



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 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.

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 virological 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 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.

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.

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.

National Viral Hepatitis Roundtable
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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 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

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 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.