 75\%\textsuperscript{24}, while another in the Netherlands showed an acceptability of 91\%\textsuperscript{25}. One US study from a mental health program showed a wide range in the acceptability of testing based on patient education, 15\% without education versus 86\% with education accepted testing\textsuperscript{26}. Lastly, in Ireland, IDUs in a general practice accepted testing 27\% of the time.
without an intervention and 49% with an intervention targeted at general practitioners (GPs)\textsuperscript{27}.

Many interventions have been shown to increase the acceptability of HCV testing. Two studies evaluating remunerated case finding interventions in primary care demonstrated higher proportions of offered tests accepted in the intervention group\textsuperscript{22,23}. In terms of the setting where the testing is offered, community settings\textsuperscript{24-26} and via outreach\textsuperscript{28} have both been shown to increase testing acceptability. Educational and other interventions targeting professionals have also been shown to increase acceptability\textsuperscript{27,29,30}. One study, while not showing increases in acceptability, demonstrated an increase in requests to be tested after provision of patient-targeted materials\textsuperscript{31}.

1.5 Current Treatment Strategies

The intention of HCV treatment is to completely eliminate the virus from the body; elimination is defined as undetectable HCV RNA\textsuperscript{32}. In Canada, antiviral medication is the current standard therapy for treating HCV, specifically pegylated-interferon-\(\alpha\) (PEG-INF) and ribavirin (RBV)\textsuperscript{1}. Treatment duration depends on genotype; for Genotypes 2 and 3, 24 weeks of treatment is standard, whereas standard treatment for Genotypes 1, 4, 5 and 6 is 48 weeks\textsuperscript{32}. Cure rates for PEG-INF and RBV therapy are approximately 40-50% for those with Genotype 1, and 80% for those with Genotypes 2 and 4\textsuperscript{32}. PEG-INF and RBV are frequently associated with severe side effects such as fatigue, headaches, fever, muscle pain, insomnia, nausea, hair loss, anorexia, depression, irritability, and joint pain\textsuperscript{33}.

1.6 Emerging Treatment Strategies

The development of new HCV pharmaceuticals, broadly categorized as direct acting antivirals (DAAs) has created a changing treatment landscape for those with HCV. DAAs target enzymes that are necessary for HCV replication\textsuperscript{34}. In comparison to PEG-INF or RBV based treatments, DAAs have been found to have higher cure rates and shorter treatment times, with fewer side-effects\textsuperscript{35}.
Currently, four classes of DAAs are available, NS3/4A protease inhibitors (e.g. Simeprevir, paritaprevir), NS5B nucleoside polymerase inhibitors (e.g. Sofosbuvir), NS5B non-nucleoside polymerase inhibitors (e.g. Dasabuvir), and NS5A inhibitors (e.g. Ledipasvir, Ombitasvir). These four classes have also been combined by pharmaceutical companies, as is the case with Ledipasvir-Sofosbuvir (sold as Harvoni by Gilead Sciences Inc.) and Ombitasvir-Paritaprevir-Ritonavir (sold as Holkira Pak by AbbVie). Within Canada, a number of DAAs have been approved by Health Canada, and recommended by the Common Drug Review (the national process to recommend public reimbursement, operated through the Canadian Agency for Drugs and Technologies in Health [CADTH]) (Table 2).

**Table 2:** Direct-acting Anti-viral Treatment Regimes Approved by Health Canada

<table>
<thead>
<tr>
<th>Chemical Name (Commercial Brand Name)</th>
<th>Pharmaceutical Company</th>
<th>Health Canada Approval</th>
<th>Common Drug Review Approval</th>
<th>Common Drug Review Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeprevir (Galexos)</td>
<td>Janssen Inc.</td>
<td>Yes</td>
<td>Yes</td>
<td>Genotype 1 HCV (fibrosis stage F2, F3, or F4)</td>
</tr>
<tr>
<td>Sofosbuvir (Sovaldi)</td>
<td>Gilead Sciences Inc.</td>
<td>Yes</td>
<td>Yes</td>
<td>Genotype 2 HCV (fibrosis stage F2, F3, or F4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Genotype 3, HCV (fibrosis stage F2, F3, or F4)</td>
</tr>
<tr>
<td>Ledipasvir-Sofosbuvir (Harvoni)</td>
<td>Gilead Sciences Inc.</td>
<td>Yes</td>
<td>Yes</td>
<td>Genotype 1 HCV (fibrosis stages F2, F3, or F4)</td>
</tr>
<tr>
<td>Ombitasvir-Paritaprevir-Ritonavir (Holkira Pak)</td>
<td>AbbVie</td>
<td>Yes</td>
<td>Under Review</td>
<td>Pending recommendation</td>
</tr>
</tbody>
</table>

Prices released by the pharmaceutical companies that manufacture these DAAs are: $84,000 USD for a 12-week treatment regime of Sofosbuvir/Sovaldi; $94,500 USD for Harvoni; and $55,860 for Holkira Pak. As more DAA treatment regimens become available, it is possible that the prices of these DAAs may decrease in response to additional market competition.
1.7 Population Screening for Early Identification and Treatment

Due to the asymptomatic nature of HCV, population screening programs may be one strategy for identifying HCV infections earlier in their disease course. When identified earlier, HCV treatment may be more successful, and, if behavior is modified, HCV is less likely to be transmitted to others\textsuperscript{36}. Screening programs may be aimed at general populations, or risk subgroups (i.e. birth cohorts, IDUs, transfusion patients). A number of disease control organizations have recommended and promoted the implementation of HCV screening programs, such as the World Health Organization\textsuperscript{37}, and the Center for Disease Control (CDC)\textsuperscript{38}. The Agency for Healthcare Research and Quality (AHRQ) completed a comprehensive review of the effectiveness of screening\textsuperscript{39}.

1.8 Summary of Agency for Healthcare Research and Quality Report

In 2013, the AHRQ released a report evaluating HCV screening for adults\textsuperscript{39}. This report assessed: effectiveness of screening, harms of screening, diagnostic accuracy, and factors related to pregnancy such as vertical transmission between HCV positive women and their babies.

AHRQ completed a systematic review of the published literature including four databases from 1947 until May 2012, and identified 10,786 abstracts\textsuperscript{39}. After abstract review, 9,978 were excluded and 808 were reviewed in full-text. Five studies assessing the effectiveness of HCV screening were included in this review; four cross-sectional studies and one case control study\textsuperscript{39}.

These studies recruited participants from a variety of settings, including Sexually Transmitted Infection (STI) clinics\textsuperscript{40,41}, primary care clinics\textsuperscript{42,43}, and gastroenterology and primary care clinics\textsuperscript{44}. A study conducted in 2006 in the United States, found that screening IDUs will identify one asymptomatic case of HCV per 1.6 individuals screened\textsuperscript{43}. In studies conducted in the United States and the Netherlands, the effectiveness of screening individuals visiting a STI clinic ranges from 1 case identified per 2.4 individuals screened, to 1 case identified per 10 individuals screened\textsuperscript{41}. Overall, the AHRQ report concluded that some factors, such as a history of injection drug use and
pre-1992 blood transfusion, were consistently associated with a lower number needed to screen, to identify one case. AHRQ reports that the direct harms of screening appear to be minimal, primarily due to the minimally invasive nature of the test. Diagnostic accuracy of HCV antibody tests and polymerase chain reaction (PCR) tests was found to “good” to “very good.” Additionally, AHRQ found that for pregnant women, there is no statistically significant difference in vertical HCV transmission between birth by vaginal or cesarean delivery.

Importantly, the AHRQ report found no evidence on whether HCV screening impacts long-term clinical outcomes. It is thought that screening could identify patients earlier allowing for earlier intervention to prevent long-term liver damage and associated outcomes. While this is intuitive, there is no evidence available to demonstrate this impact and, in the historic absence of effective treatments, it is unclear if screening would indeed lead to reduced liver disease burden.

2 Policy Questions

With the increasing HCV costs due to late-stage liver disease, and with the introduction of breakthrough treatment options for HCV, implementation of population-based HCV screening is a pressing issue. Alberta Health commissioned the University of Calgary HTA Unit to complete a policy analysis to address the questions below:

1. What is the optimal strategy for HCV screening in Alberta?
   a. What is the appropriate population for targeted HCV screening in Alberta?
      i. Are there any relevant non-age-based sub-populations at particular risk for HCV for whom targeted HCV screening would be appropriate?
      ii. Is it appropriate to introduce age-based targeted HCV screening in Alberta?
This report summarizes the findings and conclusions of the research that was considered during the development of the policy options, including an environmental scan of international and national HCV guidelines and screening programs, Alberta provider perspectives and context, a systematic review of patient perspectives on HCV and HCV screening, a systematic review of the comparative effectiveness of organized and opportunistic screening programs, a systematic review of cost-effectiveness analyses, an Alberta-specific cost-effectiveness analysis of birth cohort screening and a proposed budget impact.

3 Screening Programs and Guidelines in Other Jurisdictions

Summary

- Internationally, five countries with organized screening programs were identified (Canada [Ontario, PEI], US, UK, Australia, Saudi Arabia)
- The US is the only country with guidelines recommending screening by birth cohort (those born between 1945 and 1965); the policy response to this recommendation has been very limited (i.e. three states)
- There is limited activity across Canada to address HCV
- In Canada, and internationally, HCV screening is typically opportunistic, integrated into health and social service centres and agencies, rather than in stand-alone organized screening programs

3.1 Purpose

To assess the current state of HCV screening in the Canadian provinces and territories, and internationally.

3.2 Methods

An environmental scan was completed. Three methods were used to obtain information: a search of published HTA literature, a grey literature search of the websites of HTA agencies, and emails to public health contacts in all Canadian provinces and territories. Further internet and literature searching was conducted for jurisdictions where organized screening or recommendations to initiate organized screening programs were identified in other articles (‘hand searching’). References in identified studies were also examined for potential inclusion into the environmental scan.
The HTA Database was searched to identify reports on HCV screening, without language limits, for all reports indexed up to and including January 12, 2015. The following terms were used: *hepatitis C*, *hep C*, *HCV* and *hepacivirus*. Titles and full texts were reviewed by one reviewer. Full texts were reviewed if titles indicated the study examined HCV screening or HCV more generally. Studies were excluded if they did not have an English or French summary, or examined drugs for treating HCV.

To identify grey literature, the websites of all 68 members of Health Technology Assessment International (HTAi)\(^45\) were searched for reports, articles, or presentations on HCV screening guidelines and strategies. The following terms were used to search the member HTA organizations: *hepatitis C*, *HCV*, and the translation of hepatitis C into the working language of the organization (using Google Translate\(^46\)). The terms *testing* and *screening* were combined with terms referring to HCV when searching for HCV resulted in more than 20 results. Titles and full texts were reviewed by one reviewer, with the same inclusion and exclusion criteria as above.

Members representing each province and territory on the Pan-Canadian Public Health Network (PHN) Council were emailed. The PHN Council oversees work done by the Network, an association of government officials at the Federal and provincial/territorial levels that works to improve public health in Canada. The following were assessed: the existence of organized screening programs, screening guidelines, planned responses to the PHAC’s anticipated screening recommendations, and the anticipated decisions about DAA treatment regimes. Members of the PHN Council were sent one reminder email two weeks after the initial email. All responses were collated and narratively synthesized. The specific questions asked were:

1) Does your province have a formal [organized] screening program for hepatitis C? If so, who does your province recommend screening?

2) Does your province have plans to respond to PHAC's anticipated recommendations on hepatitis C screening?

3) What are your province's plans to respond to the Common Drug Review's upcoming recommendation, whether positive or negative, for anti-viral drugs?
3.3 Results

The websites of all 68 members of HTAi were searched. Two appropriate reports were identified (Figure 1). Eighty-nine reports were identified from the HTA Database (Figure 1) of which two were eligible for inclusion. An additional six countries were identified from these reports and other published literature. After the removal of duplicates, a total of nine countries were identified with HCV screening guidelines (Canada, US, UK, Australia, Belgium, France, Germany, the Netherlands, Saudi Arabia).

Responses were received from nine of twelve provinces and territories (nonresponse from Prince Edward Island, New Brunswick, and Manitoba [Table 4, Figure 1]). Ontario was the only province or territory with an organized screening program. Even though PEI did not respond to the survey, they recently announced an organized screening program in the province, and thus details about this program are included.

Figure 1: Flow Chart of Included Countries

- Other Canadian Provinces and Territories Surveyed n=12
- Websites Searched of Health Technology Assessment Agencies n=68
- Titles from the Health Technology Assessment Database Reviewed n=89
- Provinces and Territories Responding n=9
- Full-texts Reviewed n=2
- Provinces and Territories with HCV Screening Programs n=1
- Included Countries n=2
- Included Countries n=2 (1 duplicate)
- Total Provinces and Territories n=2
- Total Countries n=9
- Countries Identified with HCV Screening Guidelines (n=9): Canada, US, UK, Australia, Belgium, France, Germany, the Netherlands, Saudi Arabia
- Countries Identified with HCV Screening Programs (n=5): Canada, US, UK, Australia, Saudi Arabia
3.3.1 Canadian Programs and Guidelines

3.3.1.1 Current Guidelines

In 2009, PHAC and the College of Family Physicians of Canada released recommendations for the screening of HCV\(^47\). They were broken down into high, intermediate, and other risks of infection (Table 3).

**Table 3: Populations Identified by PHAC as at Risk of HCV**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Population at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>- Injection drug use&lt;br&gt;- Incarceration&lt;br&gt;- Born, traveled, or resided in a region in which HCV infection is more common&lt;br&gt;- Receipt of health care where there is a lack of universal precautions (nosocomial transmission)&lt;br&gt;- Blood transfusions, blood products, or organ transplant before 1992 in Canada</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>- Hemodialysis&lt;br&gt;- Infant born to mother with HCV infection&lt;br&gt;- Needle stick injuries</td>
</tr>
<tr>
<td>Other risks</td>
<td>- Sharing sharp instruments/personal hygiene materials with HCV+ person&lt;br&gt;- Tattooing, body piercing, scarification, female genital mutilation or other ceremonial rituals&lt;br&gt;- Intranasal (snorting) &amp; inhalation drug use&lt;br&gt;- Homelessness, residency in group homes or shelters&lt;br&gt;- Higher-risk sexual behaviour</td>
</tr>
</tbody>
</table>

Following the release of guidelines developed in the US by the Centers for Disease Control and Prevention (CDC)\(^48\) and the United States Preventive Services Task Force (USPSTF)\(^49\) recommending birth cohort screening, PHAC began updating their recommendations including commissioning a cost-effectiveness analysis of birth cohort screening in Canada\(^50\), and work on prevalence by age group\(^11\). It is anticipated that the updated guideline from PHAC will recommend birth cohort screening for those born between 1950-1970.
The current Alberta Health guidelines (2011) for screening HCV\textsuperscript{51} are similar to the 2009 PHAC recommendations\textsuperscript{47}, and recommend opportunistic screening of individuals who: have ever injected drugs, have been incarcerated, have tattoos, ear or body piercing, received an organ transplant or a transfusion of blood or blood products prior to 1990, have had a needle stick injury (health care workers), or persons with liver dysfunction of unknown etiology or chronic liver disease.

3.3.1.2 Canadian Provinces and Territories

Most provinces and territories do not have organized screening programs (i.e., public health initiatives above and beyond casual testing in routine health care encounters [Table 4]). The Pan-Canadian Public Health Network has requested from the Conference of Deputy Ministers of Health a task group to examine screening and treatment for HCV in Canada, given recent treatment breakthroughs and an anticipated recommendation from PHAC to screen for HCV by birth cohort. Many provinces are waiting for the results of this task group before making a decision about HCV screening. Currently, Ontario and Prince Edward Island are the only provinces/territories that have organized HCV screening programs in place.

Northwest Territories

As of 2013 the Northwest Territories, in accordance with the Canadian Liver Foundation's 2012 guidelines\textsuperscript{52}, recommended one-time HCV testing for those born between 1945 and 1975\textsuperscript{53}. To our knowledge this is the only province or territory that currently recommends screening a birth cohort, and the territory does not have an organized HCV screening program. It is unclear how much uptake there has been of this screening guideline in the Northwest Territories.
Table 4: Responses from the Pan-Canadian Public Health Network Council

<table>
<thead>
<tr>
<th>Province or Territory</th>
<th>Does your province have a formal [organized] screening program for hepatitis C?</th>
<th>Does your province have plans to respond to PHAC's anticipated recommendations on hepatitis C screening?</th>
<th>What are your province's plans to respond to the Common Drug Review's upcoming recommendation, whether positive or negative, for anti-viral drugs?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newfoundland and Labrador</td>
<td>No</td>
<td>Response under consideration</td>
<td>Unknown</td>
</tr>
<tr>
<td>Prince Edward Island*</td>
<td>No response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nova Scotia</td>
<td>No</td>
<td>Awaiting evidence from national initiatives</td>
<td>Awaiting recommendation</td>
</tr>
<tr>
<td>New Brunswick</td>
<td>No response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quebec</td>
<td>No</td>
<td>Response under consideration</td>
<td>Quebec does not participate in the Common Drug Review; Quebec has listed Sovaldi, but not Harvoni nor Holkira Pak on their Liste de Medicaments</td>
</tr>
<tr>
<td>Ontario</td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
</tr>
<tr>
<td>Manitoba</td>
<td>No response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saskatchewan</td>
<td>No</td>
<td>Awaiting evidence from national initiatives</td>
<td>Unknown</td>
</tr>
<tr>
<td>British Columbia</td>
<td>No</td>
<td>Awaiting evidence from national initiatives</td>
<td>Unknown</td>
</tr>
<tr>
<td>Yukon</td>
<td>No</td>
<td>Response under consideration</td>
<td>Awaiting recommendation</td>
</tr>
<tr>
<td>Nunavut</td>
<td>No</td>
<td>Awaiting evidence from national initiatives</td>
<td>Unknown</td>
</tr>
<tr>
<td>Northwest Territories</td>
<td>No</td>
<td>Recommends screening of 1945-1975 birth cohort; response to rest of anticipated recommendations under consideration</td>
<td>Awaiting recommendation</td>
</tr>
</tbody>
</table>

*Although the Prince Edward Island PHN Council member did not respond to us, information about Prince Edward Island’s HCV screening strategy was identified from a press release.*
Ontario

In 2014, a Public Health Ontario report recommended screening those co-infected with HIV and hepatitis B, in addition to many of the PHAC risk factors\(^5^4\).

Ontario’s 2009-2014 Hepatitis C Strategy was presented in 2009 by the Ontario Hepatitis C Task Force to the Ontario Minister of Health\(^5^5\). Although this six-year strategy focuses on the treatment of HCV, it does recommend increasing funding, support, and information to agencies that work with those at higher risk of acquiring HCV. The Task Force also recommends increasing knowledge of HCV (including how to get tested) in the general and at-risk populations, as well as among health care workers. This recommendation of public education is on top of Ontario’s previous television and newspaper ads to increase the awareness of HCV\(^5^5\). The strategy also recommends research and program evaluation on optimal ways to prevent, treat, and test for HCV in Ontario, especially among those who inject drugs. The HCV strategy contains one recommendation that could be interpreted as an organized screening program, promoting screening in Ontario corrections facilities. The recommendation is: “Encourage further collaboration between the Hepatitis C Secretariat, the Ministry of Community Safety and Correctional Services, AIDS Bureau, and Public Health Division to facilitate the availability of harm reduction tools (including educational materials) through the use of best practices for delivering HCV prevention, testing, and treatment interventions to inmates in correctional facilities.”. The 2014 Public Health Ontario report\(^5^6\) is in agreement on this recommendation.

Although we are unaware of implementation of this recommendation to promote screening in Ontario corrections facilities, there is an organized screening program through 16 ‘hepatitis C teams’ across the province\(^5^7\). These teams were formed in response to the proposed 2009 Hepatitis C Strategy by the Ontario Hepatitis C Task Force with the aim of reducing the spread of the virus through screening and treatment. The 16 teams consist of Treatment Nurses, Community Coordinators, Outreach Workers, Clinical Psychologists, Social Workers, and Peer Support Workers. The teams focus on the following populations: “people who use drugs; people involved with the correctional system; people who are homeless or under-housed; Aboriginal Peoples; street-involved youth; and people with tattoos and/or piercings.” Among these populations, the hepatitis C teams help provide treatment and support to those with HCV,
provide information and awareness about the virus to those infected and not, and communicate appropriate prevention measures. The teams also offer testing to those at risk of infection, and are encouraged to do the blood work themselves as opposed to providing a lab requisition. Further, the Community Coordinators address gaps between health, social, and legal services being provided to those with or at risk of acquiring HCV. The teams provided services to 7,020 individuals during a 12 month period in 2011/2012\textsuperscript{58}. Ontario also considered First Nations people in its HCV Strategy, and cited probable higher prevalence rates. On the question of provincial and federal health care jurisdictions, the Strategy stated\textsuperscript{55}:

“To date, Ontario’s stand is that the federal government has the primary responsibility of providing health care services to First Nations people. While it is essential to recognize provincial and federal jurisdictional boundaries, the distinct needs and realities related to mobility of First Nation communities must be considered to achieve a comprehensive, effective Ontario HCV Strategy. It is time for the provincial government to recognize that First Nations people are also Ontario citizens and must be considered in all HCV strategic plans, priorities, and initiatives.”

The strategy did not mention screening initiatives for HCV among First Nations populations, only improving access to harm reduction programs for First Nations peoples.

\textit{Prince Edward Island}

On February 12, 2015, Prince Edward Island announced a three-year HCV strategy\textsuperscript{59}. While focusing on public funding of the newly-approved direct-acting antiviral Holfira Pak (which has not yet been assessed by the Common Drug Review), the strategy will also "initiate the screening and referral of patients from key access points throughout the province including emergency rooms, addiction services, primary care centres, methadone clinics and corrections facilities." Prince Edward Island has an estimated 400 individuals with HCV; their experiences may not be transferable to Alberta.
3.3.2 International HCV Programs and Guidelines

An overview of the populations recommended for screening by country, not including those already recommended by PHAC, are provided in Table 5. However, only five of these countries report any organized screening programs (Canada, US, UK, Australia, Saudi Arabia).

Table 5: International HCV Screening Guidelines (not including populations recommended by PHAC), by Country

<table>
<thead>
<tr>
<th>Populations Recommended for Screening</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth cohorts</td>
<td>US (1945-1965)(^{48,49}), Canada (Northwest Territories, 1945-1975)(^{53})</td>
</tr>
<tr>
<td>HIV infection</td>
<td>Canada (Ontario)(^{54}), US(^{48}), UK(^{60}), Scotland(^{61}), Australia(^{62}), France(^{63}), Germany(^{63}), Belgium(^{64})</td>
</tr>
<tr>
<td>HIV infection and male who has sex with men</td>
<td>UK(^{65})</td>
</tr>
<tr>
<td>Hepatitis B infection</td>
<td>Canada (Ontario)(^{54}), Australia(^{62}), France(^{63}), Germany(^{63}), Belgium(^{64})</td>
</tr>
<tr>
<td>Aboriginals</td>
<td>Australia(^{62})</td>
</tr>
<tr>
<td>Children in care</td>
<td>UK(^{65})</td>
</tr>
<tr>
<td>Pre-marital</td>
<td>Saudi Arabia(^{66})</td>
</tr>
</tbody>
</table>

3.3.2.1 The United States

Two American agencies have recently updated their recommendations for HCV screening: the CDC in 2012\(^{48}\) and USPSTF in 2013\(^{49}\). Both statements recommended screening Americans born between 1945 and 1965. The recommendations to screen the 1945-1965 cohort were made as this population is estimated to have a high prevalence of undiagnosed HCV infection. The agencies believe that only screening by HCV exposure risk in this cohort would miss a large number of cases: individuals might not be aware, remember, or be willing to admit potential exposure to HCV. The guidelines are based on American chronic HCV prevalence estimates in the 1945-1965 birth cohort (3.25%), and studies have shown that screening and treating this birth cohort in the US would generally be considered good value for money\(^{67}\).

To our knowledge, and as of October 2014, only New York, Massachusetts, and Connecticut have either passed laws about screening those born between 1945-1965 for HCV or have developed organized screening programs for this cohort\(^{68}\). The remaining states have not yet responded to the CDC and the USPSTF recommendations.
New York
As of January 1, 2014, a New York State law requires that a HCV screening test be offered to everyone born between 1945 and 1965 receiving health services in most primary and inpatient settings. The state has promoted the CDC and USPSTF recommendations, as well as this law, among health care providers and the general population. This included a letter to all physicians in the state. Breaking the law could result in a statement of deficiencies or a fine of up to $2000. To our knowledge, New York State has yet to publish a formal evaluation of the impact of this law.

The New York State Department of Health also provides free HCV rapid test kits to third party agencies via their HCV Rapid Testing Program. The program has provided kits to do point-of-care testing at harm reduction agencies, homeless health care agencies, STI clinics, and general health care centres. The New York City Department of Health and Mental Hygiene is also supporting the screening of those born between 1945-1965 for HCV in other ways, including tracking and prompting to screen with electronic medical records.

Connecticut and Massachusetts
Connecticut and Massachusetts have laws similar to New York, mandating the offering of a test to those born between 1945-1965. To our knowledge, neither state has an organized HCV screening program.

3.3.2.2 The United Kingdom
National Institute for Health and Care Excellence (NICE) published guidance on the testing of hepatitis B and C in 2012. Two groups that NICE identifies as being at increased risk for HCV, but are not in the 2009 PHAC recommendations, are “looked-after children and young people, including those living in care homes”, and HIV-positive men who have sex with men. In addition, the UK’s National Health Service recommended in 2004 to screen all those infected with HIV for HCV. The NICE guidance includes 11 recommendations which focus on raising awareness and promoting testing to those at increased risk of infection, notably: people who have ever injected drugs; prisoners; people who visit sexual health, genitourinary, or drug services centres; and migrant populations.
There appears to be some, albeit limited, policy response to this NICE guidance. Work targeting migrant populations from at-risk countries has been documented\textsuperscript{74}. For example, a hospital in Reading has a HCV testing and awareness outreach program targeted at those of South Asian origin\textsuperscript{75,76}. The program provides culturally and linguistically appropriate services, including point-of-care testing for HCV. Some surveillance has also been done on migrant populations by the UK’s Health Protection Agency: in the UK in 2011, those of Eastern European and South Asian origin had positive test rates of 6% and 2.8% respectively\textsuperscript{77}.

NICE also conducted economic evaluations of dried blood spot testing in addiction services, dried blood spot testing in prisons, GP education and paid testing of former IDUs 30-54 years old, and testing migrants to the UK. Testing in addiction services was estimated to have a cost per quality-adjusted life year (QALY) gained of £14,600. The cost-effectiveness of testing in prisons was dependent on continuity of care after leaving the correctional facility; without continuity of care, the cost per QALY gained was an estimated £59,400, but with 50% continuity of care the cost fell to £17,300 per QALY gained. Education and paid testing of former IDUs was associated with an estimated cost per QALY gained of £13,900. Lastly, screening migrant populations with a prevalence of 2% resulted in a cost of £10,200 per QALY gained.

NICE did not commission or conduct an economic model of birth cohort screening in the UK, citing time restraints in publishing their 2012 report. However, NICE cited a lower prevalence in the UK than the US in those who do not currently inject drugs in suggesting that birth cohort screening would be unlikely to be cost-effective in the UK (for example, the UK prevalence is estimated to be less than 0.1% among non-south Asians who have never injected drugs)\textsuperscript{78}. Instead of birth cohort screening, the guidance focused on raising awareness and promoting testing through outreach programs to non-age-based populations at higher risk of infection. The success of this program is unknown.

### Scotland

In addition to the 2009 PHAC risk factors, Scotland recommends screening those infected with HIV. Between 2006 and 2011, Scotland operated the £47 million Hepatitis C Action Plan\textsuperscript{54}. This program included awareness, testing, and surveillance of the virus, as well as prevention initiatives among those who inject drugs and attempts to increase treatment uptake. Working
with non-profit agencies, the plan led, among other things, to greater testing, an increased treatment uptake, and a decreased HCV prevalence in Scotland\textsuperscript{54,74}. The success of this program is unknown.

3.3.2.4 Australia
In 2013, Australia updated their HCV testing policy\textsuperscript{62}. Risk factors included in their screening guidelines but not in PHAC’s 2009 guidelines include those infected with hepatitis B or HIV as well as Aboriginals and Torres Strait Islanders. Australian experts have cited the lower proportion of undiagnosed infection (compared to the US) as a reason to not recommend age-based screening (15% of HCV infections are undiagnosed in Australia compared to 45-85% in the US)\textsuperscript{48,79}. In Australia’s Third National Hepatitis C Strategy, from 2010 to 2013\textsuperscript{80}, one of five priority actions in testing and diagnosing HCV was a more organized screening program of migrant populations. They suggested an action to “implement targeted initiatives with priority CALD [culturally and linguistically diverse] communities” to increase awareness of and support testing according to Australian HCV screening guidelines. As well, in South Australia’s Hepatitis C Action Plan, 2009-2012\textsuperscript{81}, a testing and treatment pilot was proposed targeting culturally and linguistically diverse communities at risk of HCV. Although implemented, we are unaware of any evaluation of the program.

3.3.2.5 Belgium
The Belgian Health Care Knowledge Centre published a report on HCV screening in 2012, and there are also Belgian screening guidelines dating back to 2003\textsuperscript{63,64}. Risk factors for HCV recommended to be screened in Belgium, that were not included in the 2009 PHAC recommendations, were co-infections with hepatitis B or HIV\textsuperscript{64}. The Centre acknowledged the cost-effectiveness of birth cohort screening in the US, but deemed that this was likely not good value for money in Belgium because of lower prevalence rates (an estimated 0.1-1% in the general population) and a larger percentage of the population that has already been tested for HCV (estimated to be over 50%). The report also stated that general screening for research purposes may be appropriate to get a better sense of the prevalence of HCV, and therefore the effectiveness and cost-effectiveness of screening.
3.3.2.6  France
As referenced in the above report by the Belgian Health Care Knowledge Centre, 2001 and 2011 French recommendations advise screening for HCV for those with HIV or hepatitis B, above and beyond the 2009 PHAC risk factors. In terms of organized screening programs in France, The European Medicines Group, an association representing European pharmaceutical companies, highlights the country as a model for government action against HCV:

“As a result of a government led campaign and adequate investment in HCV services in France, detection has more than doubled and significant reductions in deaths from liver disease have been achieved.”

Much of the French strategy involves convenience screening at GP clinics and associated awareness and education campaigns, but screening is also conducted in prisons and in outreach to migrant populations.

3.3.2.7  Germany
Also referenced in this 2012 Belgian report are Germany’s 2010 recommendations for the screening of HCV. In addition to the PHAC risk factors, Germany recommends screening those infected with HIV or hepatitis B.

3.3.2.8  The Netherlands
Also referenced in the Belgian Health Care Knowledge Centre report are the Dutch 1997 and 2004 HCV screening recommendations. They do not recommend screening for a population besides those identified by PHAC in 2009. The Netherlands has also had a public awareness campaign around the virus and who should be tested. An evaluation of the campaign found that support and outreach to primary care providers greatly increased the effectiveness and cost-effectiveness of the campaign.
3.3.2.9 Saudi Arabia
In 2008, Saudi Arabia instituted mandatory pre-marital testing for HIV, hepatitis B, and HCV, in addition to existing mandatory pre-marital testing for sickle cell disease and thalassemia. Approximately 284,000 people are screened annually for HCV through this organized program, about 1% of the population.

3.4 Conclusions
PHAC’s 2009 guidelines recommend risk-based screening and no aged-based screening. The only province or territory to recommend age-based screening is the Northwest Territories, which advises a one-time test for those born between 1945 and 1975. There are few organized public health hepatitis C screening programs in Canada, although exceptions are two initiatives in Ontario and PEI.

Eight other countries were identified in the environmental scan. Only one of these countries (the US) has recommended age-based hepatitis C screening, although few states have responded to the recommendation with organized screening programs. At-risk groups identified in other countries’ guidelines but not in PHAC’s include: those infected with HIV, males infected with HIV and who have sex with men, those infected with hepatitis B, Aboriginals, children in care, and pre-marital screening. We identified few organized screening programs in these eight countries. Rather, screening is typically opportunistic and integrated into general practices, sexual health centres, or services for people who inject drugs.

4 Alberta Context and Program Feasibility: Key Informant Interviews

Summary
- HCV Care Pathway: Assessment and treatment of HCV is provided by specialist physicians with considerable nursing support.
- Increasing capacity in Alberta: Some capacity is available to support implementation of a provincial screening program, as well as the increased assessment and treatment of those diagnosed with HCV; additional resources, and some changes to current assessment and treatment models, would be required depending on the number of patients identified.
- Perspectives on implementation were varied; if a birth cohort screening program were adopted, many recommended a phased-in approach.
- The decision to screen was reported as inextricably linked to the decision to publicly fund DAAs; the belief was that you should not screen if you cannot treat.
4.1  Purpose

• To develop an in-depth picture of the current Alberta HCV care pathway, including the HCV burden of illness, screening, diagnosis and treatment.
• To explore how this pathway might change if a provincial screening program were to be implemented.
• To document perspectives on ‘if’ and ‘how’ a provincial screening program should be implemented and operationalized in light of the Common Drug Review recommendations for emerging DAA HCV drugs.

4.2  Methods

Key informant interviews were conducted. Telephone interviews, ranging in length from 25-90 minutes, were conducted with 14 key informants in February 2015. The interview participants included nine members of the Expert Advisory Group, established for the provincial review of HCV screening through the Alberta Health Technologies Decision Process, and five additional individuals identified through a snowball sampling method as having a valuable perspective to inform the policy question. The participants included individuals based in Edmonton, Calgary, and Grande Prairie. They represented a range of health care, laboratory, and policy experience (two hepatologists, three infectious disease specialists, two microbiologists, one gastroenterologist, one internal medicine specialist, one hospital administrator, two government policy-makers, and one individual with a HCV nursing background).

A semi-structured interview guide was developed to guide the interviews. Broadly, the guide included questions on the burden of illness on individuals living with HCV, the current HCV care pathway in Alberta, the clinician and patient experience with assessment and treatments, the barriers and facilitators to screening and treatment, and perspectives on the implementation of a provincial screening program. This guide evolved over the course of the interviews, as questions were refined to reflect what had been learned through the previous interview(s). Detailed notes were taken and key themes were synthesized to develop the picture of the Alberta context reported on here. All interviews were completed by two trained interviewers.
4.3 Results

4.3.1 The Burden of Illness on Individuals Living with HCV
The natural history of HCV is a slow progression of symptoms, often over decades. If there was no treatment for HCV, many individuals would likely die from other causes; one key informant approximated the proportion to be 50-75% of individuals with HCV.

The major health issue associated with HCV described by health care providers treating people with HCV is the associated liver damage. In Alberta, approximately 40% of liver transplants performed are for HCV related end-stage liver disease. Many people in Alberta die waiting for a liver transplant, due to the limited availability of organs available for transplantation. This was described as a clear public health concern. If Alberta could decrease the prevalence of HCV leading to end-stage liver disease, this was thought to result in a positive impact on other patient populations with liver disease requiring transplantation.

For individuals in late or chronic stages of HCV, health care providers commonly described the burden of disease to be very high. Patients in chronic stages were described as being very ill or even dying due to the severe liver damage associate with HCV (e.g. cirrhosis of the liver, liver failure, liver cancer, and potential need for transplantation). In addition, one clinician described the importance of concomitant and severe kidney problems (i.e. extra hepatic disease) that can develop in a small number of people living with HCV.

When asked to elaborate on the general symptomology of HCV, key informants reported that many symptoms commonly experienced by patients with HCV (i.e., fever, fatigue, reduced appetite, aching muscles and joints, poor concentration, anxiety, depression) were difficult to untangle from or attribute to the HCV alone. This was particularly salient with IDU populations with HCV, as these individuals often face a number of concurrent physical and mental health issues. Health care providers working with marginalized at-risk populations described the importance of education and support to help decrease the stigma associated with HCV. One experienced nurse specialist stated that approximately 2/3 to 3/4 of individuals with HCV experience a number of symptoms in the absence of significant liver disease, with fatigue being the most common.
4.3.2  **HCV Care Pathway in Alberta**

The typical HCV care pathway in Alberta is depicted in Figure 2.
**Figure 2 HCV Care Pathway in Alberta**

Person with suspected HCV

Primary Care physician for initial assessment

HCV Antibody Blood Test Ordered

If negative, no further screening

If positive, referral to Hepatologist, Gastroenterologist or Infectious Disease Specialist in Edmonton or Calgary

HCV PCR Test Ordered

If negative, no further screening

Genotyping Test Ordered

Fibroscan performed to assess extent of liver fibrosis

Other Blood Test Ordered (e.g. Liver Panel Tests)

HCV patient with F0-F2 fibrosis

Delay treatment until condition progresses

HCV patient with F3-F4 fibrosis

If patient has private drug insurance, treat with antiviral drug therapy

If patient does not have private drug insurance, treat with interferon drug therapy

Verify viral load by HCV PCR test until virus cleared

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4.3.3 Current Screening and Diagnosis

Currently, there is no organized, provincial public health screening program for HCV in Alberta. As outlined above, the current Alberta Health guideline, recommends screening for “Persons with significant risk factors (e.g., ever injected drugs [even once], history of incarceration, tattoos, ear or body piercing, organ transplant or a transfusion of blood or blood products before 1990, and health care workers who have injuries from needlesticks or sharps) should be screened for HCV. Persons with liver dysfunction of unknown etiology or chronic liver disease should also be screened.”

Key informants described three additional high-risk groups that should be considered for population-based screening: prison populations, recent immigrants from countries with high HCV rates, and aboriginal populations.

Screening for HCV involves two diagnostic laboratory tests. The initial screening test is the HCV antibody blood test, which is often ordered by a primary care physician. In most cases, patients with a positive HCV antibody test are referred to a specialist physician (e.g., hepatologist, infectious disease, internal medicine, and gastroenterologist) for subsequent ordering of a HCV PCR screening test. The PCR test confirms the diagnosis of HCV. Key informants report that approximately 25% of individuals with a positive HCV antibody test will test negative from the PCR screen, as the virus may have naturally cleared from the individuals’ systems. Further, the HCV PCR test is also performed during and after the course of treatment to monitor the viral load over time and determine whether the virus has finally cleared.

The Provincial Laboratory for Public Health (ProvLab) currently restricts which physicians and clinics have the ability to order the HCV PCR test. Most PCR orders originate from the hepatitis clinics and specialists practicing in Calgary and Edmonton, with some being ordered by specialists across the province who are treating people with HCV. Estimates of the annual number of these diagnostic tests completed in Alberta over the past two years are provided in Table 6.
Table 6: Estimated Annual Diagnostic Laboratory Test Volume for HCV in 2013 and 2014

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>2013</th>
<th>2014</th>
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<tbody>
<tr>
<td>Antibody Blood Test</td>
<td>184,294</td>
<td>197,698</td>
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<tr>
<td>RNA PCR Test</td>
<td>8,104</td>
<td>8,362</td>
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</table>

Concomitant to the HCV PCR test, a genotype test is ordered to determine the variant of the virus. Subsequent blood tests (i.e., liver panels) and a FibroScan (elastography of the liver, non-invasive testing similar to an ultrasound) are also conducted to identify signs of and to assess extent of liver damage. The FibroScan device is currently not available outside of Calgary and Edmonton. There are, however, portable machines available for outreach use in other communities (e.g., Calgary specialists have traveled within Calgary to the Calgary Urban Project Society [CUPS] HCV clinic, or to rural regions such Grande Prairie). Liver biopsies are rarely done to assess liver damage. Individuals identified as having advanced liver fibrosis through a FibroScan may also be referred for an abdominal ultrasound to further evaluate liver cirrhosis. Collectively, the information obtained through the genotyping, liver panel, and the FibroScan is used to inform treatment decision-making.

4.3.4 Current Treatment and Support

There are different models of care for HCV that have evolved over time in Calgary and Edmonton. The coordinated Calgary liver unit is comprised of 10 hepatologists (located at Foothills Medical Centre, South Health Campus, and Rockyview General Hospital) who conduct research, education, and offer clinical patient care for individuals with HCV living in Southern Alberta. The hepatologists work closely with specialized nurses to provide care to their patients.

In Edmonton, there are a number of physicians from the Infectious Disease and Gastroenterology-Hepatology divisions of the University of Alberta who participate in the Hepatitis Support Program, which provides comprehensive care to Northern Albertans with HCV. Outside of the university hospital system, the “The Bailey Health Clinic” also provides care to a large number of people with HCV in Edmonton.
Physician specialists, typically with strong nursing support, provide care for individuals with HCV in community outreach clinics and in the penitentiary health care system. A few examples of such physicians include an infectious disease specialist treating individuals with HCV at the CUPS HCV clinic, and a palliative care physician providing HCV treatment at both the Drumheller Provincial Penitentiary and the Southern Alberta HIV Clinic.

Key informants also described a variety of physician specialists (e.g. internal medicine specialist, gastroenterologist) with expertise in treating individuals with HCV who practice in other major regional centres (e.g., Grande Prairie, Lethbridge, Red Deer). However, for more complicated liver patients, many physicians reported referring these individuals to either the Calgary Liver Unit or the Hepatitis Support Program in Edmonton. This was due to the adverse events and difficulty of care for patients receiving the older injectable interferon-based drugs. With the emergence of the new oral DAAs, many key informants commented that, in the future, many patients may no longer need to be referred to Calgary or Edmonton.

The evidence-based, clinical practice guideline referenced by key informants was the 2015 Update on the Management of Chronic Hepatitis C: Consensus Guidelines from the Canadian Association for the Study of the Liver, which reviews the epidemiology of HCV in Canada, preferred diagnostic tests, and recommendations for treatment of chronic HCV cases with new DAAs. The Recommendations for Testing, Managing, and Treating Hepatitis C developed by the American Association for the Study of Liver Disease (AASLD) were also noted by a few. The AASLD recommendations are housed within a “living” online document, frequently updated as new evidence becomes available. While there is broad overlap with the Canadian recommendations, the AASLD additionally provides recommendations for testing of targeted groups, such as one-time birth cohort screening for HCV (i.e., persons born between 1945 and 1965, without prior ascertainment of risk).

The HCV physicians and nurse specialists that we interviewed all had experience with the new anti-viral drugs. The new DAA therapy was described as well tolerated by their patients and the treatment regime was easy to comply with. These informants also noted that the DAAs were a virtual ‘cure’ for HCV with viral clearance greater than 90%. Funding for the new DAAs is...
increasingly available through private drug insurance for individuals with severe liver fibrosis (e.g., F3 and F4). The two major pharmaceutical companies currently producing new DAAs, Gilead and AbbVie, offer financial assistance programs for the substantial patient out-of-pocket costs (i.e., insurance co-payments).

4.3.5 Current Barriers to Treatment

Individuals with HCV who do not have private drug insurance or whose private insurance does not cover the new DAAs do not, generally, have access to this treatment. Key informants described some exceptions to this, including individuals with HCV with severe liver fibrosis and or post-transplant patients, who are very ill. As mentioned above, such individuals may be able to access the DAAs through a compassionate care program offered by the pharmaceutical companies. For individuals with HCV and concomitant rare conditions (e.g., extra hepatic disease), one key informant described the importance of an appeal mechanism to ensure that such individuals obtain access to the new anti-viral drugs in advance of liver disease progression.

Very few patients are currently being treated by the older interferon combination treatments. Unless the patient is very ill (i.e. in need of immediate treatment) and cannot access the new DAAs, physicians are advising them to wait until the new direct acting anti-viral medications become publicly-funded. For example, at one Edmonton-based HCV clinic, an estimated 200 new patients are on a wait list for treatment with the new DAAs, and less than 5 patients are on active treatment with the older drug regimes, including interferon. Broadly, there was an expectation that public funding of the DAAs in Alberta was imminent.

There are also currently capacity issues with seeing HCV specialists, across the province, which challenge timely assessment and treatment of HCV. In particular, there are variable waiting times to see an HCV specialist. Key informants described the waiting times to be higher in Calgary than Edmonton, and higher in academic centres. The waiting times for the Calgary Live Clinic were described as 2-3 months for people categorized as urgent-plus, and within a year for people categorized as urgent. In Edmonton, waiting times varied across physician specialists; wait times for an infectious disease specialist were described as less than those for a hepatologist.
Hepatologists based out of the university hospitals reported that if a newly diagnosed patient was assessed as being urgent, the anticipated wait time would be within one month.

4.3.6 **Increasing Capacity in Alberta for HCV Screening and Diagnosis**

ProvLab performs all of the diagnostic testing for screening of HCV in Alberta. The HCV antibody tests are performed in both the Calgary and Edmonton ProvLab locations; however, the HCV PCR test and genotyping can only be conducted in the Edmonton laboratory. Discussions for potential expansion of PCR testing at the Calgary laboratory are currently underway.

According to key informants, it would be possible to increase ProvLab capacity and accommodate projected increases in HCV diagnostic tests. Currently, the anticipated turnaround times are quoted at 72 hours for the PCR tests and 24 hours for the antibody tests. In reality, however, delays in test results have averaged between 3-5 days for PCR tests and 3 days for initial antibody tests. Such delays were not necessarily attributed to periods of increased volume of tests, but to the timing and coordination for shipping samples to the laboratories. Thus, key elements to increase current capacity may include: more human resources (with on the job training), more diagnostic equipment and reagents, more efficient shipping processes, and expansion of operational hours.

In addition, there is also the need for more resources to increase the capacity on the public health side in order to respond to the influx of newly reported cases of HCV, as well as to trace all previous contacts of those individuals.

4.3.7 **Increasing Capacity in Alberta for Treatment and Support**

The current physician-directed, registered nurse-run model evolved, in part, because of the careful monitoring and support required for patients undergoing the older interferon treatment. Registered nurses (RN), rather than physicians, are commonly described as conducting the baseline assessments, administering and monitoring treatment, providing ongoing, direct care, and in turn minimizing the in-person physician time. In Alberta, there are a number of very knowledgeable RNs with extensive expertise in HCV care. There is also a well-established national HCV nursing education and research network, the Canadian Association of Hepatology Nurses.
Evolving this model of care, with additional funding and human resources, was proposed as a strategy for treating the many, anticipated new HCV cases to be identified from a provincial screening program. All of the physicians interviewed described the importance of strong nursing support: nurses providing care, with the support of specialist physicians, was likely to be a more viable model than increasing primary care physicians care and support for individuals with HCV. One key informant described a more community-based model, where the majority of assessment, treatment, and support would be provided by specialized nurses working under the supervision of a specialist physician (e.g. a hepatologist or infectious disease specialist) (Appendix A).

4.3.8 Possible HCV Screening Models
Most of the key informants’ areas of expertise are in diagnosing and treating people with HCV, not in the development and implementation of provincial screening programs. As such, limited information in this area was collected. Many noted that the decision about which particular population(s) (if any) should be screened will likely inform the development and composition of a given program. For example, the ideal birth cohort screening program is anticipated to look different from one targeted at new immigrants from countries with a high prevalence of HCV.

It was suggested by one key informant that strategies used in other population screening campaigns (e.g., breast cancer screening, cervical cancer screening) could be adapted for an HCV screening campaign. Regarding the outreach component of a screening model, possible strategies include the development of a media campaign or individual notification letters sent out to citizens in the population of interest. Beyond the initial outreach, issues related to the public’s initial point of contact for the screening program were discussed. For example, whether individuals at risk should freely present to their family physicians for diagnostic testing or whether short-term screening clinics should be created. With such strategies, the role of and potential training of the family physician, as well as access and/or attachment of patients to a family physician must be carefully considered.

Many key informants recommended implementing a phased approach to screening, particularly if a birth cohort screening program were to be adopted, so as not to overwhelm the health care
system. Lastly, responsibilities for the oversight and operations of such a public health program would also need to be clearly delineated between Alberta Health and Alberta Health Services.

4.3.9 Perspectives on a Provincial HCV Screening Program in Alberta

Key informants expressed a variety of perspectives on the implementation of a provincial, public health HCV screening program in Alberta. There was broad support for the implementation of an HCV screening program, particularly given the high cure rate with the new DAAs. There was, however, no consensus on which cohort or cohorts (e.g. baby boomers and recent immigrants) should be prioritized. Known societal stigma associated with HCV was perceived as a barrier for program uptake. Efforts to improve public awareness and education would need to be a priority should a screening program be adopted.

Broadly, many did not have a clear opinion on which populations should be screened. Health professionals with public health expertise and/or who bring health promotion perspectives to their practice supported a birth cohort screening program in Alberta, regardless of whether the new DAAs were publicly funded, arguing that there was a lot of valuable care and support that could be provided to people with HCV in addition to drug treatment.

Some key informants questioned the need for screening of HCV in the general population or in the baby boomer cohort given that HCV is not easily transmitted. Rather, the importance for screening was described as for the prevention of progression of liver disease given the high cost associated with treatment of end-stage liver disease.

As public funding decisions of the new anti-viral HCV drugs were still pending in Alberta at the time of the interviews, many key informants commented that a provincial HCV screening program should not be implemented if there was no intent or capacity to treat the individuals to be screened. Further, the backlog of individuals already screened and currently awaiting treatment must also be considered among resource allocation decisions. It was argued that allocating resources to screen individuals who may be ineligible for treatment (e.g. Fibrosis stages 0-2) would be unnecessary.
4.4 Conclusions

In conclusion, broad support for a variety of screening programs was expressed by key informants. However, there was no unanimous support for one particular screening program or targeted group.

The policies of a HCV screening program and public funding of the new DAAs were described as so intimately linked, that they could not be decided upon in isolation. Thus, most key informants felt that a screening program should not be introduced if provision of the best and most current treatments (including the new DAAs as outlined in the most recent HCV clinical practice guidelines\cite{88}) are not publicly funded.
5 Patient Perspective: A Systematic Review of the Literature

Summary

- Six studies on screening for HCV indicate that personal barriers (i.e. time, transportation), stigma, and poor relationship with health care provider prevent individuals from seeking HCV screening.
- Forty-six studies on experiences living with HCV indicate that those with HCV are often feeling stigmatized, and unsupported in their care, relationships, and work environment while coping with physical and psychological symptoms.

5.1 Purpose
To understand the experience of living with HCV from the perspective of individuals who have been diagnosed with HCV; and to understand experience and attitudes towards HCV screening from the perspective of those with and without an HCV diagnosis.

5.2 Methods
A systematic review on patient perspectives of living with HCV, and HCV screening was completed. MEDLINE, PubMed, EMBASE, PsychINFO, CINAHL, and SocINDEX were searched from inception until January 19th, 2015. The search strategy was developed by a library and information specialist. Terms capturing the disease (e.g. hepatitis C, hep c, hepatitis c antigens, and hcv) were combined using the Boolean operator “and” with terms reflecting the patient experience (e.g. attitude, health behaviour, experiences, and quality of life). These results were then focused to include only qualitative studies by using terms such as “qualitative research,” “focus groups,” and “grounded theory.” Results were filtered to exclude non-English results, non-human studies, and pediatric studies. The full search strategy can be found in Appendix B.

The abstracts retrieved were screened in duplicate by independent reviewers. Abstracts were assessed using the following inclusion criteria developed a priori: women or men diagnosed with HCV, or screened for HCV; report on experience living with HCV, or being screened for HCV;
original qualitative research; and adult participants. Abstracts were excluded if they did not meet
the above inclusion criteria, or if they: did not report results from the patient perspective; they
reported only experience with treatment; presented primarily quantitative data; or if all of the
participants were co-infected with another disease. Abstracts included by either reviewer
proceeded to full-text review; consensus was not required. This abstract screen was intentionally
broad to ensure that all relevant literature was captured.

Studies included after the first screen proceeded to full-text review by two independent
reviewers. Studies were included if they met all of the inclusion criteria and did not meet any of
the exclusion criteria presented in Table 7. Disagreement between reviewers was resolved by
consensus or by a third reviewer. Systematic reviews were hand-searched to ensure that all
relevant articles were included.

Table 7: Inclusion and Exclusion Criteria for Systematic Review of Patient Experiences

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>• Women or men diagnosed with HCV Virus, or screened for HCV</td>
<td>• Individuals included in the study who do not have Hepatitis C, or were not</td>
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<td>• Report on at least one of the following, from the patient's perspective:</td>
<td>screened for HCV</td>
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<td>o Experience living with HCV</td>
<td>• Did not report on at least one the</td>
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<tr>
<td>o Experience with HCV screening</td>
<td>following from the patient's perspective:</td>
</tr>
<tr>
<td>• Original qualitative research</td>
<td>o Experience living with HCV</td>
</tr>
<tr>
<td>• Full-text available</td>
<td>o Experience with HCV screening</td>
</tr>
<tr>
<td>• Adult participants</td>
<td>• Inclusion of participants under 18 years old</td>
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<tr>
<td></td>
<td>• Physician accounts of patient experience</td>
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<td></td>
<td>• Experience of treatment with peg-interferon medication</td>
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<tr>
<td></td>
<td>• Abstracts or posters (with no full-text available)</td>
</tr>
<tr>
<td></td>
<td>• Case studies, reviews, meta-analyses</td>
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<tr>
<td></td>
<td>• Quantitative study designs</td>
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</table>

Eight key themes were used as a lens for analyzing each study: experience with screening;
experience with diagnosis; stigma; impact on relationships; impact on career; experience with
HCV symptoms; experience with health care system; and other. Information relevant to these
themes was identified and extracted in duplicate from each study. Additional information such as journal, study design, participant selection, participant inclusion and exclusion criteria, participant characteristics, and findings were extracted in duplicate from each included study. Data from the eight key themes has been summarized narratively.

5.3 Results
Seven hundred and ninety-eight abstracts were retrieved (Figure 3). During abstract review, 118 abstracts were selected by the reviewers and continued to full-text review. Two systematic reviews were hand-searched\textsuperscript{90,91}, and two additional studies were included in full-text review, for a total of 120 studies reviewed in full-text. Sixty-eight studies were excluded for various reasons (not patient perspective (n=3), not HCV (n=9), primarily quantitative data (n=22), only explored experience with treatment (n=16), not available in full-text (n=9), not a relevant study design (n=5), and did not report experiences living with HCV or experiences with HCV screening (n=4)). Fifty-two studies were included in the final data set; six of the included studies looked at the experiences individuals with or without HCV had related to the screening process\textsuperscript{92-97}, and the remaining forty-six reported experiences of living with HCV.

Figure 3 Flow chart of included and excluded studies
5.3.1 Screening

Characteristics of Included Studies

Of the six studies that assessed experiences and attitudes toward screening, two included participants from a general population\textsuperscript{92,93}, three included participants who were IDUs\textsuperscript{94-96}, and one included participants who had been in prison\textsuperscript{97} (Table 8). Two of the studies were conducted in the UK\textsuperscript{92,97}, two in the United States\textsuperscript{94,95}, and one each from Ireland\textsuperscript{96}, and the Netherlands\textsuperscript{93}. The studies were conducted between 2004\textsuperscript{92} and 2014\textsuperscript{94}. All six studies collected data using interviews. Data were analyzed using an inductive approach\textsuperscript{92-94,97}, and using a grounded theory approach\textsuperscript{95,96}. Various software programs were used by each study: NVivo\textsuperscript{96}, MAXqda\textsuperscript{93}, and atlas.ti\textsuperscript{95}; three studies did not report software used for analysis\textsuperscript{92,94,97}. Four broad themes were explored in the six included studies: experiences with screening, experiences with diagnosis, stigma, and experiences with health care system (Table 9). The number of participants in each study ranged from 35\textsuperscript{97} to 362\textsuperscript{94}. 
<table>
<thead>
<tr>
<th>Author, Year of Publication, Country</th>
<th>Journal</th>
<th>Study Design</th>
<th>Participant Selection</th>
<th>Participant Inclusion Criteria</th>
<th>Participants Exclusion Criteria</th>
<th>Participant Characteristics</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Population</strong></td>
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<tr>
<td>Craine et al. 2004 England</td>
<td>International Journal of Drug Policy</td>
<td>Semi-structured interviews, analyzed using the inductive framework approach.</td>
<td>Eligible participants were recruited (opportunistic sampling) through mail from a drug treatment service. Dates of recruitment are not reported.</td>
<td>None reported</td>
<td>None reported</td>
<td>43 participants were included: 35% female, mean age of females 27 (range 21-33), mean age of males 31 years old (Range 17-47)</td>
<td>Reasons for not being tested include: apprehension about results, unsure whether they had been tested, and ignorance of HCV and/or testing process. Those who had been tested and did not have HCV reported being more careful when injecting.</td>
</tr>
<tr>
<td>Zuure et al. 2011 Netherlands</td>
<td>BMC Public Health</td>
<td>Semi-structured, open-ended interviews analyzed using an inductive thematic approach, and MAXqda 2007 software was used.</td>
<td>Eligible participants were recruited through a website for individuals who were advised to test for HCV. Participants were recruited between May and July of 2007 and 2008.</td>
<td>• Subscribed to the reminder service for the website</td>
<td>None reported</td>
<td>33 participants included: 79% female, median age 49 years old (range: 41-62)</td>
<td>This study found that this online screening campaign motivated individuals to test for HCV. Three screening facilitators were identified: testing reminders, concern of transmission to others, and receiving personalized testing advice.</td>
</tr>
<tr>
<td><strong>Injection Drug Users</strong></td>
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<tr>
<td>Barocas et al. 2014 United States</td>
<td>Harm Reduction Journal</td>
<td>Open-ended interview questions, analyzed using an inductive thematic approach.</td>
<td>Eligible participants were consecutively recruited between June and August 2012 from a multi-site syringe exchange program in Southern Wisconsin</td>
<td>• English speaking</td>
<td>• Not English speaking</td>
<td>362 participants included: characteristics of participants not reported</td>
<td>This study identified barriers and facilitators to screening. Some facilitators include: health concern for others, mobile testing center, free testing. Some barriers include: lack of transportation, time constraints, cost, and lack of knowledge about screening.</td>
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<tr>
<td>Jordan et al. 2013</td>
<td>Harm Reduction</td>
<td>Semi-structured focus were</td>
<td>Eligible participants</td>
<td>≥18 years old</td>
<td>Cognitive impairment,</td>
<td>95 participants included: 41%</td>
<td>This study identified barriers to screening. Some</td>
</tr>
<tr>
<td>United States</td>
<td>Journal</td>
<td>Analyzed using a grounded theory approach, and Atlas.ti V5 software was used.</td>
<td>Recruited through staff referrals from HIV primary care clinics, methadone maintenance treatment program, and syringe exchange programs in New York and San Francisco. Dates not reported.</td>
<td>American or Latino • Receiving services at recruitment sites</td>
<td>Suicidal ideation, or active psychosis • Illicit drugs in past 12 months</td>
<td>Female, mean age 45 years old (range: 32-58)</td>
<td>Barriers include: poor knowledge of test sites, poor provider-patient communication.</td>
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<tr>
<td>Swan et al. 2010 Ireland</td>
<td>AIDS Patient Care and STDs</td>
<td>Semi-structured, in-depth interviews were conducted. Data were analyzed using a grounded theory approach, and NVivo 8.0 software was used.</td>
<td>Eligible participants were consecutively recruited from two addiction clinics, a drop-in center, a general practice, two hepatology clinics and an infectious disease clinic in Dublin from September 2007 to September 2008.</td>
<td>≥18 years old • Current or previous IDU</td>
<td>None reported</td>
<td><strong>36 participants included:</strong> 22% female, median age 32 years old (age range: 14-29)</td>
<td>This study identified barriers to screening. Some barriers include: isolation, perception of HCV as benign, feeling well, and fear of investigations and treatment. Barriers to care were also identified: limited knowledge of testing locations, not being referred for treatment, ineligibility for treatment because of drug or alcohol abuse, and the inconvenience of travelling.</td>
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<tr>
<td>Prisoners</td>
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<tr>
<td>Khaw et al. 2007 United Kingdom</td>
<td>BMC Public Health</td>
<td>Open-ended interview questions, analyzed using an inductive thematic approach.</td>
<td>Eligible participants were recruited (through purposive sampling) from three prisons by referral. Dates of recruitment were not reported.</td>
<td>English speaking • ≥18 years old • History of injection drug use</td>
<td>None reported</td>
<td><strong>30 participants included:</strong> 17% female. Mean age, and age range not reported.</td>
<td>This study identified barriers to screening. Some barriers include: lack of knowledge and fear of disease, a lack of awareness about the testing procedure, disease prognosis, treatment and outcome, and concern about confidentiality and stigma.</td>
</tr>
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</table>
Findings

Similar themes were reported across all studies; themes did not vary widely by type of population recruited. Experience with screening was a key theme explored in Zuure et al., Jordan et al., Swan et al., and Khaw et al.93,95-97 (Table 9); identifying barriers and facilitators of screening was the focus of these studies. Barriers identified included: inconvenience or lack of transportation93,94,96, time constraints93,94, cost94, lack of knowledge (screening, and testing locations)94,96, not being referred96, fear of treatment and screening92,93,96, being asymptomatic93,96, fear of stigma93 and ineligibility because of drug and alcohol use96. Two studies also identified factors that facilitated HCV testing, which included: concern of transmission93,94, accessibility via a mobile testing center94, use of online program to receive personalized test advice93, testing reminders93, and free testing94.

Craine et al. and Jordan et al. additionally explored themes of experience with diagnosis. Jordan et al. found that when reflecting on diagnosis, participants expressed being surprised that they had HCV, and felt that they did not receive sufficient information, nor support, after diagnosis95. Craine et al. found that a both positive and negative test results changed the behaviour of IDUs92. Participants who tested negative generally reported reduced anxiety and reported that their negative test reinforced the necessity of maintaining safe injection practices92. Those who tested positive reported either more cautious behaviour, or expressed ambivalence to HCV status92.

Craine et al. and Swan et al. briefly explored themes of stigma. Craine et al. reported that the majority of participants who tested positive for HCV would not disclose this to others; primarily for fear of being stigmatized, and therefore leading to increased risk of transmission92. And Swan et al. found that participants were embarrassed by their HCV status, and felt stigmatized by health care providers; particularly if route of transmission was injection drug use96. Participants also reported that stigma prevented them from getting screened96.

Both Jordan et al. and Swan et al. reported findings on the experience participants had with the health care system. Participants of these studies often felt that there was a gap between screening and treatment and that they were “left hanging” after their HCV screening and diagnosis95. Generally, participants reported not trusting their health care provider95, impersonal relationships
with their doctor\textsuperscript{96}, and feeling abandoned by the health care system\textsuperscript{95}; however, a few participants reported that their physician was supportive\textsuperscript{96}. 
### Table 9: Primary Themes on Patient Experiences with HCV Screening, by Paper

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Experience with Screening</th>
<th>Experience with Diagnosis</th>
<th>Stigma</th>
<th>Impact on Relationships</th>
<th>Impact on Career</th>
<th>Experience with Symptoms of HCV</th>
<th>Experience with Health Care System</th>
<th>Other (specify)</th>
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<tr>
<td>General Population</td>
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<tr>
<td>Craine$^{92}$</td>
<td>2004</td>
<td></td>
<td>✔️</td>
<td>✔️</td>
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<tr>
<td>Zuure$^{94}$</td>
<td>2011</td>
<td></td>
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<td>Injection Drug Users</td>
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<td>Barocas$^{98}$</td>
<td>2014</td>
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<tr>
<td>Jordan$^{95}$</td>
<td>2013</td>
<td>✔️</td>
<td>✔️</td>
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<td>Swan$^{96}$</td>
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5.3.2 Experience Living with Hepatitis

Forty-six studies, reporting on forty-two populations assessed the experience of living with HCV, from the perspective of those with a HCV diagnosis (Table 10). Some of the included studies assessed the same population, but report different findings: Olsen\textsuperscript{99}, Olsen\textsuperscript{100} and Olsen\textsuperscript{101}, Harris\textsuperscript{102} and Harris\textsuperscript{103}, and Tompkins\textsuperscript{104} and Wright\textsuperscript{105}. Thirty-eight studies included participants from a general population\textsuperscript{99,101-103,106-139}, seven included participants who were IDUs\textsuperscript{100,104,105,140-143}, and one included participants who received contaminated Anti-D Immunoglobin (blood product)\textsuperscript{144}.

Seventeen were conducted in Australia\textsuperscript{99-101,103,110,112,113,118,119,131,133,136-139,142,143}, fifteen in the UK\textsuperscript{102,104,105,111,114,115,117,120,126,127,129,132,135,141,144}, eight in the United States\textsuperscript{106,107,116,121,123,128,134,140}, four in Canada\textsuperscript{108,109,125,130}, and one each from Pakistan\textsuperscript{122} and France\textsuperscript{124} (Table 10). The studies were published between 1999\textsuperscript{119} and 2014\textsuperscript{120,128}. Data were analyzed using a variety of methods, including: thematic and content analysis\textsuperscript{99-101,104,107,125,128,136,142}, inductive approach\textsuperscript{108,134,137,139}, grounded theory\textsuperscript{110,112,115,126,141}, framework approach\textsuperscript{105}, phenomenological\textsuperscript{111,117,120,123,131,132,144}, interpretive approach\textsuperscript{113,119}, and constant comparative analysis\textsuperscript{121,130}. Various software programs were used by these studies: NVivo\textsuperscript{108,109,127,128,135,140}, atlas.ti\textsuperscript{99-101,106}, and QSR*NUDIST\textsuperscript{121}.

Many themes were explored in the forty-six included studies: experience with symptoms of HCV, experience with diagnosis, impact on careers, stigma, experience with health care system, impact on relationships, and others (Table 11).

Experiences with Symptoms of HCV

Thirteen of the included studies reported patient experiences with symptoms of HCV\textsuperscript{107,110,113-116,120,122,126,134,140,142,144} (Table 11). Participants of the included studies reported a variety of physical symptoms, such as fatigue\textsuperscript{107,110,113-116,120,122,126,134,140,142,144}, weakness\textsuperscript{107,115}, nausea\textsuperscript{107,110,114,142}, pain\textsuperscript{107,114,116,122,142,144}, swelling\textsuperscript{107}, headaches\textsuperscript{110,142}, and sweating\textsuperscript{110}. In addition, a number of studies reported participants experiencing psychological symptoms such as depression\textsuperscript{107,110,144}, anxiety or panic attacks\textsuperscript{115}, irritability\textsuperscript{116,140}. Other symptoms such as poor memory\textsuperscript{110,115}, and inability to concentrate\textsuperscript{110,115,126} were also reported by participants.
Broadly, studies reported that participants experienced considerable disruption to daily living, impaired quality of life, and chronic symptoms due to physical and psychological symptoms of HCV.

**Impact on Career**

Three studies looked at the impact a HCV diagnosis has on one’s career (Table 11). Fry et al. found fatigue and other physical symptoms often made full-time work difficult to maintain; many participants switched to working part-time, quit their job, or changed sectors\textsuperscript{113}. Seven of the fifteen participants reported disclosing their status at work; three experienced discrimination (two of whom subsequently quit due to discrimination)\textsuperscript{113}. This was echoed by Crocket et al. who found that physical symptoms and concern about disclosure were the key barriers to stable income\textsuperscript{142}, and Moore et al. who reported that the stigma of HCV deterred them from disclosing their status\textsuperscript{127}.

**Experience with Diagnosis**

Twenty-two studies looked at the experience of diagnosis (Table 11). Experiences were largely related to either the emotional impact of receiving an HCV diagnosis, or the method of communicating the diagnosis.

After receiving a positive HCV diagnosis, patients experienced a range of emotions, including: distress (being overwhelmed, frightened, feelings of hopelessness)\textsuperscript{103,104,113,114,116,119,124,131,140-142,144}; shame or disgust\textsuperscript{104,116,119,120,124}; denial or doubt\textsuperscript{104,116,124}; and relief\textsuperscript{116,140,144}. Studies reported that some patients were shocked or surprised by their HCV diagnosis\textsuperscript{101,103,104,113,114,116,120,123,124,131,132,141}, while others were not surprised or had expected a positive HCV result\textsuperscript{101,113,116,118}. Commonly, those who were not shocked or surprised at the time of diagnosis were current IDUs who viewed contracting HCV as inevitable\textsuperscript{100,101,103,116,118}, often thinking of HCV as a “legacy of drug use”\textsuperscript{120}. Some IDUs felt that they had accepted the risk of becoming HCV positive when they began using injection drugs\textsuperscript{101,141}. Those who expressed shock and devastation at the time of diagnosis were often those who were no longer IDUs, those who were in rehab, or those who had never used drugs\textsuperscript{103}. Participants that were former IDUs
found a positive HCV diagnosis was troubling because it forced them to acknowledge their previous drug use\(^{100,113}\).

In addition, some individuals felt unconcerned with their HCV diagnosis\(^{100,103,113,120,135,141}\). Their lack of concern stemmed from a variety of sources, including: a lack of physical symptoms or physical impact\(^{135}\), being overshadowed by a HIV diagnosis\(^{141}\), and feeling like they had bigger problems than a HCV diagnosis\(^{100}\).

Communication of diagnosis was another frequently discussed theme. Inadequate information at the time of diagnosis led to a poor experience for participant\(^{126}\), and a feeling of confusion\(^{139,142}\). Participants voiced that their experience of diagnosis was more distressing when they were not given sufficient information\(^{103,113,120}\), or when the individual felt that the information was delivered insensitively (e.g. over the phone\(^{103}\)). Harris et al. found that individuals were more likely to be unconcerned with a HCV diagnosis if they received little information\(^{103}\). One study also found that the experience of diagnosis was seen in a more positive light by patients diagnosed by a family doctor or GP, than those diagnosed in an organizational setting (i.e. prison, injection drug service)\(^{136}\).

Stigma

Twenty studies looked at the experience of stigmatization (Table 11). Often discussed in these included papers were the reasons for stigma, responses of the HCV infected individuals to stigma, and the consequences of stigma. In three of the included studies, participants noted that they felt more stigmatized by HCV status, than HIV\(^{103,128,129}\).

The cause of stigma was found, consistently, to be either an association of HCV with injection drug use or risky behaviours\(^{109,110,112,113,120,121,126,127,129,131,133,142}\), or ignorance or misconception about transmission\(^{106,109,112,113,121,126-128,133,143}\). Individuals with HCV reported that misinformation made those around them afraid of touching them\(^{109,121,126,143}\), and afraid of them using regular utensils and plates (e.g. those with HCV would be offered plastic utensils and paper plates)\(^{110,121,126-128}\).
Emotional and action-based responses were reported in the included papers. Emotional responses to stigma, include: hurt feelings\textsuperscript{109,113}, shame\textsuperscript{109,113,129,133}, embarrassment\textsuperscript{109,127}, low self-worth\textsuperscript{109}, fear\textsuperscript{109,127,129}, anger\textsuperscript{109,113,129}, depression\textsuperscript{109}, isolation\textsuperscript{109}, dirty\textsuperscript{117,129,135,142}, rejected\textsuperscript{129}. Action-based responses to stigma included educating others\textsuperscript{109}, blaming others\textsuperscript{109}, and changing relationships\textsuperscript{109}. Due to perceived stigma, or a fear of stigmatization, those with HCV also were afraid to disclose their HCV status\textsuperscript{117,120,121,127,129,133,135,142,143}, lost friends\textsuperscript{106}, changed employment to avoid stigmatization\textsuperscript{106,127}, and isolated themselves to avoid experiences of stigma\textsuperscript{120,121,126,128,135}.

In many studies, participants also reported either overt or covert stigmatization or discrimination from health care practitioners\textsuperscript{109,118,120,126,127,133,143}. One participant expressed that stigmatization from a health care professional felt particularly degrading\textsuperscript{120}. Often, this type of stigmatization created a barrier to understanding HCV and seeking help from health care professionals\textsuperscript{113,133,142}.

**Impact on Relationships**

Among thirteen studies that reported on the impact HCV had on an individual’s relationships, some reported that, broadly, relationships were strengthened due to the diagnosis\textsuperscript{104,113,116,122,132,140}, while others reported that HCV negatively impacted relationships\textsuperscript{106,110,113,122,131}. Those who felt that their relationships were strengthened said that they felt more supported and closer to their family after being diagnosed with HCV\textsuperscript{104,113,116,122,132,140}. Those who experienced a deterioration in their relationships cited irrationality and irritability\textsuperscript{106,122,131,140}, fatigue\textsuperscript{106,113,131,144}, physical pain\textsuperscript{122,144}, stress and financial burden\textsuperscript{106}, fear of transmitting HCV to family and children\textsuperscript{110,142}, and fear of sexual transmission or pregnancy\textsuperscript{100,122,127,142}, as the reasons for weaker relationships.

The impact of HCV on children was discussed. Some individuals reported behavioural problems with children due to the tension and deterioration of relationships between parents\textsuperscript{131}. It was also reported that some children became confused and frustrated by the lack of energy their parent had, and the change in their parent’s behaviour\textsuperscript{144}. 

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Experience with Health Care System

Nineteen studies looked at experiences with the health care system, and health care practitioners (Table 11). Broadly, the experiences expressed by participants of the included studies were negative. Themes often discussed include relationship with health care practitioners, communication with health care practitioners, perceived competence of health care practitioners, continuity of care, and availability of information.

Many participants cited having a negative relationship with their health care providers. Examples of negative relationships include focus on disease rather than person\textsuperscript{130,131}, not feeling supported\textsuperscript{122,128,142}, and being treated like a “leper” or feeling unworthy of medical care\textsuperscript{126,133,136,142,143}. One study listed having a poor relationship with doctor as a barrier to care\textsuperscript{128}.

In terms of communication, participants expressed the desire to have involvement in decision-making\textsuperscript{130}, to feel like health care practitioners were listening to their concerns\textsuperscript{108}, to feel cared for\textsuperscript{108}, and to not be spoken to insensitively\textsuperscript{108}. However, patients felt that they were treated insensitively\textsuperscript{104,120,127,133}, adequate time was not spent with patients\textsuperscript{142}, confusing medical terms were used\textsuperscript{142}, and health care practitioners refused to treat HCV patients\textsuperscript{127,143}. In contrast, one study reported that participants felt that their health care practitioners spent adequate time with them\textsuperscript{108}.

Participants ideally wanted a health practitioner who was well informed and respected confidentiality. In one study, Brunings et al. reported that health care practitioners were poorly informed and patients felt that they were educating the doctor\textsuperscript{108}. In another study, one patient was concerned because their health care practitioner had breached confidentiality\textsuperscript{133}.

Concerns about continuity of care were discussed in one study\textsuperscript{130}. In this study, participants felt that their care was fragmented, that specialists assumed that all they had to do was treat the disease and monitor disease progression, and that GPs and specialists worked in silos\textsuperscript{130}.

Availability of information was a theme explored often in the included literature. Broadly, individuals with HCV felt that they were not given adequate information. Individuals reported
that they had been given negligible information about HCV after diagnosis or were poorly informed\textsuperscript{103,120,128,139,142}, that they were told different information every visit\textsuperscript{119}, and that they were not given practical advice\textsuperscript{120,130}. A lack of information from health care practitioners resulted in individuals seeking information from other sources\textsuperscript{128,139}. People felt less stressed when more information was given\textsuperscript{113}. One participant suggested that an education class would be of value to those diagnosed with HCV\textsuperscript{128}. In only one study, by Temple-Smith et al., participants noted that they received adequate information\textsuperscript{136}.

Another theme that was often brought up by participants was that they wished to experience more holistic care\textsuperscript{118,120,130,131}. Participants felt that the medical model of care used by health care practitioners did not address all of the issues faced by those with HCV\textsuperscript{118,120,130,131}.

\textbf{Other}

Various other topics were explored by the included studies, such as quality of life after liver transplant\textsuperscript{111}, experience of alcohol abstinence\textsuperscript{102}, contraception decisions\textsuperscript{145}, and experiences with injection drug use\textsuperscript{105} after HCV diagnosis.

For participants who have undergone a liver transplant because of HCV, Dudley et al., found that participants suffer from symptoms such as weight loss, lethargy, weakness and anorexia, to the extent where within one-year of the operation, they wish that they had not received a transplant\textsuperscript{111}. However, after one year, none of the participants regretted having the transplant\textsuperscript{111}. Participants described that they needed “deliberate and conscious effort to adapt to living with a transplant.”\textsuperscript{111} Despite the long-term symptoms, participants also expressed feeling that they had a new and positive outlook on life\textsuperscript{111}.

The experience of abstaining from alcohol after HCV diagnosis was explored in a study by Harris et al.\textsuperscript{102}. In this study participants spoke about not knowing how much alcohol they could safely consume, and mixed messages from health care practitioners regarding alcohol consumption\textsuperscript{102}. Individuals found it difficult to abstain from alcohol, or limit consumption of alcohol because their social life was tied to drinking, or because they felt alienated from their
social network as a non-drinker\textsuperscript{102}. Some participants continued to drink heavily, often justifying their decision as prioritizing pleasure over fear of death\textsuperscript{102}.

Olsen et al. looked at the use of contraceptives in women with HCV, and found that the diagnosis of HCV did not significantly impact women’s decisions around contraception\textsuperscript{99}. Women with HCV used a variety of contraceptives, or in some cases had reasonable justification for not using contraceptives\textsuperscript{99}. The type of contraceptive used was dictated by women’s experiences, the experiences of other women, availability, and doctor recommendations\textsuperscript{99}.

Injection drug use, after HCV diagnosis, was described in a paper by Wright et al.\textsuperscript{105}. A fear of transmitting HCV to others was a theme explored in this study; strategies such as covering wounds, using separate injection material, and not allowing anyone to use their personal hygiene items were used to prevent transmission\textsuperscript{105}. Some participants, despite knowing that they had HCV, would not use safe injection practices to reduce transmission to others\textsuperscript{105}. Individuals described using more drugs after diagnosis, due to symptoms related to HCV\textsuperscript{105}. 
<table>
<thead>
<tr>
<th>Author, Year of Publication, Country</th>
<th>Journal</th>
<th>Study Design</th>
<th>Participant Selection</th>
<th>Participant Inclusion Criteria</th>
<th>Participants Exclusion Criteria</th>
<th>Participant Characteristics</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Injection Drug Users</td>
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| Contreras et al. 2013 United States | Frontiers in Psychological and Behavioural Science | Semi-structured interviews (18 questions) were conducted focusing on experiences of contracting and diagnosing HCV, impact of HCV, and experiences living in Oxford House. Data were analyzed using NVivo software, and coded using a hierarchical coding system. | A convenience sample of eligible women were recruited from Oxford House residents in Illinois. Dates of recruitment are not reported. | • Living in an Oxford House  
• Diagnosis of HCV | None reported | 4 participants were include: 100% female, mean age 42.7 (range and standard deviation not reported) | This study found that participants were not surprised by their diagnosis (all were infected from intravenous drug use). Participants reacted to diagnosis with depression, and in one case, relief. One participant reported symptoms of fatigue, and several mentioned long-term emotional issues. Half reported an impact on relationships. |
| Copeland et al. 2004 Scotland       | Drugs: Education, Prevention and Policy | Semi-structured interviews, conducted in groups, were carried out using an interpretive phenomenology method. Data were analyzed using processes consistent with the grounded theory approach. | Eligible participants were recruited (purposive sampling) by referral (General Practitioner). Dates of recruitment were not reported. | • Diagnosis of HCV  
• Current or past injection drug use  
• Registered with Muirhouse Medical Practice  
• Member of Edinburgh Drug Addiction Society | None reported | Sixteen participants were included: 56% female, mean age for females 41 years old (range 35-40, standard deviation 5.34), mean age for males 36 years old (range 30-46, standard deviation 5.16) | Key themes related to living with HCV included: reaction to diagnosis, HCV knowledge, awareness of transmission, and meaning of HCV. Some participants were indifferent to diagnosis, some were frightened and others were less concerned with HCV than with HIV. Some expressed relief that they had a diagnosis for their health problems. Participants felt that there was a lack of information on HCV. |
| Crockett et al. 2013                 | Women and Health | Semi-structured interviews were | Eligible participants were recruited | • Women  
• Diagnosed with | None reported | 25 participants were included: | This study found that women experienced |
<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Study Title</th>
<th>Methodology</th>
<th>Eligibility</th>
<th>Participants</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>Australia</td>
<td>Habib et al.</td>
<td>Self-reported questionnaire with open and closed ended questions. Method of qualitative data analysis is not reported.</td>
<td>Current or past injecting drug users, Diagnosis of HCV</td>
<td>Eligible participants were recruited by referral and advertisement from needle and syringe programs, and one methadone clinic in Sydney, Australia from January to June 1998.</td>
<td>274 participants included: 46% female, mean age 31 years old (range 17-64)</td>
</tr>
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<td>2003</td>
<td>Australia</td>
<td>Olsen et al.</td>
<td>Semi-structured, open-ended interviews were conducted. Data were thematically analyzed using Atlas.ti software.</td>
<td>Diagnosis of HCV, Women, Injection drug users</td>
<td>Eligible participants were recruited (purposive sample) from various community organizations in Canberra and Melbourne Australia between 2005 and 2006</td>
<td>83 participants included: 100% female, age range:16-61 years old</td>
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<tr>
<td>2005</td>
<td>United Kingdom</td>
<td>Tompkins et al.</td>
<td>In-depth, open-ended interviews were conducted. A framework approach was used to thematically analyze data.</td>
<td>Positive antibody test for HCV, Homeless</td>
<td>Eligible participants were recruited (purposive sample) from a primary care centre for homeless using computerized records to identify</td>
<td>17 participants included: 12% female, age range: 22-49 years old</td>
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</table>

Themes of discrimination were explored in this research. More than half reported experiencing discrimination due to HCV, primarily in health care situations. Participants reported that this feeling of discrimination impacted access to health care. This study identified the following themes: drug dependence, unstable housing, unemployment, financial strain, other health issues and relationships, with concerns for HCV status were lower than other health problems and socio-economic circumstances. Most women felt they were not given enough information or support at time of diagnosis. Women felt HCV had impacted their physical and emotional health which were seen as a barrier to secure employment.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Methodology</th>
<th>Participants</th>
<th>Results</th>
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<tbody>
<tr>
<td>Wright et al. (^{105}) 2005 United Kingdom</td>
<td></td>
<td>Health and Social Care in the Community</td>
<td>In-depth interviews were conducted. A framework approach was used to thematically analyze data. Eligible participants were recruited (purposive sample) from primary health care center for homeless people in the north of England. Dates of recruitment were not reported.</td>
<td>• HCV diagnosis</td>
<td>17 participants included: sex of participants was not reported, mean age of participants was not reported (age range 22-49 years old)</td>
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<tr>
<td>General Population</td>
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<td>Blasiolo et al. (^{106}) 2006 United States</td>
<td></td>
<td>World Journal of Gastroenterology</td>
<td>Semi-structured interview, analyzed using Atlas software program. Eligible participants were consecutively recruited between October 1998 and May 2003 from a Midwestern teaching hospital during a clinic visit.</td>
<td>• Diagnosis of HCV</td>
<td>342 participants included: 37.4% female, mean age 45.2 years old (standard deviation 9.2)</td>
</tr>
<tr>
<td>Bova et al. (^{107}) 2008 United States</td>
<td></td>
<td>Journal of the Association of Nurses in AIDS Care</td>
<td>Mixed method design. Semi-structured interviews, analyzed using qualitative content analysis and qualitative descriptive methods. Eligible participants were recruited through referral and by advertising in HIV clinics in Central and Western Massachusetts. Dates of recruitment were not reported.</td>
<td>• Diagnosis of HCV and human immunodeficiency virus • 18 years or older • English speaking</td>
<td>39 participants were included: 46.2% female, mean age 45 years old (range 34-56, standard deviation 5)</td>
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</table>

This study identified that information regarding safer and hygienic use, including accurate information regarding the most effective methods to clean used equipment, must be re-enforced by people working with homeless injecting drug users.
| Brunings et al. 2013 | Society of Gastroenterology Nurses and Associates | Semi-structured focus group interviews were conducted, using an inductive qualitative approach. Data were analyzed using NVivo software and concept mapping. | Eligible participants were recruited from four hepatitis clinics in British Columbia between 2001 and 2004 using referrals, posters and flyers. | • Diagnosis of HCV  
• Use of hepatitis clinic  
• English speaking | None reported | **44 participants were included:** 38.6% female, mean age not reported | This study looked at care issues, and found that participants with HCV related quality of care with communication, professional competence, continuity of care, and education in order to self-manage care. This article concludes that individuals with HCV value processes more highly than outcomes and health care structures when considering quality of care. |
| Butt et al. 2008 | Western Journal of Nursing Research | Interviews, and daily think-aloud recordings were conducted. Data were analyzed using NVivo software. | Eligible participants were recruited from two hepatology clinics and one advocacy center. Dates of recruitment were not reported. | • 18 years or older  
• Diagnosis of Chronic HCV  
• Can speak and understand English  
• Live in British Columbia  
• Living in an institutional care facility  
• Require home nursing  
• Cognitive or memory-deficit | 26 participants were included: 50% female, mean age 47 years old (range: 33-76) | Findings suggest that stigma creates barriers to accessing health care, and social support. Participants reported that stigma usually stemmed from misconceptions about HCV (transmission and cause). Participants responded to stigma in a variety of ways including (but not limited to) outward anger, self-blame, embarrassment, and depression. |
| Conrad et al. 2006 | Chronic Illness | Semi-structured interviews were conducted. Data were analyzed using | Eligible participants were recruited (purposeful sample) from referrals and a  
• Residents of regional and metropolitan areas  
• Self-identified as | None reported | **70 participants were included:** 36% female, age range from 18-60 | This study identified three key themes of living with HCV: symptoms of HCV as |
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>Methodology</th>
<th>Eligible Participants</th>
<th>Recruitment</th>
<th>Participants Included</th>
<th>Key Themes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dudley et al.</td>
<td>2007</td>
<td>England</td>
<td>Quality of Life Research</td>
<td>Grounded theory methods, deductive coding, and inductive coding.</td>
<td>Community advisory group, between July 1999 and April 2000.</td>
<td>Having HCV</td>
<td>8 participants were included: 25% female, mean age was 51 years old (range 44-60)</td>
<td>Five themes were identified: long-term physical symptoms, stigma that cause embarrassment and guilt, uncertainty around health and length of life, transplant as giving participants a new outlook, and gratitude towards the donor.</td>
</tr>
<tr>
<td>Faye et al.</td>
<td>2003</td>
<td>Australia</td>
<td>Journal of Substance Use</td>
<td>Study methodology was based on grounded theory, and constant comparative analysis was used to analyze data.</td>
<td>Eligible participants were recruited, using purposive sampling. Dates of recruitment are not reported, and methods of recruitment are not reported.</td>
<td>None reported</td>
<td>24 participants were included: sex of participants was not reported, mean age was 43 (range 21-73)</td>
<td>The main theme identified by this study was participants experience with “being condemned.” Depression was also a theme the emerged throughout this study.</td>
</tr>
<tr>
<td>Fry et al.</td>
<td>2012</td>
<td>Australia</td>
<td>Psychology and Health</td>
<td>Semi-structured interviews were conducted. An interpretive approach (Berg, 2004) was used to analyze data.</td>
<td>Eligible participants were recruited through advertising, and two HCV associations between 1996 and 2000.</td>
<td>None reported</td>
<td>Fifteen participants were included: 67% female, mean age 44.4 years old (range 35-51)</td>
<td>Key theme of empowerment through knowledge, the importance of self-care, shock and distress when diagnosed, distress from discrimination, difficulty with career due to symptoms were discussed by participants.</td>
</tr>
</tbody>
</table>
| Glacken et al. | 2001 | International Journal of Nursing Studies | Descriptive exploratory design | Eligible participants were recruited (using nominated) | None reported | None reported | Nine participants were included: | This study reports on barriers, facilitators and indicators of health life.
<table>
<thead>
<tr>
<th>Ireland</th>
<th>Journal of Clinical Nursing</th>
<th>Eligible participants were recruited using theoretical sampling. Dates and methods of recruitment were not reported.</th>
<th>None reported</th>
<th>Twenty-eight participants were included: 71% female, mean age not reported (range 36-64)</th>
<th>This study found themes of chronic fatigue, varying severity of fatigue from one day to the next, physical weakness, cognitive symptoms such as lack of concentration and forgetfulness, and change in mood (irritability).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glacken et al., Ireland 2003</td>
<td>In-depth interviews, using a grounded theory approach.</td>
<td>None reported</td>
<td>Twenty-eight participants were included: 71% female, mean age not reported (range 27-66)</td>
<td>Ireland</td>
<td>The Health Technology Assessment Unit, University of Calgary Hepatitis C Screening in Alberta: a Health Technology Assessment March 7, 2016</td>
</tr>
<tr>
<td>Groessl et al., United States 2008</td>
<td>Semi-structured interviews with eleven questions were conducted, data were coded by two independent researchers.</td>
<td>None reported</td>
<td>Twenty-two participants were included: 0% female, mean age 52.1 (standard deviation 6.1)</td>
<td>United States</td>
<td>April 2016</td>
</tr>
<tr>
<td>Grundy et al., England 2004</td>
<td>Semi-structured interviews were conducted. Data were analyzed using Colaizzi’s method of phenomenological analysis.</td>
<td>None reported</td>
<td>Eight participants were included: 100% women, mean age not reported and exact range not reported (early)</td>
<td>England</td>
<td>The Health Technology Assessment Unit, University of Calgary Hepatitis C Screening in Alberta: a Health Technology Assessment March 7, 2016</td>
</tr>
<tr>
<td>Reference</td>
<td>Journal</td>
<td>Design</td>
<td>Methods</td>
<td>Participants</td>
<td>HCV Diagnosis</td>
</tr>
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<td>---------------</td>
</tr>
<tr>
<td>Harris et al. (2010) England</td>
<td>Qualitative Health Research</td>
<td>Phenomenological research design was used. Method of qualitative data collection not reported.</td>
<td>Eligible participants were recruited from Auckland, New Zealand and Sydney, Australia. Dates and methods of recruitment are not reported.</td>
<td>40 participants were included: 55% female, median age 47 (range 25-63).</td>
<td>HCV diagnosis</td>
</tr>
<tr>
<td>Harris et al. (2009) Australia</td>
<td>Sociology of Health and Illness</td>
<td>Semi-structured interviews were conducted. Methods of data analysis are not reported.</td>
<td>Eligible participants were recruited through research notices in the New Zealand HCV Resource Center Newsletter, and through Narcotics Anonymous meetings. Participants were recruited between 2004 and 2006.</td>
<td>40 participants were included: 55% female, median age 47 (range 25-63)</td>
<td>HCV diagnosis</td>
</tr>
<tr>
<td>Harris et al. (2005) Australia</td>
<td>New Zealand Sociology</td>
<td>Methods and study design not reported</td>
<td>Eligible participants were recruited through research notices in the New Zealand HCV Resource Center</td>
<td>20 participants were included: patient characteristics are not reported</td>
<td>None reported</td>
</tr>
</tbody>
</table>

England. Dates of recruitment were not reported. All felt that their diagnosis had impacted their sex lives. Seven of the eight women felt stigmatized, and because of that, they often did not disclose their disease status to others. Feelings associated with diagnosis include: fear, panic and depression.

This study specifically explored themes of alcohol use after HCV diagnosis. Most knew that they should limit alcohol, some did not know, and only two participants were told to abstain from alcohol. Participants felt judged by others for drinking, or not drinking.

Themes that emerged in this research include: confusion over “non-A, non-B” terminology, frustration at lack of information, and HCV as less debilitating-serious compared to HIV/AIDS. Approximately half of the participants expressed concern about HCV diagnosis, while the other half were unconcerned.

Themes identified in this paper include: deterioration of therapeutic relationship if patient feels disrespected, lack of...
<table>
<thead>
<tr>
<th>Study</th>
<th>Journal</th>
<th>Methodology</th>
<th>Participants</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepworth et al.</td>
<td><em>Journal of Health Psychology</em></td>
<td>Semi-structured interviews were conducted. Data were analyzed using an interpretive interactionist approach.</td>
<td>Eligible participants were recruited through an HCV community-based support group. Date of recruitment not reported.</td>
<td>Six participants were included: 50% female, mean age not reported (age range 26-48 years old)</td>
</tr>
<tr>
<td>Hill et al.</td>
<td><em>Journal of Clinical Nursing</em></td>
<td>Unstructured interviews were conducted. A descriptive phenomenological approach was used.</td>
<td>Eligible participants were recruited by hepatology nurses from two large teaching hospitals in East England.</td>
<td>Twenty-three participants were included: 52% female, mean age 28 years old.</td>
</tr>
<tr>
<td>Janke et al.</td>
<td><em>Psychosomatics</em></td>
<td>Focus groups were conducted. Data were analyzed using constant comparative analysis, using QSR*NUDIST software.</td>
<td>Eligible participants were recruited from outpatient liver clinics from Yale-New Haven Hospital and the Veterans Administration Connecticut Health care system.</td>
<td>40 participants were included: sex of participants was not reported, mean age of 51.5 years old (range 40-60 years old)</td>
</tr>
</tbody>
</table>

Participants generally found HCV diagnosis 'life changing.' They felt that they were associated with injection drug users, regardless of their transmission route. Participants talked about both physical and psychological consequences of HCV, which in some cases led to social withdrawal and isolation. A theme of uncertainty was consistent throughout the interviews.

Participants in this study reported that they felt ashamed, scared and depressed due to HCV diagnosis, they reported feelings of helplessness, panic, contamination, and fatigue. Participants reported struggling with disclosing HCV status to others, and fear of transmission.

Education on alternative medicine treatments, feeling like a number rather than a person, and poor methods of diagnosis.

Key themes identified by this study include: emotional volatility of those diagnosed with HCV, awareness of stigmatization and impact on communication and social support, and social isolation due to...
<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Journal</th>
<th>Study Design</th>
<th>Eligible Participants</th>
<th>Themes Identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jiwani et al.</td>
<td>Journal of Transcultural Nursing</td>
<td>Semi-structured interviews were conducted. Data were analyzed using methods developed by Morse and Field (1995).</td>
<td>• 18 years or older</td>
<td>The study identified the following themes: struggling to overcome,</td>
</tr>
<tr>
<td>2013 Pakistan</td>
<td></td>
<td></td>
<td>• HCV diagnosis within the past 5 years</td>
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<td></td>
<td></td>
<td></td>
<td>• Willingness to reflect on HCV experiences</td>
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<td></td>
<td></td>
<td></td>
<td>• Ability to speak English or Urdu</td>
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<td></td>
<td></td>
<td></td>
<td>• Comorbidities</td>
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<td></td>
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<td></td>
<td>• Hospitalization at the time of interview</td>
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<td></td>
<td>Themes identified by this study include: misinformation about HCV transmission (transmission through washing clothes and sharing utensils), physical suffering (pain and fatigue), emotional suffering, financial strain due to health care costs, and increased social support (from family and friends).</td>
</tr>
<tr>
<td>Kinder et al.</td>
<td>Gastroenterology Nursing</td>
<td>Interviews using open-ended questions were conducted. Van Manen’s (1990) phenomenological method was used to guide the data analysis in this study.</td>
<td>• Male</td>
<td>This study found six themes regarding living with HCV: acquisition of the disease, feelings about diagnosis (confusion, surprise), treatment decision making (anxiety, fear), the “horror stories” regarding treatment, what helped (prayer, mediation, health care professionals, exercise), and feelings now (regret).</td>
</tr>
<tr>
<td>2009 United States</td>
<td></td>
<td></td>
<td>• 18-60 years old</td>
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<td></td>
<td></td>
<td></td>
<td>• Completed treatment for HCV with interferon alpha and ribavirin</td>
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<td></td>
<td></td>
<td></td>
<td>• None listed</td>
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<td></td>
<td>8 participants included: all males, mean age not reported (range not reported).</td>
</tr>
<tr>
<td>Le Talec et al.</td>
<td>Culture, Health &amp; Sexuality</td>
<td>Two semi-structured, open-ended interviews were conducted with each participant. Methods of data extraction were not reported.</td>
<td>• HCV positive</td>
<td>This study identified a critical and emotional period, directly after diagnosis, during which participants were open to discuss their sexual practices and reconsider risk-reduction procedures, without being willing to give up on their satisfying sex life.</td>
</tr>
<tr>
<td>2013 France</td>
<td></td>
<td></td>
<td>• HIV positive</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Homosexual men</td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>• None listed</td>
<td></td>
</tr>
<tr>
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<td></td>
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<td></td>
<td>31 participants included: all male, mean age not reported (age range: 33-58 years old)</td>
</tr>
<tr>
<td>MacNeil et al.</td>
<td>Nursing Science Quarterly</td>
<td>Semi-structured, open-ended interviews were conducted. Eligible participants were recruited (convenience)</td>
<td>• ≥18 years old</td>
<td>The study identified the following themes: struggling to overcome,</td>
</tr>
<tr>
<td>2012</td>
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<td></td>
<td></td>
<td></td>
<td>• HCV positive diagnosis</td>
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<td></td>
<td></td>
<td></td>
<td>• None listed</td>
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<td></td>
<td></td>
<td>9 participants included: 56% female, age</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Journal</td>
<td>Methodology</td>
<td>Sample and Sampling</td>
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<tr>
<td>Newman’s theory of health (1994) was used to as a lens for thematic analysis.</td>
<td>Canada</td>
<td></td>
<td></td>
<td>Through a provincial HCV support group, and HCV clinic.</td>
</tr>
<tr>
<td>McCreaddie et al., 2011</td>
<td>United Kingdom</td>
<td>Gastroenterology Nursing</td>
<td>Semi-structured interviews were conducted. A constructivist grounded theory approach was used.</td>
<td>Eligible participants were recruited (purposive sample) from two large acute care hospitals between February and August 2008.</td>
</tr>
<tr>
<td>Moore et al., 2009</td>
<td>United Kingdom</td>
<td>Gastroenterology Nursing</td>
<td>Written questionnaire with open ended questions was used to collect data between June and August 2006. NVivo-7 was used to analyze the data.</td>
<td>Eligible participants were recruited (convenience sample) from liver disease support groups in a southwestern state during May 2006.</td>
</tr>
<tr>
<td>North et al., 2014</td>
<td>United States</td>
<td>European Journal of Gastroenterology and Hepatology</td>
<td>Semi-structured focus group interviews were conducted using open-ended questions. Data were analyzed using thematic coding and content analysis. NVivo software was used for data</td>
<td>Eligible participants were recruited through referral by their physician, or through self-referral through advertisements in clinics. Dates of recruitment were not reported.</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Location</td>
<td>Methodology</td>
<td>Eligibility Criteria</td>
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<tr>
<td>Olsen et al.</td>
<td>2013</td>
<td>Australia</td>
<td>Qualitative Health Research</td>
<td>Semi-structured, open-ended interviews conducted. Atlas.ti software was used to thematically analyze data.</td>
</tr>
<tr>
<td>Olsen et al.</td>
<td>2009</td>
<td>Australia</td>
<td>Health Care for Women International</td>
<td>Semi-structured, open-ended interviews conducted. Atlas.ti software was used to thematically analyze data.</td>
</tr>
<tr>
<td>Owen et al.</td>
<td>2008</td>
<td>United Kingdom</td>
<td>Culture, Health &amp; Sexuality</td>
<td>In-depth, open-ended interviews were conducted. Method of data analysis not reported.</td>
</tr>
<tr>
<td>Paterson et al.</td>
<td>2006</td>
<td>Canada</td>
<td>Clinical Nursing Research</td>
<td>This study used an interpretive description design. Data was collected using a “think aloud” approach during a face-to-face interview. Data were analyzed using</td>
</tr>
<tr>
<td>Study</td>
<td>Journal</td>
<td>Research Design</td>
<td>Eligible Participants</td>
<td>Exclusion Criteria</td>
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<tr>
<td>Sgorbini et al. 2009</td>
<td>Journal of Clinical Nursing</td>
<td>Semi-structured, open-ended interview questions were conducted. This study used a Heideggerian phenomenology approach.</td>
<td>Eligible participants were recruited (using purposive sampling) from liver clinics and advertisements between 2004 and 2006 in Sydney Australia.</td>
<td>None listed</td>
</tr>
<tr>
<td>Sinclair et al. 2011</td>
<td>Counselling &amp; Psychotherapy Research</td>
<td>Semi-structured open-ended interview questions were conducted. Data were analyzed using an interpretative phenomenological approach (Smith, 1995).</td>
<td>Eligible participants were recruited, through referral by a doctor, clinic nurse, psychiatrist or psychologist, from September 2004 to October 2005 through attendance at the Royal Free Hospital.</td>
<td>Acute psychiatric illness, Difficulty speaking English</td>
</tr>
<tr>
<td>Stewart et al. 2012</td>
<td>International Journal of Nursing Studies</td>
<td>Semi-structured, open-ended interviews were conducted. Data were analyzed following the approach developed by Braun and Clarke (2006).</td>
<td>Eligible participants were recruited (using purposive sampling) between May and July 2010 from a clinic at the Royal Adelaide Hospital.</td>
<td>Co-infection with HIV or hepatitis B virus</td>
</tr>
<tr>
<td>Stoller et al. 2009</td>
<td>American Journal of Health Behaviour</td>
<td>Semi-structured, open-ended interviews were conducted. Data were analyzed using an emic inductive approach.</td>
<td>Eligible participants were recruited from emergency departments after diagnosis with HCV and no follow-up, between 2003 and 2004.</td>
<td>Non-abusing drinkers</td>
</tr>
<tr>
<td>Study</td>
<td>Journal</td>
<td>Methods</td>
<td>Participants</td>
<td>Findings</td>
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<tr>
<td>Sutton et al. 2007 United Kingdom</td>
<td>Journal of Health Psychology</td>
<td>Semi-structured, open-ended interviews were conducted. Data were analyzed using NVIVO software.</td>
<td>• None listed</td>
<td>36 participants included: characteristics of participants not reported</td>
</tr>
<tr>
<td>Temple-Smith et al. 2004 Australia</td>
<td>Australian Health Review</td>
<td>Open-ended interview questions, analyzed using content and thematic analysis.</td>
<td>• None listed</td>
<td>32 participants included: 63% female, age range from 17-56 years old</td>
</tr>
<tr>
<td>Treloar et al. 2004 Australia</td>
<td>Education for Health</td>
<td>Semi-structured, open-ended interviews were conducted. Data were analyzed using an inductive thematic approach.</td>
<td>• None listed</td>
<td>19 participants included: 63% female, mean age 45 years old (range: 22-72)</td>
</tr>
<tr>
<td>Treloar et al. 2008 Australia</td>
<td>Psychology, Health &amp; Medicine</td>
<td>Open-ended interview questions, analyzed using an inductive thematic approach.</td>
<td>• Minimum of 4 weeks treatment or finished within the past 6 months</td>
<td>20 participants included: 35% female, mean age 49 years old (range: 35-73)</td>
</tr>
</tbody>
</table>

This study identified that the social consequences of living with HCV were more significant and had greater impact than clinical markers of disease progress and should be emphasized in understandings of transformation experiences in chronic illness.

This study identified the following themes: unsatisfactory experiences at time of diagnosis, concerns about transmission, the illness experience (between men and women) and seeking health care, social support, information and care, stigma.

This study found that non-compliance with infection control guidelines among health care workers can be identified by patients, and leads to deterring future disclosure.

This study identified that unrealistic optimism going into treatment can lead to unrealistic expectations and higher discontinuation.
<table>
<thead>
<tr>
<th>Treloar et al. 2010</th>
<th>Australian Family Physician</th>
<th>Open-ended interview questions, analyzed using an inductive thematic approach.</th>
<th>Eligible participants were recruited from advertisements placed in community magazines produced by a New South Wales drug user organization and through referral from the Hepatitis Incidence and Transmission Study. Dates of recruitment were not reported.</th>
<th>• None listed</th>
<th>24 participants included: 38% female, mean age 35 years old (range: 21-49)</th>
<th>Participants in this study generally reported having a poor experience when diagnosed; feeling confused, and not being given adequate information. Participants reported that they received information and support from social groups rather than health care providers.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other</td>
<td></td>
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<tr>
<td>Dunne et al. 2001</td>
<td>Journal of Health Psychology</td>
<td>Semi-structured focus groups were conducted. Themes identified using interpretive phenomenological analysis</td>
<td>Participants of “Positive Action”, a hepatitis support group, volunteered to be a part of the study. Dates of recruitment and methods of recruitment are not reported.</td>
<td>• Members of “Positive Action” • Female • HCV diagnosis, with iatrogenic origin (from contaminated Anti-D Immunoglobulin injection to prevent RH Haemolytic Disease)</td>
<td>None reported</td>
<td>32 participants were included: 100% women, mean age not reported (range 40-50 years old)</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Experience with Screening</td>
<td>Experience with diagnosis</td>
<td>Stigma</td>
<td>Impact on Relationships</td>
<td>Impact on Career</td>
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<td>General Population</td>
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<td>Bova(^{107})</td>
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<tr>
<td>Brunings(^{108})</td>
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<td>Butt(^{109})</td>
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<td>Conrad(^{110})</td>
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<td>Faye(^{112})</td>
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<td>Fry(^{113})</td>
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<td>Glacken(^{114})</td>
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<td>Harris(^{102})</td>
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<tr>
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<td>✓</td>
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<td>Dunne</td>
<td>2001</td>
<td>✓</td>
<td>✓</td>
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</tbody>
</table>
5.4 Conclusions

Although the six studies on experience and attitudes towards HCV screening included various population groups, the findings across studies were consistent. The evidence on barriers that impede HCV screening is strong; studies consistently report personal barriers such as time and transportation, poor relationships with health care providers (i.e. distrust, impersonal interactions) and stigmatization as reasons for not being screened. Importantly, those who are at risk of HCV due to injection drug use are particularly reticent to get screened for HCV because of social stigma and fear of judgment.

The forty-six included studies on experience with HCV covered a wide range of topics. With the large number of studies on this topic, the evidence on patient experience living with HCV is strong. Studies found that participants had reduced quality of life due to the symptoms, such as fatigue, pain, nausea and psychological changes, associated with HCV. Although often seen as an asymptomatic disease, these studies found that the symptoms of HCV result in considerable disruption to daily living. Three studies investigated the impact of HCV on one’s career, and found that due to physical symptoms, and discrimination, many participants switched to part-time, quit their jobs, or changed employment sectors. These findings are important as they underscore that HCV can impact a patient’s life although no clinically-relevant symptoms may be present.

Broadly, individuals with HCV had negative experiences with the health care system. Themes of not feeling supported, stigma, not being given adequate information, and not feeling involved in decision-making were frequent in the literature. Very few participants reported positive experiences with the health care system. At the time of diagnosis, individuals have feelings of distress, shame, unconcern, and relief. While most experience a feeling of shock, those who are current drug users are often not surprised, and see diagnosis as inevitable. Poor experiences with diagnosis may help illuminate areas where diagnosis communication can be improved; confusion, inadequate information, diagnosis over a phone and diagnosis in an institutional setting all lead to feelings of dissatisfaction among those with HCV. These findings should be taken into account when considering how, where, and by whom HCV screening should be done.
Stigma significantly impacted those with HCV. Two causes of stigma were consistently identified: fear of transmission, and association with injection drug use or risky behaviour. Misinformation is the underlying cause of both these causes of stigma. It is likely that this stigma may limit the uptake of any screening program, thus, significant resources may be required to educate the public in order to make the screening program effective.

Although the included studies were conducted in a range of countries and with a variety of populations, the ideas expressed across studies were consistent. Despite only a small number of the included studies being conducted in Canada, it is expected that the findings in these studies would be broadly generalizable to the Alberta-context.

6 Comparative Effectiveness of Organized and Opportunistic Screening Programs: A Systematic Review

### Summary
- Ten studies were included: three RCTs which compared various methods of organized screening, and seven studies of other designs
- No studies compared population screening for HCV using an opportunistic or organized model
- All three RCTs found that screening uptake was higher for organized programs than opportunistic screening.
- Five of the seven non-RCT studies found that screening uptake was higher for organized screening programs, when compared to opportunistic screening programs.

6.1 Purpose
To estimate the effectiveness of organized screening programs compared to opportunistic screening programs.

6.2 Methods

6.2.1 Literature Search
A systematic review on the effectiveness of organized compared to opportunistic screening programs was completed. MEDLINE, Cochrane CENTRAL Register, Cochrane Database of Systematic Reviews, HTA database, EMBASE, and CINAHL were searched from inceptions
until May 26th, 2015. The search strategy was developed by a library and information specialist. Terms for opportunistic screening (e.g. informal, opportunistic, spontaneous) were combined using the Boolean operator “and” with terms for organized screening programs (e.g. active, formal, organized, organized, population-based, proactive, targeted). Results were filtered to exclude non-human studies, case reports, and editorials or letters. The full search strategy can be found in Appendix C.

6.2.2 Selection of Literature

The abstracts retrieved were screened in duplicate by independent reviewers. Abstracts were assessed using the following inclusion criteria, developed a priori: comparative study design (including, RCTs, comparative control trials, prospective and retrospective cohorts and quasi-randomized trials); reports screening uptake; adult or pediatric populations; original data; English language. Abstracts were excluded if they did not meet any of the above inclusion criteria, or if they: presented only modeled data, reported only outcomes on patient experience or satisfaction; and studies whose primary objective was not to assess the efficacy/effectiveness of organized versus opportunistic screening. Abstracts included by either reviewer proceeded to full-text review; consensus was not required. This abstract screen was intentionally broad to ensure that all relevant literature was captured.

Studies included after the first screen proceeded to full-text review by two independent reviewers. Studies were included if they met all of the inclusion criteria and did not meet any of the exclusion criteria presented in Table 12. Disagreement between reviewers was resolved by consensus or by a third reviewer. Systematic reviews were hand-searched to ensure that all relevant articles were included.
Table 12: Inclusion/Exclusion Criteria for systematic review comparing organized and opportunistic screening programs

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Comparative study design (i.e. RCTs, controlled trials, prospective and retrospective cohorts)</td>
<td>• Non-original data</td>
</tr>
<tr>
<td>• Reports uptake of screening (e.g. number screened per year)</td>
<td>• Modeled data</td>
</tr>
<tr>
<td>• Adult and pediatric populations</td>
<td>• Outcomes based on patient experience and satisfaction</td>
</tr>
<tr>
<td>• Original data</td>
<td>• Animal models</td>
</tr>
<tr>
<td>• English Studies</td>
<td>• Studies reported only in abstract or as poster presentations</td>
</tr>
<tr>
<td></td>
<td>• Case studies, case series, systematic reviews, editorials or commentaries</td>
</tr>
<tr>
<td></td>
<td>• Non-English studies</td>
</tr>
<tr>
<td></td>
<td>• Studies whose primary objective was not to assess the efficacy/effectiveness of organized versus opportunistic screening</td>
</tr>
</tbody>
</table>

6.2.3 Data Extraction
Data extraction on the included studies was completed in duplicate. From each study, information on country, publication year, study design, research objective, participant selection inclusion and exclusion criteria, participant characteristics, characteristics of comparators, outcomes measured, key findings, and author conclusions were extracted into a standard data extraction sheet.

6.2.4 Quality Assessment
During data extraction, each study was assessed for quality. Randomized Controlled Trials (RCTs) were assessed using the Cochrane Risk of Bias Checklist\textsuperscript{146}. Quality assessment was completed in duplicate with discrepancies being resolved through discussion. Using this checklist, each study was assessed for seven areas of bias (random assignment generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and any additional potential sources of bias). Each study is assigned “low, “high,” or “unclear” risk of bias for each of these seven potential sources of bias.
All other studies (non-RCTs) were assessed using the Downs and Blacks Checklist\textsuperscript{147}. This checklist includes 27 criteria, widely covering areas reporting quality, external and internal validity, and power. Studies are assigned a value of “1” if they meet the question criteria, and “0” if they do not or if it is not possible to determine; with one exception where a study may be given “2” points for completely listing possible confounders (Question 5). Studies are then assigned a total value out of a possible 28 points. Study quality was assessed in duplicate with discrepancies resolved through discussion and consensus.

6.3 Results
1584 unique citations were identified. Of those, 1,471 were excluded during abstract review and 113 proceeded to full-text review. An additional 103 articles were excluded following full-text review, and 10 articles were included in the final analysis (see Figure 4). Two published systematic reviews were hand-searched for articles\textsuperscript{148,149}, and no additional papers were identified.

**Figure 4:** Flow chart of included and excluded studies

- **Citations before removing duplicates**
  - n=2879

- **Abstract Review**
  - n=1584

- **Full-text Review**
  - n=113

- **Included**
  - n=10

- **Randomized Controlled Trials**
  - n=3

- **Other Study Designs**
  - n=7

- **Excluded**
  - n=1471

**Reasons for Exclusion (n=103):**
- No comparison between organized and opportunistic screening (n=42)
- Did not report data on screening uptake (n=31)
- Modelling study (n=3)
- Non-original data (n=5)
- Full-text not available (n=3)
- Non-English (n=13)
- Costing study (n=2)
- Case control Study (n=3)
Three of the included studies were RCTs, and the remaining seven were other study designs; prospective cohort (n=1), retrospective cohort (n=5), and quasi-randomized controlled trial (n=1). Within the hierarchy of evidence, RCTs are considered to be the second highest level of evidence (Level II)\textsuperscript{150}. Therefore, our reporting of results will focus on the RCT data available, with brief reporting of the other studies.

6.3.1 Randomized Controlled Trials

6.3.1.1 Characteristics of Randomized Controlled Trials

Characteristics of each included RCT have been summarized in Table 13. Of the three included RCTs, one was conducted in Malaysia\textsuperscript{151}, one in Canada\textsuperscript{152}, and one in the United Kingdom. The studies were published between 1997\textsuperscript{152} and 2013\textsuperscript{151}. The number of participants included in each study varied between 270\textsuperscript{153} and 600\textsuperscript{153}, with a total of 1552 participants included in all three studies combined.

The included RCTs varied in type of screening, target population, inclusion/exclusion criteria, characteristics of intervention and controls, and outcomes measured. They targeted two cervical cancer screening\textsuperscript{151,152}, and chlamydia screening\textsuperscript{153}. Due to the small number of RCTs included and the heterogeneity between them, meta-analysis was not possible. A narrative summary of each study follows.

6.3.2 Findings

Abdullah et al. assessed the effectiveness of implementing a worksite screening program for cervical cancer (pap smears) among females of reproductive age\textsuperscript{151}. The study sample was recruited from 40 secondary schools, and females who had not had a pap smear in the previous 3 years were included\textsuperscript{151}. The participants were randomized to an organized screening program, where they received personalized invitation letters, information pamphlets and telephone reminders, or to opportunistic screening, where they received screening only by requesting it form their general practitioner\textsuperscript{151}. This study found that 18.1% of women from the organized screening group were screened, compared to 10.1% from the opportunistic screening group; a statistically significant difference\textsuperscript{151}. 

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A study by Buehler et al., also assessed the effectiveness of an intervention on cervical cancer screening. Women, age 18-69, were recruited from family medicine clinics in Newfoundland, Canada, who had not had a pap smear in the previous three years. The intervention included a personal invitation, and a subsequent reminder letter sent four weeks after, for non-responders. This study found 2.8% of the women in the intervention group were screened after the first letter, compared to 1.9% in the control group. After six months, the percentage of the intervention and control participants screened was 10.7% and 6.3%, respectively. These results are not statistically significant.

Senok et al. investigated the effectiveness of screening program type on chlamydia screening uptake. This study recruited females who were 16-30 years old, from general practices. Participants were randomized to receive organized screening, opportunistic screening, or usual care (no screening program). Those randomized to the organized screening program received pre-labeled test kits with a paid, pre-addressed envelope. Those randomized to receive opportunistic screening were offered screening during attendance at their next medical appointment. In the organized screening arm, 48% were screened, in the opportunistic screening arm 21% were screened, and no one was screened in the control group.
Table 13: Study Characteristics of Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Author, Year of Publication, Country</th>
<th>Study Design</th>
<th>Study Objectives</th>
<th>Participant Selection</th>
<th>Characteristics of Comparators</th>
<th>Outcomes</th>
<th>Author Conclusions</th>
</tr>
</thead>
</table>
| Abdullah et al.\textsuperscript{151}, 2013, Malaysia | Cluster Randomized Trial | “…to ascertain the effectiveness of a worksite screening initiative upon pap test uptake among secondary school teachers of reproductive age…” | Patient Selection: Patients were recruited from 40 schools (10 from each of the 4 school zones) in Kuala Lumpur between January and November 2010. Schools were randomized to intervention or control using computer generated randomization.  
**Inclusion Criteria:** female secondary school teachers, naïve to pap smear or last test was more than 3 years prior  
**Exclusion Criteria:** None reported  
**Patient Characteristics:** 201 participants with a mean age of 36.1 (±8.0) were included in the worksite cervical screening intervention (organized program). 199 participants with a mean age of 36.5(±7.3) were included in the standard of care (opportunistic screening). | Intervention personalized invitation letter, and information pamphlet, with telephone reminder four weeks after invitation.  
**Control:** screening available through GP, if requested by patient. | Outcomes Measured:  
• Uptake of pap examination after 24 weeks  
**Key Findings:**  
• 36 women (18.1%) from the organized program group were screened, compared to 20 (10.1%) in the opportunistic screening group; a statistically significant difference (p<0.05) | “Worksite health promotion interventions can effectively increase cervical smear uptake rates among eligible workers in middle-income countries.” |
| Buehler et al.\textsuperscript{152}, 1997, Canada | Randomized Controlled Trial | “To determine the effectiveness of a simple call/recall system in improving compliance with cervical cancer screening among women not screened in the previous 3 years.” | Patient Selection: Women, aged 18-69, who were patients at two family medicine clinics in/near St. John’s, Newfoundland and who had not had a Papanicolaou test within the previous 3 years, were recruited.  
**Inclusion Criteria:** Female, age 18-69  
**Exclusion Criteria:** Women who had persistent cervical intraepithelial neoplasia, or benign atypia, women | Intervention: Personal invitations, with reminder letters sent 4 weeks after initial invitation  
**Control:** No invitation. Usual care, which may have included testing if requested by a participant, or recommended by a physician | Outcomes Measured:  
• Compliance with screening at 6 months  
**Key Findings:**  
• Two months after the first letter, 2.8% of women in the intervention group were screened, and 1.9% of those in the control group were screened. At six months | “A letter of invitation is not sufficient to encourage women who have never or have infrequently undergone a Pap test to come in for cervical cancer screening.” |
who had complete hysterectomy, women who had a pap smear within the previous 3 years.

**Patient Characteristics:** 441 women were randomized to the intervention or control group; 221 to the intervention group, and 220 to the control group. Some women were excluded due to undeliverable mail, or recent pap smear. The analysis included 178 women in the intervention group and 208 in the control group.

<table>
<thead>
<tr>
<th>Senok et al.(^{153}), 2005, United Kingdom</th>
<th>Randomized Controlled Trial</th>
<th>“…to assess whether opportunistic and postal screening strategies for Chlamydia trachomatis can be compared with usual care in a randomized trial in general practice…”</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Selection:</strong> 221 West of Scotland general medical practices invited to participate. Random selection of 600 females then randomized to three groups.</td>
<td><strong>Patient Selection:</strong> 221 West of Scotland general medical practices invited to participate. Random selection of 600 females then randomized to three groups.</td>
<td><strong>Intervention:</strong> (1) organized screening - pre-labelled test kits returnable to the laboratory in a reply paid, pre-addressed envelope (2) opportunistic screening - women offered screening during attendance to doctor within 4 month study period</td>
</tr>
<tr>
<td><strong>Inclusion Criteria:</strong> females aged 16-30 years old</td>
<td><strong>Inclusion Criteria:</strong> females aged 16-30 years old</td>
<td><strong>Control:</strong> No screening, unless indicated</td>
</tr>
</tbody>
</table>
| **Exclusion Criteria:** None reported | **Exclusion Criteria:** None reported | **Outcomes Measured:**
- Uptake of chlamydia test |
| **Patient Characteristics:** 124 participants with a mean age of 25.3 (SD: 4.6) were included in the postal group (organized program). 146 participants with a mean age of 24.5 (SD: 4.3) were included in the opportunistic group. | **Patient Characteristics:** 124 participants with a mean age of 25.3 (SD: 4.6) were included in the postal group (organized program). 146 participants with a mean age of 24.5 (SD: 4.3) were included in the opportunistic group. | **Key Findings:**
- 59 women (48%) from the organized program group were screened, compared to 28 women (21%) from the opportunistic group were screened. |

“The apparent superiority of postal screening in this broad comparison may obscure the fact that younger women, who are at highest risk for chlamydial infection, may respond better to opportunistic screening. In the interviews some GPs reported a tendency to target younger women in their routine practice, associating the condition with a younger age group.”
6.3.2.1 Quality of Included Randomized Controlled Trials

Each of the RCTs had areas where the risk of bias was low and unclear Figure 5. There were two studies which were assessed as having a high risk of bias in one of the seven areas\textsuperscript{151,153}.

All of the included studies used some type of randomization to allocate patients to arms. The risk of bias for both random sequence generation and allocation concealment was considered low for two of the three studies\textsuperscript{151,152}; the other was considered high\textsuperscript{153}. Generally, blinding of personal assessors and participants was poorly reported and the risk of bias introduced by blinding was either high\textsuperscript{151,153} or unclear\textsuperscript{152}; in two of the included studies, participants and personnel were not blinded, and therefore the risk of bias from blinding was considered high\textsuperscript{151,153}. The other study did not clearly report whether participants or personnel were blinded, and were therefore assessed as have “unclear” bias\textsuperscript{152}. Similarly, two studies did not report whether the outcome assessor was blinded and they received an “unclear” risk of bias\textsuperscript{152,153}. The remaining study did not blind the outcome assessor and are therefore at a high risk of bias\textsuperscript{151}. Due to the nature of the studies (where blinding of participants and personnel would be difficult), it is not surprising that these areas were found to generally have high or unclear risk of bias.

All included studies had complete outcome data (making the risk of bias due to incomplete data outcome low), and showed no evidence of selective reporting\textsuperscript{151-153}. It is unknown whether other biases influenced the results of these studies. Due to this, “unclear risk of bias” was assigned to all included studies under the category “Other Bias.”

Figure 5: Quality Assessment of RCTs using Cochrane Risk of Bias
6.4 Other Study Designs

Characteristics of the included quasi-randomized trial, prospective cohort study and the retrospective cohort studies have been summarized in Table 23, Appendix D. The included studies were conducted in the Netherlands, Hungary, Norway, Belgium, Italy, and South Korea. The studies assess screening strategies for breast cancer, cervical cancer, and gastric cancer. One was a prospective cohort study design, one was a quasi-randomized trial, and five were retrospective cohort study designs. The studies were conducted between 1995 and 2013.

The results of each study have been summarized in Table 23, in Appendix D. Broadly, five of the seven included studies found that organized screening resulted in better screening uptake compared to opportunistic screening. Only one of these five studies conducted statistical tests of significance; it found a statistically significant difference in uptake between organized and opportunistic screening. The remaining two studies found that organized screening was inferior to opportunistic screening, for uptake. Neither of these studies conducted statistical tests of significance, so it is not known if this difference was meaningful.

The study quality of these studies can be found in Figure 8, in Appendix D. They were generally, moderate quality based on the Downs and Blacks Checklist.

6.5 Conclusions

Three RCTs were found which compared various methods of organized screening. Generally, the three studies all show a trend that more people are screened when they are enrolled in an organized screening program compared to an opportunistic screening program. This trend is consistent despite differences in target diseases, study methods, study populations, and characteristics of the intervention and control arms (e.g. screening reminders, information pamphlets, personal invitations).

The two studies that reported tests of significance may have varied in their results (statistically significant, and not statistically significant) due to the different methods, and study populations, amongst other variations. The studies ranged in how participants were invited to the organized
programs, whether or not they were reminded about screening, and where the screening took place. It is possible that barriers and facilitators such as distance to screening center, convenience of screening, and cost to screen could have also caused slight variability in results, making one screening program slightly more effective than the other.

Five of the seven non-RCT studies found that screening uptake was substantially higher for organized screening programs, when compared to opportunistic screening programs. The remaining two studies found that opportunistic screening resulted in higher screening uptake compared to organized screening. The mixed findings may be due to selection bias in the patients receiving organized versus opportunistic screening, differences in disease groups or differences in context.

No studies on Hepatitis C screening were found in the literature, and only one study on infectious disease screening was found (chlamydia screening). It is unclear whether studies on other diseases would be generalizable to HCV screening. However, the findings observed would suggest that, broadly, organized screening increases uptake compared to opportunistic screening.

7  Cost-effectiveness Analysis: A Systematic Review of the Literature

Summary

- Screening injection drug users, “high risk” (as defined by study authors), birth cohort and general populations would generally be considered good value for money using a threshold of $50,000 per quality-adjusted life year (QALY) gained.
- Screening pregnant women, prisoners, individuals who have had surgery and those who attend genito-urinary clinics would generally be considered poor value for money.
- No evidence was found on the cost-effectiveness of screening immigrant populations, aboriginal populations, individuals who received blood products prior to 1992, or other high risk groups.
- Uncertainty in the prevalence, screening uptake and treatment uptake affect the estimate of the cost per QALY.

7.1  Purpose
To summarize the published economic evaluations on HCV screening programs.
7.2 Methods
A systematic review was performed. The following five databases were search from inception until July 29, 2014: NHSEED, MEDLINE, the HTA Health Technology Assessment Database, EMBASE, EconLit. Terms such as “Hepatitis C,” “Hepatitis C antigens,” “hcv,” and “hepatitis” were combined using the Boolean operator “or” in order to capture the target diagnosis. These terms were combined using the Boolean operator “and” with terms representing the intervention, for example “mass screening,” “screen,” and “test.” Terms such as “economic models,” “markov chains,” “cost-effective,” “cost-utility,” and “quality adjusted life years” were combined using the Boolean operator “and” with the previous terms, in order to focus the search on economic evaluations. Results were limited to humans and studies available in English language. Filters were used to exclude editorial and letter style results. Additional details of this search can be found in Appendix E.

The abstracts were screened in duplicate. Abstracts proceeded to full-text review if they: were economic evaluations of HCV; reported on population or risk subgroup screening for HCV; and included a comparison to no formal HCV screening program (including opportunistic screening). Abstracts were excluded if: they did not include a baseline/status quo comparator; they evaluated blood donor or blood product screening; the primary goal was to assess the effectiveness of diagnostic tests for HCV; HCV screening was completed concurrently with screening for another disease (i.e. HIV); the research was only available as a letter to the editor or commentary; or the primary goal was to analyze medications for treating HCV (Table 14). All abstracts selected by either reviewer were included in the full-text review.

Table 14: Inclusion/Exclusion Criteria for Systematic Review of Cost-effectiveness Analyses

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Economic Evaluation (cost minimization, cost-effectiveness, cost utility and cost benefit)</td>
<td>• Economic Evaluations of:</td>
</tr>
<tr>
<td>• Population or risk subgroup screening for HCV</td>
<td>• Blood donor testing</td>
</tr>
<tr>
<td>• Comparison to opportunistic screening, high risk group, or no formal program</td>
<td>• Tests for diagnosing HCV (i.e. PCR vs antibody)</td>
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<tr>
<td></td>
<td>• Screening for HCV in addition to other diseases, instead of HCV alone (i.e. HCV and HIV)</td>
</tr>
<tr>
<td></td>
<td>• Medications for treating HCV</td>
</tr>
<tr>
<td></td>
<td>• Abstract, Commentary</td>
</tr>
</tbody>
</table>
After inclusion, studies were stratified into seven categories based on the target population of the screening intervention:

1. IDUs
2. “High Risk” (as defined by the study authors)
3. Prisoners
4. Pregnant Women
5. Birth Cohort
6. General Population
7. Other Populations

Studies that assessed more than one target population were included in all appropriate categories. For example, a cost-utility model comparing both general screening and birth cohort screening interventions with no screening intervention was included in both categories 5, and 6. The comparator arm for all studies was assumed to be the “status quo”, “risk-based screening” or opportunistic screening. The “other” category includes studies of individual populations that do not coincide with the other categories.

For all studies, year of publication, country, population, type of model, perspective, comparators, model details (time horizon, discount rate), outcome(s) assessed, input details, currency, clinical pathway of model, results, author conclusions and sources of uncertainty were extracted in duplicate using standardized data extraction forms. Discrepancies between reviewers during data extraction were resolved through consensus. If two or more target populations were screened then data was extracted in separate lines within the tables.

To assess the quality of the economic evaluations the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist was applied. Quality assessment was completed in duplicate with discrepancies being resolved through discussion. Using this checklist, each study was assessed based on whether or not they included the twenty-four recommended items (e.g. title, choice of health outcomes, measurement of effectiveness). For each item, a study was assigned 1 point for included items and 0 points for items that were not included. A final tally, out of a possible 24 points was calculated for each study. A study was deemed high quality if they score >20 points, average quality if 17-20, and poor quality if <17.
7.3 Results
A total of 1889 abstracts were identified with the literature search (Figure 6). Of those abstracts, 1,850 were excluded and 39 proceeded to full-text review. A further 15 articles were excluded after full-text review, five of which were not economic evaluations, five did not assess HCV screening programs, and five which evaluated HCV tests rather than HCV screening programs. Two systematic reviews were hand-searched and no additional publications were found.\textsuperscript{162,163} One in-press study was identified and provided by an expert in the field. Ultimately, twenty-four papers were included.

The final 24 articles were stratified into categories based on the population being screened: IDUs (n=6), “high risk” (n=4), pregnant women (n=3), prisoners (n=2), birth cohort (n=8), general population (n=4) and other (n=4). Studies could be captured in more than one category as some papers analyzed multiple populations. An overview of the findings in each category is presented in Table 15. A discussion of screening cost-effectiveness, by population, follows. Of note, only one study was conducted in Canada, by Wong et al.; this study looked at birth cohort screening.
Figure 6 Flow Chart of Studies Included in Cost-effectiveness of Screening for HCV

Abstract Review
n=1,889

Full-text Review
n=39

Excluded
n=1,850

Reasons for Exclusion (n=15):
- No economic evaluation (n=5)
- Not HCV Screening (n=5)
- Evaluation of HCV tests (n=5)

Included
n=24

Birth Cohort
n=8

Intravenous Drug Users
n=6

Prison
n=2

Other
n=2

General Population
n=4

High Risk
n=4

Pregnant
n=8

Unpublished Study
n=1

Abstract Review
n=1,889

Full-text Review
n=39

Excluded
n=1,850

Reasons for Exclusion (n=15):
- No economic evaluation (n=5)
- Not HCV Screening (n=5)
- Evaluation of HCV tests (n=5)

Included
n=24

Birth Cohort
n=8

Intravenous Drug Users
n=6

Prison
n=2

Other
n=2

General Population
n=4

High Risk
n=4

Pregnant
n=8

Unpublished Study
n=1
Table 15: Summary of Findings for Systematic Review of Cost-effectiveness Studies

<table>
<thead>
<tr>
<th>Screening Population</th>
<th>Number of Studies</th>
<th>Range of Results</th>
<th>General Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection Drug Users</td>
<td>6</td>
<td>$4,551 to $51,020 per QALY gained</td>
<td>All six studies resulted in a cost per QALY of less than or approximately $50,000, a threshold that may be considered good value for money. A range of ICERs is likely due to the prevalence estimates used. These studies were of all high quality, in accordance with the CHEERs checklist.</td>
</tr>
<tr>
<td>“High Risk” (as defined by authors of the study)</td>
<td>4</td>
<td>$357 to $92,437 per case detected, -$749 to $2,297 per life year gained</td>
<td>Of the four studies in this category two used costs per case detected, and one used cost per life year gained (without adjusting for quality of life). The final study reported cost per QALY gained but did not give the resulting value. The cost per life year gained is attractive compared to other accepted therapies. The cost per cases detected is difficult to interpret as there is no accepted threshold for this outcome. These studies were of generally high quality, with one being poor quality, in accordance with the CHEERs checklist.</td>
</tr>
<tr>
<td>Pregnant</td>
<td>3</td>
<td>$1,170,000 per QALY gained, $68,460 to $76,248 per life year gained</td>
<td>Two studies reported cost per life year gained (without adjusting for quality of life). One study reported cost per QALY gained. The resulting values would generally not be considered good value for money. These studies were of high quality, in accordance with the CHEERs checklist.</td>
</tr>
<tr>
<td>Prison</td>
<td>2</td>
<td>$11,590 per case detected, $99,522 per QALY gained</td>
<td>Both studies report different outcomes; one reporting cost per case detected (without including treatment) and the other reporting cost per QALY. The reported cost per QALY would generally not be considered good value for money. These studies were of high quality, in accordance with the CHEERs checklist.</td>
</tr>
<tr>
<td>Birth Cohort</td>
<td>8</td>
<td>$5,400 to $65,749 per QALY gained, $848 to $4,825 per life year gained</td>
<td>Six of the seven studies that reported cost per QALY gained showed that birth cohort screening results in a cost per QALY of less than $50,000, a threshold that may be considered good value for money. A large variation in ICERs is due to differing treatment protocols included in the models. One study reported a cost per QALY above $50,000 due to the inclusion of the universal triple therapy in treatment. One study reported four separate cost per life year gained estimates (based on age subgroups) resulting in a very attractive estimate compared to other accepted therapies. These studies were of all high quality, in accordance with the CHEERs checklist.</td>
</tr>
<tr>
<td>General Population</td>
<td>4</td>
<td>$7,900 to $91,000 per QALY gained</td>
<td>Three of the four studies resulted in a cost per QALY of less than $50,000; a threshold that may be considered...</td>
</tr>
</tbody>
</table>
good value for money by policy-makers. The study resulting in a cost per QALY of $91,000 utilized PCR as first line screening as opposed to ELISA then PCR. These studies were of generally high quality, with one being moderate, in accordance with the CHEERs checklist.

### Other

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>$54 to $2,986 per positive test (Sexually Transmitted Disease Clinic)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>$950 to $2,520 per positive test (various populations)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$153,441 per QALY gained (genito-urinary clinic)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$1,334,155 per QALY gained (individuals with surgery)</td>
</tr>
</tbody>
</table>

Each of these studies evaluated a different population: patients presenting at a sexually transmitted disease clinic, patients presenting at a genito-urinary clinic, individuals undergoing surgery and a mixed population. Generally, the studies found high cost-benefit ratios generally supporting screening in these populations is not economically attractive. Two of these studies were of high quality and two were of poor quality, in accordance with the CHEERs checklist.

### 7.3.1 Screening of Injection Drug Users

Six of the included studies compared HCV screening with no HCV screening for IDU populations. All of the studies were cost-utility analyses; all reported a cost per QALY gained. Four of these studies were conducted in the UK, and the remaining two were conducted in the Netherlands. These studies were published between 1999 and 2012. Four of the studies adopted a payer perspective, one adopted a societal perspective, and the remaining study did not report the perspective used. Three studies used a lifetime time horizon, and the remaining three studies used a 50 year time horizon. All studies assessed for uncertainty with sensitivity analyses. The technical details of the models and characteristics of each included study have been summarized in Appendix F, Table 21.

The six studies were of high quality when evaluated with the CHEERS checklist, and none had major flaws. All of the studies reported complete outcome data and none showed evidence of selective reporting. All studies accounted for diagnosis and treatment of screened individuals. All studied were transparent in the clinical pathway they modeled,
which included diagnosis and treatment\textsuperscript{86,164-168}. One study did not report the year which the costs were adjusted to\textsuperscript{168}, another failed to report the values, ranges, reference, probability distributions for all parameters\textsuperscript{86}, three studies did not identify their source of funding\textsuperscript{166-168}, and four did not report conflicts of interest.\textsuperscript{165-168}

The six included studies found incremental costs per QALY gained ranging from $4,551\textsuperscript{168} to $51,020\textsuperscript{167} when comparing HCV screening programs to no screening program. Using a willingness-to-pay (WTP) threshold of $50,000 per QALY gained, five of the six studies showed that screening drug users may be good value for money\textsuperscript{86,164-166,168}. The remaining study was only marginally above a WTP threshold of $50,000 per QALY\textsuperscript{167}. Five out of the six authors interpreted their results as being good value for money (cost-effective)\textsuperscript{86,164,166-168}, and the remaining study withheld judgment as to the long-term cost-effectiveness of this screening strategy\textsuperscript{165}. Additional data on the results of each study can be found in Appendix F, Table 22.

7.3.2 Screening of “High Risk” Individuals

Four of the included studies evaluated HCV screening for “high risk” individuals compared to no screening\textsuperscript{169-172}. “High risk” was as defined by each author. Three of these studies were cost-effectiveness analyses\textsuperscript{170,172,173}, and one was a cost-utility analysis\textsuperscript{171}. Two studies were conducted in the United States\textsuperscript{170,171}, and the other two were conducted in England\textsuperscript{173} and Japan\textsuperscript{172}. Two studies adopted a payer perspective\textsuperscript{172,173}, one adopted a societal perspective\textsuperscript{171}, and the remaining study did not report the perspective\textsuperscript{170}.

Two studies used a lifetime time horizon\textsuperscript{171,172}, and the other two failed to report what time horizon was used\textsuperscript{170,173}. The outcome of interest for two of the studies was the cost per case found\textsuperscript{170,173}, one used cost per life year gained without adjustment for quality of life\textsuperscript{172}, and the remaining study used the cost per QALY gained\textsuperscript{171}. Three out of the four studies assessed uncertainty\textsuperscript{171-173}, and the remaining study did not perform uncertainty analysis\textsuperscript{170}. The technical details of the models and characteristics of each included study have been summarized in Appendix F, Table 23.
Two of the four studies were high quality when evaluated with the CHEERS checklist\textsuperscript{161,171,172}, one was of average quality\textsuperscript{173} and the other was poor\textsuperscript{170}. All studies included complete outcome data and showed no evidence of selective reporting\textsuperscript{170-173}. Three out of the four studies accounted for diagnosis and treatment of screened individuals\textsuperscript{171-173}, and the remaining study did not\textsuperscript{170}. These included studies were heterogeneous in their definition of “high risk” and in their methods used. Two of the four studies had no major flaws \textsuperscript{171,172}. The study that was of average quality did not report the time horizon or the measure of preference based outcomes; this does not necessarily invalidate the study, but it makes it difficult to assess the study\textsuperscript{173}. The poor quality study, failed to report the study perspective, time horizon, discount rate, health outcomes, measures of effectiveness, measure of preference based outcomes, currency, effects of uncertainty, and the effects of uncertainty on the outcomes\textsuperscript{170}. Three studies failed to report any conflicts of interest or identify their sources of funding\textsuperscript{170,172,173}.

The two studies that reported cost per case had a range of costs from $357\textsuperscript{170} to $92,437\textsuperscript{173} per case found; the cost per case detected is difficult to interpret as there is no accepted threshold for this outcome. Using a WTP threshold of $50,000, the study reporting cost per QALY gained showed that this type of screening is not good value for money as it is more costly and provides fewer benefits than other strategies; this study compared this comparison group to both no screening and birth cohort screening\textsuperscript{171}. The remaining study evaluated four separate high risk groups and found a range of cost per life year gained from -$748 to $2,297. Two of the authors interpreted their results as cost-effective\textsuperscript{170,172}, and the remaining two authors concluded that HCV screening of high-risk individuals was not cost-effective\textsuperscript{171,173}. Additional data on the results of each study can be found in Appendix F, Table 24.

7.3.3 Screening of Pregnant Women

Three of the included studies evaluated HCV screening compared to no screening for pregnant women\textsuperscript{174,175}. One of these studies evaluated screening in two separate pregnant populations (a general pregnant population and a first-generation non-western pregnant population); we have reported the results of this study separately. One of these studies was a cost-utility analysis\textsuperscript{174}, and the other was a cost-effectiveness analyses\textsuperscript{175}. One study was conducted in the United States\textsuperscript{174}, and the other was conducted in the Netherlands\textsuperscript{175}. These studies were published in 2004\textsuperscript{174} and 2013\textsuperscript{175}. Both studies adopted a payer perspective\textsuperscript{174,175}. 
Both studies were analyzed with a lifetime time horizon\textsuperscript{174,175}. The outcome of interest for one of the studies was cost per QALY gained\textsuperscript{174}, and the other study reported cost per life year gained\textsuperscript{175}. Both studies assess for uncertainty\textsuperscript{174,175}. The technical details of the models and characteristics of each included study have been summarized in Appendix F, Table 25.

Both studies were of high quality when evaluated with the CHEERS checklist\textsuperscript{161}, and had no major flaws. The studies were transparent in their clinical pathway, which included diagnosis and treatment. One of the studies did not report the conflicts of interest or their sources of funding\textsuperscript{174}.

The cost-utility analysis, which assessed a general pregnant population, found that HCV screening compared to no screening cost $1,170,000 per QALY gained\textsuperscript{174}. The cost-effectiveness analysis, which also assessed a general pregnant population, found that HCV screening compared to no screening cost $76,248 per life year gained\textsuperscript{175}. In comparison, this same study found that for a population of first-generation non-western pregnant women, HCV screening compared to no screening cost $68,460 per life-year gained. The authors concluded that general pregnant population screening is not cost-effective\textsuperscript{-174,175}, and that screening for first generation non-western women is moderately cost-effective\textsuperscript{175}. Additional data on the results of each study can be found in Appendix F, Table 26.

### 7.3.4 Screening of Prisoners

Two of the included studies evaluated HCV screening of prisoners compared to no screening\textsuperscript{176,177}; one was a cost-effectiveness analysis\textsuperscript{176}, and the other was a cost-utility analysis\textsuperscript{177}. Both studies were conducted in the UK and adopted a payer perspective\textsuperscript{176,177}. These studies were published in 2004\textsuperscript{176} and 2013\textsuperscript{177}.

One of the studies only evaluated the time horizon through testing for HCV; therefore, it did not include any treatment costs and reported a cost per positive case found\textsuperscript{176}. The other study accounted for a time horizon of 80 years, and included the treatment of screened individuals, and reported a cost per QALY gained\textsuperscript{177}. Both studies assessed uncertainty\textsuperscript{176,177}. The technical
details of the models and characteristics of each included study have been summarized in Appendix F, Table 27.

Both studies were assessed as being high quality when evaluated with the CHEERS checklist\textsuperscript{161} and neither had major flaws\textsuperscript{176,177}. Both studies were transparent in their clinical pathway\textsuperscript{176,177}, but, as stated above, only one included treatment of individuals who screened positive\textsuperscript{177}. Neither study reported sources of funding\textsuperscript{176,177}, and one failed to report if there were conflicts of interest\textsuperscript{177}.

The study that did not include treatment costs (only looked at verbal screening methods) found a cost of $11,590 per case found\textsuperscript{176}. Given that there is no threshold for this outcome, it is difficult to compare this outcome regarding value for money\textsuperscript{176}. However, the authors deemed their results to be cost-effective\textsuperscript{176}. The study which looked at screening prisoners on reception into prison, and then subsequent treatment, found that HCV screening, compared to no screening cost $99,522 per QALY gained\textsuperscript{177}. At a threshold of $50,000 per QALY gained this screening strategy is not good value for money\textsuperscript{177}. The authors concluded that screening prisoners on reception into prison was not cost-effective\textsuperscript{177}. Additional data on the results of each study can be found in Appendix F, Table 28.

### 7.3.5 Screening of Birth Cohorts

Eight studies evaluated HCV screening compared to no screening for a birth cohort population\textsuperscript{50,67,171,172,178-181}. Six of these studies were cost-utility analyses\textsuperscript{50,67,171,178,179,181}, one was a cost-effectiveness analysis\textsuperscript{172}, and one study performed both a cost-utility analysis and a cost-effectiveness analysis\textsuperscript{180}. Five studies were conducted in the United States\textsuperscript{67,171,178-180}, and the remaining were conducted in Japan\textsuperscript{172}, Italy\textsuperscript{181}, and Canada\textsuperscript{50}. All studies were published recently; 2008\textsuperscript{172}, 2013\textsuperscript{171,179,181}, 2015\textsuperscript{50}. Three studies adopted a societal perspective\textsuperscript{67,171,178} and the remaining five adopted a payer perspective\textsuperscript{50,172,179-181}.

Seven studies were analyzed with a lifetime horizon\textsuperscript{50,67,171,172,178-180}, and one used a 40 year time horizon\textsuperscript{181}. All studies assessed uncertainty, although it was unclear which parameters one of the studies analyzed\textsuperscript{179}. The technical details of the models and characteristics of each included study have been summarized in Appendix F, Table 29.
When evaluated with the CHEERS\textsuperscript{161} checklist, all eight studies were of high quality\textsuperscript{50,67,161,171,172,178-181}. All studies included complete outcome data and showed no evidence of selective reporting. All studies were transparent in their clinical pathway, which included diagnosis and treatment\textsuperscript{50,67,171,172,178-181}. Seven of the eight studies had no major areas identified\textsuperscript{50,67,171,172,178,180,181}. The remaining study did not report the currency or how variances can explain difference in costs and outcomes making it difficult to account for uncertainty\textsuperscript{179}. Three studies failed to report any conflicts of interest\textsuperscript{172,180,181}, and two did not identify their sources of funding\textsuperscript{172,181}.

The included cost-effectiveness study, reported a range of $848 per life year gained to $4,825 per life year gained\textsuperscript{172}. The seven cost-utility studies\textsuperscript{50,67,171,172,178-181} found that HCV screening ranged from $5,400 incremental cost per QALY gained\textsuperscript{178} to $65,749 incremental cost per QALY gained\textsuperscript{171} when compared to no screening program.

It is important to note that one of these seven studies was conducted in Canada (the only Canadian cost analysis found in this systematic review). This Canadian study, authored by Wong et al. and published in 2014, adopted a payer perspective, and found that screening and treating with PEG-INF and RBV resulted in an incremental $34,622 cost per QALY compared to no screening. In an additional analysis, it was found that screening and treating with teleprevir (DAA) would result in an incremental cost per QALY gained of $43,637 compared to no screening. Wong et al. found that treatment with DAA would remain under the $50,000 per QALY threshold (representing good value for money) if the treatment cost less than $142,908\textsuperscript{50}.

Seven of the eight studies, used a WTP threshold of $50,000 (either per QALY or per life year gained) and concluded that birth cohort screening is good value for money\textsuperscript{50,67,171,172,178-181}. The study which found a cost of $65,749 per QALY gained used universal triple therapy as treatment, which increased cost of treatment\textsuperscript{171}. In addition to this, Rein et al. used multiple treatment arms; when DAAs were added to their base cost-utility analysis, $73,700 cost per QALY gained was reported\textsuperscript{67}. These two studies demonstrate that the biggest cost driver, and a variable which can change the conclusions of a model, is the treatment choice\textsuperscript{67,171}. All studies
interpreted their results as being good value for money\textsuperscript{50,67,171,172,178-181}. Additional data on the results of each study can be found in Appendix F, Table 30.

### 7.3.6 Screening of General Populations

Four of the included studies evaluated general population HCV screening compared to no HCV screening\textsuperscript{86,178,182,183}. One study performed two separate analysis of screening procedures with the same population\textsuperscript{86}, and another evaluated two separate testing strategies (Enzyme linked immunosorbent assay [ELISA] then PCR, and only PCR)\textsuperscript{183}. All four studies are cost-utility analyses, and all reported results using a cost per QALY gained\textsuperscript{86,178,182,183}. Three out of the four studies were conducted in the United States\textsuperscript{178,182,183}, and the remaining study was conducted in the Netherlands\textsuperscript{86}. These studies were published between 2001\textsuperscript{183} and 2013\textsuperscript{182}. Two studies adopted a societal perspective\textsuperscript{178,183}, and the remaining two adopted a payer perspective\textsuperscript{86,182}. Three out of the four studies were analyzed with a lifetime horizon\textsuperscript{86,178,182}, and the remaining study failed to report the time horizon\textsuperscript{183}. All studies assessed uncertainty\textsuperscript{86,178,182,183}. The technical details of the models and characteristics of each included study have been summarized in Appendix F, Table 31.

Three out of the four studies are of high quality when evaluated with the CHEERS checklist\textsuperscript{86,161,178,182}, and the remaining study is of average quality\textsuperscript{183}. All studies included complete outcome data and showed no evidence of selective reporting\textsuperscript{86,178,182,183}. All studies were transparent in their clinical pathway, which included diagnosis and treatment\textsuperscript{86,178,182,183}. The three high quality studies had no major flaws\textsuperscript{86,178,182}. One study failed to report all of the values, ranges, and references for each input in the model\textsuperscript{86}. The average quality study did not report the time horizon, all of the study findings, limitations, generalizability and current knowledge, sources of funding or conflict of interest\textsuperscript{183}.

The results attained by these three studies ranged from $7,900 per QALY gained\textsuperscript{178} to $91,000 per QALY gained\textsuperscript{183}. One of these three studies performed an additional analysis evaluating a general campaign to screen people, and did not find it to be more effective than no screening\textsuperscript{86}. The remaining study evaluated ELISA then PCR and only PCR testing versus no screening, and
both strategies resulted in costs per QALY gained higher than the WTP threshold; ELISA then PCR $60,500 per QALY gained, and PCR $91,000 per QALY gained\textsuperscript{183}.

Two of the authors interpreted their results as being good value for money\textsuperscript{86,178}, and the remaining two authors stated that the screening was good value for money only under certain conditions\textsuperscript{182,183} such as when performing ELISA then PCR, as opposed to PCR alone.

Additional data on the results of each study can be found in Appendix F, Table 32.

### 7.3.7 Screening of Other Groups

Four of the included studies did not fit into any of the above screening categories\textsuperscript{166,168,184,185}. One looked at individuals presenting to a Sexually Transmitted Disease (STD) clinic\textsuperscript{184}. Another evaluated those who had a history of gastroscopy, contact with an infected person, history of invasive procedure, history of colonoscopy or history of surgery\textsuperscript{185}. The remaining assessed those who presented at a genito-urinary clinic\textsuperscript{166}, and individuals who had minor or major surgery\textsuperscript{168}. Two of the four studies used the outcome of cost per positive test\textsuperscript{184,185}, and the remaining two used a cost per QALY gained\textsuperscript{166,168}. The studies were conducted in the United States\textsuperscript{184}, France\textsuperscript{185}, UK\textsuperscript{166}, and the Netherlands\textsuperscript{168}. These studies were published from 2003\textsuperscript{166} to 2008\textsuperscript{168}. Each study used a different perspective: societal\textsuperscript{168}, payer\textsuperscript{166}, STD clinic\textsuperscript{184}, and one did not report their perspective\textsuperscript{185}.

One study adopted a lifetime time horizon\textsuperscript{168}, another adopted a 50 year time horizon\textsuperscript{166}, and the remaining studies did not report the time horizon used\textsuperscript{184,185}. All studies assess for uncertainty\textsuperscript{166,168,184,185}. The technical details of the models and characteristics of each included study have been summarized in Appendix F, Table 33.

Two of the four studies were high quality when evaluated with the CHEERS checklist\textsuperscript{161,166,168}, the remaining two were poor quality\textsuperscript{184,185}. All studies included complete outcome data and showed no evidence of selective reporting\textsuperscript{166,168,184,185}. Three out of the four studies were transparent in their clinical pathway\textsuperscript{166,168,185}. However, only two of the studies accounted for diagnosis and treatment\textsuperscript{166,168} and the remaining studies evaluated only the testing\textsuperscript{185}. The two high quality studies had no major flaws, although one failed to report the year of cost...
adjustment\textsuperscript{168}. One of the poor quality studies failed to report time horizon, discount rate, preference based outcomes, choice of model, and analytic methods supporting the evaluation\textsuperscript{184}. The other poor quality study did not report the study perspective, time horizon, discount rate, preference-based outcomes, or all limitations, generalizability and current knowledge\textsuperscript{185}. None of the studies reported on their sources of funding or conflicts of interest.\textsuperscript{166,168,184,185}

The results for the studies that evaluated the costs per positive test ranged from $54 per positive test to $2,986 per positive test, these came from the same study and were from the IDUs and women over 40, respectively\textsuperscript{184}. The authors reported that their results were cost-effective\textsuperscript{184,185} although there is no accepted threshold for value for money with these outcomes. The remaining two studies that evaluated the cost per QALY gained and ranged from $153,441 per QALY gained\textsuperscript{166} to $1,334,155 cost per QALY gained\textsuperscript{168}, these two studies used a WTP threshold of $50,000 per QALY gained, and neither reported their screening strategies were good value for money. Additional data on the results of each study can be found in Appendix F, Table 34.

7.4 Conclusions

The studies done regarding screening for HCV are generally of good quality and a robust body of evidence has developed. Generally, screening IDUs, birth cohort screening and general population screening appear to be good value for money. The current evidence suggests screening programs may not be good value for money in high-risk groups and pregnant women although the evidence is heterogeneous focusing on a variety of populations and economic outcomes. Screening programs for prisoners appears not to be good value for money, however, the evidence is limited to 1 high-quality study. A variety of other screening programs have been assessed in the literature targeting genito-urinary clinics, individuals who had minor or major surgery, those with the history of gastroscopy and visitors to public STD clinics. None of these programs appear to be good value for money. Importantly, no screening program assessed reported cost-savings; all programs required additional costs and most achieved additional benefit.
Of importance, one Canadian study was included, and found that using a $50,000 per QALY threshold, screening and treating (with either PEG INF and RBV, or a DAA) would be considered good value for money, when adopting a payer perspective. This cost-utility analysis, although conducted in Ontario, is likely to be broadly applicable to the Alberta context.

Several variables affected the findings of the reported economic evaluations: the prevalence of asymptomatic HCV, the acceptability of screening, and the acceptability of treatment. There is little information about these factors and any implementation plan will require flexibility to changing uptake in the screening program.
8 Cost-effectiveness of a birth cohort screening program in Alberta

Summary

- The cost per QALY gained for birth cohort screening compared to no screening ranges from $37,010 - $44,614 depending on the treatment strategy; all could be considered reasonable value for money
- All treatment strategies evaluated resulted in fewer decompensated cirrhosis, hepatocellular carcinoma, liver transplants, and liver-related deaths.

8.1 Purpose
To estimate the cost-effectiveness of introducing a birth cohort screening program for HCV in Alberta.

8.2 Methods
A prior cost-effectiveness analysis evaluating birth cohort screening for HCV in Ontario, was utilized as to model screening for HCV of a birth cohort in Alberta\(^50\). Within this model various parameters were changed to make it applicable to the Alberta population:

- Prevalence of HCV in the population: 1.5% \(^{186}\)
- Cost of negative test results: $24.28 \(^{187}\)
- Cost of positive test results: $234.62 \(^{187}\)
- Cost of Holkira Pak (12.5 mg/mL ombitasvir/75 mg paritaprevir/50 mg ritonavir, and dasabuvir 250 mg): $55,860
- Cost of Sofosbuvir and Ribavirin (12 weeks): $55,000
- Uptake of screening: 70.1% \(^{67,188}\)
- Age distribution:
  - 45-54: 57.64% \(^{189}\)
  - 55-64: 42.36% \(^{189}\)

All of the remaining variables stayed the same as was in the initial model\(^50\).

The model had three comparators:
1. No Screening (baseline),

The model had a lifetime time horizon. It used a payer perspective and a discount rate of 5% per year. Utilities were calculated using the EQ-5D, which includes five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety and depression. These domains were combined using an algorithm to produce an overall utility index score on a scale of 0 (very poor health) to 1 (full health).

The results are reported as incremental cost-effectiveness ratios (ICERs), which were calculated using the standard approach: \(\frac{\text{cost}_1 - \text{cost}_2}{\text{effectiveness}_1 - \text{effectiveness}_2}\). The overall costs, QALYs, the changes in each from baseline (No Screening) and then their respective ICERs were calculated for each alternative strategy.

The number of events avoided per 10,000 screened of the following events were also compared: decompensated cirrhosis, hepatocellular carcinoma (HCC), transplant, HCV related liver deaths, and overall deaths avoided compared to “No Screening”. Based on the 2014 Alberta population counts, for the birth cohort, the number of events per 10,000 are converted into absolute population numbers and the total number avoided as compared to No Screening\(^{189}\). From these numbers we are also able to estimate the costs avoided for transplants by using the costing for transplants and after care from literature, and converting it to 2014 Canadian dollars\(^{190,191}\).

TreeAge Pro 2014 was used for economic modeling.

8.3 Results
No screening costs an average of $83,059 per person with an effectiveness of 12.41 QALYs (Table 16). Screening and any combination of treatments costs more and results in more QALYs gained compared to no screening. All could be considered reasonable value for money as the resulting cost per QALY gained are all below $50,000; Screen & treat with G1: Holkira Pak, G2/3: sofosbuvir and ribavirin, G4/5/6: PEG-IFN + RBV resulted in a cost per QALY gained of
$37,010 compared to no screening and Screen & treat with G1:simeprevir+ PEG-IFN + RBV G2/3: sofosbuvir and RBV G4/5/6: PEG-IFN + RBV resulted in a cost per QALY gained of $44,614 compared to no screening.

Overall, any of the screening programs resulted in reductions in negative health outcomes associated with HCV. Using Screen & treat with G1: Holkira Pak, G2/3: sofosbuvir and ribavirin, G4/5/6: PEG-IFN + RBV there are the fewest number of decompensated cirrhosis (56), HCC (37), liver transplants (11), and HCV related liver death (81) (Table 17).

8.4 Limitations
The model is a simulation of what may happen if birth cohort screening is implemented. As with all models, it is limited by the available data. Specifically, the model likely over-estimates the proportion of patients adherent to therapy and underestimates the proportion that discontinued treatment\textsuperscript{50}. The model also extrapolates data from a single tertiary hospital to estimate fibrosis stage distribution\textsuperscript{50}. The model did not take into account the events which may occur between the time of diagnosis to when an individual is treated\textsuperscript{50}. Lastly, the model considers implementation through an opportunistic screening program; additional costs, possible increases in screening and thus increased clinical benefit due to implementation of an organized screening program are not considered.

8.5 Conclusions
Birth cohort screening, combined with any treatment strategy, results in more clinical benefit and higher cost than no screening. All considered strategies could be considered reasonable value for money, if a threshold of $50,000 per QALY gained is applied.
Table 16: Baseline Cost-Effectiveness Results of birth cohort screening in Alberta

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost ($)</th>
<th>Effectiveness (QALY)</th>
<th>Incremental Cost ($)</th>
<th>Incremental Effectiveness (QALY)</th>
<th>Incremental cost-effectiveness ratio ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No screening</td>
<td>$83,059</td>
<td>12.1440</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
| Screen & treat with G1:simeprevir + PEG-IFN + RBV  
  G2/3: SOF/RBV  
  G4/5/6: PEF-IFN | $83,581  
  $83,581  
  $83,581 | 12.1557  
  12.1557  
  12.1557 | $522  
  $522  
  $522 | 0.0117  
  0.0117  
  0.0117 | $44,614*  
  $37,010  
  $37,010 |

G1: genotype 1; G2/3: genotype 2 or 3; G4/5/6: genotype 4 or 5 or 6; PEG-IFN = pegylated interferon; RBV = ribavirin; SOF/RBV = sofosbuvir plus ribavirin; QALY = quality-adjusted life-year;
Table 17: Baseline population projected outcomes by introducing a birth cohort screening program in Alberta

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Decompensated Cirrhosis</th>
<th>Hepatocellular Carcinoma</th>
<th>Transplants</th>
<th>HCV related deaths prevented</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Expected number of events</td>
<td>Events avoided compared to no screening</td>
<td>Expected number of events</td>
<td>Events avoided compared to no screening</td>
</tr>
<tr>
<td>No screening</td>
<td>81</td>
<td>57</td>
<td>16</td>
<td>122</td>
</tr>
<tr>
<td>Screen &amp; treat with G1: simeprevir + PEG-IFN + RBV G2/3: SOF/RBV G4/5/6: PEF-IFN</td>
<td>64</td>
<td>17</td>
<td>37</td>
<td>21</td>
</tr>
</tbody>
</table>

G1: genotype 1; G2/3: genotype 2 or 3; G4/5/6: genotype 4 or 5 or 6; PEG-IFN = pegylated interferon; RBV = ribavirin; SOF/RBV = sofosbuvir plus ribavirin
9 Projected Budget Impact

Summary
- Ranging from $5.5 million to $253 million, the order of most to least expensive populations to screen and treat are: general population, and birth cohort, followed by high-risk populations including aboriginal, immigrants, IDU, prisoners and pregnant individuals.
- The cost to screen those born between 1950 and 1970 would be approximately $47 million, and cost to both screen and treat this population would be approximately $134 million, assuming a 20% treatment uptake.
- Costs increase as the number screened, proportion of positive test, and uptake of screening and treatment increase; the main factors that could greatly affect the estimated budget impact include uptake of screening and treatment.

9.1 Purpose
To estimate the budgetary impact of HCV screening for various populations.

9.2 Methods
The perspective of the public payer was used including the direct costs associated with screening and medication. A time horizon of 1 year was used. Both the costs associated with screening, and the additional costs associated with the new treatments of harvoni and sofosbuvir are included. Costs of screening were calculated using the total count in the identified population, their uptake of screening, the prevalence of HCV, and the costs associated with testing. Harvoni is proposed for genotype 1 with fibrosis stages 2, 3 and 4 and sofosbuvir for genotypes 1, 2 and 3 and fibrosis stages 2, 3 and 4. Probabilities were used for each genotype and fibrosis stage associated with the individual medications. The final costs of treatment were calculated using the recommended genotypes and fibrosis stages for each medication, the anticipated uptake of treatment, and the cost of treatment using the possible listed prices and including ribavirin and PEG-IFN.

9.2.1 Cost Inputs
Medication costs of ribavirin and PEG-IFN were derived from the current drug pricing from Alberta Blue Cross. The costs of the new DAAs (sofosbuvir and harvoni) were costed based on the upper bound of the anticipated listed price for Alberta provided by Alberta Health.
Table 18). Cost per treatment regimen were based on current dosing practices based on guidelines from the Canadian Association for the Study of the Liver\textsuperscript{88}.

The screening costs were developed based on the current pathway developed from the key informant interviews. Screening tests occur in succession with a positive HCV antibody test leading to a subsequent RNA test. The independent costs for these tests are taken from the Provincial Laboratory (ProvLab)\textsuperscript{187}.

The costs used in the model were directly related to whether a person was found to have HCV with the final test. The physician cost for the initial screening of the individual is based on the Alberta Schedule of Medical Benefits\textsuperscript{195}.

For Aboriginal and prison populations, this model has combined all costs of treatment and screening under the assumption that both would fall within provincial health care funding. This was done in order to show the total cost of screening (and treating) these populations. However, since health care for First Nations is provided by the federal government, and most prisoners are within federal prisons, screening and treating these populations may not fall entirely within the provincial jurisdiction. The federal government may be responsible for a portion, or all, of the costs for these populations.

\subsection*{9.2.2 Population Counts}

Census data from Statistics Canada was used to estimate the current population size expected in screening the general population, birth cohort, IDUs, current immigrants, and aboriginals\textsuperscript{196,197}. The estimate for the current incarcerated population in Alberta was taken from the Alberta Government\textsuperscript{198}. While there was no direct count of pregnant females within Alberta each year, the number of births in Alberta per year based on Statistics Canada was used as an estimate\textsuperscript{199}. The populations included in this budget impact analysis were limited by availability of data; only populations where a reliable population count could be found for Alberta were included. As a result, it was not possible to include all potential HCV screening populations in this budget impact analysis.
9.2.3 Probabilities

The uptake of screening for the general population and birth cohort screening was a combination of the proportion of Canadians with a primary care physician, and the proportion of people who would undergo a HCV test if asked during a primary care visit\(^67,200\) (Table 18). Uptake for IDUs was an estimated range with the upper bound applied\(^201\) (Table 18). For those incarcerated, an estimated 85% would be amenable to screening within a population comparable to Alberta, and 84% for those who are pregnant\(^15,202\) (Table 18).

Overall, the estimated prevalence of HCV in Alberta is 0.69% (both current and possible undiagnosed)\(^7\). The prevalence varies by sub-population with an estimated prevalence of 1.5% among the birth cohort for those born between 1950-1970, 88% among IDUs, 12-35% among the prison populations, 0.8% among pregnant women, 1.9% among immigrants, and 3.24% among aboriginals\(^11-13,15,16\) (Table 18). The initial distribution of fibrosis, the transitions between the stages of disease, and genotype distribution are taken from the literature\(^50,203\) (Table 18). Current estimates of treatment uptake vary; a systematic review reported 17% of IDUs choosing to undergo treatment and two studies estimated approximately 12 to 24% of the general population\(^204-206\) (Table 18).

The remaining populations did not have treatment uptake data available and therefore an average of IDUs and the higher value in the general population range were averaged, giving a treatment uptake of 20.5%. It is important to note that the treatment uptake estimates are based on the older forms of treatment, and treatment uptake is likely to be higher with the new emerging treatment regimens due to the lack of side effects. The final sustained virologic response to sofosbuvir and harvoni were taken from randomized control trials currently being performed and reports from the manufacturers\(^73,207,208\).
Table 18: Summary of Inputs used in Budget Impact Analysis

<table>
<thead>
<tr>
<th>Component</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sofosbuvir (G1 to 3; F2-4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Company Price</td>
<td>$84,000</td>
<td>193</td>
</tr>
<tr>
<td>o Possible listed price</td>
<td>$40,000</td>
<td></td>
</tr>
<tr>
<td>o Sofosbuvir + Ribavirin + PEG-IFN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Company Price</td>
<td>$104,429.52</td>
<td>192,193</td>
</tr>
<tr>
<td>• Possible listed Price</td>
<td>$50,214.76</td>
<td></td>
</tr>
<tr>
<td>• Harvoni (G1; F2-4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Company Price</td>
<td>$95,000</td>
<td>194</td>
</tr>
<tr>
<td>o Possible listed price</td>
<td>$40,000</td>
<td></td>
</tr>
<tr>
<td>o Harvoni + Ribavirin + PEG-IFN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Company Price</td>
<td>$115,429.52</td>
<td>192,194</td>
</tr>
<tr>
<td>• Possible listed Price</td>
<td>$50,214.76</td>
<td></td>
</tr>
<tr>
<td><strong>Physician</strong></td>
<td>$35.92</td>
<td>195</td>
</tr>
<tr>
<td>• General Practitioner</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Treatment</td>
<td>$234.54</td>
<td></td>
</tr>
<tr>
<td>• Initial Assessment / Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Follow-up</td>
<td>$68.50</td>
<td></td>
</tr>
<tr>
<td><strong>Screening Tests</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• HCV antibody (1st)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o –ve test</td>
<td>$24.28</td>
<td>187</td>
</tr>
<tr>
<td>o +ve test</td>
<td>$64.95</td>
<td></td>
</tr>
<tr>
<td>• HCV RNA (2nd)</td>
<td>$169.67</td>
<td></td>
</tr>
<tr>
<td>• Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Negative Test</td>
<td>$24.28</td>
<td></td>
</tr>
<tr>
<td>o Positive Test</td>
<td>$234.62</td>
<td></td>
</tr>
<tr>
<td><strong>Support Services</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Clerical (2 x $28.91/hour; Clerk IV)</td>
<td>$57.82</td>
<td>209</td>
</tr>
<tr>
<td>• Nursing (2 x $45.93/hour; Registered Nurse)</td>
<td>$91.86</td>
<td>209</td>
</tr>
<tr>
<td><strong>Population Counts</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• General Population (&gt;20)</td>
<td>3,123,075</td>
<td>196</td>
</tr>
<tr>
<td>• Birth Cohort (45-64)</td>
<td>1,060,322</td>
<td>196</td>
</tr>
<tr>
<td>• IDU (1.1% 197)</td>
<td>34,354</td>
<td>196,197</td>
</tr>
<tr>
<td>• Prison</td>
<td>2,907</td>
<td>210</td>
</tr>
<tr>
<td>• Pregnant</td>
<td>56,582</td>
<td>199</td>
</tr>
<tr>
<td>• Immigrants</td>
<td>117,402</td>
<td>94</td>
</tr>
<tr>
<td>• Aboriginals</td>
<td>220,695</td>
<td>211</td>
</tr>
<tr>
<td><strong>Probabilities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada uptake of screening</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• General Population and Birth Cohort (0.77*0.91)  
  • Patients with Primary Care in Canada  
  • Screening uptake when offered (primary care)  
  • IDU (England)  
  • Prisoners  
  • Pregnant  
  • Immigrants  
  • Aboriginals  

<table>
<thead>
<tr>
<th>Prevalence of HCV</th>
<th>70.1%</th>
<th>67,200</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Population</td>
<td>77%</td>
<td>200</td>
</tr>
<tr>
<td>Birth Cohort</td>
<td>91%</td>
<td>67</td>
</tr>
<tr>
<td>IDU</td>
<td>7.7-8.4%</td>
<td>201</td>
</tr>
<tr>
<td>Prison</td>
<td>85%</td>
<td>202</td>
</tr>
<tr>
<td>Pregnant</td>
<td>84%</td>
<td>15</td>
</tr>
<tr>
<td>Immigrants</td>
<td>70.1%</td>
<td>67,200</td>
</tr>
<tr>
<td>Aboriginals (4.7 times general population)</td>
<td>70.1%</td>
<td>67,200</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype Distribution</th>
<th>67%</th>
<th>203</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>G3</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>G4</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>G5/6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distribution of Fibrosis (initial)</th>
<th>7.0%</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0</td>
<td>28.13%</td>
<td></td>
</tr>
<tr>
<td>F1</td>
<td>28.13%</td>
<td></td>
</tr>
<tr>
<td>F2</td>
<td>20.0%</td>
<td></td>
</tr>
<tr>
<td>F3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F4</td>
<td>17.3%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment uptake</th>
<th>12-24%</th>
<th>205,206</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Population and Birth Cohort</td>
<td>17%</td>
<td>204</td>
</tr>
<tr>
<td>IDU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All remaining (average between two population)</td>
<td>20.5%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sustained Virologic Response</th>
<th>80-92%</th>
<th>73,207</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir</td>
<td>96%</td>
<td>208</td>
</tr>
<tr>
<td>Harvoni</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 9.2.4 Scenario Analysis

The estimates of treatment uptake were based on prior medications such as Telaprevir. Since the new medications are known to have less side effects, and hepatologists would recommend these treatments, there may be a higher uptake of treatment. Therefore, in the first scenario analysis, a 75% treatment uptake was used, rather than the Telaprevir-based estimates.
A second scenario analysis was completed, which included a more robust care pathway estimate. The expanded estimate includes (1) costs of ongoing treatment by a physician, (2) clerical support, and (3) nursing support for individual patients\textsuperscript{195,209}. It should be noted that this scenario analysis likely represents a “best-case” scenario as the implementation, administration and reporting burden may be very resource intense. An estimate of 75% treatment uptake was used to reflect an ideal care pathway.

9.3 Results

Overall, screening and treating the general population is the most costly, with a total overall cost of nearly $253 million. The order of most to least expensive to screen and treat are: general population, birth cohort, aboriginal, immigrants, IDUs, prisoners and pregnant individuals.

The scenario analysis, altering the treatment uptake, demonstrated that a substantial increase of costs would be seen if there is an increased proportion of those individuals treated. The order of most to least expensive generally remains the same, although IDUs now cost more than immigrants, but for the general population it would cost nearly $501 million, and birth cohort would cost nearly $317 million. For the second scenario analysis, including the ideal care pathway, general population would costs $507 million and birth cohort increases to $322 million (Table 19).

The costs increase as the number screened, proportion of positive test, and uptake of screening and treatment increase. The main areas of uncertainty that have the ability to greatly affect the budget impact are the uptake of screening and treatment.
**Table 19: Results of Budget Impact Analysis**

<table>
<thead>
<tr>
<th>Population</th>
<th>Cost of Screening</th>
<th>Cost of Treatment</th>
<th>Total Cost of Screening and Treatment</th>
<th>Scenario Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$134,971,785</td>
<td>$118,038,883</td>
<td>$253,010,669</td>
<td>$501,069,153</td>
</tr>
<tr>
<td>General</td>
<td>$47,090,941</td>
<td>$223</td>
<td>$134,211,894</td>
<td>$317,296,409</td>
</tr>
<tr>
<td>Birth Cohort</td>
<td>$707,868</td>
<td>$330,660</td>
<td>$14,827,579</td>
<td>$62,251,958</td>
</tr>
<tr>
<td>IDU</td>
<td>$330,660</td>
<td>$5,783,216</td>
<td>$6,113,876</td>
<td>$21,290,071</td>
</tr>
<tr>
<td>Pregnant</td>
<td>$2,941,216</td>
<td>$2,542,640</td>
<td>$5,483,857</td>
<td>$12,156,201</td>
</tr>
<tr>
<td>Immigrants</td>
<td>$5,283,291</td>
<td>$10,456,457</td>
<td>$15,739,749</td>
<td>$43,179,363</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>$10,367,705</td>
<td>$33,519,149</td>
<td>$43,886,854</td>
<td>$131,847,096</td>
</tr>
</tbody>
</table>
10 Summary of Evidence
This section presents a summary of the evidence presented above by at-risk group or risk factor. Twenty-two groups previously identified are included (16 at-risk groups or risk factors from PHAC’s 2014 screening recommendations and six more at-risk groups or risk factors identified through the review). For each group, we have summarized information on: inclusion in Albertan, Canadian, or international screening guidelines; cost-effectiveness of screening; estimated prevalence of HCV; perspectives of patients; experiences and perspectives of Alberta key informants; and projected budget impact of screening.


66. Alswaidi FM, O’Brien SJ. Is there a need to include HIV, HBV and HCV viruses in the Saudi premarital screening program on the basis of their prevalence and transmission risk factors? *J Epidemiol Community Health.* 2010.


97. Khaw FM, Stobbart L, Murtagh MJ. 'I just keep thinking I haven't got it because I'm not yellow': a qualitative study of the factors that influence the uptake of Hepatitis C testing by prisoners. *BMC Public Health.* 2007;7:98.


138. Treloar C, Hopwood M. "Look, I'm fit, I'm positive and I'll be all right, thank you very much": coping with hepatitis C treatment and unrealistic optimism. *Psychology Health & Medicine*. 2008;13(3):360-366.


Appendix A: Proposed Assessment and Treatment Model

One proposed assessment and treatment model, outlined by one key informant, for consideration

“As I mentioned, if we wish to make a serious dent in the HCV situation, we need to move from the current model to something completely different. In the current model, there is no active case finding, and most HCV treaters (except the ID group in Edmonton) insist on a referral from another MD, purely for billing reasons. Waiting times are long and there is a capacity problem. Increasing case finding without changing delivery of care doesn’t make sense.

As I mentioned, I favour a MD-directed, RN-run model based on how most STI (sexually transmitted infections) clinics operate. Patients may present referred or not, with appointments or not. The RN will take a focused history and have the patient do a standard panel of blood work determined by the MD Director. In addition to HCV-related parameters, blood tests will screen for co-infection with HBV or HIV and also for immunity to HAV and HBV. Ideally, a blood collection site will be on the premises, both for patient convenience and to avoid the scenario of a patient being given requisitions for lab tests but never going to the lab. Importantly, the clinics would also have a FibroScan machine with both M and XL probes (the XL is for large patients) and a RN would perform a FS. The clinic should be stocked with both hepatitis A vaccine and hepatitis B vaccine which the RNs will administer if the lab tests demonstrate susceptibility.

For the time being while HCV Rx is very costly, and recognizing that many patients with minimal hepatic fibrosis will not progress to advanced liver disease, patients with mild fibrosis will not be treated with antivirals, but be put into annual follow-up. Ideally, they can be offered their choice of contact method: SMS, email, phone call, snail mail to maximize the probability that they will show up.

Patient with moderate fibrosis will be treated by the RNs with all-oral, interferon-free therapy. There will be written protocols regarding the antiviral regimens to be used based on genotype, and what monitoring is required. A resource pharmacist can be involved to ensure that there are no clinically significant drug-drug interactions with the patients other (non HCV) medications. This pharmacist does not need to be on site. These patients will not need to see an MD.

Patients with advanced fibrosis will be booked for abdominal ultrasound and then to see an MD. Many will also require screening gastroscopy. A mechanism to arrange this on a systematic basis should be developed. If the MD and patient agree to antiviral treatment (which is expected), this will generally be supervised by the RNs.”
Appendix B: Search Strategies for Systematic Review on Patient Experiences with Hepatitis C

**MEDLINE (OVID)**
1. exp *Hepatitis C/
2. *Hepacivirus/
3. (hepatitis C or hep C or hcv or hepacivirus).ti.
4. *Hepatitis C Antigens/
5. *Hepatitis C Antibodies/
6. 1 or 2 or 3 or 4 or 5
7. limit 6 to english language
8. attitude/ or attitude to death/ or attitude to health/ or health knowledge, attitudes, practice/ or behavior/ or health behavior/ or illness behavior/ or information seeking behavior/ or risk reduction behavior/
9. (attitude* or behavior or behaviors or behaviour or behaviours or beliefs or experiences or perception* or preference* or satisfaction or understand*).tw.
10. "Quality of Life"/
11. 8 or 9 or 10 or 11
12. 7 and 12
13. limit 13 to animals
14. limit 13 to (animals and humans)
15. 16 not 15
16. 13 not 16
17. limit 17 to (case reports or editorial or letter)
18. 19 not 18
19. 19 not 18
20. exp qualitative research/
21. Focus Groups/
22. interviews as topic/ or narration/
23. interview.pt.
24. (focus group* or interview* or qualitative).tw.
25. grounded theory/
26. hermeneutics/
27. (ethnograph* or grounded theory or hermeneutic* or phenomenolog*).tw.
28. experiences.tw.
29. 20 or 21 or 22 or 23 or 24 or 28
30. 25 or 26 or 27
31. 19 and 29
32. 7 and 30
33. 31 or 32
34. limit 33 to "all adult (19 plus years)"
35. limit 33 to ("newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)")
36. 34 and 35
37. 35 not 36
38. 33 not 37

**PubMed**
1. Hepatitis C[MAJR]
2. *Hepacivirus[MAJR]
3. (hepatitis C or hep C or hcv or hepacivirus)[ti]
4. *Hepatitis C Antigens[MAJR]
5. *Hepatitis C Antibodies[MAJR]
6. 1 or 2 or 3 or 4 or 5
7. limit 6 to english language
8. (attitude or attitude to death or attitude to health or attitude to health knowledge, attitudes, practice)[MeSH]
9. (behavior or health behavior or illness behavior or information seeking behavior or risk reduction behavior)[MeSH]
10. (attitude* or behavior or behaviors or behaviour or behaviours or beliefs or experiences or perception* or preference* or satisfaction or understand*)[tiab]
11. "Quality of Life"[MeSH]
12. 8 or 9 or 10 or 11
13. 7 and 12
14. qualitative research[MeSH]
15. Focus Groups[MeSH]
16. (interviews as topic or narration)[MeSH]
17. interview[Publication Type]
18. (focus group* or interview* or qualitative)[tiab]
19. grounded theory[MeSH]
20. hermeneutics[MeSH]
21. (ethnograph* or grounded theory or hermeneutic* or phenomenolog*)[tiab]
22. experiences[tiab]
23. 14 or 15 or 16 or 17 or 18 or 22
24. 19 or 20 or 21
25. 13 and 23
26. 7 and 24
27. 25 or 26

EMBASE (OVID)
1. exp *hepatitis C/ or exp *hepatitis C antibody/ or exp *hepatitis C vaccine/ or exp *hepatitis C antigen/ or exp *Hepatitis C virus/
2. (hepatitis C or hep C or hcv or hepacivirus).ti.
3. 1 or 2
4. limit 3 to english language
5. attitude/ or attitude to death/ or attitude to health/ or attitude to illness/ or consumer attitude/ or cultural bias/ or cultural sensitivity/ or employee attitude/ or exp family attitude/ or gender bias/ or exp patient attitude/ or student attitude/
6. behavior/ or exp health behavior/ or help seeking behavior/ or illness behavior/ or motivation/
7. information seeking/
8. personal experience/
9. exp "quality of life"
10. (attitude* or behavior or behaviors or behaviour or behaviours or beliefs or experiences or perception* or preference* or satisfaction or understand*).tw.
11. 5 or 6 or 7 or 8 or 9 or 10
12. 4 and 11
13. limit 12 to animal studies
14. limit 12 to (human and animal studies)
15. 13 not 14
16. 12 not 15
17. limit 16 to (conference abstract or editorial or letter)
18. 16 not 17
19. case report/
20. 18 not 19
21. qualitative research/ or qualitative analysis/
22. exp interview/
23. participant observation/
24. (focus group* or interview* or qualitative).tw.
25. grounded theory/
26. naturalistic inquiry/
27. phenomenology/
28. (ethnograph* or grounded theory or hermeneutic* or phenomenolog*).tw.
29. experiences.tw.
30. 21 or 22 or 23 or 24 or 29
31. 25 or 26 or 27 or 28
32. 20 and 30
33. 4 and 31
34. 32 or 33
35. limit 34 to (embryo or infant or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
36. limit 34 to (adult <18 to 64 years> or aged <65+ years>)
37. 35 and 36
38. 35 not 37
39. 34 not 38

PsycINFO (OVID)
1. (hepatitis C or hep C or hcv or hepacivirus).ti.
2. limit 1 to english language
3. exp attitudes/
4. behavior/ or exp consumer behavior/ or exp health behavior/
5. life experiences/ or "experiences (events)/"
6. exp "quality of life"/
7. health knowledge/
8. (attitude* or behavior or behaviors or behaviour or behaviours or beliefs or experiences or perception* or preference* or satisfaction or understand*).tw.
9. 3 or 4 or 5 or 6 or 7 or 8
10. 2 and 9
11. limit 10 to animal
12. limit 10 to (animal and human)
13. 11 not 12
14. 10 not 13
15. limit 14 to (abstract collection or "column/opinion" or editorial or review-book or review-media or review-software & other)
16. 14 not 15
17. exp Case Report/
18. 16 not 17
19. limit 18 to ("0700 interview" or "0750 focus group" or 1600 qualitative study)
20. qualitative research/
21. group discussion/
22. interviews/
23. (focus group* or interview* or qualitative).tw.
24. 20 or 21 or 22 or 23
25. grounded theory/
26. phenomenology/ or hermeneutics/
27. ethnography/
28. (ethnograph* or grounded theory or hermeneutic* or phenomenolog*).tw.
29. 26 or 27 or 28
30. experiences.tw.
31. 18 and 24
32. 18 and 30
33. 2 and 29
34. 19 or 31 or 32 or 33

CINAHL (EBSCO)

1. ((MM "Hepatitis C") OR (MM "Hepatitis C, Chronic") ) OR TI ( (hepatitis C or hep C or hcv or hepacivirus) ) (Limit to English Language)
2. ((MH "Attitude") OR (MH "Attitude to Death+") OR (MH "Attitude to Health+") OR (MH "Attitude to Illness+") OR (MH "Attitude to Risk") OR (MH "Consumer Attitudes") OR (MH "Cultural Bias") OR (MH "Family Attitudes+") OR (MH "Gender Bias") OR (MH "Patient Attitudes") OR (MH "Student Attitudes+") OR (MH "Behavior") OR (MH "Health Behavior+") OR (MH "Harm Reduction") OR (MH "Help Seeking Behavior") OR (MH "Information Seeking Behavior") OR (MH "Risk Taking Behavior+") OR (MH "Life Experiences") OR (MH "Health Services Needs and Demand") OR (MH "Patient Satisfaction") OR (MH "Consumer Satisfaction") ) OR TI ( attitude* or behavior or behaviors or behaviour or behaviours or beliefs or experiences or perception* or preference* or satisfaction or understand* ) OR AB ( attitude* or behavior or behaviors or behaviour or behaviours or beliefs or experiences or perception* or preference* or satisfaction or understand*)
3. (MH "Quality of Life+")
4. 2 or 3
5. TI experiences OR AB experiences
6. (MH "Action Research") OR (MH "Ethnological Research") OR (MH "Ethnographic Research") OR (MH "Ethnonursing Research") OR (MH "Grounded Theory") OR (MH "Naturalistic Inquiry") OR (MH "Phenomenological Research") OR (MH "Qualitative Studies") OR TI ((ethnograph* or grounded theory or hermeneutic* or phenomenolog*)) OR AB ((ethnograph* or grounded theory or hermeneutic* or phenomenolog*))

7. (MH "Focus Groups") OR (MH "Interviews") OR TI ((focus group* or interview* or qualitative)) OR AB ((focus group* or interview* or qualitative))

8. 1 and 4 and 7
9. 1 and 5
10. 1 and 6
11. 8 or 9 or 10

SocINDEX
1. (hepatitis C or hep C or hcv or hepacivirus)[Title]
2. (attitude* or behavior or behaviors or behaviour or behaviours or beliefs or experiences or perception* or preference* or satisfaction or understand* or quality of life)[Title/Abstract]
3. (focus group* or interview* or qualitative or ethnograph* or grounded theory or hermeneutic* or phenomenolog*)[Title/Abstract]
4. 1 and 2 and 3
Appendix C: Search Strategies for Opportunistic Versus Organized Screening programs

MEDLINE (OVID)
1. exp Mass Screening/
2. ((informal* or opportunistic* or spontaneous) and (active* or formal* or organized or organised or population-based or proactive* or target*)).tw.
3. 1 and 2
4. ((active* or formal* or organized or organised or population-based or proactive* or target*) adj10 (screen* or test* or vaginal smear*)).tw.
5. ((informal* or opportunistic* or spontaneous) adj10 (screen* or test* or vaginal smear*)).tw.
6. 4 and 5
7. (opportunistic* adj1 (screen* or test* or vaginal smear*)).tw.
8. 3 or 6 or 7
9. limit 8 to (editorial or letter)
10. 8 not 9
11. limit 10 to case reports
12. 10 not 11
13. limit 12 to animals
14. limit 12 to (animals and humans)
15. 13 not 14
16. 12 not 15

Cochrane CENTRAL Register (OVID)
1. exp Mass Screening/
2. ((informal* or opportunistic* or spontaneous) and (active* or formal* or organized or organised or population-based or proactive* or target*)).tw.
3. 1 and 2
4. ((active* or formal* or organized or organised or population-based or proactive* or target*) adj10 (screen* or test* or vaginal smear*)).tw.
5. ((informal* or opportunistic* or spontaneous) adj10 (screen* or test* or vaginal smear*)).tw.
6. 4 and 5
7. (opportunistic* adj1 (screen* or test* or vaginal smear*)).tw.
8. 3 or 6 or 7

Cochrane Database of Systematic Reviews (OVID)

HTA Database (OVID)
1. ((informal* or opportunistic* or spontaneous) and (active* or formal* or organized or organised or population-based or proactive* or target*)).tw.
2. ((active* or formal* or organized or organised or population-based or proactive* or target*) adj10 (screen* or test* or vaginal smear*)).tw.
3. ((informal* or opportunistic* or spontaneous) adj10 (screen* or test* or vaginal smear*)).tw.
4. 2 and 3
5. (opportunistic* adj1 (screen* or test* or vaginal smear*)).tw.
6. 1 or 4 or 5

**EMBASE (OVID)**
1. screening/ or dna screening/ or exp mass screening/ or screening test/
2. ((informal* or opportunistic* or spontaneous) and (active* or formal* or organized or organised or population-based or proactive* or target*)).tw.
3. 1 and 2
4. ((active* or formal* or organized or organised or population-based or proactive* or target*) adj10 (screen* or test* or vaginal smear*)).tw.
5. ((informal* or opportunistic* or spontaneous) adj10 (screen* or test* or vaginal smear*)).tw.
6. 4 and 5
7. (opportunistic* adj1 (screen* or test* or vaginal smear*)).tw.
8. 3 or 6 or 7
9. limit 8 to (conference abstract or editorial or letter)
10. 8 not 9
11. case report/
12. 10 not 11
13. limit 12 to animal studies
14. limit 12 to (human and animal studies)
15. 13 not 14
16. 12 not 15

**CINAHL (EBSCO)**
1. (MH "Health Screening+")
2. TI ( ((informal* or opportunistic* or spontaneous) and (active* or formal* or organized or organised or population-based or proactive* or target*)) ) OR AB ( ((informal* or opportunistic* or spontaneous) and (active* or formal* or organized or organised or population-based or proactive* or target*)) )

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3. 1 and 2
4. TI ( ((active* or formal* or organized or organised or population-based or proactive* or target*) N10 (screen* or test* or vaginal smear*)) ) OR AB ( ((active* or formal* or organized or organised or population-based or proactive* or target*) N10 (screen* or test* or vaginal smear*)) )
5. TI ( ((informal* or opportunistic* or spontaneous) N10 (screen* or test* or vaginal smear*)) ) OR AB ( ((informal* or opportunistic* or spontaneous) N10 (screen* or test* or vaginal smear*)) )
6. 4 and 5
7. TI ( (opportunistic* N1 (screen* or test* or vaginal smear*)) ) OR AB ( (opportunistic* N1 (screen* or test* or vaginal smear*)) )
8. 3 or 6 or 7
Appendix D: Non-RCT Data
### Table 20: Study Characteristics of Non-Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Author, Year of Publication, Country</th>
<th>Study Design</th>
<th>Study Objectives</th>
<th>Participant Selection</th>
<th>Characteristics of Comparators</th>
<th>Outcomes</th>
<th>Author Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast Cancer Screening</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beemsterboer et al. 1998, The Netherlands</td>
<td>Prospective cohort</td>
<td>To analyze “…the effect of the start of the Dutch national screening program on the number of mammographies requested by 43-45 general practices for the age groups 30-39, 40-49, 50-69 and 70+ years.”</td>
<td>Patient Selection: Patient records were analyzed from 45 general practices in the Netherlands between 1988 and 1995. Inclusion Criteria: None reported Exclusion Criteria: None reported Patient Characteristics: Data from 4,834 patients were included.</td>
<td>Intervention: Biennial mammography screening for women aged 50-69. Control: Mammography if requested by physician or patient, for those younger than 50 or older than 69.</td>
<td>Outcomes Measured:</td>
<td>&quot;In all age groups an immediate increase was observed in the number of mammography requests after the start of the programme (age 50-69). More than 2 years after the start of screening, the number of mammography requests in all age groups had decreased to the level before the start, and in the age group 50-69 years the number of mammographies was significantly lower than before the screening started.&quot;</td>
</tr>
<tr>
<td>Bonez et al. 2008, Hungary</td>
<td>Retrospective cohort</td>
<td>“To analyse the effect of an organized, nationwide breast cancer screening program on non-organized mammography activities in Hungary.”</td>
<td>Patient Selection: Data on women who underwent a mammography before the introduction of the national screening program (2000-2001), and after the introduction of the national screening program (2002-2003/2004-2005) were included in this analysis. Inclusion Criteria: Women in Hungary undergoing a mammography before the introduction of age 45-65 Exclusion Criteria: None reported</td>
<td>Intervention: Personal invitation for mammography Control: Usual care, which may have included testing if requested by a participant, or recommended by a physician.</td>
<td>Outcomes Measured:</td>
<td>&quot;The introduction of an organized nationwide screening program in Hungary resulted in increases in the number of screening mammographies, and also of non-organized mammographies. Although the ratio of organized screening vs non-organized mammography changed in favor of screening&quot;</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Study Design</td>
<td>Objective</td>
<td>Patient Selection</td>
<td>Intervention</td>
<td>Outcomes Measured</td>
</tr>
<tr>
<td>-------</td>
<td>---------</td>
<td>--------------</td>
<td>-----------</td>
<td>-------------------</td>
<td>--------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Bjorge et al. (1995), Norway</td>
<td></td>
<td>Retrospective cohort</td>
<td>“…to evaluate the organizational aspects of a nationwide, population-based screening program for cervical cancer in Norway.”</td>
<td>Data between November 1991 and October 1994 from women who had opportunistic smears, was included in the analysis. Data between January 1993-October 1994 from women who lived in Vestfold or Sor-Trondelag and received tests within the organized program, was included in the analysis.</td>
<td>Personal invitations for cervical smear testing to women in the counties of Vestfold and Sor-Trondelag, who had not had a cervical smear within the previous 3 years. Reminder invitations were sent 10 months after initial invitation, if no smear was registered. Invitation includes an information brochure. Information about the program was also disseminated through various media outlets (e.g. newspapers, magazine, television). Women in these areas, who were outside the target groups, were still able to request testing through a physician.</td>
<td></td>
</tr>
</tbody>
</table>
| Bos et al. (1998), The Netherlands | | Retrospective cohort | “…to study coverage and excessive smear taking for program and spontaneous | Data was collected through the National Health Interview Survey, on women who answered questions | Invitation for cervical cancer screening (self-reported) | | “…we conclude that despite a long tradition of cervical cancer screening
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patient Selection</th>
<th>Intervention</th>
<th>Outcomes Measured</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Jonge et al., 2007, Belgium</td>
<td>Quasi-randomized Trial</td>
<td>Data on women aged 25-64 who had not had a pap smear within the previous 30 months</td>
<td>Selective invitations to non-attenders</td>
<td>Additional pap smears due to invitation</td>
<td>Of women invited, 91% had one smear within the previous 5 years. Of the women not invited, 68% had one smear within the previous 5 years. 66% reported receiving an invitation; 9% of these women had no smear within the previous 5 years. Of the women who had not received an invitation, 32% had no smear within the previous 5 years. Coverage rate for invited women was 91%, coverage rate for uninvited women was 68%. Of women who had been invited, 16% had 3+ smears in the previous 5 years; of women who had not been invited, 12% had 3+ smears in the previous 5 years. Not statistical tests of significance were conducted.</td>
</tr>
<tr>
<td>De Jonge et al., 2007, Belgium</td>
<td>Quasi-randomized Trial</td>
<td>Data on women aged 25-64, no pap smear within past 30 months</td>
<td>Selective invitations to non-attenders</td>
<td>Additional pap smears due to invitation</td>
<td>Of women invited, 91% had one smear within the previous 5 years. Of the women not invited, 68% had one smear within the previous 5 years. 66% reported receiving an invitation; 9% of these women had no smear within the previous 5 years. Of the women who had not received an invitation, 32% had no smear within the previous 5 years. Coverage rate for invited women was 91%, coverage rate for uninvited women was 68%. Of women who had been invited, 16% had 3+ smears in the previous 5 years; of women who had not been invited, 12% had 3+ smears in the previous 5 years. Not statistical tests of significance were conducted.</td>
</tr>
</tbody>
</table>

“In The Netherlands and despite the fact that both organised and spontaneous screening are performed by the general practitioner, an organised programme is still required to achieve high coverage.”
### Exclusion Criteria:
None reported

### Patient Characteristics:
- **87,654 eligible women were identified; 43,523 were randomized to be in the intervention group, and 44,131 were randomized to be in the control group**

- **Women who were 46 years and older were significantly more likely to attend screening after an invitation, than those under 46 years old (OR:1.19, 95% CI: 1.14-1.24, p<0.001)**

### Key Findings:
- **6249 women (12.7%) from the organized program group were screened, compared to 145,564 (50.4%) in the opportunistic screening group.**

**“Implementation of organized cervical cancer screening did not decrease the volume of opportunistic screening.”**

### Veerus et al. 159, 2010, Italy

**Retrospective Cohort Study**

“…to describe the organized cervical cancer screening program stated in 2006, to compare its performance with the opportunistic screening and to define requirements for the improvement of national implementation in the future…”

### Patient Selection:
Data on patients was obtained from Estonian Cancer society and Estonian Health Insurance Fund

### Inclusion Criteria:
- women who had pap-smears within the organized screening program in 2006, or had a pap smear from 2004-2006 outside the organized program.

### Exclusion Criteria:
None reported

### Patient Characteristics:
- **49,385 participants in organized screening program and 288,596 outside of organized screening program.**

### Organized Screening program:
Invitations mailed to insured women.

### Opportunistic Screening:
Usual care, which may have included testing if requested by a participant, or recommended by a physician.

### Outcomes Measured:
- **Uptake of pap examination**
- **Gastric cancers detected**

**“Implementation of organized cervical cancer screening did not decrease the volume of opportunistic screening.”**

---

### Gastric Cancer Screening

**Kim et al. 160, 2013, South Korea**

**Retrospective Cohort Study**

“…we investigated the current features of gastric cancer screening programs in South Korea, in terms of the outcome and effectiveness of National Cancer Screening Program and Opportunistic Screening conducted at a single center…”

### Patient Selection:
Data was collected on patients who underwent upper endoscopy in the Chung-Ang University Healthcare System in South Korea from January 2007 through December 2010.

### Inclusion Criteria:
- subjects over 40 years old, Medicaid recipients and benefit from the National Health Insurance Corporation.

### Exclusion Criteria:
Previous gastric or endoscopic resection

### Organized Screening program:
National Cancer Screening Program were invitations for screening are issued.

### Opportunistic Screening:
Unknown

**Key Findings:**
- **19.1% were screened in organized screening arm and 27.1% were screened in opportunistic screening arm (p<0.05)**
- **0.3% in organized screening had gastric**

**“…this study demonstrated that National Cancer Screening Program was an effective screening system comparable to opportunistic screening in the early detection of gastric cancer. The results suggest that compliance to the screening program is more important than the type of screening**
**Patient Characteristics:** 34,416 participants with a mean age of 56.2 (±9.2) were included in the National Cancer Screening Program (organized program). 11,238 participants with a mean age of 50 (±8.0) were included in opportunistic screening.

cancer and 0.2% in opportunistic screening (p=0.299) system itself. However, further studies on the efficiency and analysis of cost-effectiveness will be needed for successful progression of both systems…”
Figure 7: Quality Assessment of non-RCT studies using Downs and Black Checklist
Appendix E: Search Strategies for Systematic Review of Screening Economic Evaluations

**NHSEED**
1. exp Hepatitis C/di [Diagnosis]
2. Hepacivirus/
3. (hepatitis c or hcv or hepacivirus*).tw.
4. exp Hepatitis C Antigens/ or exp Hepatitis C Antibodies/ or exp Hepatitis C/
5. 2 or 3 or 4
6. Mass Screening/
7. (screen* or test*).tw.
8. 6 or 7
9. 5 and 8
10. 1 or 9

**MEDLINE**
1. exp Hepatitis C/di [Diagnosis]
2. Hepacivirus/
3. (hepatitis c or hcv or hepacivirus*).tw.
4. exp Hepatitis C Antigens/ or exp Hepatitis C Antibodies/ or exp Hepatitis C/
5. 2 or 3 or 4
6. Mass Screening/
7. (screen* or test*).tw.
8. 6 or 7
9. 5 and 8
10. 1 or 9
11. exp Hepatitis C/ec [Economics]
12. exp "Costs and Cost Analysis"/
13. exp models, economic/
14. markov chains/
15. Quality-Adjusted Life Years/ or choice behavior/
17. (economic evaluation* or cost benefit* or cost effective* or cost utilit* or cost minimization or cost or costs or costing or (economic adj5 model*) or economics).tw.
18. 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 10 and 18
20. limit 19 to english language
21. limit 20 to animals
22. limit 20 to (animals and humans)
23. 21 not 22
24. 20 not 23
25. limit 24 to (editorial or letter)
26. 24 not 25

**HTA Database**

The Health Technology Assessment Unit, University of Calgary
Hepatitis C Screening in Alberta: a Health Technology Assessment

March 7, 2016

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1. exp Hepatitis C/di [Diagnosis]
2. Hepacivirus/
3. (hepatitis c or hcv or hepacivirus*).tw.
4. exp Hepatitis C Antigens/ or exp Hepatitis C Antibodies/ or exp Hepatitis C/
5. 2 or 3 or 4
6. Mass Screening/
7. (screen* or test*).tw.
8. 6 or 7
9. 5 and 8
10. 1 or 9
11. limit 10 to english language

EMBASE
1. exp hepatitis C/di [Diagnosis]
2. exp Hepatitis C virus/di [Diagnosis]
3. 1 or 2
4. exp hepatitis C/ or exp Hepatitis C virus/
5. exp hepatitis C antibody/
6. exp hepatitis C antigen/
7. (hepatitis c or hcv or hepacivirus*).tw.
8. 4 or 5 or 6 or 7
9. exp screening/
10. (screen* or test*).tw.
11. 9 or 10
12. 8 and 11
13. 3 or 12
14. exp economic evaluation/
15. exp economic aspect/
16. hidden markov model/
17. (economic evaluation* or cost benefit* or cost effective* or cost utilit* or cost minimization or cost or costs or costing or (economic adj5 model*) or economics).tw.
18. 14 or 15 or 16 or 17
19. 13 and 18
20. limit 19 to english language
21. limit 20 to animal studies
22. limit 20 to (human and animal studies)
23. 21 not 22
24. 20 not 23
25. limit 24 to (editorial or letter)
26. 24 not 25
27. limit 26 to conference abstract
28. 26 not 27

Econlit
(hepatitis c or hcv or hepacivirus*)
AND
(screen* or test*)
### Table 21: Characteristics of Studies Assessing Screening for Injection Drug Using Populations

<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Population</th>
<th>Model</th>
<th>Perspective</th>
<th>Comparators</th>
<th>Time Horizon</th>
<th>Discount Rate</th>
<th>Outcome</th>
<th>Clinical Inputs</th>
<th>Prevalence Estimate</th>
<th>Adherence Estimate</th>
<th>Preference measurement</th>
<th>Included Cost Inputs</th>
<th>Assessment of Uncertainty</th>
<th>Currency (Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castelnuovo et al., 2006, United Kingdom</td>
<td>Hypothetical cohort of 1,000 people age 37 years old, based on data from the Trent HCV Study Cohort Database</td>
<td>CUA</td>
<td>Payer</td>
<td>Systematic case-finding (screening program) compared to no systematic case finding (no screening program). Treatment with PEGIFN and ribavirin in all diagnosed cases.</td>
<td>Lifetime</td>
<td>Costs: 6%</td>
<td>Benefits: 1.5%</td>
<td>Costs and consequences of case-finding and no-case-finding, cost per life-year-gained, QALY</td>
<td>Pooled estimate of HCV prevalence in intravenous drug users (Bird et al.): 49% (95% CI 38-61%)</td>
<td>Acceptance of testing rate for IDU population using ELISA test (Serfaty et al): 49%</td>
<td>EQ-5D (UK algorithm) from the HTA mild HCV Trial and cost-effectiveness model (reference)</td>
<td>ELISA test, communicating results, PCR, genotyping, liver biopsy, counselling and harm reduction, treatment, referral to treatment, annual cost by disease state, liver transplant, annual cost for liver transplant wait list, costs related to case-finding (health promotion information session, communication of results, referral, pre-test discussion)</td>
<td>Sensitivity Analysis (all parameters varied in one-way sensitivity analysis)</td>
<td>€ (2004)</td>
</tr>
<tr>
<td>Helsper, 2012, Netherlands</td>
<td>Drug Users</td>
<td>CUA</td>
<td>Payer</td>
<td>No screening program compared to &quot;drug user campaign&quot; which targeted drug users through addiction care centers</td>
<td>Lifetime</td>
<td>Costs: 4%</td>
<td>Benefits: 1.5%</td>
<td>Costs and consequences of screening strategies and no screening strategy, cost per life-year-gained, QALY</td>
<td>Distribution of fibrosis stage, patients eligible for treatment</td>
<td>Not reported</td>
<td>Referral rate: 71.43%</td>
<td>Not reported</td>
<td>Diagnostic tests and consultations before treatment, medication and diagnostic tests during treatment (by fibrosis stage), campaign costs (training, project organization, material and travel expenses, consultation costs)</td>
<td>Sensitivity Analysis</td>
</tr>
<tr>
<td>Author, Year, Country</td>
<td>Population</td>
<td>Model</td>
<td>Perspective</td>
<td>Comparators</td>
<td>Time Horizon</td>
<td>Discount Rate</td>
<td>Outcome</td>
<td>Clinical Inputs</td>
<td>Prevalence Estimate</td>
<td>Adherence Estimate</td>
<td>Preference measurement</td>
<td>Included Cost Inputs</td>
<td>Assessment of Uncertainty</td>
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<tr>
<td>Local**, 1999, United Kingdom</td>
<td>Hypothetical cohort of 246,636 attending a genito-urinary clinic annually (61% former intravenous drug users)</td>
<td>CUA</td>
<td>Not reported</td>
<td>Screening program or no screening program for intravenous drug users who use the health care system</td>
<td>50 years</td>
<td>Costs: 6%</td>
<td>Benefits: 6%</td>
<td>Costs and consequences of screening strategies and no screening strategy, cost per life-year-gained, QALY</td>
<td>Stage of liver disease, complications, response to treatment, costs</td>
<td>HCV positive: 60%</td>
<td>Acceptance of testing: 80%</td>
<td>Failure to complete liver biopsy: 45%</td>
<td>Acceptance of initial treatment: 50%</td>
<td>From Bennett et al.</td>
</tr>
<tr>
<td>Stein**, 2003, United Kingdom</td>
<td>Hypothetical cohort of former intravenous drug users attending a genito-urinary clinic compared to no screening program</td>
<td>CUA</td>
<td>Payer</td>
<td>Screening program of former intravenous drug users attending a genito-urinary clinic compared to no screening program</td>
<td>50 years</td>
<td>Costs: 6%</td>
<td>Benefits: 1.5%</td>
<td>Costs and consequences of screening strategies and no screening strategy, cost per life-year-gained, QALY</td>
<td>Sensitivity and specificity of ELISA and PCR, proportion with mild, moderate or severe disease, complications, progression to cirrhosis, decompensated cirrhosis, hepatic carcinoma, death, transplant, second transplant</td>
<td>HCV prevalence at genito-urinary clinic (Goldberg et al.): 1.5%</td>
<td>Acceptance of testing rate for individuals using ELISA test (Serfaty et al.): 49%</td>
<td>Acceptance of testing rate for individuals using biopsy (Jowett et al.): 77%</td>
<td>Acceptance of treatment (Jowett et al.): 50%</td>
<td>ELISA, PCR, Counselling, liver biopsy, medical visits, medications, inpatient day, hepatocellular carcinoma inpatient cost, chronic HCV infection, hepatic encephalopathy inpatient, varicled bleed inpatient, liver transplant</td>
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<tr>
<td>Stein**, 2004, United Kingdom</td>
<td>Hypothetical cohort of former intravenous drug users</td>
<td>CUA</td>
<td>Payer</td>
<td>Screening program of former intravenous drug users compared to no screening program</td>
<td>50 years</td>
<td>Costs: 6%</td>
<td>Benefits: 1.5%</td>
<td>Costs and consequences of screening strategies and no screening strategy, cost per life-year-gained, QALY</td>
<td>Sensitivity and specificity of ELISA and PCR, probabilities of cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver</td>
<td>HCV of individuals who go to drug services (Department of Health): 32%</td>
<td>Adherence to treatment (Barbato et al.): 100%</td>
<td>VAS for HCV patients (Corder et al.)</td>
<td>ELISA, PCR, Counselling, liver biopsy, medical visits, medications, inpatient day, hospitalization, liver transplant</td>
<td>Sensitivity Analysis (current intravenous drug users, prevalence of HCV, acceptance of ELISA or PCR, sensitivity and specificity of</td>
</tr>
<tr>
<td>Author, Year, Country</td>
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<tr>
<td>Tramarin², 2008, Netherlands</td>
<td>Hypothetical cohort of intravenous drug users living in the Veneto Region in 2007</td>
<td>CUA</td>
<td>Societal</td>
<td>Screening program of intravenous drug users compared to no screening.</td>
<td>Lifetime</td>
<td>Costs: 3%</td>
<td>Benefits: 3%</td>
<td>Costs and consequences of screening strategies and no screening strategy, cost per life-year-gained, QALY</td>
<td>Probabilities of symptomatic and asymptomatic HCV, spontaneous clearance, progression, cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, death, and liver transplant</td>
<td>Randomized control trial HCV prevalence estimate of symptomatic and asymptomatic (Manns et al): 0.16, 0.84</td>
<td>Complete compliance</td>
<td>A variety of literature-based sources were used to provide utility data (Short Form 36 Health Survey data).</td>
<td>Screening, annual costs (screening, cirrhosis, transplantation in hepatocellular carcinoma), monthly costs (acute therapy, chronic therapy)</td>
<td>Sensitivity Analysis (prevalence of genotypes 1 and 4)</td>
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</table>
### Table 22: Results of Studies Assessing Screening for Injection Drug Using Populations

<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Target Population of Screening Program</th>
<th>Population Definition</th>
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<th>Clinical Pathway</th>
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<th>Sources of Uncertainty</th>
<th>Critical Appraisal (Our Interpretation of the Study)</th>
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<tr>
<td>Castelnuovo**, 2006, United Kingdom</td>
<td>Former intravenous drug users (excludes current drug users)</td>
<td>Hypothetical cohort of 1,000 people age 37 years old, based on data from the Trent HCV Study Cohort Database</td>
<td>Systematic case-finding (screening program) compared to no systematic case finding (no screening program). Treatment with PegIFN and ribavirin in all diagnosed cases.</td>
<td>Screening or no screening (natural history of disease), positive or negative ELISA test, PCR test if positive ELISA test, diagnosis, treatment</td>
<td>• Case-finding in 1,000 people prevents: 3 cases of cirrhosis, 3 deaths and 1 case of hepatocellular cancer for an incremental £70,000 ($127,000)</td>
<td>&quot;Case-finding for hepatitis C is likely to be considered cost-effective by NHS commissioners. Further improvements in the effectiveness of treatments to slow or halt disease progression are likely to improve the cost-effectiveness of case-finding. Case-finding is likely to be most cost-effective if targeted at people who HCV disease is probably more advanced.&quot;</td>
<td>Rates of acceptance of testing and treatment, distribution of disease severity in population, discount rates</td>
<td>This study is high quality; it adheres to all of the 24 guidelines established in the CHEER checklist. It demonstrates that for intravenous drug users within the UK, screening is likely to be more costly and more effective than no screening program. Using a threshold of £50,000 per QALY gained, this screening program would be considered good value for money. Although there is uncertainty in this model, it is not likely that the cost-effectiveness will exceed the threshold of £50,000 per QALY gained.</td>
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<tr>
<td>Helper*, 2012, Netherlands</td>
<td>Drug Users</td>
<td>Cohort of drug users recruited between May 2007 and September 2008</td>
<td>No screening program compared to &quot;drug user campaign&quot; which targeted drug users through addiction care centers</td>
<td>Screening or no screening (natural history of disease), positive or negative test result, diagnosis or no diagnosis, treatment or no treatment, response to treatment or no response to treatment</td>
<td>• 7,331k ($10,638) incremental cost per QALY gained for drug user screening program compared to no screening program</td>
<td>&quot;In The Netherlands, an informal threshold for cost-effectiveness often quoted is €20000 per QALY. Considering this cut-off point, the ICERs of the support campaign and the drug users campaign indicate that both these campaign strategies should be considered cost-effective.&quot;</td>
<td>Age at testing, costs and disease progression</td>
<td>This study is high quality; it adheres to 23 of the 24 guidelines established in the CHEER checklist. It demonstrates that screening drug users populations living in the Netherlands is likely to be more costly and more effective than no screening program. Using a threshold of €50,000 per QALY gained, this screening program would be considered good value for money, Although there is uncertainty in this model, it is not likely that the cost-effectiveness will exceed the threshold of €50,000 per QALY gained.</td>
</tr>
<tr>
<td>Leal**, 1999, United Kingdom</td>
<td>Intravenous drug users</td>
<td>Intravenous drug users in south west health region of the UK.</td>
<td>Screening program compared to no screening program for intravenous drug users who use the health care system</td>
<td>Screening or no screening (natural history of disease), acceptance or test or no acceptance of test, ELISA and PCR testing, biopsy or no biopsy to confirm, diagnosis, treatment or no treatment, response or no response to treatment.</td>
<td>• £9,300 ($16,874) incremental cost per QALY for screening program, compared to no screening program</td>
<td>&quot;Although potentially cost effective, many important uncertainties surround the assumptions used to estimate the long term effectiveness of screening and treatment. There is insufficient evidence to inform policy development and further research is required in this rapidly changing field.&quot;</td>
<td>Benefit discounting, acceptance rates for biopsy, acceptance rates for treatment and acceptance rates of treatment, treatment cost</td>
<td>This study is high quality; it adheres to 22 of the 24 guidelines established in the CHEER checklist. It demonstrates that screening intravenous drug users living in the UK is likely to be more costly and more effective than no screening program. Using a threshold of £50,000 per QALY gained, this screening program would be considered cost-effective. Uncertainty in the variables results in a range from £3,333 ($6,047) to £81,438 ($147,759); this uncertainty therefore may strongly impact the cost-effectiveness of this program.</td>
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<tr>
<td>Stein**, 2003, United Kingdom</td>
<td>Former intravenous drug users in genito-urinary medicine</td>
<td>Hypothetical cohort of 246,636 attending a genito-urinary clinic annually (61%)</td>
<td>Screening or no screening (natural history of disease), positive or negative ELISA test, PCR test if positive</td>
<td>Screening results in a £27,138 ($49,238) cost per QALY gained compared to no screening</td>
<td>&quot;The evidence suggests that the most cost-effective approach to screening for HCV in GUM clinics would be to restrict&quot;</td>
<td>Utility of people who present symptomatically or are screened asymptptomatically with HCV, utility of those</td>
<td>This study is high quality; it adheres to 22 of the 24 guidelines established in the CHEER checklist. It demonstrates that screening former intravenous drug users in genito-urinary clinics in the UK is likely to be...</td>
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<tr>
<td>Author, Year, Country</td>
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<tr>
<td>Stein*, 2004, United Kingdom</td>
<td>Intravenous drug users</td>
<td>Hypothetical cohort of intravenous drug users living in the Veneto Region in 2007</td>
<td>Screening program of former intravenous drug users compared to no screening program</td>
<td>Screening or no screening (natural history of disease), positive or negative for HCV, transition through stages of cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, or die</td>
<td>Screening results in a -$3,132 ($4,551) cost per QALY gained compared to no screening</td>
<td>&quot;Screening for HCV in intravenous drug users in contact with services is moderately cost effective (around £30,000 per QALY) and reasonably stable when explored in extensive one-way sensitivity analyses&quot;</td>
<td>Current intravenous drug users, prevalence of HCV, acceptance of ELISA or PCR, sensitivity and specificity of ELISA or PCR, adherence to treatment, utility increase associated with successful treatment</td>
<td>This study is high quality; it adheres to 22 of the 24 guidelines established in the CHEER checklist. It demonstrates that screening former intravenous drug users in the UK is likely to be more costly and more effective than no screening program. Using a threshold of a $50,000 per QALY gained this screening program would be considered reasonable value for money. The cost per QALY changes significantly due to uncertainty in the proportion of people who will accept a biopsy ($26,528-74,497), and acceptance of treatment ($16,196-92,969).</td>
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</table>

| Tramarin*, 2008, Netherlands | Intravenous drug users | Hypothetical cohort of intravenous drug users living in the Veneto Region in 2007 | Screening program of intravenous drug users compared to no screening program | Screening or no screening (natural history of disease), positive or negative for HCV, transition through stages of cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, or die | Screening results in a -$28,120 ($51,020) cost per QALY gained compared to no screening | "Screening to those with a history of intravenous drug use but that cost effectiveness remains relatively high." with chronic HCV, acceptance of liver biopsy among intravenous drug users | more costly and more effective than no screening program. Using a threshold of a $50,000 per QALY gained this screening program would be considered reasonable value for money. There is significant uncertainty in this model; if fewer than 70% of the population are treated the cost per QALY gained is over £100,000; and as the number of people with severe or moderate disease decreases the program becomes less economically attractive. |

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*Note: The data and conclusions are based on a hypothetical scenario for illustrative purposes and do not reflect real-world clinical practice or outcomes.
<table>
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<tr>
<td>Batra 23, 2001, England</td>
<td>Real cohort of 1879 people in West Kent, England, tested for HCV in 1998/1999 (former drug users, received clotting factors, long term hemodialysis, abnormal alanine aminotransferase, prior recipients of transfusion or organ transplants, exposed health care workers, children of HCV women)</td>
<td>CEA</td>
<td>Payer</td>
<td>No screening and liver transplant compared to opportunistic screening and treatment</td>
<td>Not reported</td>
<td>Costs: 6% Benefits: 6%</td>
<td>Screening effectiveness, number needed to screen to prevent 1 patient developing cirrhosis, marginal cost of preventing 1 case of cirrhosis, net present value of opportunistic HCV screening compared to liver transplant</td>
<td>Distribution of fibrosis stage, sensitivity and specificity of tests, risk of developing cirrhosis</td>
<td>8%</td>
<td>Acceptance of treatment given diagnosis: 61%</td>
<td>Not reported</td>
<td>Medications, tests</td>
<td>Sensitivity analysis (proportion of high risk people accepting testing, proportion who receive RNA test, proportion who accept liver biopsy proportion who are Knodell &gt;6, proportion who accept treatment requiring genotyping)</td>
<td>₤ (1999)</td>
</tr>
<tr>
<td>Lapane 24, 1998, United States</td>
<td>Real cohort of patients (n=13,997) who self-referred for HCV screening were assessed based on risk factor and modeled (former IV drug use, sex with IV drug user, history of blood transfusion, age, gender, hemodialysis, hepatitis B vaccination, health care professional)</td>
<td>CEA</td>
<td>Not Reported</td>
<td>Comparing no screening with four screening strategies/models: 1. Screening only when predicted probability of infection exceeds 7%, 2. Screening only for individuals who have significant risk based on all questionnaire questions 3. Screening only using questions that did not carry stigma (no questions about drug use etc.) 4. Screening only for patients with elevated</td>
<td>Not Reported</td>
<td>Not reported</td>
<td>Cost per case detected and average cost per 100 people screened (Primary data collection)</td>
<td>Model 1: 20% Model 2: 29% Model 3: 25% Model 4: 12%</td>
<td>Not reported</td>
<td>Not Reported</td>
<td>Average cost of testing (primary data collection)</td>
<td>Not Reported</td>
<td>USD (Not Reported)</td>
<td>USD (Not Reported)</td>
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<td>Author, Year, Country</td>
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<tr>
<td>Liu, 2013, United States</td>
<td>High risk individuals who are 40-74 years old (drug history use, blood transfusion before 1992, and multiple sexual partners)</td>
<td>CUA</td>
<td>Societal</td>
<td>No screening versus risk-factor guided screening</td>
<td>Lifetime</td>
<td>Costs: 3%</td>
<td>Benefits: 3%</td>
<td>Costs and consequences of screening strategies and no screening strategy, cost per lifetime-year-gained, QALY</td>
<td>Mortality rates (NHANESIII data), disease progression rates (Liu et al)</td>
<td>Various estimates (by sex and race) calculated using the National Health and Nutrition Examination Survey (2001-2008)</td>
<td>Acceptance of treatment for those with fibrosis stage F0-F1: 30%</td>
<td>Acceptance of treatment for those with fibrosis stage F2-F4: 39%</td>
<td>Derived from the Medical Expenditure Panel Survey</td>
<td>Screening (ELISA, RIBA and RNA tests, counselling, liver biopsy, FibroTest), drug and medical care related to treatment, and annual care by fibrosis stage</td>
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<tr>
<td>Nakamura, 2008, Japan</td>
<td>Cohort of 42,538 high-risk individuals from 2003 to 2006 (showing a high level of aminotransferase, undergone major operation, or received a blood transfusion during child birth)</td>
<td>CEA</td>
<td>Payer</td>
<td>Screening program of high-risk individuals compared to no screening program</td>
<td>Lifetime</td>
<td>Costs: 3%</td>
<td>Benefits: 3%</td>
<td>Costs and consequences of screening strategies and no screening strategy, cost per lifetime-year-gained (not adjusted for quality of life)</td>
<td>Probability of compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, death</td>
<td>HCV prevalence per age group: 0.81% 40-49: 0.38% 50-59: 0.31% 60-69: 0.66% &gt;70: 1.60%</td>
<td>Acceptance of treatment (assumption): 100%</td>
<td>Life expectancy</td>
<td>HCV antibody test, core antigen test, PCR test, combination therapy (inpatient and outpatient), post SVR (outpatient), chronic hepatitis (outpatient), compensated cirrhosis (outpatient), decompensated cirrhosis (inpatient and outpatient), hepatocellular carcinoma (inpatient and outpatient)</td>
<td>Sensitivity analysis (treatment effectiveness, transition probabilities, infection rates of HCV, price of drugs)</td>
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<tr>
<td>Author, Year, Country</td>
<td>Target Population of Screening Program</td>
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<tr>
<td>Batra*, 2001, England</td>
<td>High Risk population (former drug users, received clotting factors, long term hemodialysis, abnormal alanine aminotransferase, prior recipients of transfusion or organ transplants, exposed health care workers, children of HCV women)</td>
<td>Real cohort of 1879 people in West Kent, England, tested for HCV in 1998/1999</td>
<td>No screening and liver transplant compared to opportunistic screening and treatment</td>
<td>Screening or no screening (natural history of disease), test positive or negative, liver biopsy or no biopsy, biopsy positive or negative, diagnosis and staging or no diagnosis and staging, treatment or no treatment</td>
<td>113,479 high risk individuals have to be screened at a cost of £50,947 ($92,437) to prevent 1 case of cirrhosis</td>
<td>“HCV screening and drug treatment is more expensive than liver transplantation.”</td>
<td>Drop out, screening effectiveness, cost</td>
<td>This study is high quality; it adheres to 20 of the 24 guidelines established in the CHEER checklist. It demonstrates that screening high risk populations within England is likely to be more costly than a strategy of providing liver transplants but not screening. There is uncertainty in this model. The interpretation of the cost per case prevented is unclear as there are no accepted thresholds to represent good value for money with this outcome.</td>
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<tr>
<td>Lapane*, 1998, United States</td>
<td>High Risk (former IV drug use, sex with IV drug user, history of blood transfusion, age, gender, hemodialysis, hepatitis B vaccination, health care professional)</td>
<td>Real cohort of patients (n=13,997) who self-referred for HCV screening were assessed based on risk factor and modelled</td>
<td>Comparing no screening with four screening strategies/models: 1. Screening only when predicted probability of infection exceeds 7%, 2. Screening only for individuals who have significant risk based on all questionnaire questions 3. Screening only using questions that did not carry stigma (no questions about drug use etc.) 4. Screening only for patients with elevated ALT levels</td>
<td>Not Reported</td>
<td>Model one costs $357 per case detected and $1,571 per 100 people screened Model two costs $439 per case detected, and $2,020 per 100 people screened Model three costs $487 per case detected, and $1,706 per 100 people screened Model four costs $1047 per case detected, and $4,292 per 100 people screened</td>
<td>“The yield and cost of screening for HCV compares favorably with accepted current screening practices for other diseases. Models 1, 2, and 3 may be appropriate in certain clinical and epidemiological settings. Selective screening by a risk factor questionnaire (first three models) is more cost-effective than blood testing with ALT.”</td>
<td>Not reported</td>
<td>This study is poor quality; it adheres to only 12 of the 24 guidelines established in the CHEER checklist. It demonstrates that the cost per case detected is lowest when only screening individuals with a high probability of being HCV positive. This study is limited because it does not clearly report methods and inputs used, and appears to only include limited costing data. Sources of uncertainty were not reported, a limitation of this study.</td>
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| Liu, 2013, United States | High risk individuals 40-74 years old (drug history use, blood transfusion before 1992, and multiple sexual partners) | Hypothetical cohort of 50 year old adults who are asymptomatic (age range 40-74) | Risk-factor based screening program compared to no screening program for asymptomatic individuals who are 40-74 | Screening or no screening (natural history of disease), treatment with standard therapy, universal triple therapy or IL-28B-guided triple therapy | • by birth cohort screening (cost per QALY not reported)  
• costs more than no screening and provides fewer benefits than other strategies  
• Risk-factor based screening averted 4-7 liver transplants, 13-27 liver cancers at a cost of $17-30 million dollars per 100,000 people screened compared to no screening | “We closely examined risk-factor guided HCV screening and found that it is not preferred to birth-cohort screening…” | Fibrosis stage distribution | This study is high quality; it adheres to 24 of the 24 guidelines established in the CHEER checklist. It demonstrates that screening asymptomatic adult populations living in the United States is likely to be more costly and more effective than no screening program, but more costly and less effective than birth-cohort screening. The interpretation of the cost per case prevented is unclear as there are no accepted thresholds to represent good value for money with this outcome. |
| Nakamura, 2008, Japan | High– risk group over 40 years old (showing a high level of aminotransferase, undergone major operation, or received a blood transfusion during child birth) | Cohort of 42,538 high-risk individuals from 2003 to 2006 | Screening program of high-risk individuals compared to no screening program. | Screening or no screening, diagnosis, treatment, cirrhosis, decompensated cirrhosis, death | • 40-49: screening results in a -$749 cost per life year gained compared to no screening.  
• 50-59: screening results in a $523 cost per life year gained compared to no screening.  
• 60-69: screening results in a $2,297 cost per life year gained compared to no screening.  
• >70: not done | “The ICERs of the screening strategies in both the general population and high-risk group would be below $50,000/LE gained, therefore, the screening strategy was cost-effective in comparison to the no-screening strategy.”  
“Our results indicated that the national screening programs for HCV in both the general population and high-risk group would be cost-effective in comparison to each no-screening case. Especially, the younger age groups would gain more benefit by the screening and the combination therapy despite the low infection rates” | Prevalence of HCV | This study is high quality; it adheres to 24 of the 24 guidelines established in the CHEER checklist. It demonstrates that screening a high-risk cohort is likely to be more costly and more effective than no screening program. There is no accepted reasonable cost per life year gained, however, the estimates in this study are substantially less than other accepted therapies which have costs per life year gained of $100,000. Although there is uncertainty in this model, it is not likely that the cost per life year gained would become economically unattractive. |
<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Population</th>
<th>Model</th>
<th>Perspective</th>
<th>Comparators</th>
<th>Time Horizon</th>
<th>Discount Rate</th>
<th>Outcome</th>
<th>Clinical Inputs</th>
<th>Prevalence Estimate</th>
<th>Adherence Estimate</th>
<th>Preference measurement</th>
<th>Included Cost Inputs</th>
<th>Assessment for Uncertainty</th>
<th>Cost (Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plunkett*, 2004, United States</td>
<td>Hypothetical cohort of low-risk pregnant women</td>
<td>CUA</td>
<td>Payer</td>
<td>Screening program of low-risk pregnant women (treatment, treatment and elective C-section) compared to no screening.</td>
<td>Lifetime</td>
<td>Costs: 3%</td>
<td>Benefits: 3%</td>
<td>Costs and consequences of screening strategies and no screening strategy, cost per life-year gained, QALY</td>
<td>Sensitivity and specificity of ELISA and PCR, probability of mild to moderate hepatitis for mother and child, cirrhosis, decompensated cirrhosis, hepatocellular cancer, transplant, death, response to treatment, delivery (elective, emergent, vaginal), transmission (elective, emergent, vaginal)</td>
<td>HCV infection (Centers for Disease Control and Prevention, Alter et al, Silverman et al): 1%</td>
<td>Receive treatment if screened (McHutchinson et al): 70%</td>
<td>A variety of literature-based sources were used to provide utility data (Short Form 36 Health Survey data). Pregnancy delivery utilities (assumption)</td>
<td>Counselling, ELISA, PCR, genotype, delivery cost, annual cost (cirrhosis, decompensated cirrhosis, hepatocellular cancer, transplant, treatment, delivery)</td>
<td>Sensitivity Analysis (all parameters in one-way analysis and HCV transmission and prevalence in multi-way)</td>
</tr>
<tr>
<td>Urbanus**, 2013, Netherlands</td>
<td>Hypothetical cohort of all pregnant women</td>
<td>CEA</td>
<td>Payer</td>
<td>Screening of pregnant women over 31 years of age compared to no screening.</td>
<td>Lifetime</td>
<td>Costs: 4%</td>
<td>Benefits: 1.5%</td>
<td>Costs and life years of screening pregnant women, cost per life-year gained</td>
<td>Probability of HCV infections, successful treatments, new protease inhibitor by genotype, standard of care by genotype possible future regimen by genotype, transition to cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, death</td>
<td>Prevalence estimate of all women (Lindenburg et al): 0.2%</td>
<td>Not Reported</td>
<td>Life years</td>
<td>Antibody HCV test, RNA-test, chronic infection (per year), New protease inhibitor by genotype, standard of care by genotype possible future regimen by genotype, costs related to disease progression (decompensated cirrhosis, hepatocellular carcinoma, liver transplant, after liver transplant)</td>
<td>Sensitivity Analysis (all parameters in one-way analysis)</td>
</tr>
<tr>
<td>Urbanus**, 2013, Netherlands</td>
<td>Hypothetical cohort of first-generation non-Western pregnant women</td>
<td>CEA</td>
<td>Payer</td>
<td>Screening of pregnant women 29 for first-generation non-western women to no screening.</td>
<td>Lifetime</td>
<td>Costs: 4%</td>
<td>Benefits: 1.5%</td>
<td>Costs and life years of screening pregnant women, cost per life-year gained</td>
<td>Probability of HCV infections, successful treatments, new protease inhibitor by genotype, standard of care by genotype possible future regimen by genotype, transition to cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, death</td>
<td>Prevalence estimate of first-generation non-western pregnant women (Lindenburg et al): 0.43%</td>
<td>Not Reported</td>
<td>n/a</td>
<td>Antibody HCV test, RNA-test, chronic infection (per year), New protease inhibitor by genotype, standard of care by genotype possible future regimen by genotype, costs related to disease progression (decompensated cirrhosis, hepatocellular carcinoma, liver transplant, after liver transplant)</td>
<td>Sensitivity Analysis (all parameters in one-way analysis)</td>
</tr>
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</table>
### Table 26: Results of Studies Assessing Pregnant Populations

<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Target Population of Screening Program</th>
<th>Population Definition</th>
<th>Comparators</th>
<th>Clinical Pathway</th>
<th>Results</th>
<th>Author’s Conclusions</th>
<th>Sources of Uncertainty</th>
<th>Critical Appraisal (Our Interpretation of the Study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plunkett, 2004, United States</td>
<td>Low-risk pregnant women</td>
<td>Hypothetical cohort of low-risk pregnant women</td>
<td>Screening program of low-risk pregnant women (treatment, treatment and elective C-section) compared to no screening.</td>
<td>Screening or no screening (natural history of disease), diagnosis, treatment, cirrhosis, decompensated cirrhosis, transplant, death</td>
<td>Screening with treatment results in a dominated (more costly and less effective) cost per QALY compared to no screening. Screening with treatment and C-section results in a $1,170,000 cost per QALY compared to no screening.</td>
<td>“As our model demonstrates, a screening strategy is not a cost-effective intervention even in the unique circumstances of pregnancy, when 2 individuals potentially could access the benefits of treatment and 1 individual could even avoid the disease altogether.”</td>
<td>Pregnancy delivery utilities</td>
<td>This study is high quality; it adheres to 22 of the 24 guidelines established in the CHEER checklist. It demonstrates that screening low-risk pregnant women within the United States is likely to be more costly and less effective than no screening program, and treatment with C-section is more costly and more effective. Using a threshold of a $50,000 per QALY gained, this screening program would not be considered good value for money. Although there is uncertainty in this model, the conclusions are robust to changes in all costs, probability and utility variables.</td>
</tr>
<tr>
<td>Urbanus, 2013, Netherlands</td>
<td>Pregnant woman</td>
<td>Hypothetical cohort of all pregnant women</td>
<td>Screening of pregnant women over 31 years of age compared to no screening.</td>
<td>Screening or no screening (natural history of disease), positive or negative for HCV, transition through stages of cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, or die</td>
<td>Screening results in a $52,473€ ($76,248) cost per life-year compared to no screening.</td>
<td>Screening all pregnant women in Amsterdam for HCV within the existing screening program for other infections during pregnancy is probably not cost-effective.</td>
<td>Discount rates</td>
<td>This study is high quality; it adheres to 24 of the 24 guidelines established in the CHEER checklist. It demonstrates that screening a pregnant population within the Netherlands is likely to be more costly and more effective than no screening program. There is no accepted reasonable cost per life year gained, however, the estimates in this study are substantially less than other accepted therapies which have costs per life year gained of $100,000. Although there is uncertainty in this model, the conclusions are robust to changes in all costs, probability and utility variables.</td>
</tr>
<tr>
<td>Urbanus, 2013, Netherlands</td>
<td>Pregnant first-generation non-Western women</td>
<td>Hypothetical cohort of all first-generation non-Western pregnant women</td>
<td>Screening of pregnant women 29 for first-generation non-Western women to no screening.</td>
<td>Screening or no screening (natural history of disease), positive or negative for HCV, transition through stages of cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, or die</td>
<td>Screening results in a 47,113€ ($68,460) cost per life-year compared to no screening.</td>
<td>“Screening first-generation non-Western women was moderately cost-effective. These findings are partially due to the slow progression of HCV infection to cirrhosis, especially for women and the relatively high costs for patients treated with new protease inhibitors”</td>
<td>Discount rates</td>
<td>This study is high quality; it adheres to 24 of the 24 guidelines established in the CHEER checklist. It demonstrates that screening a pregnant population within the Netherlands is likely to be more costly and more effective than no screening program. There is no accepted reasonable cost per life year gained, however, the estimates in this study are substantially less than other accepted therapies which have costs per life year gained of $100,000. Although there is uncertainty in this model, the conclusions are robust to changes in all costs, probability and utility variables.</td>
</tr>
<tr>
<td>Author, Year, Country</td>
<td>Population</td>
<td>Model</td>
<td>Perspective</td>
<td>Comparators</td>
<td>Time Horizon</td>
<td>Discount Rate</td>
<td>Outcome</td>
<td>Clinical Inputs</td>
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<tr>
<td>Sutton**, 2006, United Kingdom</td>
<td>Hypothetical cohort of prisoners on reception into prison</td>
<td>CEA</td>
<td>Payer</td>
<td>Case-finding (screening program) compared to no Case finding (no screening program).</td>
<td>Through testing (no markov model)</td>
<td>Costs: 3.5% Benefits: 3.5%</td>
<td>Costs and consequences of case-finding and no-case-finding, cost per HCV infection identified</td>
<td>Identify as HCV positive (whether have positive test or not), report intravenous drug use, sensitivity and specificity of ELISA and PCR</td>
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<tr>
<td>Sutton**, 2008, United Kingdom</td>
<td>Hypothetical cohort of prisoners on reception into prison</td>
<td>CUA</td>
<td>Payer</td>
<td>Screening program of prisoners on reception into prison compare to no screening program.</td>
<td>80 years</td>
<td>Costs: 3.5% Benefits: 3.5%</td>
<td>Costs and consequences of screening strategies and no screening strategy, cost per life-year-gained, QALY</td>
<td>Sensitivity and specificity of ELISA, probabilities of cirrhosis, decompensated cirrhosis hepatocellular carcinoma, liver transplant, death, overdose mortality, HCV prevalence in prisoners (Weild et al): 7%</td>
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</table>
Table 28: Results of Studies Assessing Screening for Prison Populations

<table>
<thead>
<tr>
<th>Author, Year, Country, Model</th>
<th>Target Population of Screening Program</th>
<th>Population Definition</th>
<th>Comparators</th>
<th>Clinical Pathway</th>
<th>Results</th>
<th>Author’s Conclusions</th>
<th>Sources of Uncertainty</th>
<th>Critical Appraisal (Our Interpretation of the Study)</th>
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</thead>
</table>
| Sutton 176, 2006, United Kingdom | Prisoners on reception into prison | Hypothetical cohort of prisoners on reception into prison | Case-finding (screening program) of prisoners on reception into prison, three separate scenarios of verbal screening questions (Q1 and Q2, Q1, or Q2) and one only test with no question compared to no case finding (no screening program) | Three scenarios of verbal screening questions or no questions, ELISA and if positive then PCR, only screening followed. No treatment included. | - Verbal screening (Q1 and Q2) results in a £2,102 ($3,814) cost per case found compared to no screening  
- Verbal screening (Q1) results in a dominated cost per case found compared to no screening  
- Verbal screening (Q2) results in a £6,388 ($11,590) cost per case found compared to no screening  
- All screened results in a £6,388 ($11,590) cost per case found compared to no screening | “It has been shown here that verbally screening for ever injecting illicit drugs and for ever having received a past positive HCV test is the most cost effective approach to establishing prisoners eligible for HCV serological testing. The results from sensitivity analysis show the importance of encouraging eligible prisoners to accept ELISA testing with this having a significant impact on the cost-effectiveness of the case-finding scenarios.” | Prisoners that accept the ELISA or PCR test, other members of staff taking part in testing (i.e. guards) | This study is high quality; it adheres to 23 of the 24 guidelines established in the CHEER checklist. It demonstrates that screening prisoners in the UK is likely to be more costly and more effective than no screening program. As this is an analysis of cost per case found there is no accepted threshold value. The variables that have the strongest effect on the cost-effectiveness include: number of prisoners that attend lecture, proportion of prisoners who are tested with ELISA test. |
<p>| Sutton 177, 2008, United Kingdom | Prisoners on reception into prison | Hypothetical cohort of prisoners on reception into prison | Screening program of prisoners on reception into prison compared to no screening program | Screening or no screening (natural history of disease), cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, death | - Screening results in a £54,852 ($99,522) cost per QALY gained compared to no screening | “Taking parameter values at baseline values, the analysis here suggests that HCV screening and treatment in a prison setting is not cost-effective with an estimated cost/QALY gained of £54,852. Given the high prevalence of HCV in prisons as described in many previous studies, this may be seen as a surprising result.” | Discount rates, utilities, progression rates | This study is high quality; it adheres to 22 of the 24 guidelines established in the CHEER checklist. It demonstrates that screening prisoners in the UK is likely to be more costly and more effective than no screening program. Using a threshold of a $50,000 this screening program would not be considered reasonable value for money. Uncertainty in a number of areas significantly impacts the cost-effectiveness of this intervention: increased acceptance rate of the ELISA test makes it more cost-effective; faster HCV progression makes it cost-effective (£13,408/QALY); and discount rates set at 3.5% make it cost effective (£13,408/QALY). |</p>
<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Population</th>
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<th>Comparators</th>
<th>Time Horizon</th>
<th>Discount Rate</th>
<th>Outcome</th>
<th>Clinical Inputs</th>
<th>Prevalence Estimate</th>
<th>Adherence Estimate</th>
<th>Preference measurement</th>
<th>Included Cost Inputs</th>
<th>Assessment of Uncertainty</th>
<th>Currency (Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coffin**, 2012, United States</td>
<td>Hypothetical cohort of individuals born between 1945-1965</td>
<td>CUA</td>
<td>Societal</td>
<td>No screening program compared to screening program for those born between 1945-1965 and living in the United States</td>
<td>Lifetime</td>
<td>Costs: 3% Benefits: 3%</td>
<td>Costs and consequences of screening strategies and no screening strategy, cost per life-year-gained, QALY</td>
<td>Distribution of fibrosis stage at time of diagnosis, rate of progression through each stage of fibrosis, spontaneous presentation outside screening, rates of sustained viral response</td>
<td>Proportion of general US adult population HCV positive: 0.16% (range: 0.13-0.20%)</td>
<td>Assumption that 15% of the population born between 1945-1965 would be screened, based on 5-60% uptake of screening (Bassett et al.).</td>
<td>A variety of literature-based sources were used to provide utility data (Short Form 36 Health Survey data).</td>
<td>HCV antibody screening, RNA polymerase chain reaction test cost, Telaprevir-based therapy cost, boceprevir-based therapy costs, physician costs, disease management costs, and liver transplant and management costs</td>
<td>Sensitivity Analysis (all parameters varied in one-way sensitivity analysis) Scenario Analysis (varying all parameters to be unfavorable) Probabilistic Sensitivity Analysis (all parameters varied)</td>
<td>USD (2010)</td>
</tr>
<tr>
<td>Liu**, 2013, United States</td>
<td>Individuals who are 40-74 years old as of ?</td>
<td>CUA</td>
<td>Societal</td>
<td>No screening versus birth-cohort screening program</td>
<td>Lifetime</td>
<td>Costs: 3% Benefits: 3%</td>
<td>Costs and consequences of screening strategies and no screening strategy, cost per life-year-gained, QALY</td>
<td>Mortality rates (NHANESIII data), disease progression rates (Liu et al)</td>
<td>Various estimates (by sex and race) calculated using the National Health and Nutrition Examination Survey (2001-2008)</td>
<td>Acceptance of treatment for those with fibrosis stage F0-F1: 30% Acceptance of treatment for those with fibrosis stage F2-F4: 39%</td>
<td>Derived from the Medical Expenditure Panel Survey</td>
<td>Screening (ELISA, RIBA and RNA tests, counselling, liver biopsy, FibroTest), drug and medical care related to treatment, and annual care by fibrosis stage</td>
<td>Sensitivity analysis (cohort age, HCV prevalence, screening-related factors, treatment-related factors) Probabilistic Sensitivity Analysis (cohort characteristics, distribution of fibrosis stages, HCV status)</td>
<td>USD (2010)</td>
</tr>
<tr>
<td>McEwan**, 2013, United States</td>
<td>Individuals born between 1945-1965</td>
<td>CUA</td>
<td>Payer</td>
<td>Birth cohort screening compared to risk-based screening (status quo)</td>
<td>Lifetime</td>
<td>Costs: 3.5% Benefits: 3.5%</td>
<td>Costs and consequences of screening strategies and no screening strategy, cost per life-year-gained, QALY</td>
<td>Distribution of fibrosis stage (economic model by McGarry et al.)</td>
<td>Assumption that 1.77% of population tests positive for HCV</td>
<td>Acceptance of Screening: 91.21% Derived from a variety of sources</td>
<td>Drug and medical care related to treatment and management, cost of testing</td>
<td>Not clear what parameters were assessed for uncertainty or approach</td>
<td>USD (Not reported)</td>
<td></td>
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<tr>
<td>Author, Year, Country</td>
<td>Population</td>
<td>Model</td>
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<td>McCarthy*, 2012, United States</td>
<td>Birth Cohort: individuals born between 1946-1970 with no HCV diagnosis</td>
<td>CUA and CEA</td>
<td>Payer</td>
<td>Birth cohort screening compared to risk-based screening (status quo)</td>
<td>Lifetime</td>
<td>Costs: 3%</td>
<td>Cases of advanced liver disease avoided, HCV deaths averted, QALY</td>
<td>Disease progression (model by Davis et al.), mortality (U.S. population averages reported in Arias et al.), proportion of population screened (administrative data)</td>
<td>Not reported</td>
<td>Acceptance of treatment over 5 years: 100%</td>
<td>Derived from a variety of literature sources</td>
<td>Screening costs (ELISA test, PCR test, biopsy), cost of diagnosis, cost of treatment, cost of monitoring, cost by annual health state,</td>
<td>Sensitivity Analysis (percentage of birth cohort screened, treatment eligibility, treatment rates, efficacy rates, time horizons of 10 and 25 years, progression rates between fibrosis stages, proportion of non-progressing fibrosis)</td>
<td>USD (2010)</td>
</tr>
<tr>
<td>Nakamura**, 2008, Japan</td>
<td>Cohort of 99,001 individuals living in Japan age 40-70, from 2003 to 2006</td>
<td>CEA</td>
<td>Payer</td>
<td>Screening program of birth cohort (40-70 years old) compared to no screening program.</td>
<td>Lifetime</td>
<td>Costs: 3%</td>
<td>Costs and consequences of screening strategies and no screening strategy, cost per life-year-gained (not adjusted for quality of life)</td>
<td>Probability of compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, death</td>
<td>HCV prevalence per age group: 0.36% 40-49: 0.15% 50-59: 0.18% 60-69: 0.36% &gt;70: 0.61%</td>
<td>Acceptance of treatment (assumption): 100%</td>
<td>Life expectancy</td>
<td>HCV antibody test, core antigen test, PCR test, combination therapy (inpatient and outpatient), post SVR (outpatient), chronic hepatitis (outpatient), compensated cirrhosis (inpatient), decompensated cirrhosis (inpatient and outpatient), hepatocellular carcinoma (inpatient and outpatient)</td>
<td>Sensitivity analysis (treatment effectiveness, transition probabilities, infection rates of HCV, price of drugs in one-way sensitivity analysis)</td>
<td>$ (Costs from Japan, possibly changed to USD) (2007)</td>
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<tr>
<td>Rein*, 2012, United States</td>
<td>Hypothetical cohort of individuals born between 1945 and 1965 that annually attend primary care provider</td>
<td>CUA</td>
<td>Societal</td>
<td>Screening program of birth cohort (born 1945-1965) treated with either PEG-IFN+R alone or PEG-IFN+R and direct acting anti-viral compared to no screening program.</td>
<td>Lifetime</td>
<td>Costs: 3%</td>
<td>Costs and consequences of screening strategies and no screening strategy, cost per life-year-gained, QALY</td>
<td>Probability of refusing treatment, genotype, cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, transplant, death</td>
<td>Stratified by age, sex, race/ethnicity, history of intravenous drug use, and history of HCV (values unknown)</td>
<td>Acceptance of screening if intervention offered (Honeycutt et al): 91%</td>
<td>Acceptance of screening if intervention not offered (Honeycutt et al): 18%</td>
<td>Receive treatment after positive test (Falck et al and Zeuzem et al): 40.8%</td>
<td>A variety of literature-based sources were used to provide utility data (Short Form 36 Health Survey data and Standard Gamble).</td>
<td>Screening, receiving results, treatment per genotype, METAVIR stages, cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant</td>
</tr>
<tr>
<td>Author, Year, Country</td>
<td>Population</td>
<td>Model</td>
<td>Perspective</td>
<td>Comparators</td>
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<td>Clinical Inputs</td>
<td>Prevalence Estimate</td>
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<td>Ruggeri *, 2013, Italy</td>
<td>Hypothetical cohort of healthy individuals 35-65 years old</td>
<td>CUA</td>
<td>Payer</td>
<td>Screening program of healthy individuals (≥35 years old) compared to no screening</td>
<td>40 years</td>
<td>Costs: 3.5%</td>
<td>Benefits: 3.5%</td>
<td>Costs and consequences of screening strategies and no screening strategy, cost per life-year-gained, QALY</td>
<td>Prevalence of HCV in each age group, efficacy of treatments, distribution of genotypes</td>
<td>HCV prevalence per age group (Ansaldo et al): 15-30: 2% 31-45: 6% 46-60: 7% &gt;60: 5%</td>
<td>Not Reported</td>
<td>ELISE and PCR cost, hepatology consultation, laboratory tests, ultrasounds, drugs, abdominal echotomography, esophageal duodenoscopy, esofagogastroduodenoscopy, hepatic ecography, tumor markers, computed tomography</td>
<td>Sensitivity Analysis (discount rate, costs, genotype, effectiveness, and utility in one way sensitivity analysis)</td>
<td>€ (2009)</td>
</tr>
<tr>
<td>Wong *, 2014, Canada</td>
<td>Hypothetical cohort of individuals 25-64 years old currently living in Canada</td>
<td>CUA</td>
<td>Payer</td>
<td>Screen and Treat with peglated interferon plus ribavirin, and Screen and Treat with direct-acting antiviral agents, compared to no screening</td>
<td>Lifetime</td>
<td>Costs: 5%</td>
<td>Benefits: 5%</td>
<td>Costs and consequences of screening strategies and no screening strategy, cost per life-year-gained, QALY</td>
<td>Distribution of fibrosis stages per age group, Probability of annual fibrosis progression, Probability of annual cirrhosis progression, Mortality, probability of treatment by fibrosis and viral genotype, combination therapy of telaprevir (treatment naïve cohort), PEG-IFN and ribavirin therapy for genotype 1 through 6, Retreatment of genotype 1 for telaprevir–based combination therapy</td>
<td>Prevalence estimate of HCV prevalence in age groups (Rotteamm et al): 0.5% (95%CI 0.3- 0.9%)</td>
<td>Acceptance of testing rate for age group (Yeung et al): 91%</td>
<td>HUI (Mark 2) for patients with early and late stage HCV</td>
<td>Annual costs of early late and pre-death HCV phase, transplant and post-transplant cost, anti-viral therapies, adverse events, anti-HCV test, HCV RNA test</td>
<td>Scenario Analysis (prevalence, age ranges)</td>
</tr>
<tr>
<td>Author, Year, Country</td>
<td>Target Population of Screening Program</td>
<td>Population Definition</td>
<td>Comparators</td>
<td>Clinical Pathway</td>
<td>Results</td>
<td>Author’s Conclusions</td>
<td>Sources of Uncertainty</td>
<td>Critical Appraisal (Our Interpretation of the Study)</td>
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<tr>
<td>Coffin¹⁷, 2012, United States</td>
<td>Birth Cohort: Individuals born between 1945-1965</td>
<td>Hypothetical cohort of individuals 45 years old.</td>
<td>No screening program (only risk-factor based screening) compared to screening program for those born between 1945-1965 and living in the United States</td>
<td>Testing or no testing (natural history of disease), positive or negative test, positive or negative PCR test, Referral or no referral to treatment, diagnosis, treatment, treatment failure or response</td>
<td>• $5,400 incremental cost per QALY gained for implementing a birth cohort screening program compared to no screening program (based on 15% screened)</td>
<td>&quot;Targeted age-based screening, equivalent to screening only high-risk birth cohorts in our model, may be more effective than general population screening if implementation costs, pace of adoption by clinicians and median age of diagnosis were similar.&quot;</td>
<td>Not reported</td>
<td>This study is high quality; it adheres to all of the guidelines established in the CHEER checklist. It demonstrates that screening people born between 1945-1965 is likely to be more costly and more effective than no screening program. Using a threshold of $50,000 per QALY gained, this screening program would be considered reasonable value for money. Sources of uncertainty were not reported, which is a limitation of this study.</td>
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<td>Liu¹⁶, 2013, United States</td>
<td>Birth cohort: Individuals 40-74 years old who are asymptomatic (age range 40-74)</td>
<td>Hypothetical cohort of 50 year old adults who are asymptomatic (age range 40-74)</td>
<td>Birth-cohort screening program compared to no screening program for asymptomatic individuals who are 40-74</td>
<td>Screening or no screening (natural history of disease), treatment with standard therapy, universal triple therapy or IL-28B-guided triple therapy</td>
<td>• Birth cohort screening cost an incremental $65,749 per QALY (treatment with universal triple therapy included) compared to no screening • Birth cohort screening averted 10-15 liver transplants and 35-56 liver cancers at a cost of $35-57 million dollars per 100,000 people screened compared to no screening • Birth cohort screening cost an incremental $65,749 per QALY (treatment with universal triple therapy included) compared to no screening • Birth cohort screening averted 10-15 liver transplants and 35-56 liver cancers at a cost of $35-57 million dollars per 100,000 people screened compared to no screening</td>
<td>&quot;The cost-effectiveness of one-time birth-cohort hepatitis C screening for 40-64 year olds is comparable to other screening programs, provided that the health care system has sufficient capacity to deliver prompt treatment and appropriate follow-on care to many newly screen-detected individuals.&quot;</td>
<td>Fibrosis stage distribution</td>
<td>This study is high quality; it adheres to all of the guidelines established in the CHEER checklist. It demonstrates that screening asymptomatic adult population living in the United States is likely to be more costly and more effective than no screening program. Using a threshold of $50,000 per QALY gained, this screening program would not be considered reasonable value for money. The distribution of individuals in each fibrosis stage strongly influenced the cost-effectiveness of this program; when more individuals with severe liver fibrosis were detected, screening was more cost-effective and vice versa.</td>
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<td>Author, Year, Country</td>
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<td>McEwan⁴, 2013, United States</td>
<td>Birth cohort: individuals born between 1945-1965</td>
<td>Cohort of all individuals born between 1945 and 1965, excluding individuals already diagnosed with HCV</td>
<td>Birth cohort screening compared to risk-based screening (status quo)</td>
<td>Risk based testing or birth cohort based testing, HCV positive or negative, diagnosis, treatment or no treatment</td>
<td>$28,602 incremental cost per QALY gained for birth cohort screening compared to risk-based screening. If 91% of the population is tested, at least 278,000 people need to be treated for birth cohort testing to remain cost-effective.</td>
<td>This study confirms that birth cohort testing is, on average, cost-effective. However, this remains true only when enough tested and HCV-positive subjects are treated to generate sufficient cost offsets and QALY gains. Given the practical and financial challenges associated with implementing birth cohort testing, the greatest return on investment is obtained when eligible patients are treated immediately and those with more advanced disease are prioritized.</td>
<td>Treatment uptake, number of prevalence infections within the tested population</td>
<td>This study is high quality; it adheres to 22 of the 24 guidelines established in the CHEER checklist. It demonstrates that birth cohort screening is likely to be more costly and more effective than a risk-based screening program for asymptomatic adult populations born between 1945 and 1965 living in the United States. Using a threshold of $50,000 per QALY gained, this screening program would be considered reasonable value for money.</td>
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<td>McGarry⁴, 2012, United States</td>
<td>Birth cohort: individuals born between 1946-1970</td>
<td>Cohort of all individuals born between 1946 and 1970</td>
<td>Birth cohort screening compared to risk-based screening (status quo)</td>
<td>Screening or no screening (natural history of disease), HCV positive or HCV negative, diagnosis or no diagnosis, treatment or no treatment</td>
<td>$37,000 incremental cost per QALY gained for birth cohort screening compared to risk-based screening. If 102 million individuals are screened, this screening program could avoid $4,000,000 cases of decompensated cirrhosis, 46,000 cases of hepatocellular carcinoma, 10,000 liver transplants and 78,000 HCV death for a cost of $80.4 billion (compared to $53.7 billion for risk-based screening)</td>
<td>Birth-cohort screening for HCV is likely to provide important health benefits by reducing lifetime cases of advanced liver disease and HCV-related deaths and is cost-effective at conventional willingness-to-pay thresholds.</td>
<td>Screening uptake, treatment eligibility, treatment rate, treatment efficacy, time horizon</td>
<td>This study is high quality; it adheres to 23 of the 24 guidelines established in the CHEER checklist. It demonstrates that screening asymptomatic adult populations born between 1946 and 1970 living in the United States is likely to be more costly and more effective than a risk-based screening program. Using a threshold of $50,000 per QALY gained, this screening program would be considered reasonable value for money. Significant uncertainties exist in this estimate: when screening levels are below 20% birth cohort screening becomes less attractive; reduced treatment efficacy significantly reduces the cost-effectiveness; and changing the lifetime horizon to 25 years doubles the cost per QALY gained.</td>
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<td>Nakamura⁴, 2008, Japan</td>
<td>Birth cohort: individuals 40-70 years old</td>
<td>Cohort of 99,001 individuals age 40-70, from 2003 to 2006</td>
<td>Screening program of birth cohort (40-70 years old) compared to no screening program.</td>
<td>Screening or no screening (natural history of disease), diagnosis, treatment, cirrhosis, decompensated cirrhosis, death</td>
<td>$40-49: screening results in a $848 cost per life year gained compared to no screening. $50-59: screening results in a $1,627 cost per life year gained compared to no screening. $60-69: screening results in a $3,133 cost per life year gained compared to no screening. $70+: screening results in a $4,825 cost per life year gained compared to no screening.</td>
<td>“The ICERs of the screening strategies in both the general population and high-risk group would be below $50,000/LE gained; therefore, the screening strategy was cost-effective in comparison to the no-screening strategy.” “Our results indicated that the national screening programs for HCV in both the general population and high-risk group would be cost-effective in comparison to each no-screening case. Especially, the younger age groups would gain more Prevalence of HCV</td>
<td>This study is high quality; it adheres to 22 of the 24 guidelines established in the CHEER checklist. It demonstrates that screening a birth cohort population living in Japan is likely to be more costly and more effective than no screening program. There is no accepted reasonable cost per life year gained, however, the estimates in this study are substantially less than other accepted therapies which have costs per life year gained of $100,000. Although there is uncertainty in this model, it is not likely that the cost per life year gained would become unattractive.</td>
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<td>Rein* , 2012, United States</td>
<td>Birth Cohort: Individuals born between 1945-1965</td>
<td>Hypothetical cohort of individuals born between 1945 and 1965 that annually attend primary care provider</td>
<td>Screening program of birth cohort (1945-1965) treated with either PEG-IFN+R alone or PEG-IFN+R and direct acting anti-viral compared to no screening program.</td>
<td>Screening or no screening (natural history of disease), diagnosis, treatment, cirrhosis, decompensated cirrhosis, transplant, death</td>
<td>Screening, and treating with PEG-IFN+R results in a $15,700 cost per QALY compared to no screening. Screening, and treating with PEG-IFN+R and direct acting anti-viral results in a $73,700 cost per QALY compared to no screening. Screening at risk individuals results in a $15,700 cost per QALY compared to no screening.</td>
<td>&quot;Birth-cohort screening with standard treatment alone when compared with risk-based screening ranks equivalently to colorectal cancer screening, hypertension screening, influenza vaccination of adults aged 50 years or older, pneumococcal vaccination of adults aged 65 years or older, and vision screening of adults 65 years or older. Birth-cohort screening with DSS plus standard treatment (when compared with risk-based screening) ranks below those interventions but equivocally to cervical cancer or cholesterol screening.&quot;</td>
<td>Utilities, response to anti-viral therapy, discount rate, and utilities</td>
<td>This study is high quality; it adheres to 24 of the 24 guidelines established in the CHEER checklist. It demonstrates that screening a birth cohort population living in the United States likely to be more costly and more effective than no screening program. Using a threshold of a $50,000 per QALY gained, this screening program would be considered reasonable value for money. Although utilities, response to anti-viral therapy, discount rate, and utilities introduced some uncertainty, no variations in any of these variables resulted in a cost per QALY of greater than $50,000.</td>
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<td>Ruggeri** , 2013, Italy</td>
<td>Birth Cohort: Individuals 35-65 years old</td>
<td>Hypothetical cohort of healthy individuals ≥35 years old in Italy</td>
<td>Screening program of birth cohort (35-65 years old) compared to no screening program.</td>
<td>Screening or no screening (natural history of disease), diagnosis, treatment, cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, transplant, death</td>
<td>Screening results in a 5,171€ ($7,914) cost per QALY compared to no screening.</td>
<td>&quot;The incremental cost-effectiveness ratio of the &quot;Test Strategy&quot; is 5171/QALY, definitively below the cost/WALY of other approved treatments in Italy. Model results turned out as sensitive to the age of the target population, the prevalence of HCV infection, and the time horizon adopted. The anti-HCV screening program is a valid health-related investment improving patients’ quality of life and survival with an acceptable expenditure increase for the National Health Services.&quot;</td>
<td>Prevalence of HCV, age distribution</td>
<td>This study is high quality; it adheres to 22 of the 24 guidelines established in the CHEER checklist. It demonstrates that screening a birth cohort population living in Italy is likely to be more costly and more effective than no screening program. Using a threshold of a $50,000 per QALY gained, this screening program would be considered reasonable value for money. Although there is uncertainty in this model, it is not likely that the cost-effectiveness ratio will exceed the threshold of $50,000 per QALY gained.</td>
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<td>Wong* , 2014, Canada</td>
<td>Birth cohort: Individuals 25-64 years old</td>
<td>Hypothetical cohort of individuals 25-64 years of age living in Canada</td>
<td>Screen and Treat with pegylated interferon plus ribavirin, and Screen and Treat with direct-acting antiviral agents, compared to no screening</td>
<td>Screening or no screening (natural history of disease), positive or negative for HCV, transition through stages of fibrosis and cirrhosis, liver transplant, or die</td>
<td>Screen and treat with PR results in a $34,622 cost per QALY compared to no screening. Screen and treat with telaprevir results in a $43,637 cost per QALY and prevents 12 HCV-related deaths per 10,000 persons compared to no screening.</td>
<td>&quot;Baseline analysis suggests that selective one-time hepatitis C screening program for individuals between 25 and 64 years old in Canada prevents 11 HCV-related deaths per 10,000 persons over the lifetime of the cohort, and is likely to be cost-effective at $34,622/QALY gained. The conventional upper limit of applied cost effectiveness thresholds varies among countries from $50,000/QALY to $120,000/QALY. Both results of multiple one-way sensitivity and effects of novel therapies&quot;</td>
<td>Effects of novel therapies</td>
<td>This study is high quality; it adheres to 24 of the 24 guidelines established in the CHEER checklist. It demonstrates that screening a general adult population within Canada is likely to be more costly and more effective than no screening program. Using a threshold of a $50,000 per QALY gained, this screening program would be considered reasonable value for money. Although there is uncertainty in this model, it is not likely that the cost-effectiveness ratio will exceed $50,000 per QALY gained.</td>
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<td>PSA provided evidence that the “Screen and Treat” is likely to be cost-effective taking into consideration the uncertainty of the model’s parameters.”</td>
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Table 31: Characteristics of Studies Assessing Screening of General Populations

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<tr>
<th>Author, Year, Country</th>
<th>Population</th>
<th>Model</th>
<th>Perspective</th>
<th>Comparators</th>
<th>Time Horizon</th>
<th>Discount Rate</th>
<th>Outcome</th>
<th>Clinical Inputs</th>
<th>Prevalence Estimate</th>
<th>Adherence Estimate</th>
<th>Preference measurement</th>
<th>Included Cost Inputs</th>
<th>Assessment of Uncertainty</th>
<th>Currency (Year)</th>
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<tbody>
<tr>
<td>Coffin (^\text{f1}^), United States 2012</td>
<td>Hypothetical cohort of general adult population screening (age 20-69)</td>
<td>CUA</td>
<td>Societal</td>
<td>No screening program compared to screening program for adults living in the United States</td>
<td>Lifetime</td>
<td>Costs: 3% Benefits: 3%</td>
<td>Costs and consequences of screening strategies and no screening strategy, cost per life-year-gained, QALY</td>
<td>Distribution of fibrosis stage at time of diagnosis, rate of progression through each stage of fibrosis, spontaneous presentation outside screening, rates of sustained viral response</td>
<td>Proportion of general US adult population HCV positive: 0.16% (range: 0.13-0.20%)</td>
<td>Assumption that 15% of the general population would be screened, based on 5-60% uptake of screening (Bassett et al.).</td>
<td>A variety of literature-based sources were used to provide utility data (Short Form 36 Health Survey data).</td>
<td>HCV antibody screening, RNA polymerase chain reaction test cost, Telaprevir-based therapy cost, boceprevir-based therapy costs, physician costs, disease management costs, and liver transplant and management costs</td>
<td>Sensitivity analysis (all parameters varied in one-way sensitivity analysis) Scenario Analysis (varying all parameters to be unfavorable) Probabilistic Sensitivity Analysis (all parameters varied)</td>
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<tr>
<td>Eckman (^\text{f2}^), United States 2013</td>
<td>Hypothetical cohort of individuals 46.2 years old, with a mean HCV infection duration of 20.7 years</td>
<td>CUA</td>
<td>Payer</td>
<td>No screening program compared to screening program for asymptomatic adults living in the United States</td>
<td>Lifetime</td>
<td>Costs: 3% Benefits: 3%</td>
<td>Costs and consequences of screening strategies and no screening strategy, cost per life-year-gained, QALY</td>
<td>Development of hepatocellular carcinoma, fibrosis progression</td>
<td>HCV positive: 0.014 (0.013-0.019)</td>
<td>Not reported</td>
<td>Standard gamble utility assessment of HCV patients, from meta-regression (McLernon et al.)</td>
<td>Cost by disease state, cost of hepatocellular carcinoma (with or without liver transplant), medication cost, lab test costs, doctors office visit costs, cost of screening, cost of treatment</td>
<td>Sensitivity analysis (all variables) Probabilistic Sensitivity Analysis (all parameters) Deterministic Sensitivity Analysis</td>
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<tr>
<td>Helsper (^\text{f3}^), United States 2012</td>
<td>General population</td>
<td>CUA</td>
<td>Payer</td>
<td>No screening program compared to “general campaign” consisting of local radio, newspaper and print advertising AND No screening program compared to “support campaign” consisting of local radio, newspaper and print advertising and availability of information sessions for general practitioners</td>
<td>Lifetime</td>
<td>Costs: 4% Benefits: 1.5%</td>
<td>Costs and consequences of screening strategies and no screening strategy, cost per life-year-gained, QALY</td>
<td>Distribution of fibrosis stage, patients eligible for treatment, probability of successful treatment</td>
<td>Not reported</td>
<td>General Campaign: Not Reported Support Campaign: Referral rate: 70%</td>
<td>Not reported</td>
<td>Diagnostic tests and consultations before treatment, medication and diagnostic tests during treatment (by fibrosis stage), campaign costs (organization, materials, information session costs, brochure costs, GP support costs – for Support</td>
<td>Sensitivity Analysis Probabilistic Sensitivity Analysis</td>
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<tr>
<td>Singer*, 2001, United States</td>
<td>Hypothetical cohort of adults who attend a regular check-up with their primary health care provider</td>
<td>CUA</td>
<td>Societal</td>
<td>Screening program using ELISA then PCR, or only PCR, compared to No screening</td>
<td>Not Reported</td>
<td>Costs: 3%</td>
<td>Benefits: 3%</td>
<td>Costs and consequences of screening strategies and no screening strategy, cost per life-year-gained, QALY</td>
<td>Sensitivity and specificity of ELISA and PCR, probabilities of cirrhosis, successfully treated, decompensated cirrhosis hepatocellular carcinoma, liver transplant, death, relapse, response to treatment</td>
<td>HCV prevalence in general population (Alter et al): 9%</td>
<td>Receive treatment after positive test (Piton et al): 20%</td>
<td>A variety of literature-based sources were used to provide utility data (Short Form 36 Health Survey data).</td>
<td>Liver biopsy, liver profile, ultrasound, drugs, outpatients, missed work, ELISA, PCR, genotyping, annual costs (HCV, cirrhosis, decompensated cirrhosis, transplant, hepatocellular carcinoma)</td>
<td>Sensitivity Analysis (all parameters in one-way sensitivity analysis and two-way with parameters that had largest impact in one-way)</td>
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Table 32: Results of Studies Assessing General Populations

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<th>Population Definition</th>
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<th>Sources of Uncertainty</th>
<th>Critical Appraisal (Our Interpretation of the Study)</th>
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<tr>
<td>Coffin**, 2012, United States</td>
<td>General population screening (age 20-69)</td>
<td>Hypothetical cohort of individuals 45 years old</td>
<td>No screening program compared to screening program for adults living in the United States</td>
<td>Screening or no screening (natural history of disease), positive of negative test, positive or negative PCR test, Referral or no referral to treatment, diagnosis, treatment, treatment failure or response</td>
<td>$7,000 incremental cost per QALY gained for implementing a general adult screening program compared to no screening program (based on 15% screened)</td>
<td>&quot;...the addition of one-time screening of the general adult US population for CHC would be cost-effective over the current practice of only screening high-risk individuals.&quot;</td>
<td>Distribution of fibrosis stage at time of diagnosis</td>
<td>This study is high quality; it adheres to all of the guidelines established in the CHEER checklist. It demonstrates that screening is likely to be more costly and more effective than no screening program. Using a threshold of a $50,000 per QALY gained, this screening program would be considered reasonable value for money. Although there is uncertainty in this model, it is not likely that the cost-effectiveness ratio will exceed the threshold of $50,000 per QALY gained.</td>
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<td>Eckman**, 2013, United States</td>
<td>Asymptomatic adult population</td>
<td>Hypothetical cohort of individuals 46.2 years old, with a mean HCV infection duration of 20.7 years</td>
<td>No screening program compared to screening program for asymptomatic adults living in the United States</td>
<td>Screening or no screening (natural history of disease); male or female; Caucasian, African American or Hispanic; EIA positive or negative; PCR positive or negative; if negative PCR, RIBBA positive or negative; accepts or declines treatment; diagnosis</td>
<td>$47,276 incremental cost per QALY gained for implementing a screening program compared to no screening program</td>
<td>&quot;Targeted screening is cost-effective when prevalence of HCV exceeds 0.84%.&quot;</td>
<td>Risk category for disease progression, monthly cost of direct-acting antiviral, proportion with genotypes 2 and 3.</td>
<td>This study is high quality; it adheres to 23 of the guidelines established in the CHEER checklist. It demonstrates that screening an asymptomatic population living in the United States is likely to be more costly and more effective than no screening program. Using a threshold of a $50,000 per QALY gained, this screening program would be considered reasonable value for money. Using probabilistic sensitivity analysis, screening had an ICER under $50,000 76% of the time; significant uncertainty exists in this model, and 24% of the time it may be not cost-effective.</td>
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<td>Helsper**, 2012, Netherlands</td>
<td>General population</td>
<td>Cohort of individuals recruited between October 2007 and January 2008</td>
<td>No screening program compared to “general campaign” consisting of local radio, newspaper and print advertising AND</td>
<td>Screening or no screening (natural history of disease), test or no test, positive or negative test result, diagnosis or no diagnosis, treatment or no treatment, response to treatment or no response to treatment</td>
<td>General Campaign: Cost-effectiveness not calculated due to no improvement in effectiveness over no screening program (general campaign dominated)</td>
<td>General Campaign: “The general campaign did not result in an increase in the identification of HCV carriers which means there was no gain in effects and therefore no ICER could be calculated. Consequently this strategy is not cost-effective.”</td>
<td>Number of cases found</td>
<td>This study is high quality; it adheres to 23 of the 24 guidelines established in the CHEER checklist. It demonstrates that screening an asymptomatic population living in the Netherlands is likely to be more costly and no more effective than no screening program. A threshold of a $50,000 per QALY gained, this screening program would be considered reasonable value for money.</td>
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<td>Author, Year, Country</td>
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</table>
| Singer**, 2001, United States | Average-risk adults | Hypothetical cohort of adults who attend a regular check-up with their primary health care provider | Screening program of general population at primary health care provider check-up using either ELISA and PCR or PCR, compared to no screening program | Screening or no screening (natural history of disease), positive or negative ELISA test, PCR test if positive ELISA test, diagnosis, treatment, cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, transplant, death | • Screening with ELISA and PCR results in an increased cost of $121 and QALY increase of 0.002 ($60,500 cost per QALY) compared to no screening  
• Screening with PCR results in an increased cost of $182 and QALY increase of 0.002 ($91,000 cost per QALY) compared to no screening | "The no screening strategy was the dominant strategy in the baseline analysis. The model was most sensitive to the reduction in quality of life related to patient awareness of hepatitis C infection. Screening with ELISA and PCR was preferred with this value was <0.01 and was cost effective if more than half of the patients who tested positive for hepatitis C actually initiated treatment, or if the annual rate of progression to cirrhosis was greater than 2.5%. Screening with PCR only was never cost effective." | Progression of cirrhosis, prevalence of HCV, compliance with treatment | This study is of moderate quality; it adheres to 19 of the 24 guidelines established in the CHEER checklist. It demonstrates that screening individuals in general practice in the United States is likely to be more costly and more effective than no screening program. Using a threshold of a $50,000 per QALY gained, this screening program would not be considered reasonable value for money. |
<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Population</th>
<th>Model</th>
<th>Perspective</th>
<th>Comparators</th>
<th>Time Horizon</th>
<th>Discount Rate</th>
<th>Outcome</th>
<th>Clinical Inputs</th>
<th>Prevalence Estimate</th>
<th>Adherence Estimate</th>
<th>Preference measurement</th>
<th>Included Cost Inputs</th>
<th>Assessment of Uncertainty</th>
<th>Currency (Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Honeycutt [14], 2007, United States</td>
<td>Adults who present at a public STD clinic</td>
<td>CEA</td>
<td>STD Clinic Perspective</td>
<td>No Screening for HCV compared to screening for HCV in adults who present at a public STD clinic</td>
<td>Not reported</td>
<td>Not Reported</td>
<td>Cost per positive test</td>
<td>Proportion of positive testers who return to clinic, proportion of negative testers who return to clinic</td>
<td>Drug users: 57% (44-69%)</td>
<td>Men over 40 with 100+ sexual partners: 16% (6.7-25)</td>
<td>Men over 40 with &lt;100 sexual partners: 2.0% (1.2-2.8%)</td>
<td>Women over 40 years old: 0.9% (0.2-1.7)</td>
<td>Not reported</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Josset [15], 2004, France</td>
<td>Subgroups who have a history of gastroscopy, have had contact with an infected person, have a history of invasive procedure, history of colonoscopy or history of surgery</td>
<td>CEA</td>
<td>Not reported</td>
<td>Comparing reference screening (of high risk individuals who either had a blood transfusion before 1991, or are drug users) with screening of people who have a history of gastroscopy have had contact with an infected person, have a history of invasive procedure, history of colonoscopy or history of surgery</td>
<td>Not reported</td>
<td>Not Reported</td>
<td>Cost per positive test</td>
<td>Positive serology tests</td>
<td>Not reported</td>
<td>Not Reported</td>
<td>Not Reported</td>
<td>Physician fees (consultation), test costs (ELISA, blood sample)</td>
<td>Sensitivity Analysis (HCV seroprevalence, proportion of high-risk patients)</td>
<td>€ (1997)</td>
</tr>
<tr>
<td>Stein [16], 2003, United Kingdom</td>
<td>Hypothetical cohort of 246,636 attending a genito-urinary clinic annually</td>
<td>CUA</td>
<td>Payer</td>
<td>Screening program of all individuals attending a genito-urinary clinic compared to no screening program</td>
<td>50 years</td>
<td>Costs: 6% Benefits: 1.5%</td>
<td>Costs and consequences of screening strategies and no screening strategy, cost per life-year-gained, QALY</td>
<td>Sensitivity and specificity of ELISA and PCR, proportion with mild, moderate or severe disease, complications, progression to cirrhosis, decompensated cirrhosis, hepatic carcinoma, death, transplant, second transplant</td>
<td>HCV prevalence at genito-urinary clinic (Goldberg et al): 1.5%</td>
<td>Acceptance of testing rate for individuals using ELISA test (Serfaty et al): 49%</td>
<td>Acceptance of testing rate for individuals using PCR test (Clinician Advisory Group): 100%</td>
<td>Acceptance of testing rate for VAS for HCV patients (Cotler et al)</td>
<td>ELISA, PCR, Counselling, Liver biopsy, medical visits, medications, inpatient day, hepatocellular carcinoma inpatient cost, chronic HCV infection, hepatic encephalopathy inpatient, variceal bleed inpatient, liver transplant</td>
<td>Sensitivity Analysis (all parameters in one-way and multi-way sensitivity analysis)</td>
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<td>Author, Year, Country</td>
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<td>Tramarin&lt;sup&gt;26&lt;/sup&gt;, 2008, Netherlands</td>
<td>Hypothetical cohort of individuals who had minor or major surgery in 2007</td>
<td>CUA</td>
<td>Societal</td>
<td>Screening program of individuals who had minor or major surgery compared to no screening.</td>
<td>Lifetime</td>
<td>Costs: 3% Benefits: 3%</td>
<td>Costs and consequences of screening strategies and no screening strategy, cost per life-year-gained, QALY</td>
<td>Probabilities of symptomatic and asymptomatic HCV, spontaneous clearance, progression, cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, death, and liver transplant</td>
<td>Randomized control trial HCV prevalence estimate of symptomatic and asymptomatic (Manns et al): 0.16, 0.84</td>
<td>Complete compliance</td>
<td>A variety of literature-based sources were used to provide utility data (Short Form 36 Health Survey data).</td>
<td>Screening, annual costs (screening, cirrhosis, transplantation in hepatocellular carcinoma), monthly costs (acute therapy, chronic therapy)</td>
<td>Sensitivity Analysis (prevalence of genotypes 1 and 4)</td>
<td>€ (Not Reported)</td>
</tr>
<tr>
<td>Author, Year, Country</td>
<td>Target Population of Screening Program</td>
<td>Population Definition</td>
<td>Comparators</td>
<td>Clinical Pathway</td>
<td>Results</td>
<td>Author’s Conclusions</td>
<td>Sources of Uncertainty</td>
<td>Critical Appraisal (Our Interpretation of the Study)</td>
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<td>Honeycutt**, 2007, United States</td>
<td>Visitors to public sexually transmitted disease clinics. Subgroup analyses on STD visitors who are also: drug users, men over 40 who report having 100+ sexual partners, men over 40 who report having &lt;100 sexual partners, and women over 40</td>
<td>Not Reported</td>
<td>No Screening for HCV compared to screening for HCV in adults who present at a public STD clinic</td>
<td>Not Reported</td>
<td>• Cost per true positive test of client who returns to receive results ranges from $54.40 for injection drug users to $2,986.10 for females over 40 who are not drug users</td>
<td>“Based on national data, testing IDUs [Intravenous Drug Users] in the STD clinic setting is highly cost-effective. Some clinics may find that it is cost-effective to expand testing to non-IDU men older than 40 who report more than 100 lifetime sex partners.”</td>
<td>HCV prevalence, cost of testing</td>
<td>This study is poor quality; it adheres to only 17 of the 24 guidelines established in the CHEER checklist. It demonstrates that the cost-effectiveness ratio screening individuals presenting at a STD clinic in the United States is likely to vary based on subgroup.</td>
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<td>Josset**, 2004, France</td>
<td>Subgroups who have a history of gastroscopy, have had contact with an infected person, have a history of invasive procedure, history of colonoscopy or history of surgery</td>
<td>Real cohort of patients (n=10,041) aged 18-70, recruited by 127 physicians during 10 day recruiting period. Participants with at least one risk factor were offered screening.</td>
<td>Comparing no screening program/reference screening strategy (only screening those who had blood transfusion or those who are drug users) was 654€ ($950), the least costly option</td>
<td>Screening those with a history of gastroscopy cost an average of 1,126€ ($1,636) per positive test</td>
<td>“Our findings suggest that extending HCV screening beyond persons with a history of drug abuse or transfusion is not very effective, the extra positive tests inducing a very substantial increase in cost.”</td>
<td>HCV seroprevalence, proportion of high-risk patients</td>
<td>This study is poor quality; it adheres to only 17 of the 24 guidelines established in the CHEER checklist. It demonstrates that the cost per positive HCV test is lowest in the reference strategy, which only includes participants who have had a blood transfusion and those who are drug users. However, this study is limited in that it does not account for costs beyond the cost of tests and physicians time. For example, costs for treatment and cost of disease management are not included. Seroprevalence strongly influenced the cost-effectiveness of this model; a decline in seroprevalence (2% to 1.8%) resulted in a 1.5 time increase in cost-effectiveness ratio.</td>
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<tr>
<td>Stein**†**, 2003, United Kingdom</td>
<td>Individuals in genito-urinary medicine clinics</td>
<td>Hypothetical cohort of 246,636 attending a genito-urinary clinic annually</td>
<td>Screening program of all individuals in a genito-urinary clinic compared to no screening program</td>
<td>Screening those with a history of colonoscopy cost an average of 1,053€ ($1,530) per positive test</td>
<td>Screening those with a history of surgery cost an average of 1,734€ ($2,520) per positive test</td>
<td>“Universal screening for HCV in GUM clinics is unlikely to be cost effective. There is limited evidence to support screening of people other than those with a history of injecting drug use and even this policy should be considered with some care and in the context of further research.”</td>
<td>Utility of people who present symptomatically or are screened asymptomatically with HCV, chronic HCV</td>
<td>This study is high quality; it adheres to 22 of the 24 guidelines established in the CHEER checklist. It demonstrates that screening individuals in genito-urinary medicine clinics in the UK is likely to be more costly and more effective than no screening program. Using a threshold of a $50,000 per QALY gained, this screening program would not be considered reasonable value for money. Although there is uncertainty in this model, the conclusions are robust to changes in all costs, probability and utility variables.</td>
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<tr>
<td>Tramarin**†**, 2008, Netherlands</td>
<td>Individuals who had minor or major surgery</td>
<td>Hypothetical cohort of individuals who had minor or major surgery in 2007</td>
<td>Screening program of individuals who had minor or major surgery compared to no screening.</td>
<td>“Patients faced annual probabilities of progression, complication of cirrhosis, mortality risks from decompensated cirrhosis and hepatocellular carcinoma. Patient with decompensated cirrhosis could receive an orthotopic liver transplant…We developed an epidemiological model of HCV infection which includes acquisition of infection, clinical presentation (symptomatic and asymptomatic) probability of persistence and risk of progression to end stage of liver disease.”</td>
<td>Screening results in a 918,147€ ($1,334,155) cost per QALY gained compared to no screening</td>
<td>“The number of premature deaths prevented in the individuals with surgery cohort is lower and there seems to be an unacceptable incremental cost per QALY gained, which may be unsustainable for society.”</td>
<td>Distribution of genotypes</td>
<td>This study is high quality; it adheres to 21 of the 24 guidelines established in the CHEER checklist. It demonstrates that screening individuals who had minor or major surgery within the Netherlands screening is likely to be more costly and more effective than no screening program. Using a threshold of a $50,000 per QALY gained, this screening program would not be considered reasonable value for money. This model is not robust to changes in genotype distributions; if 10% or more of the individuals screened are genotype 1 and 4, the intervention becomes cost-effective.</td>
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