

Hepatitis C Screening — Getting It Right

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Abstract

Hepatitis C is the most prevalent bloodborne viral disease in the United States and the deadliest. This year, the U.S. Preventive Services Task Force (USPSTF) will update its 2004 hepatitis C guideline, which recommends against screening asymptomatic adults for hepatitis C. This guideline has hampered public health efforts to encourage screening and identify and refer infected persons for care by declaring that such interventions were not supported by the evidence. A draft revision of the guideline, released on November 26, 2012, concludes that testing persons born between 1945 and 1965 probably has at least a small net benefit, but stops short of definitively recommending that this cohort be screened. This article examines the Task Force's process for writing its guidelines. It recommends that the Task Force adopt a balanced approach to evaluating the benefits and harms of screening; use the preponderance of the evidence as a standard for evaluating interventions that target serious public health problems; be transparent about the value judgments that go into its decisions; consider the wide variation in disease prevalence in diverse patient populations; and recommend screening asymptomatic adults for hepatitis C. By taking a broader view of the evidence, the Task Force can write new guidelines that will serve efforts to curb the hepatitis C epidemic, rather than frustrate them.

214 words

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Hepatitis C is a major public health threat. It is already the most common cause of death from liver disease and the leading indication for liver transplantation in the United States.¹ Deaths from hepatitis C are increasing year by year; in 2007, we now know,² they exceeded 15,000, surpassing deaths from HIV/AIDS and making hepatitis C not only the most prevalent bloodborne viral disease in the U.S. but also the deadliest.

This year, the U.S. Preventive Services Task Force (USPSTF) is reviewing and updating its recommendations about screening asymptomatic adults for hepatitis C. This will provide the group the opportunity to avoid the confusion and controversy that arose when its current guideline was issued in 2004. That statement concluded that the harms of screening asymptomatic adults for hepatitis C outweighed the benefits. This opinion was based on a perceived lack of evidence that treatment resulted in clinical benefit, along with concerns about the potential harms of labeling, liver biopsies, and adverse treatment effects in those screening positive.³

That guideline contradicted the position taken by every other authoritative body that had examined the same evidence.⁴ The National Institutes of Health (NIH),^{5,6} the Centers for Disease Control and Prevention (CDC),⁷ the Veterans Health Administration,⁸ the American Association for the Study of Liver Disease,⁹ the Infectious Diseases Society of America,⁹ the American College of Gastroenterology,⁹ the American Gastroenterological Association,¹⁰ and

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the Institute of Medicine¹ all recommended hepatitis C screening and treatment, and the Food and Drug Administration (FDA) has approved nine antiviral regimens for hepatitis C since 1991. The Task Force attempted to clarify its statement in a second article published 8 months later,¹¹ but the second statement simply restated the first. The Task Force had found insufficient evidence of the benefits of treating hepatitis C and recommended against screening asymptomatic adults. The evidence was insufficient, it said, to support screening even high-risk adults for hepatitis C, which it recommended neither for nor against.

On November 26, 2012, the USPSTF released for public comment a draft of its new hepatitis C screening guideline.¹² The new statement concludes that testing asymptomatic persons born between 1945 and 1965 probably has at least a small net benefit, but says only that screening should be “considered” in this cohort. This is a “grade C” recommendation, meaning that patients in this age group should not be screened routinely because the net benefit is likely to be small. The new draft does, however, endorse screening people who inject illicit drugs or received a blood transfusion before 1992 with a grade B recommendation.

The Task Force’s 2004 guideline set back public health efforts to encourage screening and create programs to identify and refer infected persons for care by declaring that such interventions were not supported by the evidence. USPSTF recommendations carry considerable weight with healthcare payers and public health agencies, who look to the USPSTF as the authority on what interventions are supported by the evidence, and the guideline has led to missed opportunities to identify thousands if not millions of infected people. A CDC-funded study, for example, estimated that 66.9 million Americans born from 1945 through 1965 visited a primary care provider at least once in 2006; screening them for hepatitis C would have detected 1.2 million infections and averted 82,000 deaths.¹³ The Affordable Care Act has now amplified the consequences of USPSTF decisions by mandating universal

insurance coverage for all USPSTF grade A or B (but not grade C) recommendations. The new draft guideline moves closer to the consensus of the medical and public health community, but still refrains from definitively recommending screening asymptomatic adults for hepatitis C, passing up the opportunity to substantially reduce the burden of disease and death that will be caused by hepatitis C. This article reviews key steps in the USPSTF process and makes recommendations to strengthen the process and the nation's hepatitis C screening policy.

Why the discordance? And what does the evidence really say?

Somewhere between 5 and 8 million Americans have been infected with the hepatitis C virus (HCV).^{14,15} Most suffer clinical sequelae, including chronic hepatitis, which progresses in some patients to cirrhosis, liver failure, or liver cancer; and a variety of extrahepatic manifestations ranging from chronic fatigue and cognitive impairment to mixed cryoglobulinemia, type 2 diabetes mellitus, and others.¹⁶ A single course of antiviral therapy with peginterferon and ribavirin, available since 2001, results in durable loss of viremia — termed sustained virologic response (SVR) — in 40%-50% of patients,⁵ with concomitant improvements in liver histology¹⁷ and quality of life.¹⁸ When added to this regimen, protease inhibitors, approved in 2011, raise the SVR rate to 65%-75% in patients infected with HCV genotype 1.^{19,20} The new regimens have drawbacks, including troublesome side effects, high adherence burdens, numerous drug-drug interactions, high costs, and suboptimal response rates in patients with cirrhosis. Better regimens are still needed. But followed long-term, patients with SVR rarely experience recurrence of viremia or progression of disease; for all intents and purposes, they appear to be cured of their infection.²¹⁻²⁷ The life-threatening sequelae of hepatitis C, however — liver failure, liver cancer, and death — unfold over decades, much longer than the duration of clinical trials, and data from randomized, controlled trials are not available on the impact of antiviral regimens on these clinical events.

The USPSTF attempts to base its evaluation of interventions on direct evidence — data from randomized trials with clinical endpoints — as it should. The objective of medical care is to prevent sickness and death, not to correct abnormal laboratory test results, and randomized trials are the gold standard for assessing effects of interventions. For hepatitis C treatment, however, such data are neither available nor will they be forthcoming. It will never be acceptable to randomize patients to a control group that does not receive treatment and follow them long enough to count the number who get sick and die of liver disease. Treatment already exists that can eradicate the infection in most patients, and in the decades it would take to do such a study even more effective and less toxic regimens will become available.^{28,29} In short, we will never have the direct evidence the Task Force would like because the medical and scientific communities have already accepted what the Task Force has not, namely, that HCV infection causes serious clinical sequelae and that its eradication prevents those sequelae.

Where the USPSTF departs from the other groups that have written hepatitis C guidelines is that it believes screening must meet a higher burden of proof than interventions for persons seeking care for a clinical illness^{30,31} and finds evidence that fails to meet the highest standard unpersuasive. Because direct evidence of the benefit of hepatitis C treatment was not available — regardless of how remote the possibility of obtaining such evidence — the Task Force concluded that primary care practitioners should spend their limited time on other interventions instead.¹¹

In the real world, however, physicians, patients, and policymakers must make decisions, no matter what the quality of the available data — decisions that gain urgency as the death toll from hepatitis C mounts. To guide such decisions, evidence-based guidelines must consider all the available evidence, including that which fails to meet the gold standard. The consequences

of not screening must be weighed as seriously as the consequences of screening. Indirect evidence of benefit must be weighed against indefinite evidence of harm.

Such decisions require judgment. But simply dismissing evidence that does not meet the highest standard does not make guidelines more evidence-based; it just assures that they will be based on less evidence. Indeed, writing guidelines always requires weighing and comparing the relative importance of harms and benefits that are dissimilar in nature and frequency. There is no objective method to do this. The Task Force believes that it “stands as an independent arbiter of the evidence, and, as such, has set the standard for evidence-based recommendations for the delivery of clinical preventive services.”³² But although it uses a rigorous, systematic process to review the evidence about preventive services, its procedures for weighing the data and drawing conclusions from them are opaque and subjective. Indeed, the Task Force acknowledges that writing guidelines requires making value judgments — which it does by “striving to consider what it believes are the general values of most people,”^{30,33} a procedure that is anything but rigorous or evidence-based. In the case of hepatitis C screening, the Task Force’s judgment — that the harms of labeling, liver biopsies, and adverse treatment effects outweigh any benefits of eradicating infections that are detected — though informed by a careful review of the evidence, was also based on a series of value-laden, subjective choices.

Balance in assessment of benefits and harms

Some of these choices are embedded in the analytic framework the Task Force uses to examine indirect evidence when data from randomized trials of screening are unavailable.^{30,33} The framework is skewed to emphasize the potential harms of screening over its benefits. The Task Force is committed to assuming that screening causes harm, for example, regardless of whether there is evidence of such harm.^{30,33} It will not consider the benefits of screening,

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however, unless there is solid evidence that meets a list of criteria.^{30,33} In addition, the Task Force is aware that referral bias can cause natural history studies to overestimate the sequelae of a condition and clinical trials to overestimate the benefits of treatment, and automatically discounts such studies, regardless of whether there is evidence for such bias.^{3,30,33} Labeling and referral bias are important concerns, and the USPSTF is wise to take them into consideration. But how much weight to give them is a matter of opinion, not evidence.

Most Americans infected with the hepatitis C virus (HCV) are unaware of their infection.¹ Screening allows infected persons to learn their status and be offered potentially curative treatment. 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 HCV drug development; to obtain health insurance so that treatment will be an option in the future; to be vaccinated against hepatitis A and B; to take other steps to avoid complications of hepatitis C, such as avoiding or getting treated for HIV infection or alcohol consumption; and, not least, to take steps to avoid transmitting the infection to others, including loved ones.

But the Task Force's analytic framework does not consider the value to patients of these opportunities. This decision reflects a particular approach to medical diagnosis that is out of step with current thinking by either doctors or patients, who consider the right to know one's diagnosis paramount, regardless of the anxiety that might be caused by the information and regardless of whether it leads to any specific intervention. Ethical guidelines emphasize disclosure of diagnoses to patients to maximize their autonomy, and there is abundant evidence that patients value this kind of information for its own sake and want to receive it.³⁴⁻³⁶ By using an analytic framework that considers the potential harms of knowing one's diagnosis but not any

inherent benefits, the Task Force has chosen to attach a particular set of weights to these harms and benefits, values that are skewed and anachronistic.

Evidence for the benefit of antiviral treatment

Fortunately, evidence is mounting that antiviral treatment does indeed reduce clinical illness and death.^{22-27,37} These findings make the strongest argument for the benefits of screening. In a study of 34,480 veterans with hepatitis C, for example, mortality was 59% lower in those who received a 48-week course of antiviral treatment than in untreated patients, with intermediate rates in those who received shorter courses.²² But although the investigators controlled for comorbidities that might have confounded the result, this was a retrospective study, not a randomized trial, and thus was subject to selection bias. Indeed, most of the evidence of the clinical benefits of hepatitis C treatment is indirect: antiviral treatment unequivocally eradicates viremia in most patients,^{19,20} and patients without viremia do not progress to develop clinical complications.²³⁻²⁷ Dozens of studies show that achieving an SVR is associated with reductions in histological fibrosis and inflammation,^{17,24} hepatic decompensation,²⁴⁻²⁶ hepatocellular carcinoma,²⁴⁻²⁷ and death.²³⁻²⁶ Based on this evidence, CDC, FDA, and the professional societies have concluded that SVR is a valid surrogate endpoint for judging the benefit of antiviral therapy. The new draft guideline indicates that the USPSTF has now accepted this as well, an important step forward.

Access to quality care

In some studies of clinical populations, only a small proportion of patients testing positive for hepatitis C received antiviral therapy. The Task Force considers this proportion in estimating the value of screening, since patients who do not receive antiviral therapy cannot benefit from it. But

the proportion of patients who undergo antiviral therapy will depend on the knowledge and attitudes of patients and their physicians. Primary care physicians in general lack knowledge about hepatitis C.³⁸ But this can be remedied.^{39,40} Hepatitis C is receiving increasing public attention, and increasing resources are being devoted to education of both physicians and the public. The problem with the Task Force's approach can be illustrated by considering the evidence of racial and ethnic disparities in the evaluation and treatment of patients for hepatitis C. Patients belonging to ethnic minorities are less likely than patients of majority ethnicity to receive treatment for hepatitis C.⁴¹⁻⁴⁵ This would hardly be an appropriate reason to recommend that patients of minority ethnicity not be screened for hepatitis C. Poor quality care can best be addressed by interventions that improve care, not by recommendations against screening. Indeed, recommendations that primary care physicians screen for hepatitis C will undoubtedly spur more widespread physician education.

Variation in patient populations

Whatever the harms and benefits of screening, their balance will depend on the prevalence of the infection in the population under consideration. Screening for a condition is of greater value in populations with a higher prevalence of the condition, because more disease will be prevented and because those screening positive are more likely to be truly at risk of suffering from the condition. Because it intends its guidelines for physicians practicing in "the general primary care situation," the Task Force emphasizes studies "generalizable to the general population."^{30,33,46} But no physician provides care to the "general population." Each physician cares for patients who have a particular set of geographic, demographic, and socioeconomic characteristics. The prevalence of hepatitis C varies widely according to demographic, clinical, behavioral, and epidemiologic factors. Among African American men born in the 1950s, for example, 14% are HCV-positive — even after those who are homeless or incarcerated have

been excluded.⁴⁷ Groups with an elevated risk of HCV infection include persons born between 1945 and 1965 (“baby boomers”); persons lacking health insurance; persons born in a high-prevalence country; and persons with diabetes or other medical illnesses, mental health conditions, illicit substance use (injected or noninjected), homelessness, incarceration, poverty, or a history of any of these conditions (Table 1).^{1,14,47} The Task Force concluded that hepatitis C screening was not warranted in part because the condition was uncommon in the “general population.”³ Primary care physicians serving patients in any of these groups who look to the current USPSTF guideline for guidance will not find it.

The new guideline should do better. But the new draft, unfortunately, does not. It recognizes the increased benefit of screening persons who have injected illicit drugs but none of the other groups listed above. It judges the net benefit of screening baby boomers “small” because their HCV prevalence is “only” 3%-4% (while grading the benefit “moderate” in persons who received blood transfusions before 1992, of whom only 4%-5% are infected⁴⁷). It acknowledges that 10% to 30% of hemodialysis patients have hepatitis C but does not recommend screening that group either. No justification, or evidence, is offered for choosing this threshold, which appears to be entirely arbitrary. (The juxtaposition is striking with the USPSTF’s draft HIV guideline, released one week earlier, which recommends screening all persons aged 15-65, a group in whom undetected HIV infections are present at a frequency of about 0.1%.⁴⁹) Two studies have estimated that screening baby boomers for hepatitis C will avert 78,000-121,000 deaths,^{13,50} a benefit that can hardly be considered “small,” and a third estimated that screening the entire US population aged 20-69 years could save 200,000 lives.⁵¹ These studies also calculated that screening baby boomers would avert 10,000-19,000 liver transplants,^{13,50} which carries an added dividend that each unused organ would be freed up to save another life and relieve the shortage of livers for transplantation. The distinction between grade B and grade C

recommendations has extensive ramifications for healthcare systems, public health agencies, and policymakers and should be made with careful attention to the evidence.

Basing recommendations on evidence

Six measures would strengthen the nation's hepatitis C screening policy (Table 2). USPSTF should adopt a balanced approach to evaluating the benefits and harms of screening, acknowledge the validity of SVR as a surrogate endpoint for evaluating hepatitis C interventions, and consider the wide variation in hepatitis C prevalence in diverse patient populations. USPSTF should use the preponderance of the evidence as a standard for evaluating interventions that target serious public health problems, rather than considering only evidence meeting the highest standard, and it should be more transparent about the value judgments that have gone into its decisions. Providing quantitative estimates of the likelihood of positive and negative outcomes,^{52,53} for example, can be more helpful than simply deciding for everyone which are greater. Federal insurance mandates should consider guidelines written by CDC and NIH, and not solely those of the USPSTF.

The Task Force has stood by controversial recommendations against breast and prostate cancer screening.^{53,54} But treatment for these conditions can cause permanent disability, and many cancers detected by screening would cause symptoms before they became untreatable. Neither of these is true for hepatitis C. By the time patients develop symptoms of advanced liver disease, a liver transplant is usually the only hope for long-term survival.

In writing guidelines, evidence should always be measured against the highest standards. But holding out for the best imaginable evidence – knowing it is impossible to obtain — serves no purpose. It only renders USPSTF guidelines irrelevant to those trying to reduce the suffering

caused by hepatitis C. It has been argued that Task Force recommendations differ from those of other groups because its perspective is that of the primary care practitioner rather than that of the public's health.³¹ But this is a false dichotomy. HCV screening benefits the health of the public only because it benefits the individual patient. Conflicting guidelines serve neither primary care providers nor the public.

The USPSTF's indifference toward hepatitis C screening is only one factor driving the nation's anemic response to the hepatitis C epidemic.^{14,55,56} Four times the size of the HIV epidemic, now known to kill more Americans, the hepatitis C epidemic receives less than 3% of the Federal funding allotted to HIV.¹⁴ Depending on how health reform proceeds, hepatitis C will likely overwhelm the already overtaxed, fragile, and fragmented publicly funded healthcare system. But the USPSTF recommendation against hepatitis C screening has further handicapped public health efforts to control the epidemic. In New York, for example, the "Bronx Knows" and "Brooklyn Knows" campaigns are testing more than a million New Yorkers for HIV, in order to identify, and refer for treatment, the remaining HIV-infected persons in New York who still don't know their HIV status. If these campaigns simultaneously screened for HCV, they would probably identify 15 previously undiagnosed HCV infections for each new HIV infection detected.¹⁴ But funding for hepatitis C screening was not available, and the campaigns have not tested a single person for hepatitis C. Soon they will end, and the opportunity to identify, and refer for care, tens of thousands of New Yorkers with hepatitis C will have been lost.

Lost opportunities such as this one have already translated into thousands of deaths, and stand to cause many thousands more. Without a change in policy, annual deaths from hepatitis C are expected to quadruple in the next two decades.⁵⁷ The overwhelming preponderance of the evidence suggests that the benefits of hepatitis C screening and treatment outweigh the harms. The lives saved and liver disease averted are considerable, and the risks minimal. Economic

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analyses, using the best available data, have found one-time screening of baby boomers,¹³ which CDC has now recommended,⁵⁸ and even of the entire US population aged 20-69 years,⁵¹ to be life-saving and cost-effective. The USPSTF serves a critically important function, providing a fresh, unbiased set of eyes on issues of central importance to patients, physicians, and health systems. By taking a broader view of the evidence, they can write new hepatitis C screening guidelines that will serve efforts to curb the epidemic, rather than frustrate them.

Accepted Article

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Table 1. Groups in the United States with an increased prevalence of hepatitis C

Persons born between 1945 and 1965 (“baby boomers”)

Men

African Americans

Persons with diabetes or other medical illnesses

Persons with mental health conditions

Persons with illicit substance use (injected or noninjected)

Hemodialysis patients

Persons lacking health insurance

Persons living in poverty

Homeless persons

Persons in correctional institutions

Persons receiving unsafe medical injections

Persons born in a high-prevalence country

Source: Refs 1,12,47,48.

Table 2. The author's recommendations to improve national hepatitis C screening policy

1. USPSTF should adopt a balanced approach to evaluating the benefits and harms of screening.
 2. USPSTF should consider the preponderance of the evidence as a standard for evaluating interventions that target serious public health problems when ideal data (from randomized clinical trials with clinical endpoints) cannot be obtained.
 3. USPSTF should acknowledge the validity of SVR as a surrogate endpoint for evaluating hepatitis C interventions.
 4. USPSTF should consider the wide variation in hepatitis C prevalence in diverse patient populations.
 5. USPSTF should be transparent about the value judgments that go into its decisions.
 6. Federal insurance mandates should take into consideration guidelines written by CDC and NIH and not solely those of the USPSTF.
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