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Screening for Hepatitis C Virus Infection in Adults: A Systematic Review for the U.S. Preventive Services Task Force

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Background: Identification of hepatitis C virus (HCV)–infected persons through screening could lead to interventions that improve clinical outcomes.

Purpose: To review evidence about potential benefits and harms of HCV screening in asymptomatic adults without known liver enzyme abnormalities.

Data Sources: English-language publications identified from MEDLINE (1947 to May 2012), the Cochrane Library Database, clinical trial registries, and reference lists.

Study Selection: Randomized trials and cohort, case–control, and cross-sectional studies that assessed yield or clinical outcomes of screening; studies reporting harms from HCV screening; and large series reporting harms of diagnostic liver biopsies.

Data Extraction: Multiple investigators abstracted and checked study details and quality by using predefined criteria.

Data Synthesis: No study evaluated clinical outcomes associated with screening compared with no screening or of different risk- or prevalence-based strategies. Three cross-sectional studies in higher prevalence populations found that screening strategies that targeted multiple risk factors were associated with sensitivities greater than 90% and numbers needed to screen to identify 1 case of HCV infection of less than 20. Data on direct harms of screening were sparse. A large study of percutaneous liver biopsies ($n = 2740$) in HCV-infected patients with compensated cirrhosis reported no deaths and a 1.1% rate of serious adverse events (primarily bleeding and severe pain).

Limitations: Modeling studies were not examined. High or unreported proportions of potentially eligible patients in the observational studies were not included in calculations of screening yield because of unknown HCV status.

Conclusion: Although screening tests can accurately identify adults with chronic HCV infection, targeted screening strategies based on the presence of risk factors misses some patients with HCV infection. Well-designed prospective studies are needed to better understand the effects of different HCV screening strategies on diagnostic yield and clinical outcomes.

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The prevalence of anti–hepatitis C virus (HCV) antibody in the United States is about 1.6% (1). Approximately 78% of affected patients have viremia, indicating chronic infection. About two thirds of patients with HCV infection were born between 1945 and 1964, with the highest prevalence (4.3%) in people 40 to 49 years of age in 1999–2002 (1). There were 16 000 new cases of HCV infection in 2009 (2).

In 2007, HCV infection was associated with an estimated 15 000 deaths in the United States (3). Liver disease related to HCV is the most common indication for liver transplantation among U.S. adults (4, 5) and is a leading cause of hepatocellular carcinoma (6).

The virus is primarily acquired via percutaneous exposures to infected blood, such as injection drug use (7–13). Transfusions before 1992 and high-risk sexual behaviors are also associated with increased risk, although the efficiency of sexual transmission seems to be relatively low (7, 8, 14, 15).

The natural course of HCV infection varies. Studies of community cohorts estimate cirrhosis in 7% of people after 20 years of infection, with rates about twice as high in clinical and referral cohorts (16, 17). Studies with longer follow-up suggest that disease progression accelerates after 20 years (18).

Screening for HCV infection could identify persons at earlier stages of disease, before they develop serious or irreversible liver damage, and lead to treatments to improve clinical outcomes or reduce transmission risk. Up to three quarters of HCV-infected persons are unaware of their status (19).

In 2004, the U.S. Preventive Services Task Force (USPSTF) recommended against HCV screening in adults not at increased risk (D recommendation) and found insufficient evidence to recommend for or against screening in high-risk adults (I recommendation) (20). Although the USPSTF found that screening tests are accurate and that antiviral treatments improve viremia (21), the recommendations were based on the lower prevalence of HCV infection in persons without risk factors; the relatively low rate of long-term progression, potentially resulting in overtreatment; and lack of evidence that screening improves important health outcomes or reduces transmission risk. Other groups recommend screening in higher-risk patients (22–24). The Centers for Disease Control and Prevention

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(CDC) also recently recommended screening all persons born between 1945 and 1965 (25).

The purpose of this report is to review the evidence on HCV screening in asymptomatic adults without known liver enzyme abnormalities (26). This review focuses on research gaps identified in the 2004 USPSTF review (21) and will be used together with a separate review on antiviral treatments (27) by the USPTF to update its HCV screening recommendations.

METHODS

Scope

We developed a review protocol and analytic framework that included the following key questions:

1. Does screening for HCV infection in nonpregnant adults without known abnormal liver enzymes reduce mortality and morbidity due to HCV infection, affect quality of life, or reduce incidence of HCV infection?

2. What is the effectiveness of different risk- or prevalence-based methods for screening for HCV infection on clinical outcomes?

3. What is the sensitivity and number needed to screen to identify 1 case of HCV infection of different risk- or prevalence-based methods for screening for HCV infection?

4. What are the harms associated with screening for HCV infection, including diagnostic liver biopsies?

Detailed methods and data for the review, including search strategies, detailed inclusion criteria, data abstraction tables, and tables with quality ratings of individual studies, are available in the full report, which includes the analytic framework and additional key questions (26). The protocol was developed using a standardized process with input from experts and the public. The analytic framework focuses on direct evidence that HCV screening improves important health outcomes compared with not screening, as well as the chain of indirect evidence (diagnostic accuracy of screening, clinical utility and harms of subsequent testing in HCV-infected persons, and benefits and harms of treatments) linking screening with improved health outcomes. Key questions related to risk modification of mother-to-infant transmission are presented in the full report (26) and in a separate article (28). We did not re-review the diagnostic accuracy of HCV antibody testing, which the 2004 USPSTF review found to be high (21).

Data Sources and Searches

A research librarian searched Ovid MEDLINE (1947 to May 2012), Embase, the Cochrane Library Database, Scopus, and PsycINFO; clinical trial registries (including ClinicalTrials.gov); and grants databases. We supplemented electronic searches by reviewing reference lists of retrieved articles.

Study Selection

At least 2 reviewers independently evaluated each study to determine inclusion eligibility. Papers were selected for full review if they were relevant to a key question and met the predefined inclusion criteria. For screening, we included randomized trials, cohort studies, case–control studies, and cross-sectional studies that compared different screening strategies in asymptomatic adults without known liver enzyme abnormalities and reported clinical outcomes or sufficient information to compute the sensitivity and number needed to screen to identify 1 HCV-infected person. We also included large studies (sample size >1000 participants) reporting harms associated with diagnostic liver biopsy published since 2004 and uncontrolled or controlled studies reporting direct harms associated with screening.

Clinical outcomes were mortality, end-stage liver disease, cirrhosis, hepatocellular carcinoma, need for transplantation, quality of life, HCV transmission, harms associated with screening (such as anxiety, labeling, and effects on quality of life), and harms associated with liver biopsy (including death, bleeding, and severe pain).

We restricted inclusion to English-language articles and excluded studies published only as abstracts. We excluded studies of posttransplant patients, HIV-infected patients, patients undergoing hemodialysis, and persons with occupational exposures, in whom screening and treatment considerations may differ from those in the general population (29–33).

Data Abstraction and Quality Rating

One investigator abstracted details about the study design, patient population, setting, interventions, analysis, follow-up, and results. A second investigator reviewed data for accuracy. Two investigators independently applied predefined criteria (34–36) to assess the quality of each study as good, fair, or poor. Discrepancies were resolved through a consensus process.

Data Synthesis

For studies reporting the diagnostic yield of different screening strategies, we computed the number needed to screen to identify 1 case of HCV infection by dividing the number of screening tests performed by the number of HCV cases identified. The proportion screened was the number of patients screened upon application of a particular screening strategy, divided by the total number of patients assessed.

We assessed the overall strength of each body of evidence as "high," "moderate," "low," or "insufficient" in accordance with the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (37), based on the quality of studies, consistency between studies, precision of estimates, and directness of evidence.

Role of the Funding Source

This research was funded by AHRQ's Effective Health Care Program. Investigators worked with AHRQ staff to develop and refine the scope, analytic framework, and key

Table 1. **Studies of Alternative Screening Strategies**

Study, Year; Country (Reference)	Study Design	Sample Size, *n*	Setting Population Characteristics	HCV Screening Strategies	Quality
Gunn et al, 2003; United States (38)	Cross-sectional	3367	STD clinic Age ≥30 y: 4.6% Female: Not reported Self-reported injection drug use: 5.7%	A: Screen all B: Ever injected drugs (self-report) C: Ever injected drugs or blood transfusions before 1992 (self-report) D: Same as C, or sex partner used injection drugs (self-report) E: Same as D (self-report or identified by clinic staff) F: Same as E, plus bacterial STD in last 5 y G: Same as F, plus age ≥30 y	Fair
McGinn et al, 2008; United States (39)	Cross-sectional	1000	Urban primary care clinic Age: Mean, 50 y Female: 73% Nonwhite: 90%	A: Screen all B: Positive findings in ≥1 of 3 domains C: Positive findings in ≥2 domains D: Positive findings in 3 domains	Fair
Nguyen et al, 2005; United States (42)	Case–control	429 (225 HCV-positive, 204 HCV-negative)	Gastroenterology and primary care clinics Born 1940–1949: 20% Born 1950–1959: 38% Back 1960–1969: 18% Female: 58% Nonwhite: 37% Reports seeing use of injecting drugs: 34%	A: Screen all B: ≥1 risk factor, based on 7-item instrument (self-report history of sex with a prostitute, history of exposure to potentially infected blood during transfusion, rejection as a blood donor, refused life insurance, witnessing use of injection drugs, sexual intercourse with an injection drug user, self-report of HBV infection) C: ≥2 risk factors D: ≥3 risk factors E: ≥4 risk factors	Poor
Zuniga et al, 2006; United States (40)	Cross-sectional	2263	Urban primary care clinics Age 40–54 y: 31% White: 78% Female: 3.9% Vietnam-era veteran: 50% Blood transfusion before 1992: 17% Any injection drug use: 4.5% Abnormal liver function test results: 9.1%	A: Any of 11 risk factors (Vietnam-era veteran, multiple sexual contacts, tattoo or body piercing, intemperate alcohol use, blood transfusion before 1992, intranasal cocaine use, blood exposure [mucous membranes], abnormal liver enzyme levels, injection drug use [past or present], unexplained liver disease, hemodialysis) B: Any of 5 risk factors (Vietnam-era veteran, tattoo or body piercing, blood transfusion before 1992, abnormal liver enzyme levels, injection drug use) C: Self-reported injection drug use (past or present)	Fair
Zuure et al, 2010; the Netherlands (41)	Cross-sectional	985	STD clinics Population characteristics not reported	A: Screen all B: ≥1 risk factor, based on 20-item questionnaire*	Fair

HBV = hepatitis B virus; HCV = hepatitis C virus; STD = sexually transmitted disease.
* Injection drug use, born in HCV-endemic country, blood transfusion before 1992, HCV-infected mother, mother is/was injection drug user, living with HCV-infected individual, living with injection drug user, needle exposure to high-risk person, needle exposure in HCV-endemic country, patient with hemophilia, hemodialysis patient, organ recipient, received blood products in medium- or high-risk country, exposure of health care workers to blood or tissue in medium- or high-risk country, surgical or dental procedure in medium- or high-risk country, ritual intervention (circumcision, scarification) in medium- or high-risk country, tattoo in medium- or high-risk country, body piercing in medium- or high-risk country, HIV-positive status, noninjection drug use ≥3 times/wk for ≥3 mo.

questions. AHRQ staff had no role in study selection, quality assessment, synthesis, or development of conclusions. AHRQ staff provided project oversight, distributed the draft report for peer review, and reviewed the draft report and manuscript. The investigators are solely responsible for the content of the manuscript and the decision to submit for publication.

RESULTS

The **Appendix Figure** (available at www.annals.org) shows the results of the search and study selection process. No study compared clinical outcomes between individuals screened and not screened for HCV infection or between individuals screened by using different risk- or prevalence-based strategies.

Yield of Risk-Based Screening Methods

Four cross-sectional studies (samples sizes ranging from 985 to 3367) provided data to calculate the diagnostic accuracy and yield of alternative HCV screening criteria (**Table 1**) (38–41). Two studies evaluated patients attending sexually transmitted disease clinics (38, 41) and 2 evaluated patients attending urban primary care clinics (39, 40). Three studies evaluated higher-prevalence populations (HCV prevalence, 4.6% to 8.3%) (38–40) and 1 a lower-

Table 2. **Screening Strategies: Effects of Applying Alternative Screening Criteria on Proportion Screened, Sensitivity, Specificity, and Number Needed to Screen to Identify 1 Case of HCV Infection**

Study, Year; Country (Reference)	HCV Prevalence, % (*n*/*N*)	Screening Strategy	Proportion Screened, % (*n*/*N*)	Sensitivity, % (*n*/*N*)	Specificity, % (*n*/*N*)	Number Needed to Screen to Identify 1 Case of HCV Infection, *n* (*n*/*N*)*
Gunn et al, 2003; United States (38)	4.9 (165/3367)	A: Screened all B: Injection drug use (self-report) C: Injection drug use or blood transfusions (self-report) D: Injection drug use, blood transfusions, or sex partner was an injection drug user (self-report) E: Same as D (self-report or identified by clinic staff) F: Same as E, plus bacterial STD in last 5 y G: Same as F, plus age ≥30 y	A: 100 (3356/3356) B: 5.8 (193/3356) C: 7.5 (253/3356) D: 10 (347/3356) E: 12 (413/3356) F: 34 (1145/3356) G: 63 (2127/3356)	A: 100 (165/165) B: 60 (99/165) C: 64 (105/165) D: 67 (110/165) E: 70 (116/165) F: 81 (134/165) G: 97 (160/165)	A: 0 (0/3191) B: 97 (3097/3191) C: 95 (3043/3191) D: 93 (2954/3191) E: 91 (2894/3191) F: 68 (2180/3191) G: 38 (1224/3191)	A: 20 (3356/165) B: 1.9 (193/99) C: 2.4 (253/105) D: 3.2 (347/110) E: 3.6 (413/116) F: 8.5 (1145/134) G: 13 (2127/160)
McGinn, 2008; United States (39)	8.3 (83/1000)	A: Screen all B: Positive findings in ≥1 of 3 domains C: Positive findings in ≥2 domains D: Positive findings in 3 domains	A: 100 (1000/1000) B: 71 (709/1000) C: 23 (228/1000) D: 5.6 (56/1000)	A: 100 (83/83) B: 92 (76/83) C: 65 (54/83) D: 34 (28/83)	A: 0 (0/917) B: 31 (284/917) C: 81 (743/917) D: 97 (889/917)	A: 12 (1000/83) B: 9.3 (709/76) C: 4.2 (228/54) D: 2.0 (56/28)
Nguyen et al, 2005; United States (42)	Case–control design: 225 HCV-positive, 204 HCV-negative	A: Screen all B: ≥1 risk factor, based on 7-item instrument C: ≥2 risk factors D: ≥3 risk factors E: ≥4 risk factors	A: 100 (429/429) B: 78 (335/429) C: 48 (207/429) D: 28 (118/429) E: 13 (56/429)	A: 100 (225/225) B: 94 (212/225) C: 79 (178/225) D: 51 (115/225) E: 24 (55/225)	A: 0 (0/204) B: 35 (81/204) C: 86 (175/204) D: 99 (201/204) E: 100 (203/204)	Not applicable (case–control design)
Zuniga et al, 2006; United States (40)	4.6 (103/2263)	A: Any of 11 risk factors B: Any of 5 risk factors C: Self-reported injection drug use (past or present)	A: 100 (2263/2263) B: 78 (1776/2263) C: 3.0 (68/2263)*	A: 100 (103/103) B: 97 (100/103) C: 41 (42/103)	A: 0 (0/2160) B: 22 (484/2160) C: 99 (2134/2160)	A: 22 (2263/103) B: 18 (1776/100) C: 1.6 (68/42)
Zuure et al, 2010; the Netherlands (41)	1.0 (98/985)	A: Screen all B: ≥1 risk factor, based on 20-item questionnaire	A: 100 (985/985) B: 21 (207/985)	A: 100 (98/98) B: 90 (88/98)	A: 0 (0/887) B: 87 (768/887)	A: 10 (985/98) B: 2.4 (207/88)

HCV = hepatitis C virus; STD = sexually transmitted disease.
* Number of screening tests performed/number of HCV cases identified.

prevalence population (HCV prevalence, 1.0%) (41). One study of patients in primary care and gastroenterology clinics ($n = 429$) also evaluated alternative screening criteria but used a case–control design (42). All of the studies applied and evaluated alternative screening criteria retrospectively. Other limitations of the studies were that high proportions of potentially eligible patients were not included in analyses because of unknown HCV status or that the study did not report the proportion with unknown HCV status. Although the studies used different criteria for targeted screening, several factors (a personal history of injection drug use, sexual intercourse with an injection drug user, and pre-1992 blood transfusion) were consistently used across studies to identify higher-risk individuals.

One cross-sectional study of a lower-prevalence population in a Dutch sexually transmitted disease clinic ($n = 985$; HCV seroprevalence, 1%) found that screening based on presence of 1 or more positive items on a 20-item questionnaire was associated with a sensitivity of 90% for identifying persons with HCV infection and a number needed to screen to identify 1 case of HCV infection of 2.4 (**Table 2**) (41).

Three cross-sectional studies in higher-prevalence populations found that screening strategies targeting multiple risk factors were associated with sensitivities of more than 90% and numbers needed to screen of 9.3 to 18 (**Table 2**) (38–40). One cross-sectional study in a sexually transmitted disease clinic ($n = 3367$; HCV seroprevalence, 4.9%) found that screening patients with 1 of 5 risk factors (injection drug user, sex partners of injection drug user, received a pre-1992 blood transfusion, bacterial sexually transmitted disease in last 5 years, or age ≥30 years) would

have resulted in testing 63% of clinic attendees, with a sensitivity of 97% for identifying HCV infection and a number needed to screen of 13 (38). One study of patients in an inner-city primary care clinic ($n = 1000$; HCV seroprevalence, 8.3%) found that screening patients with positive findings in at least 1 of 3 domains (medical history, exposure history, or social history) would have resulted in screening 71% of the population, with a sensitivity of 92% and a number needed to screen of 9.3 (39). A study of U.S. veterans ($n = 2263$; HCV seroprevalence, 4.6%) found that screening patients according to presence of 1 or more of 5 risk factors (Vietnam-era veteran, tattoo/body piercing, blood transfusion before 1992, abnormal liver enzyme levels, past or present injection drug use) would have resulted in screening of 78% of the population compared with screening based on the presence of these or 6 additional risk factors (multiple sexual contacts, intemperate alcohol use, intranasal cocaine use, blood exposure [mucous membranes], unexplained liver disease, hemodialysis), with a sensitivity of 97% and number needed to screen of 18 (40).

More narrowly targeted screening strategies evaluated in these studies were associated with specificities of more than 95% and numbers needed to screen of less than 2, but missed up to two thirds of infected patients (38–40). Two studies found screening only injection drug users would have resulted in testing of 3.0% or 5.8% of the population, with sensitivities of 41% and 60%, and numbers needed to screen of 1.6 and 1.9, respectively (38, 40). One study found screening patients with positive findings in 3 domains (medical, exposure, or social history) would have resulted in testing of 5.6% of the population, with a sensitivity of 34% and number needed to screen of 2.0 (39).

A case–control study (222 cases) found screening based on presence of 4 or more of 7 risk factors (self-reported history of sex with a prostitute, history of exposure to potentially infected blood transfusion, rejections as a blood donor, refused life insurance, witnessed use of injecting drugs, sexual intercourse with an injection drug user, or self-reported hepatitis B virus infection) would have identified 24% of HCV-infected persons, with a specificity of nearly 100% (203 of 204) (42). Screening patients with 1 or more risk factors would have identified 94% of infected persons, with a specificity of 35%.

The 2004 USPSTF review (21) included a post hoc analysis of National Hepatitis Screening Survey data that found that screening using 1 of 3 risk factor models would have identified 53% to 69% of HCV-infected persons (43).

Potential Harms Associated With Screening

Three studies ($n = 15$ to 161) found diagnosis of HCV infection associated with some negative effects on psychological status, strain on spousal relationships, or binge drinking, but these studies had important shortcomings, including no control group of HCV-infected persons unaware of their status, reliance on retrospective recall, and poorly defined outcomes (44–46). A small, fair-quality cross-sectional study ($n = 34$) included in the 2004 USPSTF review found that HCV-infected intravenous drug users aware of their status reported worse quality of life than those who were unaware (47) of their status.

One study of percutaneous liver biopsies ($n = 2740$) in HCV-infected patients with compensated cirrhosis and at least moderate fibrosis reported a 1.1% rate of serious adverse events, most commonly bleeding or severe pain, with no deaths (48). Two other small studies ($n = 126$ and $n = 166$) included in the 2004 USPSTF review reported no episodes of bleeding, perforation, or death after percutaneous liver biopsy in HCV-infected persons (49, 50).

In patients undergoing liver biopsy for various indications, large series ($n = 1398$ to 61 184) published since 2004 reported periprocedural mortality rates of 0% to 0.2% and major complications (primarily bleeding) in 0.3% to 1.0% (51–55), consistent with studies included in the 2004 USPSTF review (56–62).

Discussion

The evidence reviewed in this report is summarized in **Table 3**. As in the 2004 USPSTF review (21), we found no direct evidence on effects of HCV screening versus no screening on clinical outcomes, or on the comparison of clinical effects of alternative screening strategies. Retrospective studies found that screening strategies targeting multiple risk factors were associated with sensitivities exceeding 90% and numbers needed to screen to identify 1 case of HCV infection of less than 20 (38–41). More narrowly targeted alternative screening strategies (such as screening only persons with a history of injection drug use) were associated with numbers needed to screen of less than 2, but they missed up to two thirds of infected patients.

Although direct harms of screening seem minimal, such harms as labeling, anxiety, and stigmatization remain poorly studied and difficult to quantify (63–65). Harms of biopsy include a risk for death of less than 0.2% and serious complications (primarily bleeding and severe pain) in about 1% (48, 51–55). As detailed in our full report, noninvasive tests have fair to good accuracy for diagnosing fibrosis and good to excellent accuracy for diagnosing cirrhosis compared with liver biopsy (26). Although clinical practice has evolved toward less routine use of liver biopsy before antiviral therapy and the proportion of HCV-infected patients undergoing liver biopsy has decreased overall, no study reported the proportion of screen-detected patients who undergo biopsy. Thus, it is difficult to determine the magnitude of harms associated with liver biopsy subsequent to screening.

In the absence of direct evidence on clinical outcomes associated with screening, an indirect chain of evidence showing the availability of accurate diagnostic tests and effective treatments could link screening with improve-

Table 3. **Summary of Evidence**

Strength of Evidence of Findings From 2012 AHRQ Report*	Studies Identified and Participants	Overall Quality	Consistency (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Summary of Findings
Does screening for HCV infection in nonpregnant adults without known abnormal liver enzymes reduce mortality and morbidity due to HCV, affect quality of life, or reduce transmission of HCV?						
No evidence	No studies	No studies	No studies	No studies	No studies	No study compared clinical outcomes between individuals screened and not screened for HCV infection.
What is the effectiveness of different risk- or prevalence-based methods for screening for HCV infection on clinical outcomes?						
No evidence	No studies	No studies	No studies	No studies	No studies	No study compared clinical outcomes associated with different risk- or prevalence-based strategies for targeted HCV screening.
What is the sensitivity and number needed to screen to identify 1 case of HCV infection of different risk- or prevalence-based methods for screening for HCV infection?						
Overall strength of evidence: low	5 studies (4 cross-sectional, 1 case–control) 8044 participants	Poor	High	Direct	High	Five studies found screening strategies that targeted multiple risk factors were associated with sensitivities of >90% and numbers needed to screen to identify 1 case of HCV infection of <20. More narrowly targeted screening strategies were associated with numbers needed to screen of <2, but with the tradeoff of missing up to two thirds of infected patients.
What are the harms associated with screening for HCV infection, including diagnostic liver biopsies?						
Screening: overall strength of evidence: low	Screening: 5 studies (1 cross-sectional, 3 intervention series, and 1 controlled trial) 288 participants	Screening: poor	Screening: unable to assess (assessed different outcomes)	Screening: direct	Screening: low	Screening: Five studies of patients with diagnosis of HCV infection suggested potential negative psychological and social effects, but results are difficult to interpret because of small sample sizes and methodological shortcomings, including no unscreened comparison group.
Liver biopsies: overall strength of evidence: moderate	Liver biopsies: 6 studies (intervention series) 88 587 participants	Liver biopsies: fair	Liver biopsies: moderate	Liver biopsies: direct	Liver biopsies: moderate	Liver biopsies: One study (n = 2740) of patients with chronic HCV infection and compensated cirrhosis reported serious adverse events in 1.1%, including 0.6% serious bleeding episodes and 0.3% severe pain, with no deaths. Five large (n = 1398–61 184) intervention series of percutaneous liver biopsy for a variety of conditions reported periprocedural mortality in <0.2% and serious complications in 0.3%–1.0%.

AHRQ = Agency for Healthcare Research and Quality; HCV = hepatitis C virus.
* Additional questions are addressed in the full report (26). Questions related to prenatal screening are addressed in a separate article (28).

ments in clinical outcomes. The 2004 USPSTF review found HCV antibody testing to be highly accurate (21). Much of the benefits from screening are likely to be based on the effectiveness of antiviral treatments, including newly approved direct-acting antiviral agents, which are addressed in a separate review (27). Therefore, screening recommendations should be based on the evidence for screening and treatment in totality (27). Studies showing that screening or subsequent interventions are associated with decreased transmission risk could also significantly affect estimates of potential benefits, but these are not yet available (26).

Our study has limitations. We excluded non–English-language articles, which could result in language bias, although we identified no non–English-language studies that would have met inclusion criteria. We could not formally assess for publication bias because of small numbers of studies. We also excluded modeling studies, which might be informative for understanding benefits and harms of screening, given the challenges in conducting the large, long-term studies needed to assess clinical outcomes associated with screening. Available evidence regarding screening yield is derived from a few retrospective studies. High or unreported proportions of potentially eligible patients in these observational studies were not included in calculations of screening yield because of unknown HCV status.

The CDC recently recommended that all persons born between 1945 and 1965 be screened for HCV infec-

tion, in addition to persons with risk factors for HCV infection (25). The CDC based its recommendation on the prevalence of patients with HCV infection in this birth cohort (accounting for about three quarters of patients with HCV infection in the United States), the high proportion of patients with undiagnosed HCV infection, projected disease burden after several decades of infection, and estimated benefits from antiviral treatments. Although cost-effectiveness analyses suggest that the birth cohort screening approach is highly cost-effective, no clinical data are yet available (13). The CDC's birth cohort approach was not evaluated in the studies included in our review on the yield of alternative screening strategies. Clinical studies that prospectively evaluate the accuracy, yield, and outcomes of alternative HCV screening strategies, including the birth cohort approach, are needed.

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References

1. **Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ.** The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med. 2006;144:705-14. [PMID: 16702586]

2. **National Center for HIV/AIDS, Viral Hepatitis, STD & TB Prevention.** Disease burden from viral hepatitis A, B, and C in the United States. Updated 13 September 2011 and 31 May 2012. Accessed at www.cdc.gov/hepatitis/pdfs/disease_burden.pdf on 30 August 2012.

3. **Ly KN, Xing J, Klevens RM, Jiles RB, Ward JW, Holmberg SD.** The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. Ann Intern Med. 2012;156:271-8. [PMID: 22351712]

4. **Busch MP.** Insights into the epidemiology, natural history and pathogenesis of hepatitis C virus infection from studies of infected donors and blood product recipients. Transfusion Clinique et Biologique. 2001;8:200-6. [PMID: 11499958]

5. **Kim WR.** The burden of hepatitis C in the United States. Hepatology. 2002; 36:S30-4. [PMID: 12407574]

6. **El-Serag HB.** Hepatocellular carcinoma: recent trends in the United States. Gastroenterology. 2004;127:S27-34. [PMID: 15508094]

7. **Alter H.** Discovery of non-A, non-B hepatitis and identification of its etiology. Am J Med. 1999;107:16S-20S. [PMID: 10653450]

8. **Kaur S, Rybicki L, Bacon BR, Gollan JL, Rustgi VK, Carey WD.** Performance characteristics and results of a large-scale screening program for viral hepatitis and risk factors associated with exposure to viral hepatitis B and C: results of the National Hepatitis Screening Survey. National Hepatitis Surveillance Group. Hepatology. 1996;24:979-86. [PMID: 8903363]

9. **Yawn BP, Gazzuola L, Wollan PC, Kim WR.** Development and maintenance of a community-based hepatitis C registry. Am J Manag Care. 2002;8:253-61. [PMID: 11915975]

10. **Austin GE, Jensen B, Leete J, De L'Aune W, Bhatnagar J, Racine M, et al.** Prevalence of hepatitis C virus seropositivity among hospitalized US veterans. Am J Med Sci. 2000;319:353-9. [PMID: 10875289]

11. **Cheung RC.** Epidemiology of hepatitis C virus infection in American veterans. Am J Gastroenterol. 2000;95:740-7. [PMID: 10710068]

12. **Garfein RS, Vlahov D, Galai N, Doherty MC, Nelson KE.** Viral infections in short-term injection drug users: the prevalence of the hepatitis C, hepatitis B, human immunodeficiency, and human T-lymphotropic viruses. Am J Public Health. 1996;86:655-61. [PMID: 8629715]

13. **Rein DB, Smith BD, Wittenborn JS, Lesesne SB, Wagner LD, Roblin DW, et al.** The cost-effectiveness of birth-cohort screening for hepatitis C antibody in U.S. primary care settings. Ann Intern Med. 2012;156:263-70. [PMID: 22056542]

14. **Bellentani S, Pozzato G, Saccoccio G, Crovatto M, Crocè LS, Mazzoran L, et al.** Clinical course and risk factors of hepatitis C virus related liver disease in the general population: report from the Dionysos study. Gut. 1999;44:874-80. [PMID: 10323892]

15. **Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ.** The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study. N Engl J Med. 1996;334:1685-90. [PMID: 8637512]

16. **Thein HH, Yi Q, Dore GJ, Krahn MD.** Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008;48:418-31. [PMID: 18563841]

17. **Freeman AJ, Dore GJ, Law MG, Thorpe M, Von Overbeck J, Lloyd AR, et al.** Estimating progression to cirrhosis in chronic hepatitis C virus infection. Hepatology. 2001;34:809-16. [PMID: 11584380]

18. **Wiese M, Grüngreiff K, Güthoff W, Lafrenz M, Oesen U, Porst H; East German Hepatitis C Study Group.** Outcome in a hepatitis C (genotype 1b) single source outbreak in Germany—a 25-year multicenter study. J Hepatol. 2005;43:590-8. [PMID: 16237783]

19. **Hagan H, Campbell J, Thiede H, Strathdee S, Ouellet L, Kapadia F, et al.** Self-reported hepatitis C virus antibody status and risk behavior in young injectors. Public Health Rep. 2006;121:710-9. [PMID: 17278406]

20. **U.S. Preventive Services Task Force.** Screening for hepatitis C virus infection in adults: recommendation statement. Ann Intern Med. 2004;140:462-4. [PMID: 15023712]

21. **Chou R, Clark EC, Helfand M; U.S. Preventive Services Task Force.** Screening for hepatitis C virus infection: a review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2004;140:465-79. [PMID: 15023713]

22. **Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases.** Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009;49:1335-74. [PMID: 19330875]

23. **Dienstag JL, McHutchison JG.** American Gastroenterological Association medical position statement on the management of hepatitis C. Gastroenterology. 2006;130:225-30. [PMID: 16401485]

24. Hepatitis C virus infection. American Academy of Pediatrics. Committee on Infectious Diseases. Pediatrics. 1998;101:481-5. [PMID: 9499195]

25. **Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Ward JW.** Hepatitis C virus testing of persons born during 1945–1965: recommenda-

tions from the Centers for Disease Control and Prevention. Ann Intern Med. 2012;157:817-22. [PMID: 22910836]
26. **Chou R, Cottrell EB, Wasson N, Rahman B, Guise JM.** Screening for Hepatitis C Virus Infection in Adults: A Comparative Effectiveness Review (Prepared by Oregon Evidence-based Practice Center under contract no. 290-2007-10057-I.) 2012. Accessed at www.effectivehealthcare.ahrq.gov on 28 November 2012.
27. **Chou R, Hartung D, Rahman B, Wasson N, Cottrell EB, Fu R.** Comparative effectiveness of antiviral treatment for hepatitis C virus infection in adults: a systematic review. Ann Intern Med. 2013;158:114-23.
28. **Cottrell EB, Chou R, Wasson N, Rahman B, Guise JM.** Reducing risk for mother-to-infant transmission of hepatitis C virus: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2013;158:109-13.
29. **Furusyo N, Hayashi J, Kanamoto-Tanaka Y, Ariyama I, Etoh Y, Shigematsu M, et al.** Liver damage in hemodialysis patients with hepatitis C virus viremia: a prospective 10-year study. Dig Dis Sci. 2000;45:2221-8. [PMID: 11215743]
30. **Kliem V, van den Hoff U, Brunkhorst R, Tillmann HL, Flik J, Manns MP, et al.** The long-term course of hepatitis C after kidney transplantation. Transplantation. 1996;62:1417-21. [PMID: 8958266]
31. **Rostaing L, Rumeau JL, Cisterne JM, Izopet J, Chabannier MH, Durand D.** Liver histology in renal transplant patients after more than 10 years of hepatitis C virus infection. Transplant Proc. 1996;28:2836-7. [PMID: 8908089]
32. **Soto B, Sánchez-Quijano A, Rodrigo L, del Olmo JA, García-Bengoechea M, Hernández-Quero J, et al.** Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. J Hepatol. 1997; 26:1-5. [PMID: 9147999]
33. **Sánchez-Quijano A, Andreu J, Gavilán F, Luque F, Abad MA, Soto B, et al.** Influence of human immunodeficiency virus type 1 infection on the natural course of chronic parenterally acquired hepatitis C. Eur J Clin Microbiol Infect Dis. 1995;14:949-53. [PMID: 8654444]
34. **Downs SH, Black N.** The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;52:377-84. [PMID: 9764259]
35. **Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al; Methods Work Group, Third US Preventive Services Task Force.** Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20:21-35. [PMID: 11306229]
36. **Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al; QUADAS-2 Group.** QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155:529-36. [PMID: 22007046]
37. **Agency for Healthcare Research and Quality.** Methods guide for effectiveness and comparative effectiveness reviews. AHRQ publication no. 10(12)-EHC063-EF. April 2012. Accessed at www.effectivehealthcare.ahrq.gov/ehc/products/60/318/MethodsGuide_Prepublication-Draft_20120523.pdf on 19 June 2012.
38. **Gunn RA, Murray PJ, Brennan CH, Callahan DB, Alter MJ, Margolis HS.** Evaluation of screening criteria to identify persons with hepatitis C virus infection among sexually transmitted disease clinic clients: results from the San Diego Viral Hepatitis Integration Project. Sex Transm Dis. 2003;30:340-4. [PMID: 12671556]
39. **McGinn T, O'Connor-Moore N, Alfandre D, Gardenier D, Wisnivesky J.** Validation of a hepatitis C screening tool in primary care. Arch Intern Med. 2008;168:2009-13. [PMID: 18852403]
40. **Zuniga IA, Chen JJ, Lane DS, Allmer J, Jimenez-Lucho VE.** Analysis of a hepatitis C screening programme for US veterans. Epidemiol Infect. 2006;134: 249-57. [PMID: 16490127]
41. **Zuure F, Davidovich U, Kok G, Depla AC, Hoebe C, van den Hoek A, et al.** Evaluation of a risk assessment questionnaire to assist hepatitis C screening in the general population. Euro Surveill. 2010;15:19539. [PMID: 20429995]
42. **Nguyen MT, Herrine SK, Laine CA, Ruth K, Weinberg DS.** Description of a new hepatitis C risk assessment tool. Arch Intern Med. 2005;165:2013-8. [PMID: 16186472]
43. **Lapane KL, Jakiche AF, Sugano D, Weng CS, Carey WD.** Hepatitis C infection risk analysis: who should be screened? Comparison of multiple screening strategies based on the National Hepatitis Surveillance Program. Am J Gastroenterol. 1998;93:591-6. [PMID: 9576453]
44. **Anderson EM, Mandeville RP, Hutchinson SJ, Cameron SO, Mills PR, Fox R, et al.** Evaluation of a general practice based hepatitis C virus screening intervention. Scott Med J. 2009;54:3-7. [PMID: 19728405]
45. **Fabris P, Tositti G, Giordani MT, Baldo V, Grasso A, Pignattari E, et al.** Assessing patients' understanding of hepatitis C virus infection and its impact on their lifestyle. Aliment Pharmacol Ther. 2006;23:1161-70. [PMID: 16611277]
46. **Trepka MJ, Zhang G, Leguen F, Obiaja K, Malow RM, De La Rosa M.** Benefits and adverse effects of hepatitis C screening: early results of a screening program. J Public Health Manag Pract. 2007;13:263-9. [PMID: 17435493]
47. **Rodger AJ, Jolley D, Thompson SC, Lanigan A, Crofts N.** The impact of diagnosis of hepatitis C virus on quality of life. Hepatology. 1999;30:1299-301. [PMID: 10534353]
48. **Seeff LB, Everson GT, Morgan TR, Curto TM, Lee WM, Ghany MG, et al; HALT–C Trial Group.** Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. Clin Gastroenterol Hepatol. 2010;8:877-83. [PMID: 20362695]
49. **Saadeh S, Cammell G, Carey WD, Younossi Z, Barnes D, Easley K.** The role of liver biopsy in chronic hepatitis C. Hepatology. 2001;33:196-200. [PMID: 11124836]
50. **Farrell RJ, Smiddy PF, Pilkington RM, Tobin AA, Mooney EE, Temperley IJ, et al.** Guided versus blind liver biopsy for chronic hepatitis C: clinical benefits and costs. J Hepatol. 1999;30:580-7. [PMID: 10207798]
51. **Atwell TD, Smith RL, Hesley GK, Callstrom MR, Schleck CD, Harmsen WS, et al.** Incidence of bleeding after 15,181 percutaneous biopsies and the role of aspirin. AJR Am J Roentgenol. 2010;194:784-9. [PMID: 20173160]
52. **Huang JF, Hsieh MY, Dai CY, Hou NJ, Lee LP, Lin ZY, et al.** The incidence and risks of liver biopsy in non-cirrhotic patients: An evaluation of 3806 biopsies [Letter]. Gut. 2007;56:736-7. [PMID: 17440193]
53. **Myers RP, Fong A, Shaheen AA.** Utilization rates, complications and costs of percutaneous liver biopsy: a population-based study including 4275 biopsies. Liver Int. 2008;28:705-12. [PMID: 18433397]
54. **van der Poorten D, Kwok A, Lam T, Ridley L, Jones DB, Ngu MC, et al.** Twenty-year audit of percutaneous liver biopsy in a major Australian teaching hospital. Intern Med J. 2006;36:692-9. [PMID: 17040353]
55. **West J, Card TR.** Reduced mortality rates following elective percutaneous liver biopsies. Gastroenterology. 2010;139:1230-7. [PMID: 20547160]
56. **Cadranel JF, Rufat P, Degos F.** Practices of liver biopsy in France: results of a prospective nationwide survey. For the Group of Epidemiology of the French Association for the Study of the Liver (AFEF). Hepatology. 2000;32:477-81. [PMID: 10960438]
57. **Froehlich F, Lamy O, Fried M, Gonvers JJ.** Practice and complications of liver biopsy. Results of a nationwide survey in Switzerland. Dig Dis Sci. 1993; 38:1480-4. [PMID: 8344104]
58. **Garcia-Tsao G, Boyer JL.** Outpatient liver biopsy: how safe is it? [Editorial]. Ann Intern Med. 1993;118:150-3. [PMID: 8416312]
59. **Gilmore IT, Burroughs A, Murray-Lyon IM, Williams R, Jenkins D, Hopkins A.** Indications, methods, and outcomes of percutaneous liver biopsy in England and Wales: an audit by the British Society of Gastroenterology and the Royal College of Physicians of London. Gut. 1995;36:437-41. [PMID: 7698705]
60. **Janes CH, Lindor KD.** Outcome of patients hospitalized for complications after outpatient liver biopsy. Ann Intern Med. 1993;118:96-8. [PMID: 8416324]
61. **McGill DB, Rakela J, Zinsmeister AR, Ott BJ.** A 21-year experience with major hemorrhage after percutaneous liver biopsy. Gastroenterology. 1990;99: 1396-400. [PMID: 2101588]
62. **Vautier G, Scott B, Jenkins D.** Liver biopsy: blind or guided? [Editorial]. BMJ. 1994;309:1455-6. [PMID: 7804036]
63. **Stewart BJ, Mikocka-Walus AA, Harley H, Andrews JM.** Help-seeking and coping with the psychosocial burden of chronic hepatitis C: a qualitative study of patient, hepatologist, and counsellor perspectives. Int J Nurs Stud. 2012;49: 560-9. [PMID: 22154094]
64. **Zickmund S, Ho EY, Masuda M, Ippolito L, LaBrecque DR.** "They treated me like a leper". Stigmatization and the quality of life of patients with hepatitis C. J Gen Intern Med. 2003;18:835-44. [PMID: 14521647]
65. **Conrad S, Garrett LE, Cooksley WG, Dunne MP, MacDonald GA.** Living with chronic hepatitis C means 'you just haven't got a normal life any more'. Chronic Illn. 2006;2:121-31. [PMID: 17175655]

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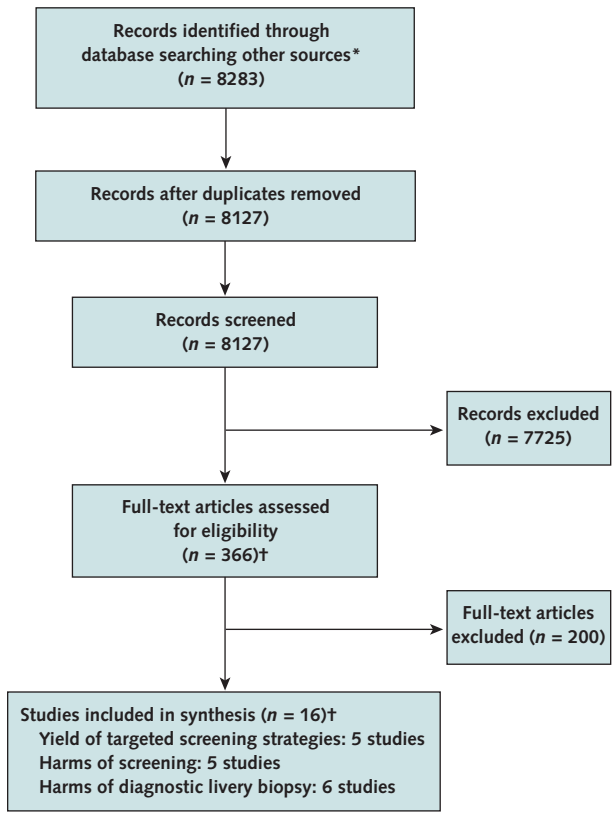
Appendix Figure. **Summary of evidence search and selection.**



The flow diagram summarizes the search and selection of articles addressing the following key questions: 1. Does screening for hepatitis C virus (HCV) infection in nonpregnant adults without known abnormal liver enzymes reduce mortality and morbidity due to HCV, affect quality of life, or reduce transmission of HCV? 2. What is the effectiveness of different risk- or prevalence-based methods for screening for HCV infection on clinical outcomes? 3. What is the sensitivity and number needed to screen to identify 1 case of HCV infection of different risk- or prevalence-based methods for screening for HCV infection? 4. What are the harms associated with screening for HCV infection, including diagnostic liver biopsies? Reproduced from reference 26.
* Includes hand searches and gray literature searches.
† The total number of studies included in the full report, which addresses additional key questions, is 166.