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Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965



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CONTENTS

Introduction 2
 Background 3
 Rationale for Augmenting HCV Testing Recommendations 3
 Consideration of a New HCV Testing Strategy 5
 Methods 6
 Results 9
 Factors Considered When Determining the Recommendations 11
 Recommendations 13
 Public Health Testing Criteria 13
 Testing Methods 14
 Management of Persons Tested for HCV Infection 14
 Future Directions 16
 Appendix A 19
 Appendix B 23
 Appendix C 25
 Appendix D 26
 Appendix E 27
 Appendix F 28
 Appendix G 28
 Appendix H 29

CONTENTS (Continued)

Appendix I 30
 Appendix J 31

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Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965

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Summary

Hepatitis C virus (HCV) is an increasing cause of morbidity and mortality in the United States. Many of the 2.7–3.9 million persons living with HCV infection are unaware they are infected and do not receive care (e.g., education, counseling, and medical monitoring) and treatment. CDC estimates that although persons born during 1945–1965 comprise an estimated 27% of the population, they account for approximately three fourths of all HCV infections in the United States, 73% of HCV-associated mortality, and are at greatest risk for hepatocellular carcinoma and other HCV-related liver disease. With the advent of new therapies that can halt disease progression and provide a virologic cure (i.e., sustained viral clearance following completion of treatment) in most persons, targeted testing and linkage to care for infected persons in this birth cohort is expected to reduce HCV-related morbidity and mortality. CDC is augmenting previous recommendations for HCV testing (CDC. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. MMWR 1998;47[No. RR–19]) to recommend one-time testing without prior ascertainment of HCV risk for persons born during 1945–1965, a population with a disproportionately high prevalence of HCV infection and related disease. Persons identified as having HCV infection should receive a brief screening for alcohol use and intervention as clinically indicated, followed by referral to appropriate care for HCV infection and related conditions. These recommendations do not replace previous guidelines for HCV testing that are based on known risk factors and clinical indications. Rather, they define an additional target population for testing: persons born during 1945–1965. CDC developed these recommendations with the assistance of a work group representing diverse expertise and perspectives. The recommendations are informed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework, an approach that provides guidance and tools to define the research questions, conduct the systematic review, assess the overall quality of the evidence, and determine strength of the recommendations. This report is intended to serve as a resource for health-care professionals, public health officials, and organizations involved in the development, implementation, and evaluation of prevention and clinical services. These recommendations will be reviewed every 5 years and updated to include advances in the published evidence.

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Introduction

In the United States, an estimated 2.7–3.9 million persons (1.0%–1.5%) are living with hepatitis C virus (HCV) infection (1), and an estimated 17,000 persons were newly infected in 2010, the most recent year that data are available (2). With an HCV antibody prevalence of 3.25%, persons born during 1945–1965 account for approximately three fourths of all chronic HCV infections among adults in the United States (3). Although effective treatments are available to clear HCV infection from the body, most persons with HCV do not know they are infected (4–7), do not receive needed care (e.g., education, counseling, and medical monitoring), and are not evaluated for treatment. HCV testing is the first step toward improving health outcomes for persons infected with HCV.

Since 1998, routine HCV testing has been recommended by CDC for persons most likely to be infected with HCV (8) (Box). These recommendations were made on the basis of a

known epidemiologic association between a risk factor and acquiring HCV infection. However, many persons with HCV infection do not recall or report having any of these specific risk factors.

In a recent analysis of data from a national health survey, 55% of persons ever infected with HCV reported an exposure risk (e.g., injection-drug use or blood transfusion before July 1992), and the remaining 45% reported no known exposure risk (CDC, unpublished data, 2012). Other potential exposures include ever having received chronic hemodialysis, being born to an HCV-infected mother, intranasal drug use, acquiring a tattoo in an unregulated establishment, being incarcerated, being stuck by a needle (e.g., in health care, emergency medical, home, or public safety settings) and receiving invasive health-care procedures (i.e., those involving a percutaneous exposure, such as surgery before implementation of universal precautions). Although HCV is inefficiently transmitted

BOX. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic diseases

Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born during 1945–1965*

- Adults born during 1945–1965 should receive one-time testing for HCV without prior ascertainment of HCV risk.
- All persons with identified HCV infection should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment services for HCV infection and related conditions.

Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents†

- HIV-infected patients should be tested routinely for evidence of chronic HCV infection. Initial testing for HCV should be performed using the most sensitive immunoassays licensed for detection of antibody to HCV (anti-HCV) in blood.

Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection and HCV-Related Chronic Disease‡

Routine HCV testing is recommended for

- Persons who ever injected illegal drugs, including those

who injected once or a few times many years ago and do not consider themselves as drug users.

- Persons with selected medical conditions, including
 - persons who received clotting factor concentrates produced before 1987;
 - persons who were ever on chronic (long-term) hemodialysis; and
 - persons with persistently abnormal alanine aminotransferase levels.
- Prior recipients of transfusions or organ transplants, including
 - persons who were notified that they received blood from a donor who later tested positive for HCV infection;
 - persons who received a transfusion of blood or blood components before July 1992; and
 - persons who received an organ transplant before July 1992.

Routine HCV testing is recommended for persons with recognized exposures, including

- Health care, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-positive blood.
- Children born to HCV-positive women.

* Source: CDC. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945–1965. MMWR 2012;61 (No. RR–4).

† Source: CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR 2009;58 (No. RR–4).

‡ Source: CDC. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. MMWR 1998;47 (No. RR–19).

through sexual activity, the prevalence of HCV antibodies among persons who report having had ≥ 20 sex partners is 4.5 times greater compared with the general population (1).

These birth-year-based recommendations are intended to augment, not replace, the 1998 HCV testing guidelines (8). They were developed by the HCV Birth Cohort Testing Work Group, which consisted of experts from CDC and other federal agencies, professional associations, community-based organizations, and medical associations. The Work Group used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework (9–17) to inform the development of these recommendations. The GRADE approach provides guidance and tools to define the research questions, conduct systematic reviews, assess the overall quality of the evidence, and determine the direction and strength of the recommendations. Following this evidence review, CDC's Division of Viral Hepatitis (DVH) developed this report, which was then peer-reviewed by external experts and posted for public comment (www.regulations.gov). CDC reviewed and considered all public comments in developing the final recommendations.

Background

HCV causes acute infection, which can be characterized by mild to severe illness but is usually asymptomatic. In approximately 75%–85% of persons, HCV persists as a chronic infection, placing infected persons at risk for liver cirrhosis, hepatocellular carcinoma (HCC), and extrahepatic complications that develop over the decades following onset of infection (18).

Because HCV is a bloodborne infection, risks for HCV transmission are primarily associated with exposures to contaminated blood or blood products (8). In 1998, the highest prevalence of antibody to HCV (anti-HCV) was documented among persons with substantial or repeated direct percutaneous exposures, such as persons who inject drugs (PWID), those who received blood from infected donors, and persons with hemophilia (60%–90%); moderate rates were found among those with repeated direct or unapparent percutaneous exposures involving smaller amounts of blood, such as hemodialysis patients (10%–30%). Persons with unapparent percutaneous or mucosal exposures, including those with high-risk sexual behaviors, sexual and household contacts of persons with chronic HCV infection (1%–10%), and persons with sporadic percutaneous exposures (e.g., health-care workers [1%–2%]), had lower rates. According to American Red Cross Blood Service systems in the United States, prevalence among first time blood donors was even lower (0.16% in 2008) (19).

Before 1965, the estimated incidence of HCV infection (then known as Non A-Non B hepatitis) was low (18 cases per 100,000 population). However, the incidence of HCV infection increased steadily into the 1980s and remained high (130 cases per 100,000 population), representing an average of 230,000 infections per year during that decade (20). In 1988, HCV was identified, and by 1992, sensitive multiantigen serologic assays for testing the blood supply had been developed and licensed. During 1992–2004, the number of reported cases of new HCV infection decreased 78.4% (2), and during 1999–2008, HCV prevalence among first-time blood donors decreased 53%. Much of this decline can be attributed to a decrease in cases among PWID (21). Safer injection practices among PWID contributed to some of this decline, but the downward trend was most likely related to HCV infection saturation of the injection-drug-using population (21). A smaller proportion of the overall decline in HCV infection incidence was attributed to effective screening of blood donors to prevent HCV transmission. Since 2004, HCV incidence has remained stable (21). In 2010, the estimated number of newly acquired (i.e., acute) infections in the United States was 17,000 (2,22).

The overall prevalence of anti-HCV in the general population of the United States can be estimated by analyzing National Health and Nutrition Examination Survey (NHANES) data, a representative sample of the civilian noninstitutionalized population. NHANES data indicate that HCV infection prevalence was 1.6%–1.8% during 1988–2002, consistent with the finding that the incidence of infection declined and then remained stable during this time (1,20,21,23). Considering NHANES data collected from 1999–2008, the anti-HCV prevalence estimate is 1.5%, or 3.9 million persons (95% confidence interval [CI] = 1.3–1.7; 3.4–4.4 million persons). NHANES data underestimate the actual national prevalence because these surveys do not include samples of incarcerated or homeless persons, populations known to have high prevalence of HCV infection. Although no systematic surveys comparable to NHANES have sampled these populations, their inclusion has been estimated to increase the number of infected persons by 500,000–1,000,000 (24).

Rationale for Augmenting HCV Testing Recommendations

In 1998, recommendations for identifying HCV-infected persons were issued as part of a comprehensive strategy for the prevention and control of HCV infection and HCV-related chronic disease (8). HCV testing was recommended for persons at high risk for HCV transmission, including

persons who 1) had ever injected drugs, 2) were ever on chronic hemodialysis, 3) received blood transfusions or organ transplants before July 1992, or 4) received clotting factor concentrates produced before 1987 (Box). Screening also was recommended for persons who had a recognized exposure (i.e., health-care, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures and children born to HCV-infected mothers) and persons with laboratory evidence of liver inflammation (i.e., persistently elevated alanine aminotransferase levels). In 1999, HCV testing also was recommended for persons infected with HIV (25).

Limited Effectiveness of Current Testing Strategies

Current risk-based testing strategies have had limited success, as evidenced by the substantial number of HCV-infected persons who remain unaware of their infection (26). Of the estimated 2.7–3.9 million persons living with HCV infection in the United States, 45%–85% are unaware of their infection status (4–7); this proportion varies by setting, risk level in the population, and site-specific testing practices. Studies indicate that even among high-risk populations for whom routine HCV testing is recommended, prevalence of testing for HCV seromarkers varies from 17%–87% (4,5); according to one study, 72% of persons with a history of injection-drug use who are infected with HCV remain unaware of their infection status (27). Barriers to testing include inadequate health insurance coverage and limited access to regular health care (7); however, risk-based testing practices have not been successful in identifying most HCV-infected persons, even those covered by health insurance (6).

Barriers exist at the provider level, limiting the success of the risk-based approach to HCV testing. Providers lack knowledge about hepatitis serology and treatment; studies indicate that providers' level of knowledge regarding HCV infection prevalence, natural history, available tests, and testing procedures is low (28–30). Although up-to-date professional guidelines on HCV testing are available from the American Association for the Study of Liver Disease (AASLD) (18,31), one survey found that 41.7% of primary care physicians reported being unfamiliar with these guidelines (32). In addition, accuracy of patient recall of risk behaviors, including drug use and sexual encounters, decreases over time (33).

Increasing HCV-Associated Morbidity and Mortality

HCV-associated disease is the leading indication for liver transplantation and a leading cause of HCC in the

United States (26,34–36). HCC and cirrhosis have been increasing among persons infected with HCV (37,38), and these outcomes are projected to increase substantially in the coming decade (39,40). HCC is the fastest growing cause of cancer-related mortality, and infection with HCV accounts for approximately 50% of incident HCC (41). A CDC review of death certificate data found that the hepatitis C mortality rate increased substantially during 1999–2007 (annual mortality rate change: +0.18 deaths per 100,000 population per year); in 2007, HCV caused 15,106 deaths (42). Of the HCV-related deaths, 73.4% occurred among persons aged 45–64 years, with a median age of death of 57 years (approximately 20 years less than the average lifespan of persons living in the United States).

On the basis of data from prospective and retrospective cohorts, an estimated 20% of infected persons will progress to cirrhosis 20 years after infection, and up to 5% will die from HCV-related liver disease (43). Modeling studies forecast substantial increases in morbidity and mortality among persons with chronic hepatitis C as they age into their third, fourth, and fifth decades living with the disease (44,45). These models project that during the next 40–50 years, 1.76 million persons with untreated HCV infection will develop cirrhosis, with a peak prevalence of 1 million cases occurring from the mid-2020s through the mid-2030s (40); approximately 400,000 will develop HCC (40). Of persons with hepatitis C who do not receive needed care and treatment, approximately one million will die from HCV-related complications (40,46).

Benefits of HCV Testing and Care

Clinical preventive services, regular medical monitoring, and behavioral changes can improve health outcomes for persons with HCV infection. HCV care and treatment recommendations have been issued by AASLD and endorsed by the Infectious Disease Society of America (IDSA) and the American Gastroenterological Association (AGA) (18). Because co-infection with HIV, hepatitis A virus (HAV), or hepatitis B virus (HBV) and consumption of alcohol hasten the progression of HCV-related disease (47), professional practice guidelines (18) include counseling to decrease or eliminate alcohol consumption and vaccination against HAV and HBV for susceptible persons. Additional guidance includes counseling and education to reduce interactions between herbal supplements and over-the-counter and prescription medications (18,31). Because elevated body mass index (BMI) (weight [kg]/height [m]²) has been linked to increased disease progression among HCV-infected persons, counseling to encourage weight loss for persons who have BMI scores ≥ 25 is recommended to reduce the likelihood of insulin resistance and disease progression (18,48). As HCV-associated liver disease progresses, the likelihood of sustaining a treatment response

decreases (48,49); therefore, early identification, linkage to care, and clinical evaluation are critical disease prevention interventions.

Benefits of HCV Treatment

AASLD recommends considering antiviral treatment for HCV-infected persons with histological signs of bridging fibrosis, septal fibrosis, or cirrhosis (18). In 2011, the first generation of direct-acting antiviral agents (DAAs), the HCV NS3/4A protease inhibitors telaprevir and boceprevir, were licensed in the United States for treatment of HCV genotype 1 (the most common genotype in the United States). Compared with conventional pegylated interferon and weight-based ribavirin therapy (PR) alone, the addition of one of these two protease inhibitors in clinical trials increased rates of sustained virologic response (SVR) (i.e., viral clearance following completion of treatment) from 44% to 75% and 38% to 63%, respectively, in persons with HCV (50,51). In a study of veterans with multiple co-morbidities, achieving an SVR after treatment was associated with a substantial reduction in risk for all-cause mortality of >50% (52) and substantially lower rates of liver-related death and decompensated cirrhosis (i.e., cirrhosis with the diagnosis of at least one of the following: ascites, variceal bleeding, encephalopathy, or impaired hepatitis synthetic function) (18). Because of the recent introduction of these treatment regimens, the long-term effects of DAA treatment in clinical practice have yet to be established, and the benefits might be different in community settings. In addition to the new Food and Drug Administration (FDA)-approved medications, approximately 20 HCV treatments (protease and polymerase inhibitors) are undergoing Phase II or Phase III clinical trials (53); treatment recommendations are expected to change as new medications become available for use in the United States.

Consideration of a New HCV Testing Strategy

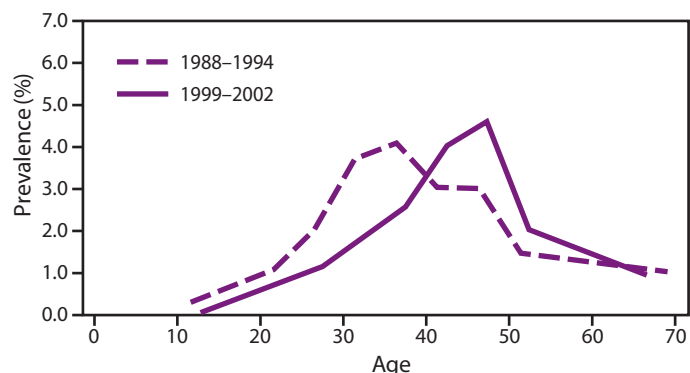
Because of the limited effectiveness of risk-based HCV testing, the rising HCV-associated morbidity and mortality, and advances in HCV care and treatment, CDC has evaluated public health strategies to increase the proportion of infected persons who know their HCV infection status and are linked to care. Several analyses of nationally representative data have found a disproportionately high prevalence of HCV infection among persons who were born during the mid-1940s through the mid-1960s. In an analysis of 1988–1994 NHANES data, 65% of 2.7 million persons with HCV infection were aged 30–49 years (23), roughly corresponding to this birth cohort.

In an analysis of NHANES data during 1999–2002, a similarly high proportion of persons with HCV antibody had been born during 1945–1964 (Figures 1 and 2) (1). A recent analysis of 1999–2008 NHANES data found that the prevalence of HCV antibody among persons in the 1945–1965 birth cohort was 3.25% (95% CI = 2.80–3.76); persons born during these years accounted for more than three fourths (76.5%) of the total anti-HCV prevalence in the United States (3).

Selection of a Target Birth Cohort

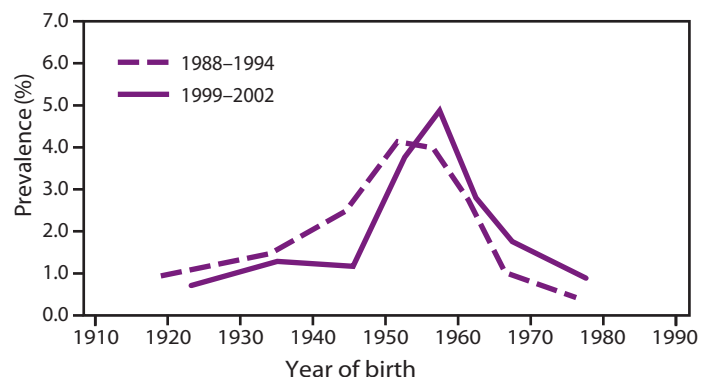
To select a target birth cohort for an expanded testing strategy, CDC considered various birth cohorts with increased HCV prevalence (Table 1). For each proposed cohort, CDC

FIGURE 1. Prevalence of hepatitis C virus antibody, by age at time of survey — National Health and Nutrition Examination Survey, United States, 1988–1994 and 1999–2002



Source: Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Internal Med* 2006;144:705–14. Modified and reprinted with permission from *Annals of Internal Medicine*.

FIGURE 2. Prevalence of hepatitis C virus antibody, by year of birth — National Health and Nutrition Examination Survey, United States, 1988–1994 and 1999–2002



Source: Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Internal Med* 2006;144:705–14. Modified and reprinted with permission from *Annals of Internal Medicine*.

determined the weighted, unadjusted anti-HCV prevalence and the size of the population.

On the basis of HCV prevalence and disease burden, the 1945–1965 birth cohort was selected as the target population. Three birth cohorts (1945–1965, 1950–1970, and 1945–1970) were additionally stratified by race/ethnicity and sex (Table 2). The differences in the male-to-female ratio were not substantial and were not critical in selecting the birth cohort. However, the difference in prevalence by race/ethnicity between the birth cohorts is notable. Both the 1950–1970 and 1945–1970 cohorts have a lower prevalence of HCV-infected non-Hispanic black populations than the 1945–1965 cohort. Of the 210,000 anti-HCV-positive persons in the 1945–1949 cohort, approximately 71,000 (35%) were black. Because non-Hispanic black populations account for a substantial proportion of the 1945–1965 birth cohort, these birth years were included to better address this health disparity.

When examining the possibility of including persons born during 1966–1970 with the target population (i.e., 1945–1965 cohort), it was determined that such a strategy would direct testing to approximately 20 million additional persons at a cost of approximately \$1.08 billion, resulting in identification of an additional 300,000 persons with chronic infection. The number needed to screen to avert a single HCV-related death was lower in the 1945–1965 birth cohort compared with the 1945–1970 birth cohort (607 and 679, respectively). Data collected through a series of 12 consumer focus groups in three different U.S. cities demonstrated that the 1945–1965 birth cohort is a recognized subpopulation known as the “baby boomers;” familiarity with this subpopulation and the term used to describe it likely will facilitate adoption of the recommendation. On the basis of these assessments, CDC selected the 1945–1965 birth cohort as the target population.

Prevalence of HCV Infection in the 1945–1965 Birth Cohort

The prevalence of anti-HCV among persons born during 1945–1965 is 3.25% (3), five times higher than among adults born in other years. The high prevalence of HCV among persons in this birth cohort reflects the substantial number of incident infections throughout the 1970s and 1980s and the persistence of HCV as a chronic infection. Males in this cohort had almost twice the prevalence as their female counterparts; HCV infection prevalence was highest among non-Hispanic black males (8.12%), followed

TABLE 1. Number and prevalence of persons born during 1945–1970 positive for anti-HCV and with chronic HCV infection, by birth cohort — National Health and Nutrition Examination Survey, United States, 1999–2008

Birth cohort	U.S. population (in millions)*	Anti-HCV		Chronic HCV infection	
		No. (in millions)	(Weighted %) [†]	No. (in millions) [§]	(%)
1945–1965	84.2	2.74	(3.25)	2.06	76.6
1950–1970	89.2	2.89	(3.24)	2.17	80.6
1945–1970	105.1	3.15	(3.00)	2.36	87.3
1950–1965	68.3	2.47	(3.61)	1.85	69.9
1950–1960	45.6	1.83	(4.01)	1.37	52.3
1945–1949	13.2	0.21	(1.58)	0.16	6.7
1966–1970	20.9	0.41	(1.94)	0.30	10.8

Abbreviations: HCV = hepatitis C virus; anti-HCV = antibody to hepatitis C virus.

* Source: U.S. Census Bureau. 2010 Census: Single years of age and sex: summary file 1, table PCT12. Available at http://factfinder2.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=DEC_10_SF1_PCT12&prodType=table. Accessed April 27, 2012.

[†] Not adjusted by age or other covariates.

[§] An estimated 75% of anti-HCV-positive persons have chronic HCV infection. (Source: Ghany MG, Strader DB, Thomas DL, Seeff LB, American Association for the Study of Liver D. Diagnosis, management, and treatment of hepatitis C: an update. [Practice Guideline.] *Hepatology* 2009;49(4):1335–74.)

TABLE 2. Prevalence of anti-HCV among three birth cohorts, by sex and race/ethnicity* — National Health and Nutrition Examination Survey, United States, 1999–2008

Characteristic	Anti-HCV (weighted %)		
	1945–1965	1950–1970	1945–1970
Sex			
Male	4.34	4.12	3.89
Female	2.19	2.34	2.14
Race/ethnicity			
White, non-Hispanic	2.89	3.01	2.77
Black, non-Hispanic	6.42	5.73	5.60
Mexican American	3.26	2.56	2.71

Abbreviation: anti-HCV = antibody to hepatitis C virus.

* Not adjusted by age or other covariates.

by non-Hispanic white males (4.05%) and Mexican-American males (3.41%).

Complicating health outcomes among HCV-infected persons born during 1945–1965 are a lack of health insurance (31.5%) and use of alcohol (3). Of all anti-HCV positive persons in the 1945–1965 birth cohort who self-reported alcohol use, 57.8% reported consuming an average of two or more alcoholic drinks per day (3).

Methods

CDC employed the GRADE methodology to inform the guideline development process. In April 2011, CDC convened the HCV Birth Cohort Testing Work Group to explore the practicality of developing a recommendation for one-time HCV testing for persons unaware of their infection status. Epidemiologic data exist to support the consideration of a birth year testing strategy; however, the GRADE process

dictated that a formal review of the literature be conducted to examine the effect that this testing would have on diagnosing persons unaware of their HCV infection status, as well as the potential benefits and harms that this strategy would have on persons tested. The Work Group consisted of 1) a steering committee within CDC's DVH, which led and conducted the evidence reviews; 2) representatives from DVH's Laboratory, Prevention, and Epidemiology and Surveillance Branches, who were tasked with reviewing and providing input on the evidence compiled by the steering committee through biweekly meetings; and 3) external (to CDC) representatives, who provided input on materials compiled by the steering committee through teleconferences, an evidence grading methodology training workshop, and a consultation. External representatives were selected on the basis of expertise with viral hepatitis; members included representatives from hepatitis C-related community-based organizations, persons living with HCV infection, hepatologists, economists, infectious disease specialists, and guideline methodologists. A wide range of disciplines, organizations, and geographic regions was represented, to include

- federal organizations (Agency for Healthcare Research and Quality, National Cancer Institute, Food and Drug Administration, Veteran's Affairs, Health Resources and Services Administration, Substance Abuse and Mental Health Services Administration, and National Institute of Diabetes Digestive and Kidney Diseases),
- professional associations (American Medical Association, American College of Physicians, American Academy of Family Physicians, Association of Public Health Laboratories, and Council of State and Territorial Epidemiologists),
- community-based organizations (Adult Viral Hepatitis Prevention Coordinator Program, National Viral Hepatitis Roundtable, CopeHealth, National Association of State and Territorial AIDS Directors, and Hepatitis Education Project), and
- organizations of medical specialists who frequently see patients in consultation or referral (AASLD, AGA, and IDSA).

Several subject matter experts (e.g., hepatologists, economists, infectious disease specialists, and guideline methodologists) also served as members of the external group. Work Group participants were required to disclose conflicts of interest and were notified of the restrictions regarding lobbying during the recommendation development process (Appendix A). No members' activities were restricted based on the information disclosed.

Comprehensive systematic reviews of the literature were conducted, analyzed, and assessed in two stages to examine the availability and quality of the evidence regarding HCV infection prevalence and the health benefits and harms associated with one-time HCV testing for persons unaware of their status.

Work Group members communicated through teleconferences and attended an in-person workshop on GRADE methodology. Initial evidence from the systematic review of the prevalence data was shared during the teleconferences, and the target birth years were selected. Following that selection, the systematic review focused on the HCV-associated morbidity and mortality that might be altered by a recommendation for one-time testing of persons born during 1945–1965.

In August 2011, CDC convened a 2-day consultation with Work Group members to 1) review and evaluate the quality of the evidence for the proposed birth cohort-based strategy, 2) consider benefits versus harms of patient-important outcomes, 3) weigh the variability between the values and preferences of HCV testing among potential patients, and 4) consider resource implications. During the consultation, a summary of findings table addressing each patient-important outcome was presented to consultation attendees for discussion (Appendix B). Work Group members later provided input on the quality of the evidence and strength of the recommendations. Following the consultation, the DVH Steering Committee and other DVH representatives reviewed the information and reached a decision regarding the strength of the recommendations. At that time, a recommendations statement and qualifying remarks were developed in accordance with GRADE methodology.

Feedback from the public was solicited through conference presentations, meetings with national stakeholders, and public comment. Further, the proposed guidelines were peer-reviewed by external experts in viral hepatitis. A Federal Register notice was released on May 18, 2012, announcing the availability of the draft recommendations for public comment through June 8, 2012. In addition, external Work Group members were asked to comment on the recommendations statement and remarks during the public comment process. Feedback from the public comment period was reviewed by the DVH Steering Committee, and the draft was modified accordingly. Throughout the development process, CDC also sought input from participants at national conferences, including AASLD's 2011 Single Topic Conference, the 2010 Annual Meeting of the American Public Health Association, the 2010 AASLD Conference, the 2011 Guidelines International Network Conference, and Digestive Disease Week 2012.

GRADE Methodology

These recommendations were developed using GRADE methodology (9–17), which has been adopted by approximately 60 organizations, including CDC federal advisory committees (i.e., the Advisory Committee on Immunization Practices and the Healthcare Infection Control Practices Advisory

Committee), the World Health Organization, IDSA, AGA, and the Cochrane Collaboration (www.gradeworkinggroup.org). GRADE provides guidance and tools to define research questions, develop an analytic framework, conduct systematic reviews, assess the overall quality of the evidence, and determine the direction and strength of the recommendations.

Research questions were formulated to guide the development of the recommendations using a population, intervention, comparator, and outcome (PICO) format (9). The research questions were developed to support a two-stage approach to the evidence review: 1) determine the baseline prevalence of HCV infection and 2) measure the effects of an intervention (i.e., patient-important benefits and harms).

Per the GRADE process, the HCV Birth Cohort Testing Work Group designed an analytic framework (Appendix C), which was used to examine patient-important outcomes associated with each step of the testing effort, from the identification of the target population to the treatment of persons found to be infected with HCV. To measure the benefits and harms of HCV screening and treatment, patient-important outcomes were compiled. These outcomes were ranked, each according to its relevance to the recommendation (a rating of 1–3 being of low importance; 4–6 being important but not critical to decision making; and 7–9 as critical to decision making). Literature reviews were conducted on outcomes identified as important or critical to decision making. Work Group members had three opportunities to rank the outcomes: 1) when the outcomes were first identified, 2) after the evidence was presented, and 3) during the discussion of the benefits and harms, allowing the Work Group to weigh the relative importance of the outcomes based on the evidence presented and the benefits and harms.

The quality of the evidence for each patient-important outcome was assessed collectively by individual outcome, not by individual studies, in the GRADE profiler software (GRADEpro 3.6). The quality of the evidence was categorized as being “high,” “moderate,” “low,” or “very low” depending on the established criteria for rating the quality up or down. The quality of evidence for each of the outcomes was rated down if it met at least one of the following five criteria: 1) risk of bias; 2) inconsistency or heterogeneity; 3) indirectness (addressing a different population than the one under consideration); 4) imprecision; or 5) publication bias. Conversely, the quality of the evidence was rated up if it met any of three criteria: 1) large effect size; 2) dose-response; or 3) plausible residual confounders (i.e., when biases from a study might be affecting the estimated apparent intervention effect) (Appendix B). Outcomes were reranked for importance after consideration of evidence by the Work Group members.

The following four factors are considered when determining the relevance and strength of a GRADE-based recommendation:

1) quality of evidence, 2) balance between benefits and harms, 3) values and preferences, and 4) resource implications. During the consultation, the Work Group considered each of these factors in light of the evidence presented. A statement based on the direction and strength of the recommendation was developed using the GRADE criteria; statements were either “for” or “against” an intervention and were either strong (designated by a “should” statement) or conditional (designated by a “may consider” statement).

Research Questions

To facilitate a succinct, systematic review of the evidence, the Work Group developed the following review questions to be considered when examining prevalence data and patient-important outcomes:

- What is the effect of a birth-year based testing strategy versus the standard of care (i.e., risk-based testing) for identification of hepatitis C virus (HCV) infection?
- Should HCV testing (versus no testing) be conducted among adults at average risk for infection who were born during 1945–1965?
- Among persons tested and identified with HCV infection, is treatment-related SVR (versus treatment failure) associated with reduced liver-related morbidity and all-cause mortality?
- Should HCV testing followed by brief alcohol interventions (versus no intervention) be carried out to reduce or cease drinking among HCV-infected persons?

Review questions were aligned with the analytic framework and were formed in accordance with PICO. The division of these questions into two topics, prevalence data and patient-important outcomes, reflects the two-stage approach that was used to 1) define the testing strategy and birth years of interest, and 2) examine the effects of testing persons born during 1945–1965 for HCV infection. Because the patient-important outcomes questions encompass many outcomes, they are formed without listing one specific outcome; they present only the population, intervention, and comparator.

Literature Review

The DVH Steering Committee reviewed current HCV testing guidelines (8,18,54–58) and existing scientific evidence; systematic reviews and meta-analyses were conducted to synthesize the evidence available for the review questions. This evidence was compiled and presented to the Work Group throughout the development process.

The systematic review process for these recommendations was separated into two stages: 1) a review of HCV infection prevalence to determine the effect of a birth-year testing strategy, and 2) a review of the effects of testing persons born during

1945–1965 on patient-important outcomes. Search strategies varied for each stage; however, following the initial collection of results from the search, titles and abstracts were reviewed by two persons. If disagreement on the inclusion of an article occurred, an independent third reviewer decided whether the article would be included. For the titles and abstracts that met the inclusion criteria, the full article was retrieved and reviewed. Information from the full articles was extracted for the GRADE profiles to conduct the meta-analyses.

Prevalence Data

The review of prevalence data was conducted to identify literature addressing a birth-year-based strategy or providing additional support for the prevalence estimates (see Selection of a Target Birth Cohort). The DVH Steering Committee reviewed all literature regarding the effect of a birth-year-based testing strategy for HCV infection that had been considered and published after CDC's 1998 recommendation. To be selected for review, articles had to have been published during 1995–2011, describe results of U.S.-based studies, and include participants within the target population (i.e., the 1945–1965 birth cohort). Case studies and studies of persons co-infected with HBV or HIV were excluded. Six databases were searched for primary research, including grey literature and conference abstracts: MEDLINE, EMBASE, Sociological Abstracts, Cochrane Library (e.g., Database of Systematic Reviews, Central Register of Controlled Trials, and Economic Evaluation Database), CINAHL, and Database of Abstracts of Reviews of Effects (DARE) (Appendix D).

Patient-Important Outcomes

A literature search for the effect of HCV testing and treatment on patient-important outcomes was conducted (Appendix E). A search of previously published systematic reviews and meta-analyses was conducted initially and used to address the patient-important outcomes when available and of high quality. When systematic reviews or meta-analyses were unavailable, primary studies were sought and added to the results. When possible, data from primary studies were entered into systematic review software (Review Manager, 2008) to produce meta-analyses for estimation of effect sizes. Otherwise, effect size data were extracted directly from published meta-analyses.

Separate, targeted literature reviews were conducted for those outcomes considered important or critical to decision-making (i.e., given a GRADE rating of ≥ 4); these outcomes included:

- all-cause mortality;
- HCC;
- SVR (a marker of virologic cure);
- serious adverse events (SAEs) (i.e., treatment-related side effects);

- quality of life (QoL);
- HCV transmission; and
- brief alcohol interventions.

Systematic reviews for all-cause mortality, SVR, SAEs, QoL, HCV, and brief alcohol interventions were conducted for literature published in MEDLINE from 1995 through July 2011. For HCC, a comprehensive search for HCC was conducted for literature published during 1946–2011 in MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, CINAHL, Web of Science, and DARE.

The selection criteria for the primary literature search included intervention studies (i.e., controlled trials, cohort studies, and case-control studies) conducted worldwide and published in English. Case studies were excluded, along with studies of transplant recipients and persons co-infected with HBV or HIV, if they were not controlled for in the analysis. To be selected, studies needed to present data inclusive of persons born during 1945–1965. Because DAAs have only recently been licensed, evidence was insufficient on their long-term effect on the patient-important outcomes. Therefore, only studies providing treatment regimens with pegylated interferon (with and without ribavirin) or interferon (with or without ribavirin) were examined.

A systematic, targeted review was conducted to examine potential harmful and beneficial patient-important outcomes associated with HCV testing and treatment. A similar review also was conducted to examine reduction or cessation of alcohol use associated with brief interventions provided to persons identified as HCV-infected. Only those outcomes considered critical to decision making (i.e., all-cause mortality, HCC, SVR, treatment-related SAEs, QoL, HCV transmission, and alcohol use) were graded on their quality and used to inform the strength of the recommendations.

Results

Review of HCV Infection Prevalence Data

Of the 10,619 articles that met the search criteria for the HCV infection prevalence review, 31 provided data on HCV infection prevalence by birth year (Appendix F). Three of those articles (1,23,59) examined nationally representative data from NHANES. Because data from population-based NHANES is nationally representative, the quality of the NHANES data was deemed higher than that from the other 28 articles. Therefore, NHANES data for 1999–2008 were used to determine the most effective birth years to target when testing persons for HCV infection. The NHANES analysis revealed a 3.25% prevalence of anti-HCV among persons born during 1945–1965 (95% CI = 2.80–3.76). The prevalence data

were presented to the Work Group early in the development process. The results were reviewed again during a discussion of patient-important outcomes at the consultation.

Patient-Important Outcomes

Of the patient-important outcomes determined by the Work Group to be either important or critical for decision making (see GRADE Methodology), evidence was found in the literature for all-cause mortality, HCC, SVR, SAEs, QoL, and alcohol use. However, for several other important or critical outcomes (i.e., HCV transmission, insurability, reassurance of testing negative, false reassurance of testing negative, and worry or anxiety caused by testing true positive), no studies examining their importance and relevance to a birth cohort recommendation could be identified. With the exception of HCV transmission, these outcomes were re-ranked as not critical to decision-making. For HCV transmission, the Work Group decided to keep the categorization as critical to decision-making to highlight the need for future research.

All-Cause Mortality

Previously published systematic reviews and meta-analyses did not provide all-cause mortality information relevant to this population, so a systematic review was conducted (Appendix G). A total of 22 published articles examined all-cause mortality among persons tested and treated for HCV infection. However, a review of the full articles revealed weaknesses in 21 of these studies resulting from insufficient sample sizes, unrepresentative study populations, and other sources of confounding, thus they did not meet the inclusion criteria (Appendix G). One study was identified as directly applicable to the target population (52). The study had a large sample size and rigorously controlled for covariates in post hoc analysis, which improved the Work Group's confidence in the estimate of the effect. This study, which included a sample size of 16,864 HCV-infected persons identified through the U.S. Department of Veterans Affairs, found that treatment-related SVR was associated with a reduction in risk for mortality among persons who had HCV infection diagnosed (Relative risk [RR] = 0.45; 95% CI = 0.41–0.51). However, this study only compares persons who responded to therapy with those who did not respond and does not address a screened population or an untreated population. Differences in stage of liver disease between the groups had the potential to bias these findings, but those data were not available. Therefore, the confidence in the estimate of effect was deemed to be low, and no change in rating of the quality of evidence was performed despite a large estimated treatment effect (Appendix B).

Hepatocellular Carcinoma

A meta-analysis was conducted to examine HCC as a patient-important outcome. A total of 12 observational studies (n=25,752) providing adjusted relative risk measures examined the incidence of HCC among persons achieving an SVR versus those who did not respond to treatment (60–71) (Appendix H, Appendix I, Appendix J). Data from these studies revealed that treatment-related SVR was associated with a reduced risk for HCC (>75%) among persons at all stages of fibrosis (RR = 0.24; 95% CI = 0.18–0.31). Minimal heterogeneity was reported (I²=22%), mainly attributed to the few occurrences of HCC and small sample sizes in the studies. No other criteria were fully met to justify downgrading the quality of the evidence for this outcome. Instead, the quality of the evidence was rated up to moderate because of the substantial measure of relative risk (Appendix B).

Sustained Virologic Response

Achieving SVR is the first step toward reducing future HCV morbidity and mortality. The combination of PR with a DAA increases the rate of SVR in treated persons with hepatitis C genotype 1 when compared with PR alone. Pooled estimates comparing boceprevir- and telaprevir-based regimens with PR suggest that these regimens are associated with 28% increases in SVR rates (RR = 0.28, 95% CI = 0.24–0.32) (50,51,72–74). Although SVR was initially judged by the Work Group to be directly associated with patient-important outcomes (e.g., reduced viral transmission), further deliberation resulted in SVR being defined as an intermediary outcome that is predictive of a reduction in morbidity and mortality, particularly from HCC. Thus, rating down the quality of the evidence for SVR from high to moderate was justified given the indirectness of the outcome (Appendix B).

Treatment-Related Serious Adverse Events

Treatment for HCV infection with PR can result in serious adverse events (SAEs).^{*} In May 2011, triple-drug therapy with PR and DAA became the standard of care for patients with HCV genotype 1, but limited data are available for systematic reviews on SAEs for regimens including these new agents. In the telaprevir phase III clinical trial, the most common adverse events included gastrointestinal disorders, pruritus, rash, and anemia, and 11% of those receiving telaprevir discontinued therapy because of SAEs compared with 1% of those receiving

^{*} Defined by the Food and Drug Administration (FDA) as any undesirable experience associated with the use of a medical product in a patient. The event is serious and should be reported to FDA when the patient outcome is: death, hospitalization, disability or permanent damage, congenital anomaly/birth defect, or required intervention to prevent permanent impairment or damage. SAEs can include nausea, anemia, rash, and neuropsychiatric disturbances. (<http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm>).

PR alone (50). In the boceprevir phase III clinical trial, the most common adverse events included fatigue, headache, nausea, and anemia. No differences in discontinuation rates between study arms were observed (51). The harms of these new treatments might be different in community settings.

Although the addition of boceprevir and telaprevir to standard treatment with PR increases the rate of SVR in persons with HCV genotype 1, it also has been shown to result in an increased rate of adverse events that are severe enough to lead to treatment discontinuation (RR = 1.34; 95% CI = 0.95–1.87) (50,51,72–74). The quality of the evidence for SAEs was rated down because of imprecision and judged to be moderate (Appendix B).

Quality of Life

One systematic review was identified that examined the effect of HCV testing and treatment on patients' QoL (75). This study included seven observational studies. Although analysis of these studies did not yield an effect size, the mean QoL associated with the SVR in the intervention group was 6.6 points higher on the SF-36 Health Survey (a standard tool used to measure QoL) (<http://www.sf-36.org/tools/sf36.shtml>) compared with the control group. On the basis of study design and the limited evidence available regarding QoL, the quality of the evidence for this outcome was rated as low (Appendix B).

HCV Transmission

Literature searches were conducted for previously published systematic reviews, meta-analyses, and articles that addressed HCV transmission. No intervention studies examining the effect of HCV testing on the patient-important outcome of HCV transmission were identified. However, HCV transmission was a critical factor when determining the strength of the recommendations, despite the absence of related intervention studies. Future research is needed to address this gap in knowledge.

Alcohol Use

A literature search was conducted for systematic reviews, meta-analyses, and articles on the effect of an intervention to reduce alcohol use among persons found to be infected with HCV. Because evidence is limited, the search was broadened to include reviews focused on alcohol interventions for persons tested for HCV, not just those found positive. Recently, a meta-analysis of 22 randomized, controlled trials (n=7,619) examined the effects of HCV testing followed by a brief alcohol intervention (i.e., an assessment of the drinking behaviors of patients and provision of brief, one-on-one counseling if the health-care provider determines it to be clinically indicated) on drinking behaviors versus testing alone (76). The mean reduction of drinking alcohol (grams/week) in the intervention groups was 38.42%

lower (95% CI = 30.91–65.44) than in the control groups after follow-up at ≥ 1 year. The quality of this evidence was initially rated as high because it was derived from randomized, controlled trials without major risk for bias. However, because the body of evidence was not specifically derived from persons with HCV infection, the quality of evidence was rated down to moderate because of indirectness (Appendix B).

Factors Considered When Determining the Recommendations

Four factors must be considered when determining the relevance and strength of a GRADE-based recommendation: quality of evidence, balance between benefits and harms, values and preferences, and resource implications. During the consultation, the Work Group considered each of these factors in light of the evidence presented.

Determining the Quality of the Evidence Across Outcomes Critical for Decision Making

The systematic reviews revealed a lack of evidence directly comparing the effectiveness of birth-year based testing to risk-based testing. Thus, the Work Group considered available evidence from studies examining 1) nationally representative observational data on HCV prevalence among varying birth cohorts, 2) clinical trial data on the effect of HCV treatment on achieving SVR, 3) observational data on the association of SVR with HCC and all-cause mortality, and 4) data from a meta-analysis of randomized controlled trials on the effectiveness of brief alcohol interventions in reducing alcohol use. Evidence from these studies was reviewed comprehensively to infer that birth-year based testing, in combination with alcohol reduction interventions, will lead to enhanced identification and treatment of the infected population and result in reduced morbidity and mortality.

The GRADE framework follows the principle that the overall quality of evidence should be determined based on the lowest quality of evidence of any outcome deemed critical for decision making. For the proposed HCV testing recommendation, critical factors included all-cause mortality, HCC, SVR, and SAEs (77). However, two factors were considered when rating the overall quality of evidence: 1) the desirable effects of testing and treatment (the low quality evidence of mortality reduction and the moderate quality evidence of reducing HCC) and 2) the harms of testing and treatment (the moderate quality evidence of adverse events associated with HCV eradication). Thus, if the reduction in HCC alone is a sufficiently desirable

outcome to support testing and treatment (moderate quality evidence), and minimal uncertainty exists regarding the effect of the undesirable consequences (i.e., moderate quality evidence of SAEs), then the overall quality of evidence supporting testing and treatment in this cohort is determined to be moderate.

Benefits versus Harms

A review of published and anecdotal evidence conducted in accordance with GRADE methodology indicated that the benefits of testing and treating persons with HCV infection were greater than the harms. Published evidence was predominantly drawn from the summary of findings tables (Appendix B) and additional literature shared by the Work Group. To supplement that information, anecdotal evidence on the benefits and harms associated with several factors was considered, including undergoing a liver biopsy, the receipt of a false-positive test result, the need to wait or return for test results, access to treatment, and the effect of HCV-infection notification on insurance and employment.

Although certain harms (i.e., worry or anxiety while waiting for test results, concern about insurability, and occurrence of SAEs during treatment) can be uncomfortable for patients, effective treatment can result in SVR, which is associated with reductions in liver-related morbidity and all-cause mortality. Liver biopsy also can result in complications, the most common of which is pain. Other less common complications include bleeding, intestinal perforation, and death (reported in <0.1% of persons) (78); therefore, the benefits associated with HCV treatment were judged to be greater than the harms. Additional factors support this judgment. For example, concerns about receipt of inaccurate HCV antibody test results can be assuaged by the accuracy of HCV RNA testing, and the time and resources needed to screen, provide a brief alcohol intervention, and refer patients to care is outweighed by the efficacy of these interventions in reducing alcohol use.

Values and Preferences

Available data are limited regarding the acceptability by patients of HCV testing in the United States (79). However, this can be addressed during physician-patient discussions about individual preventive care.

Resource Implications

Only two U.S.-based studies specifically examined the cost effectiveness and resource implications of birth-year-based HCV testing linked to HCV care and treatment; both studies found the interventions to be cost effective (46,80). These

studies, which evaluated slightly different definitions of birth cohort, compared birth-cohort testing and treatment with the status quo of risk- and medical indication-based testing recommendations; both studies demonstrated nearly identical cost-effectiveness results. The first study, which defined the birth cohort as persons born during 1945–1965, estimated a cost per quality-adjusted life year (QALY) gained of \$35,700 on the basis of a 12-week, response-guided course of telaprevir and PR; cost per QALY was an estimated \$15,700 when assuming treatment with PR alone (46). The second study defined the birth cohort as persons born during 1946–1970 and estimated a cost per QALY gained of \$39,963 for patients treated with telaprevir in addition to PR (80). Both modeling studies assumed that liver disease progression would not continue for those who achieve SVR.

These cost-effectiveness studies had different assumptions about the timing of HCV testing and treatment. The study that examined the 1945–1965 birth cohort included all possible costs and benefits in a single year (46), whereas the study that examined the 1946–1970 birth cohort assumed 20% of the eligible population would be screened and treated each year for 5 years (46,80). Testing costs (including antibody testing, nucleic acid testing of antibody positives, and post-test counseling) were estimated at \$54 per person tested (40).

The birth-cohort testing strategy will reduce morbidity and mortality (Table 3), saving future HCV-related medical expenditures. However, in the immediate future, the increase in testing and treatment of persons born during 1945–1965 will cost more than that associated with current risk-based testing and treatment strategies. Several factors contribute to projected increases in treatment costs, including an expected increase in the number of persons tested and treated for HCV and the higher costs associated with combination PR/DAA therapy versus PR alone (Table 4). Costs can be compared using four different scenarios: risk-based testing with PR therapy; risk-based testing with PR therapy and DAA; birth-cohort testing with PR therapy; and birth-cohort testing with PR therapy and DAA, the current standard of care (Table 4).

To inform cost projections for the birth cohort HCV testing strategy, colorectal screening rates were reviewed to estimate the testing costs associated with one-time HCV testing for persons in the 1945–1965 birth cohort. Both interventions focus on screening at a single time point in time (i.e., at age 50 years for colorectal screening); therefore, data from colorectal screening programs are useful for estimating the rate of adoption of a recommendation for one-time prevention services. In an analysis of 2005 National Health Interview Survey data (a nationally representative household survey), 19.8% of women and 23.7% of men reported receiving colorectal screening during the preceding 3 years (the time

since implementation of the United States Preventive Services Task Force [USPSTF] screening recommendation) (78,81). These percentages were obtained after years of updated colorectal screening recommendations and implementation of educational campaigns, so they likely are higher than those expected to follow adoption of HCV testing recommendations. However, adopting the birth-cohort recommendations at the same level would result in testing approximately 5.6 million women and 6.7 million men for HCV within the first 3 years

of implementation, at a cost of \$664 million; approximately 400,000 persons with HCV infection would be identified.

Recommendations

The following recommendations for HCV testing are intended to augment the *Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection and HCV-Related Chronic Disease* issued by CDC in 1998 (8). In addition to testing adults of all ages at risk for HCV infection, CDC recommends that:

- Adults born during 1945–1965 should receive one-time testing for HCV without prior ascertainment of HCV risk (Strong Recommendation, Moderate Quality of Evidence), and
- All persons identified with HCV infection should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment services for HCV infection and related conditions (Strong Recommendation, Moderate Quality of Evidence).

Providers and patients can discuss HCV testing as part of an individual's preventive health care. For persons identified with HCV infection, CDC recommends that they receive appropriate care, including HCV-directed clinical preventive services (e.g., screening for alcohol use, hepatitis A and hepatitis B vaccination as appropriate, and medical monitoring of disease). Recommendations are available to guide treatment decisions (31). Treatment decisions should be made by the patient and provider after several factors are considered, including stage of disease, hepatitis C genotype, comorbidities, therapy-related adverse events, and benefits of treatment.

Public Health Testing Criteria

HCV testing of persons in the 1945–1965 birth cohort is consistent with established general public health screening criteria (82) as evidenced by the following factors: 1) HCV infection is a substantial health

TABLE 3. Comparison of risk-based testing with PR treatment strategy and birth cohort testing with PR and DAA treatment strategy, by outcome

Outcome	HCV testing and treatment strategy		
	Risk-based testing* with PR therapy	Birth-cohort [†] testing with PR and DAA therapy	Difference (birth cohort – risk based)
No. of antibody tests administered	14,793,816	60,404,514	45,610,698 more tests conducted
No. of positive results delivered to patient	262,260	1,070,840	808,580 more cases identified
No. of patients treated	135,089	551,800	416,711 more patients treated
No. of patients who achieved a sustained viral response	53,160	310,855	257,695 more patients achieved SVRs
No. of patients who ever developed compensated cirrhosis	994,291	791,053	203,238 cirrhosis cases averted
No. of patients who ever developed DCC	360,388	286,699	73,689 DCC cases averted
No. of patients who ever developed HCC	230,784	183,595	47,189 HCC cases averted
No. of patients who ever received a transplant	75,752	60,268	15,484 transplants averted
No. of HCV-related deaths	591,172	470,293	120,879 deaths averted

Abbreviations: DCC = decompensated cirrhosis; DAA = direct-acting antiviral; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; PR = pegylated interferon with ribavirin; SVR = sustained virologic response.

Source: Rein D, Smith BD, Wittenborn JS, Lesesne SB. The cost-effectiveness of birth cohort hepatitis C antibody screening in U.S. primary care settings. *Ann Intern Med* 2012;156:263–70. Modified and reprinted with permission from *Annals of Internal Medicine*.

* Risk-based testing applies to all persons with an identified risk regardless of year of birth and has been the standard of care for HCV screening since 1998.

[†] Birth-cohort testing applies to all persons born during 1945–1965 regardless of risk.

TABLE 4. Selected medical cost, by HCV testing and treatment strategy — United States, 2012

Medical cost	Testing and treatment strategy			
	Risk-based testing* with PR therapy (in millions)	Birth-cohort [†] testing with PR therapy (in millions)	Risk-based testing with PR and DAA (in millions)	Birth-cohort testing with PR and DAA (in millions)
Testing	\$754	\$3,078	\$754	\$3,078
Treatment	\$1,508	\$6,162	\$5,133	\$20,662
Total	\$2,262	\$9,240	\$5,887	\$23,740

Abbreviations: HCV = hepatitis C virus; PR = pegylated interferon plus ribavirin; DAA = direct-acting antivirals. **Source:** Rein D, Smith BD, Wittenborn JS, Lesesne SB. The Cost-effectiveness of birth cohort hepatitis C antibody screening in U.S. primary care settings. *Ann Intern Med* 2012;156:263–70. Modified and reprinted with permission from *Annals of Internal Medicine*.

* Risk-based testing applies to all persons with an identified risk regardless of year of birth and has been the standard of care for HCV screening since 1998.

[†] Birth-cohort testing applies to all persons born during 1945–1965 regardless of risk.

problem that affects a large number of persons, causes negative health outcomes, and can be diagnosed before symptoms appear; 2) testing for HCV infection is readily available, minimally invasive, and reliable; 3) benefits include limiting disease progression and facilitating early access to treatments that can save significant life years; and 4) testing is cost effective. Such testing would help identify unrecognized infections, limit transmission, and help HCV-infected persons receive beneficial care and treatment before onset of severe HCV-related disease (82).

Testing Methods

Hepatitis C Antibody Testing

Laboratory testing methods for HCV included in these recommendations were established by CDC's *Guidelines for Laboratory Testing and Result Reporting of Antibody to Hepatitis C Virus* in 2003 (83). No new methods are introduced in these recommendations. HCV testing should be initiated with an FDA-approved test for antibody to HCV (anti-HCV). These assays are highly sensitive and specific. An HCV point-of-care assay that can provide results in <1 hour is available for clinical use (84). An immunocompetent person without risks for HCV infection who tests anti-HCV negative is not HCV-infected and no further testing for HCV is necessary. Additional testing might be needed for persons who have ongoing or recent risks for HCV exposure (e.g., injection-drug use) and persons who are severely immunocompromised (e.g., certain patients with HIV/AIDS or those on hemodialysis).

A person whose anti-HCV test is reactive should be considered to either 1) have current HCV infection or 2) have had HCV infection in the past that has subsequently resolved (i.e., cleared). To identify persons with active HCV infection, persons who initially test anti-HCV positive should be tested by an HCV nucleic acid test (NAT).

Hepatitis C Nucleic Acid Testing

An FDA-approved HCV NAT (also referred to as an "HCV RNA test") should be used to identify active HCV infection among persons who have tested anti-HCV positive; FDA-approved tests include both quantitative HCV NATs (for HCV viral load) and qualitative NATs (for presence or absence of viremia). Persons who test anti-HCV positive or have indeterminate antibody test results who are also positive by HCV NAT should be considered to have active HCV infection; these persons need referral for further medical evaluation and care. A person who is anti-HCV positive but who tests negative by HCV NAT should be considered to not have active HCV infection.

Other HCV-Related Testing Issues

Quantitative NATs assess the level of viremia in the bloodstream expressed as HCV viral load. Although viral load is a critical marker for the effectiveness of treatment, it is not a reliable indicator of stage of disease. Similarly, liver enzyme tests (i.e., alanine aminotransferase [ALT]) reflect the level of liver inflammation at the time of the test, but are not correlated consistently with the stage of liver disease. ALT levels are subject to fluctuations associated with many factors other than infection, including BMI and use of alcohol or medication.

Management of Persons Tested for HCV Infection

Communicating Test Results to Persons Tested for HCV

Negative Anti-HCV Test Results

Persons with negative anti-HCV test results should be informed of their test results and reassured that they are not infected unless they were recently at risk for infection (e.g., current injection-drug use). Repeat testing should be considered for persons with ongoing risk behaviors.

Positive Anti-HCV and Negative HCV RNA Test Results

Persons who are anti-HCV positive but have an HCV RNA-negative test result should be informed that they do not have HCV infection and do not need follow-up testing.

Positive Anti-HCV and HCV RNA Test Results

Persons who test positive for both HCV antibody and HCV RNA should be informed that they have HCV infection and need further medical evaluation for liver disease, ongoing medical monitoring, and possible treatment. At the time positive test results are communicated to patients, health-care providers should evaluate the patient's level of alcohol use and provide a brief alcohol intervention if clinically indicated (see Alcohol-use Reduction). Persons with HCV infection also should be provided information (either through face-to-face sessions, video, or written materials) about 1) HCV infection, 2) risk factors for disease progression, 3) preventive self-care and treatment options, and 4) how to prevent transmission of HCV to others. HCV-infected persons also should be informed about the resources available to them within their communities, including providers of medical evaluation and social support.

Post-Test Counseling Messages

Persons infected with HCV can benefit from the following counseling messages.

- Contact a health-care provider (either a primary-care clinician or specialist [e.g., in hepatology, gastroenterology, or infectious disease]), for
 - medical evaluation of the presence or development of chronic liver disease;
 - advice on possible treatment options and strategies; and
 - advice on how to monitor liver health, even if treatment is not recommended.
- Protect the liver from further harm by,
 - considering hepatitis A and B vaccination if susceptible and if liver disease is present;
 - reducing or discontinuing alcohol consumption;
 - avoiding new medicines, including over-the-counter and herbal agents (18), without first checking with their health-care provider; and
 - obtaining HIV risk assessment and testing.
- For persons who are overweight (BMI ≥ 25 kg/m²) or obese (BMI ≥ 30 kg/m²) (85),
 - consider weight management or losing weight and
 - follow a healthy diet and stay physically active.
- To minimize the risk for transmission to others,
 - do not donate blood, tissue, or semen and
 - do not share appliances that might come into contact with blood, such as toothbrushes, dental appliances, razors, and nail clippers.

Alcohol-Use Reduction

Messages to decrease alcohol use should be provided to persons infected with HCV. Alcohol screening and brief interventions (SBI) for referral for treatment can reduce the number of drinks consumed per week and episodes of binge drinking. SBI includes screening patients for excessive alcohol consumption, brief counseling for those who screen positive, and referral to specialized alcohol treatment for patients with possible alcohol dependence. The brief intervention is also an opportunity to communicate the HCV-associated risks posed by alcohol consumption and provide options for behavioral change. The U.S. Preventive Services Task Force (USPSTF) recommends screening and behavioral counseling interventions to reduce alcohol misuse by adults in primary-care settings (86). Screening tools shown to be effective in eliciting a history of alcohol use from patients include the Alcohol Use Disorders Identification Test (AUDIT). Screening tools are available from the National Institute on Alcohol Abuse and Alcoholism (http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide.htm), and

WHO has published intervention tools to help patients adopt healthy behaviors regarding alcohol use (http://www.who.int/substance_abuse/activities/sbi/en/index.html).

Linkage to Care and Treatment

Many persons identified as HCV-infected do not receive recommended medical evaluation and care after the diagnosis of HCV infection (30); this gap in linkage to care can be attributed to several factors, including being uninsured or underinsured, failure of providers to provide a referral, failure of patients to follow up on a referral, drug or alcohol use, and other barriers. The lack of such care, or substantial delays before care is received, negatively impacts the health outcomes of infected persons. Routine testing of persons born during 1945–1965 is expected to lead to more HCV-infected persons being identified earlier in the course of disease. However, to improve health outcomes, persons testing positive for HCV must be provided with appropriate care and treatment. Linking patients to care and treatment is a critical component of the strategy to reduce the burden of disease.

Strategies are needed for HCV-infected persons who are experiencing barriers to care. These persons might benefit from the replication of effective linkage-to-care models and the development of other evidence-based interventions. Active linkage-to-care programs provided in a culturally sensitive manner (87–89) (e.g., the use of case managers to schedule appointments, bring infected patients to doctors' appointments, and follow-up with patients) have been found to be more effective (87) than passive referral methods (e.g., providing patients with information about the disease and a list of resources or referrals to medical care). Such linkage creates opportunities for patients to receive information, vaccinations, and prevention counseling messages and to more fully engage in care (90). Once patients receive care, case management can provide active linkage (91–93) to social services (88,94), referral to substance abuse services (95–98), and assistance with transportation and housing (92,95). Recommendations for the medical management of HCV infection and disease are updated regularly by AASLD. Notable advances are being made in the care, management, and treatment of HCV infection at the time of publication of this recommendation. Although primary care clinicians can readily provide much of the care necessary for initial evaluation and management of persons with HCV infection, antiviral treatment is complex, and collaboration between primary-care providers and specialists facilitates delivery of optimal care. CDC is working with academic and clinical partners and with other federal and state agencies to replicate best practices and develop new models for HCV care (99).

Future Directions

CDC will conduct demonstration projects to expand access to HCV testing and evaluate implementation of HCV testing in clinical and public health settings; data from these projects will identify best practices. In addition, CDC will employ national health surveys (e.g., NHIS) to assess implementation of this recommendation at the national level.

CDC is conducting systematic reviews of other testing and prevention recommendations that were included in the 1998 HCV testing recommendations (3). In addition, CDC will be reviewing evidence related to the potential benefits and harms of testing persons who were determined to be of “uncertain need” in the 1998 recommendations (i.e., those with risks that have not been well defined, such as intranasal drug use or a history of multiple sex partners). On completion of these reviews, recommendations for HCV testing and linkage to care will be revised as necessary. The revised guidelines, which will incorporate the present birth-cohort-based recommendations as well as risk-based strategies, will provide updated, comprehensive recommendations for the identification and management of HCV infection in the United States.

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Appendix A Conflicts of Interest

External Work Group Members

Miriam Alter, PhD

For the work under consideration: No financial conflict of interest reported
Other relevant financial activities: No financial conflict of interest reported

Sanjeev Arora, MD

For the work under consideration: No financial conflict of interest reported
Other relevant financial activities: *Consultancy:*
Served on Advisory Board of Vertex Pharmaceuticals in 2009
Grants/Grants Pending:
Grants from Vertex Pharmaceuticals, Roche/ Genentech, Gilead, Zyrnogenetics, Bristol Myers, Pharmasset, and Abbott paid to institution for clinical trials
Lectures/ Speakers Bureaus:
Scherring Corp., served on September Bureau for Roche Pharmaceuticals until mid-2009

Bruce Bacon, MD

For the work under consideration: No financial conflict of interest reported
Other relevant financial activities: No financial conflict of interest reported

Doug Campos-Outcalt, MD

For the work under consideration: No financial conflict of interest reported
Other relevant financial activities: No financial conflict of interest reported

Alfred DeMaria, Jr., MD

For the work under consideration: No financial conflict of interest reported
Other relevant financial activities: No financial conflict of interest reported

Janet Durfee, MSN

For the work under consideration: No financial conflict of interest reported
Other relevant financial activities: No financial conflict of interest reported

Yngve Falck-Ytter, MD

For the work under consideration: No financial conflict of interest reported
Other relevant financial activities: No financial conflict of interest reported

Colleen Flanigan, MS

For the work under consideration: *Support for Travel:*
CDC Foundation
Other relevant financial activities: No financial conflict of interest reported

Marc Ghany, MD

For the work under consideration: No financial conflict of interest reported
Other relevant financial activities: No financial conflict of interest reported

Robert Gish, MD

For the work under consideration: No financial conflict of interest reported
Other relevant financial activities: *Board Membership:*
Hepahope
Consultancy:
Performed as a consultant to Abbott, Anadys Pharmaceuticals, Inc., Bayer AG, Bristol-Myers Squibb Company, Durect, Hepahope, Hoffman-LaRoche Ltd., Genentech, Gilead Sciences, GlaxoSmithKline, Globelimmune, Human Genome Sciences, Merck, Metabasis Therapeutics, OSI/Astellas Parmasset, Schering-Plough Corporation, Three Rivers Pharma, VitalTherapies, and ZymoGenetics; payments directed to an SPF fund for research and education.
Lectures/ Speakers Bureaus:
Speakers bureau activities for Bayer, Bristol-Myers Squibb Company, F. Hoffman-LaRoche Ltd., Gilead Sciences, Inc., GlaxoSmithKline, Onyx, Merck/Schering-Plough Corporation, Three Rivers, Salix, SciClone Pharmaceuticals focused on HBV, HCV, and liver cancer, specifically epidemiology, diagnosis, and treatment, with additional program presentations for HBV and management of complications of cirrhosis; has a speakers contract to do promotional talks for BMS, Roche, Schering-Plough, Gilead Sciences, Bayer and Onyx; payments are directed to an SPF fund for research and education.
Grants/ Grants Pending:
Support from Bayer-Onyx, Bristol-Myers Squibb Company, Genentech/ F. Hoffman-LaRoche, Ltd., Gilead Sciences, Genentech, Pharmasset, Zymogenetics; payments directed to an institutional fund under contract to CPMC.
Stock/ Stock Options:
Major stock shareholder for Hepahope

Fasiha Kanwal, MD

For the work under consideration: No financial conflict of interest reported
Other relevant financial activities: No financial conflict of interest reported

Recommendations and Reports

Emmett Keeffe, MD

For the work under consideration: No financial conflict of interest reported
Other relevant financial activities: *Consultancy:*
Vertex
Travel/ Accommodations:
Vertex

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For the work under consideration: No financial conflict of interest reported
Other relevant financial activities: No financial conflict of interest reported

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For the work under consideration: No financial conflict of interest reported
Other relevant financial activities: No financial conflict of interest reported

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For the work under consideration: No financial conflict of interest reported
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Other relevant financial activities: No financial conflict of interest reported

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For the work under consideration: No financial conflict of interest reported
Other relevant financial activities: No financial conflict of interest reported

Barbara McGovern, MD

For the work under consideration: No financial conflict of interest reported
Other relevant financial activities: *Employment:*
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Other:
Editor at Infectious Diseases Society of America

Rachel McLean, MPH

For the work under consideration: No financial conflict of interest reported
Other relevant financial activities: No financial conflict of interest reported

Michael Ninburg

For the work under consideration: No financial conflict of interest reported
Other relevant financial activities: *Consultancy:*
Vertex, Abbott, Genentech, GlaxoSmithKline, Merck, Hoffman LaRoche, Tibotec, Boehringer Ingelheim
Grants/ Grants Pending:
Grants from Vertex, Merck, Genentech, Hoffman La Roche, Schering Plough, Gilead, Novartis, and Human Genome Sciences paid to institution
Payment for the Development of Educational Presentations:
Vertex, Hoffmann La Roche, and Schering Plough, paid to institution

Phillip Reichert, MPH

For the work under consideration: No financial conflict of interest reported
Other relevant financial activities: No financial conflict of interest reported

Vinod Rustgi, MD

For the work under consideration: No financial conflict of interest reported
Other relevant financial activities: *Consultancy:*
Merck, Vertex
Grants/ Grants Pending:
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Appendix B Evidence Tables

Table 1. GRADE evidence profile for HCV testing followed by antiviral treatment versus no antiviral treatment

Outcome	Quality assessment			Summary of findings								
				Study event rates				Anticipated absolute effects*				
	No. Participants	No. Studies	Overall quality of evidence	Failed or no treatment		SVR		Relative effect		Risk with failed or no treatment	Absolute effect with SVR	
				No./N	%	No./N	%	HR	CI		No.	CI
All-cause mortality	16,864 (ref 1)	1	Low	1,126/9,430	(11.9)	409/7,434	(5.5)	0.7	(0.59–0.83)	119	34 fewer	(19–47)
HCC	25,906 (ref 2–13)	12	Moderate [†]	145/9,185	(1.6)	1,012/16,721	(6.1)	0.24	(0.18–0.31)	46	23 fewer	(21–24)
QoL	5,978 (ref 14)	7	Low	— [§]	—	— [§]	—	—	—	—	6.6 higher [¶]	(—)**

Abbreviations: GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; HCV = hepatitis C virus; SVR = sustained virologic response; HR = hazard ratio; CI = 95% confidence interval; HCC = hepatocellular carcinoma; QoL = quality of life.

* Per 1,000 persons tested for HCV infection.

[†] Rated up due to large relative risk effect: 0.24; 95% CI = 0.18–0.31.

[§] Total number of participants = 5,978; distribution between participants and controls not available.

[¶] The mean QoL associated with sustained viral response-vitality sub-score in the intervention groups.

** 95% CI not provided. Effect was reported as significant. Minimally clinically important difference estimated to be 4.2 (range: 3–5). Effect size results: 0.2; effect sizes are classified as small (≤ 0.2); moderate (0.5); and large (≥ 0.8) (Spiegel BMR, Younossi Z, Hays R, Revicki D, Robbins S, Kanwal F. Impact of hepatitis C on health related quality of life: a systematic review and quantitative assessment. *Hepatology*. 2005;41[4]:790–800.)

Table 2. GRADE evidence profile for HCV testing followed by boceprevir or telaprevir (with PR) compared with PR alone

Outcome	Quality assessment			Summary of findings								
				Study event rates				Anticipated absolute effects*				
	No. Participants	No. Studies	Overall quality of evidence	Failed or no treatment		SVR		Relative effect		Risk with failed or no treatment	Absolute effect with SVR	
				No./N	%	No./N	%	RR	CI		No.	CI
SAEs	2,704 (ref 15–19)	5	Moderate [†]	105/985	(10.7)	235/1,719	(13.7)	1.34	(0.95–1.87)	107	36 more	(5–93)
Failure to achieve SVR [§]	2,527 (ref 15–19)	5	Moderate [¶]	582/985	(59.1)	493/1,542	(32.0)	0.53	(0.47–0.60)	591	278 fewer	(236–313)

Abbreviations: GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; HCV = hepatitis C virus; PR = pegylated interferon plus ribavirin; SAEs = serious adverse events; RR = risk ratio; CI = confidence interval; SVR = sustained virologic response.

* Per 1,000 persons receiving HCV treatment.

[†] Rated down for imprecision. 95% CI includes harms as well as benefits. Sensitivity analysis: excluding one trial (SPRINT 2) that showed a lower discontinuation rate in the triple therapy group in one of the treatment arms compared with standard of care, the results would be as follows: RR=1.60 (95% CI = 1.16–2.22) (no imprecision).

[§] Failure of viral negativity at 24 weeks post treatment.

[¶] Rated down for indirectness. SVR considered an intermediary outcome for long-term benefit.

Table 3. GRADE evidence profile for HCV testing followed by a brief alcohol intervention versus no intervention

Outcome	Quality assessment			Summary of findings				
	No. Participants	No. Studies	Overall quality of evidence	Study event rates		Anticipated absolute effects		
				HCV testing followed by no intervention No.	HCV testing followed by intervention No.	Risk with failed or no treatment Mean	Absolute effect with SVR Mean CI	
Alcohol use	5,860 (ref 20)	22	Moderate	2,922	2,938	313 g alcohol/week*	38.42 g lower	(54.16–22.67)

Abbreviations: GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; HCV = hepatitis C virus; CI = 95% confidence interval.

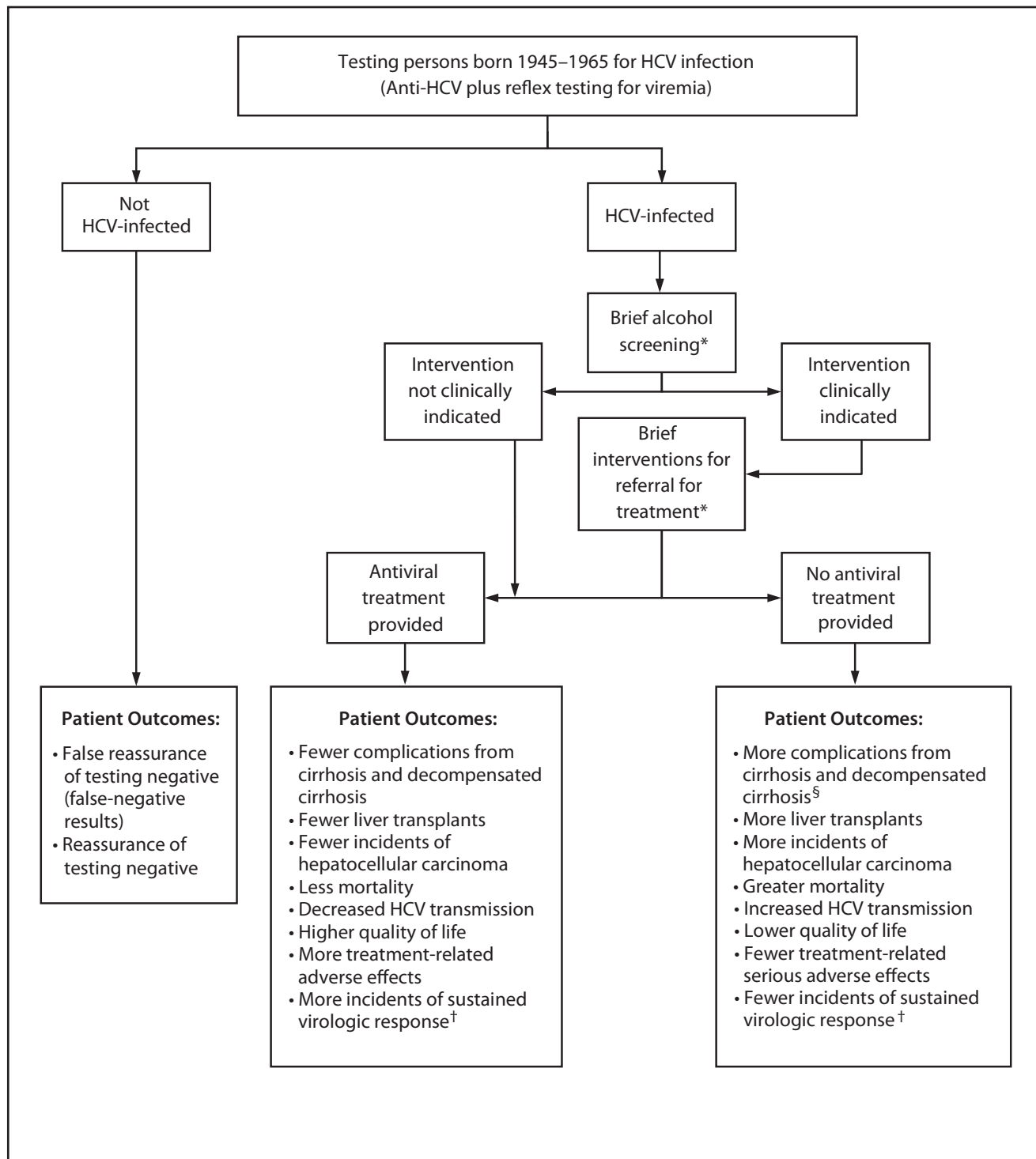
* A total of 21 trials reported baseline alcohol consumption: range: 89–456 g/week; overall mean = 313 g/week (26 standard U.S. drinks [approximately 12 g each] per week; average: 3.7 drinks per day).

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Appendix C

Analytic Framework for Guiding HCV Testing Among Persons Born During 1945–1965



* Together, these interventions are known as alcohol screening and brief interventions (SBI) for referral for treatment.

† Viral eradication after treatment completion.

§ Cirrhosis with the diagnosis of at least one of the following: ascites, variceal bleeding, encephalopathy, or impaired hepatitis synthetic function.

Appendix D

Search Strategy for Literature Addressing HCV Prevalence,* by Database

Database [†]	Search terms	No. hits	No. with abstracts
Cochrane Database	1. (Hepatitis C OR Hep C OR HCV) t.ti,ab,kw	Cochrane reviews:32 Economic evaluations:223 Clinical trials:1,720	1,648
	2. Hepatitis C.kw		
CINAHL	1. (MM "Hepatitis C+")	3,236	647
	2. (MH "Hepatitis C+")	4,503	
	3. (MH "Antibodies+")	16,891	
	4. (MH "Antibodies +") and (S2 and S3)	304	
	5. TX prevalence OR frequen*	115,230	
	6. Cohort* or cross-section* or cross section*	78,023	
	7. (MH "Epidemiological Research+"# OR #MH "Epidemiology+"#)	217,794	
	8. (MH "Environment and Public Health (Non-Cinah!)"	6,696	
	9. 1 OR 4	3,298	
	10. 5 OR 6 OR 7 OR 8	339,418	
	11. (5 OR 6 OR 7 OR 8) and (9 and 10)	793	
MEDLINE	1. Hepatitis C [majr] OR Hepatitis C Antibodies [majr]	22,809	6,159
	2. 1 AND (Prevalence OR frequen*)	9,134	
	3. 2 AND (Cohort or cross-sectional OR "cross-sectional" or Epidemiologic Studies [mesh])	4,005	
EMBASE	1. *Hepatitis C/ or *Hepatitis C Antibody/	35,963	6,159
	2. (prevalence OR frequen*).mp	890,278	
	3. (cohort OR cross-sectional or "cross adj sectional").mp	346,055	
	4. *epidemiology/	10,345	
	5. 1 AND (2 OR 3 OR 4)	6,835	
Sociological Abstracts	1. Hep C OR hepc or hepatitis C (ti, kw, au, de)	— [§]	160 [¶]
	2. HCV (ti)	—	
	3. 1 OR 2	—	
Database of Abstracts of Reviews of Effects	1. Explode Hepatitis C	279	171
	2. Explode Hepatitis C Antibodies	11	
	3. Explode Hepatitis C, Chronic	144	
	4. 1 OR 2 OR 3	280	

Abbreviations: HCV = hepatitis C virus.

* The HCV-prevalence literature search was conducted to determine the effect of a birth-year based testing strategy versus the standard of care (i.e., risk-based testing) for identification of HCV infection.

[†] Search was conducted for literature published during 1995–2011.

[§] Unavailable.

[¶] Of these hits, 159 were de-duplicated (i.e., remained after duplicate study reports were identified).

Appendix E

Search Strategy for Literature* Addressing Patient-Important Outcomes† Associated with HCV Testing Among Persons Born During 1945–1965§

Outcome	Search terms	No. hits
All-cause mortality	Clinical query	
	1. ("hepatitis C" PR HCV) and (mortality)	123
	Search	
	1. Hepatitis C [majr] OR Hepatitis C Antibodies [majr]	33,186
	2. mortality	480,636
	3. #1 AND #2	1,857
Sustained virologic response	Clinical query	
	1. ("hepatitis C" OR HCV) AND ("sustained virologic response" or SVR)	127
	Search	
	1. Hepatitis C [majr] OR Hepatitis C Antibodies [majr]	33,186
	2. "sustained virologic response" OR SVR	2,849
	3. #1 AND #2	1,607
Serious adverse events	Clinical query	
	1. (("hepatitis C" OR HCV) AND ("adverse effects"))	215
Quality of life	Clinical query	
	1. (("hepatitis C" OR HCV) AND ("quality of life"))	45
HCV transmission	Clinical query	
	1. (("hepatitis C" OR HCV) AND (transmission))	166
	Search	
	1. Hepatitis C [majr] or Hepatitis C Antibodies [majr]	33,186
	2. transmission	207,262
	3. #1 AND #2	4,166
Alcohol use	Clinical query	
	1. (("hepatitis C" OR HCV) AND ("alcohol use"))	5
	Search	
	1. Hepatitis C [majr] OR Hepatitis C Antibodies [majr]	33,186
	2. Alcohol use	108,559
	3. #1 AND #2	1,018

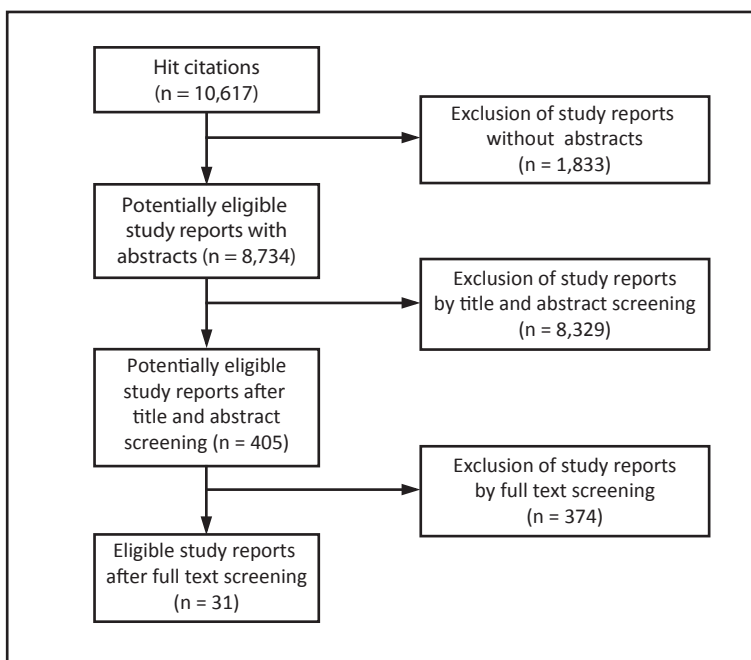
* Literature searches include all types of publications (e.g., conference abstracts, clinical trials, systematic reviews, and meta-analyses), whereas clinical queries include only systematic reviews and meta-analyses.

† Although hepatocellular carcinoma (HCC) is considered a patient-important outcome associated with HCV testing, a separate search strategy was used for this outcome (see Appendix H).

§ The search aimed to answer the following questions: 1) Should HCV testing (versus no testing) be conducted among adults at average risk for infection who were born during 1945–1965? 2) Among persons tested and identified with HCV infection, is treatment-related SVR (versus treatment failure) associated with reduced liver-related morbidity and all-cause mortality? 3) Should HCV testing followed by brief alcohol interventions (versus no intervention) be carried out to reduce or cease drinking among HCV-infected persons?

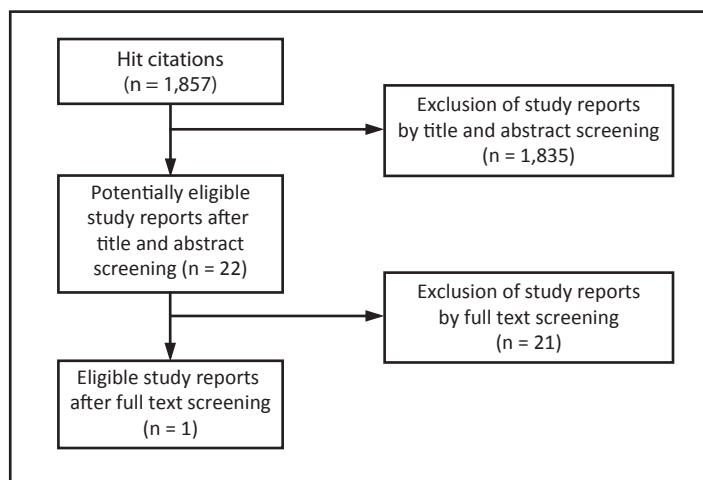
Appendix F

Flow Chart for Review of Literature Searches Addressing Hepatitis C Virus Prevalence



Appendix G

Flow Chart for Review of Literature Searches Addressing All-cause Mortality Data



Appendix H

Search Strategy for Literature Addressing Development of HCC among Persons with HCV Who Either Achieve an SVR or Have No Response to Treatment,* by Database

Database	Search terms	No. hits	Dates covered
MEDLINE	<ol style="list-style-type: none"> Hepatitis C[mesh] or "hepatitis c" OR "hep c" OR HCV HCC OR hepatocellular #1 AND #2 Treatment OR therapy OR treat* OR therap* #3 AND #4 Limit 5 to English language 	<ol style="list-style-type: none"> 57,231 71,033 6,788 7,698,358 3,717 3,238 Total[†]: 3,275 De-duplicated[§]: 3,273	1946–02/2012
EMBASE (Ovid)	<ol style="list-style-type: none"> (hcc or hepatocellular carcinoma).mp Limit #1 to English language (hepatitis c or hep c or hcv).mp #2 and #3 (treatment or therapy).mp #4 and #5 	<ol style="list-style-type: none"> 46,546 38,765 80,415 7,359 3,710,093 3,414 Total[†]: 3,439 De-duplicated[§]: 1,483	1988–02/2012
Web of Science	<ol style="list-style-type: none"> Topic=(hcc OR hepatocellular) AND topic=("hepatitis c" OR hep-c OR hcv) Limit #1 to English language Topic=(treatment OR therapy) #3 AND #2 	<ol style="list-style-type: none"> 8,352 8,069 2,908,801 3,290 Total[†]: 3,317 De-duplicated[§]: 1,421	1950–02/2012
CINAHL	<ol style="list-style-type: none"> (Hep c OR hep-c OR hepatitis-c OR hepatitis C) AND (HCC or hepatocellular) AND (treatment OR therapy) 	<ol style="list-style-type: none"> 198 De-duplicated[§]: 54	1937–2012
Cochrane	<ol style="list-style-type: none"> Hepatitis c OR hcv OR hepc OR hepatitis-c OR hep-c HCC OR hepatocellular 	Cochrane Reviews: 3 Other Reviews: 10 Clinical Trials: 177 Methods Studies: 1 Technical Assessments: 1 Economic Evaluations: 7 Total[†]: 199 De-duplicated[§]: 69	2012
Database of Abstracts of Reviews and Effects	<ol style="list-style-type: none"> (hcc OR hepatocellular) AND (hepatitis-c OR hepc OR hep-c OR hepatitis c OR hcv) 	<ol style="list-style-type: none"> 152 De-duplicated[§]: 107	2012

Abbreviations: HCC = hepatocellular carcinoma; HCV = hepatitis C virus; SVR = sustained viral response.

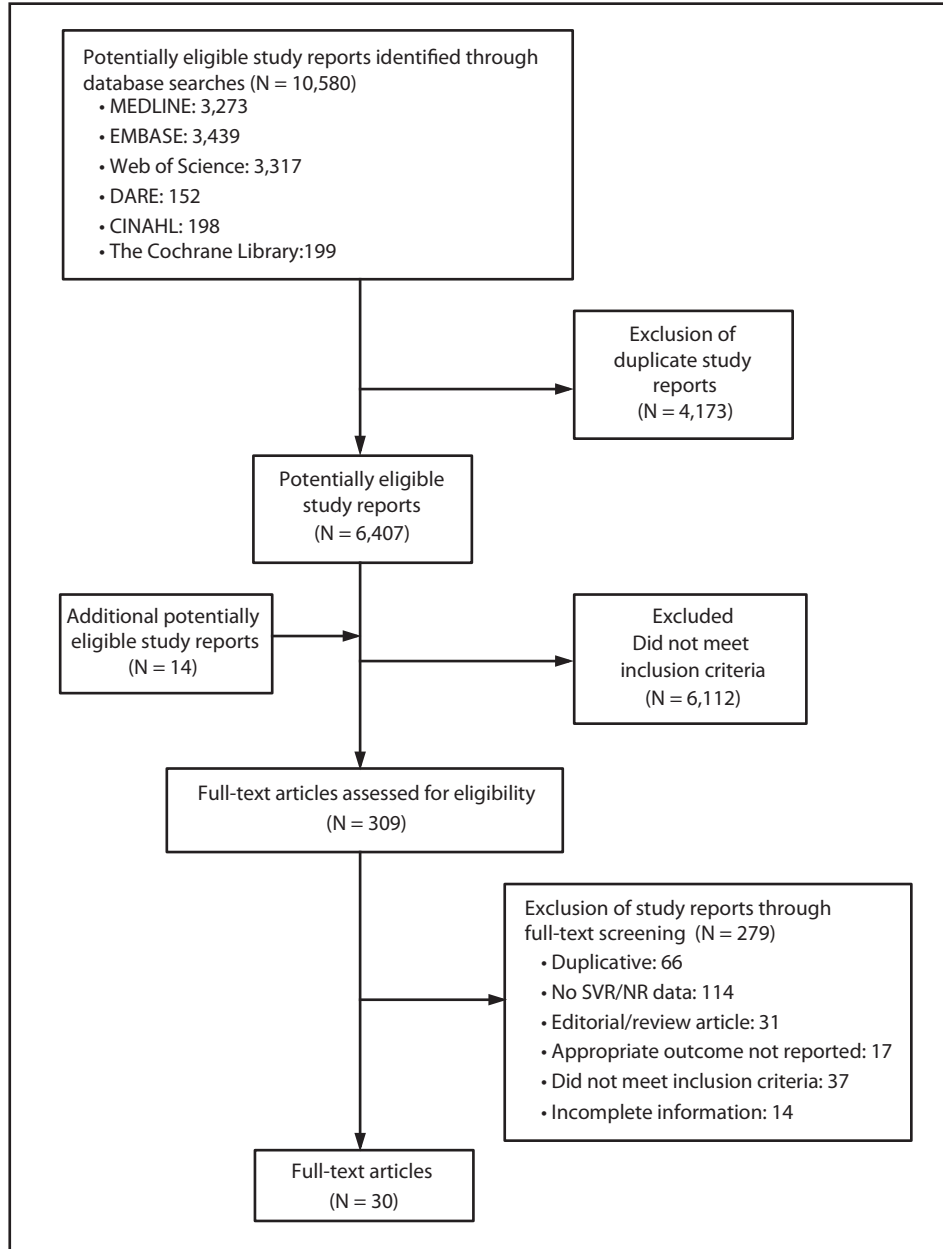
* This literature search was conducted to determine the effect of a birth-year-based testing strategy versus the standard of care (i.e., risk-based testing).

[†] Search totals were updated in February 2012.

[§] The number of reports remaining after duplicate study reports were identified.

Appendix I

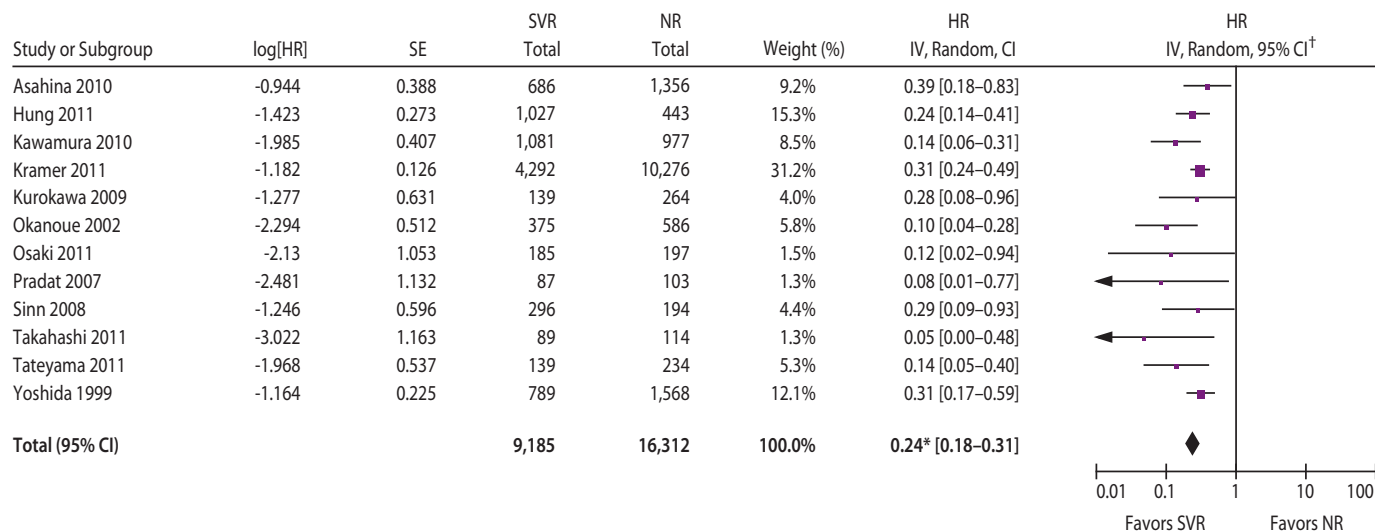
Flow Chart for Review of Literature Searches Addressing Hepatocellular Carcinoma



Abbreviations: SVR = sustained viral response; NR = non-response.

Appendix J

Meta-analysis of the Effects of Treatment Response on Incidence of Hepatocellular Carcinoma



Abbreviations: CI = 95% confidence interval; HR = hazard ratio; SE = standard error; SVR = sustained virologic response; NR = non-response; IV = inverse variance.

* Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 14.05$; degrees of freedom = 11 ($P=0.23$); $I^2 = 22\%$; test for overall effect: $Z = 10.80$ ($P<0.00001$).

[†] The HR is designated by the squares and diamond, whereas 95% CI is designated by a line.

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