Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Screening for Hepatitis C Virus Infection in Adults*

Draft review available for public comment from December 09, 2011 to January 06, 2012.

Research Review Citation: Chou R, Cottrell EB, Wasson N, Rahman B, Guise J-M. Screening for Hepatitis C Virus Infection in Adults. Comparative Effectiveness Review No. 69. (Prepared by the Oregon Evidence-based Practice Center under Contract No. 290-2007-10057-I.) AHRQ Publication No. 12(13)-EHC090-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
Donna Geiger	Structured Abstract	"There was no direct evidence on clinical benefits associated with screening compared with no screening (or comparing different screening approaches) in nonpregnant or pregnant adults." ?What would be "direct evidence" = please define "Targeted screening strategies based on the presence of risk factors for HCV infection resulted in numbers needed to screen to identify on case of HCV infection of less than 15…." WOW! I think you meant to print "one" not 'on"- IF so That is one POWERFUL POWERFUL Statistic. "…..but missed from 10 percent to up to two-thirds of infected people, depending on how narrowly screening was targeted" – I am not clear on this rationale. Cohort studies have shown that most individuals with this disease are in the so-called "boomer" group – doesn't it make sense to universally screen this group? Data on harms of screening (such as labeling and anxiety) were sparse. You cite this in your summary as "labeling" causing anxiety and effects on relationships" – aren't these commonly the result of the diagnosis of all chronic medical conditions? Limited evidence suggested that knowledge of HCV status and counseling interventions may reduce alcohol use and risky injection drug use behaviors, but more evidence is needed to demonstrate long-term sustainability and to understand effects on clinical outcomes and transmission risk. In that case perhaps we should rethink screening for chlamydia or giving the HPV immunization amongst adolescents and older young adults.. when do you NOT do something in the prevention realm of healthcare because "long term sustainability" is not possible?	We corrected the text to read "identify one case" in the final report. Thank you for bringing this to our attention. Direct evidence is defined on page 8 of the Methods section. The proportion missed is simply based on the studies that evaluated targeted strategies and reported how many patients with hepatitis C virus (HCV) infection would have been missed by the various strategies. The report does not say that screening should not be done because of no evidence of long-term sustained behavior changes; it simply states that there is no evidence to show that such changes are sustained, which has a big impact on estimations of reduced transmission risk from knowing about HCV-positive status.
Bellinda Schoof, MHA, CPHQ Scientific Affairs Manager AAFP bschoof@aafp.org	Structured Abstract	The evidence report is very well done. There is a type on page v of the structured abstract (should be "on" rather than "one").	Thank you for making us aware of this. We have corrected this in the final report.
Public Reviewer #1	Executive Summary	1. Page ES-1, paragraph 2, line 2: this is 2006 data. The updated CDC data was presented at the 2011 Liver Meeting. The annual mortality is higher than stated in the document. The CDC also recognizes that these figures are marred by significant underreporting. Morbidity has already increased significantly, particularly with hepatocellular carcinoma.	This was updated in the final report. Thank you.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1	Executive Summary	2. Page ES-2, paragraph 4, line 4: these references are old and we would suggest the following as potential additions/substitutions: Colvin HM, et al. Hepatitis and liver cancer: A national strategy for prevention and control of hepatitis B and C. Washington, D.C.: Committee on the prevention and control of viral hepatitis infections; Institute of Medicine; 2010.; McHutchison JG, et al. Chronic hepatitis C: an age wave of disease burden. Am J Manag Care. 2005;11:S286–95.; Pyenson BS, et al. Consequences of hepatitis C virus (HCV): Costs of a baby boomer epidemic of liver disease. Milliman Report. New York, NY; May 2009.; Volk ML, et al. Public health impact of antiviral therapy for hepatitis C in the United States. Hepatology. 2009 Dec; 50(6):1750-5.	This was updated from the IOM report (though the IOM report itself is based on only a single study).
Public Reviewer #1	Executive Summary	3. Page ES-3, paragraph 1, line 12: there have now been two studies looking at the cost-effectiveness of birth cohort screening. The first was by Rein et al. Ann Int Med 2011; Nov 4 [Epub] and the other by McGarry, et al. Hepatology 2011; Dec 2 [Epub].	Thank you for bringing these references to our attention. These are both cost-effectiveness/modeling studies that do not meet the inclusion criteria for this review. Our search strategy was broad, and we sought to include evidence about birth cohort screening that met our inclusion criteria. Our search yielded only one published report on birth cohort screening, but it did not report clinical data, and for that reason did not meet criteria for inclusion in the review.
Public Reviewer #1	Executive Summary	4. Same page, paragraph 3, fourth from last line: reference 8 is incorrect.	Thank you for your comment. This was updated with the most recent CDC estimate.
Public Reviewer #1	Executive Summary	5. Page ES –11, Table A: key question 1A – there will never be prospective data on this. Only modeling can address this topic. Key question 2a - see references in comment above. Key question 3 - the reference Stewart, et al. International J Nurs Stud 2011; Dec 6 [Epub] may address this.	Thank you for your comment. Retrospective studies would also be includable if available; in addition we do not believe that prospective studies could never be done. Modeling studies were excluded as they do not assess actual clinical data.

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Public Reviewer #1	Executive Summary	6. Page ES-14, paragraph 1: The potential benefits of screening lie in identification of infected persons, providing access of those persons to medical care, availability of tolerable and effective treatment, and documentation of durable eradication of virus. There are now several studies that clearly demonstrate that sustained virological response is associated with improved survival, a lower chance of hepatocellular carcinoma, and near complete reduction of the risk of liver failure. It is unlikely that any screening study would be large enough or long enough in duration to link the screening event to such morbidity and mortality outcomes. Thus, the greater challenge comes in linking screening to access to care. There is reasonably good data on the proportion of patients who see a specialist and eventually come to antiviral treatment. Given the superb results with direct acting antiviral agents and the likelihood that interferon will be eliminated from such treatment regimens in the near future, we must assume that the proportion of identified patients who will successfully eradicate virus and reduce their risk for later complications of liver disease or death will be dramatically increased. This is likely still 3 to 5 years away.	Thank you. Evidence on the association between intermediate and clinical outcomes is reviewed in the separate report on antiviral treatments for HCV.
John Ward, CDC	Executive Summary	The review process also appears not to take into consideration the long incubation period between HCV infection and development of disease. On page ES-10, the reviewers note that "there was no direct evidence on clinical benefits associated with screening compared with no screening (or of different screening approaches) in nonpregnant or pregnant adults," implying that this evidence should be available. However, conducting a study that follows patients from screening to illness and death is not feasible. Such a study would take years to conduct, would be prohibitively expensive, and raises ethical concerns because HCV-infected persons in a no-screening group would suffer harm. Because it is not feasible to design a study to determine long-term outcomes, it is critical for the review process to evaluate HCV screening and treatment with the surrogate markers associated with positive health outcomes, such as entry into care and sustained virologic response with treatment	Thank you for commenting. The report describes the long natural history of HCV infection in the Introduction as well as in the Future Research Needs section. The reviewer seems to indicate that only prospective studies would meet inclusion criteria, which is not accurate; retrospective studies would also be included as well. Sustained virologic response (SVR) is evaluated as an outcome in a separate but complementary report about treatment of hepatitis C that will be available concurrently.
John Ward, CDC	Executive Summary	Background (ES-1)- Strike "large or repeated percutaneous exposures to blood.". Multiple studies of health-care associated outbreaks and other transmission settings associate HCV transmission with single and small exposures to contaminated blood. This comment also relates to Introduction page 1.	Thank you for your comment. We revised this to state, "HCV is primarily acquired via percutaneous exposures to infected blood."

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John Ward, CDC	Executive Summary	ES-2 first paragraph. The background data should note recent increases in HCV reporting associated with injection drug use among young persons and the frequent reports of healthcare-associated transmission of HCV. 4th paragraph: Some studies have found more than 50% of unaware of their status. These studies should be included as references.	Thank you for your comment. The Introduction provides a broad range of HCV prevalences in injection drug users and we did not feel adding more detail about recent trends was necessary. We changed the estimate for those unaware of their status to use the estimate from the IOM report, which itself is based on a single study of young injection drug users.
John Ward, CDC	Executive Summary	The Executive Summary, Document, and Annex are repetitive. The recommendations would be easier to read and more effective if they were more succinct.	The Executive Summary is intended to be a summary of the Document. We are not sure what the reviewer is referring to as the "Annex"; if it is the Appendices these are supplemental tables and include information that is otherwise not in the report. This report presents the evidence on hepatitis C screening. The intent of the report is not to make recommendations or guidelines for screening. This is beyond the intent and purpose of this report. Recommendations about screening will be made by a separate and distinct independent body charged with this specific task.

Commentator & Affiliation	Section	Comment	Response
John Ward, CDC	Executive Summary	In the first paragraph of the results section in the Executive Summary, the document states "Limited evidence suggested that knowledge of HCV status and counseling interventions may reduce alcohol use and risky injection drug use behaviors, but more evidence is needed to demonstrate long-term sustainability and effects on clinical outcomes and transmission risk." Multiple behavioral studies have It has been shown repeatedly in behavioral research shown that knowledge alone does not change behavior. However, when a physician or other care provider encourages behavior change based on that knowledge, behavior change (in the short term) does occur. Perhaps it would be best to look at ways to extend the effect of the brief intervention with the provision of booster interventions. THE USPSTF endorses brief alcohol interventions, and there is no evidence than an HCV-infected patient would be less likely to benefit from such an intervention than others. CDC encourages the evidence-based review to recognize this body of literature as applicable to for HCV-infected persons. This concern also relates to key question 6C. For this question, Strength of evidence is listed as insufficient; however, counseling interventions were analyzed and outcomes were listed, including the benefit of a counseling intervention to reduce alcohol use. An insufficient conclusion doesn't seem appropriate.	The review includes key questions that address the evidence on effects of knowledge of HCV Infection (KQ 6b) as well as on counseling interventions (KQ 6c). We focused on evidence on alcohol interventions in HCV-positive persons as it is not known if data from general populations is applicable to HCV-infected persons. A sentence was added to the Discussion to this effect. Finally, we stand by the insufficient grade for KQ 6c, as there are two conflicting randomized trials and a weak observational study only.
John Ward, CDC	Executive Summary	ES-4 The key question should be revised to assess the knowledge of HCV infection status rather than impact of only a positive HCV test. Knowledge of no HCV infection is also of value. Study data have shown persons at-risk for HCV who receive a negative HCV tests result prompt the adoption of protective behaviors than persons who are unaware of their status. This comment also relates to the statement in paragraph 3, ES-14. T The target population of the testing strategy under consideration by CDC is a birth cohort, and not an age cohort. The birth cohort strategy calls for testing of all persons born from 1945 through 1965 (rather than testing of persons aged 45-65). There are several references to this strategy that need to be revised.	KQ 6b addresses impacts of a positive test on risky behaviors. Effects of screening on primary prevention (behaviors in non-infected people) is outside the scope of this review. We revised the description of the CDC screening strategy to refer to screening of persons born in 1945 to 1965. Thank you for your input.

Commentator & Affiliation	Section	Comment	Response
Phillip Coffin	Executive Summary	Thank you for your work on this important subject. While the document thoroughly addresses specific questions, the overall conclusions must consider the bigger picture of the U.S. HCV epidemic. As a public health HCV investigator, I disagree with the conclusion that more research is needed without also noting that broadened screening is urgently needed. The Summary should consider several aspects of the HCV epidemic that are key to determining the utility of broadened screening. 1) Most studies considering the relative benefit and costs of broadened screening were conducted many years ago or relied upon data and models developed many years ago. Two new models (one by Rein et al in Annals of Internal Medicine 2011, the other Coffin et al in Clinical Infectious Diseases currently in press) consider the updated circumstances of 2010/2011. HCV in the U.S. is an evolving epidemic in which a rapidly growing proportion of new diagnoses already have advanced fibrosis. As fibrosis advances, treatment is the only option to avoid complications of HCV-liver disease and yet many treatments appear to decline in effectiveness with advancing fibrosis, increasing the urgency with which we need to identify this population. Studies that considered circumstances 10 years ago were not addressing the same degree and risk of morbidity (i.e. many people infected in the 1970s were still doing okay in the 1990s) and are simply not relevant to the current situation. 2) As the conclusion suggests, evolving HCV treatment must be considered in any evaluation of HCV screening. Treatment is rapidly evolving and we may well have an interferon-free, 3-month, all-oral regimen with few side effects and a very high cure rate within the next 3 years. With such a large population progressing toward end-stage liver disease we need to find these people now in order to establish the infrastructure to treat them as soon as appropriate treatments become available. We don't have time to wait for years of trials that will quickly become irrelevant as new treatments emerge - our best option would be to rely on models that can be modified to the latest circumstances. Too many people will needlessly suffer and our healthcare system will be further overburdened and, frankly, overrun, with end-stage HCV-related liver disease, if we don't act now. 3) HCV has been ignored for so long because it can be - there has rightly been little urgency in diagnosing this chronic disease. However, (a) the aging population of infected persons has forced the sudden realization that we should have acted several years ago, (b) the development of new treatments has given hope for better outcomes for those with timely diagnosis, and (c) the prospect of interferon-free treatments raises the possibility of eventually treating active drug users to break the epidemic through "treatment as prevention". There are real hopes to blunt the epidemic of HCV-related disease we are currently experiencing, but none of these efforts will make a meaningful difference if we do not broaden screening to detect many more HCV-infected persons. Please consider incorporating these concerns.	Thank you for your comment. The report of the review does not make recommendations, but rather it summarizes the available evidence on screening. Modeling studies that don't report actual clinical results do not meet inclusion criteria for this review.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 4	Executive Summary	ES-page 2: The authors note a very long lag time 20-40 years from infection to hepatocellular carcinoma (and presumably death). The lag time to cirrhosis (another potentially important outcome) is also quite long in that cohort studies suggest cirrhosis in 0-10% of patients after at least 10 years of follow-up and another among community cohorts (most relevant to the Task Force) of about 7% at 20 years. These points are important when trying to assess the net benefit of detection of asymptomatic HCV infection, diagnostic/prognostic liver biopsies and treatments with agents that have serious and frequent early adverse effects (and are costly) but no potential for benefit for at least 10-20 years. Thus there is likely to be considerable overdiagnosis and overtreatment resulting in harms. They also note that 50% of HCV+ patients are unaware of their HCV status. This is not a sufficient reason for testing and actually can lead to labeling and harms.	Thank you for your comment. We found that the undiagnosed rate has been estimated at up to 70%.
Public Reviewer # 4	Executive Summary	ES-page 3: Prior Task Force D recommendation in “low risk individuals” was based on low prevalence HCV infection, natural history studies showing that most patients with HCV do not develop major long-term negative health outcomes and lack of direct evidence showing that screening or antiviral treatment improve important health outcomes…” – I agree and do not find any evidence in this report that changes those facts. Furthermore, with the decreasing incidence of HCV and lower risk of transfusion borne infection future screening in “low risk” individuals is likely to be of less benefit than when previously considered.	Thank you for your comment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 4	Executive Summary	ES-14: Discussion: The one study of no difference in virological status according to biopsy status is of uncertain clinical importance. Of greater importance is whether treating those with cirrhosis (or according to biopsy status or noninvasive scores predictive or cirrhosis status) improves clinical outcomes-this portion of the review does not provide evidence for that. I disagree that harms of biopsy "appear to be small". The rate of complications are as high as for some therapeutic or preventive procedures (e.g. radical prostatectomy for prostate cancer, colonoscopy with polypectomy for adenomatous polyps) and higher and more serious than for most "diagnostic" procedures. (e.g. breast biopsy, prostate biopsy etc …). This is particularly important because the vast majority of patients with HCV infection will not have adverse consequences from the condition, and if they did they do not occur for 10-20 years and not all patients who undergo biopsy are candidates for treatment. Benefits due to antiviral treatments and associated between sustained virologic response and improved clinical outcomes are not addressed in this report and require evaluation. As noted in my first paragraph it is difficult to assess benefits and harms of screening in any population without this information-in particular because knowledge of HCV status has limited impact on modes of pregnancy delivery and limited impact (if at all) on behavioural risk factors or universal secretion precautions or blood transfusion usage. Only 15-30% of screen detected patients with HCV receive treatment. Even in this cohort it is not clear if they "benefit" from treatment… and if they do…the time to benefit is extremely long and occurs in few patients. The remainder are likely either overdiagnosed, ineffectively treated or not otherwise candidates/refuse yet still suffer the consequences of diagnosis and possible treatment. The authors note assessing that is difficult due to populations studies and reported. It would be helpful to understand how the percent eligible for treatment has changed over time and by avg or low risk population detected screening (vs. high risk populations) and by age/race.	Antiviral treatments are covered in a separate complementary review that will be available concurrently. We disagree that the harms of prostatic biopsy are comparable to radical prostatectomy, which is associated with a 0.5% perioperative mortality (the largest series of patients with HCV infection found no deaths) as well as risks of CV events, and large risks of long-term impotence/ incontinence). Compared to prostate biopsy the harms appear comparable (prostate biopsy 3.5% fever, 0.4% urinary retention, 0.5% hospitalization for prostatitis or sepsis). We do not have data to assess trends in proportion of screen-detected patients with chronic HCV infection who are treated.
Belinda Schoof	Executive Summary	The evidence report is very well done. There is a type on page v of the structured abstract (should be "on" rather than "one"). Also, the AAFP recommendation for Hepatitis C are: Hepatitis C Virus Infection, Adults The AAFP recommends against routine screening for hepatitis C virus (HCV) infection in asymptomatic adults who are not at increased risk (general population) for infection. (2004) (Grade: D recommendation) Grade Definition: http://www.uspreventiveservicestaskforce.org/uspstf/grades.htm Clinical Consideration: http://www.uspreventiveservicestaskforce.org/uspstf/uspshepc.htm Hepatitis C Virus Infection, Adults The AAFP found insufficient evidence to recommend for or against routine screening for hepatitis C virus (HCV) infection in adults at high risk for infection. (2004) (Grade: I recommendation) Grade Definition: http://www.uspreventiveservicestaskforce.org/uspstf/grades.htm Clinical Consideration: http://www.uspreventiveservicestaskforce.org/uspstf/uspshepc.htm It would be important to consider integrating the results of the review regarding effectiveness of antiviral regimens when that is available.	Thank you for your comment. We corrected the text to read "identify one case" in the final report.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 1	Introduction	The introduction has been well written and sets the scene. It reviews the arguments for and against screening, and nicely highlights the controversies. The introduction supports and feeds into the clinical questions.	Thank you for your comment.
Peer Reviewer # 2	Introduction	I see only one typo. p6 line 42-43 "on" should be "one"	Thank you for noting this. We corrected the text to read “identify one case” in the final report.
Peer Reviewer # 3	Introduction	The introduction is thorough. It provides current epidemiologic data on incidence and prevalence of hep C. It discusses risk factors and natural history and provides a review of the previous USPSTF recommendation.	Thank you for your comment.
Peer Reviewer # 4	Introduction	Provides sufficient background on the HCV issue, the past recommendations from the USPSTF and other current relevant issues that prompted the review.	Thank you for your comment.
Peer Reviewer # 5	Introduction	Written very well.	Thank you for your comment.
Peer Reviewer # 6	Introduction	This statement is incorrect. The prevalence of anti-HCV antibodies (based on data from 1999-2002) is 1.6%. This is not the same as chronic infection; as discussed further down, approximately 20-25% of seropositive individuals do not have chronic infection.	Thank you. We revised the text to state (p 1 and ES-1): "The prevalence of anti-HCV antibody infection in the United States is estimated at 1.6 percent. Approximately 78 percent of those who test positive for anti-HCV antibody have the HCV detectable in the blood (viremia), indicating chronic infection; those with anti-HCV antibody but no viremia are considered to have cleared the infection."
Peer Reviewer # 6	Introduction	This highly precise estimate is not appropriate; different studies have found different proportions of seropositive patients to be viremic depending on factors such as age at infection, race, and sex.	Thank you for your comment. The Introduction notes that the highest prevalence is in people 40 to 49 years of age and discusses risk factors for infection. We believe the background provides sufficient detail about general prevalence of HCV.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 6	Introduction	Given the decrease in annual incidence and generally low anti-viral treatment rates, this statement immediately suggests that the decline in prevalence is due to all-cause mortality. All-cause mortality is decreased in HCV patients who receive anti-viral treatment. Is this taken into account in either this synthesis or the companion review of anti-viral treatment? In addition, this trend also has implications for the Future Directions section. Given the increasing incidence of HCV-related liver disease, there is a limited window available to fill in evidence gaps before screening becomes irrelevant because a substantial proportion of HCV patients will have developed end-stage liver disease.	Thank you. Antiviral treatments are covered in a companion review, including effects on mortality (and the association between SVR and mortality).
Peer Reviewer # 6	Introduction	Complications of HCV should be de-scribed in a separate paragraph, given their mortality, morbidity, and rapidly rising incidence.	Thank you for your comment. Complications are discussed in a separate paragraph (paragraph 2) in the Introduction.
Peer Reviewer # 6	Introduction	This statement omits information on how great this increase in HCC has been; it has tripled over the last two decades in the U.S. It also omits in-formation on the poor survival associated with HCC. Use of the word 'suggests' tends to minimize the magnitude of the association between progression of HCV infection and HCC, with a RR of 15 in HCV-positive vs. HCV-negative individuals.	Thank you. We revised the Introduction to state: "Studies suggest that about half of the recently observed three-fold increase in incidence of hepatocellular carcinoma is related to acquisition of HCV infection 2 to 4 decades earlier."
Peer Reviewer # 6	Introduction	As written, this statement is misleading. Although blood pro-ducts administered in the U.S. are not currently a significant source of *incident* cases of chronic HCV, this risk factor accounts for a substantial number of existing cases. In Armstrong's study, individuals older than 60 with a history of blood transfusion prior to 1992 had a RR of 4.9 (95% CI, 1.7-14.1) for chronic HCV. In a large cohort of U.S. Veterans with chronic HCV, 25% had a history of blood transfusion prior to 1990.	Thank you. We revised the Introduction to state: "Transfusions prior to 1992 are a risk factor for HCV infection but transfusions after 1992 are no longer an important source of infection due to the implementation of effective screening programs for donated blood."
Peer Reviewer # 6	Introduction	This paragraph does not address a significantly higher rate of progression to cirrhosis in the Veterans Affairs cohort, with a prevalence of 18.5% in 2006. The VA National HCV Clinical Case Registry reports a prevalence at some VA medical centers (which served as community hospitals for the local Veteran population) as high as 30%.	Thank you for your comment. The estimates are based on prospective studies with known time of initial infection; not cross-sectional or prevalence studies.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 6	Introduction	The focus of this analysis on individuals with normal LFT results is extremely confusing. Blood donor studies have shown a high prevalence of chronic HCV infection among individuals with normal LFTs. Normal transaminase levels have a low negative predictive value for chronic HCV infec-tion (one reason that the strategy of using elevated transaminases as a surrogate for non-A, non-B hepatitis in screening the blood supply was so unsuccessful.) In addition, a substantial number of HCV-infected individuals with fibrosis may have persistently normal transaminase levels. While there is much debate about whether this subpopulation progresses more slowly, LFTs are a much weaker predictor of HCV infection than are epidemiologic risk factors. Finally, it is not clear whether a "normal" transaminase level really translates into a reduced risk of liver-related mortality.	Thank you for your comment. Testing for HCV infection in people with elevated LFTs or signs/symptoms suggesting HCV infection is considered case-finding, not screening.
Peer Reviewer # 6	Introduction	I am very concerned about the decision to separate the discussion of anti-viral therapy from diagnosis, linkage to care, and risk stratification. Given the absence of RCTs for many of the key questions (at this point, RCTs for these questions are impractical and potentially unethical due to lack of clinical equipoise), the separation of diagnosis and therapy introduces an unavoidable bias against any testing. By way of analogy, screening for cervical carcinoma has never been shown via an RCT to reduce mortality; if one were to analyze Pap smears without reference to available treatments for carcinoma in situ, one would be quite likely to conclude (incorrectly) that such screening should not be performed.	Both the screening review and the complementary treatment review will be available for decisionmakers so antiviral therapy can be considered along with other issues related to screening.
Peer Reviewer # 8	Introduction	Page 10, lines 40-41. "HCV infection… associated with an estimated 12,000 deaths each year in the United States." This is an old estimate. The number exceeded 15,000 in 2007 and has been climbing year by year.9 Page 10, lines 55-56. "Studies of injection drug users report prevalences ranging from 33 to 81 percent." The upper bound of the prevalences is higher. For example, a study in San Francisco found a prevalence of 95%.10 Age, duration of injection drug use, and calendar year, however, are all strong predictors of prevalence.11 Among young injection drug users, who began using after needle exchange was introduced, prevalence rates are often < 50%.12-14 Among old drug users, and those studied in the 1980s, rates are considerably higher.10,15 Thus, a single range may not be an ideal way to describe these prevalences in injection drug users; it may be preferable to report the prevalences in the two groups separately.	Thank you. We revised the Introduction to state: "HCV infection is a leading cause of complications from chronic liver disease, and is associated with an estimated 15,000 deaths in the United States in 2007" with the updated reference cited by the reviewer; and "The prevalence of HCV infection in injection drug users varies widely depending on age, duration of injection drug use, and other factors (such as availability and use of needle exchange programs). Prevalences range from <50% in more recent studies of younger injection drug users to over 90% in older studies of older injection drug users."

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Peer Reviewer # 8	Introduction	Page 11, lines 42-44. “It is thought that up to 50 percent of adults with chronic HCV infection in the United States are unaware of their status.” This may be a selective reading of the literature. The Institute of Medicine examined the problem of viral hepatitis and concluded that 75% of persons with hepatitis C in the United States were unaware of their status.16	The IOM report is based on a single study of young injection drug users. We were unable to find studies reporting other estimates. We revised this section to state, "A high proportion of persons with chronic HCV infection are thought to be unaware of their status. One study of young injection drug users in the U.S. found that 72 percent were unaware of their HCV-positive status."
Public Reviewer #1	Introduction	7. Introduction, page 2, paragraph 2, line 3: the references provided in the second and third comments speak to this issue. Data suggest that well over 50%, perhaps 70% or more, of infected persons do not know that they have hepatitis C infection.	We updated the Introduction with the reference from the IOM report (a single study).
Public Reviewer #3	Introduction	Please correct the reference to the CDC recommendations. Instead of "among persons age 45 to 65", these recommendations address screening among persons born between 1945 and 1965. This is a more accurate and less dated way of stating the population of interest.	Thank you for your comment. We have corrected this.
Dolph Chianchiano	Introduction	The scope of the report is limited to HCV infection and liver disease. On the other hand, HCV infection is associated with an increased prevalence of reduced kidney function and albuminuria and an increased risk of developing End Stage Renal Disease. Moreover, HCV infection is associated with increased mortality in patients on hemodialysis therapy and kidney transplant recipients. (Please see: KDOQI US Commentary on the KDIGO Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in CKD; American Journal of Kidney Diseases, Vol 52, No 5 (November), 2008: pp 811-825.) These risks should be noted in the background section.	Thank you for your comment. Effects of HCV screening on renal disease was outside the scope of this report, which focuses on the hepatic outcomes.
Peer Reviewer # 1	Methods	The inclusion and exclusion criteria are justifiable. Lower quality and broader inclusions had to be permitted given the paucity of direct evidence to support or refute the principle clinical questions. The statistical methods are appropriate. As above, the outcome measures with regard to fibrosis assessment should be more vlearly delineated.	Thank you for your comment.
Peer Reviewer # 2	Methods	Criteria, search strategies, defs, etc are all stated and logical. I am not qualified to address the stats	Thank you for your comment.
Peer Reviewer # 3	Methods	The methods are clearly stated, appropriate, and well justified. I don't see any deficiencies in the methodology.	Thank you for your comment.
Peer Reviewer # 4	Methods	Because this was for HCV screening in a non high risk population, the inclusion criteria was specific to that. So in terms of that criteria, the rest made sense. Statistical methods appropriate.	Thank you for your comment. As clarification, the review did include studies of screening in high-risk as well as non-high-risk populations.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 5	Methods	The inclusion/exclusions are very appropriate and the search strategies quiet logical (and easy to follow the justification.)	Thank you for your comment.
John Ward, CDC	Methods	The methods section highlights the use of a PICO(TS) format to direct the development of the key questions. None of the key questions use the PICO format occasionally but often leave out elements, and the time and setting elements are never used. are formatted with a population, intervention, comparator, outcome, time, or setting. Since they key questions were not developed based on the full PICO(TS) framework, they are less effective in asking a measurable question, which in turn leads to a greater inability to answer the questions in a standardized manner.	The Key Questions are not intended to each outline every element of the PICOTS, which are described in more detail on pages 10-12. This PICOTS delineates the population and conditions, interventions, comparators, and outcomes that were used to guide our evidence review. The PICOTS and elements of the research protocol were developed with input from key informants and technical experts; these stakeholder groups included individuals with expertise in hepatology and public health, as well as representatives from Federal agencies with an interest in the topic.
Peer Reviewer # 1	Results	The results section is detailed, reflects the key questions and has the relevant studies.	Thank you for your comment.
Peer Reviewer # 2	Results	The detail is incredible. The tables are the largest I have ever seen.	Thank you for your comment.
Peer Reviewer # 3	Results	The results are clearly stated in appropriate detail. Longer would not be better. I like the bullet points at the beginning of each section of Results, as they help to summarize the findings. The tables are sufficiently detailed. I am not aware of any studies that should have been included or excluded.	Thank you for your comment.
Peer Reviewer # 4	Results	Yes, much, much detail. Each article that was considered was clearly outlined and reasons why it was used. How results arrived at were clearly documented. Numerous tables used and referred to in article to make the authors points explicit.	Thank you for your comment.
Peer Reviewer # 5	Results	Appropriate studies are included. The tables and figures are quite complete and perhaps more than needed.	Thank you for your comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 6	Results	I would strongly recommend collaboration with large health care organizations that have substantial numbers of HCV patients (Department of Veterans Affairs and Kaiser-Permanente) to examine data that is not contained in the published literature that may be informative.	Thank you. We did not include unpublished studies. We did assess grey literature to qualitatively identify potential publication bias or unpublished data on harms, but we did not include unpublished studies in the report because the searches did not yield additional high quality or usable data beyond the evidence available in the body of peer reviewed literature.
Peer Reviewer # 6	Results	It is not clear why this testing algorithm was chosen. In many systems, a positive ELISA is reflexively tested by nucleic acid testing, without RIBA.	We revised the results to state: "Our review assumed screening with a later-generation HCV enzyme-linked immunoassay (ELISA) as the initial test, with confirmatory recombinant immunoblot assay (RIBA) or nucleic acid testing for HCV infection for positive ELISA. We considered patients to have chronic HCV infection if they had hepatitis C viremia based on reverse transcriptase polymerase chain reaction (PCR) or nucleic acid testing."
Peer Reviewer # 6	Results	Liver biopsy is no longer regarded as being absolutely essential for treatment eligibility determinations, particularly for patients with genotype 2 or 3 infection.	Thank you. This is discussed in the Interventions section.
Peer Reviewer # 6	Results	Suggestions for additional studies to review that are relevant to NNT among at-risk groups	The team reviewed the suggested references; none met inclusion criteria, primarily because they did not perform (or attempt to perform) screening in a defined population and evaluate the yield/sensitivity of different screening strategies.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 8	Results	Key Question 2b Page 48, lines 18-19. The CDC study that evaluated a screening strategy targeted at the highest-prevalence birth cohort (those born between 1945 and 1965) has been completed and published.	Thank you. The CDC study referred to by the reviewer is a modeling study, and it did not evaluate actual clinical outcomes with the birth cohort approach. Therefore it did not meet the inclusion criteria for this review.
Connie Chiang, PharmD Associate Director, Medical Information Janssen Scientific Affairs, LLC 1125 Trenton-Harbourton Road Titusville, NJ 08560	Results	Key Question 1a: As noted in the conclusions from Smith 2011 (Abstract 241), while most persons who are chronically infected with HCV and have persistently normal ALT (PNALT) levels have significantly less liver fibrosis than persons whose ALT levels are elevated, 20-30% of chronically-infected persons with PNALT do have significant fibrosis progression and are candidates for prevention and care. Reference:Smith DB, Patel N, Beckett, and Ward JW. Comparison of hepatitis C virus infection screening strategies: Elevated alanine aminotransferase levels versus birth cohort. Oral presentation at the 62nd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); San Francisco, CA, November 4-8, 2011. Abstract 241.	Thank you for this information.
Public Reviewer # 4	Results	KQ2: Both targeted and universal screening in the reported populations appear to have relatively acceptable NNS to identify a case of HCV. I do not believe this is the key point. Furthermore, this presumably is a 1x screen. Additional comments could be made re: the age of cohorts, the conceptual validity (or lack of) for starting, stopping or more than one screen and the potential harm of a negative screen in someone later on goes and becomes infected. If a recommendation for screening is made it will be important to be more specific about age to start, stop and frequencies and the benefits and harms of that.	Thank you for your comment.
Connie Chiang, PharmD Associate Director, Medical Information Janssen Scientific Affairs, LLC 1125 Trenton-Harbourton Road Titusville, NJ 08560	Results	Key Question 2a and 2b: Consider including data from current CDC projects on birth cohort screening. Ref: *Smith BD, Patel N, and Ward J. Hepatitis C virus antibody prevalence, correlates and predictors among persons born from 1945 through 1965, United States, 1999-2008. Poster presented at the 62nd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); San Francisco, CA, November 4-8, 2011. Abstract 394. Rein DB, Smith BD, Wittenborn JS, et al. The Cost-Effectiveness of Birth-Cohort Screening for Hepatitis C Antibody in U.S. Primary Care Settings. Ann Intern Med published ahead of print November 4, 2011. *Spradling PR, Rupp LB, Moorman, et al. Predictors of testing for and infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) in four United States health care organizations (HCOs), 2006-2008. Poster presented at the 62nd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); San Francisco, CA, November 4-8, 2011. Abstract 1749.	Thank you. These are modeling studies, and so these references do not meet inclusion criteria.

Commentator & Affiliation	Section	Comment	Response
John Ward, CDC	Results	Key Question 2a examines the tools used to screen for HCV among different risk- /and prevalence-based populations, but doesn't specify examine the issue of which risk-/and prevalence-based populations were included in this review. are at greatest need for screening. AHRQ investigators conclude contends that evidence is insufficient to warrant the routine HCV screening of high -risk populations should not receive routine HCV screenings; however, none of the key questions look at the proportion of HCV among persons in risk-/and prevalence-based populations. The report should be explicit about which risk and prevalence-based populations were considered. CDC has multiple studies that show demonstrating the high prevalence of HCV among persons with a history of current or past IDU and of high prevalence in in certain age groups the 1945-1965 birth cohort (e.g., persons in the birth cohort). CDC believes that this conclusion is flawed in part because of the dichotomy that has been created separating treatment and screening. This limitation is compounded and because intermediate outcomes have not been considered.	This report makes no conclusions about whether screening is warranted or not; it simply summarizes the evidence on benefits and harms and yield of screening. Risk factors for HCV infection as well as the increased prevalence in certain age groups is discussed in the Background; however, no clinical study has evaluated clinical outcomes associated with screening in such populations.
Public Reviewer #1	Results	Question 2b: The reference by McGarry (see comment 3) also addresses this question and their sensitivity analysis also addresses the cost-effectiveness of screening by various methods depending a population prevalence.	This is a modeling study and does not meet inclusion criteria.
Public Reviewer # 4	Results	KQ4a: See comment in opening paragraph. Again the bullets are helpful-is cirrhosis or fibrosis the key factor in making treatment decisions. Presumably this KQ was developed because treatment is primarily focused on patients with cirrhosis. Several problems come with this: a) the data suggest fair to good diagnostic accuracy-is their evidence to indicate that clinicians are willing to forego biopsy in making treatment decisions or conversely what has been the impact of using these scores to guide treatment decisions on clinical outcomes and the prevalence of potential candidates for therapy; b) there was insufficient evidence that clinical outcomes varied by biopsy status (as measured by sustained virological rates…of greater importance would be the impact on true clinical outcomes-rather than just virological efficacy). I do not believe that virological outcomes are a clinical outcome-they are intermediate.	See response to previous comment by this reviewer.
Public Reviewer #1	Results	Question 4a: This question is based on previous recommendations from the NIH consensus conference at which treatment was most strongly recommended for those with advanced fibrosis. Clearly, clinical practices have changed significantly over the last 10 years and the degree of fibrosis plays a much smaller role in selecting patients for treatment. This will become even more the case as the efficacy of new therapies improves even further. This is not to say, however, that these assessments of fibrosis are not important since they do influence the urgency of treatment and need for clinical follow-up. Thus, the diagnostic evaluation of patients found to be positive for antibody to the hepatitis C virus includes confirmation of viremia (HCV-RNA) and viral genotype, not liver biopsy.	The most recent practice guidelines from the AASLD and others still recommend biopsy for most patients being considered for treatment. The KQ makes no judgment about the need for biopsy or not, it simply summarizes the evidence on clinical outcomes associated with biopsy vs. no biopsy prior to treatment, and the diagnostic accuracy of non-invasive assessment methods compared to biopsy.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 4	Results	KQ4b: All patients addressing the question were identified via risk based testing. The applicability to low risk individuals is not known from these data. Between 15-33% of patients received treatment suggesting much over diagnosis even if one presumes that all treated patients "needed or benefited" from treatment. In the 2 studies that reported-57-71 percent of test + patients were classified as eligible (though being classified as treatment eligible does not necessarily translate into benefitting from treatment-it merely implies someone thinks they should get a treatment-we need a better linkage between treatment eligible, treatment received and benefits in clinical (not virological or biochemical) outcomes. Additionally, adherence to treatment (not covered here) would make "treated" even lower than the 15-33%.	Thank you for your comment.
Public Reviewer #1	Results	Key question 4b: It needs to be qualified that screening has been limited to at risk populations. The patient subsets must be outlined to understand why so few identified proceeded to treatment. If screening was implemented in a STD clinic or prison system with limited follow-up it is not an accurate reflection of how many patients may be eligible for therapy if screening was performed in a primary care office.	As described in the report, two of the studies were large Veterans Affairs studies and the third of active and former drug users; the results also describe challenges in interpreting the results including unclear or poorly defined eligibility criteria.
Public Reviewer #1	Results	Key question 5, harm of work-up: Most of these studies center on liver biopsy. Only a minority of patients require a biopsy when formulating treatment decisions. This proportion will grow even smaller once more effective and better tolerated therapy is available. It is true that biopsy has a real and well established risk, but key question 5 must be qualified by the number of patients that actually require a biopsy.	The KQ simply reports harms associated with biopsy.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 4	Results	KQ5: the serious AE events reported for workup appear to be high given that these are workup (NOT treatment) harms and that most patients are still not candidates for treatment (which have harms) and any benefit from treatment on average is at least 10-20 years in the future. Serious AE occurred in approximately 1% with 0.6% having a serious bleed and periprocedure mortality of around 0.2%. The types of serious AE are very real and clinically relevant. On page 39 the authors state "no study of percutaneous liver biopsies specifically examined asymptomatic patients … who may be at lower risk." 1) it is not clear that all patients with "cirrhosis" are symptomatic-I would correct the statement to probably say something like-no studies of patients without symptoms, liver function abnormalities or other evidence of cirrhosis…or from screened populations… 2) while the actual rate of complications might be less the overall number would be higher because of the marked increase in frequency of liver biopsies needed in evaluating the large number of asymptomatic patients with normal LFTs and no other evidence of cirrhosis. Additionally, these patients presumably have a better long-term natural history and thus have less to gain and more to lose from complications. An essential point will be for this review to help us determine in whom and how frequently do patients undergo liver biopsy, are all antiviral treatment trials based on patients who have undergone a liver biopsy, and has there been treatment "creep"…such that even in the absence of evidence patients without cirrhosis (or a biopsy to determine cirrhosis status) are receiving treatment.	The periprocedural mortality cited by the reviewer is not in patients specifically with HCV infection; they include patients with conditions such as cancers who most would assume to be more ill. The largest study of HCV patients showed no deaths. Although we agree with the reviewer that the rate of harms may be similar with liver biopsy and other diagnostic tests following screening, they are generally short-term and self-limited.
John Ward, CDC	Results	Key Question 6a: Narrative in first paragraph should define the number needed to determine a significant change in quality of life (QOL) among persons evaluated with the SF-36 (i.e., a one-point difference does not indicate a significant change in a person's QOL).	We previously stated that the reported differences (2 to 5 points) were slight.
Public Reviewer # 4	Results	KQ 6a: The improvements in vitality scores are based on a subscale of the SF-36 and unlikely to be clinically meaningful. I would clarify this. (p40)	Thank you for your comment. It is reported as a subscale in the Results.
Public Reviewer # 4	Results	KQ6b-c Little evidence that counseling or awareness improve long-term risk behavior. Furthermore, it is not clear that knowledge of HCV status is important to initiate counseling or receive benefits of counseling re: risk behavior.	Thank you for your comment.
Public Reviewer #1	Results	Key question 6a: Several studies have shown that effectively treating HCV improves quality of life. This should also be factored into this question.	Effects of antiviral treatments on QoL are addressed in a separate review.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1	Results	Key question 6c: data does suggest that needle exchange programs decrease the transmission rates of several blood borne pathogens. http://students.umf.maine.edu/marc.chiavon/public.www/The%20effect%20of%20clean%20needle%20exchange%20programs%20in%20the%20United%20States.pdf This sections should be expanded to include any information we have regarding NEP and HCV transmission http://aje.oxfordjournals.org/content/149/3/214.full.pdf	Studies of needle exchange programs generally did not specifically evaluate effectiveness of needle exchange programs in persons with HCV infection, and therefore did not meet inclusion criteria. Reviewing the general efficacy of needle exchange was outside the scope of this review, though readers may choose to extrapolate.
NVHR	Results	To take one example of the rapidly shifting landscape, the draft CER devotes considerable attention to the comparative effectiveness and diagnostic accuracy of tests used for the workup to guide treatment decisions. The majority of this section considers the diagnostic accuracy of various tests when compared to liver biopsy. It should be noted that more than a dozen additional studies evaluating the performance of various tests as alternatives to liver biopsy were presented in November, 2011 at the AASLD Liver Meeting, with additional data slated for release in 2012. More importantly, the role of liver biopsy in clinical practice is shifting due to advancements in HCV treatment. The AASLD noted in their 2009 Practice Guidelines ("Diagnosis, Management, and Treatment of Hepatitis C: An Update"): "A liver biopsy may be unnecessary in persons with genotypes 2 and 3 HCV infection, since more than 80% of them achieve a sustained virlogical response (SVR) to standard-of-care treatment. There is,however, an ongoing debate about whether a biopsy is warranted for persons infected with HCV, genotype 1, whose response to such treatment approximates 50% among Caucasians and 30% among African Americans. Even more uncertain is whether there is need for a liver biopsy in persons infected with the other less common genotypes (4 through 6). "Thus, although the liver biopsy was previously regarded as routine for defining the fibrosis stage in persons with genotype 1 infection, the issue is now in a state of flux and possible transition." Hepatitis C protease inhibitors approved in May, 2011 for the treatment of genotype 1 HCV infection now offer SVR rates of up to 79%, well in the range of SVR rates achieved with standard of care therapy for genotypes 2 and 3. While liver biopsy still plays a role in clinical practice, its relative importance in guiding treatment decision-making is declining in parallel with substantial improvements in SVR rates. Therefore, the relative weight of liver biopsy in considerations regarding the relative effectiveness and potential harms of tests involved in the workup to guide treatment decisions should correspondingly diminish, and perhaps be obviated completely in the near future.	The 2009 AASLD guideline still recommends considering biopsy prior to treatment, though acknowledging changes in practice. Regardless, KQ 4a addresses evidence on outcomes of treatment with biopsy vs. without biopsy (only one study available). The rest of the KQ simply summarizes the available evidence on the diagnostic accuracy of noninvasive tests vs. liver biopsy and makes no judgment regarding the need for liver biopsy.

Commentator & Affiliation	Section	Comment	Response
Dolph Chianchiano	Results	In its analysis of comparative effectiveness of HCV screening, the AHRQ evidence center excluded dialysis patients (page 11) but the evidence review by the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline development program (and the Kidney Disease Outcomes Quality Initiative US Commentary) resulted in a recommendation for routine testing of dialysis patients and kidney transplant candidates for HCV, based on "strong" evidence. The Kidney Disease Outcomes Quality Initiative (KDOQI) US Commentary on the KDIGO HCV Guideline concluded that the KDIGO recommendation is applicable in the US context because the prevalence of HCV in patients on maintenance hemodialysis therapy is tenfold greater than that of the general population. In addition, the KDOQI Commentary on the KDIGO HCV Guideline makes the following recommendation for individuals with earlier stages of CKD: "HCV testing of patients with CKD should be performed in patients with unexplained proteinuria, microscopic hematuria, increased aminotransferase levels, or risk factors for HCV acquisition." These recommendations should be noted in the report. Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of Hepatitis C in chronic kidney disease. Kidney International 2008; 73 (Suppl 109): S1–S99. KDOQI US Commentary on the KDIGO Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in CKD American Journal of Kidney Diseases, Vol 52, No 5 (November), 2008: pp 811-825.	Persons with kidney failure were outside the scope of this report.
Peer Reviewer # 1	Discussion/ Conclusion	The implications of the major findings are clearly stated. Unfortunately there are still major gaps in the evidence base, but these have been highlighted. The future research section is clear, and most importantly, highlights the challenges in obtaining data to support or refute screening.	Thank you for your comment.
Peer Reviewer # 2	Discussion/ Conclusion	Yes [sic]	Thank you for your comment.
Peer Reviewer # 3	Discussion/ Conclusion	The discussion was well written, with a summary of the findings and paragraphs on limitations and future research. The findings were fairly presented. I liked the Summary Table, with the key questions, strength of evidence and conclusion. That was succinct and clear. A comparison of the findings of this review with the CDC's birth cohort approach would be helpful.	Thank you for your comment. The only data available from the CDC birth cohort approach is a modeling study. The need for studies evaluating the clinical accuracy and effectiveness of this (and other) screening strategies is mentioned in the Future Research section.
Peer Reviewer # 4	Discussion/ Conclusion	Limitations appropriately stated. Review was hampered due to the lack of research in the area of what the key questions asked for. And clearly stated the in the section for future research what is needed in order to advance this science.	Thank you for your comment.
Peer Reviewer # 5	Discussion/ Conclusion	Nothing omitted that I would have included. The future research needed is quite adequately stated.	Thank you for your comment.

Commentator & Affiliation	Section	Comment	Response
Donna Geiger	Discussion/ Conclusion	"Much of the benefits from screening are likely to occur as a result of antiviral treatments, which have become increasingly effective at achieving a sustained virologic response (a strong predictor of long-term virological response)" I very much disagree with this assessment. Harm reduction advice in the form of weight loss and avoidance of ETOH and tobacco are powerful recommendations for any patient infected chronically with HCV. HCVHCV remains primarily a disease of duration. Individuals infected for less than 5-10 years often have only mild liver disease, if any. Studies of the cohort of Irish pregnant women infected in the 1970s has consistently shown low incidence of cirrhosis AND low rates of ETOH consumption which is often quoted as one of the primary reasons women do better than men with this disease. Maintaining a normal weight and limited EOTH intake can be within the control of the individual as opposed to actually obtaining viral clearance which is a complex and miserable process with our current therapies and one many patients cannot even afford. When I advise patients with minimal liver disease they can safely await better therapies that depends to a large extent on follow-up regarding ETOH and working towards a normal BMI. Our media rich society soaks us all with messages to eat and drink alcohol multiple times a day. Though we all know these behaviors are not healthy, once a clinical diagnosis is given as a result (eg. Diabetes would be an excellent example) behaviors may not change. Do we not then screen for diabetes ! I have seen many many hospitalized patients with end stage liver disease who are alcoholics AND have chronic HCV. In fact, that is the first thing I try to find out when I see such a patient. And typically their HCV status is buried in the record. I have to do some sleuthing to find it. Many people drink too much – the patients who end up destroying their livers with ETOH usually have a co-morbidity –either HCV, or now Obesity. I think that your report requires evidence that would take years to obtain to meet your strict criteria. In the healthcare system in which I have participated for decades now, unchanging evidence has not been required for mammography, cervical cancer screening, many of the commonly administered immunizations, prostate cancer screening and so many others I cannot list them all. I do have to wonder whether this disease of essentially individuals with substance abuse histories that includes primarily IV drug use colors the decisions made by your organization. I am very disappointed, Thank you for allowing comments.	KQ 6a addressed benefits of counseling (including for alcohol) in persons with HCV infection. We are not aware of any studies evaluating specific effects of weight loss or tobacco use in persons with HCV infection.
Public Reviewer #3	Discussion/ Conclusion	Please correct the reference to the CDC recommendations. Instead of "among persons age 45 to 65", these recommendations address screening among persons born between 1945 and 1965. This is a more accurate and less dated way of stating the population of interest.	We revised the description of the CDC screening strategy to refer to screening of persons born from 1945 to 1965.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 8	Future Research Needs	More research is needed on how to overcome the barriers to treatment that result in a low proportion of persons screening positive for hepatitis C benefiting from antiviral treatment. This research gap is not mentioned in the review. More research is also needed on the experiences of persons testing positive to better understand the potential benefits of screening. The review mentions the need for more research on the harms of screening but not the benefits.	The Future Research section states: "Studies that compare clinical outcomes in patients screened and not screened for HCV infection would provide the most direct evidence…." Clinical outcomes include beneficial outcomes, such as improvements in quality of life and morbidity. Addressing barriers to screening was not within the scope of this review.

Commentator & Affiliation	Section	Comment	Response
John Ward, CDC	Future Research Needs	The first paragraph of the Future Research section contains this sentence: "Studies that compare clinical outcomes in patients screened and not screened for HCV infection would provide the most direct evidence, but would require large sample sizes and long duration of follow up." It is possible to say that the cost, in terms of time and financial resources, precludes a study that would compareing screening strategies based solely on clinical outcomes; this is not a realistic suggestion for future research. Further, any benefit derived from the findings of such a long-term study would no longer be relevant or have value to the large population of chronicallyHCV- infected persons born from 1945 through 1965 because the study would take too long to conduct.	Retrospective studies would also be includable if available, and we do not believe that a prospective study is completely precluded. In fact, there is no reason why the birth cohort approach by the CDC shouldn't be prospectively evaluated. We revised the Research Gaps section to state: "Studies that compare clinical outcomes in patients screened and not screened for HCV infection would provide the most direct evidence, but would require large sample sizes and long duration of followup. However, studies would not necessarily need to be prospective, as well-conducted retrospective studies could also be informative. In addition, in lieu of direct evidence on effects of screening on clinical outcomes, studies that prospectively evaluate the accuracy and efficiency of alternative screening strategies (such as the CDC birth-cohort approach of screening all adults born between 1945 and 1965) would help fill important research gaps and provide some evidence to help guide strategies for targeted screening."

Commentator & Affiliation	Section	Comment	Response
John Ward, CDC	Future Research Needs	The next sentence in the first paragraph of the Future Research section states that “No studies have adequately assessed the harmful impacts due to anxiety, labeling, or relationships with family and sexual partners that may result from screening for HCV infection in these patients, and whether these harmful impacts can be minimized by appropriate counseling.” While the sentence does state these harms may result, the overall thrust of the sentence suggests that these harms do exist. However, no studies support even though no studies were found to support that this assertion., and Iit appears that the statement about the potential harms of testing is not supported by the data. at h. Evidence regarding harms are getgetstings the benefit of the doubt, whilereas benefits are set to an unattainable standard. WeHence, CDC would recommends toning down the de-emphasisizing on harms given the absence of data. and given the poor quality of the studies regarding harms included in this report.	Balanced reviews of screening interventions require consideration of both harms and benefits. The statement in question simply reports that no studies were found.
Public Reviewer #3	Future Research Needs	Please correct the reference to the CDC recommendations. Instead of "among persons age 45 to 65", these recommendations address screening among persons born between 1945 and 1965. This is a more accurate and less dated way of stating the population of interest.	We revised the description of the CDC screening strategy to refer to screening of persons born in 1945 to 1965.
Genentech	Future Research Needs	Given the potentially high cost burden when HCV is left untreated, this draft Report is being released at a critical juncture. It will be used by the U.S. Preventive Services Task Force (USPSTF) to update its recommendations on HCV screening for asymptomatic adults. The USPSTF recommendations have important implications for access to care in the Medicare and Medicaid programs, as we" as in private health plans. As such, the basis for the updated recommendations should reflect the most current data and evidence relevant to screening for chronic HCV. As discussed above, the CDC is currently evaluating the potential of a new screening strategy to identify individuals with the hepatitis virus. Researchers are reviewing medical records to better understand the effectiveness of the current risk-based approach and collecting data on a birth-year based approach (one-time screening for everyone born from 1945 to 1965). The findings are expected to be published in 2012 and could provide the scientific foundation for new screening recommendations on hepatitis C. A birth-year based screening could have a significant impact; a recent analysis suggested that screening all people in the United States ages 46-64 years would identify more than 800,000 individuals previously undiagnosed with hepatitis C.? Such early identification, combined with treatment, could prevent the severe - or fatal -- complications associated with the disease. The Report acknowledges that the CDC's initiative could address an existing gap in the evidence. In the discussion about Future Research, the Report states that U[i]n lieu of direct evidence on effects of screening on clinical outcomes, studies that prospectively evaluate the accuracy and efficiency of alternative screening • strategies (such as the CDC birth-cohort approach of screening all adults 45 to 65 years of age) would help guide strategies for targeted screening."s Given the importance of the CDC's study to achieve the goal of better identification and treatment of hepatitis C, we urge AHRQ to fully consider this important data in the Report.	See responses to similar comments; the CDC's birth cohort approach has only been evaluated in a modeling study without actual clinical outcomes.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 1	Clarity and Usability	The report was well thought out and presented. The key questions were well delineated and evidence presented well. the conclusions were appropriate and it was easy to read. The conclusion can inform clinical practice, but add little to the previous report because of continuing evidence gaps.	Thank you for your comment.
Peer Reviewer # 2	Clarity and Usability	The document is so massive and repetitive that I doubt it will be read. The page number alone is daunting and will lead most would-be readers to forget about it. The table of contents is helpful. The focus on pregnancy is massive and unlike I have ever seen before. I have no MPH. Perhaps pregnancy is the top priority of all such studies. I have no idea.	Thank you for your comment. The comparative effectiveness reviews are often summarized in a journal article that may be more accessible to some readers.
Peer Reviewer # 3	Clarity and Usability	Yes, overall very well written and organized. The report will be very helpful to policy-making/guideline groups.	Thank you for your comment.
Peer Reviewer # 4	Clarity and Usability	Very clear and well organized. Tables were appropriate in order to clarify the topics discussed in the narrative. The conclusions can clearly be used by providers in discussions with patients that fit the inclusion criteria of the review.	Thank you for your comment.
Peer Reviewer # 5	Clarity and Usability	It will be difficult for the conclusions to inform practice decisions, only because of the lack of good data (no RCT's).	Thank you for your comment.
Donna Geiger	Appendix	In your Appendix you define “high risk groups” as Substance-abuse, Intravenous/ Needle Sharing/Opioid-Related Disorders/Unsafe Sex/Sexual Behavior/HIV/HIV Infections. You do not include alcoholics!	Alcoholics are not at higher risk for HCV infection (they are at higher risk for progression if they have chronic HCV infection).

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 8	Figures and Tables	Problems with Analytic Framework The analytic framework is imbalanced with respect to the benefits and harms of detecting HCV infection. Subjective harms of screening, such as anxiety, labeling, effects on partner relationships, etc., are considered, but subjective benefits of an infected person's knowing one's HCV status are not. Potential benefits of knowing one's status include the opportunity to access antiviral treatment; to educate oneself and make an informed choice about antiviral treatment; to monitor developments in the rapidly evolving field of new HCV drug development; to obtain health insurance so that treatment will be an option in the future; to take other steps to avoid complications of hepatitis C, such as avoiding or treating HIV infection and avoiding or receiving treatment for alcohol consumption; and, not least, to take steps to avoid transmitting the infection to others, including one's loved ones. The extent to which patients avail themselves of these opportunities will differ from patient to patient. The extent to which patients value having these opportunities will also differ from patient to patient. The analytic framework does not consider the value of patients' having these opportunities. Authorities on medical ethics emphasize autonomy as one of the guiding principles of medical practice. Patients cannot have autonomy to address threats to their health if they do not have complete information about them. The value of knowing about an infection that one has may be very different for different people. The decision to be tested is therefore, one that autonomous persons should be able to choose for themselves. They cannot make this decision if they are not offered testing. The analytic framework does not acknowledge or address the value of this autonomy to patients.	The "subjective benefits" referred to by the reader are included in morbidity and quality of life. As discussed in the results, very few studies have evaluated such outcomes. A number of the potential benefits mentioned by the reviewer, such as effectiveness of alcohol treatment and transmission risk, are included outcomes in the review. Beneficial effects on "patient autonomy" could be measured by outcomes assessing effects on quality of life, but no studies did so.
Public Reviewer #3	Figures and Tables	Centers for Disease Control and Prevention Recommendations for prevention and control of HCV infection and HCV related chronic disease (2002) *Note - recommendations were released in 1998, not 2002.	Thank you for your comment. This was corrected in the final report.
Public Reviewer # 4	Figures and Tables	**Table 3** is busy and hard to follow. Any way to make this picture-wise or graphically. Difficult I know. Perhaps a "bottom line" Several of the studies include AST/ALT ratios (presumably because one or the other or both are abnormal)-however our screened population must have normal LFTs…thus presumably all patients identified by screening would not be candidates for treatment or necessarily would have to undergo biopsy or there would be a long delay and monitoring of LFTs among identified individuals. Has this been considered in the potential harms and clinical implications/applicability.?	The screened population is asymptomatic persons not known to have abnormal liver enzymes, so persons undergoing screening may or may not have elevated liver enzymes. The proportion of screen-detected patients who receive treatments is reviewed as a key question.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 2	References	There are 3 key references that I can't find in the massive list of refs. Two are recent huge liver Bx studies--Clin Gastro & Hep 2010;8:877-83 and Gastroenterology 2010;139:1230-7. One is in press in Hepatology Hoefs, et al regarding perhaps the best noninvasive test that predicts mortality, the perfused hepatic mass. The list of excluded studies is also massive.	Thank you. The two references on biopsies were included (ref: 70 Seeff 2010 et al, ref. 72 West 2010 et al). The study on perfused hepatic mass is not yet published and therefore not includable; if It were published we would need to verify that this is an FDA-approved test before making a decision to include it or not.
Dolph Chianchiano	References	We recommend addition of these two references. Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of Hepatitis C in chronic kidney disease. Kidney International 2008; 73 (Suppl 109): S1–S99. KDOQI US Commentary on the KDIGO Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in CKD American Journal of Kidney Diseases, Vol 52, No 5 (November), 2008: pp 811-825.	Thank you. Renal failure patients were outside the scope of this report.

Commentator & Affiliation	Section	Comment	Response
Vertex	References	Recent work by the Centers for Disease Control and Prevention (CDC) has shown that of the Americans who are most likely to have HCV infection in the US, 80 percent were born from 1945 through 1965.8 IfHCV screening mechanisms target both the birth cohort between 1945 and 1965 and patients with elevated levels of the alanine aminotransferase (ALT) liver enzyme, screening can identify 90 percent of people in the US with HCV.9 As acknowledged in the AHRQ report, the CDC is in the process of evaluating a proposed expansion to their current guideline to include anti-HCV antibody testing for the birth cohort of people born 1945 through 1965. Furthermore, two additional prominent research studies have been published supporting age-based screening and demonstrating the cost-effectiveness of this approach. Part of the cost-effectiveness of the approach is due to the use of direct-acting antiviral therapy for genotype 1 HCV patients who are identified by screening. 10,11 The AHRQ draft report reviewed only one study that evaluated age-based screening but ultimately excluded the study based on its failure to meet the review's inclusion criteria. The study found that the greatest predictor ofHCV seropositivity, other than intravenous drug use, was being 40 to 80 years old, further supporting age-based screening. Because the majority of infected individuals in the birth cohort from 1945 through 1965 are unaware of their risk status, without a screening program that specifically targets them, these patients will likely remain undiagnosed until symptomatic with manifestations of severe liver disease; even compensated cirrhotic patients often do not have signs or symptoms that would lead to testing for HCV. McGarry, et al. estimates that approximately 70 percent of infected people will remain undiagnosed under current screening practices until they progress to advanced liver disease or die. 12 Given that new studies demonstrate the benefit of age-based targeted screening, we urge AHRQ to include a review of these studies as part of the final report treatments are in development that may further improve SVR rates. While the draft report does acknowledge that the screening recommendations must be viewed in the context of the effectiveness of antiviral treatments, by omitting newly available evidence on improved treatments, the report recommendations are out-of-date and do not reflect current standards of care. Though we eagerly await the publication of the AHRQ reports on HCV treatment and adherence interventions, we are concerned that these two reports will similarly not reflect the most recent evidence on new FDA approved therapies and current standards of care which is critical to the United States Preventive Services Task Force (USPSTF) review and update of the current HCV screening guidelines. We urge AHRQ to consider the most up-to-date evidence on treatments and clinical standards in order to ensure that the reports on HCV treatment and adherence, as well as the update of the USPSTF recommendations on screening, are of maximum utility to physicians and patients.	Antiviral treatments including the recently approved protease inhibitors are included in the separate review on antiviral treatments. The CDC birth-cohort approach entails modeling studies, excluded from this review since they lack clinical data.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 8	Cited References		Thank you for identifying these references. All of the references were reviewed for potential inclusion, but none met the inclusion criteria. See the list of references below for specific reasons for exclusion
Peer Reviewer # 8	Cited References	1. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med 2006;144(10):705-14.	Background
Peer Reviewer # 8	Cited References	2. Edlin BR. Perspective: Test and treat this silent killer. Nature 2011;474:S18-9.	No original data
Peer Reviewer # 8	Cited References	3. Edlin BR. Five million Americans infected with the hepatitis C virus: a corrected estimate [abstract #44]. Hepatology 2005;42(4 Suppl 1):213A.	Background
Peer Reviewer # 8	Cited References	4. Butt AA, Justice AC, Skanderson M, Rigsby MO, Good CB, Kwoh CK. Rate and predictors of treatment prescription for hepatitis C. Gut 2007;56(3):385-9. PMID: 17005764.	Wrong population (not screen-detected)
Peer Reviewer # 8	Cited References	5. Rousseau CM, Ioannou GN, Todd-Stenberg JA, Sloan KL, Larson MF, Forsberg CW, Dominitz JA. Racial differences in the evaluation and treatment of hepatitis C among veterans: a retrospective cohort study. Am J Public Health 2008;98(5):846-52. PMID: 18382007.	Not relevant (doesn't address a KQ)
Peer Reviewer # 8	Cited References	6. Davila JA, El-Serag HB. Racial differences in survival of hepatocellular carcinoma in the United States: a population based study. Clin Gastroenterol Hepatol 2006;4(1):104-10; quiz 4-5. PMID: 16431312.	Not relevant (doesn't address a KQ)
Peer Reviewer # 8	Cited References	7. Siegel AB, McBride RB, El-Serag HB, Hershman DL, Brown RS, Jr., Renz JF, Emond J, Neugut AI. Racial disparities in utilization of liver transplantation for hepatocellular carcinoma in the United States, 1998-2002. Am J Gastroenterol 2008;103(1):120-7. PMID: 18005365.	Not relevant (doesn't address a KQ)
Peer Reviewer # 8	Cited References	8. Sonnenday CJ, Dimick JB, Schulick RD, Choti MA. Racial and geographic disparities in the utilization of surgical therapy for hepatocellular carcinoma. J Gastrointest Surg 2007;11(12):1636-46; discussion 46. PMID: 17912593.	Not relevant (doesn't address a KQ)
Peer Reviewer # 8	Cited References	9. Holmberg SD, Ly KN, Xing J, Klevens M, Jiles R, Ward JW. The growing burden of mortality associated with viral hepatitis in the United States, 1999-2007 [abstract #243]. Hepatology 2011;54(4 suppl):483A.	Background
Peer Reviewer # 8	Cited References	10. Lorvick J, Kral AH, Seal K, Gee L, Edlin BR. Prevalence and duration of hepatitis C among injection drug users in San Francisco, Calif. Am J Public Health 2001;91(1):46-7.	Background
Peer Reviewer # 8	Cited References	11. Tseng FC, O'Brien TR, Zhang M, et al. Seroprevalence of hepatitis C virus and hepatitis B virus among San Francisco injection drug users, 1998 to 2000. Hepatology 2007;46(3):666-71.	Background
Peer Reviewer # 8	Cited References	12. Hahn JA, Page-Shafer K, Lum PJ, Ochoa K, Moss AR. Hepatitis C virus infection and needle exchange use among young injection drug users in San Francisco. Hepatology 2001;34(1):180-7.	Background

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 8	Cited References	13. Thorpe LE, Ouellet LJ, Levy JR, Williams IT, Monterroso ER. Hepatitis C virus infection: prevalence, risk factors, and prevention opportunities among young injection drug users in Chicago, 1997-1999. J Infect Dis 2000;182(6):1588-94.	Background
Peer Reviewer # 8	Cited References	14. Diaz T, Des Jarlais DC, Vlahov D, et al. Factors associated with prevalent hepatitis C: differences among young adult injection drug users in lower and upper Manhattan, New York City. Am J Public Health 2001;91(1):23-30.	Background
Peer Reviewer # 8	Cited References	15. Garfein RS, Vlahov D, Galai N, Doherty MC, Nelson KE. Viral infections in short-term injection drug users: the prevalence of the hepatitis C, hepatitis B, human immunodeficiency, and human T-lymphotropic viruses. Am J Public Health 1996;86(5):655-61.	Background
Peer Reviewer # 8	Cited References	16. Institute of Medicine. Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C (National Academies Press, 2010).	No original data
Peer Reviewer # 8	Cited References	17. Rein DB, Smith BD, Wittenborn JS, Lesesne SB, Wagner LD, Roblin DW, Patel N, Ward JW, Weinbaum CM. The Cost-Effectiveness of Birth-Cohort Screening for Hepatitis C Antibody in U.S. Primary Care Settings. Ann Intern Med 2011 Nov 4. [Epub ahead of print] PMID: 22056542.	Wrong study type (modeling study)
Peer Reviewer # 6	Cited References		Thank you for identifying these references. All of the references were reviewed for potential inclusion, but none met the inclusion criteria. See the list of references below for specific reasons for exclusion.
Peer Reviewer # 6	Cited References	Armstrong GL, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Annals of Internal Medicine. 2006;144(10):705-14.	Background
Peer Reviewer # 6	Cited References	Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. Int J Med Sci. 2006;3(2):47-52.	Background
Peer Reviewer # 6	Cited References	Backus et al. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol. 2011 Jun; 9(6) 509-516.e1.	Not relevant (doesn't address a KQ)—but is included in the hepatitis C treatment review.
Peer Reviewer # 6	Cited References	Wong JB, et al. Estimating future hepatitis C morbidity, mortality, and costs in the United States. Am J Public Health. 2000 Oct;90(10):1562-9.	Background
Peer Reviewer # 6	Cited References	El-Serag H. Hepatocellular Carci¬noma. NEJM 2011 Sep 22: 365:1118-1127.	Background
Peer Reviewer # 6	Cited References	Armstrong GL, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Annals of Internal Medicine. 2006;144(10):705-14.	Background
Peer Reviewer # 6	Cited References	Bini EJ et al. Prospective Multi-Center Study of Eligibility for Anti-Viral Therapy among 4,084 Veterans with chronic Hepatitis C Virus Infection. Am J Gastroenterol 2005 Aug; 100:1772-9.	Wrong population (not screen-detected)
Peer Reviewer # 6	Cited References	Kanwal F et al. Increasing preva¬lence of HCC and cirrhosis in patients with chronic hepatitis C virus infection. Gastroenterology. 2011 Apr; 140(4):1182-1188.e1. State of Care for Veterans with Hepatitis C (SOC), p. 18, available at http://www.hepatitis.va.gov/pdf/HCV-State-of-Care-2010.pdf	Background

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 6	Cited References	Kanwal F et al. Increasing prevalence of HCC and cirrhosis in patients with chronic hepatitis C virus infection. Gastroenterology. 2011 Apr; 140(4):1182-1188.e1. State of Care for Veterans with Hepatitis C (SOC), p. 18, available at http://www.hepatitis.va.gov/pdf/HCV-State-of-Care-2010.pdf	Background
Peer Reviewer # 6	Cited References	Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. Int J Med Sci. 2006;3(2):47-52. Marcellin P, et al. Treatment of hepatitis C patients with normal aminotransferases levels. Clin Liver Dis. 1999 Nov; 3(4):843-53. Pradat P, et al. Predictive value of ALT levels for histologic findings in chronic hepatitis C: a European collaborative study. Hepatology. 2002 Oct;36(4 Pt 1):973-7. Dufour DR. Alanine aminotransferase: is it healthy to be "normal"? Hepatology. 2009 Dec;50(6):1699-701 CDC. Guidelines for Laboratory Testing and Result Reporting of Antibody to Hepatitis C Virus. MMWR 2003 Feb 7; 52(RR03):1-16. Ghany M et al. AASLD Practice Guidelines: Diagnosis, Management, and Treatment of Hepatitis C - An Update. Hepatology 2009 April; 49:1335-1374. Cheung RC, et al. Viral hepatitis and other infectious diseases in a homeless population. J Clin Gastroenterol. 2002 Apr;34(4):476-80. Desai RA, et al. Prevalence of Hepatitis C virus infection in a sample of homeless veterans. Soc Psychiatry Psychiatr Epidemiol. 2003 Jul;38(7):396-401. Kilbourne AM, et al. Guideline-concordant hepatitis C virus testing and notification among patients with and without mental disorders. Gen Hosp Psychiatry. 2008 Nov-Dec;30(6):495-500.	None address the key questions for this review.
Peer Reviewer # 6	Cited References	Bini EJ et al. Prospective Multi-Center Study of Eligibility for Anti-Viral Therapy among 4,084 Veterans with chronic Hepatitis C Virus Infection. Am J Gastroenterol 2005 Aug; 100:1772-9.	See above
Peer Reviewer # 6	Cited References	Lindenburg CE et al. Hepatitis C testing and treatment among active drug users in Amsterdam: results from the DUTCH-C project. Eur J Gastroenterol Hepatol. 2011 Jan;23(1):23-31. Knott A, et al. Integrated psychiatric/medical care in a chronic hepatitis C clinic: effect on antiviral treatment evaluation and outcomes. Am J Gastroenterol. 2006 Oct;101(10):2254-62.	Neither address key questions for this review.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 6	Cited References	Mallette C, et al. Outcome of screen¬ing for hepatitis C virus infection based on risk factors. Am J Gastroenterol. 2008 Jan;103(1):131-7. Drumright LN, et al. Predictors and effects of alcohol use on liver function among young HCV-infected injection drug users in a behavioral intervention. J Hepatol. 2011 Jul;55(1):45-52. Epub 2010 Nov 24. Bini EJ, et al.; VA HCV-001 Study Group. National multicenter study of HIV testing and HIV seropositivity in patients with chronic hepatitis C virus infection. J Clin Gastroenterol. 2006 Sep;40(8):732-9. Wong JB, et al. Estimating future hepatitis C morbidity, mortality, and costs in the United States. Am J Public Health. 2000 Oct;90(10):1562-9.	None of the references address key questions for this review. Wong is a background reference.
NVHR	Cited References	Appendix: Additional research for consideration Key Question 1a. Does screening for hepatitis C virus (HCV) infection in nonpregnant adults without known abnormal liver enzymes reduce mortality and morbidity due to HCV infection, affect quality of life, or reduce incidence of HCV infection? While the CER acknowledges the paucity of data comparing screening to non-screening on long-term clinical outcomes, this analysis should also consider emerging data from modeling studies indicating that HCV treatment can have an impact on incidence rates of HCV infection among people who inject drugs: Martin NK, Vickerman P, Foster GR, Hutchinson SJ, Goldberg DJ, Hickman M. Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility. J Hepatol. 2011 Jun;54(6):1137-44. Martin NK, Pitcher AB, Vickerman P, Vassall A, Hickman M. Optimal control of hepatitis C antiviral treatment programme delivery for prevention amongst a population of injecting drug users. PLoS One. 2011;6(8):e22309. Martin NK, Vickerman P, Miners A, Foster GR, Hutchinson SJ, Goldberg DJ, Hickman M. Cost effectiveness of hepatitis C virus antiviral treatment for injection drug user populations. Hepatology. 2012 Jan;55(1):49-57. Matser A, Urbanus A, Geskus R, Kretzschmar M, Xiridou M, Buster M, Coutinho R, Prins M. The effect of hepatitis C treatment and HIV coinfection on the disease burden of hepatitis C among injecting drug users in Amsterdam. Addiction. 2011 Sep 15. doi: 10.1111/j.1360-0443.2011.03654.x. [Epub ahead of print] As indicated by the publication dates, this is an avenue of research that has emerged very recently, is rapidly evolving, and must be considered by the USPSTF in making its determination about this topic. Key Questions 2a & 2b. What is the effectiveness of different risk- or prevalence-based methods for screening for HCV infection on clinical outcomes? and What is the sensitivity and number needed to screen to identify one case of HCV infection of different risk- or prevalence-based methods for screening for HCV infection? These questions address a rapidly developing area of research, driven in part by the	Thank you for identifying these references. All of the references were reviewed for potential inclusion, but none met the inclusion criteria. See the list of references below for specific reasons for exclusion.

Commentator & Affiliation	Section	Comment	Response
		availability of new diagnostic tools and by recent and on-going studies to inform the development of new screening guidelines by the CDC. Relevant literature published or in press over the last six months which should be included in the CER include: Rein DB, Smith BD, Wittenborn BS et al. The Cost-Effectiveness of Birth-Cohort Screening for Hepatitis C Antibody in U.S. Primary Care Settings.Ann Intern Med. 2011 Nov 4. [Epub ahead of print] Roblin DW, Smith BD, Weinbaum CW et al. HCV Screening Practices and Prevalence in an MCO, 2000-2007. Am J Manag Care. 2011;17(8):548-555. Smith BD, Teshale E, Jewett A et al. Performance of Premarket Rapid Hepatitis C Virus Antibody Assays in 4 National Human Immunodeficiency Virus Behavioral Surveillance System Sites. Clinical Infectious Diseases. 2011;53(8):780–786. Southern WN, Drainoni ML, Smith BD et al. Hepatitis C testing practices and prevalence in a high-risk urban ambulatory care setting. Journal of Viral Hepatitis. 2011;18(7):474-481; July. In addition, another article currently in press at Clinical Infectious Disease by P. Coffin et al. provides a separate analysis, using a different model, of the comparative effectiveness of different HCV screening strategies. Moreover, presentations from the AASLD Liver Meeting in November 2011, currently being prepared for publication, also address this question (Drainoni M. et al., Effectiveness of a Risk Screener 5 in Identifying Hepatitis C Virus in Primary Care; Smith B. et al., Comparison of Hepatitis C Virus Infection Screening Strategies: Elevated Alanine Aminotransferase Levels Versus Birth Cohort). The rapid growth in the evidence base on the utility of HCV screening strategies underscores the crucial question of whether the USPSTF review is premature. Key Question 6b. Does becoming aware of positive HCV infection status decrease high risk behaviors? The CER understates the strength of the evidence supporting reduced risk behaviors among those aware of positive HCV infection status. Two recent studies not addressed in the review provide additional support for the adoption of injection risk reduction strategies based on serostatus knowledge: Burt RD, Thiede H, Hagan H. Serosorting for hepatitis C status in the sharing of injection equipment among Seattle area injection drug users. Drug Alcohol Depend. 2009 Dec 1;105(3):215-20. Hahn JA, Evans JL, Davidson PJ, Lum PJ, Page K. Hepatitis C virus risk behaviors within the partnerships of young injecting drug users. Addiction. 2010 Jul;105(7):1254-64. These studies add weight to the evidence for the benefit of HCV screening in decreasing high risk behaviors. In addition, recent studies report success in reducing alcohol consumption among patients diagnosed with hepatitis C: Proeschold-Bell RJ, Patkar AA, Naggie S, Coward L, Mannelli P, Yao J, Bixby P, Muir AJ. An Integrated Alcohol Abuse and Medical Treatment Model for Patients with Hepatitis C. Dig Dis Sci. 2011 Dec 2. [Epub ahead of print] Dieperink E, Ho SB, Heit S, Durfee JM, Thuras P, Willenbring ML. Significant reductions in	

Commentator & Affiliation	Section	Comment	Response
		drinking following brief alcohol treatment provided in a hepatitis C clinic. Psychosomatics. 2010 Mar;51(2):149-56. Collectively, these studies suggest that the evidence in support of reduction in risk behaviors subsequent to HCV diagnosis is stronger than indicated in the CER.	
NVHR	Cited References	1. Burt RD, Thiede H, Hagan H. Serosorting for hepatitis C status in the sharing of injection equipment among Seattle area injection drug users. Drug Alcohol Depend. 2009 Dec 1;105(3):215-20.	Not relevant
NVHR	Cited References	2. Coffin P et al. Cost-Effectiveness and Population Outcomes of General Population Screening for Hepatitis C. Clin Infect Dis () (2012) PMID 22412061	Not relevant
NVHR	Cited References	3. Dieperink E, Ho SB, Heit S, Durfee JM, Thuras P, Willenbring ML. Significant reductions in drinking following brief alcohol treatment provided in a hepatitis C clinic. Psychosomatics. 2010 Mar;51(2):149- 56.	Background
NVHR	Cited References	4. Drainoni M. et al., Effectiveness of a Risk Screener in Identifying Hepatitis C Virus in Primary Care;	Unable to find
NVHR	Cited References	5. Hahn JA, Evans JL, Davidson PJ, Lum PJ, Page K. Hepatitis C virus risk behaviors within the partnerships of young injecting drug users. Addiction. 2010 Jul;105(7):1254-64.	Not relevant
NVHR	Cited References	6. Proeschold-Bell RJ, Patkar AA, Naggie S, Coward L, Mannelli P, Yao J, Bixby P, Muir AJ. An Integrated Alcohol Abuse and Medical Treatment Model for Patients with Hepatitis C. Dig Dis Sci. 2011 Dec 2. [Epub ahead of print]	Background
NVHR	Cited References	7. Martin NK, Vickerman P, Foster GR, Hutchinson SJ, Goldberg DJ, Hickman M. Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility. J Hepatol. 2011 Jun;54(6):1137-44.	No original data
NVHR	Cited References	8. Martin NK, Pitcher AB, Vickerman P, Vassall A, Hickman M. Optimal control of hepatitis C antiviral treatment programme delivery for prevention amongst a population of injecting drug users. PLoS One. 2011;6(8):e22309.	No original data
NVHR	Cited References	9. Martin NK, Vickerman P, Miners A, Foster GR, Hutchinson SJ, Goldberg DJ, Hickman M. Cost effectiveness of hepatitis C virus antiviral treatment for injection drug user populations. Hepatology. 2012 Jan;55(1):49-57.	Not relevant
NVHR	Cited References	10. Matser A, Urbanus A, Geskus R, Kretzschmar M, Xiridou M, Buster M, Coutinho R, Prins M. The effect of hepatitis C treatment and HIV coinfection on the disease burden of hepatitis C among injecting drug users in Amsterdam. Addiction. 2011 Sep 15. doi: 10.1111/j.1360-0443.2011.03654.x. [Epub ahead of print]	Non-English language
NVHR	Cited References	11. Rein DB, Smith BD, Wittenborn BS et al. The Cost-Effectiveness of Birth- Cohort Screening for Hepatitis C Antibody in U.S. Primary Care Settings.Ann Intern Med. 2011 Nov 4. [Epub ahead of print]	No original data
NVHR	Cited References	12. Roblin DW, Smith BD, Weinbaum CW et al. HCV Screening Practices and Prevalence in an MCO, 2000-2007. Am J Manag Care. 2011;17(8):548-555.	No original data
NVHR	Cited References	13. Smith BD, Teshale E, Jewett A et al. Performance of Premarket Rapid Hepatitis C Virus Antibody Assays in 4 National Human Immunodeficiency Virus Behavioral Surveillance System Sites. Clinical Infectious Diseases. 2011;53(8):780–786.	Background

Commentator & Affiliation	Section	Comment	Response
NVHR	Cited References	14. Smith B. et al., Comparison of Hepatitis C Virus Infection Screening Strategies: Elevated Alanine Aminotransferase Levels Versus Birth Cohort).	Background
NVHR		15. Southern WN, Drainoni ML, Smith BD et al. Hepatitis C testing practices and prevalence in a high-risk urban ambulatory care setting. Journal of Viral Hepatitis. 2011;18(7):474-481; July.	Background
Vertex	Cited References	I McHutchison, J.G. & Bacon, B.R. Chronic hepatitis C: an age wave of disease burden. Am J Manag Care 11, S286-295; quiz S307-2II (2005). 2 Annstrong, G., et al. The Prevalence of Hepatitis C Virus Infection in the United States, 1999 through 2002. Annals of Internal Medicine. May 2006. 3 Pyenson, B. & Fitch, K. & Iwasaki, K. Consequences of Hepatitis C Virus: Costs of a Baby Boomer Epidemic of Liver Disease. Milliman, Inc. May 2009. 4 Srocynski G, Esteban E, Conrads-Frank A, Schwarzer R, et. al. Long-term effectiveness and cost-effectiveness of screening for Hepatitis C virus infection. European Journal of Public Health, Vol. 19, No.3, 245-253. February 2009. 5 Annstrong, G., et al. The Prevalence of Hepatitis C Virus Infection in the United States, 1999 through 2002. Annals of Internal Medicine. May 2006. 6 Bruce, MG, et al. Hepatitis C infection in Alaska Natives with persistently normal, persistently elevated or fluctuating alanine aminotransferase levels. Liver International. 2006. 7 Colvin, H and Mitchell, A. Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C. Institute of Medicine. 2010. 8 Rein, DB, et al. The Cost-Effectiveness of Birth Cohort Hepatitis C Antibody Screening in U.s. Primary Care Settings. American Association for the Study of Liver Diseases. 2011. 9 Smith, B. Comparison of Hepatitis C Virus Infection Screening Strategies: Elevated Alanine Aminotransferase Levels Versus Birth Cohort. Presented at the American Association for the Study of Liver Diseases Hepatitis Single Topic Conference. 10 Rein, et al. The Cost-Effectiveness of Birth-Cohort Screening for Hepatitis C Antibody in U.S. Primary Care Settings. Annals of Internal Medicine. November 2011. 11 McGarry, et al. "Economic model of a birth cohort screening program for hepatitis C virus" Hepatology December 2011. 12 McGarry, et al., "Economic model of a birth cohort screening program for hepatitis C virus" Hepatology 2011. 13 Morgan, TR, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology, 2010 Sep;S2(3):833-44 . 14 Sroczynski G. & Esteban E et. al. Long-term effectiveness and cost-effectiveness of screening for Hepatitis C virus infection. European Journal o/Public Health. Vol. 19, No.3, 245-253. 15 Davis G, Alter M, El-Serag H, Poynard T, & Jennings L. Aging of Hepatitis C Virus-Infected Persons in the United States: A Multiple Cohort Model ofHCV Prevalence and Disease Progression. Gastroenterology 2010; 138: 513-521. 16 Davis G, Alter M, El-Serag H, Poynard T, & Jennings L. Aging of Hepatitis C Virus-	Thank you for identifying these references. All of the references were reviewed for potential inclusion, but none met the inclusion criteria. See the list of references below for specific reasons for exclusion.

Commentator & Affiliation	Section	Comment	Response
		Infected Persons in the United States: A Multiple Cohort Model of HCV Prevalence and Disease Progression. Gastroenterology 2010; 138: 513-521.	
Vertex	Cited References	1. Armstrong, G., et al. The Prevalence of Hepatitis C Virus Infection in the United States, 1999 through 2002. Annals of Internal Medicine. May 2006.	Background
Vertex	Cited References	2. Bruce, MG, et al. Hepatitis C infection in Alaska Natives with persistently normal, persistently elevated or fluctuating alanine aminotransferase levels. Liver International. 2006.	Not relevant
Vertex	Cited References	3. Colvin, H and Mitchell, A. Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C. Institute of Medicine. 2010. (Mayer 2010)	Background
Vertex	Cited References	4. Davis G, Alter M, El-Serag H, Poynard T, & Jennings L. Aging of Hepatitis C Virus-Infected Persons in the United States: A Multiple Cohort Model of HCV Prevalence and Disease Progression. Gastroenterology 2010; 138: 513-521.	Excluded at abstract review
Vertex	Cited References	5. Pyenson, B. & Fitch, K. & Iwasaki, K. Consequences of Hepatitis C Virus: Costs of a Baby Boomer Epidemic of Liver Disease. Milliman, Inc. May 2009.	No original data
Vertex	Cited References	6. Rein, DB, et al. The Cost-Effectiveness of Birth Cohort Hepatitis C Antibody Screening in U.s. Primary Care Settings. AASLD. 2011.	No original data
Vertex	Cited References	7. Rein, et al. The Cost-Effectiveness of Birth-Cohort Screening for Hepatitis C Antibody in U.S. Primary Care Settings. Annals of Internal Medicine. November 2011.	No original data
Vertex	Cited References	8. Smith, B. Comparison of Hepatitis C Virus Infection Screening Strategies: Elevated Alanine Aminotransferase Levels Versus Birth Cohort. Presented at the AASLD Hepatitis Single Topic Conference.	Unable to find
Vertex	Cited References	9. McHutchison, J.G. & Bacon, B.R. Chronic hepatitis C: an age wave of disease burden. Am J Manag Care 11, S286-295; quiz S307-2II (2005).	Background
Vertex	Cited References	10. McGarry, et al. "Economic model of a birth cohort screening program for hepatitis C virus" Hepatology December 2011.	No original data
Vertex	Cited References	11. Morgan, TR, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology, 2010 Sep;S2(3):833-44	Not relevant
Vertex	Cited References	12. Srocynski G, Esteban E, Conrads-Frank A, Schwarzer R, et. al. Long-term effectiveness and cost-effectiveness of screening for Hepatitis C virus infection. European Journal of Public Health, Vol. 19, No.3, 245-253. February 2009.	No original data
Genentech	Cited References		Thank you for identifying these references. All of the references were reviewed for potential inclusion, but none met the inclusion criteria. See the list of references below for specific reasons for exclusion.
Genentech		1. Centers for Disease Control and Prevention (CDC) Viral Hepatitis Action Coalition, "Birth-cohort Evaluation to Advance Screening and Testing for Hepatitis C, last accessed December 22, 2011. Available at www.viralhepatitisaction.org	Not relevant
Genentech		2. Centers for Disease Control and Prevention, Hepatitis C FAQs for Health Professionals, last accessed December 23, 2011 . Available at www.cdc.gov/hepatitis/HCV/HCVfaq.htm.	Not relevant

Commentator & Affiliation	Section	Comment	Response
Genentech		3. Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis Band C, Heather M. Colvin and Abigail E. Mitchell, Editors; Committee on the Prevention and Control of Viral Hepatitis Infections; Institute of Medicine, pg. 21 (2010). Available at http://www.nap.edu/catalog/12793.html.	Background
Genentech		4.Rein et al. The Cost-Effectiveness of Birth Cohort Hepatitis C Antibody Screening in U.S. Primary Care Settings. 62nd Annual Meeting of the American Association for the Study of Liver Diseases ~AASLD 2011). San Francisco, November 4-8.2011. Abstract 479.	No original data
Peer Reviewer # 1	General	The report is clinically meaningful. The target populations are clearly defined. The audience is broad and implied rather than explicitly stated. The key questions are clinically relevant, important and very well defined. My only concern here is the question comparing invasive and non-invasive markers of fibrosis. I think there needs to be more introduction to why this is important. Are we considering that patients with early or non-progressive fibrosis should not be treated (one school of though)? As is quoted on page ES-1, these patients have symptoms and poorer QOL and may warrant treatment. Or are we looking for cirrhosis because we are trying to predict complications with interferon based treatment regimens. In which case we are most interest in tools which determine cirrhosis from other stages of fibrosis. In both cases, but particularly the latter, fibroscan should certainly be included as a non-invasive fibrosis assessment tool. Having said that, and given the presumed knowledge gap, the key questions have been well chosen to find evidence to inform clinical practice.	As stated in the section on Interventions and Comparators, liver biopsy is still recommended as a standard part of the workup for guiding decisions regarding eligibility for antiviral treatments, but it is invasive and associated with potential complications as well as other issues. Therefore, non-invasive alternatives have been developed and it is important to understand their accuracy. We added a sentence to clarify the issue regarding interpretation of liver biopsies for guiding treatment decisions (p 11, paragraph 3): "The absence of bridging fibrosis (METAVIR F0-F2, Ishak stage 0-3, or equivalent) on liver biopsy is associated with a low likelihood for liver-related complications over the next 10 to 20 years and is an important consideration when making individualized treatment decisions."

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 2	General	Incredibly comprehensive document, too long for many readers to actually read every word. There is much repetition, including whole sections. Target pop and audience are stated as are the key questions--repeatedly. Hepatologists oppose the use of the phrase "liver function tests". AST, ALT do not measure liver function. INR does measure synthetic function, but is seldom thought of as an "LFT" by non-Hepatologists. "Liver tests" is preferable, short, and difficult to object to. Is 1990 or 1992 the best year to consider as the beginning of the optimal screening of blood? The recommendation to vaccinate hep C pts for A & B was industry driven to sell vaccines, in my opinion, and is not data-supported, as pointed out here. Vaccination always sounds good, but who will deliver it and who will pay for it? Our PCPs are expected to give the vaccinations, but they do not do it effectively. My Hepatology clinic will not let me vaccinate. They no longer stock vaccines. There was an industry-funded effort to get federal agencies to agree to vaccinate all obese pts for A & B. I helped squelch that effort.	Thank you. We revised text throughout the report to replace "liver function test" or "LFT" with the term "liver test" as suggested by the reviewer. Specific blood donor screening for HCV was introduced in 1990; by 1992 the risk had dropped to 1 in 100,000. We went through the text and revised to use the 1992 date which seems more clinically on target. Comments on vaccination noted. Thank you.
Peer Reviewer # 3	General	The report provides clinically useful and meaningful information. The target population and audiences are explicitly defined. The key questions are appropriate and clearly stated.	Thank you for your comment.
Peer Reviewer # 4	General	This report is clinically meaningful to providers. It does serve to give them information to discuss with their patients relative to HCV screening. The key questions address a large portion of the adult population as well as the pregnant population thus it can be widely used. The key questions are explicit and a provider can easily fit their patients into one of the categories.	Thank you for your comment.
Reviewer 5	General	The key questions are very well stated. Unfortunately, there are few studies that actually contribute to definitive answers.	Thank you for your comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 8	General	This comparative effectiveness review is somewhat hypothetical, since it omits consideration of the main benefit of screening, namely antiviral therapy. It concludes that no randomized trials of screening with clinical endpoints exist, a somewhat gratuitous observation, since such studies are neither possible (ethically or logistically), nor would they be of any utility in the real world in which hepatitis C treatments are undergoing serial increases in effectiveness. It omits certain considerations, discussed below, that would make it more relevant and clinically meaningful. In general, the key questions do not address central, important, or meaningful issues relevant to hepatitis C screening or to its utility for the control of the hepatitis C epidemic. It does not address the benefits of screening, the barriers to achieving these benefits, or potential strategies to overcoming these barriers. It does not identify populations or groups of patients in whom the benefits of screening would be of particular value. The conclusions of the review are overly pessimistic and of limited applicability or utility to inform policy or practice decisions.	As stated in the abstract and in the review, antiviral therapy was reviewed in a separate report which will be used together with this review by the USPSTF and others. Studies comparing clinical outcomes associated with screening versus no screening provide the most direct evidence and are always sought by the USPSTF and others when evaluating screening interventions. As stated in the Methods and Results, we did not restrict inclusion to randomized trials; observational studies would have been included as well. The key questions synthesized the evidence on benefits and harms of screening as outlined in the key questions.

Commentator & Affiliation	Section	Comment	Response
Connie Chiang, PharmD Associate Director, Medical Information Janssen Scientific Affairs, LLC 1125 Trenton-Harbourton Road Titusville, NJ 08560	General	New and emerging information on HCV screening and treatment will change the landscape in this area and can have a major impact on the conclusions in this report. Recent studies in HCV screening, as well as emerging HCV treatments that do not require interferon and ribavirin should be considered before final conclusions on this topic are made. New and emerging information on HCV screening and treatment will change the landscape in this area and can have a major impact on the conclusions in this report. Recent studies in HCV screening, as well as emerging HCV treatments that do not require interferon and ribavirin should be considered before final conclusions on this topic are made. References *Smith BD, Patel N, and Ward J. Hepatitis C virus antibody prevalence, correlates and predictors among persons born from 1945 through 1965, United States, 1999-2008. Poster presented at the 62nd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); San Francisco, CA, November 4-8, 2011. Abstract 394. Rein DB, Smith BD, Wittenborn JS, et al. The Cost-Effectiveness of Birth-Cohort Screening for Hepatitis C Antibody in U.S. Primary Care Settings. Ann Intern Med published ahead of print November 4, 2011. *Spradling PR, Rupp LB, Moorman, et al. Predictors of testing for and infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) in four United States health care organizations (HCOs), 2006-2008. Poster presented at the 62nd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); San Francisco, CA, November 4-8, 2011. Abstract 1749.	Thank you for your comment. Antiviral treatments for HCV are reviewed in a separate report. Non-interferon based therapies are not currently FDA approved and are outside the scope of that review. Thank you for suggesting these references. We reviewed the studies and they do not meet the inclusion criteria—two of the suggested references are abstracts only, and the Rein study is a cost-effectiveness/modeling study.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1	General	Our main comments regarding the AHRQ HCV screening recommendations pertain to the fact that, in a disease like HCV that progresses over several decades, the effect of HCV screening on outcomes will be impossible to determine based on randomized controlled trials or observational studies, the types of studies that are considered valid in the systematic review performed by the Evidence-based Practice Center. Additionally, several practice guidelines (including our own) and the CDC have recommended HCV screening in high-risk populations. As this is the assumed standard, it is not surprising to find a paucity of literature to either dispute or support this recommendation. It will be very difficult to perform a study where one population is offered less than what is considered the standard of care. Thus, many of the key questions posed in the document will likely remain unanswered. Rather than explore screening vs. no screening, it would be more useful to compare different screening strategies. Despite the acceptance of current screening recommendations, implementation is difficult. Primary care providers may fail to ask questions to identify high-risk patients, and patients may be less than forthright about their answers. As a result at least 50% of individuals with HCV are unaware of their disease. Research in this area should include the likelihood that primary care providers ask (and receive accurate answers) about the risk factors for HCV. A screening strategy based on age would be easier to implement and would broaden the population that would be appropriate candidates for therapy. Importantly, the outcome of screening cannot be isolated from the effect of treatment. Since the last AHRQ review in 2004, this is the area that has accumulated the most new data. Eradication of HCV has been associated with a decreased progression to cirrhosis and cirrhosis decompensation, a decreased risk of hepatocellular carcinoma and improved survival. A recent U.S. study by Backus and colleagues in the Veterans Administration showed that sustained virological response reduces risk of all-cause mortality in the cohort of veterans with HCV and numerous co-morbidities. (Backus et al. Clin Gastroenterol Hepatol. 2011;9(6):509-516). With current therapies, viral eradication occurs in 70-100% of HCV-infected patients. Over the next 5 years it is anticipated that these percentages will increase further with an oral (interferon-free) treatment that will be more acceptable for patients and providers. If left unidentified and untreated, patients with HCV will progress to cirrhosis, cirrhosis decompensation and hepatocellular carcinoma which will impact healthcare costs significantly. A cost-analysis would be necessary to assess the impact of HCV screening and treatment. Our screening recommendations should mirror the disease burden. In 2008 chronic liver disease was the 12th leading cause of death in the United States (www.cdc.gov/nchs/data/nvsr/nvsr59/nvsr59_10.pdf). In addition, the annual incidence rate of liver and bile duct malignancies have increased more than any other cancer (www.atsdr.cdc.gov/risk/cancer/cancer-trends.html). HCV is a leading cause of hepatobiliary malignancies.	The review has key questions relevant for screening vs. no screening as well as for comparing different screening strategies (KQ 2a), for which there is also little evidence. Evidence on benefits of screening vs. no screening would provide the most direct evidence on benefits of screening and should always be sought and included if available. Effectiveness of treatment is covered in a separate review. This report presents the available evidence about screening for hepatitis C. A separate independent organization will weigh the benefits and harms, and make a determination about screening.

Commentator & Affiliation	Section	Comment	Response
John Ward, CDC	General	Effective hepatitis C virus (HCV) screening is a public health priority. As the investigators documented in the Executive Summary of this Report, chronic Hepatitis C virus (HCV) hepatitis C virus (HCV) infection is a major public health problem in the United States; an estimated 3.2 million Americans are living with hepatitis C infections, and with the aging of the infected cohort, the disease burden is expected to continue to increase dramatically over at least the next ten10 years. The Institute of Medicine estimates that as many as 75% of HCV-infected persons are unaware of their infection status, and an even larger percentage of these persons are not receiving medical care for their condition. Consequently, while effective treatments are available to stop and even reverse the adverse effects of hepatitis C, the rates of liver cancer and other diseases caused by hepatitis C continue to increase. Treatment is most effective for HCV-infected persons early in the course of infection, before they develop late-stage clinical manifestations of their infection (e.g., cirrhosis). Timely HCV testing is necessary and prompt medical evaluation and appropriate treatment are needed to maximize the benefits of HCV care and treatment and prevent morbidity and mortality among persons living with HCV infection. Accordingly, this review of evidence regarding HCV screening is timely. However, CDC has a number of concerns and comments, as follows:	Thank you for your comment.
John Ward, CDC	General	CDC is concerned that the evidence review of hepatitis C screening is being conducted separately from the review of hepatitis C treatment effectiveness. The separation of these two reviews is problematic, because it does not permit an analysis that links screening to clinical outcomes associated with treatment. As stated on ES-14 of the review, “much of the benefits from screening are likely to occur as a result of antiviral treatments.” How can screening be evaluated in the absence of treatment? Screening in itself is not of benefit; rather, it yields information that prompts intervention (e.g., medical management and therapy), ultimately benefiting persons living with HCV. The first step to getting an HCV-infected person evaluated and treated is identification of HCV infection through effective testing programs. There is ample evidence that HCV treatment is more effective if initiated prior to the onset of symptoms associated with end-stage liver disease.	Thank you for your comments. We agree that evidence about treatment is an important consideration in screening. We have therefore timed a separate complementary report about hepatitis C treatment to be available concurrently to allow for more informed decisionmaking.
John Ward, CDC	General	CDC views screening and linkage to care and treatment as equally critical components of the same intervention. To update public health guidelines for HCV testing, the agency is reviewing evidence for both screening and treatment. To harmonize the approach to development of HCV screening recommendations across agencies, CDC recommends that the AHRQ-supported review and framework should be revised to bring together testing and treatment before it is submitted to USPSTF for a recommendation. Alternatively, it will be important for AHRQ to present how the outcomes of the two separate reviews will be considered in revising the position statement regarding HCV screening.	See above response.

Commentator & Affiliation	Section	Comment	Response
John Ward, CDC	General	The evidence review also confuses issues regarding treatment eligibility and the proportion of patients receiving treatment. In the description of the overview of the analytical framework, the authors state, "The proportion of patients with HCV infection that receives antiviral treatment is important for understanding potential benefits of screening, as not all patients will be eligible for treatment." This quote suggests that because treatment rates are low, perhaps screening is unnecessary. CDC strongly maintains that access to care begins with testing; studies demonstrate that many patients eligible for treatment never receive it. Inadequate testing represents a barrier to treatment. Because most cases of chronic HCV infection are asymptomatic and because early diagnosis is critical to preventing end-state liver disease and hepatocellular carcinoma, we believe that effective screening is a public health priority. The U.S. Department of Health and Human Services (HHS) recognizes the need to address the silent epidemic of viral hepatitis as evidenced by the 2011 publication of the HHS Action Plan for the Prevention, Care, and Treatment of Viral Hepatitis.	We agree that benefits of screening will depend in part on how many patients are treated, which is why it is important to understand how many screen-detected patients are treated in real-world practice (KQ 4b).

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2	General	Thank you for your work on this important subject. While the document thoroughly addresses specific questions, the overall conclusions must consider the bigger picture of the U.S. HCV epidemic. As a public health HCV investigator and clinician, I disagree with the conclusion that more research is needed without also noting that broadened screening is urgently needed. On a very personal level, I see patients every week who present with hepatocellular carcinoma or end-stage liver disease and that is when the diagnosis of hepatitis C is made. Clearly, that is too late to do anything meaningful or cost-effective for them.The Summary should consider several aspects of the HCV epidemic that are important to determining the utility of broadened screening. 1) Most studies considering the relative benefit and costs of broadened screening were conducted many years ago or relied upon data and models developed many years ago. Two new models (one by Rein et al in Annals of Internal Medicine 2011, the other Coffin et al in Clinical Infectious Diseases currently in press) consider the updated circumstances of 2010/2011. HCV in the U.S. is an evolving epidemic in which a rapidly growing proportion of new diagnoses already have advanced fibrosis. As fibrosis advances, treatment is the only option to avoid complications of HCV-liver disease and yet many treatments appear to decline in effectiveness with advancing fibrosis, increasing the urgency with which we need to identify this population. Studies that considered circumstances 10 years ago were not addressing the same degree and risk of morbidity (i.e. many people infected in the 1970s were still doing okay in the 1990s) and are simply not relevant to the current situation. Moreover, your analysis only considered randomized clinical trials. Given the expense and time required for such studies, I would request that the authors consider modeling studies. 2) The paper concludes that there is insufficient evidence to answer many of the posed questions. Is it fair to say this when the federal government has devoted very little funds to studying the question? For example, the Institute of Medicine report of 2010 states that there are more patients dying from hepatitis C compared to HIV, yet the CDC budget spends nearly 70% on HIV and only 1-2% on hepatitis C. I am not aware of any requests for applications from the NIH, AHRQ, or CDC to study those questions for which there is insufficient evidence. It therefore seems duplicitous for a publication sponsored by the US federal government to come to this conclusion.3) The authors are referred to a published report on patient preferences for hepatitis C screening (Coffin P, et al. Patient acceptance of universal screening for hepatitis C virus infection. BMC Infectious Diseases 2011; 11:160). In this survey of 200 patients, we found that patients support universal screening for HCV, even if that screening involves testing without prior consent or the routine provision of negative test results. In other words, patients want hepatitis C screening to occur in a similar fashion as HIV.	It is not correct that the review only included randomized trials. Observational studies were included as well. Modeling and cost-effectiveness studies are not within the scope of this review. As a typical part of our evidence reviews, we include a section on evidence gaps and priorities for future research. It is our hope that researchers and funders will use these recommendations in considering future research.

Commentator & Affiliation	Section	Comment	Response
Goldschimdt	General	This amazingly comprehensive and accurate review is extremely helpful, yet leaves some important holes for current practice. This is in part because the review has to stand in isolation from current drug developments, which appear to be impressive and are not yet reflected in such a review. The typical problem of excellent studies lagging behind advances (or presumed advances) or decrements (or presumed decrements) in treatment and/or diagnosis is, of course, discouraging for a primary care physician such as myself. Thus, the timing of the review (not the quality of the review) is unfortunate. I trust the complementary review of effectiveness of therapy balances this off. Overall, the review provides excellent background information, much of which challenged my preconceptions and knowledge base! I have a slightly different take on the way the effectiveness of risk-based testing is described. Although the facts seem correctly stated from the review's findings, it seems there is a subtle diminishing of the value of being able to identify infected persons through risk-based screening. There are two reasons the review made me think that. First, I think that by using the word, "although," as the first word of the Conclusion, it substantially influences the rest of the sentence, diminishing the important clause, “screening can accurately identify adults with chronic HCV infection.” The word, “although,” seems unnecessary and – to the clinician-reader – implies that the next phrase is somehow less important. For the review to serve as a guiding document, I think the conclusion would be better if it captured the sum of the review. To me, the review more accurately says something like (paraphrased): screening can identify many infected folks, screening also will miss many infected folks (so beware, it’s not as sensitive as we would like), no single screening tool is established as the right tool to use for screening. Second, I think a bit too much emphasis is based on the finding that from 10-67% of infected persons are not identified with those methodologies. If therapies are indeed found in the long term to be more effective and less toxic than earlier therapies (which seems will be the case, but is not part of this review), the identification of the patients who are infected will have great value. Thus, the false negatives are not all that bothersome to me. That the screening is not as sensitive as one would want should not diminish the value of risk based testing (if treatment is effective) unless there is a compelling cost reason to avoid it or the risks of screening are substantial. The review did not make the case that there was evidence of either of those factors.	We believe that the wording of the conclusions accurately summarizes the evidence presented in the report. The false-reassurance rates from targeted screening are simply reported and can be interpreted by readers as appropriate.
NVHR	General	The Draft Comparative Effectiveness Review, Screening for Hepatitis C Virus Infection in Adults, raises a number of significant concerns which must be addressed before this document is finalized. The hepatitis C epidemic poses a major public health crisis in the United States, with hepatitis C associated deaths now exceeding annual mortality from HIV/AIDS, and steadily increasing. The 2010 Institute of Medicine report Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C documents the failure to address the hepatitis C epidemic through established measures and proven interventions. The absence of consistent and coordinated HCV screening guidelines and measures undermines detection and disease control measures and contributes to the growing mortality attributable to HCV. Public health and liver disease experts and patient advocates widely criticized the	Antiviral treatments are covered in a separate companion review. Rapid testing is not in widespread use yet, and it is believed to be similar in diagnostic accuracy to standard testing, which was felt to be well-established as highly accurate in the prior USPSTF review and therefore not re-reviewed. There are also no studies as yet that

Commentator & Affiliation	Section	Comment	Response
		2004 USPSTF review of HCV screening for adopting a narrow and conservative approach to assessing the available evidence, resulting in no favorable recommendation for screening. Given the significance of USPSTF recommendations in guiding clinical practice and reimbursement, the panel bears responsibility for the continued underdiagnosis of HCV over the past several years, placing hundreds of thousands, if not millions, of undiagnosed patients at considerable risk for disease progression and death. The body of evidence supporting HCV screening has grown considerably since 2004, and the pace of new research has accelerated dramatically over the past two years. Since the release of the Institute of Medicine report, the FDA has approved two new treatments for hepatitis C which dramatically improve cure rates, along with approval of a new rapid HCV antibody screening test with the potential to significantly expand rates of diagnosis and entry into care. Further therapeutic advances currently far along in development promise to transform the HCV landscape, opening up the possibility of effectively eradicating HCV in the United States. However, these new therapies will only benefit those who have been diagnosed; screening remains the largest bottleneck, and a revolution in screening guidelines must accompany the revolutions in therapeutics and diagnostics now underway. This is a crucial time in the HCV epidemic, and the patient advocacy community regards the USPSTF review of HCV screening recommendations as a pivotal moment in determining whether we will stem the tide of morbidity and mortality in this decade. The National Viral Hepatitis Roundtable (NVHR) believes that the draft CER is incomplete and premature. In the Appendix below, we outline several critical pieces of evidence supporting HCV screening which were not considered in the draft review. In particular, we note the renewed research interest in robust models and studies to compare and evaluate HCV screening strategies, along with an emerging body of research on the efficacy and diagnostic accuracy of rapid HCV antibody testing. Much of this research has been published or presented over the past six months, demonstrating the accelerated pace of research and rapid shifts in the field. A significant body of research remains still in progress, with salient results expected throughout 2012. This highlights the risks of drawing premature conclusions in an area undergoing substantial transformation: any screening recommendations based only on a review of data available through June, 2011 will quite likely be rendered outdated and obsolete by the time of publication.	have evaluated clinical effects of rapid testing on test uptake or clinical outcomes.

Commentator & Affiliation	Section	Comment	Response
Bellinda Schoof, MHA, CPHQScientific Affairs ManagerAAFPbschoof@aafp.org	General	AAFP recommendation for Hepatitis C are: Hepatitis C Virus Infection, AdultsThe AAFP recommends against routine screening for hepatitis C virus (HCV) infection in asymptomatic adults who are not at increased risk (general population) for infection. (2004)(Grade: D recommendation) Grade Definition: http://www.uspreventiveservicestaskforce.org/uspstf/grades.htm Clinical Consideration: http://www.uspreventiveservicestaskforce.org/uspstf/uspshepc.htm Hepatitis C Virus Infection, AdultsThe AAFP found insufficient evidence to recommend for or against routine screening for hepatitis C virus (HCV) infection in adults at high risk for infection. (2004) (Grade: I recommendation) Grade Definition: http://www.uspreventiveservicestaskforce.org/uspstf/grades.htm Clinical Consideration: http://www.uspreventiveservicestaskforce.org/uspstf/uspshepc.htm It would be important to consider integrating the results of the review regarding effectiveness of antiviral regimens when that is report is available.	Thank you. Recommendations regarding screening will be made by a separate independent body. This report presents the evidence about screening for hepatitis C. As noted above, a separate but complementary report about treatment of hepatitis C will be available concurrently. The body making recommendations about screening for hepatitis C will consider the evidence presented in both of these reports in their deliberations.
Vertex	General	Vertex applauds AHRQ for recognizing the importance of HCV screening by conducting this review. We commend AHRQ for undertaking this investigation of screening and the complementary reviews of HCV treatment and medication adherence. HCV infection is the most common long-term blood-borne infection in the United States.1 Although new Hev infections have declined over the last two decades, at least three million Americans are chronically infected with HCV. Most Americans were infected in the 1960s t01980s and have had HCV infection for 20 to 40 years? They are at increased risk for complications of cirrhosis, including decompensated liver disease, liver cancer (hepatocellular carcinoma), and need for liver transplantation. 3 Screening for HCV may help to identify HCV -infected patients prior to the onset of liver failure or liver cancer, allowing them to be adequately monitored and potentially treated.4 Furthermore, by allowing for the detection of HCV, screening may assist in further reducing transmission of the virus.	Thank you for your comment.
Vertex	General	AHRQ should ensure that the appropriate population is targeted for HCV screening. Screening for HCV infection in the general population of asymptomatic adults is unlikely to be an effective strategy, given the low prevalence of HCV infection among adults between 20 to 29 years of age. 5 In addition, including adults with no known liver function test abnormalities may dilute the effectiveness of screening programs, as evidence suggests that over 90 percent of adults with chronic HCV have abnormal liver function test levels at some point during follow Up.6 Thus, it is doubtful that studies performed to assess the effectiveness of HCV screening for asymptomatic adult patients in the general population with no known liver function test abnormalities will be useful, given that the prevalence of HCV in the nontargeted population is low.	The review included key questions on the effectiveness and diagnostic yield of targeted screening (KQ's 2a and 2b).

Commentator & Affiliation	Section	Comment	Response
Vertex	General	We encourage AHRQ to include the recently published data on the utility of birth cohort screening for HCV as part of this review. There is a growing body of evidence supporting birth cohort screening for HCV. Studies included in the AHRQ report rely on the previously understood populations with higher prevalence of HCV infection, such as individuals who report injecting drugs, high risk sexual behaviors, transfusions prior to 1990, and other percutaneous exposures. A wide variety of screening approaches have been considered for these populations, but there is no clear consensus on which approaches can be best implemented in primary care practices. This is in part because many of these behaviors are stigmatizing, which leads to suboptimal disclosure.7	The only published report on birth cohort screening is a cost-effectiveness modeling study by Rein, et al., that does not meet inclusion criteria; modeling studies were excluded because they do not report actual clinical data. Our search strategy was broad, and we sought to include evidence about birth cohort screening that met our inclusion criteria. However we found that the only published report on birth cohort screening did not report clinical data outcomes and thus it did not meet criteria for inclusion.
GENENTECH	General	I. Data Suggests That Current Screening Guidelines for Hepatitis C Fail to Adequately Capture the Infected Population In the United States, 2.7-3.9 million people are chronically infected with the hepatitis C virus (HCV).1 However, approximately 75 percent of those infected are unaware of their status.2 Given the asymptomatic nature of hepatitis C, some patients may not know they have the disease until they experience symptoms of more severe liver disease, which can take decades to emerge. Current risk-based screening efforts include people (1) with history of injection drug use; (2) who have persistently elevated liver function tests; and (3) who received a blood transfusion before 1992.3 However, despite existing screening guidelines and efforts to increase awareness among both physicians and populations in which hepatitis C infection is prevalent, only 25 percent to 50 percent of patients with chronic hepatitis C are aware of their infections.4 Low case identification may result from difficulty in implementing risk-based screening given the limited time available in primary care visits and the awkwardness of discussing the behavioral risks associated with hepatitis C.5 Unfortunately, individuals who remain undiagnosed and without treatment are at greater risk for serious chronic conditions, including liver failure, cirrhosis and liver cancer. In addition, HCV-related liver disease is a leading reason for liver transplants.6 Patients who are made aware of their status and do seek treatment can see a positive impact on their liver health and may be able to avoid these serious consequences, including liver failure. Informed patients are also less likely to risk spreading the disease. II. The Final Report Should Incorporate Important New Evidence That Will Be Released in 2012	Thank you for your comment.

Commentator & Affiliation	Section	Comment	Response
CAP	General	Thank you for the opportunity to comment on your recent review, Screening for Hepatitis C Virus Infection in Adults. We respect your position is to look at this as a healthcare quality issue but hepatitis C is an infectious disease of epidemic proportions with huge public health implications. An infectious disease that impacts more than 3 million Americans and up to 75% are unaware of their infection. Dare we ask you? If you had a potentially life threatening disease, that has a cure, that may cause cancer, or kill you, or you may unintentionally spread to your family, would you want to know about it? Do you tell patients with cancer, they only have a little cancer and let's wait? The Caring Ambassadors Program is a public charity whose mission is to help improve the lives of those affected by hepatitis C. The charity was founded after my-brother was diagnosed with hepatitis C in 1999. My brother's doctor missed testing him for 10 years even though he had elevated liver enzymes, he did not "fit the profile" in his doctors mind to warrant a hepatitis C test. He thought he was in great physical health running marathons and coaching his kids in sports. Little did he know his liver disease was progressing, he had late stage 2 fibrosis. The good news was he was diagnosed and was able to seek treatment. He is now cured. Without the initial diagnosis, he was without options to change the outcome of this disease. The CDC has recognized that the current risk-based screening approach is not working and will be releasing new guidelines in 2012. We have a very short window period to address this epidemic before the death rate triples and we have more than a million people living with cirrhosis. One of the most detrimental things AHRQ could do would be to release conflicting USPSTF guidelines. Physicians and the general public are confused. This confusion has lead to inaction and the loss of life. A recent study, not included in your review, by Rein et al, found if birth-cohort and risk-based screening were adapted it would decrease deaths by 82,000 people compared to risk-based alone. Yet your review found no evidence? The Federal government has provided too little resources to effectively study this issue which results in the lack of evidence you site.	Thank you. The Rein analysis is a cost-effectiveness/modeling study and thus did not meet inclusion criteria. Our search strategy was broad, and we sought to include evidence about birth cohort screening that met our inclusion criteria. However we found that the only published report on birth cohort screening did not report clinical outcomes and it did not meet criteria for inclusion.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 4	General	Overall, well written and clear. The bulleted summaries at the beginning of each KQ are helpful. The evidence tables are in general clear and conclusions valid and well presented. The findings are limited by the lack of evidence or limited quality/consistency of findings. In particular this is insufficient evidence (lac of any studies on KQ1a, b and 2aI believe there needs to be a better linkage between the screening accuracy and harms questions and the effectiveness and harms of therapies (while I realize this is a two part review it is difficult to determine the balance of benefits and harms without knowing the impact of therapies on clinical outcomes (including harms) and the role that the diagnostic tests/strategies play in selecting patients for therapies and the impact these tests have on clinical outcomes. KQ4 assesses the diagnostic accuracy of tests and strategies to guide treatment decisions. Presumably treatment decisions are based on whether a patient has cirrhosis or not…however this is not clearly delineated and should be…furthermore it would be helpful here to know the characteristics of populations enrolled in treatment trials and how they might compare to patients detected by broad based screening (increased risk vs. low risk) and how current clinical practice might be deviating from the patients enrolled in trials (e.g. are all patients in treatment trials those with abnormal LFTs, evidence of cirrhosis or some of these surrogates for cirrhosis-and is there evidence that screening is leading to expansion of treatment to patients with “less severe” disease that might have a much better natural history than patients enrolled in treatment trials-and thus a less favorable benefits to harms ratio.The authors examined evidence to determine if screening could identify and improve clinical outcomes or reduce transmission risk of hepatitis C. The population was asymptomatic adults with no known liver enzyme abnormalities. The literature search went through June 2011. They identified no direct evidence on clinical benefits associated with screening. Targeted screening had a low NNS to identify one case of HCV but missed infected patients. Several noninvasive indices had fair to good operating characteristics for diagnosing cirrhosis, an important point in that diagnostic liver biopsies are invasive and associated with serious harms and rarely death. Treatment is primarily focused on individuals with cirrhosis, though even this outcome is an intermediate (as shown in their analytic framework) one that is not consistently characterized or reproducible. Limited evidence suggests that knowledge of HCV status and counseling may reduce risky behaviors (though even this limited evidence is weakened by the fact that it is not clear if counseling alone would have similar effects and not require HCV screening/knowledge status). There was no clear difference in delivery management practices and risk of HCV infection. Prevalence is 1.6% though the largest cohort is for individuals born between 1945-1964 calling into question the need to screen individuals age > 65 or less 50 in particular because the incidence has declined markedly since 2001 (this latter point should be emphasized in that repeated screening and screening in younger cohorts are likely to have very low incidence.) Mortality is 12,000 deaths per year. HCV is apparently associated with worse QOL even in the absence of cirrhosis.	The Interventions of the Methods section was revised to more clearly explain the potential utility of liver biopsy and other diagnostic testing. In general, treatment decisions are informed in part by findings on biopsy, which can provide information about likelihood of progression. However, clinical practice has been moving towards more selected use of biopsy to inform treatment decisions.The separate antiviral treatment review includes information on characteristics of patients enrolled in the trials. Thank you for your comments.

Commentator & Affiliation	Section	Comment	Response
CAP	General	cont. The Institute of Medicine Report from 2010, Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C wrote; "Upon reviewing evidence on the prevention and control of hepatitis B and hepatitis C, thecommittee identified the underlying factors that impede current efforts to prevent and control these diseases. Three major factors were found: • There is a lack of knowledge and awareness about chronic viral hepatitis on the part of health-care and social-service providers. • There is a lack of knowledge and awareness about chronic viral hepatitis among at-risk populations, members of the public, and policy-makers. • There is insufficient understanding about the extent and seriousness of this public-health problem, so inadequate public resources are being allocated to prevention, control, and surveillance programs. That situation has created several consequences: • Inadequate disease surveillance systems underreport acute and chronic infections, so the full extent of the problem is unknown. • At-risk people do not know that they are at risk or how to prevent becoming infected. • At-risk people may not have access to preventive services. • Chronically infected people do not know that they are infected. • Many health-care providers do not screen people for risk factors or do not know how to manage infected people. • Infected people often have inadequate access to testing, social support, and medical management services. Your recommendations will have an impact on all healthcare settings. After reviewing the entire report, we respectfully suggest that you look again at the questions asked and the data that was missed in this review. Hepatitis C is a virus we can cure. We have an opportunity in our lifetime to eliminate a virus. We cannot do this without the first step, screening. Did you look at the harm of not knowing? Everyone living with hepatitis C has the right to that knowledge and the opportunity to seek a cure.	Thank you for your comment. The intent of this report is not to make recommendations; it presents the evidence which will be used by the USPSTF to make recommendations.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 8	Major Comments	Hepatitis C is a major problem, as described in the background section of the review. Data from large, randomized controlled trials with clinical endpoints would be an ideal tool to make evidence-based decisions about screening and treatment. Unfortunately, such data are neither available nor will they be forthcoming. Decisions — because physicians, patients and public health organizations must make decisions no matter what the quality of the data available — must be based on a lesser standard. In the face of this large and growing epidemic, making no decision, which is of course itself a decision, is not an option. It is critical therefore, to examine all possible sources of information and lines of evidence to assess the benefits of screening. Overall, the benefits of screening (in saved lives and liver disease averted) are considerable, and the risks minimal. A recommendation against screening would therefore require fairly strong justification. This comparative effectiveness review provides an important service in reviewing and summarizing the literature relevant to screening for hepatitis C. The comments in this document attempt to focus constructively on several weaknesses of the work and not its strengths and are not intended to be dismissive of its strengths.	The review was not restricted to randomized trials of benefits of screening versus no screening (observational studies were also included). In addition, the review also evaluated the indirect chain of evidence that could also demonstrate clinical benefits of screening, as indicated in the analytic framework and key questions.
Peer Reviewer # 8	Additional Comments	**Problems with the Organization of the Review:** A decision was made to divide the comparative effectiveness review for hepatitis C screening into two parts by removing considerations of antiviral treatment into a separate review. A second decision was made to conclude the review of "screening-minus-treatment," and obtain no further comments on it from reviewers or the public, before the review of treatment was made available. The consequence of these decisions was to make it extremely difficult to assess the value of this review. Because the greatest benefits from screening will result from treatment, and screening recommendations will be driven by the perceived benefits of treatment, it is impossible to fully evaluate the issues addressed in this review (or omitted from it) without knowing the results of the review of the effectiveness of treatment. The results of that review will determine what questions about screening are most meaningful and relevant and most need to be answered. Thus, peer reviewers and members of the public wishing to comment on this comparative effectiveness review are hamstrung in their ability to provide cogent commentary. Without the results of the treatment effectiveness review, the "screening minus-treatment" effectiveness review can only be considered hypothetically, in abstraction from real-world considerations.	The antiviral treatment review is currently in process and is expected to be available when the screening review is released, or shortly after.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 8	Additional Comments	Problems with Key Questions: **Key Questions 2a and 2b:** These questions do not address the range of meaningful issues related to differing screening strategies in different patient populations. The prevalence of hepatitis C varies widely according to demographic, clinical, behavioral, and epidemiologic factors. According to NHANES data from the National Health and Nutrition Examination Survey, for example, 14% of African American men born in the 1950s — excluding those who are homeless and incarcerated — are HCV-positive.1 Persons with medical illnesses; mental health conditions; a history of illicit substance use (injected or noninjected), homelessness, or incarceration; current incarceration; poverty; or birth in a high-prevalence country have increased prevalences.1-3 A great deal of epidemiologic data provide a basis for identifying patients or patient groups in whom the number needed to screen would be considerably lower than in the general population. In high prevalence groups, screening strategies differ because of the low likelihood of false positive results. The review omits any consideration of these issues. Consequently, it misses the opportunity to be relevant for practitioners caring for patients in these groups.	The review did include studies that evaluated targeted screening strategies, including many of the risk factors described by the reviewer. The numbers needed to screen with the targeted strategies, as described in the Results (KQ 2b), are quite low (though the more targeted the strategy, the more infections are missed).
Peer Reviewer # 8	Additional Comments	Problems with Key Questions: **Key Questions 4a and 4b**: Step #4 in the analytic framework, eligibility for treatment, does not appear to be well served by the key questions assigned to it. Eligibility for hepatitis C treatment is a complex question that the review does not define and does not appear to examine well. Most authorities, and most guidelines, consider any person infected with HCV to be eligible for antiviral treatment unless there are specific contraindications. (The contraindications may differ widely among physicians who treat hepatitis C. For example, some will not treat patients with any history of substance use or mental health conditions, although there is little or no evidence to support this practice. Others have little difficulty treating the vast majority of such patients if the nature and severity of these problems are assessed and monitored individually.) Instead, the review extensively examines the ability of various tests to identify patients with progressive fibrosis. Presumably this was done because the authors believe that only patients with advancing fibrosis are eligible for antiviral treatment, or perhaps because they believe that only patients with advancing fibrosis should be eligible for antiviral treatment. In fact, while treatment is generally considered more urgent or more clearly necessary in patients with advancing fibrosis, few authorities consider progressive fibrosis a requirement for treatment eligibility. Instead of addressing treatment eligibility, the review examined several papers to see what proportion of patients in those practices were treated. Patients' actual experiences will differ greatly depending not only on the practices of the physicians to whom they may be referred for treatment, but also on the practices of the referring physicians who performed the testing. There is good evidence, which the review did not examine, that primary care physicians in general lack knowledge about hepatitis C. Moreover, the actual experience of patients will depend on a variety of other barriers to treatment (including structural barriers, such as lack of insurance, lack of supportive services, lack of access to trained providers, etc.) which the	Understanding the proportion of screen-detected patients that receives antiviral treatment (Key Question 4b) is important for understanding benefits and harms of screening because the clinical benefits of screening are highly dependent on receipt of antiviral therapy and attaining a sustained virologic response. Screen-detected patients who do not receive antiviral treatments cannot benefit from these treatments. We did not make assumptions regarding which patients should be eligible for treatment or reasons for treatment eligibility. Rather, Key Question 4b reports the proportion of patients who received treatment. As discussed in the Results for KQ 4b, eligibility criteria were not well-standardized, and varied between studies. The studies included in the review report

Commentator & Affiliation	Section	Comment	Response
		review also did not examine. Thus, the experience of the patients in the studies the review examined would be expected to bear little relation to actual patient eligibility for treatment. It could be argued that patients' actual experiences are more relevant than their theoretical eligibility for treatment, since the purpose of screening is for patients to actually be treated. But physician behavior is highly variable and highly dependent on their education, training, and experience. In an era when hepatitis C is receiving increasing attention, and increasing resources are being devoted to physician education and referral, past observations cannot substitute for future expectations. With the approval of more effective antiviral treatment regimens during 2011, physician awareness and referral practices, and the proportion of patients treated, are expected to increase. Studies conducted before these drugs became available will therefore have limited applicability for the future.	actual data on treatment rates from populations of screen-detected patients with HCV infection. While issues related to access to treatment, barriers to treatment, differences in physician knowledge regarding HCV, etc, may have an important impact on the proportion who are treated, we found no studies showing that interventions addressing these factors impacts the proportion of patients who receive treatment. Nonetheless, this is an important area of research and should be considered by decisionmakers as they weigh the evidence. The Discussion section (see Applicability) notes that treatment eligibility criteria continue to evolve and treatment rates are likely to vary depending on many factors.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 8	Additional Comments	**Key Questions 4a and 4b cont.:** Moreover, the rational response to physician ignorance or inaction is physician education (in which issuing clinical practice guidelines play an important role) — not the issuance of recommendations against screening. It is hard to understand why evidence that physicians provide poor quality care and fail to act appropriately on positive results of screening tests (or because of other barriers are unable to do so) was considered relevant information about "patient eligibility" that should be applied to inform decisions about the utility of screening. The problem with this approach can be further illustrated by considering the evidence — also not examined in this review — of racial and ethnic disparities in the evaluation of and treatment for HCV infection.4-8 Patients belonging to ethnic minorities are more likely than patients of majority ethnicity to be judged "ineligible" for treatment. This would clearly not be an appropriate basis for recommending that patients of minority ethnicity not be screened for hepatitis C. This information could be more appropriately used in a caveat to screening recommendations indicating that the value of screening will be limited if the opportunity to link patients to care where they have true access to antiviral treatment is limited or is not taken advantage of. This more relevant type of analysis would require an analytic framework in which this evidence was considered for detailed examination, in its own right, rather than being categorized as evidence of patient ineligibility for treatment. In this respect, the review would be of greater utility if it reviewed the extensive literature on barriers to treatment, including physician factors (such lack of knowledge about hepatitis C), patient factors, and structural barriers, and on the feasibility of overcoming them, rather than simply reporting the observations in the literature that suffer from these barriers. Ultimately, the benefits of screening will be determined by the ease or difficulty of overcoming these barriers. This comparative effectiveness review, because of the design of its analytic framework and key questions, misses this key set of issues of core relevance to the value of screening.	Thank you for commenting. As described above, the review simply reports the proportion of screen-detected patients who received treatment in clinical practice. It is outside of the scope of this review to speculate about best-case scenarios, reduction in disparities, and/or how physician education might affect treatment rates.
Peer Reviewer # 8	Additional Comments	Problems with Key Questions: **Key Questions 6a and 6b:** The review appears to have considered only studies of counseling interventions for persons testing positive for HCV infection. It appears to have omitted consideration of the entire field of alcohol treatment research.	The CER does focus on benefits of alcohol treatment in HCV-positive patients, as it is not certain that benefits in the general population would be the same as for HCV-positive patients.
Peer Reviewer # 8	Additional Comments	Problems with the Process The issues raised here could easily have been raised by members of the Technical Expert Panel, before the analytic framework and key questions were finalized and the review conducted, had they been allowed the opportunity to provide input. Unfortunately, the process for obtaining input from the Technical Expert Panel allowed several members a few minutes of oral comments and prevented most from having any input at all.	Thank you for your comment. Technical Expert Panel members had opportunities to provide input on multiple calls and electronically, and also to serve as peer reviewers on the report.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 8	Additional Comments	The review omitted mention of one of the biggest developments in HCV screening to emerge during the past year, which was the availability of rapid HCV testing technology. Rapid HCV antibody testing has now been approved by FDA and received a CLIA waver for point-of-care use. This new technology will overcome several of the barriers to effective HCV screening and dramatically affect its potential availability and applicability in a variety of settings. The fact that these developments escaped notice by the review is further evidence of its irrelevance and its obliviousness to the key issues surrounding HCV screening. This undoubtedly resulted from the failure to obtain appropriate input from subject matter experts.	We did not assess diagnostic accuracy of rapid testing because it is not yet commonly used in clinical practice and because the diagnostic accuracy appears similar to standard testing, which was previously already found to be highly accurate. We did revise the "Interventions" section to describe the rapid tests: "A rapid HCV test was approved by the FDA in 2011 for point-of-care testing, based on comparable diagnostic accuracy to standard HCV testing, but is not yet in widespread use."
John Ward, CDC	Additional Comments	Pg 4. CDC recommendations were published in 1998, not 2002. CDC recommendations include testing of persons with a history of injection drug use. Pg 118. Author for reference 96 is Centers for Disease Control and Prevention. This should be cited in similar format to reference 8.	Thank you for your comment. We have made corrections in the final report.

Commentator & Affiliation	Section	Comment	Response
NVHR	Additional Comments	The National Viral Hepatitis Roundtable also has concerns about the standards of evidence required in the draft review. As patient advocates, we see a clear and logical association between testing, treatment, and clinical outcomes: patients can't be treated unless they have been diagnosed, and patients who are diagnosed late or not at all face substantial morbidity and mortality – risks which can be significantly reduced by successful treatment. We have struggled to explain to our communities the basis on which in 2004 the USPSTF found insufficient evidence to recommend HCV screening for adults at high risk, and recommended against screening in asymptomatic adults not at increased risk. Amongst our members, we have countless stories and testimony to the value and power of HCV screening; indeed, had they not been screened, some of our members would not be alive today. 3 But the evidence for screening is more than anecdotal: the question is how the available research is interpreted. The Draft CER presents a narrow and conservative interpretation of multiple lines of evidence which should otherwise support a favorable recommendation of sufficient evidence for HCV screening, particularly in groups at risk (e.g., injection drug users) and/or with elevated prevalence (e.g., the 1945-1965 birth cohort). However, the draft review repeatedly fixates on methodological limitations and perceived gaps in the evidence, placing undue weight on its purported failure to meet an unrealistic burden of proof, to the detriment of its conclusions and the very credibility of the USPSTF itself.	The report adheres to standards developed by AHRQ for evaluating research evidence. The Methods Guide for Effectiveness and Comparative Effectiveness Reviews outlines in detail the methods used for this review. This can be found on the Effective Health Care website at http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&mp=1&productID=318. The Effective Health Care program seeks methodological rigor and consistency across all reviews, and does so in a transparent manner by posting their methods manual and protocols for their reviews. In addition the USPSTF is a separate independent body from AHRQ that will make determination regarding screening based on evidence outlined in this report and the separate complementary evidence report on Hepatitis C treatment.

Commentator & Affiliation	Section	Comment	Response
NVHR	Additional Comments	In summary, NVHR believes that the aggregate body of currently available data clearly provides sufficient evidence to support a recommendation of HCV screening for those at risk and/or with elevated prevalence. Regardless of interpretations of individual studies addressing particular questions, there is an overwhelming preponderance of research consistently favoring screening. We urge AHRQ to reconsider its assessments in this draft CER and incorporate key research published and presented in recent months. NVHR further calls upon AHRQ to recognize the rapid pace of change in an evolving landscape, and defer finalizing the CER and developing new USPSTF HCV screening recommendations if there are reasonable grounds to expect that additional data in 2012 would render the current assessment of the evidence obsolete. In particular, NVHR calls attention to the importance of the CDC's forthcoming revision to its HCV screening guidelines, as well as further diagnostic and therapeutic developments and research currently underway. The reviewers, the USPSTF, and AHRQ bear a heavy responsibility for taking a thoughtful approach to this process, and any updated recommendations will come under considerable scrutiny. NVHR is a strong proponent of evidence-based public health and health care policy; we also hold ourselves accountable to the millions of undiagnosed Americans living with chronic hepatitis C, and urge AHRQ to hold itself to the same standard.	Thank you for your comment.
Vertex	Additional Comments	Vertex appreciates this opportunity to comment on this important draft paper, and we look forward to continuing to collaborate with AHRQ. Of note, at your request, we are currently working on submitting a Scientific Information Packet on INCIVEKTM (telaprevir) to support AHRQ's two additional studies on HCV treatment and adherence to treatment. We appreciate your consideration and are available to provide further information or assist with any additional questions.	Thank you for submitting a Scientific Information Packet (SIP). This is most relevant to the Hepatitis C treatment review.
Vertex	Additional Comments	In addition to assessing the harms of HCV screening, AHRQ should consider the harms of not screening for HCV. While the AHRQ report assesses the benefits and harms of HCV screening, it is important to also consider the harms associated with not screening for HCV. Some studies state that 70 percent of patients who are currently infected with HCV are unaware of their infection. Without screening, these patients could progress to advanced liver disease and experience a reduced life expectancy, a reduced quality of life, and high treatment costS.14 One study projects that the proportion of chronic HCV patients with cirrhosis is currently about 25 percent; this is expected to reach 45 percent by 2030.15 This same study estimates that treatment of all infected patients in 2010 could reduce the risk of cirrhosis, liver decompensation, liver cancer, and liver related deaths by 2020 with the current antiviral therapy response rates. 16 However, unless these asymptomatic HCV infected patients are identified by screening or other methods, they will not receive treatment which has been shown to significantly reduce patient risk of death due to liver decompensation and liver cancer. Given the abundant evidence that supports improved outcomes from appropriate identification and treatment of HCV, we urge AHRQ to consider the harms associated with not screening for HCV in the final report.	Consequences of not screening are already addressed by the key questions (e.g., KQ 1 addresses screening vs. no screening; other KQ's address counseling interventions vs. no counseling interventions [which might occur as a result of no screening]; etc.)

Commentator & Affiliation	Section	Comment	Response
Genentech	Additional Comments	Treatment for hepatitis C is a dynamic field; new therapies are increasingly effective at inducing sustained virological response and research continues on promising new molecules. Screening is the critical first step in identifying millions of individuals currently unaware of their status and linking them to important treatments. Therefore, we urge AHRQ to ensure this Report provides a comprehensive review of all available evidence, including the outcomes of the CDC study, in the final report. This will provide a strong foundation for USPSTF as it undertakes the process of updating its recommendations and facilitates creation of a comprehensive and uniform national strategy for HCV screening.	Thank you for your comment. There are as yet no clinical data from the CDC study.