A population-based US study of hepatitis C diagnosis rate

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Background Underdiagnosis of HCV infection may hinder the obtainment of 2030 elimination goal.
Objective To estimate the pre-DAA HCV diagnosis rate to inform future public health effort.
Methods Data were obtained from three nationwide databases (Truven Health MarketScan Research Database 2007–2014, US Census Bureau 2012–2016 and NHANES 2007–2014). HCV diagnosis was defined with either one inpatient or two outpatient HCV International Classification of Disease 9 codes, providing the number of patients with diagnosed HCV (Truven). US Census Bureau data were used for age- and sex-standardization. We derived the total (diagnosed and undiagnosed) HCV infection using the NHANES database. To determine the rate and number of undiagnosed HCV, we subtracted diagnosed HCV burden (Truven) from the total HCV burden (NHANES).
Results Of the 198 073 302 privately insured Americans, 1.49% (2 951 490 persons) had HCV infection. However, only 362 672 (12.29%) persons were diagnosed with HCV, leaving 2 588 818 (87.71%) undiagnosed. About two-third (68.04%) and one-third (33.04%) of diagnosed HCV patients had HCV RNA or genotype tests overall, with even lower rates for the ≥65 age group, respectively.
Conclusion In the pre-DAA era, only 12% of insured Americans with HCV were diagnosed. While this grim statistic is expected to rise, much more effort is needed to enhance the HCV care cascade. Eur J Gastroenterol Hepatol XXX: 00–00

Introduction

Hepatitis C virus (HCV) infection is a leading cause of hepatocellular carcinoma (HCC) and liver-related death globally [1,2]. In late 2013 and early 2014, new medications [all-oral interferon-free, direct-acting antiviral agents (DAAs)] were approved for treatment and cure of HCV with high efficacy [3,4]. These new medication regimens significantly reduced the pill burden, the side effect profile and expanded the population that was eligible for HCV treatment while producing high cure rates (>85%) even in patients with HCC as well as reducing the incidence of HCC and HCV-associated mortality in those treated [5–12]. However, a large proportion of the world HCV population remains undiagnosed, a challenge that is now further threatened by the COVID-19 pandemic, with lower numbers of medical visits and monitoring for liver patients already in care, including those with viral hepatitis and HCC [13].

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The WHO established a goal of eliminating HCV by 2030 [14]. A recent modeling study indicated the significant economic benefit through investing in HCV elimination [15]. In response to the WHO's call for elimination of HCV by 2030, the National Academies of Science, Engineering and Medicine put together its national action plan, which centered on several key strategies – HCV treatment without restrictions on the severity of liver disease; a consistent ability to diagnose new cases, even as the prevalence of HCV decreases and diagnosing at least 110 000 cases a year until 2020, almost 89 000 a year between 2020 and 2024 and over 70 000 each year between 2025 and 2030 [16]. Considering disease screening is the biggest challenge in the cascade of care, the Centers for Disease Control (CDC) and US Preventive Services Task Force (USPTF) recently expanded its HCV testing recommendation to include all adults over the age of 18 get tested at least once but more often if engaging in risky behaviors as well as testing women during each pregnancy [17].

To date, the diagnosis rate of HCV infection in the USA at the population level prior to these recommendations remains largely unknown, which hinders the true capture of the progress of meeting both the WHO and the USA goal of HCV elimination. Therefore, the purpose of this study was to use three nationwide databases in the USA to determine the diagnosis rate of HCV in Americans with private insurance.

Methods

Data sources

We used three databases in this study: The Truven Health MarketScan Research Database 2007–2014 (Truven),

the US Census Bureau 2012–2016 American Community Survey (ACS) and the National Health and Nutrition Examination Survey 2007–2014 (NHANES). The Truven database is an administrative claims database for privately insured Americans. It collected data on inpatient and outpatient claims as well as relevant healthcare expenditures from more than 100 employers, government agencies and public organizations. Therefore, clinical diagnoses and utilization records of enrollees can be retrieved and analyzed. The Truven data were obtained from the Population Health Science Center at Stanford University, California, USA. The population data of 2014 was obtained from the 2011–2015 ACS 5-year estimate. US Census Bureau is the agency of the federal government to delineate the US population in terms of social, economic and geographic aspects. The Census Bureau publishes their population estimates online at the website (https://www.census.gov). The data were accessed from the US Census Bureau website (https://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=ACS_17_5YR_B27002&prodType=table). We categorized the data by age, and sex, which allowed us to perform age- and sex-standardization of HCV prevalence.

NHANES is a program that conducts questionnaire surveys, imaging and laboratory examination to gauge the nutritional and health status of both adults and children in the USA. It is approved by the institutional review board of the CDC. NHANES participants underwent blood test for anti-HCV and HCV RNA levels. Serum specimens from participants were drawn, processed and shipped to the Division of Viral Hepatitis, National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention, Centers for Disease Control and Prevention. In terms of sampling method, NHANES adopts a complex, multistaged sampling method to ascertain that the participants are representative of the noninstitutionalized general population. All patients have signed informed consent.

The current study was approved by the Institutional Review Board at Stanford University, California, USA. All participants of NHANES had provided written consent. This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

Study design – diagnosis rate

The use of these databases to estimate the diagnosis rate was described in a previous study [18]. In brief, individuals with HCV infection in the Truven database were identified using International Classification of Disease (ICD)-9 CM codes for HCV infection (07044, 07054, 07070, 07071 and v0262). Each patient had to have either one inpatient or two outpatient diagnoses during the period of 2007–2014. The estimated prevalence of patients diagnosed with HCV was determined by dividing the number of patients with HCV by the total number of patients enrolled. The ACS database was used to compute the age- and sex-standardized prevalence of HCV. The NHANES database was used to identify the true prevalence (both diagnosed and undiagnosed) of HCV infection in the private insurance population. We included participants who reported yes to the question 'Are you covered by private insurance?' and determine the prevalence of HCV using data on anti-HCV stratified by age and sex. To determine the undiagnosed rate of HCV, the difference between the total number of HCV patients (from NHANES) and the number of diagnosed HCV patients (from Truven database) was calculated.

Proportion of diagnosed patients with hepatitis C viral confirmatory test

We calculated the proportion of diagnosed HCV patients who received a viral confirmatory test (HCV RNA or HCV genotype) during the study period (2007–2014). We used CPT codes to identify patients who had received HCV RNA (87521, 87522) or HCV genotype (87902, 3266F) tests from 12 months before HCV diagnosis date to the end of the study period.

Statistical analysis

Using descriptive analysis, we reported counts and percentages for categorical variables. The prevalence of HCV infection was categorized by various demographic characteristics and clinical characteristics such as the severity of liver disease by the presence of cirrhosis or HCC and the proportion with HIV or HBV coinfection. The Pearson chi-squared test was used to compare the categorical variables among subgroups. The two-tailed P values set to be significant were <0.05.

A sensitivity analysis was completed to determine the diagnosis rate using one inpatient or one outpatient encounter. R (3.5.0) was used for all statistical analyses in this article.

Results

Study patients

In total, 138 634 154 individuals aged 6 years or above were enrolled in the Truven database during 2007–2014. Among them, 67 312 312 (48.6%) were men and 71 321 842 (51.4%) were women. A total of 73% of the enrollees were aged between 18 and 64 years. Enrollees with preferred provider organization (PPO) and health maintenance organization (HMO) constituted 63.1 and 12.5% of all participants, respectively.

Number of diagnosed hepatitis C virus burden

Using one inpatient or two outpatient diagnoses as criteria, we identified 239 385 patients with HCV in the Truven database (Table 1), yielding a prevalence of 0.1727% (0.1720–0.1734%) for diagnosed cases of HCV. When subgrouped by age, the prevalence was higher in older age groups from 0.0079% (0.0076–0.0083%) in the age group of 6–17 to 0.5027% (0.4993–0.5061%) in the age group 55–64, then was lower in the age group 65 years and older at 0.0087% (0.0081–0.0094%). The prevalence was 0.2206% (0.2195–0.2217%) in men and 0.1274% (0.1266–0.1283%) in women. By insurance plan, the prevalence of HCV in individuals with a HMO plan was 0.2200% (0.2177–0.2222%), while it was 0.1682% (0.1673–0.1691%) in individuals with a PPO plan and 0.1599% (0.1586–0.1613%) in those with non-HMO and non-PPO insurance. The prevalence of HCV infection

Table 1. The prevalence of diagnosed HCV infection in privately insured Americans, by diagnosis criteria

			One inpatient/two outpatient		One inpatient/one outpatient	
Patient group		No. of population	No. of patients with HCV diagnosis	Diagnosed HCV prevalence (%, 95% CI)	No. of patients with HCV diagnosis	Diagnosed HCV prevalence (%, 95% CI)
Overall		138 634 154	239 385	0.1727 (0.1720–0.1734)	353 112	0.2547 (0.2539–0.2555)
Age group (years)	6–17	28 520 831	2266	0.0079 (0.0076–0.0083)	4371	0.0153 (0.0149–0.0158)
	18–34	39 866 980	18 756	0.0470 (0.0464–0.0477)	34 783	0.0872 (0.0863–0.0882)
	35–44	22 576 301	27 461	0.1216 (0.1202–0.1231)	45 013	0.1994 (0.1975–0.2012)
	45–54	22 678 600	104 553	0.4610 (0.4582–0.4638)	145 139	0.6400 (0.6367–0.6433)
	55–64	17 038 737	85 654	0.5027 (0.4993–0.5061)	118 725	0.6968 (0.6928–0.7007)
	≥65	7 952 705	695	0.0087 (0.0081–0.0094)	5081	0.0639 (0.0621–0.0656)
Sex	Men	67 312 312	148 499	0.2206 (0.2195–0.2217)	212 545	0.3158 (0.3144–0.3171)
	Women	71 321 842	90 886	0.1274 (0.1266–0.1283)	140 567	0.1971 (0.1961–0.1981)
Insurance plan	PPO	87 512 508	147 197	0.1682 (0.1673–0.1691)	216 866	0.2478 (0.2468–0.2489)
	HMO	17 372 574	38 211	0.2200 (0.2177–0.2222)	56 274	0.3239 (0.3213–0.3266)
	Other	33 749 072	53 977	0.1599 (0.1586–0.1613)	79 972	0.2370 (0.2353–0.2386)
Region	North East	24 686 367	48 830	0.1978 (0.1960–0.1996)	73 965	0.2996 (0.2975–0.3018)
	North Central	30 796 745	36 630	0.1189 (0.1177–0.1202)	53 982	0.1753 (0.1738–0.1768)
	South	52 785 069	97 758	0.1852 (0.1840–0.1864)	142 238	0.2695 (0.2681–0.2709)
	West	25 568 826	48 663	0.1903 (0.1886–0.1920)	71 954	0.2814 (0.2794–0.2835)

HCV, hepatitis C virus; HMO, health maintenance organization; PPO, preferred provider organization.

Table 2. The proportion of advanced liver diseases and coinfection among diagnosed HCV patients, by diagnosis criteria

		One inpatient/two outpatient			One inpatient/one outpatient		
Disease	Subgroup	No. of HCV patients	Proportion (%)	*P* value	No. of HCV patients	Proportion (%)	*P* value
Severity	Non-cirrhosis	229 027	95.6731	<0.0001	339 869	96.2496	<0.0001
	Cirrhosis	9342	3.9025		11 909	3.3726	
	HCC	1016	0.4244		1334	0.3778	
Coinfection	HIV	3077	1.2854	<0.0001	4665	1.3211	<0.0001
	HBV	698	0.2916	<0.0001	2881	0.8159	<0.0001

HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

by geographical area was 0.1978% (0.1960–0.1996%) in the Northeast, 0.1189% (0.1177–0.1202%) in the North Central, 0.1852% (0.1840–0.1864%) in the South, and 0.1903% (0.1886–0.1920%) in the West. Table 2 shows the proportion of diagnosed HCV patients with cirrhosis (3.90%), HCC (0.42%) and coinfection (HBV 0.29%, HIV 0.52%). The far-right panels of Tables 1, 2 shows data for sensitivity analysis with HCV diagnostic criteria requiring only one inpatient or one outpatient HCV diagnosis code. In this sensitivity analysis, the diagnosed HCV prevalence was higher but still dismal at 0.2547% (0.2539–0.2555%) overall.

Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/EJGH/A678* displays the age- and sex-standardized prevalence of diagnosed HCV using the 'one inpatient or two outpatient HCV diagnoses' criteria, resulting in an age- and sex-standardized prevalence of diagnosed HCV of 0.1831% and a total of 362 672 diagnosed HCV cases. Supplementary Table 2, Supplemental digital content 1, *http://links.lww.com/EJGH/A678* shows the age- and sex-standardized prevalence of diagnosed HCV for the sensitivity analysis requiring only 'one inpatient or one outpatient' HCV code to define HCV diagnosis. The resulting age- and sex-standardized prevalence was 0.2719%, yielding a respective total of 538 561 individuals with known HCV infection.

Number of total hepatitis C virus disease burden (diagnosed and undiagnosed)

Using the positivity of HCV antibody data from NHANES, we estimated the age- and sex-standardized prevalence of HCV infection (both diagnosed and undiagnosed) to be 1.4901% (Fig. 1). Combined with the total number of privately insured Americans from the ACS registry in 2014, we estimated the total number of persons with HCV and private insurance in the USA in 2014 to be 2 951 490 (Fig. 1).

Number of undiagnosed hepatitis C virus burden

Since only 362 672 HCV patients have been diagnosed out of the total of 2 951 490, the resulting diagnosis rate for HCV was 12.29% (362 672 out of 2 951 490) (Fig. 1). This left a total of 2 588 818 (87.71%) Americans with private insurance and HCV undiagnosed. In the sensitivity analysis that used the number of known HCV infections based on the 'one inpatient or one outpatient' criteria, the diagnosis rate was still only 18.25% (538 561 out of 2 951 490), leaving an undiagnosed rate of 81.75%.

Proportion of diagnosed hepatitis C virus patients who underwent viral confirmatory tests

A total of 68.04% of diagnosed HCV patients had HCV RNA tests during the study period. The proportion was higher in patients who were younger, female (69.27%), PPO insured (68.65%), and residents of the West (70.10%) and South of the USA (68.47%) (Table 3). A total of 33.04% of HCV patients underwent HCV genotype testing during the study period, and the trend among subgroups was similar to that of HCV RNA testing, with a higher proportion of young and PPO insurers as well as

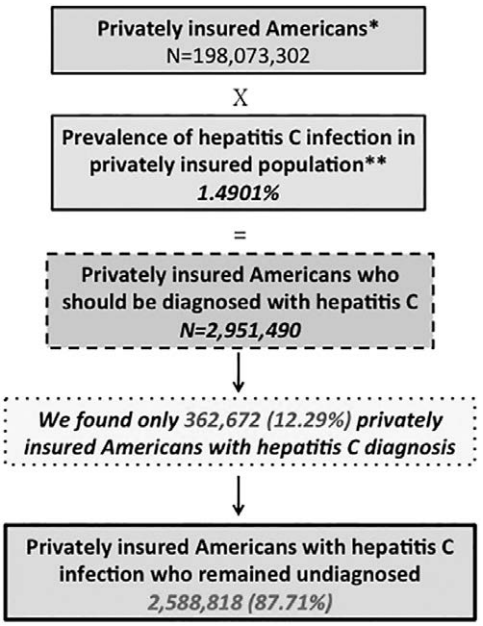

Fig. 1. Graphical study overview and summary. *Based on US Census Bureau data. **Based on National Health and Nutrition Examination Survey data. Age- and sex-standardized prevalence of patients with hepatitis C diagnosis as derived from Truven Health MarketScan Research Database was 0.1831%, yielding a total number of 362 672 patients diagnosed with hepatitis C in the population of 198 073 302 privately insured individuals. 362 672 patients constituted 12.29% of the total number of privately insured Americans who should be diagnosed (both diagnosed and undiagnosed) with hepatitis C (2 951 490).

residents of the West and South of the USA but less female having HCV genotype test.

When using the 'one inpatient or one outpatient diagnosis' criteria, the proportions of HCV RNA and genotype tests were lower at 55.51 and 24.60%, respectively. However, the trend of the test in the different subgroups remained generally the same.

Discussion

Overall, among the 198 073 302 privately insured Americans, 2 951 490 persons had HCV infection. However, we found that only 362 672 (12.29%) of these individuals with HCV infection have been diagnosed, leaving 2 588 818 (87.71%) undiagnosed. Sensitivity analysis using less stringent diagnostic criteria yielded an HCV diagnosis rate of 18.25% and an undiagnosis rate of 81.75%. Our results are similar to what the WHO reported in 2015 when they estimated that only 20% of patients with HCV were actually diagnosed [19]. A recent US study also reported an HCV screening rate of less than 20% among persons with opioid disorder from a national sample of US federally qualified health centers [20]. Additionally, we also found that only about two-third of patients with known HCV diagnosis underwent HCV RNA testing, and only about one-third had HCV genotype test.

These are disturbing findings as recent data from the CDC have also indicated that cases of acute hepatitis are

Table 3. The proportion of viral confirmatory test in diagnosed HCV patients, by diagnosis criteria

		One inpatient or two outpatient diagnosis code			One inpatient or one outpatient diagnosis code		
Patient group		No. of patients with HCV diagnosis	Proportion of patients with HCV RNA test (%)	*P* value	No. of patients with HCV diagnosis	Proportion of patients with HCV RNA test (%)	*P* value
HCV RNA test							
Overall		239 385	68.04		353 112	55.51	
Age group (years)	6–17	2266	77.71	<0.001	4371	56.97	<0.001
	18–34	18 756	73.41		34 783	54.56	
	35–44	27 461	71.13		45 013	55.11	
	45–54	104 553	69.97		145 139	59.37	
	55–64	85 654	63.56		118 725	53.33	
	≥65	695	31.66		5081	4.80	
Sex	Men	148 499	67.29	<0.001	212 545	55.74	<0.001
	Women	90 886	69.27		140 567	55.15	
Insurance plan	PPO	147 197	68.65	<0.001	216 866	56.27	<0.001
	HMO	38 211	65.93		56 274	53.36	
	Other	53 977	67.88		79 972	54.93	
Region	North East	48 830	68.54	<0.001	73 965	54.90	<0.001
	North Central	36 630	65.39		53 982	53.03	
	South	97 758	68.47		142 238	56.81	
	West	48 663	70.10		71 954	56.54	
HCV genotype test							
Overall		239 385	33.04		353 112	24.60	
Age group (years)	6–17	2266	48.24	<0.001	4 371	29.31	<0.001
	18–34	18 756	39.55		34 783	25.28	
	35–44	27 461	35.47		45 013	24.30	
	45–54	104 553	34.24		145 139	26.78	
	55–64	85 654	29.14		118 725	22.67	
	≥65	695	10.65		5081	1.54	
Sex	Men	148 499	33.33	<0.001	212 545	25.47	<0.001
	Women	90 886	32.56		140 567	23.29	
Insurance plan	PPO	147 197	33.75	<0.001	216 866	25.20	<0.001
	HMO	38 211	30.42		56 274	22.53	
	Other	53 977	32.93		79 972	24.44	
Region	North East	48 830	31.93	<0.001	73 965	23.15	<0.001
	North Central	36 630	31.68		53 982	23.48	
	South	97 758	35.54		142 238	26.98	
	West	48 663	30.76		71 954	22.68	

HCV, hepatitis C virus; PPO, preferred provider organization; HMO, health maintenance organization.

increasing rapidly [21]. Though the CDC attributes some of the increase to case ascertainment, the majority of new cases are the result of the opioid epidemic. A recent report suggested that given the extensive underreporting of HCV, the actual number of acute hepatitis C cases is estimated to be 13.9 times the number reported to CDC [22]. As such, the goal of hepatitis elimination by 2030 is severely challenged by the continual increase in new cases as well as the low diagnosis rate of old cases; and despite the increased availability of DAA agents, HCV diagnosis and treatment remain barriers to obtaining the WHO elimination goal for the USA [23]. A recent article that investigated the policy of HCV elimination in countries with a heavy burden, the rank of the USA was 14th among included countries/territories, far behind many industrialized counterparts [24]. Treatment uptake rate among HCV patients already diagnosed and linked to care at an Urban Health Network in the Philadelphia area was only 15% according to a recent study [25], though various interventions had been proposed with some degree of success, including task shifting to community-based nonspecialist providers [26].

Although the prevalence of HCV infection among those with private insurance is lower than the prevalence in the general population, the predominance in men and those aged 45–64 years is similar [2]. By estimating the prevalence of HCV by subgroups, we provided important baseline results for use when determining the impact of changes in DAA treatment eligibility across different types of insurance as well as the changes that may occur as a result of the new expanded testing guidelines recommended by the CDC and the USPTF as discussed above. As we found in this study that the highest prevalence rates in those ages 45 years and older, this is not surprising as the prior CDC and USPTF HCV testing guidelines recommended screening of all patients born between 1945 and 1965 [27,28]. Now that the guidelines recommend testing everyone 18 years and older and testing more frequently those who engage in risky behavior [17], we may find a shift in the HCV prevalence to a younger cohort and potentially capture the group that is having the most rapid increase in acute HCV cases.

However, despite these changes, many challenges remain in improving the rate of diagnosis. The challenges most recently reported include lack of community awareness of HCV, lack of enough rapid results testing equipment, lack of follow-up of patients after test results were received, stigma, and cost of treatment [29,30]. Others have reported that among those with health care coverage, especially among HMO participants, the characteristics independently associated with being tested and testing positive for HCV infection included being less than 59 years old and being Black or Native American [31]. Another report found similar results but also found that electronic health engagement, attending a residency teaching clinic, and having more than one clinic visit were all associated with higher odds of screening [32]. Both studies found that being female was associated with being significantly less likely to be tested. These reported findings are also reflected in our results, where the prevalence of diagnosed HCV among men was about twice that of women, and the prevalence of HCV among those belonging to an HMO was higher than among those in a PPO or other insurance type. Data from an interventional study aiming at improving HCV screening and care for the baby boomers in safety-net primary care practices through May 2018 showed that HCV screening rates were as high as 50% on average, ranging from 20 to 71% among the practices included in the study [33].

In this study, there were only two-thirds and one-third of diagnosed HCV patients underwent HCV RNA and HCV genotype testing, respectively, during study period. Pediatric patients (6–17 years) had the highest proportion of tests, although this could have been due to older patients had their confirmatory testing done before their enrolment in the Truven database. The lower rates of viral confirmatory tests in older patients may also have been due to older patients were generally not considered good candidates for interferon-based therapies. The lower proportion of HMO patients who underwent testing may manifest an ineffective referral to a specialist for further management after the initial diagnosis. This could contribute to the challenge in the care cascade of HCV.

The diagnosis rate in this study is significantly lower than the rate of HCV awareness in a prior study that used the NHANES database [34]. However, this could be due to participants in NHANES are more motivated and proactive in their healthcare leading to higher diagnosis rates than real-world patients from the Truven database. NHANES participants may also have better recall about their condition and bias toward a higher proportion of disease awareness.

There are several strengths to our study. Through the use of the Truven MarketScan database and the ACS data, we were able to determine the prevalence of diagnosed HCV at a nationwide level. Second, the use of serological data in NHANES provided the opportunity to estimate the true total number of HCV infected patients and thus allowed us to determine the difference between true disease burden and the number of persons with HCV infection who remained undiagnosed. Finally, the robustness of the data retrieved from Truven allowed us to assess certain characteristics of patients with HCV. Our data are also timely to help maintain public awareness and the need for improved HCV screening and diagnosis now that this poor linkage to care of people affected by chronic hepatitis C is further threatened by the COVID-19 pandemic. Indeed, since government shelter-in-place order came into effect, the number of medical visits and HCC surveillance for people already known to have hepatitis and HCC have declined significantly [13].

Our study is not without limitations. Our results are the only representative of the population with private insurance, so our results cannot be generalized to populations who are more likely to be uninsured, including incarcerated individuals and people who inject drugs. However, given the lower rate of access to healthcare and treatment among those without private insurance, we suggest that the diagnosis and viral confirmatory test rates within that population would be lower. The Truven database is a claim database; therefore, we did not have access to race/ethnicity and laboratory data. However, using ICD codes to define HCV infection (in which case we may have

included patients with both positive and negative HCV antibodies) would only increase the diagnosis rate.

Conclusion

Using data from nationwide databases, we found that only 12% of privately insured Americans with HCV infection were actually diagnosed with HCV, leaving 88% (2 588 818 persons) undiagnosed and thus potentially untreated and at a greater risk for end-stage liver disease. Therefore, with the advent of the all-oral interferon-free DAA therapy and the expanded recommendations for HCV screening, policymakers and other stakeholders should identify and curb the hurdles to enhance the cascade of care of HCV infection to achieve the WHO 2030 goal of viral hepatitis elimination. As the COVID-19 pandemic continues to ravage many areas of the USA, additional commitment to viral elimination is needed so that this important long-term public health effort is not sidelined by other more acute priorities.

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M.H.N. supervised and is the guarantor of the study. Y.H.Y. and M.H.N. conceptualized and designed the study. L.K., M.H.L., D.J., N.D., Y.H.Y. and M.H.N. analyzed the data. Y.H.Y., L.H., R.C. and M.H.N. drafted the manuscript. All authors collected and interpreted the data and reviewed and revised the article.

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Conflicts of interest

R.C. received a research grant from Gilead. M.H.N. received grant\research support from Pfizer, Gilead Sciences, Enanta and is the advisory board member and/or consultant of Gilead Sciences, Janssen. For remaining authors, there are no conflicts of interest.

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