

# Screening for Hepatitis C Virus Infection: A Review of the Evidence for the U.S. Preventive Services Task Force

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**Background:** Hepatitis C virus (HCV) is the most common bloodborne pathogen in the United States and is an important cause of patient morbidity and mortality, but it is unclear whether screening to identify asymptomatic infected persons is appropriate.

**Purpose:** To synthesize the evidence on risks and benefits of screening for HCV infection.

**Data Sources:** MEDLINE (through February 2003), Cochrane Clinical Trials Registry (2002, Issue 2), reference lists, and experts.

**Study Selection:** Controlled studies of screening and antiviral therapy and observational studies on other interventions, risk factors, accuracy of antibody testing, work-up, harms of biopsy, and long-term outcomes.

**Data Extraction:** Using preset criteria, the authors assessed the quality of included studies and abstracted information about settings, patients, interventions, and outcomes.

**Data Synthesis:** There are no published trials of screening for HCV infection. Approximately 2% of U.S. adults have HCV anti-

bodies, with the majority having chronic infection. Risk factor assessment could identify adults at substantially higher risk. Antiviral treatment can result in a sustained virologic response rate of 54% to 56%, but no trials have been done specifically in asymptomatic patients likely to be identified by screening. Data are insufficient to determine whether treatment improves long-term outcomes. There are no data to estimate the benefit from counseling or immunizations. Although risks of biopsy and treatment appear minimal or self-limited, data on other adverse effects of screening, such as labeling or anxiety, are sparse.

**Conclusions:** Antiviral treatment can successfully eradicate HCV, but data on long-term outcomes in populations likely to be identified by screening are lacking. Although the yield from targeted screening, particularly in intravenous drug users, would be substantially higher than in the general population, data are inadequate to accurately weigh the overall benefits and risks of screening in otherwise healthy asymptomatic adults.

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**H**epatitis C virus (HCV), the most common chronic bloodborne pathogen in the United States, is acquired primarily by large or repeated percutaneous exposures to blood (1). In the United States, approximately 2.3% of adults 20 years of age or older are positive for anti-HCV antibody. Between 55% and 84% of these have chronic infection (1–6), but only 5% to 50% of infected adults are thought to know their status (7–9).

In the United States, HCV is associated with approximately 40% of cases of chronic liver disease and 8000 to 10 000 deaths each year (1). Chronic HCV infection can also cause fatigue and decreased quality of life in the absence of cirrhosis or other complications (5, 10, 11).

The natural course of chronic HCV infection varies. Some patients never develop histologic evidence of liver disease even after decades of infection (12, 13). In a meta-analysis of community-based cohort studies, 7% of patients with chronic HCV infection developed cirrhosis after 20 years (14). Factors that may be associated with a more progressive course include older age at acquisition (14, 15); comorbid medical conditions, such as heavy alcohol use (14, 16–21), HIV infection (22–24), and other chronic liver disease (25–27); male gender (14); and longer duration of infection. Mode of acquisition, viral load, aminotransferase levels, and viral genotype have not been consistently established as predictors of disease progression (28–31). The effects of ethnicity on the course of HCV infection have not been well studied in the United States (32).

In this systematic review, commissioned by the U.S. Preventive Services Task Force (USPSTF), we focus on whether it is useful to test for anti-HCV antibodies in asymptomatic adults who have no history of liver disease.

## METHODS

The analytic framework, definitions used, key questions, literature search, and data extraction methods are described in detail in the Appendix (available at [www.annals.org](http://www.annals.org)). Briefly, relevant studies were identified from searches of MEDLINE (1989 through February 2003) and the Cochrane Clinical Trials Registry (2002, Issue 2) and from the reference list of a recent evidence report commissioned by the National Institutes of Health (33). Reference lists of retrieved articles, periodic hand searches of relevant journals, and suggestions from experts supplemented the electronic searches.

Two readers reviewed all English-language abstracts. We selected studies that provided direct evidence on the benefits of screening and studies on risk factors for HCV infection and the performance of third-generation HCV enzyme-linked immunoassay (ELISA) alone or followed by confirmatory recombinant immunoblot assay (RIBA). We focused on third-generation ELISAs because they are thought to be slightly more sensitive than second-generation tests but included data on second-generation ELISAs from large, good-quality observational studies (34). We also selected studies evaluating noninvasive methods to

evaluate active HCV infection and the harms associated with biopsy. For treatment, we focused on trials of pegylated interferon with ribavirin but included studies that examined the effect of other interferon-based treatment regimens on long-term clinical outcomes. We also reviewed studies evaluating effects of counseling on high-risk behaviors and benefits of immunizations. Good-quality meta-analyses were reviewed when available. We excluded studies of pregnant patients; children; and patients with occupational exposures, end-stage renal disease, or HIV infection, as well as studies focusing on patients who had already developed complications of chronic HCV infection.

We used predefined criteria developed by the USPSTF, described in detail elsewhere (35), to assess the internal validity of included studies, which we rated as “good,” “fair,” or “poor.” We also rated the applicability of each study to the population likely to be identified by screening. We rated the overall body of evidence for each key question using the system developed by the USPSTF (35).

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## DATA SYNTHESIS

### Studies of Screening

We identified no randomized trials or longitudinal cohort studies comparing outcomes between patients in the general adult population who were screened and not screened for HCV infection.

### Risk Factor Assessment

The identification of risk factors for the presence of HCV infection could aid in the development of selective screening strategies (8). We identified 4 large population-based studies from the United States and Europe that evaluated rates of HCV infection and risk factors associated with HCV status (2, 3, 37, 38). Among these, the National Health and Nutrition Examination Survey III (NHANES III), a good-quality nationwide sample of U.S. households that was conducted from 1988 to 1994 and had 21 241 participants, found that the prevalence of positivity for anti-HCV antibodies was 1.8% overall and 2.3% in adults older than 20 years of age (3). Although NHANES III provides the most reliable estimate of prevalence of HCV infection in U.S. households, it probably underestimates the overall prevalence of the disease because it excluded

persons without addresses, institutionalized persons, and those in military service.

Independent risk factors for HCV infection found in the 4 large population-based studies are shown in **Table 1** (2, 3, 37, 38). Intravenous drug use was the strongest independent risk factor in 3 of these studies (adjusted odds ratios, 18.4 to 29.2). The fourth study, NHANES III, did not assess intravenous drug use. However, it found that cocaine and marijuana use were associated with HCV infection, perhaps because they are surrogate markers for intravenous drug use (**Table 1**) (3). Many other smaller, cross-sectional studies in a variety of specific populations support the strong association between HCV infection and intravenous drug use (39–51). Cross-sectional studies in intravenous drug users have reported prevalence rates ranging from 50% to more than 90% (52–56).

All 4 large population-based studies also found an independent association between HCV infection and high-risk sexual behaviors (variably defined, but usually considered sex with multiple partners or sex with an HCV-infected person). In most settings with a low prevalence of intravenous drug use, high-risk sexual behaviors are the strongest risk factor for HCV infection (56–60). It is not clear whether this association is due to a high rate of sexual transmission in specific situations (61–66) or because high-risk sexual behaviors are a marker for unacknowledged drug use.

Since 1992, transfusions have not been an important mode of HCV transmission (56, 67, 68). There is insufficient evidence to determine the importance of tattoos, body piercings, shared razors, and acupuncture as risk factors (2, 67, 69–75). Nonpercutaneous risk factors such as gender, ethnicity, and socioeconomic status have inconsistent or weak associations with the prevalence of HCV infection (3, 38, 76).

In large U.S. cross-sectional studies, between 33% and 81% of patients with HCV infection reported intravenous drug use (38–40, 77). Other retrospective studies have found that 53% to 88% of infected patients had identifiable risk factors (78, 79). Sample differences, varying stringency of risk factor ascertainment, or variation in the risk factors examined could explain some of the discrepancies between studies (79). No study has prospectively applied a selective screening strategy and determined how many patients were correctly identified by it.

### Accuracy of HCV Antibody Testing

The terminology and interpretation of tests used to diagnose HCV infection are reviewed in the Appendix (available at [www.annals.org](http://www.annals.org)). A recent fair-quality systematic review of third-generation ELISA (7 studies) and RIBA (3 studies) found that only 10 of 150 studies used appropriate methods for evaluating a diagnostic test (80). We applied the USPSTF quality criteria to 9 of these 10 studies and found that all 9 had at least one important flaw: inclusion of a narrow patient spectrum, failure to perform

**Table 1. Data from Large Observational Studies on Independent Risk Factors for Positive Status on Tests for Anti-Hepatitis C Virus Antibody\***

| Study (Reference)   | Setting   | Sample Size, n | Prevalence of Anti-HCV Antibodies, %    | Risk Factors Evaluated  | Adjusted Odds Ratio for Independent Risk Factors for Positive HCV Antibody Status (95% CI)   |
|---|---|----------------|---|---|--|
| Alter et al. (National Health and Nutrition Examination Survey III) (3) | Population-based household sample in the United States            | 21 241         | 1.80 overall; 2.3 in adults $\geq 20$ y | Race or ethnicity<br>Sex<br>Marital status<br>Poverty index<br>Education<br>Urban residence<br>Region of residence<br>Military service status<br>Country of birth<br>Health care worker<br>Cocaine use<br>Marijuana use<br>Age at first sexual intercourse<br>Number of lifetime sexual partners<br>Herpes simplex virus 2 infection  | Marital status<br>Divorced or separated: 1.70 (1.08–2.66)<br>Never married, married, or widowed: 1.00<br>Education<br>$\leq 12$ y: 1.92 (1.01–3.67)<br>$> 12$ y: 1.00<br>Poverty index<br>Below poverty level: 2.99 (1.69–5.27)<br>At or above poverty level: 1.00<br>Marijuana use<br>$\geq 100$ times: 2.99 (1.69–5.27)<br>1–99 times: 1.15 (0.61–2.16)<br>Never: 1.00<br>Cocaine use<br>Ever: 4.70 (2.49–8.87)<br>Never: 1.00<br>Number of sexual partners<br>$> 50$ : 5.16 (1.80–14.73)<br>2–49: 2.54 (1.14–5.66)<br>0–1: 1.00<br>Age at first sexual intercourse<br>$< 18$ y: 2.94 (1.50–5.78)<br>$\geq 18$ y: 1.00 |
| Kaur et al. (National Hepatitis Screening Survey) (38)                  | Screening program at 40 mostly urban centers in the United States | 13 997         | 7                                       | Age<br>Sex<br>Ethnicity<br>Occupation<br>Blood transfusion<br>Hemodialysis<br>Surgery<br>Intravenous drug use<br>Sex with intravenous drug user<br>Sex with multiple partners<br>Needlestick injury<br>Born in southeast Asia or Africa<br>Vaccinated for hepatitis B virus   | Sex<br>Male: 3.60 (2.66–4.87)<br>Female: 1.00<br>Ethnicity<br>White or Hispanic: 0.57 (0.39–0.83)<br>Other: 1.00<br>Blood transfusion<br>Yes: 4.09 (2.97–5.62)<br>No: 1.00<br>Hemodialysis<br>Yes: 10.95 (3.85–31.13)<br>No: 1.00<br>Intravenous drug use<br>Yes: 23.34 (15.21–35.81)<br>No: 1.00<br>Sex with intravenous drug user<br>Yes: 7.29 (4.74–11.21)<br>No: 1.00<br>Vaccination for hepatitis B virus<br>Yes: 0.37 (0.22–0.62)<br>No: 1.00  |
| Bellentani et al. (Dionysos Study) (37)                                 | Population-based study in Northern Italy                          | 6917           | 3.2                                     | Male sex<br>Alcohol intake $> 30$ g/d<br>Hepatitis among cohabitating persons<br>Surgical procedure<br>Dental procedures<br>Intravenous drug use<br>Acupuncture<br>Blood transfusion<br>Animal bites<br>Homosexuality   | Hepatitis among cohabitating persons<br>Yes: 2.0 (1.4–2.8)<br>No: 1.00<br>Intravenous drug use<br>Yes: 18.4 (5.3–64.0)<br>No: 1.00<br>Animal bites<br>Yes: 1.6 (1.0–2.5)<br>No: 1.00<br>Blood transfusion<br>Yes: 2.2 (1.4–3.4)<br>No: 1.00  |
| Dubois et al. (2)   | Population-based study throughout France                          | 6283           | 1.2                                     | Past or present intravenous drug abuse<br>Unemployment<br>Tattoos<br>History of transfusions<br>Travel in developing countries<br>Voluntary abortion<br>Sexually transmitted disease<br>Casual sex partners<br>Sexual contact with intravenous drug users<br>Surgery with major blood loss<br>Acupuncture<br>Injection with reusable glass syringe<br>Dental surgery<br>Sexual contact with HCV-positive partner<br>Homosexual practices<br>Education level | Intravenous drug use<br>Yes: 29.2 (3.8–225.7)<br>No: 1.00<br>History of transfusion<br>Yes: 7.0 (1.7–15.1)<br>No: 1.00<br>Unemployment<br>Yes: 3.1 (1.2–8.1)<br>No: 1.00   |

\* HCV = hepatitis C virus.

a reference standard test in all samples, or lack of clarity about whether the reference standard test was interpreted independently of the screening test (81–86). The tenth

study, a study of RIBA in 51 patients receiving hemodialysis, was not referenced in the systematic review and we could not find it.

**Table 2. Additional Studies on the Diagnostic Accuracy of Third-Generation Enzyme-Linked Immunosorbent Assays for Anti-Hepatitis C Virus Antibodies\***

| Study, Year (Reference)  | Patients Studied  | Reference Assay               | Prevalence of Positive Results on Anti-HCV ELISA | Sensitivity      | Specificity    | Positive Predictive Value | Quality Rating  |
|--------------------------|---|-------------------------------|--|------------------|----------------|---------------------------|---|
|                          |   |                               | % (n/n)  | ← % →            |                |                           |   |
| Huber et al., 1996 (87)  | Patients admitted because of acute liver disease or suspected chronic hepatitis | PCR                           | 10 (107/1090)                                    | 94 (107/114)     | 97 (946/976)   | 78 (107/137)              | Good  |
| Prince et al., 1997 (89) | Blood donors with elevated alanine aminotransferase levels                      | PCR                           | 18 (54/301)                                      | 100 (51/51)      | 98.8 (247/250) | 94 (51/54)                | Fair; narrow patient spectrum   |
| Busch et al., 2000 (88)  | Blood donors with positive results on a screening test who were retested        | Second-generation RIBA or PCR | 100 (1091/1091)                                  | 99.2 (1082/1091) | Not calculable | Not calculable            | Fair; performance of reference assays not standardized, narrow patient spectrum |

\* ELISA = enzyme-linked immunosorbent assay; HCV = hepatitis C virus; PCR = polymerase chain reaction; RIBA = recombinant immunoblot assay.

Of 7 studies that evaluated the sensitivity of third-generation ELISA and involved 4674 patients, sensitivity ranged from 97.2% to 100% compared with the results of polymerase chain reaction (PCR) (a reference standard for active infection) or RIBA (a reference standard for exposure). We identified 3 additional studies of the sensitivity of third-generation ELISA using PCR as the reference standard (Table 2) (87–89). One of these was a good-quality study that found a sensitivity of 94% (107 of 114) (87). The specificity was 97% (946 of 976), and the positive predictive value (prevalence, 10%) was 78% (107 of 137). Second-generation ELISAs are thought to be slightly less sensitive than third-generation tests but may be more specific (34). In data collected by the Centers for Disease Control and Prevention in 24 012 lower-prevalence (2%) patients, the positive predictive value of current second- and third-generation ELISAs without confirmatory RIBA was 42%, using PCR as the reference standard (90).

To minimize false-positive results in low-prevalence populations, positive results on ELISA are usually followed by confirmatory RIBA tests (90). Patients with positive results on both tests are considered to have confirmed evidence of HCV exposure, although they may not have active infection. In 4 large population-based studies (prevalence, 1.2% to 3.2%), the proportion of patients with positive results on ELISA confirmed by RIBA who were found to have viremia was 73% to 86%, using second- or third-generation ELISAs (2, 3, 37, 91).

**Harms from HCV Antibody Testing**

False-positive results on screening tests could cause harms that are difficult to measure (for example, labeling, anxiety, and detrimental effects on close relationships). There are few data regarding harms in patients who have false-positive test results or HCV-positive patients who do not receive treatment, although one fair-quality observational study suggests worse quality of life in patients who

are aware of their status (92). We found no studies investigating whether harms associated with knowledge of HCV status could be reduced by effective patient education and counseling. However, data from one small trial in 34 patients found that a counseling program improved sense of well-being in women with HCV infection (93).

**Work-Up for Treatable Disease**

In addition to viral load and aminotransferase testing, the National Institutes of Health currently recommends pretreatment liver biopsy (67). Several blood tests have been proposed as noninvasive methods of predicting biopsy findings, but in a recent good-quality systematic review, no blood test predicted liver biopsy findings accurately, particularly for intermediate stages of fibrosis (94).

**Proportion of Patients Qualifying for Treatment**

In clinical practice, the number of referred patients who receive antiviral treatment depends on the degree of liver damage, the presence of serious comorbid conditions, and patient preferences regarding treatment. Antiviral therapy is recommended for patients with chronic HCV infection who are at the greatest risk for progression to cirrhosis. These persons have HCV viremia, persistently elevated aminotransferase levels, or liver biopsy findings showing significant fibrosis or inflammation and necrosis (1, 67, 95–98). In patients with minimal or no biopsy abnormalities, the benefits of treatment are not clear, and decisions about therapy are individualized (67, 69, 98, 99). Many patients identified by screening are likely to be in this category. In 3 community-based cohort studies, the rate of chronic hepatitis of minimal grade or with no inflammation was 43% to 61% (4–6). Patients with cirrhosis or serious comorbid medical or psychiatric conditions also must have the risks and benefits of antiviral treatment carefully weighed.

We identified 3 fair-quality observational studies in

Table 3. Randomized, Controlled Trials of Pegylated Interferon plus Ribavirin in Patients with Hepatitis C Virus Infection\*

| Study, Year (Reference)  | Patients Enrolled/Analyzed, n/n | Interventions   | Sustained Viral Response 6 Months after Therapy, % | Adverse Events   | Internal Validity Rating  | Relevance to Screening   |
|--------------------------|---------------------------------|---|--|--|---|--|
| Fried et al., 2002 (122) | 1149/1121                       | 1) INF- $\alpha$ 2b, 3 MU 3 times per wk, + ribavirin, 1000–1200 mg/d<br>2) Pegylated INF- $\alpha$ 2a, 180 $\mu$ g/kg of body weight once weekly<br>3) Pegylated INF- $\alpha$ 2a, 180 $\mu$ g/kg once weekly, + ribavirin, 1000–1200 mg/d   | 44<br>29<br>56†                                    | For 1 vs. 2 vs. 3<br>Dose reduction: not clear<br>Discontinuation: 32% vs. 32% vs. 22%<br>Fatigue: 55% vs. 44% vs. 54%<br>Headache: 52% vs. 51% vs. 47%<br>Fever: 56% vs. 38% vs. 43%<br>Myalgia: 50% vs. 42% vs. 42%<br>Nausea: 33% vs. 26% vs. 29%<br>Depression: 30% vs. 20% vs. 22%<br>Dermatitis: 22% vs. 11% vs. 21%<br>Deaths: 3, none thought to be related to treatment | Good  | Fair; required liver biopsy findings consistent with chronic hepatitis and elevated ALT level within the past 6 months |
| Manns et al., 2001 (123) | 1530/1530                       | 1) INF- $\alpha$ 2b, 1.5 $\mu$ g/kg 3 times per wk, + ribavirin, 1000–1200 mg/d<br>2) Pegylated INF- $\alpha$ 2b, 1.5 $\mu$ g/kg once weekly for 4 wk, then 0.5 $\mu$ g/kg for 44 wk, + ribavirin, 1000–1200 mg/d for 48 wk<br>3) Pegylated INF- $\alpha$ 2b, 1.5 $\mu$ g/kg once weekly, + ribavirin, 800 mg/d for 48 wk   | 47<br>47<br>54‡                                    | For 1 vs. 2 vs. 3<br>Dose reduction: 34% vs. 36% vs. 42%<br>Dose discontinued: 13% vs. 13% vs. 14%<br>Fatigue: 60% vs. 62% vs. 64%<br>Headache: 58% vs. 58% vs. 62%<br>Myalgia: 50% vs. 48% vs. 56%<br>Fever: 33% vs. 44% vs. 46%<br>Diarrhea: 17% vs. 16% vs. 22%<br>Depression: 34% vs. 29% vs. 31%<br>Injection site reaction: 36% vs. 59% vs. 58%<br>Death: 0                | Good  | Fair; required liver biopsy findings consistent with chronic hepatitis and elevated ALT levels                         |
| Glue et al., 2000 (124)  | 72/72                           | 1) Pegylated INF- $\alpha$ 2b, 0.35 $\mu$ g/kg once weekly<br>2) Pegylated INF- $\alpha$ 2b, 0.70 $\mu$ g/kg once weekly<br>3) Pegylated INF- $\alpha$ 2b, 1.40 $\mu$ g/kg once weekly<br>4) Pegylated INF- $\alpha$ 2b, 0.35 $\mu$ g/kg once weekly, + ribavirin, 600–800 mg/d<br>5) Pegylated INF- $\alpha$ 2b, 0.70 $\mu$ g/kg once weekly, + ribavirin, 600–1200 mg/d<br>6) Pegylated INF- $\alpha$ 2b, 1.40 $\mu$ g/kg once weekly, + ribavirin, 600–1200 mg/d | 0<br>44<br>42<br>17<br>53<br>60                    | Dose reduction: NR<br>Dose discontinued: 1 patient (treatment group not specified)<br>Influenza symptoms: 17%–44%<br>Headache: 50%–56%<br>Asthenia: 0%–22%<br>Mean reduction in hemoglobin level: 15–25 g/L  | Fair; allocation concealment inadequate, not clear if groups similar at baseline, outcomes assessors not blinded. | Unclear; numbers screened and eligible not reported, baseline characteristics inadequately described                   |

\* ALT = alanine aminotransferase; HCV = hepatitis C virus; INF = interferon; NR = not reported; PCR = polymerase chain reaction.

†  $P < 0.001$  for 1 vs. 3, 2 vs. 3.

‡  $P = 0.01$  for 1 vs. 3.

referral centers (involving 100, 327, and 557 patients, respectively) that evaluated the number of patients referred for HCV infection who received treatment (100–102). In these studies, 30% to 40% of evaluated patients received treatment. Common reasons for ineligibility were ongoing substance abuse (13% to 44%) and serious comorbid medical or psychiatric conditions (12% to 34%). Nonadherence to the protocol (37%) and declining to receive therapy (10%) were also reported in one study (102).

#### Harms from Work-up for Active HCV Infection

In the work-up of patients with chronic HCV infection, percutaneous liver biopsy has the highest risk for complications. The most common complication of liver biopsy is pain; approximately 30% of patients require strong analgesic medications (103). More serious but less common complications include bleeding (the most frequent major complication), biliary rupture, intestinal perforation, vasovagal hypotension, or infection.

Most data on the risks of percutaneous liver biopsy come from large, fair-quality series of patients undergoing liver biopsy for a variety of reasons (104–109). The study of highest quality (independent assessment, standard assessment form) evaluated consecutive percutaneous liver

biopsies in a nationwide sample in the United Kingdom (107). A bleeding rate of 26 of 1500 (1.7%) was found, with 11 of 1500 patients (0.7%) requiring transfusion. Death was definitively associated with biopsy in 2 of 1500 patients and was possibly associated with biopsy in another 3, yielding a mortality rate of 0.13% to 0.33%. Because a substantial proportion of patients in this study had malignant disease, the risks associated with percutaneous biopsy in asymptomatic patients with chronic HCV infection may have been overestimated (109). The rates of major complications in other large series were 0% to 3.7% (mortality rates were typically <0.1%) (104, 106, 110). In large series, the material obtained was inadequate for diagnosis in 1.5% to 5% of cases (107, 108).

Two small studies involving 126 and 166 patients, respectively, reported complication rates from percutaneous biopsy specifically in patients with HCV infection (111, 112). In both studies, which included patients with known or suspected cirrhosis, no major complications were reported.

Small studies suggest that ultrasonography-guided biopsies may be associated with fewer complications than blind biopsies (110, 112–115). Increased experience of the

person performing the liver biopsy has also been associated with fewer complications (105, 107, 108).

**Antiviral Treatment Efficacy for Intermediate Outcomes**

Because of the large number of patients and long duration required to demonstrate improvements in long-term clinical outcomes, intermediate outcomes have been the most common measure of treatment benefit. Sustained virologic response rates (absence of viremia 6 months after completion of a treatment course) are currently considered the best indication of successful treatment (116).

Antiviral treatment began in 1986 with the use of interferon- $\alpha$  (117). Meta-analyses of interferon trials report sustained virologic response rates of 6% to 21% for interferon monotherapy, compared with approximately 2% in untreated controls (118–121). Combination interferon plus ribavirin was approved in 1998 and was found in 3 good-quality systematic reviews to be superior (sustained virologic response, 33% to 41%) to interferon monotherapy (119–121). Treatment with pegylated interferon, alone or in combination with ribavirin, has been used for only a few years. For all interferon-based regimens, factors associated with successful treatment include genotypes other than 1, lower baseline viral load, less serious biopsy findings, and smaller body surface area or lower weight (67).

We reviewed 3 randomized, controlled trials of pegylated interferon plus ribavirin versus pegylated interferon alone for 24 to 48 weeks (Table 3). Two trials (122, 123) were large, multicenter, good-quality randomized, controlled trials, involving 1121 and 1530 patients, respectively, and the other was a small, fair-quality study involving 72 patients (124).

The 2 good-quality trials found that 54% to 56% of all patients achieved a sustained virologic response with pegylated interferon plus ribavirin versus 44% to 47% with pegylated interferon monotherapy ( $P \leq 0.01$ ) (122, 123).

One of these trials also found a higher sustained virologic response rate with pegylated interferon plus ribavirin compared with nonpegylated interferon plus ribavirin (56% vs. 44%;  $P < 0.001$ ) (122). Table 4 summarizes the relative effects of each interferon-based regimen, with estimated numbers needed to treat for benefit.

Treatment studies may not be directly applicable to the population that would be identified by screening because they evaluate patients who probably have more serious disease. In addition, a significant proportion of patients identified by screening would not meet inclusion criteria used by antiviral trials. For example, 6 (122, 123, 125–128) of 7 (124) trials of pegylated interferon used elevated aminotransferase levels as an inclusion criterion. In large, population-based studies, 46% to 67% of patients with viremia had normal aminotransferase levels (2, 37, 91).

**Antiviral Treatment Efficacy for Clinical Outcomes**

The long duration required for important complications to develop and the relatively short period that treatments have been available complicate our ability to assess the long-term benefits of antiviral treatment. There are no data on long-term benefits after treatment with pegylated interferon alone, pegylated interferon combined with ribavirin, or nonpegylated interferon combined with ribavirin (119).

One recent good-quality systematic review of 3 randomized, controlled trials and 13 cohort studies evaluated the long-term effects (viremia or clinical outcomes) of monotherapy with nonpegylated interferon (120). The studies were heterogeneous in design, had some methodologic limitations, and did not consistently show that treated patients had better long-term clinical outcomes than untreated patients.

We independently reviewed the 2 randomized, controlled trials that reported long-term clinical outcomes after treatment with interferon (Table 5). In an unblinded,

**Table 4. Sustained Virologic Response Rates with Different Antiviral Regimens for Hepatitis C Virus Infection\***

| Treatment                           | Sustained Virologic Response Rate 6 Months after Treatment, % | Number Needed To Treat for One Sustained Virologic Response, Compared with Placebo | Study, Year (Reference)   |
|-------------------------------------|---|--|---|
| Placebo                             | <2  | Not applicable   | Poynard et al., 1996 (118)*   |
| Interferon monotherapy              | 6–16  | 6–17   | Poynard et al., 1996 (118)*<br>Gebo et al., 2002 (33)*<br>Kjaergard et al., 2001 (119)*<br>Shepherd et al., 2000 (121)* |
| Interferon plus ribavirin           | 33–41   | 2.4–3.0  | Gebo et al., 2002 (33)*<br>Kjaergard et al., 2001 (119)*<br>Shepherd et al., 2000 (121)*                                |
| Pegylated interferon alone          | 25–39   | 2.6–4.0  | Heathcote et al., 2000 (125)<br>Lindsay et al., 2001 (126)<br>Reddy et al., 2001 (127)<br>Zeuzem et al., 2000 (128)     |
| Pegylated interferon plus ribavirin | 54–60   | 1.6–1.8  | Fried et al., 2002 (122)<br>Glue et al., 2000 (124)<br>Manns et al., 2001 (123)   |

\* Systematic review or meta-analysis.

**Table 5. Randomized, Controlled Trials with Long-Term Clinical Outcomes in Patients with Hepatitis C Virus Infection after Treatment with Interferon\***

| Study, Year (Reference)           | Patients Analyzed, n | Duration of Follow-up, y | Interventions  | Long-Term Outcomes   | Internal Validity   | Applicability to Screening   |
|-----------------------------------|----------------------|--------------------------|--|--|---|--|
| Nishiguchi et al., 2001 (129)     | 90                   | Mean, 8.7                | 1) INF- $\alpha$ , 6 MU 3 times weekly for 24 wk<br>2) Symptomatic treatment                                       | Hepatocellular carcinoma: 27% vs. 73% ( $P < 0.001$ ); adjusted RR, 0.256 [0.125–0.522]<br>Death: 11% vs. 58% ( $P < 0.001$ ); adjusted RR, 0.135 [0.049–0.372]<br>Adjusted RR for progression to Child B cirrhosis: 0.250 [0.124–0.505] | Fair; not blinded   | Unclear; required elevated ALT levels and liver biopsy findings consistent with active cirrhosis; incidence of hepatocellular cancer and death much higher in untreated Japanese populations than in the United States |
| Bernardinello et al., 1999 (130)† | 61                   | Up to 5                  | 1) Intramuscular INF- $\beta$ , 6 MU 3 times weekly for 6 mo, then 3 MU 3 times weekly for 6 mo<br>2) No treatment | Cumulative probability of decompensation: 24% vs. 35%<br>Risk for death: 9% vs. 4.4%<br>Hepatocellular carcinoma: 5.3% (2 cases) vs. 4.3% (1 case)   | Fair; attrition, crossovers, and contamination not reported; possibility of differential loss to follow-up not reported | Unclear; required elevated ALT levels and liver biopsy findings consistent with active cirrhosis   |

\* Numbers in square brackets are 95% CIs. ALT = alanine aminotransferase; INF = interferon; RR = relative risk.

† Differences between the groups were not statistically significant.

fair-quality Japanese trial, 90 patients were randomly assigned to receive interferon- $\alpha$  for 24 weeks or symptomatic treatment. After 8.7 years, rates of hepatocellular carcinoma (27% vs. 73%;  $P < 0.001$ ) and mortality (11% vs. 58%;  $P < 0.001$ ) were significantly reduced in the interferon-treated patients (129). The relative risk for progressing to Child B cirrhosis was 0.250 (95% CI, 0.124 to 0.505) in the treatment group versus the control group. In a fair-quality Italian randomized, controlled trial, no significant differences in long-term outcomes were found up to 5 years after randomization to interferon- $\beta$  or placebo (5.3% vs. 4.3% for hepatocellular cancer) (130).

The single randomized, controlled trial and many of the cohort studies showing significantly improved long-term outcomes after interferon monotherapy were conducted in Japan and may not be applicable to settings in the United States. Some evidence shows that chronic HCV infection in Japan is associated with substantially higher rates of serious complications (33, 129, 131, 132).

Quality of life has generally been evaluated by comparing results in patients who achieved a sustained viral response and those who did not. We identified only one randomized, controlled trial that analyzed quality-of-life outcomes according to whether patients received antiviral treatment or placebo (133). This study was rated as poor quality because results were available for only 53 of 106 patients randomly assigned to interferon, baseline quality-of-life scores appeared significantly different between groups, and it was unclear whether patients were blinded to markers of response to treatment. Patients randomly assigned to interferon had no significant change in total Sickness Impact Profile score compared with baseline.

### Efficacy of Counseling and Immunizations

Counseling asymptomatic patients found to have HCV infection might help prevent spread of disease or decrease the likelihood of progressive disease (70). Specifically, patients could be counseled to obtain immunizations for hepatitis A virus or hepatitis B virus, avoid excess alcohol, or avoid sharing needles or engaging in other risky practices (134).

Hepatitis A and hepatitis B vaccinations in patients with HCV infection have been found to be immunogenic and safe (135). We identified no studies evaluating the effect of vaccinations after diagnosis of HCV infection on subsequent clinical outcomes. Although a widely publicized Italian study (136) reported high rates of fulminant (7 of 17) and fatal (6 of 17) hepatitis in patients with HCV infection who acquired hepatitis A infection, other studies (137, 138) have reported much lower rates. According to data from the Centers for Disease Control and Prevention, mortality rates from hepatitis A virus infection are higher in patients with underlying chronic liver disease (4.6% [107 of 2311]) than in those without it (0.2% [247 of 113 009]), but it is not clear how many of these deaths were associated with HCV infection (135).

We identified no studies that evaluated the effect of postdiagnosis counseling regarding alcohol consumption or other high-risk behaviors on subsequent clinical outcomes or spread of disease. We also did not identify any studies that estimated rates of spread of disease in patients aware of their status compared with those who were unaware. One poor-quality French observational study found less “excessive” alcohol consumption after diagnosis of HCV infection, but the results may have been affected by recall bias

**Table 6. Differences in Baseline and 24-Week Scores on the 36-Item Short-Form Health Survey between Patients with Hepatitis C Virus Infection Who Had a Sustained Virologic Response Compared with Nonresponders\***

| SF-36 Categories                   | Difference in SF-36 Score†   |                              |                                 |
|------------------------------------|------------------------------|------------------------------|---------------------------------|
|                                    | Bernstein et al., 2002 (142) | Bonkovsky et al., 1999 (143) | McHutchison et al., 2001 (144)‡ |
| Physical function                  | 4.6§                         | 6                            | 2.5                             |
| Ability to perform physical roles  | 9.8§                         | 22¶                          | 5                               |
| Degree of bodily pain              | 2.9¶                         | -1                           | 1.5                             |
| Sense of general health            | 9.1§                         | 7¶                           | 5                               |
| Overall sense of vitality          | 9.6§                         | 8                            | 4.5                             |
| Social function                    | 6.2§                         | 9                            | 3                               |
| Ability to perform emotional roles | 8.4¶                         | 11                           | 3                               |
| Overall sense of mental health     | 4.6§                         | 4                            | 2.5                             |

\* Numbers in parentheses are reference numbers. SF-36 = 36-Item Short-Form Health Survey.

† Reported as difference from baseline to 24 weeks after starting treatment in responders as compared with nonresponders.

‡ Difference in standard deviation of change from baseline. Statistical significance was not reported. The other studies reported differences in absolute scores.

§  $P < 0.001$ .

¶  $P < 0.05$ .

||  $P < 0.01$ .

or patients' unwillingness to admit to current heavy alcohol use (139). One small U.S. study found no significant differences in behaviors in young injection drug users aware of their HCV status compared with those who were unaware (140).

### Harms from Antiviral Treatment

Interferon-based treatments are commonly associated with self-limited adverse events. The most common adverse event is an influenza-like syndrome involving myalgias, fevers, and fatigue. A good-quality systematic review found that serious or life-threatening side effects occurred in 1% to 2% of patients receiving interferon monotherapy (118). Patients with significant comorbid conditions were generally excluded from randomized, controlled trials. Because of the long duration (6 months) of interferon regimens, adverse effects of treatment can have significant (although usually self-limited) effects on quality of life.

Three randomized, controlled trials provided data about adverse effects associated with combination therapy with pegylated interferon plus ribavirin or pegylated interferon monotherapy (Table 3) (122–124). In all of the studies, rates of adverse events were similar in both groups (50% to 60%). No serious complications or deaths from treatment were reported. In addition to dose-related influenza-like symptoms, psychiatric, gastrointestinal, dermatologic, and mild self-limited hematologic adverse effects were also common. Withdrawal rates in the pegylated interferon plus ribavirin group in 2 good-quality studies (122, 123) were 14% and 22%, compared with 13% to 32% in the nonpegylated interferon plus ribavirin group. Two good-quality systematic reviews found withdrawal rates of 8% to 9% in trials of patients receiving nonpegylated interferon monotherapy (119, 121).

### Relationship of Intermediate Outcomes to Clinical Outcomes

In 5 uncontrolled retrospective and prospective studies of patients who received antiviral treatment, complete responders (sustained virologic response and sustained biological response) had a moderately lower risk for hepatocellular cancer and cirrhosis than those who had relapses or those who did not respond (33, 120, 141). However, these studies did not consistently find a decreased risk for hepatocellular cancer in nonresponders compared with untreated controls. These studies were heterogeneous in design and had some methodologic limitations. Specifically, this body of literature does not exclude the possibility that favorable, unknown underlying prognostic factors led to a better response to treatment and better long-term outcomes.

In 4 clinical trials of treatment-naïve patients with HCV infection, 3 of which were fair quality (142–144) and 1 of which was poor quality (133), a sustained virologic response was associated with better functional status 24 weeks after treatment (Table 6) (142–144). The 3 fair-quality studies found that sustained responders had better scores than nonresponders on the 36-Item Short-Form Health Survey (SF-36) in 5 to 8 of 8 domains. In all of these studies, patients could have been aware of the results of biochemical or virologic testing before SF-36 testing was repeated.

### DISCUSSION

The results of the evidence review are summarized in Table 7. No direct evidence shows benefits of screening for HCV infection in the general adult population. There are inadequate data with which to accurately weigh the benefits and risks of screening for HCV infection in otherwise healthy asymptomatic adults. Although screening can accurately detect chronic HCV infection and antiviral treatment can successfully eradicate viremia, there are inadequate data with which to estimate benefits of treatment for long-term clinical outcomes such as death, cirrhosis, hepatocellular cancer, and quality of life. There are also no data with which to estimate benefits from vaccinations or counseling about alcohol use and high-risk behaviors.

Clinical trials of antiviral treatment have been performed in referred patients, who generally have more serious and progressive disease than patients followed in community-based cohorts. Even if treatment is equally effective for virology end points in patients identified by screening and those studied in clinical trials, the overall clinical benefit would be expected to be smaller since the underlying progression rate is lower. Although the proportion of screened patients found to have chronic HCV infection in selected high-risk populations, particularly intravenous drug users, would be substantially higher than in the general population, there are also no data with which to accurately weigh the risks and benefits of selective

**Table 7. Summary of Findings of Evidence Synthesis on Screening for Hepatitis C Virus Infection\***

| Key Question  | Level and Type of Evidence†                           | Overall Evidence for the Link‡   | Findings  |
|---|---|--|---|
| 1. Does screening for HCV infection reduce the risk for or rate of harm and premature death and disability?                                   | None  | NA   | No direct evidence regarding benefits of screening in the general population  |
| 2. Can clinical or demographic characteristics identify a subgroup of asymptomatic patients at higher risk for infection?                     | II-3; cross-sectional studies                         | Good for persons with intravenous drug use, high-risk sexual behaviors, and transfusions before 1992; fair for other risk factors. | Intravenous drug use is the most important risk factor for HCV infection. High-risk sexual behaviors are another important risk factor. Transfusions before 1992 remain a risk factor. Other risk factors have inconsistent associations with HCV infection. No prospective study has applied a screening strategy in the general population and measured what proportion of patients was identified correctly. |
| 3. What are the test characteristics of HCV antibody testing?   | Studies of diagnostic test characteristics            | Fair   | Using viremia as the reference standard, sensitivity of third-generation ELISA testing appears to be 94% or higher. Limited data found a specificity of 97% or greater using viremia as the reference standard.   |
| 4. What is the predictive value of a positive result on a screening test, and what are the harms associated with screening for HCV infection? | II-3; cross-sectional studies                         | Good for positive predictive values; poor for harms  | Large population-based studies found that the positive predictive value for viremia of positive results on ELISA with confirmatory positive results on RIBA was 73% to 86%. There are almost no data on the harms of screening.   |
| 5a. What are the test characteristics of the work-up for treatable disease?   | One good systematic review                            | Fair   | Blood tests have only modest value in predicting fibrosis on liver biopsy.  |
| 5b. In patients found to be positive for HCV, what proportion of patients would qualify for antiviral treatment?                              | II-3; cohort studies and cross-sectional studies      | Fair   | 30%–40% of patients referred for treatment received treatment.  |
| 6. What are the harms associated with the work-up for active HCV disease?   | II-2; cohort studies                                  | Fair   | In the highest-quality trial, the risk for major complications (bleeding, death, perforation) from liver biopsy was approximately 1%–2%, with mortality less than 0.3%. The risks may be lower in patients undergoing liver biopsy specifically for evaluation of HCV infection.  |
| 7a. How well does antiviral treatment reduce the rate of viremia, improve aminotransferase levels, and improve histology?                     | I; well-designed randomized clinical trials           | Good   | Newer treatments have achieved sustained virologic response rates of 54%–60% (54%–60% with pegylated interferon + ribavirin) compared with older treatments. Trials were performed in patients referred for treatment.  |
| 7b. How well does antiviral treatment improve health outcomes in asymptomatic patients with HCV infection?                                    | I, II-2; cohort studies and clinical trials           | Fair   | Limited data, primarily from Japan, have found improved clinical outcomes in patients receiving antiviral treatment. Data on long-term quality-of-life outcomes are sparse.   |
| 7c. How well do counseling and immunizations improve outcomes in asymptomatic patients with HCV infection or prevent spread of disease?       | II-3; case-control and cross-sectional studies        | Poor   | There is insufficient evidence to estimate the effects of counseling or immunizations on intermediate or clinical outcomes.   |
| 8. What are the harms (including intolerance to treatment) associated with antiviral intervention?  | I; well-designed randomized clinical trials           | Good   | Common adverse events with interferon-based therapy are self-limited influenza-like symptoms, which occur in 50%–60%. Major complications occur in 1%–2% of patients. Withdrawals due to adverse events occurred in 14%–22% of patients taking combination therapy with pegylated interferon + ribavirin.   |
| 9. Has improvement in intermediate outcomes been shown to reduce the risk for or rate of harm from HCV infection?                             | II-2; fair-quality cohort studies and clinical trials | Fair   | There is some evidence that intermediate outcomes are associated with improved clinical outcomes, but methodologic concerns limit interpretation of this data.  |

\* ELISA = enzyme-linked immunoassay; HCV = hepatitis C virus; NA = not applicable; RIBA = recombinant immunoblot assay.

† Evidence codes are based on study design categories (35). I = evidence obtained from at least one properly randomized, controlled trial; II-1 = evidence obtained from well-designed controlled trials without randomization; II-2 = evidence obtained from well-designed cohort or case-control analytic studies; II-3 = evidence obtained from multiple time series or dramatic uncontrolled experiments; III = opinion of respected authorities, descriptive studies, case reports.

‡ Based on criteria developed by the U.S. Preventive Services Task Force (35).

screening. **Table 8** estimates the yield from screening in hypothetical cohorts of 1000 adults in the general population and 1000 intravenous drug users.

Important gaps remain in our understanding of the

natural history of untreated patients with HCV infection who are likely to be identified by screening. If untreated chronic HCV infection causes important morbidity in the absence of cirrhosis, there may be other important goals to

Table 8. Estimated Yield of Screening for Hepatitis C Virus Infection in 2 Hypothetical Cohorts\*

| Variable  | Base-Case Assumptions  | Source (Reference)  | Adults with HCV Infection among 1000 Average-Risk Adults Screened  | Adults with HCV Infection among 1000 Adults Screened Who Reported IV Drug Use      |
|---|--|---|--|--|
|   | %  |   |  | <i>n</i>   |
| Prevalence of anti-HCV antibodies in population   | 2% in general U.S. population; 50% to >90% in U.S. patients with past or current IV drug use | NHANES III (3) (1.8% in general population, 2.3% in adults > 20 y); numerous cross-sectional studies  | 20   | 500–900  |
| Proportion of patients who were positive for anti-HCV antibody (positive results on ELISA followed by confirmatory RIBA) with viremia             | 73–86  | NHANES III (3), Dionysos study (Italy) (37), French population-based study (2), Italian population-based study (91)   | 15–17  | 365–774  |
| Proportion of patients with viremia who will develop cirrhosis after 10–20 y  | 0–10   | Systematic review of community-based cohorts of patients with HCV infection (14)  | 0–1.7  | 0–77   |
| Proportion of patients with viremia who have abnormal aminotransferase levels   | 54–66  | Dionysos Study (Italy) (37), French population-based study (2), Italian population-based study (91)   | 8–11   | 197–511  |
| Proportion of patients undergoing liver biopsy who have major complications   | 1–2 for major complications (bleeding, death, perforation); <0.3% mortality rate             | 1 large fair-quality observational study with independent ascertainment of complications in patients referred for biopsy for a variety of indications (107); numerous other poor- and fair-quality observational studies (small studies of patients with HCV infection suggest a lower rate of complications) | 0.15–0.34 major complication and <0.05 death if all patients with viremia undergo biopsy; 0.08–0.22 major complication and <0.03 death if only patients with abnormal aminotransferase levels undergo biopsy | 4–15 major complications and 0–2 deaths; 2–10 major complications and 0–1.5 deaths |
| Proportion of patients referred for evaluation of HCV infection that received therapy   | 30   | 3 fair-quality observational studies of patients referred for evaluation of HCV infection (100–102)   | 4–5 if all patients with viremia referred; 2–3 if only patients with abnormal aminotransferase levels referred   | 110–232; 59–153  |
| Proportion of patients receiving interferon-based therapy who completed treatment course  | 80–90  | Numerous good-quality randomized trials and systematic reviews (33, 118–128)  | 4–5 if all patients with viremia referred; 2–3 if only patients with abnormal aminotransferase levels referred   | 88–209; 47–138   |
| Proportion of patients receiving interferon-based therapy who had a serious or life-threatening adverse event                                     | 1–2  | Numerous good-quality randomized trials and systematic reviews (33, 118–128)  | 0.04–0.09 if all patients with viremia referred; 0.02–0.06 if only patients with abnormal aminotransferase levels referred   | 1–4; 0.5–2.8   |
| Proportion of patients receiving treatment who have a sustained virologic response to best available therapy (pegylated interferon and ribavirin) | 54–60 for pegylated interferon and ribavirin combination therapy                             | 3 randomized clinical trials (2 good quality, 1 fair quality) for pegylated interferon and ribavirin (122–124)  | 2–3 if all patients with viremia referred; 1–2 if only patients with abnormal aminotransferase levels referred   | 59–139; 32–92  |

\* HCV = hepatitis C virus; IV = intravenous; NHANES III = National Health and Nutrition Examination Survey III.

be obtained from treatment, but few studies have adequately assessed the impact of treatment on quality of life or symptoms. Additional studies are needed to define the progression from asymptomatic to symptomatic HCV infection and how long symptomatic patients remain unidentified without screening.

Many studies showing improvement in long-term clinical outcomes have been conducted in Japan. Chronic HCV infection appears to follow a substantially more ag-

gressive course in Japan than in the United States. Although lead-time bias could explain some of the observed differences in disease progression rates, the case for screening would be greatly strengthened by data showing that treatment in earlier, asymptomatic stages of disease in western countries is associated with improved outcomes compared with treatment reserved for patients who have become symptomatic and could be identified without screening. Studies demonstrating important individual or

public health benefits from counseling, immunizations, and behavioral changes after a diagnosis of HCV infection would also greatly strengthen the case for screening. Little is known about the benefits and risks of treatment in patients typically excluded from or underrepresented in randomized trials, such as those with ongoing substance abuse, those with comorbid conditions, elderly persons, and persons of nonwhite ethnicity (145).

No studies have adequately assessed the potential harmful effects of screening for HCV infection, such as anxiety, labeling, or damage to close relationships, and whether these factors can be minimized by appropriate counseling. Additional studies on the long-term effects of antiviral treatment in nonresponders are important because studies have not consistently found an improved outcome in this group compared with untreated controls.

Reasonable screening strategies might be to screen adults with established risk factors, adults in settings with a high prevalence of HCV infection, or all adults in the general population. Studies that adequately assess the usefulness of risk factor assessment to guide selective screening strategies and the harms and benefits of selective versus universal screening are needed. A potential barrier to screening patients on the basis of risk factors is the difficulty in obtaining accurate histories of intravenous drug use or high-risk sexual behaviors. Little is known about patient preferences for screening. There are no data with which to estimate risks and benefits of one-time screening versus other screening strategies.

Complications from chronic HCV infection present an enormous health burden that is expected to increase 2- to 4-fold over the next 2 to 4 decades. Further research to more accurately determine the benefits and harms of screening is of paramount importance.

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## APPENDIX

### Definitions

This section summarizes terminology describing the tests used to identify patients with HCV infection, the results of these tests (Appendix Table), and the response to treatment. The Centers for Disease Control and Prevention has recently published detailed guidelines for performing laboratory testing and reporting results of anti-HCV antibody and supplemental testing (90).

**Enzyme-linked immunoassay (ELISA) or enzyme immunoassay (EIA):** The ELISA (also referred to as EIA) detects antibodies against recombinant HCV antigens. First-generation ELISAs used a single antigen; later tests added additional antigens (146–148). Second- and third-generation tests are both in standard use. Because of concerns about false-positive test results, particularly in low-prevalence populations (such as blood donors or asymptomatic adults), the Centers for Disease Control and Prevention has recommended confirming positive ELISA results with a supplemental test (recombinant immunoblot assay or polymerase chain reaction), unless the signal-to-cutoff ratio is above a predetermined threshold that has been shown to be confirmed as positive more than 95% of the time (90).

The ELISA is the least expensive diagnostic test for HCV infection, with an average charge of about \$60.00 (34).

**Recombinant immunoblot assay (RIBA):** The RIBA is a supplemental test that also detects antibodies against HCV antigens. In these assays, multiple HCV antigens are individually displayed on a nitrocellulose strip as bands. Positive RIBA results have at least 2 reactive bands; indeterminate results have one reactive band. Because positive RIBA results require reactivity to more than one HCV antigen, they are considered more specific (but not more sensitive) than ELISA for past HCV infection and are used to confirm positive ELISA results in low-prevalence populations (34). However, RIBA is not an independent gold standard for ELISA because the 2 tests use similar antigens to detect anti-HCV antibodies.

Currently available third-generation RIBAs are thought to be more specific than earlier-generation tests because they produce fewer indeterminate results (149). The interpretation of indeterminate RIBA results remains uncertain (90, 150, 151). The relative proportion of RIBA-positive, RIBA-indeterminate, and RIBA-negative test results in patients with positive results on ELISA varies according to the patients studied.

The RIBA is typically 2 to 3 times more expensive than ELISA; usual charges are approximately \$140.00 (34).

**HCV core antigen testing:** Recently developed tests to detect HCV core antigen may aid in diagnosing acute infection in the “window period” before HCV antibodies develop (152, 153). The role of HCV core antigen testing in screening has not yet been established.

**Reverse transcription polymerase chain reaction (RT-PCR or PCR):** This is a laboratory method used to detect circulating HCV RNA in blood. A PCR can be quantitative or qualitative, and under optimal conditions qualitative PCR can detect 100 IU of circulating virus per mL or less (34, 116). Because the absence of viremia in patients who test positive for anti-HCV antibodies is associated with little or no risk for HCV infection (154) or complications related to chronic HCV infection, sustained PCR-detected viremia has become the gold standard for chronic HCV infection (6, 132, 155–157). In patients who have positive results on PCR, the degree of viremia correlates poorly with degree of liver damage (157–161), although these results may help predict the likelihood of response to treatment (162).

Strict quality control is necessary for PCR testing to be reliable. False-negative test results can occur because some patients with active infection have intermittent viremia, and a small portion of patients with chronic HCV infection can become non-viremic, particularly if they develop hepatocellular cancer (163–165). For this reason, repeated PCR testing is suggested in high-risk patients who are positive for anti-HCV antibodies but have negative results on initial PCR. False-positive PCR test results may also occur because of contamination of samples (11% in one early quality-control study), but this appears to be much less frequent since standardization of assay techniques (164).

Testing with PCR is associated with charges of approximately \$130.00 for a qualitative test and \$200.00 for a quantitative test (34).

**False-positive ELISA results:** Patients who have positive results on ELISA but negative results on RIBA or negative results on both RIBA and PCR are usually considered to have false-positive results (that is, they have no evidence of past or current HCV infection). False-positive ELISA results may occur in patients with autoimmune diseases and in neonates born to mothers with chronic HCV infection, who frequently pass on antibody

Appendix Table. Results of Screening Tests for Hepatitis C Virus Infection and Usual Interpretation\*

| ELISA Results | RIBA Results                                | PCR Results   | Interpretation   |
|---------------|---|---|--|
| Positive      | Positive or indeterminate                   | Positive  | Active or chronic HCV infection                                |
| Positive      | Positive                                    | Negative  | Cleared HCV infection if PCR results are persistently negative |
| Positive      | Negative, intermediate, or not performed    | Negative  | Cleared HCV infection or false-positive results on ELISA       |
| Positive      | Negative                                    | Not usually done if RIBA results are negative   | False-positive results on ELISA                                |
| Negative      | Not performed if ELISA results are negative | Not usually done if ELISA results are negative (unless suspicion for acute infection is high)   | No evidence of past exposure to HCV                            |
| Negative      | Not performed if ELISA results are negative | Positive (test is not usually done in clinical settings unless suspicion for infection is high) | Early (<7–8 wk) HCV infection or false-negative results        |

\* ELISA = enzyme-linked immunoassay; HCV = hepatitis C virus; PCR = polymerase chain reaction; RIBA = recombinant immunoblot assay.

ies to their children but usually do not pass on the virus (34, 116).

*False-negative ELISA results:* Patients who have negative results on ELISA but positive results on PCR are usually considered to have false-negative results. False-negative results are probably most common very early after infection (it takes 6 to 8 weeks for third-generation ELISAs to yield positive results vs. 2 to 3 weeks for PCR) or in patients who have an impaired immune system (34).

*Cleared or resolved HCV infection:* Patients who have positive results on ELISA and RIBA but negative results on PCR on repeated testing are generally considered to have cleared or resolved HCV infection. This is usually not considered a false-positive finding because the positive RIBA test result provides specific evidence of past exposure to HCV (166). Patients who have positive results on ELISA, indeterminate results on RIBA (or no RIBA performed), and negative results on PCR may either have false-positive results or have cleared their HCV infection. False-positive test results are more common in low-prevalence settings (167, 168).

*Chronic or active HCV infection:* Patients who have persistent positive results on PCR are said to have chronic HCV infection. Chronic infection may present with or without symptoms, abnormal aminotransferase levels, or abnormal biopsy findings. In this review, the term *asymptomatic chronic HCV infection* refers to patients who report no symptoms of HCV infection. Like symptomatic patients, asymptomatic patients may or may not have abnormal biopsy results or aminotransferase levels.

*Liver biopsy results:* The Histologic Activity Index is used to grade histologic findings. The Knodell score and the METAVIR scoring system are common methods used to report the Histologic Activity Index (169, 170). The Knodell score is a semi-quantitative scoring system in which fibrosis and portal, periportal, and lobular necrotic and inflammatory components are assessed separately and their coding values are added. Maximum scores vary depending on exactly how the scores are totaled (171). The METAVIR system reports both the inflammatory and the fibrosis scores using separate standardized scores for activity and fibrosis (170).

*Early responders:* Patients with HCV infection who receive treatment and clear their viremia (viral load undetectable by PCR) or have a significant response (usually defined as a 2-log drop in HCV RNA level) in the first few months of treatment are referred to as early responders. People who are not early responders (usually measured at 12 weeks of therapy) have a low chance of successful treatment and may not benefit from further therapy (116). Normalization of aminotransferase levels (biochemical response) was reported in earlier trials of HCV treatment but has been replaced by assessments of virologic status, which are thought to be more accurate predictors of successful treatment.

*End-of-treatment responders:* Patients with HCV infection who receive treatment, clear their viremia, and maintain this response until the end of treatment are referred to as *end-of-treatment* responders. Presence of HCV RNA at the end of treatment is highly predictive of relapse when therapy is stopped (116).

*Sustained responders or sustained virologic responders:* Patients

with HCV infection who receive treatment and clear their viremia and maintain this response 6 to 12 months after the completion of treatment are referred to as sustained responders or sustained virologic responders.

*Nonresponders:* Patients with HCV infection who do not clear their viremia during treatment are considered nonresponders.

## Analytic Framework and Key Questions

The analytic framework in the **Appendix Figure** indicates the strategy we used to evaluate screening for HCV infection in adults without known or suspected liver disease or abnormalities on liver function tests. The key questions, which guided our literature review, were determined in conjunction with USPSTF liaisons.

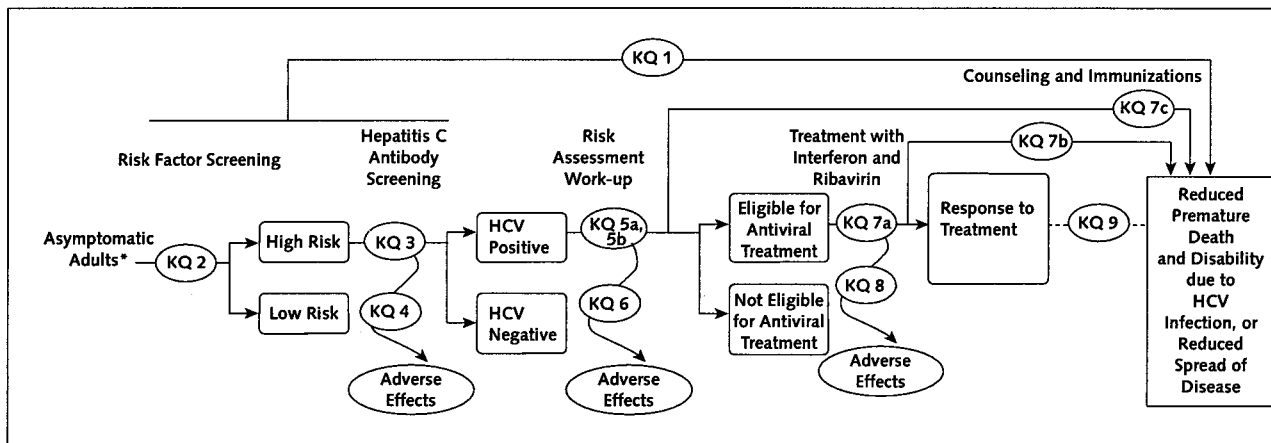
The analytic framework shows the target samples, interventions, and intermediate and health outcome measures we examined. We narrowed the scope of the literature review after a preliminary search. We excluded children from the review because of the low prevalence of anti-HCV antibodies (0.2% to 0.4% in those 6 to 19 years of age) (3) and the unclear safety and efficacy of treatment in this population (172). We also excluded pregnant women because of unclear safety of treatment and insufficient evidence regarding ability to lower vertical transmission rates (estimated at approximately 5% in mothers without HIV infection) (173–176). We excluded other specific populations, such as patients who had received transplants, HIV-infected patients, and patients receiving hemodialysis. In these patients, screening test characteristics and natural history of HCV infection may differ from those in the general population (23, 177–180). In addition, these populations have generally been excluded from large trials of treatment, and data regarding clinical outcomes are lacking. Patients with occupational exposures were also excluded because of clear consensus about screening after percutaneous exposures (1).

Our review evaluated the screening strategy in which a second- or third-generation HCV ELISA is the initial test, with confirmatory RIBA. These are the screening tests that are currently in standard use for the diagnosis of current or resolved HCV infection (90). Testing with PCR, aminotransferase testing, and liver biopsy were considered the standard work-up to determine presence of chronic HCV infection and eligibility for treatment in patients who tested positive for anti-HCV antibodies.

For treatment of chronic HCV infection, we focused on evidence regarding efficacy and safety of pegylated interferon with ribavirin, the treatment regimen found in good-quality trials to have the highest efficacy. Because this treatment regimen has been available for evaluation for only a short time, we also reviewed evidence regarding the effect of other interferon-based treatment regimens on long-term clinical outcomes. Ribavirin alone, amantadine, and corticosteroids were not included because they have not been found to be efficacious (1, 98, 181).

For outcomes, we were particularly interested in reviewing any literature on the benefit of early antiviral treatment of chronic HCV infection in asymptomatic patients. Clinical outcomes that we evaluated were mortality, end-stage liver disease, cirrhosis, and hepatocellular cancer. Quality-of-life outcomes

Appendix Figure. Key questions (KQs).



KQ 1 = Does screening for hepatitis C virus (HCV) infection reduce the risk or rates of harm and premature death and disability? KQ 2 = Can clinical or demographic characteristics identify a subgroup of asymptomatic patients at higher risk for HCV infection? KQ 3 = What are the test characteristics of HCV antibody testing? KQ 4 = What is the predictive value of a positive screening test result and what are the harms associated with screening for HCV infection? KQ 5a = What are the test characteristics of the work-up for active disease? KQ 5b = In patients found to be positive for HCV antibody, what proportion of patients would qualify for treatment? KQ 6 = What are the harms associated with the work-up for active HCV disease? KQ 7a = How well does antiviral treatment reduce the rate of viremia, improve aminotransferase levels, and improve histology? KQ 7b = How well does antiviral treatment improve health outcomes in asymptomatic patients with HCV infection? KQ 7c = How well do counseling and immunizations in asymptomatic patients with HCV infection improve clinical outcomes or prevent spread of disease? KQ 8 = What are the harms (including intolerance to treatment) associated with antiviral intervention? KQ 9 = Have improvements in intermediate outcomes (liver function tests, remission, histologic changes) been shown to reduce the risk or rate of harm from HCV infection? \* Excluding pregnant women, HIV-positive persons, transplant recipients, and patients with renal failure.

were also evaluated. Intermediate outcomes were loss of detectable viremia, improvement in histologic findings, and normalization of aminotransferase levels. We also reviewed adverse outcomes from screening and treatment, including side effects from treatment, adverse events from liver biopsy, and effects of diagnosing chronic HCV infection on quality of life.

Other reasons for screening for HCV infection might be to prevent spread of the disease or to identify those who might benefit from hepatitis A or B virus vaccination, alcohol cessation counseling, or other interventions. We performed an additional literature search and review to identify potential benefits from screening that leads to these types of interventions in patients with chronic HCV infection.

## Methods

### Search Strategy

We searched the topic of HCV in MEDLINE (1989 to July 2002, updated search in February 2003) and the Cochrane Clinical Trials Registry (2002, Issue 2). We originally performed 3 MEDLINE searches, one for screening for HCV infection, one for work-up of HCV infection, and one for treatment of HCV infection. For screening, the Medical Subject Headings (MeSH) terms *hepatitis C* and *hepacivirus* were combined with the terms *mass screening*, *hepatitis C antibodies*, *predictive value of tests*, and *sensitivity and specificity* and the text words *antibody testing*. For work-up, the MeSH terms *hepatitis C* and *hepacivirus* were combined with the terms *ultrasonography*, *liver function tests*, *liver biopsy*, and *viral load*. For treatment, the MeSH terms *antiviral agents*, *interferons*, and *ribavirin* were combined with the terms *hepatitis C* and *hepacivirus*. We conducted a search for controlled studies of treatment of HCV infection in the Cochrane Library

databases, using the phrase *hepatitis C* in title, abstract, or keywords combined with terms for clinical trials. We retrieved the complete reference list from a recent Agency for Healthcare Research and Quality evidence report commissioned by the National Institutes of Health to update its consensus statement on management of HCV infection (33). Periodic hand searching of hepatology, gastroenterology, and major medical journals; review of the reference lists of retrieved articles; and suggestions from expert reviewers supplemented the electronic searches.

We performed an additional MEDLINE search in February 2003 on counseling on alcohol use, immunizations, and risky behaviors in patients with HCV infection. For this search, we combined the MeSH terms *hepatitis C*, *hepacivirus*, or *hepatitis C*, *chronic* with the MeSH terms *patient education*, *counseling*, *alcohol drinking*, *viral hepatitis vaccines*, *hepatitis A*, or *vaccination*.

One reader reviewed all English-language abstracts. Papers were selected for full review if they were about HCV infection, were relevant to key questions in the analytic framework, and met other inclusion criteria specific to the key questions. Reviews, policy statements, and other papers with contextual value were also obtained from the searches. Studies published as abstracts were not included in the search; although pertinent abstracts may be referred to in the text, they are not included in evidence tables.

### Inclusion Criteria

For all key questions, articles were limited to those that evaluated the general adult population with chronic HCV infection. We excluded studies that focused only on patients with end-stage liver

disease, cirrhosis, or hepatocellular cancer. Although the population of interest was asymptomatic adults with chronic HCV infection who would be identified by screening, we included studies of patients with a broad spectrum of chronic HCV disease to get a picture of the benefits and adverse effects of screening and treatment in patients with different degrees of liver disease. Studies on persons with HCV who had undergone transplantation were excluded, as were studies of pregnant patients, children, or those with end-stage renal disease or HIV infection. Studies of nonhuman subjects were also excluded, and studies had to include original data. Foreign-language papers were considered if they were clinical trials and an abstract was available in English. We searched for relevant systematic reviews for all key questions.

For individual key questions, additional inclusion criteria were as follows. For key question 1, articles were included if they were clinical trials or observational studies that evaluated clinical outcomes in patients screened and not screened for HCV infection.

For key question 2, we included large observational studies that used appropriate statistical methods to assess associations between various risk factors and the presence of HCV infection. Representative smaller observational studies were also reviewed.

For key questions 3a, 3b, and 4, we included observational studies and systematic reviews that evaluated third-generation ELISA (the most recent generation) and used a credible, current reference standard (third-generation RIBA or PCR). We did not include studies that evaluated third-generation ELISA only in relationship to an earlier-generation ELISA or performed the reference standard only in “discordant” samples from 2 screening tests. We also included data from large, good-quality observational studies on diagnostic test characteristics of second-generation ELISA.

For key question 5a, we included studies that evaluated the ability of blood tests to predict liver biopsy results and performed liver biopsy as the reference standard.

For key question 5b, we included clinical trials and observational studies that reported the number of patients referred or considered for HCV treatment after a positive result on an HCV antibody test and that also provided detailed information about the reasons patients were considered ineligible for treatment.

For key question 6, we included observational studies that reported complications from percutaneous liver biopsy specifically in patients with chronic HCV infection. We also included representative large, higher-quality observational studies of complications from percutaneous liver biopsy performed for a variety of indications.

For key questions 7a and 7b, we included controlled trials of antiviral treatment that evaluated relevant intermediate or clinical outcomes in treatment-naïve samples. We included studies that evaluated pegylated interferon with or without ribavirin versus

another treatment or placebo and studies that evaluated nonpegylated interferon plus ribavirin compared with interferon alone or placebo. For question 7b, controlled trials of nonpegylated interferon without ribavirin were also included if they had more than 5 years of post-treatment follow-up and evaluated clinical or histologic outcomes. We reviewed clinical trials that were previously included in good-quality systematic reviews to ensure accuracy and reproducibility of the findings of the systematic reviews.

For key question 7c, we included controlled trials and observational studies that evaluated the effectiveness of counseling and immunizations in patients with HCV infection for improving clinical outcomes related to hepatitis A or B infection, alcohol use, or preventing spread of disease.

For key question 8, we included controlled antiviral trials and observational studies that reported adverse events in treatment-naïve samples. We included studies of pegylated interferon with or without ribavirin versus another treatment or placebo and studies of nonpegylated interferon plus ribavirin versus another treatment or placebo.

For key question 9, we included controlled antiviral trials and observational studies in which long-term outcomes were stratified by intermediate responses to treatment.

For all key questions, we reviewed meta-analyses and systematic reviews when available.

### Data Extraction

We used predefined criteria from the USPSTF to assess the internal validity of included systematic reviews, trials, and observational studies, which we rated as good, fair, or poor. We also rated the applicability of each study to the population that would be identified by screening. The rating system was developed by the USPSTF and is described in detail elsewhere (35). For included trials and systematic reviews, we also abstracted information about setting, patients, interventions, and outcomes. For clinical trials, when possible we recorded the difference between the probability of a response in the treatment and control groups for each outcome studied. We evaluated the applicability of reviewed studies to the population likely to be identified by screening. We developed evidence tables for those key questions related to antiviral treatment of HCV infection (key questions 7a and 7b). We rated the overall body of evidence for each key question using the system developed by the USPSTF (35).

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