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ORIGINAL RESEARCH

Epidemiology and Clinical Characteristics of Individuals with Hepatitis C Virus Infection in the United States, 2017–2019

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ABSTRACT

Introduction: Hepatitis C virus (HCV) is the most common bloodborne chronic infection in the US. Following approval of highly effective, direct-acting antivirals in 2014, the diagnostic and treatment rates for HCV infection in the US have evolved. This study assessed the number of individuals with HCV screening or diagnostic testing and the clinical characteristics and treatment of HCV-infected individuals between 2017 and 2019.

Methods: Individuals screened for HCV antibody and/or tested for HCV ribonucleic acid (RNA) from 2017 to 2019 by two large US laboratory companies were included in this analysis. Clinical characteristics, such as HCV genotype, fibrosis stage, HIV coinfection and demographics, were assessed in HCV RNA-positive individuals. HCV treatment and subsequent achievement of sustained virologic response were imputed using data-driven algorithms based on successive viral load decline and negativity.

Results: From 2017 to 2019, the number of individuals tested for HCV antibody increased by 5.7%, from 7,580,303 in 2017 to 8,009,081 in 2019. The percentage of individuals tested who were HCV antibody positive was stable, ranging from 5.0% in 2017 to 4.9% in 2018 and 2019. The number of HCV RNA-positive individuals decreased by 5.0% from 382,500 in 2017 to 363,532 in 2019. Of HCV RNA-positive individuals, the proportions with genotype (GT) 3 and minimal fibrosis increased over time; proportions of individuals aged < 40 years increased, while the proportion aged 50 to 59 years decreased. Treatment rates increased from 23.4% in 2017 to 26.8% in 2019.

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Conclusions: The percentage of HCV antibody-positive individuals remained stable from 2017 to 2019. The number of individuals tested HCV RNA positive decreased over the years. Demographics shifted toward a younger population with less fibrosis and higher rates of GT3. More than 70% of diagnosed individuals were not treated during this interval, highlighting a need for unfettered access to treatment.

Keywords: Epidemiology; Hepatitis C virus; Screening; Treatment

Key Summary Points

Why carry out this study?

This study describes the hepatitis C virus (HCV) care cascade from HCV antibody screening and HCV ribonucleic acid (RNA) diagnostic testing to treatment and cure in the US in 2019, based on the largest and most current dataset of non-extrapolated data using a robust study design and advanced analytical techniques

This dataset answers the important question of "what proportion of individuals received a positive HCV RNA test from 2017 to 2019?" and describes the characteristics of individuals with HCV in the US in terms of age, genotype, fibrosis stage and geographic region

What was learned from the study?

The number of individuals HCV screened and treated increased from 2017 to 2019; however, most infected individuals remain untreated

Understanding the number of individuals screened, diagnosed and treated over time and identifying gaps in care may help to orient intervention efforts and highlight the need for unfettered access to treatment for all individuals

INTRODUCTION

Hepatitis C viral (HCV) infection is one of the most common bloodborne chronic infections in the US. The treatment landscape of HCV has fundamentally improved since development and approval of direct-acting antivirals (DAAs) for treatment of chronic HCV, which offer simpler treatment that is highly effective with shorter durations [1, 2]. Using data collected early in the DAA era (2013–2016), the National Health and Nutrition Examination Survey (NHANES) estimated the overall US prevalence at 2.3 million people infected with HCV [3]. Prior analysis by our group has shown that the number of persons screened for HCV antibody increased from 2013 to 2016, with a corresponding increase in confirmatory ribonucleic acid (RNA) testing [4, 5]. Since that period, the percentage of the population that is screened, diagnosed or treated for HCV infection has likely evolved rapidly owing to changes in screening guidance, treatment options and access to therapy and the incidence of HCV in at-risk populations, namely persons who use drugs (PWUD) [6]. Rates of acute infection have risen 63% between 2015 and 2019 in the US, with 63% of cases in 2019 occurring in persons aged 20–39 years, consistent with age groups most impacted by the opioid crisis [7]. The rate of newly reported chronic infections in 2019 was 56.7 per 100,000 individuals and follows a biphasic pattern, with cases of new infections highest among those aged 20–39 years and 55–70 years [7, 8], further amplifying the need for accurate, up-to-date HCV epidemiology information. In the US, 67% of incident cases of HCV infection are believed to be due to injection drug use [7]. Furthermore, despite the availability of curative treatment and universal screening recommendations [6, 9, 10], many individuals (> 39%) with HCV are unaware of their disease, and in those who have been screened, the HCV care cascade shows few receive treatment [8, 11].

Given these developments, a better understanding of the changing landscape of HCV screening and treatment, as well as the clinical characteristics of diagnosed individuals, may

facilitate targeting of resources to increase HCV screening and treatment. Improved understanding of the care cascade of HCV individuals in the US may support the World Health Organization (WHO)'s goal of HCV elimination as a major burden by 2030. The NHANES estimates extrapolated prevalence of HCV from 15 US counties, Centers for Disease Control and Prevention (CDC) provides yearly estimates of incident infection through 2019, and state Department of Health data provide information on HCV prevalence from 2000 to 2018. However, there is a lack of real-world data sources reporting on the observed diagnostic, prevalence and treatment rates of HCV infection and clinical characteristics of individuals with HCV infection. This study utilizes data from large laboratory companies combining patient information and clinical characteristics stratified by year to fill key evidence gaps and provide the most recent data regarding the screening/testing, clinical characteristics and treatment of individuals with HCV in the US from 2017 to 2019.

METHODS

Data Source and Patient Population

This study used a secondary, de-identified dataset combined from two large laboratory companies in the US. This derived dataset represents the largest available HCV laboratory dataset in the US. Records of all individuals who were screened for HCV antibody and/or tested for HCV RNA from 2017 to 2019 were retrieved and included in this analysis. Not all included individuals had both HCV antibody and HCV RNA tests.

Patient characteristics, including age (in years), sex (female, male, or unknown) and region of residence (East, South, Midwest or West) were available for all individuals included in the analysis. An individual's region of residence was determined by the location of HCV RNA testing and diagnosis (Supplementary Material Table S1). For individuals who tested positive for HCV RNA, additional information was retrieved from both laboratory datasets for the following variables: HCV genotype; laboratory results that facilitate calculation of fibrosis stage, including liver alanine aminotransferase, aspartate aminotransferase and platelets; and human immunodeficiency virus (HIV) diagnosis.

Fibrosis Stage Calculation

Fibrosis stage was calculated among HCV RNA-positive individuals using the levels of liver alanine aminotransferase, aspartate aminotransferase and platelets as the modified fibrosis 4 (FIB-4) index and categorized as *F*0 (< 0.97), *F*1 (0.97–1.44), *F*2 (1.45–3.25), *F*3 (3.26–5.20) or *F*4 (> 5.20) [12, 13]. Individuals with *F*4 fibrosis stage were classified as cirrhotic [12].

Algorithms for Treatment Receipt and Achievement of Sustained Virologic Response

Treatment Receipt

Owing to the lack of information on treatment and continuity of medical or pharmacy benefit enrollment in the source data, receipt of HCV treatment was determined based on a viral load decline of at least 1.2 × log10 units since the first positive HCV RNA test, indicating that treatment was initiated in the immediate period prior to the decline [12, 14]. The year of treatment was assigned for the year in which such decline since a positive HCV RNA viral load was detected. Direct information on treatment timing, type or duration was not available in the data source.

Prediction of Individuals Attaining Sustained Virologic Response

Data-driven machine learning algorithms were employed to identify individuals who achieved sustained virologic response (SVR) or virologic cure based on successive decline in HCV RNA viral loads. Detailed methodology for development of the algorithm was previously described [12]. Briefly, machine learning predictive models were built and validated using a separate set of 92,099 treated HCV individuals with medical and pharmacy claims available in the Symphony Health Solutions (SHS) medical and

pharmacy claims dataset from 2017 to 2019. Individuals in the current laboratory dataset who were predicted to have achieved SVR from the machine learning algorithms were classified as cured in the year following the year of treatment (e.g., individuals flagged as initiating treatment in 2018 were classified as treated in 2018 and cured in 2019).

Viremic Status

Because individuals might have varied follow-up duration and/or inconsistent HCV RNA measurements in the years from 2017 to 2019, a longitudinal method was applied to impute their HCV viremic status over multiple years. Individuals who had two positive HCV RNA values with gap years in between were assumed to stay HCV viremic in the gap years.

Observed Rates of HCV Screening and Diagnostic Testing

Observed numbers of HCV antibody-screened, HCV antibody-positive and HCV RNA-positive individuals were assessed for each year from 2017 to 2019. The proportion of individuals who were HCV antibody positive among all individuals HCV antibody screened was calculated.

Rates per 100,000 Individuals

Observed HCV antibody-screened, HCV antibody-positive and HCV RNA-positive rates per 100,000 individuals in each year were calculated by dividing the observed number of individuals by the US Census population estimates from 2017 to 2019, respectively.

Statistical Analysis

This study was descriptive in nature. After retrieving and combining data from the two laboratory databases, observed numbers of individuals screened for HCV antibody, tested HCV antibody positive and tested HCV RNA positive were reported. The observed number of individuals who were HCV antibody screened, tested HCV antibody positive and tested HCV RNA positive was stratified by age for the year 2019; the observed rate per 100,000 individuals for those three measures was presented similarly for 2019. Cured individuals predicted from the machine learning algorithms were removed from each year's estimates. The total number of individuals who remained HCV RNA positive and not cured was reported for the respective years between 2017 and 2019. The percent change in observed number of individuals HCV antibody tested, HCV antibody positive and HCV RNA positive between each respective year (2017 to 2018, 2018 to 2019) and between 2017 and 2019 was reported. For those individuals who remained HCV RNA positive in each year, demographic and clinical characteristics, including age, gender, region, HCV genotype, fibrosis status, renal status, HIV coinfection and treatment status (treated or untreated), were summarized using descriptive statistics to describe the sample of participants. Means and standard deviations were reported for normally distributed continuous variables, medians and interquartile ranges for non-normally distributed continuous variables and frequencies and percentages (%) for categorical variables. The predictive performance of the machine learning algorithms was summarized by metrics of sensitivity, specificity and accuracy. Percentages of SVR or cure rate in the SHS and laboratory databases were calculated as well. Mortality was not determined owing to limitations of the database.

Software

Data cleaning and manipulation were performed using SAS 9.4 (Cary, NC, USA). Machine learning algorithms were developed in R software (R Foundation for Statistical Computing, Vienna, Austria).

Compliance with Ethics Guidelines

With permission, this study utilized de-identified retrospective data from two US laboratory datasets. Because the data were de-identified, no ethics committee approval was required. Additionally, as this study is based on laboratory data, it does not contain any new studies with human or animal subjects performed by any of the authors.

RESULTS

Age Distribution of Screening and Diagnostic Testing in 2019

Observed numbers of individuals in 2019 who were HCV antibody screened, HCV antibody positive and HCV RNA positive were stratified by age, and the percentage of individuals within each age category is presented in Fig. 1. In 2019, the observed number of individuals screened for HCV antibody followed a bimodal age distribution, with the percentage of individuals screened highest among individuals aged 25–34 and 55–59 years (Fig. 1A). The rate of screening per 100,000 individuals followed a similar age distribution, with observed rates highest among individuals aged 25–34 years and 55–59 years. The age distribution was similar between individuals who were HCV antibody positive and those who were HCV RNA positive. Among individuals who were HCV RNA positive, 21% were aged 30 to 39 years and 28% were aged 55 to 64 years (Fig. 1B, C). The rate of HCV RNA positivity per 100,000 individuals followed a similar age distribution as the age-stratified

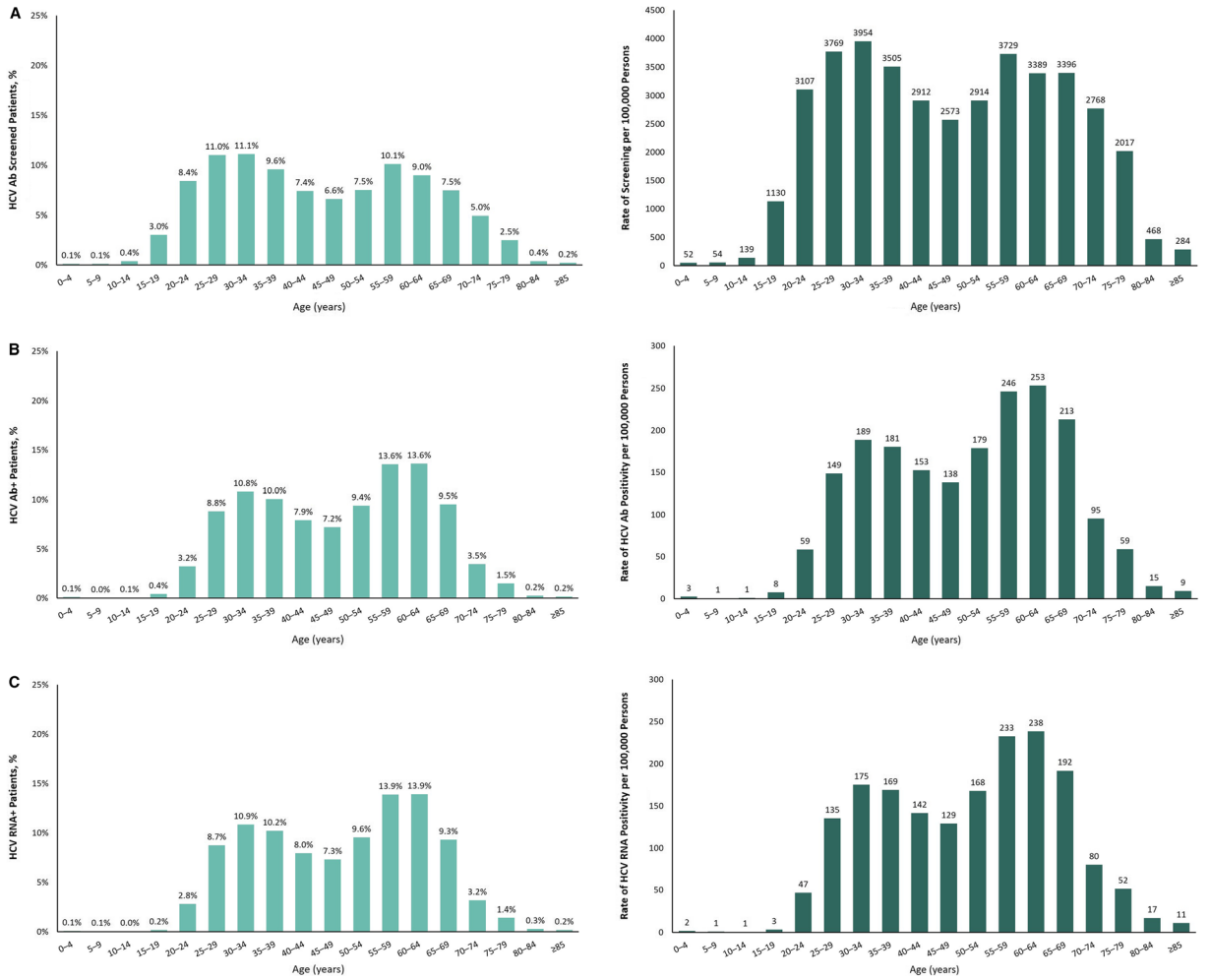

Fig. 1 Age distribution of the number of individuals as well as the observed rates per 100,000 individuals screened for HCV Ab (**A**), positive for HCV Ab (**B**) and positive for HCV RNA (**C**) in 2019. *Ab* antibody, *HCV* hepatitis C virus, *RNA* ribonucleic acid

proportions of individuals who were HCV RNA positive, with highest rates among those aged 55 to 64 years and 30 to 39 years (Fig. 1C).

Changes in Screening and Diagnostic Testing from 2017 to 2019

From 2017 to 2019, the observed number of individuals tested for HCV antibody increased from 7,580,303 in 2017 to 7,906,178 in 2018 and 8,009,081 in 2019 (Table 1). Of these, the percentage of individuals who tested HCV antibody positive remained relatively stable, from 5.0% (382,451) in 2017, 4.9% (386,016) in 2018, to 4.9% (394,666) in 2019 (Table 1). The number of individuals who were HCV RNA positive increased from 2017 to 2018 and decreased from 2017 to 2019.

Observed Screening and Diagnostic Rates per 100,000 Individuals from 2017 to 2019

The rate per 100,000 individuals screened for HCV antibody increased from 2308 in 2017 to 2423 in 2018 and remained stable from 2018 to 2019 (rate: 2417/100,000) (Table 1). The rate of HCV antibody-positive individuals per 100,000 individuals remained stable, from 117 in 2017 to 118 in 2018 and 119 in 2019. Among

Table 1 Observed number and rates per 100,000 persons of individuals screened, diagnosed and treated for HCV from 2017 to 2019

	2017	2018	2019	% Change 2017–2019
HCV Ab screened, N	7,580,303	7,906,178	8,009,081	–
Change from previous year, %	–	4.3	1.3	5.7
HCV Ab screening rate[a]	2308	2423	2417	–
Change from previous year, %	–	5.0	− 0.3	4.7
HCV Ab positive, N (% positive of screened)	382,451 (5.0)	386,016 (4.9)	394,666 (4.9)	–
Change from previous year, %	–	0.9	2.2	3.2
HCV Ab positive rate[a]	117	118	119	–
Change from previous year, %	–	0.9	0.9	1.7
HCV RNA positive, N	382,500	395,524	363,532	–
Change from previous year, %	–	3.4	− 8.1	− 5.0
HCV RNA positivity rate[a]	116	121	110	–
Change from previous year, %	–	4.3	− 9.1	− 5.2
Treated, N	89,490	94,116	97,588	–
Change from previous year, %	–	5.2	3.7	9.1
Percent treated,[b] %	23.4	23.8	26.8	–
Change from previous year, %	–	1.7	12.6	14.5

Ab antibody, *HCV* hepatitis C virus, *RNA* ribonucleic acid
[a]Rate per 100,000 persons
[b]Among HCV RNA-positive individuals

individuals with a positive HCV antibody test and a follow-up HCV RNA test in 2019, 42.4% tested positive for HCV RNA, resulting in an observed rate of 110 per 100,000 individuals, a decrease from 116 in 2017 and 121 in 2018 (Table 1).

Clinical Characteristics of Individuals Who Were HCV RNA Positive from 2017 to 2019

The total as-observed number of individuals with active HCV infection (HCV RNA positive) was 363,532 in 2019, which represents a slight decrease (− 5.0%) from the 382,500 HCV RNA-positive individuals in 2017. Individuals may have appeared in more than 1 year of observation if there was no successive decline in HCV RNA viral loads. Between 2017 and 2019, the number and proportion of individuals who were HCV RNA positive and aged < 40 years numerically increased from 97,462 (25.5%) in 2017 to 119,797 (33.0%) in 2019, while the proportion aged 50 to 69 years old decreased (Table 2). Proportions were relatively consistent for other age groups over the same time frame. Sex ratio was relatively consistent during this time frame, with males representing > 60% of all HCV RNA-positive individuals.

Of people who tested HCV RNA positive from 2017 to 2019, 78.9%, 76.6% and 77.6% had data available for HCV genotype in 2017, 2018 and 2019, respectively (Table 2). The percentage of individuals diagnosed with genotype 3 HCV increased over time (12.9% in 2017, 14.3% in 2018 and 15.0% in 2019). The percentage of individuals diagnosed with fibrosis stage *F*0 and *F*1 (no scarring/fibrosis or minimal scarring/fibrosis) increased over time (49.4% in 2017, 52.5% in 2018 and 55.8% in 2019). Correspondingly, the percentage of individuals with fibrosis stage *F*3 and *F*4 decreased over time (27.2% in 2017, 25.1% in 2018 and 22.8% in 2019) (Table 2).

The proportion of all observed individuals in the US who were HCV RNA positive decreased in the East (18.6% in 2017, 18.5% in 2018 and 16.7% in 2019) and increased in the South (44.0% in 2017, 44.6% in 2018 and 45.5% in 2019) and West (26.7% in 2017, 28.1% in 2018 and 28.3% in 2019) (Table 2).

Percentage of Individuals Treated from 2017 to 2019

According to our definition of treatment, which was based on sequential RNA viral load measurements, 26.8% of individuals who were HCV RNA positive were treated in 2019. This represents an increase from 23.4% and 23.8% for those who were treated in 2017 and 2018, respectively (Table 1).

Prediction of SVR/Cure

The predictive performance of machine learning algorithms in terms of accuracy, sensitivity and specificity is summarized in Supplementary material Table S2, along with the prediction of percentage of cured individuals who were predicted to have attained SVR. The predicted SVR rates stayed stable and > 95% across the three datasets from 2017 to 2019, demonstrating a high cure rate (Supplementary material Table S2). Of note, predicted cure rates were similar to the observed cure rates in the SHS dataset.

DISCUSSION

In this study, we examined screening, diagnosis, clinical characteristics and treatment of individuals with HCV infection in the US between 2017 and 2019. To the best of our knowledge, this is the largest study to describe the HCV care continuum based on actual confirmed antibody and HCV RNA positivity from non-extrapolated data in 2019, prior to the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Understanding screening, diagnostic and treatment rates over time and identifying gaps in care may help to orient intervention efforts and highlight the need for unrestricted access to treatment for all individuals.

This study identified 8,009,081 individuals screened for HCV antibodies, compared to the approximately 5 million previously identified from 2013 to 2016 using a similar methodology [12]. The number of individuals screened for

Table 2 Characteristics of individuals who tested HCV RNA positive from 2017 to 2019

Variable	Statistic or category	2017 *N* = 382,500	2018 *N* = 395,524	2019 *N* = 363,532
Treatment status, *n* (%)	Untreated	293,010 (76.6)	301,408 (76.2)	265,944 (73.2)
Median age	Years (IQR)	54 (39–61)	53 (37–61)	51 (36–61)
Age, *n* (%)[a]	< 40 years	97,462 (25.5)	117,084 (29.6)	119,797 (33.0)
	40–49 years	51,684 (13.5)	56,297 (14.2)	55,512 (15.3)
	50–59 years	113,702 (29.7)	104,195 (26.4)	85,211 (23.5)
	60–69 years	100,604 (26.3)	97,946 (24. 8)	84,336 (23.2)
	≥ 70 years	19,359 (5.1)	19,754 (5.0)	18,374 (5.1)
	Missing	332 (< 0.1)	248 (< 0.1)	302 (< 0.1)
Sex, *n* (%)	Female	143,904 (37.6)	147,740 (37.4)	131,680 (36.3)
	Male	238,152 (62.3)	246,954 (62.5)	231,010 (63.7)
	Unknown	444 (0.12)	180 (0.05)	193 (0.05)
Region, *n* (%)	East	71,307 (18.6)	73,008 (18.5)	60,856 (16.7)
	Midwest	40,754 (10.7)	35,053 (8.9)	34,369 (9.5)
	South	168,193 (44.0)	176,520 (44.6)	165,497 (45.5)
	West	102,246 (26.7)	110,943 (28.1)	102,810 (28.3)
Genotype, *n* (%)[a]	Genotype 1	224,146 (74.3)	220,460 (72.7)	203,310 (72.1)
	Genotype 2	34,044 (11.3)	34,641 (11.4)	31,845 (11.3)
	Genotype 3	38,902 (12.9)	43,357 (14.3)	42,407 (15.0)
	Genotype 4	3103 (1.0)	3379 (1.1)	3346 (1.2)
	Genotype 5/6	1503 (0.5)	1281 (0.4)	1035 (0.4)
	Missing	80,802 (21.1)	92,406 (23.4)	81,589 (22.4)
Fibrosis stage, *n* (%)[a]	*F*0–1	168,920 (49.4)	183,412 (52.5)	179,261 (55.8)
	*F*2	80,296 (23.5)	78,426 (22.4)	68,917 (21.4)
	*F*3	31,612 (9.3)	30,472 (8.7)	25,792 (8.0)
	*F*4	61,016 (17.9)	57,193 (16.4)	47,466 (14.8)
	Missing	40,656 (10.6)	46,021 (11.6)	42,096 (11.6)
HIV infection, *n* (%)	Yes	8988 (2.4)	8026 (2.0)	6730 (1.9)

HCV hepatitis C virus, *HIV* human immunodeficiency virus, *IQR* interquartile range, *RNA* ribonucleic acid
[a]Percentages based on non-missing values

HCV antibody increased from 2017 to 2019, while the number of individuals who tested HCV RNA positive increased from 2017 to 2018 but decreased overall from 2017 to 2019. This is in contrast to a previous analysis that found increases in the number of individuals screened for HCV antibody from 2013 to 2016 and a corresponding increase in confirmatory RNA testing, which may reflect the introduction of reflex RNA testing [5]. Increases in screening rates over time may be due to increases in injection drug use, improved surveillance [15] and universal screening recommendations [10]. The observed proportion of individuals who were HCV antibody positive observed in our study remained relatively stable between 2017 and 2019, suggesting a continued need for universal screening efforts as an essential tool in identifying HCV-infected individuals.

To understand changing characteristics of screened and diagnosed individuals, our study stratified the observed number of individuals HCV antibody screened, tested HCV antibody positive and tested HCV RNA positive by age for 2019. A bimodal age distribution was observed for all three measures of screening and diagnostic testing. Notably, in 2019, individuals aged 25–34 years made up the highest proportion of individuals who were HCV antibody screened. One potential explanation for this is that an estimated 67% of new infections are the result of illicit drug use, primarily among younger generations [7, 15]. These results reinforce the need for one-time, opt-out universal HCV testing and treatment and repeat testing among high-risk individuals, especially PWUD.

The bimodal age distribution of individuals who are HCV RNA positive in our dataset is consistent with CDC 2019 HCV surveillance data of newly diagnosed individuals with HCV [7]. In our analysis, observed rates of HCV RNA positivity were highest in individuals aged 55–64 years and second highest in individuals aged 30–39 years. In both datasets, individuals aged 30–39 years were disproportionally impacted by HCV, consistent with the age groups most impacted by the nation's opioid crisis [7]. Previous analyses by our group from 2013 to 2016 also saw increases in HCV screening and diagnosis among younger individuals, supporting the observations of the more current 2019 dataset [12]. These results also support earlier analysis of NHANES data through 2016, which found that, although HCV rates were increasing in young people, most prevalent infections occurred in people born between 1945 and 1969 [16]. One explanation for the continued high proportion of older individuals in our study is that the individuals included in this analysis are engaged in HCV care, as they have recent HCV tests, while not accounting for individuals disengaged in care, including PWUD and younger persons. Furthermore, a recent study highlighted that 17% of adults have never heard of HCV and that younger adults specifically were more likely than older adults to have no awareness of HCV [17].

We also observed an increase in the proportion of HCV genotype 3 infection among individuals who are HCV RNA positive over time in our study. This finding correlates with the increase of HCV genotype 3 infection among younger adults and injection drug users [18–20]. An additional observation was the reduction in the proportion of HCV RNA-positive individuals with cirrhosis over time. This finding is likely to be explained by the prioritization of treatment of patients with cirrhosis and restrictions on treatment access based on fibrosis stage as well as potentially increased motivation to seek treatment by patients with cirrhosis.

Although we observed moderately increased treatment rates over time, most HCV RNA-positive individuals are still not being treated, indicating a need for improved efforts to support access to treatment. Previous analysis has also demonstrated that the proportion of individuals treated remains low, even if individuals were referred to a specialist after an HCV diagnosis [4]. Removing barriers to treatment is critical in efforts to contain and to achieve the WHO's announced a goal of eliminating HCV by 2030 through increased prevention, diagnosis and treatment [21]. Despite elimination efforts, there was a growing burden of chronic liver disease between 2007 and 2017, with HCV being a primary driver of disability-adjusted life years caused by chronic liver disease in 2017

[22], highlighting the need for unfettered access to treatment.

Barriers to treatment may include stigmatization of marginalized patients, particularly PWUD, insurance denial of treatment and restrictive state Medicaid policies. In a previous analysis of 2016 to 2017 pharmacy data from 45 states, treatment was denied for individuals with Medicaid (34.5%) and private insurance (52.4%) at high levels [23]. Sobriety, prescriber and fibrosis stage restrictions, as well as policies that restrict harm reduction services, can limit efforts to achieve HCV elimination [24, 25]. As reported by the National Viral Hepatitis Roundtable and the Center for Health Law and Policy Innovation of Harvard Law School, the number of states with sobriety restrictions decreased between 2017 and 2021 [24, 25]; however, 13 states still require a period of abstinence and 15 states require drug or alcohol screening or counseling [26]. Furthermore, 12 states do not have laws authorizing syringe service program operations and 13 states criminalize hepatitis transmission [24]. Between 2017 and 2021, most states have eased restrictions based on fibrosis status (4 states have restrictions) and prescriber restrictions (18 states have restrictions), which may correlate with the moderate increases in treatment observed [26–29]. In our current study, states in the South and West had the highest proportions of individuals who were HCV RNA positive. Of the 30 states in those 2 regions, 2 have restrictions by fibrosis status, 19 have sobriety restrictions, and 9 have provider restrictions. Of note, regional data included all payer types and are not Medicaid specific, which may cloud restrictive policies that preferentially impact the Medicaid population. Updates on state-level data from 2015 through 2017 are available at the MappingHepC.com website, which reflects the most current trends in HCV epidemiology [30]. To overcome barriers to treatment, subscription or "Netflix" model programs for HCV treatments from pharmaceutical companies in Louisiana and Washington may lead to treatment increases in these states because these subscription models allow the states to treat patients at a reduced cost [31]. Future research and trends will reveal whether these policy changes and subscription models will correlate with improvements in treatment rates. Simplified treatment algorithms and treatment of individuals who are HCV positive by nonspecialists may also aid in improving treatment rates [6].

The effects of the coronavirus disease 2019 (COVID-19) pandemic may create additional barriers to treatment access and achievement of elimination targets. Impacts of COVID-19 on HCV elimination include reallocation of healthcare resources and disruptions in care and access to treatment as well as patient reluctancy to access healthcare services out of fear of contracting COVID-19 [32]. This is significant, as a 1-year delay in diagnosis and treatment efforts could result in an additional 72,300 liver-related deaths from HCV globally [32]. Furthermore, during the pandemic there may have been an increase in HCV transmission, as suggested by the increase in overdose and overdose-related deaths in the US [33].

Strengths of the study include analysis of the most recent and largest collection of data significantly contributing to efforts supporting HCV screening, testing and linkage to care in the US. This dataset includes as-observed real-world data of HCV RNA-confirmed cases and their associated clinical characteristics. The study described HCV screening and diagnostic testing among individuals from 52 states and US territories aged 0 to $>$ 85 years from 2017 to 2019. These data inform on HCV elimination efforts that were occurring before the outbreak of COVID-19 in 2020.

Limitations of this study include the selective nature of our dataset, which was limited to community-dwelling Americans. This circumstance means that no imprisoned individuals were included, which is notable because the prevalence of HCV is high among those engaged in the criminal justice system. Active drug users may be less represented in these commercial laboratories compared to those in the community with prior drug use. Other high-risk patient populations may also be underrepresented in these datasets, including persons receiving hemodialysis. We could also not assess epidemiology in veterans or determine mortality among included individuals due to

lack of data. Additional limitations are the lack of details pertaining to the specific treatment regimens that were utilized and the use of viral load as a proxy for cured individuals that could be inaccurate owing to insufficient follow-up time. The number of individuals who were HCV RNA positive in our study was obtained from commercial laboratory databases and is likely an underestimate, as individuals tested outside of these laboratories through other HCV screening endeavors were not captured. The data source does not differentiate between acute and chronic infections, although the timing between RNA tests in our data was generally consistent over time with guidelines for RNA tests (i.e., intervals of 4 weeks apart), which was indicative of treatment for chronic disease. Treatment rates by geographical region were not calculated, which limits understanding of the correlation between state Medicaid restrictions and treatment rates. Future studies will aim to extrapolate the overall prevalence of HCV infection in the US, including an estimation of both diagnosed and undiagnosed individuals.

CONCLUSION

These data inform on the observed number of individuals screened and diagnosed for HCV infection using the largest available laboratory dataset in the US. Notably, we found that numbers of younger individuals and of those with milder disease are increasing. Data from this study can inform medical and government stakeholders about HCV burden and help define current unmet needs. Future studies are needed to examine estimated prevalence and progress toward elimination after the COVID-19 epidemic.

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Compliance with Ethics Guidelines. With permission, this study utilized de-identified data from two US laboratory datasets. Because the data were de-identified, no ethics committee approval was required. Additionally, as this study is based on laboratory data, it does not contain any new studies with human or animal subjects performed by any of the authors.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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