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Screening for Hepatitis C Virus Infection in Adults: U.S. Preventive Services Task Force Recommendation Statement

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Description: Update of the 2004 U.S. Preventive Services Task Force (USPSTF) recommendation on screening for and treatment of hepatitis C virus (HCV) infection in asymptomatic adults.

Methods: The Agency for Healthcare Research and Quality commissioned 2 systematic reviews on screening for and treatment of HCV infection in asymptomatic adults, focusing on evidence gaps identified in the previous USPSTF recommendation and new studies published since 2004. The evidence on screening for HCV in pregnant women was also considered.

Population: This recommendation applies to all asymptomatic adults without known liver disease or functional abnormalities.

Recommendation: The USPSTF recommends screening for HCV infection in persons at high risk for infection. The USPSTF also recommends offering 1-time screening for HCV infection to adults born between 1945 and 1965. (B recommendation).

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The U.S. Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

Summary of Recommendation and Evidence

The USPSTF recommends screening for hepatitis C virus (HCV) infection in persons at high risk for infection. The USPSTF also recommends offering 1-time screening for HCV infection to adults born between 1945 and 1965. (B recommendation).

See the Clinical Considerations for more information on risk factors for HCV infection.

See the **Figure** for a summary of the recommendation and suggestions for clinical practice.

Appendix Table 1 describes the USPSTF grades, and **Appendix Table 2** describes the USPSTF classification of levels of certainty about net benefit (both tables are available at www.annals.org).

Rationale

Importance

Hepatitis C virus is the most common chronic bloodborne pathogen in the United States and a leading cause of complications from chronic liver disease. The prevalence of the anti-HCV antibody in the United States is approximately 1.6% in noninstitutionalized persons. According to data from 1999 to 2008, about three fourths of patients in the United States living with HCV infection were born between 1945 and 1965, with a peak prevalence of 4.3% in persons aged 40 to 49 years from 1999 to 2002 (1, 2). The most important risk factor for HCV infection is past or current injection drug use, with most studies reporting a prevalence of 50% or more. The incidence of HCV infection was more than 200 000 cases per year in the 1980s but decreased to 25 000 cases per year by 2001. According to the Centers for Disease Control and Prevention (CDC), there were an estimated 16 000 new cases of HCV infection in 2009 and an estimated 15 000 deaths in 2007. Hepatitis C–related end-stage liver disease is the most common indication for liver transplants among U.S. adults, accounting for more than 30% of cases. Studies suggest that about one half of the recently observed 3-fold increase in incidence of hepatocellular carcinoma is related to acquisition of HCV infection 2 to 4 decades earlier (1).

See also:

Print
Editorial comment

Figure. **Screening for hepatitis C virus infection in adults: clinical summary of U.S. Preventive Services Task Force recommendation.**

Annals of Internal Medicine

U.S. Preventive Services TASK FORCE
www.USPreventiveServicesTaskForce.org

SCREENING FOR HEPATITIS C VIRUS INFECTION IN ADULTS
CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

Population	Persons at high risk for infection and adults born between 1945 and 1965
Recommendation	Screen for hepatitis C virus (HCV) infection. Grade: B

Risk Assessment	The most important risk factor for HCV infection is past or current injection drug use. Additional risk factors include receiving a blood transfusion before 1992, long-term hemodialysis, being born to an HCV-infected mother, incarceration, intranasal drug use, getting an unregulated tattoo, and other percutaneous exposures. Adults born between 1945 and 1965 are more likely to be diagnosed with HCV infection, either because they received a blood transfusion before the introduction of screening in 1992 or because they have a history of other risk factors for exposure decades earlier.
Screening tests	Anti–HCV antibody testing followed by confirmatory polymerase chain reaction testing accurately identifies patients with chronic HCV infection. Various noninvasive tests with good diagnostic accuracy are possible alternatives to liver biopsy for diagnosing fibrosis or cirrhosis.
Screening interval	Persons with continued risk for HCV infection (such as injection drug users) should be screened periodically. Evidence on how often screening should occur in these persons is lacking. Adults born between 1945 and 1965 and persons who are at risk because of potential exposure before universal blood screening need only be screened once.
Treatment	Antiviral treatment prevents long-term health complications of HCV infection (such as cirrhosis, liver failure, and hepatocellular carcinoma). The combination of pegylated interferon (a-2a or a-2b) and ribavirin is the standard treatment for HCV infection. In 2011, the U.S. Food and Drug Administration approved the protease inhibitors boceprevir and telaprevir for the treatment of HCV genotype 1 infection (the predominant genotype in the United States).
Balance of Benefits and Harms	On the basis of the accuracy of HCV antibody testing and the availability of effective interventions for persons with HCV infection, the USPSTF concludes that there is a moderate net benefit to screening in populations at high risk for infection. The USPSTF concludes that there is also a moderate net benefit to 1-time screening in all adults in the United States born between 1945 and 1965.
Other Relevant USPSTF Recommendations	The USPSTF has made recommendations on screening for hepatitis B virus infection in adolescents, adults, and pregnant women. These recommendations are available at www.uspreventiveservicestaskforce.org.

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to www.uspreventiveservicestaskforce.org.

Detection

The USPSTF found adequate evidence that anti–HCV antibody testing followed by confirmatory polymerase chain reaction testing accurately detects chronic HCV infection.

In screening strategies targeting persons with risk factors for HCV infection (such as past or present injection drug use, sex with an injection drug user, or blood transfusion before 1992), anti–HCV antibody testing is associated with high sensitivity (>90%) and small numbers needed to screen to identify 1 case of HCV infection (<20 persons) (1). Anti–HCV antibody testing remains highly accurate in low-prevalence populations, although the numbers needed to screen to detect 1 case of HCV infection are higher.

The USPSTF also found adequate evidence that various noninvasive tests have good to very good diagnostic accuracy in diagnosing fibrosis or cirrhosis (3).

Benefits of Detection and Early Intervention

The USPSTF found no direct evidence on the benefit of screening for HCV infection in asymptomatic adults in reducing morbidity and mortality. However, the USPSTF found adequate evidence that antiviral regimens result in sustained virologic response (SVR) and improved clinical outcomes.

The USPSTF found inadequate evidence that counseling or immunization of patients with HCV infection against other infections improves health outcomes, reduces transmission of HCV, or changes high-risk behaviors. The USPSTF found inadequate evidence that knowledge of positive status for HCV infection reduces high-risk behaviors. The USPSTF also found inadequate evidence that labor management and breastfeeding strategies in HCV-positive women are effective at reducing risk for mother-to-child transmission.

Given the accuracy of the screening test and the availability of effective interventions for HCV infection, the USPSTF concludes that screening is of moderate benefit for populations at high risk for infection. The USPSTF concludes that 1-time screening in all adults in the United States born between 1945 and 1965 is also of moderate benefit.

Harms of Detection and Early Intervention

The USPSTF found limited evidence on the harms of screening for HCV. Potential harms of screening include anxiety, patient labeling, and feelings of stigmatization.

The USPSTF found adequate evidence on the harms associated with the diagnostic evaluation used to guide treatment decisions (liver biopsy). These harms include bleeding, infection, and severe pain in approximately 1% of persons who had a liver biopsy and death in less than 0.2%. However, the use of liver biopsy to guide treatment decisions is declining, and noninvasive tests have sufficient accuracy to diagnose fibrosis and cirrhosis. Thus, the absolute risk to persons who currently receive a diagnosis of HCV infection and subsequent treatment is probably declining.

The USPSTF found adequate evidence that antiviral therapy regimens are associated with a high rate of harms, such as fatigue, headache, flu-like symptoms, hematologic events, and rash. However, antiviral therapy is given for a defined duration, serious adverse events are uncommon, and adverse events are self-limited and typically resolve after treatment is discontinued. The USPSTF found adequate evidence that these harms of treatment are small.

USPSTF Assessment

The USPSTF concludes with moderate certainty that screening for HCV infection in adults at increased risk for infection and 1-time screening in adults in the 1945–1965 birth cohort has moderate net benefit.

Clinical Considerations

Patient Population Under Consideration

This recommendation applies to all asymptomatic adults without known liver disease or functional abnormalities.

Assessment of Risk

The most important risk factor for HCV infection is past or current injection drug use. Another established risk factor for HCV infection is receipt of a blood transfusion before 1992. Because of the implementation of screening programs for donated blood, blood transfusions are no longer an important source of HCV infection. In contrast, 60% of new HCV infections occur in persons who report injection drug use within the past 6 months (1).

Additional risk factors include long-term hemodialysis, being born to an HCV-infected mother, incarceration, intranasal drug use, getting an unregulated tattoo, and other percutaneous exposures (such as in health care workers or from having surgery before the implementation of universal precautions). Evidence on tattoos and other percutaneous exposures as risk factors for HCV infection is limited. The relative importance of these additional risk factors may differ on the basis of geographic location and other factors (1).

Large population-based studies report an independent association between high-risk sexual behaviors (multiple sex partners, unprotected sex, or sex with an HCV-infected person or injection drug user) and HCV infection. However, HCV seems to be inefficiently transmitted through sexual contact, and observed associations may have been confounded by other high-risk behaviors.

In 1998, the highest prevalence rates of the anti-HCV antibody occurred in persons with significant direct percutaneous exposures, such as injection drug users and persons with hemophilia (60% to 90%); persons with less significant percutaneous exposures involving smaller amounts of blood, such as patients receiving hemodialysis (10% to 30%), had more moderate prevalence rates. Persons engaging in high-risk sexual behaviors (1% to 10%); recipients of blood transfusions (6%); and persons with infrequent percutaneous exposures, such as health care workers (1% to 2%), had the lowest prevalence rates (4, 5).

Among patients with abnormal results on liver function tests (measurement of aspartate aminotransferase, alanine aminotransferase, or bilirubin) who were tested for reasons other than HCV screening, finding the cause of the abnormality often includes testing for HCV infection and is considered case finding rather than screening; therefore, it is outside the scope of this recommendation.

In 2010, the overall incidence rate of acute HCV infection was 0.3 cases per 100 000 persons and varied by race or ethnicity. The incidence rate for acute hepatitis C was lowest among persons of Asian or Pacific Islander descent and highest among American Indians and Alaskan natives. Blacks had the highest mortality rates from HCV, at 6.5 to 7.8 deaths per 100 000 persons, according to data from 2004 to 2008 (6).

Birth-Cohort Screening

Persons born between 1945 and 1965 are more likely to be diagnosed with HCV infection, possibly because they received blood transfusions before the introduction of screening in 1992 or have a history of other risk factors for exposure decades earlier (2). Many persons with chronic HCV infection are unaware of their condition. A risk-based approach may miss detection of a substantial proportion of HCV-infected persons in the birth cohort because of a lack of patient disclosure or knowledge about prior risk status. As a result, 1-time screening for HCV infection in the birth cohort may identify infected patients at earlier stages of disease who could benefit from treatment before developing complications from liver damage.

The USPSTF concluded that the benefit of screening for HCV infection in persons in the birth cohort is prob-

ably similar to that in persons at higher risk for infection. Birth-cohort screening is probably less efficient than risk-based screening, meaning more persons will need to be screened to identify 1 patient with HCV infection. Nevertheless, the overall number of Americans who will probably benefit from birth-cohort screening is greater than the number who will benefit from risk-based screening.

The USPSTF recognizes that increased screening and the resulting increased diagnoses and treatment could result in increased overall harms because not all treated persons will benefit from treatment, including those who will never develop signs or symptoms of disease (overdiagnosis). The USPSTF weighed this potential harm against the potential harm of undertreatment attributable to underdiagnosis. It is hoped that future research will reduce overtreatment by clarifying which persons are most likely to benefit from early diagnosis and treatment. However, given that persons in the birth cohort have been living with HCV infection for 20 or more years, the potential benefit of screening and early treatment will probably be at its highest now and in the near future before becoming smaller. After weighing the competing harms of overtreatment and underdiagnosis, the USPSTF recommends 1-time screening for this cohort.

Screening Tests

Anti–HCV antibody testing followed by polymerase chain reaction testing for viremia is accurate for identifying patients with chronic HCV infection. Various noninvasive tests with good diagnostic accuracy are possible alternatives to liver biopsy for diagnosing fibrosis or cirrhosis.

Screening Intervals

Persons in the birth cohort and those who are at risk because of potential exposure before universal blood screening and are not otherwise at increased risk need only be screened once. Persons with continued risk for HCV infection (injection drug users) should be screened periodically. The USPSTF found no evidence about how often screening should occur in persons who continue to be at risk for new HCV infection.

Screening Implementation

The USPSTF believes that screening should be voluntary and undertaken only with the patient's knowledge and understanding that HCV testing is planned. Patients should be informed orally or in writing that HCV testing will be performed unless they decline (opt-out screening). The USPSTF further believes that before HCV screening, patients should receive an explanation of HCV infection, how it can (and cannot) be acquired, the meaning of positive and negative test results, and the benefits and harms of treatment. Patients should also be offered the opportunity to ask questions and to decline testing.

Treatment

The purpose of antiviral treatment regimens is to prevent long-term health complications of chronic HCV infection (such as cirrhosis, liver failure, and hepatocellular carcinoma).

The combination of pegylated interferon (α2a or α2b) and ribavirin is the standard treatment for HCV infection. In 2011, the U.S. Food and Drug Administration approved the protease inhibitors boceprevir and telaprevir for the treatment of HCV genotype 1 infection (the predominant genotype in the United States). Trials have found increased SVR rates in patients with HCV genotype 1 infection who received triple therapy consisting of pegylated interferon, ribavirin, and boceprevir or telaprevir compared with dual therapy consisting of pegylated interferon and ribavirin. Evidence is lacking on the comparative effects of current antiviral treatments on long-term clinical outcomes. Regimens with protease inhibitors are usually of shorter duration than dual therapy (24 or 28 weeks vs. 48 weeks). Triple therapy with protease inhibitors is associated with an increased risk for hematologic events (such as anemia; neutropenia; and thrombocytopenia, particularly with boceprevir) and rash (telaprevir) compared with dual therapy. These adverse events are self-limited and typically resolve after the discontinuation of treatment (7).

Other Considerations

Research Needs and Gaps

As treatment of HCV continues to evolve, more research is needed to understand which persons benefit the most from treatment and when treatment should begin in asymptomatic persons. Research is needed on the outcomes of treatment in screen-detected patients and on treatment decisions guided by "noninvasive" assessment of cirrhosis and fibrosis because these patients may differ from those enrolled in treatment trials or described in prospective cohort studies. In addition, research should focus on the long-term harms associated with antiviral regimens. Other areas of needed research include frequency of testing in high-risk populations; demonstrating individual or public health benefits from counseling, immunizations, and behavioral changes after an HCV diagnosis in asymptomatic patients; the effect of antiviral treatments on quality of life; and the comparative effectiveness of antiviral treatments in patients with various medical and psychological comorbid conditions.

Discussion

Burden of Disease

Hepatitis C is the most common chronic bloodborne pathogen in the United States. The prevalence of the anti-HCV antibody in the United States is approximately 1.6% (1).

An estimated 78% of persons who test positive for the anti-HCV antibody have detectable levels of HCV in the blood (viremia), reflecting chronic infection. Persons who have HCV and undetectable viremia are considered

"cured," as demonstrated by the absence of serum HCV RNA (1).

The prevalence of chronic HCV infection peaked in 2001 at 3.6 million persons. According to data from 1999 to 2008, three fourths of patients in the United States living with HCV infection were born between 1945 and 1965, with a peak prevalence of 4.3% in persons aged 40 to 49 years. The incidence of HCV infection was more than 200 000 cases per year during the 1980s but decreased to 25 000 cases per year by 2001. In 2009, the CDC estimated that there were 16 000 new cases of HCV infection (1, 2).

Hepatitis C virus infection is the leading cause of complications from chronic liver disease, and HCV-related end-stage liver disease is the most common indication for liver transplants among U.S. adults. It is estimated that the total number of patients with cirrhosis will peak at 1 million in 2020; however, rates of hepatic decompensation and liver cancer are expected to increase for another 10 to 13 years because of the lengthy lag time between infection and development of cirrhosis and other complications. An estimated 15 000 deaths from HCV infection occurred in 2007 (1).

Scope of Review

The Agency for Healthcare Research and Quality commissioned 2 systematic reviews (1, 7) to update the 2004 USPSTF recommendation on screening for and treatment of HCV infection in asymptomatic adults (8). These reviews focused on evidence gaps identified in the previous USPSTF recommendation and new studies published since 2004. They also examined the evidence on screening for HCV in pregnant women.

Accuracy of Screening Tests

The USPSTF previously found that screening with later-generation enzyme immunoassay and confirmatory recombinant immunoblot assay accurately detects the anti-HCV antibody (8). In the current review, the USPSTF considered the evidence on the diagnostic accuracy of various noninvasive confirmatory tests to diagnose cirrhosis or advanced fibrosis in patients with HCV infection (1). The USPSTF found more than 100 studies (including 8 of good quality) that compared various noninvasive laboratory-based diagnostic tests with liver biopsy as the reference standard. Sensitivity and specificity varied depending on the cutoff used to define a positive test result. Several of the blood indices were associated with an area under the receiver-operating characteristic curve of 0.75 to 0.86 for fibrosis and 0.80 to 0.91 for cirrhosis (considered good to very good values for diagnostic accuracy) (1).

One study evaluated clinical outcomes associated with different strategies to evaluate patients with HCV infection for treatment. A retrospective cohort study of 156 HCV-positive patients who received interferon and ribavirin therapy found no difference in SVR rates between patients who did not have biopsy before treatment compared with matched patients who did have biopsy (41% vs. 44%; $P = 0.87$). About three quarters of the patients who did not have biopsy declined the procedure, and about one quarter had contraindications. The study was not designed or powered to evaluate longer-term clinical outcomes and did not report harms associated with biopsy (1, 9).

Clinical practice is moving toward less routine use of biopsy before antiviral treatment. No studies reported current estimates of the proportion of patients who have biopsy before treatment. Although such practice patterns will undoubtedly reduce harms associated with liver biopsy, how this will affect the number of patients considered eligible for treatment and the long-term clinical effectiveness and harms of treatment of these persons is not yet clear.

Effectiveness of Early Detection and Treatment

There is no direct evidence of the benefit of screening for HCV infection in asymptomatic adults in reducing morbidity or mortality. No randomized trials have compared clinical outcomes between persons screened and those not screened for HCV infection.

Various screening strategies have been proposed; however, no randomized trials or observational studies have compared clinical outcomes of different approaches to screening for HCV. Five studies compared screening approaches to determine the relative yield of the different strategies. Targeted screening strategies in high-risk persons were associated with high sensitivity (>90%) and small numbers needed to screen to identify 1 case of HCV infection (<20 persons). The studies used various criteria for targeted screening, but all included current or past injection drug use, sex with an injection drug user, and receipt of blood transfusion before 1992. Narrow screening strategies (such as those targeting only injection drug use) had low numbers needed to screen but missed up to two thirds of infected patients. None of the studies used the birth-cohort screening approach. The studies were retrospective and had methodological issues that limit the overall ability to compare screening strategies (1).

The USPSTF examined the evidence on benefits from counseling, immunizations, and behavioral changes after a diagnosis of HCV infection. No studies evaluated effects of counseling or immunizations on health outcomes or transmission risk. One randomized trial found that a self-management program in patients with HCV infection was associated with small increases in vitality scores on the 36-Item Short Form Health Survey compared with the use of educational materials after 6 weeks, but there were no effects on other quality-of-life measures (10).

Three retrospective studies showed reduced alcohol use after a diagnosis of HCV infection, but 2 prospective studies found no association between sustainable behavior change (alcohol or injection drug use) and knowledge of diagnosis. Two cross-sectional studies had conflicting results (1).

Evidence is limited on effective counseling methods to decrease high-risk behaviors. Two randomized trials reported mixed results on the effects of behavioral-based counseling interventions compared with simple educational interventions. A before–after study of HCV-infected patients who were heavy drinkers found that a counseling intervention was associated with a greater than 50% reduction in alcohol use (1).

Sustained virologic response is the intermediate outcome used to measure treatment efficacy in clinical trials and is the basis for U.S. Food and Drug Administration drug approval. It is defined as a decrease in HCV RNA to undetectable levels 24 weeks after antiviral treatment and is associated with a sustained loss of detectable viremia.

Sustained virologic response rate is the principal outcome used to assess the benefit of antiviral regimens because of a lack of direct evidence on long-term clinical outcomes. Two trials of boceprevir and 3 trials of telaprevir with pegylated interferon (α2a or α2b) and ribavirin found that these regimens were more effective in increasing SVR rates than dual therapy with pegylated interferon (α2a or α2b) and ribavirin. Sustained virologic response rates ranged from 60% to 92% (genotype 1) with triple therapy regimens compared with 42% to 52% (genotype 1) with dual therapy (7).

The link between SVR and clinical outcomes has been evaluated in many studies. The largest was a cohort study of 16 864 patients from the U.S. Department of Veterans Affairs that adjusted for several confounders (demographic factors, comorbid conditions, laboratory characteristics, and treatment characteristics). This fair-quality study showed a decrease in the risk for all-cause mortality compared with no SVR across patient groups stratified by genotype. Hazard ratios (HRs) were 0.71 (95% CI, 0.60 to 0.86), 0.62 (CI, 0.44 to 0.87), and 0.51 (CI, 0.35 to 0.75) for genotypes 1, 2, and 3, respectively (11). Another recently published cohort study of 530 patients from 5 hospitals in Europe and Canada that adjusted for confounding also found a positive association between SVR and reduced risk for all-cause mortality (HR, 0.26 [CI, 0.14 to 0.49]). The study also found reduced risk for liver-related mortality or transplants (HR, 0.06 [CI, 0.02 to 0.19]), with a median follow-up of 8.4 years. All patients had advanced fibrosis or cirrhosis (12). Eighteen other primarily smaller cohort studies (n = 102 to 2698) found that SVR was associated with decreased risk for all-cause mortality and hepatic complications related to chronic HCV infection, including studies of populations with baseline cirrhosis. The smaller cohort studies had methodological limitations. For example, only 5 studies evaluated important confounders (age, sex, genotype, viral load, and fibrosis); 4 studies reported patients who were excluded or lost to follow-up. In addition, 10 of the 18 studies were conducted in Asia, where the incidence of hepatocellular carcinoma in patients with chronic HCV infection is higher than in the United States, possibly limiting applicability. Hazard ratios in the 18 cohort studies also indicated an association between achievement of SVR and improvement in clinical outcomes, but these studies reported stronger estimates than the U.S. Department of Veterans Affairs cohort study (7). A recently published meta-analysis of pooled observational studies (13), most of which were included in the USPSTF review, examined the association between SVR and hepatocellular carcinoma. Overall, the review's conclusions on the association between SVR and decreased risk for hepatocellular carcinoma were consistent with the USPSTF review. The pooled adjusted HR estimates for hepatocellular carcinoma were 0.24 (CI, 0.18 to 0.31) in the general HCV population and 0.23 (CI, 0.16 to 0.35) in patients with advanced fibrosis or cirrhosis.

A recent meta-analysis of 8 randomized, controlled trials comparing antiviral therapy (interferon or pegylated interferon, alone or with ribavirin) versus placebo or no intervention showed a reduction in hepatocellular carcinoma (risk ratio, 0.53 [CI, 0.34 to 0.81]), with a more pronounced effect in virologic responders than in nonresponders. Although the trials examined older regimens, the USPSTF concluded that the benefits from newer, more effective antiviral regimens may be greater (14).

Antiviral therapy is contraindicated in pregnancy because of its potential teratogenic effects. Although evidence is limited, no labor management intervention has been clearly shown to decrease risk for mother-to-child transmission of HCV infection. Breastfeeding does not seem to be associated with increased risk for mother-to-child transmission (1).

The USPSTF also reviewed a modeling study that informed the CDC's 2012 recommendation on screening for HCV and reported large estimated reductions in HCV-related mortality with a birth-cohort approach versus risk-based screening (15). These estimates assumed a lifetime rate of progression to cirrhosis in untreated patients with HCV infection of 54% and a mortality rate from HCV infection of 22%. However, longitudinal studies with up to 20 years of follow-up report cirrhosis in 10% to 20% of HCV-infected patients, and the longest study reported HCV-related mortality in 5.9% of patients after 45 years. In addition, estimates of clinical benefit in the modeling study assumed that risk for cirrhosis and other complications of HCV infection in patients achieving SVR after antiviral therapy reverted to that of uninfected persons (5). These assumptions relate to important uncertainties about the natural history of HCV infection. If progression to cirrhosis or mortality was lower than assumed, the benefit from screening and treatment would also be lower. A recent modeling study by Liu and colleagues (16) evaluated risk factor–guided and birth-cohort screening strategies. Model assumptions seemed conservative and consistent with available data on the natural history of HCV and effectiveness of antiviral treatment. The study concluded that birth-cohort screening provides nearly twice the benefit of risk-based screening.

Harms of Screening and Treatment

Potential harms associated with screening for HCV infection include anxiety, labeling, and effect on relationships, but evidence on these harms is limited. Five studies of patients diagnosed with HCV infection suggest potential negative psychological and social effects, but the sample sizes were small and the studies had methodological flaws, such as lack of an unscreened comparison group (1).

In addition to the potential harms of screening, there are harms related to the diagnostic evaluation of patients who test positive for the anti-HCV antibody. In a study of 2740 patients with chronic HCV infection and an Ishak fibrosis score of 3 or higher (no uncompensated cirrhosis) who had liver biopsy, serious adverse events occurred in 1.1% of patients, including 0.6% who had serious bleeding and 0.3% who had severe pain (1). No deaths were reported. In 5 large intervention series published since 2004, the mortality rate was less than 0.2% and serious complications were found in 0.3% to 1.0% of more than 62 000 patients who had liver biopsy (1). Because of the availability of various noninvasive tests that have good diagnostic accuracy, liver biopsy will probably occur less frequently.

Harms are associated with the medications used to treat HCV. The most common adverse effects of antiviral regimens are fatigue, headache, and other flu-like symptoms, which occurred in as many as one half of patients in some trials. Triple therapy with protease inhibitors was associated with increased risk for hematologic events (anemia; neutropenia; and thrombocytopenia, particularly with boceprevir) and rash (telaprevir) compared with dual therapy. Although treatment-related adverse effects were common, the few serious adverse events reported in the trials were generally self-limited and typically resolved after the discontinuation of treatment (7).

Estimate of Magnitude of Net Benefit

The USPSTF concludes with moderate certainty that there is a linkage between SVR and clinical outcomes (hepatocellular carcinoma and mortality) and that the overall net benefit of screening is moderate. The evidence supporting this linkage includes consistent associations between achieving SVR and improved clinical outcomes, with most studies reporting large effect sizes, as well as evidence from studies that controlled for several confounders and found an early mortality reduction among patients with all viral genotypes who achieved SVR and are probably similar to patients detected and eligible for treatment through U.S. screening programs. In addition, evidence showed that antiviral treatment results in improved clinical outcomes. A new modeling study showed that birth-cohort screening provided nearly twice the benefit of risk-based screening.

Given the decreasing use of liver biopsy before antiviral treatment and evidence that antiviral therapy regimens have small harms, the USPSTF concludes that the net benefit of screening for HCV infection in high-risk populations with a high prevalence (injection drug users) is moderate. Populations at very high risk have a larger overall benefit from screening because of the higher prevalence of infection and greater potential for treatment benefits. Although the birth cohort has a lower prevalence of infection, the small harms of screening are outweighed by the larger benefit of receiving treatment that can prevent liver-related morbidity and mortality. Therefore, the USPSTF concludes with moderate certainty that the net benefit of 1-time screening in adults born between 1945 and 1965 is moderate.

How Does Evidence Fit With Biological Understanding?

Chronic HCV infection is defined by the presence of HCV RNA in the blood for at least 6 months after acute infection. Chronic infection occurs in 78% of infected patients; however, the ability to accurately determine which infected patients will develop cirrhosis and which will not is limited. Many patients with chronic infection do not develop histologic evidence of liver disease or have mild liver disease, whereas others progress to cirrhosis, end-stage liver disease, or hepatocellular carcinoma. Cohort studies show that approximately 7% to 24% of persons will develop cirrhosis after 20 years of infection, with possible acceleration of cirrhosis after infection for 20 years, and up to 5% will die of liver-related complications (1). Evidence is limited on the longer-term natural history of chronic HCV infection.

Sustained virologic response is associated with the absence of detectable serum HCV RNA, improved histologic changes, and normalization of liver aminotransferase levels. It is considered to reflect resolution of HCV infection.

Preparation of the Draft Recommendation Statement

In July 2012, after deliberation of the evidence, the USPSTF preliminarily voted for a B grade for screening for HCV in high-risk persons and a C grade for the birth cohort. In preparing the draft recommendation statement, the USPSTF considered the quality of evidence obtained from observational data, whether results from the cohort studies reflected a "screened population," and whether SVR is a sufficient proxy for long-term treatment response. These limitations of the evidence led the USPSTF to conclude with moderate certainty that the magnitude of the net benefit was at least small for the birth cohort. The different recommendations for high-risk versus birth-cohort screening reflected differences in the prevalence of HCV infection in the populations and the USPSTF's certainty about net benefit.

A draft version of the recommendation statement was posted for public comment on the USPSTF Web site from 27 November to 24 December 2012. Since then, new evidence has been published by van der Meer and colleagues (12), Morgan and colleagues (13), Kimer and colleagues (14), and Liu and colleagues (16) and reviewed by the USPSTF. The positive association between SVR and mortality (all-cause or liver-related) reported in the cohort study by van der Meer and colleagues strengthened the

USPSTF's confidence in the linkage of SVR and clinical outcomes. A meta-analysis of cohort studies by Morgan and colleagues showed findings consistent with those of the USPSTF's evidence review (13). Kimer and colleagues provided new evidence that antiviral treatment was associated with better clinical outcomes than placebo or no intervention, and the modeling study by Liu and colleagues showed that birth-cohort screening provided nearly twice the clinical benefit of risk-based screening.

The USPSTF also considered that risk-based screening does not work well in identifying persons who are at increased risk for HCV infection. The USPSTF recognized that increased screening and diagnoses could lead to increased harms because not all persons will benefit from treatment. The USPSTF assessed the potential harm of overdiagnosis and determined that the harms were small given the reduced use of liver biopsy, the limited duration of antiviral therapy, and the reversibility of adverse effects with discontinuation and therapy and were balanced by the larger benefit of treatment for infected persons in the birth cohort. The new studies provided evidence that the magnitude of the net benefit in the birth cohort is moderate, not small.

Response to Public Comments

A draft version of this recommendation statement was posted for public comment on the USPSTF Web site from 27 November to 24 December 2012. Some comments requested clarification about risk factors. Others addressed the costs of screening in the birth cohort and how HCV treatment may be inaccessible to persons without health insurance coverage. Many comments noted that risk-based screening would be a burden to clinical providers, is viewed as less effective, and may be a low priority for clinicians who see asymptomatic patients. Many comments disagreed with the USPSTF's assessment of the benefits and harms of screening for HCV in the birth cohort compared with high-risk persons.

In response to these comments, the USPSTF distinguished between established risk factors and less established risk factors in the Clinical Considerations section and added language about populations that are at risk. The USPSTF does not make recommendations on insurance coverage or assess or consider financial costs. The USPSTF also clarified how risk-based screening approaches may miss infected persons.

After the public comment period, the USPSTF considered new evidence that was published since its initial deliberation—specifically, studies by Kimer and colleagues (14), van der Meer and colleagues (12), Liu and colleagues (16), and Morgan and colleagues (13). After reviewing this new evidence, the USPSTF determined that the new studies support a moderate magnitude of net benefit for the birth cohort as well as for high-risk persons.

Update of the Previous USPSTF Recommendation

In 2004, the USPSTF recommended against screening for HCV infection in adults not at increased risk for infection (D recommendation) and found insufficient evidence to recommend for or against screening in adults at high risk (I statement). The D recommendation for average-risk persons was based on a low prevalence of HCV infection, the natural history of chronic HCV infection, a lack of direct evidence showing that screening or antiviral treatments improve important health outcomes, and the potential harms of screening. The USPSTF found insufficient evidence on the effects of screening or antiviral regimens on clinical outcomes and the link between improved intermediate and clinical outcomes to determine the balance of benefits and harms of screening (8).

For this update, the USPSTF reviewed the indirect chain of evidence that showed the benefits of screening through improvement of the intermediate outcome of SVR after triple-regimen antiviral treatments and reductions in all-cause and liver-related mortality and hepatocellular carcinoma. The USPSTF examined the evidence and accepted with moderate certainty the association between SVR after antiviral treatments and improved clinical outcomes. The USPSTF also found adequate evidence that antiviral treatment results in improved clinical outcomes (reduction in hepatocellular carcinoma). In addition, a recent modeling study with more conservative assumptions showed that birth-cohort screening provided nearly twice the benefit of risk-based screening.

In reviewing the prevalence data on high-risk groups and the potential for reduced transmission, the USPSTF concluded that screening in high-risk persons (prevalence $\geq$50%) and the birth cohort (prevalence of about 3% to 4%) would result in a moderate net benefit. With regard to harms, the use of liver biopsy is decreasing and the few serious adverse events reported in the trials were self-limited and typically ended after treatment discontinuation.

On the basis of the evidence, the USPSTF changed its previous recommendations to a grade B recommendation for screening for HCV infection in persons at high risk for infection and 1-time screening for HCV infection in the 1945–1965 birth cohort.

Recommendations of Others

The American Association for the Study of Liver Diseases (17), the Infectious Diseases Society of America (18), and the American College of Gastroenterology (19) recommend screening in higher-risk patients. The CDC now recommends screening in high-risk patients and age cohort–based screening for HCV in all persons born between 1945 and 1965 (5). Previous recommendations on screening for hepatitis C by the American Academy of Family Physicians, which is currently updating its recom-

mendations, have been consistent with those of the USPSTF (20).

From the U.S. Preventive Services Task Force, Rockville, Maryland.

Disclaimer: Recommendations made by the USPSTF are independent of the U.S. government. They should not be construed as an official position of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

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Requests for Single Reprints: Reprints are available from the USPSTF Web site (www.uspreventiveservicestaskforce.org).

References

1. **Chou R, Cottrell EB, Wasson N, Rahman B, Guise JM.** Screening for Hepatitis C Virus Infection in Adults. Comparative Effectiveness Review no. 69. AHRQ publication no. 12-EHC090-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2012. Accessed at www.ncbi.nlm.nih.gov/books/NBK115423 on 24 May 2013.

2. **Smith BD, Patel N, Beckett GA, Jewett A, Ward JW.** Hepatitis C virus antibody prevalence, correlates and predictors among persons born from 1945 through 1965, United States, 1999-2008 [Abstract]. Hepatology. 2011;54(Suppl 1):554A-5A.

3. **Chou R, Wasson N.** Blood tests to diagnosis fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: a systematic review. Ann Intern Med. 2013;158:807-20.

4. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Centers for Disease Control and Prevention. MMWR Recomm Rep. 1998;47(RR-19):1-39. [PMID: 9790221]

5. **Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Teo CG, et al; Centers for Disease Control and Prevention.** Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. MMWR Recomm Rep. 2012;61(RR-4):1-32. [PMID: 22895429]

6. **Centers for Disease Control and Prevention.** Viral Hepatitis Surveillance - United States, 2010. Atlanta, GA: Centers for Disease Control and Prevention; 2012. Accessed at www.cdc.gov/hepatitis/Statistics/2010Surveillance on 24 May 2013.

7. **Chou R, Hartung D, Rahman B, Wasson N, Cottrell E, Fu R.** Treatment for Hepatitis C Virus Infection in Adults. Comparative Effectiveness Review no. 76. AHRQ publication no. 12(13)-EHC113-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2012. Accessed at www.ncbi.nlm.nih.gov/books/NBK115347 on 24 May 2013.

8. **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]

9. **Myers RP, Ratziu V, Imbert-Bismut F, Charlotte F, Poynard T; MULTIVIRC Group.** Groupe d'Etude Multidisciplinaire sur les Pathologies Liées au Virus C. Biochemical markers of liver fibrosis: a comparison with historical features in patients with chronic hepatitis C. Am J Gastroenterol. 2002;97:2419-25. [PMID: 12358267]

10. **Groessl EJ, Weingart KR, Stepnowsky CJ, Gifford AL, Asch SM, Ho SB.** The hepatitis C self-management programme: a randomized controlled trial. J Viral Hepat. 2011;18:358-68. [PMID: 20529203]

11. **Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA.** A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol. 2011;9:509-516.e1. [PMID: 21397729]

12. **van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al.** Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012;308:2584-93. [PMID: 23268517]

13. **Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y.** Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann Intern Med. 2013;158:329-37. [PMID: 23460056]

14. **Kimer N, Dahl EK, Gluud LL, Krag A.** Antiviral therapy for prevention of hepatocellular carcinoma in chronic hepatitis C: systematic review and meta-analysis of randomised controlled trials. BMJ Open. 2012;2. [PMID: 23089208]

15. **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]

16. **Liu S, Cipriano LE, Holodniy M, Goldhaber-Fiebert JD.** Cost-effectiveness analysis of risk-factor guided and birth-cohort screening for chronic hepatitis C infection in the United States. PLoS One. 2013;8:e58975. [PMID: 23533595]

17. **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]

18. **European Paediatric Hepatitis C Virus Network.** Three broad modalities in the natural history of vertically acquired hepatitis C virus infection. Clin Infect Dis. 2005;41:45-51. [PMID: 15937762]

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

20. **American Academy of Family Physicians.** Clinical Preventive Services: Hepatitis. Leawood, KS: American Academy of Family Physicians; 2004. Accessed at www.aafp.org/online/en/home/clinical/exam/hepatitis.html on 24 May 2013.

Appendix: U.S. Preventive Services Task Force

Members of the U.S. Preventive Services Task Force at the time this recommendation was finalized† are Virginia A. Moyer, MD, MPH, *Chair* (American Board of Pediatrics, Chapel Hill, North Carolina); Michael L. LeFevre, MD, MSPH, *Co-Vice Chair* (University of Missouri School of Medicine, Columbia, Missouri); Albert L. Siu, MD, MSPH, *Co-Vice Chair* (Mount Sinai School of Medicine, New York, and James J. Peters Veterans Affairs Medical Center, Bronx, New York); Linda Ciofu Baumann, PhD, RN (University of Wisconsin, Madison, Wisconsin); Kirsten Bibbins-Domingo, PhD, MD (University of California, San Francisco, San Francisco, California); Susan J. Curry, PhD (University of Iowa College of Public Health, Iowa City, Iowa); Mark Ebell, MD, MS (University of Georgia, Athens, Georgia); Glenn Flores, MD (University of Texas Southwestern, Dallas, Texas); Francisco A.R. García, MD, MPH (Pima County Department of Health, Tucson, Arizona); Adelita Gonzales Cantu, RN, PhD (University of Texas Health Science Center, San Antonio, Texas); David C. Grossman, MD, MPH (Group Health Cooperative, Seattle, Washington); Jessica Herzstein, MD, MPH (Air Products, Allentown, Pennsylvania); Wanda K. Nicholson, MD, MPH, MBA (University of North Carolina School of Medicine, Chapel Hill, North Carolina); Douglas K. Owens, MD, MS (Veteran Affairs Palo Alto Health Care System, Palo Alto, and Stanford University, Stanford, California); William R. Phillips, MD, MPH (University of Washington, Seattle, Washington); and Michael P. Pignone, MD, MPH (University of North Carolina, Chapel Hill, North Carolina). Timothy Wilt, MD, MPH, a former USPSTF member, also contributed to the development of this recommendation.

† For a list of current Task Force members, go to www.uspreventiveservicestaskforce.org/members.htm.

Appendix Table 1. **What the USPSTF Grades Mean and Suggestions for Practice**

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer/provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer/provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer/provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Appendix Table 2. **USPSTF Levels of Certainty Regarding Net Benefit**

Level of Certainty*	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited generalizability of findings to routine primary care practice; and lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: the limited number or size of studies; important flaws in study design or methods; inconsistency of findings across individual studies; gaps in the chain of evidence; findings that are not generalizable to routine primary care practice; and a lack of information on important health outcomes. More information may allow an estimation of effects on health outcomes.

* The USPSTF defines *certainty* as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general primary care population. The USPSTF assigns a certainty level on the basis of the nature of the overall evidence available to assess the net benefit of a preventive service.