Hepatocellular Carcinoma in the United States: Current Epidemiological Trends

The incidence of hepatocellular carcinoma (HCC) has almost tripled since the early 1980s in the United States, where it is the fastest rising cause of cancer-related deaths. According to population-based Surveillance Epidemiology and End Results registry data, the overall HCC age-adjusted incidence rates for liver and intrahepatic ducts cancer is as high as 8 per 100,000 underlying population in 2010 (Fig. 1) of which at least 6 per 100,000 are related to HCC. Men are at approximately three times higher risk than women. Asian men (i.e., Chinese, Korean, Filipino, and Japanese) have the highest age-adjusted incidence rates. However, the largest proportional increases have occurred among Hispanics followed by blacks and non-Hispanic whites, whereas the lowest proportional increases have occurred among Asians. In contrast to Asians/Pacific Islanders, HCC incidence rates are reported to be higher among Hispanics born in the United States than among foreign-born Hispanics. HCC incidence rates have increased in each successive birth cohort born between 1900 and 1959 (Fig. 2). In addition, the age distribution of HCC patients has shifted to younger ages, with the greatest proportional increases among individuals 45-60 years old (Fig. 2). There is a south to north gradient in the incidence and mortality of HCC; southern states, including Texas, Louisiana, and Mississippi, have some of the highest HCC incidence rates in the nation (Fig. 3). In one study, Texas Latinos and, especially, South Texas Latinos had the highest age-adjusted HCC incidence rates (as high as 10.6 per 100,000).

Risk Factors for HCC

Most HCC risk factors (chronic infection with hepatitis B [HBV] and/or C virus [HCV] and alcoholic liver disease [ALD]) operate by promoting the development of cirrhosis. Exceptions are rare in HCV-related HCC and mostly represent cases with at least bridging hepatic fibrosis. Whereas most cases of HBV-related HCC also occur in the background of cirrhosis (as high as 85% in some studies), HBV can cause HCC in the absence of advanced fibrosis or cirrhosis. Although there are several mechanisms for non-alcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD-NASH)-related HCC conceivably in the presence of mild or no fibrosis, there are no systematic studies to confirm or quantify this contention. Indirect measures of severity of hepatic fibrosis, such as degree of liver stiffness using elastography, is associated with risk of HCC.

The risk of developing HCC in patients with cirrhosis varies with the underlying condition. The highest 5-year cumulative risks are observed in HCV cirrhosis (17% in the West and 30% in Japan), hemochromatosis (21%), HBV cirrhosis (10% in the West and 15% in Asia), alcoholic cirrhosis (8%-12%), and biliary cirrhosis (4%).

HBV

Most large studies and consistent data about the clinical course of HBV infection come from Asian countries, where HBV is endemic and vertical transmission is frequent. This pattern is different in areas that have low incidence of HCC (such as the United States), where HBV infection is mostly acquired in
adulthood either through sexual or parenteral routes. There have been only a few adequate studies in Europe and North America that determined the incidence of HCC in hepatitis B surface antigen (HBsAg)-positive individuals—most included only small numbers of HBsAg-positive patients. Nevertheless, the summary HCC incidence rate in these regions is approximately 0.02 per 100 person-years in inactive carriers (HBsAg-positive, but with normal levels of alanine aminotransferase [ALT]), 0.3 in subjects with chronic HBV without cirrhosis, and 2.2 in subjects with HBV-related compensated cirrhosis. On the other hand, cohort studies estimated the incidence rates of HCC among subjects with chronic HBV infection in East Asian countries to be 0.2 per 100 person-years in inactive carriers, 0.6 per 100 person-years for those with chronic HBV infection without cirrhosis, and 3.7 per 100 person-years for those with compensated cirrhosis.

Several demographic (male sex, older age, Asian or African ancestry, and family history of HCC), viral (higher levels of HBV replication, HBV genotype, longer duration of infection, coinfection with HCV, human immunodeficiency virus [HIV], or hepatitis D virus), and environmental factors (exposure to aflatoxin and heavy intake of alcohol or tobacco) increase HCC risk among individuals with chronic HBV. HBV viral load appears to be an important determinant of HCC risk. The incidence of cirrhosis and HCC increased in proportion to the serum level of HBV DNA in Asian countries as well as Alaska. HBV genotypes also seem to affect clinical outcomes. In North America and Western Europe, individuals with genotype D had a higher incidence of HCC than those with genotype A. Some data associate genotype B HBV with the development of HCC in young carriers without cirrhosis. Mutations in the region of the HBV genome that encode the basal core promoter have been associated with increased HCC risk, whereas those in the precore region have been associated with decreased HCC risk.

Aflatoxin causes a mutation at serine 249 in the tumor suppressor, p53, that was detected in 30%-60% of HCC tumor samples collected from individuals in aflatoxin-endemic areas, most of whom also had HBV.

\[ \text{Incidence Rate} = \frac{\text{Number of cases}}{\text{Total person-years}} \]

Fig. 1. Time trends (1975-2010) of population-based age-adjusted incidence and mortality rates for liver and intrahepatic bile duct cancer in the United States. Both sexes and all races are included.

Fig. 2. State-specific population-based age-adjusted incidence rates for liver and intrahepatic bile ducts cancer. Both sexes and all races are included.
infections. Aflatoxin-associated mutation is rarely detected in HCC cases diagnosed in the United States.

**HCV**

HCV infection is associated with a 15- to 20-fold increase in risk for HCC, compared with HCV-negative, subjects. The rate of HCC in cohort studies of HCV-infected persons ranges from 1% to 3% over 30 years of chronic infection. Once HCV-related cirrhosis is established, HCC develops at an annual rate of 1%-8% (average, 3.5%). Risk factors for HCC in HCV-infected individuals include male sex, coinfection with HBV or HIV, diabetes, obesity, and high level of alcohol consumption.

HCV viremia of any level is a strong risk factor for HCC, compared to no viremia; however, though few studies reported a correlation between HCV viral load levels and risk of progression to cirrhosis or HCC, most studies did not find such an association. Reports of the association between HCV genotype and HCC risk are inconsistent, but suggest a slightly greater risk of developing HCC in patients with HCV genotype 1b, and possibly genotype 3, than patients with other HCV genotypes.

Meta-analyses of observational studies from various countries report additive effects of HBV and HCV on risk for HCC (35- to 165-fold increase), although a subadditive effect has been suggested based on more recent studies, cohort studies, and studies conducted in areas in which HBV and HCV infection were not common. Persons coinfected with HCV (and, to a lesser extent, HBV) and HIV have faster progression to cirrhosis and decompensated liver disease, especially during immnosuppression, than patients with monoinfection.

For both HBV and HCV, men have 2-4 times greater risk of HCC across almost all liver disease etiologies than women. Gender-based differences in behavior and environmental exposures, such as alcohol use, might explain some of this difference. However, male and female sex hormones may also play a role. Nested case-control studies in China reported that baseline testosterone levels were higher in HBsAg-positive males, compared to age-matched controls. There is a functional polymorphism, a trinucleotide polyglutamine (CAG) short tandem repeat, in exon 1 of the androgen receptor (AR) gene, where increasing number of CAG repeats results in decreased AR signaling. Carriage of the high-risk AR allele (i.e., fewer CAGs) conveyed greater risk of HBV-related HCC in Taiwanese males, whereas increased AR CAG
repeats were associated with greater HCC risk in females. Molecular data indicate that androgens contribute to HCC development by acting as tumor promoters through induction of DNA damage and oxidative stress, whereas estrogens may act as general suppressors of HCC through reduction in the pro-inflammatory effects of myeloid differentiation primary response 88-mediated secretion of interleukin-6.

**Metabolic Syndrome**

Patients with metabolic syndrome (MetS) or with various components of MetS (e.g., diabetes or obesity) also have higher incidence of HCC than those without MetS. There are also emerging reports of HCC in the setting of MetS arising in the absence of cirrhosis; however, the true extent of this condition or its risk factors are unclear.27,28

**Diabetes.** Meta-analyses of observational studies report pooled odds ratios (ORs) of approximately 2.5 for the association between diabetes and HCC independent of viral hepatitis or alcohol use.29,30 Cirrhosis causes glucose intolerance and type 2 diabetes, and also leads to HCC, making it difficult to interpret the association between HCC and diabetes, especially in case-control and cross-sectional studies. However, this bias is less likely to be present in longitudinal studies; several cohort studies also showed a similar association between diabetes and HCC. This association is less consistent in areas with a high incidence of HBV infection than in other regions. Factors that change HCC risk among patients with diabetes are not clear, but it has been suggested that long diabetes duration and high glycated hemoglobin increase the risk, whereas metformin treatment decreases HCC risk.31

**Obesity.** A meta-analysis of 26 prospective cohort studies, including 25,337 primary liver cancer cases, demonstrated that a body mass index (BMI) ≥25 kg/m² as well as a BMI ≥30 kg/m² were associated with an increased risk of primary liver cancer. The summary relative risk (RR) for a 5-unit increment in BMI was 1.39 kg/m² (95% confidence interval [CI]: 1.25-1.55), with the most pronounced increase in risk among persons with a BMI >32 kg/m². The association between BMI and liver cancer was independent of geographic location, alcohol consumption, or history of diabetes. However, obese males had a higher risk of primary liver cancer than obese females. Furthermore, the association between increasing BMI and HCC was much stronger in individuals with concomitant HCV infection than in persons with HBV infection.

NAFLD is the hepatic manifestation of MetS, and it affects approximately one third of the U.S. adult population. Epidemiologic studies support at least a modest association between NAFLD or NASH and HCC, but this association seems to be predominantly limited to those who develop cirrhosis.

The few population-based cohort studies of patients with NAFLD are limited by a low number of HCC cases and inability to identify high-risk subgroups (such as cirrhosis, obesity, and diabetes). Several cross-sectional and case-control studies have evaluated this association indirectly by concomitantly examining the prevalence of diabetes and obesity in NAFLD/NASH-related HCC cases. Diabetes and obesity prevalence was greater in the NAFLD/NASH-related HCC cases, compared to their respective controls with other chronic liver diseases. Prevalence of cirrhosis among HCC cases attributed to NAFLD/NASH ranged between 36% and 90%, with the majority of studies reporting cirrhosis rates ≥70%. These studies are limited because of the difficulty in ascertaining the exposure (histopathological features for confirmed NAFLD/NASH diagnosis) once cirrhosis is established. Furthermore, cirrhosis causes glucose intolerance and type 2 diabetes, and also leads to HCC, rendering it difficult to interpret the association between HCC and diabetes and exclude reverse causality.

Recently, a genetic polymorphism of the patatin-like phospholipase domain-containing protein has been shown to be associated with an increase in hepatic fat deposition as well as an increase in the risk of HCC development. This and other genetic markers may serve as a part of predictive algorithms to identify high-risk groups for surveillance or chemoprevention.

**Alcohol**

Heavy alcohol intake, defined as ingestion of >50-70 g/day for prolonged periods, is a well-established HCC risk factor. However, even moderate alcohol consumption may increase the risk of HCC in women.53 There is evidence for a synergistic effect between heavy ingestion of alcohol and HCV infection and, to a lesser extent, HBV infection on HCC risk; similar synergism may be present with diabetes. These factors presumably operate together to promote cirrhosis and further increase the risk in individuals with cirrhosis.34,35

**Cigarette Smoking**

The association between cigarette smoking and HCC has been inconsistent, with few studies finding a positive association and others finding no associations. Among studies reporting positive associations, several found that effects were limited to only those with HBV or HCV infection.36
Burden of HCC Related to the Major Risk Factors in the United States

Estimates of RR, such as risk ratios or ORs, for any of the individual HCC risk factors do not describe their contribution to HCC burden, which is also driven by the prevalence of the risk factor in the general population. Population attributable fraction (PAF) accounts for both an estimate of RR as well as prevalence of a given risk factor in the population, and it describes the proportional reduction in disease that would occur if exposure to a risk factor were to be eliminated. MetS is likely to have the greatest PAF (Table 1). A population-based study of SEER-Medicare-diagnosed HCC cases reported that the highest PAF was for diabetes or obesity (36.6%), followed by alcohol-related disease (23.5%), HCV (22.4%), and HBV (6.3%). Diabetes/obesity had the greatest PAF among whites and Hispanics (38.9% and 38.1%), and HCV had the greatest PAF among Asians and blacks (35.4% and 34.9%). The second greatest PAF were alcohol-related disorders in whites, Hispanics, and blacks (25.6%, 30.1%, and 18.5%) and HBV in Asians (28.5%). Therefore, despite having the lowest RR among the risk factors examined, the high prevalence of diabetes/obesity translates into a high attributable fraction.

Among patients with HCC currently diagnosed in the United States, 50%-60% are infected with HCV, 10%-15% are infected with HBV, and 20%-25% have ALD. Approximately 20%-30% of HCC cases do not have any of the previously mentioned factors, but have some features of MetS. Several studies examined time trends of risk factors among patients with HCC in the United States; HCV-related HCC had the largest proportional increases during the 1990s and early 2000, whereas the proportion of HCC associated with HBV infection and ALD remained relatively stable. However, based on the PAF arguments, these proportions may change in the next two to three decades with declining HCV-related HCC and increasing MetS-related cases.

| Risk Estimate of HCC* | Current Prevalence in HCC Cases (%) | Population Attributable Fraction (%) |
|-----------------------|------------------------------------|-------------------------------------|
| Current Prevalence in General U.S. Population (%) |                       |                                    |
| HBV                  | 0.5-1.0                            | 20-25                               | 10-15                               | 5-10                               |
| HCV                  | 1-2                                | 20-25                               | 30-60                               | 20-25                               |
| ALD                  | 10-15                              | 2-3                                 | 20-30                               | 20-30                               |
| MetS                 | 30-40                              | 1.5-2.5                             | 20-50                               | 30-40                               |

*Relative to controls without the risk factor.

Prevention of HCC

Prevention of HCC focuses on preventing these risk factors from ever developing (primary prevention) or, once developed, treating them at an early enough stage (secondary prevention) in order to reduce the risk of HCC. On the other hand, surveillance in patients at risk for HCC is intended to detect small, treatable cancer (tertiary prevention). The section below focuses on primary and secondary prevention.

HBV Vaccination Program. National HBV vaccination programs have been the most successful prevention strategy in reducing the incidence of HCC in HBV-endemic areas. These programs have dramatically reduced the prevalence of HBV (16%-1.4% in China, 9.8%-1.3% in Taiwan, and 9.3%-0.9% in Spain) with a concomitant decrease in the incidence of HCC. Since the implementation of the universal vaccination program for newborns in Taiwan in 1986 to the early 1990s, the average annual incidence of HCC in children between 6 and 14 years of age has fallen by 65%-75%.

In these regions, HBV is the most important risk factor for HCC, and universal vaccination programs, with almost 100% penetration, have been successful in decreasing the rate of chronic HBV in the general population. In other regions (e.g., Spain) where HBV is mainly spread by different parenteral routes, a decline in HBV likely resulted from screening of blood products and use of disposable syringes and needles. However, there are still ~400 million individuals chronically infected with HBV in the world—a group that will not benefit from immunization and remains at increased risk for HCC. Of these, an estimated ~800,000 to 1.4 million live in the United States.

Antiviral Treatment. There is moderately strong evidence that successful antiviral therapy for HBV or HCV substantially reduces, but does not eliminate, the risk of HCC in patients with viral hepatitis who already developed cirrhosis; the residual annual HCC risk in those patients may exceed the 1.5% threshold required by some cost-effectiveness models for HCC surveillance.

HBV Treatment. One randomized, controlled, clinical trial evaluated the efficacy of antiviral treatment on long-term clinical outcomes in patients with HBV. In a large Taiwanese study, patients with chronic HBV infection who also had cirrhosis or advanced fibrosis were randomly assigned to receive 100 mg of lamivudine per day or placebo for up to 5 years; the incidence of HCC was significantly reduced in the lamivudine group, as compared to the placebo group (3.9% vs. 7.4%; hazard ratio [HR]: 0.49;
though these data have just started to emerge. Though these data have just started to emerge.

Newer treatments with greater potency and better risk of HCC come from studies that used lamivudine. Studies indicated that the use of lamivudine may reduce the risk of HCC in patients with HBV.

Patients with HBV who were treated with medium-term nucleos(t)ide analogs (lamivudine was the initial treatment in 19, emtricitabine in one, and adefovir in one study). Only 3 of the 21 studies included untreated HBV patients followed for at least 24 months (one from the only randomized, controlled trial on this topic, as described above). A total of 168 (4.3%) patients receiving nucleos(t)ide analog therapy were diagnosed to have HCC during a mean/median follow-up of 40 (24-102) months. In the three studies with untreated controls, which were all of high quality and large, the rate of HCC was significantly lower in the treated (22 of 779; 2.8%) than in the untreated patients (34 of 534 [6.4%]; P = 0.003). Of note, most of these data on the effect of HBV treatment on the risk of HCC come from studies that used lamivudine. Newer treatments with greater potency and better resistance profiles—such as entecavir and tenofovir—are expected to further reduce the incidence of HCC, though these data have just started to emerge.

A multinational European cohort study reported clinical outcomes in patients treated with entecavir for a median of 20 months. Patients with a virological response (defined as serum HBV-DNA levels <80 IU/mL) had a significantly lower probability of developing hepatic decompensation, HCC, or death (HR, 0.29; 95% CI: 0.08-1.00; P = 0.05). This effect was significant among patients with cirrhosis (HR, 0.22; 95% CI: 0.05-0.99; P = 0.04), but not in those without cirrhosis (HR, 0.24; 95% CI: 0.02-3.76; P = 0.27). Of the 372 patients in the trial, only 3 developed HCC. Although encouraging, this study is limited by a relatively small number of clinical events and a short follow-up. A larger study following patients for a longer duration will be required to confirm a preventive effect of entecavir treatment in patients with HBV. In the interim, the existing data show that medium-term nucleos(t)ide analog therapy significantly reduces, but does not eliminate, the risk of HCC, particularly in patients with cirrhosis. The use of all oral antiviral agents in patients with cirrhosis is associated with improved virological, biochemical, and clinical parameters at 1 year, with tenofovir and entecavir being the most efficacious.

The effect of interferon (IFN) on HCC incidence in patients with chronic HBV has also been evaluated in several studies and meta-analyses. Most of the data suggest that IFN treatment decreases overall HCC incidence in sustained responders.

HCV Treatment. A recent systematic review of observational studies examined the risk of HCC among HCV-infected adults who had been treated and either achieved a sustained virological response (SVR) or did not respond to therapy. SVR was associated with a reduction in RR for HCC for patients at all stages of liver disease (HR, 0.24; 95% CI: 0.18-0.31; P < 0.001). Approximately 1.5% of patients responding to treatment develop HCC, compared to 6.2% of those who did not respond. SVR was associated with a similar reduction in risk for HCC (HR, 0.23; 95% CI: 0.16-0.35; P < 0.001) in patients with advanced liver disease or cirrhosis; approximately 4.2% of patients with SVR developed HCC, compared to 17.8% of those without SVR. Most studies included in this systematic review were from Asia. Given the fact that rates of HCC are higher in Asian populations than in European or U.S. populations, the absolute benefit of SVR on HCC risk may have been overestimated. However, collectively, these data show a moderate protective effect of treatment-related SVR on the development of HCC among HCV-infected persons. However, the absolute risk of HCC does not revert to baseline levels among those with cirrhosis, older age, high alpha-fetoprotein (AFP) levels, low platelet counts, high fibrotic stage, and diabetes. Furthermore, HCC incidence in nonresponders to initial antiviral therapy is not reduced by maintenance IFN therapy. Newer, more effective therapies may further stem the risk of HCC in HCV-infected persons.

Treatment of NAFLD. There is currently no direct evidence to show that treatment for NAFLD/NASH by any modality (including bariatric surgery) can reduce this risk. Several agents may have potential chemopreventive effects in reducing the risk of HCC in patients at high risk for NAFLD (section below).

Chemoprevention of HCC. Diabetes treatment. Several studies indicate that the use of insulin-sensitizing agents (such as metformin) in diabetes may reduce the risk of HCC. In a meta-analysis of these observational studies, metformin use was associated with a 70% reduction in the odds of HCC in patients with diabetes (OR, 0.30; 95% CI: 0.17, 0.52; P < 0.001). The proportion of patients with NAFLD/NASH was not reported. However, given that all patients had established diabetes, one expects NAFLD to be disproportionately high in these studies. Therefore, although the extent to which metformin (or
similar insulin-sensitizing agents) may reduce HCC risk in individuals with NAFLD/NASH remains unknown.

**Statins.** Epidemiological data also suggest a potential chemopreventive effect of statins specific to HCC. In a large cohort of diabetics, we found that statin use was associated with a 54% reduction in the odds of HCC (OR, 0.46; 95% CI: 0.40-0.51). A recent study from Taiwan found a strong dose-response relationship between statin use and the risk of HCC in individuals with HBV (HR, 0.66 [95% CI: 0.44-0.99], 0.41 [95% CI: 0.27-0.61], and 0.34 [95% CI: 0.18-0.67] for statin use of 28-90, 91-365, and >365 days). A meta-analysis of observational studies and randomized trials evaluated 4,298 cases of HCC in 1,459,417 patients found a 41% overall reduction in HCC risk with the use of statins. This finding was driven entirely by observational studies that are subjected to confounding by indication and healthy patient bias. There was no benefit observed in the randomized trials; however, none of the trials were powered to detect differences in HCC.

**Coffee.** Several studies suggested an inverse relation between coffee drinking and risk of HCC. A meta-analysis combined the results from 16 studies, eight of which were case-cohort studies and the other eight of which were case-control studies. The summary RR of developing HCC with coffee consumption was 0.60 (95% CI: 0.50-0.71). The calculated summary RR was 0.72 (95% CI: 0.61-0.84) for low versus no coffee consumption and 0.80 (95% CI: 0.77-0.84) for each extra cup of coffee consumed daily. Consumption of caffeine from sources other than coffee or of decaffeinated coffee is generally not associated with reduced levels of liver enzymes, fibrosis, or HCC.

Biomarkers such as high AFP, aspartate aminotransferase and/or ALT, and low platelet counts; clinical features such as esophageal varices and type 2 diabetes have been used in various algorithms to identify and enroll patients at high HCC risk in HCC surveillance programs. A similar approach (targeting patients at high risk for HCC) may improve the effectiveness and cost-effectiveness of chemoprevention efforts in HCC.

**Future Burden of HCC**

In the United States, the incidence of HBV-related HCC is likely to remain steady. Though vaccination against HBV could prevent HCC, it does not prevent cancer in persons with chronic infections. A larger proportion is chronically infected with HCV—most of them are unaware of their infection status. Testing persons at high risk for infection, educating patients, and administering effective therapies for treating HBV and HCV is therefore an important component of prevention against HCC.

A recent mathematical model based on the prevalence and natural history of HCV in the U.S. general population of HCV-infected individuals estimated that the number of HCC cases increased from 37,697 between 1990 and 1999 to 86,765 (+130%) between 2000 and 2009, with a projected increase to 130,366 (+50%) cases between 2010 and 2019. We found similar time trends in the prevalence of HCC in a national cohort of veterans with HCV. Among HCV-infected veterans who visited the Veterans Administration in a given calendar year, the prevalence of HCC increased 19-fold from 0.07% (95% CI: 0.04-1.0) to 1.3% (95% CI: 1.23-1.35) from 1996 to 2006 (P < 0.0001). Collectively, these data show that the number of individuals with HCV-related HCC has continued to rise and is projected to peak in 2019.

Although the incidence of HCV-related HCC is expected decline after 2020, this may not translate into a parallel decrease in the number of overall HCC cases. NASH-related cirrhosis is rapidly becoming an important cause of HCC. Given the very high prevalence of MetS in the United States, even small increases in risk related to NASH could translate into a large number of cases of HCC.

The recent breakthrough in the management of HCV may indeed change the trajectory of HCC in the United States. However, data show that the benefit of antiviral treatment is primarily limited to patients with successful eradication of the virus. Recent data show that approximately 45%-70% of individuals with HCV in the United States remain unaware of their infection status. Based on the mathematical model by Davis et al., assuming an SVR rate of ~80%, antiviral treatment will decrease cases of cirrhosis by a mere 5% in 2020. However, extending the treatment of half of infected persons would reduce HCC by 30.2%; treatment of all infected individuals would reduce the risk by 60.4% after just 10 years. Thus, a reduction in the incidence of HCC may not be achieved unless an increasing number of patients are diagnosed and treated.

The Centers for Disease Control and Prevention (CDC) recently recommended to test all persons in the United States born between 1945 and 1965 with the hope that this will identify 400,000 new persons with HCV. However, issues related to patient consent, buy-in, and reimbursement may reduce its overall effectiveness. Furthermore, the degree to which
increased identification will result in treatment with new, highly potent, yet expensive, treatment remains to be seen. The success of the CDC’s plan will likely be contingent upon the use of efficient and effective means of entering and retaining individuals in HCV care—steps that will need more focused efforts in the near term.

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