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MAJOR ARTICLE

The Burden of Hepatitis C Infection–Related Liver Fibrosis in the United States

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Background. Knowledge of the estimated proportion of hepatitis C virus (HCV)-infected persons with advanced fibrosis or cirrhosis is critical to estimating healthcare needs.

Methods. We analyzed HCV-related testing conducted by Quest Diagnostics from January 2010 through December 2013. Tests included hepatitis C antibody, HCV RNA, HCV genotype (nucleic acid tests [NAT]), liver function tests, and platelet counts; patient age was also determined. Aspartate aminotransferase (AST)-to-platelet ratio (APRI) was calculated as = 100*(aspartate aminotransferase [AST]/upper limit of AST)/platelet. Fibrosis-4 (FIB-4) was calculated as (age × AST)/(platelet ×$\sqrt{}$ alanine aminotransferase [ALT]). Persons were "currently infected" if they had ≥1 positive HCV NAT; "in care" if a positive RNA test was followed <6 months by ≥1 additional NAT(s), or ALT, AST, and platelets <90 days, or any test ordered by an infectious diseases or gastroenterology specialist; and "evaluated for treatment" if they had a genotype test.

Results. Approximately 10 million HCV test results were analyzed, representing 5.6 million unique patients. Of the 2.6 million patients with data to estimate liver disease, 5% were currently infected. Among those currently infected, APRI and FIB-4 scores indicated that 23% overall—and 27% among the cohort born during 1945–1965—had advanced fibrosis or cirrhosis at first diagnosis. A total of 54% of infected were in care and 51% of infected with advanced fibrosis or cirrhosis were evaluated for treatment.

Conclusions. Testing from a large US commercial laboratory indicates that about 1 in 4 HCV-infected persons have levels of liver disease put them at highest risk for complications and could benefit from immediate antiviral therapy.

Keywords. hepatitis C virus; epidemiology; fibrosis.

Deaths as recorded on death certificates associated with hepatitis C virus (HCV) infection have steadily increased in the United States, exceeding deaths recorded on death certificates for human immunodeficiency virus since 2007 [1], even though death certificates record less than one-fifth of all persons dying with HCV [2]. Persons dying with HCV infection are 25 years younger than those dying without HCV infection [3]. The appearance of clinical complications of HCV might be the first indication of infection, as infection may be asymptomatic for decades. The early identification of asymptomatic HCV-infected persons with subsequent linkage to care and treatment, if appropriate, is estimated to prevent more than 320 000 deaths associated with HCV-related complications between 2010 and 2060 [4]. To prevent further complications and deaths, the Centers for Disease Control and Prevention (CDC) [5] and the US Preventive Services Task Force (USPSTF) [6] recommend a 1-time screening of persons born during 1945–1965 to identify and diagnose infected persons who might be unaware of their infection.

Once diagnosed, HCV-infected persons can benefit from novel, highly effective anti-HCV therapies. Current clinical guidelines recommend treatment for all patients with chronic HCV infection, unless individuals will not benefit from treatment [7]. Controlling for other factors, advanced fibrosis (Metavir stage F3) and compensated cirrhosis (Metavir stage F4) are strong predictors of progression to hepatocellular carcinoma or decompensation [8]. Biopsy had long been the gold standard to stage liver fibrosis of any etiology, but its costs and other limitations have led clinicians to use a combination of noninvasive methods to assess liver fibrosis [7, 9]. Fibrosis-4 (FIB-4) score is frequently used because of its demonstrated statistical association with HCV-related liver disease staging, especially in identifying advanced fibrosis or cirrhosis [10, 11].

In this study, we used laboratory data from a large commercial laboratory service in the United States to describe the burden of fibrosis among persons with chronic HCV infection, evaluate stage of fibrosis at first HCV diagnosis, and use laboratory measures to describe persons in care and those evaluated for HCV treatment.

METHODS

Quest Diagnostics provides laboratory testing services to approximately half of the physicians and hospitals in the United

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States. Approximately 150 million test requisitions are processed annually. Test results are routinely reported back through providers for clinical care. CDC asked 6 collaborating health departments to track the laboratory source of newly reported hepatitis C cases during 2012–2014. Quest was the source of 11%–73% of new cases.

Quest stores selected information for each test in secure databases. After finalizing a data-sharing agreement with CDC in 2013, Quest provided CDC with longitudinal, de-identified data from HCV-related tests ordered by physicians in the United States between January 2010 and December 2013. The tests analyzed were HCV antibody (Ab), HCV-RNA, genotype (LiPA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and platelet count from a complete blood count. Nucleic acid tests (NATs) included any RNA or genotype test. Hepatitis C Ab measurements were performed by immunoassay (Ortho-Clinical Diagnostics, Inc., Rochester New York). HCV viral RNA quantitative measurements were performed by polymerase chain reaction (PCR), using the COBAS Ampliprep/COBAS TaqMan HCV test kit (Roche Molecular Systems, Inc., Branchburg, New Jersey). HCV viral RNA qualitative, transcription-mediated amplification test was performed using the Versant HCV RNA qualitative assay (Gen-Probe Inc., San Diego, California). HCV Ab, recombinant immunoblot assay (RIBA) test (Chiron RIBA HCV 3.0 SIA) was used to confirm the presence of HCV antibodies (Ortho Clinical Diagnostics, Raritan, New Jersey) through 2012. As of May 2013, an option of Ab testing with reflex to RNA PCR became available.

A unique patient identification (ID) was created to extract patient data from the Quest clinical results database. SAS statistical software (version 9.3; Cary, North Carolina) was used to clean and prepare data prior to delivery to CDC via a password-protected secure ftp (file transfer protocol) site (Secure Access Management Service), hosted by CDC.

Data Analyses

The patient ID was used to structure the data such that interpretation could be made at the patient level. Patient year of birth was used to categorize persons into 1 of 3 cohorts: born before 1945, born from 1945–1965, and born after 1965. In addition to year of birth, records contained limited patient and provider characteristics including payer type, specialty of the provider ordering the test, and the first 3 digits of the patient residence zip code, which were used to define state of residence. Regions were categorized using 9 standard US Department of Health and Human Services groups as follows: New England (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont); Mid-Atlantic (New Jersey, New York State, and Pennsylvania); East North Central (Illinois, Indiana, Michigan, Ohio, and Wisconsin); West North Central (Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota); South Atlantic (Delaware, District of Columbia, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, and West Virginia); East South (ES) Central (Alabama, Kentucky, Mississippi, and Tennessee); West South (WS) Central (Arkansas, Louisiana, Oklahoma, and Texas); Mountain (Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, and Wyoming); and Pacific (Alaska, California, Hawaii, Oregon, and Washington).

We defined a person as "'currently infected'" if they had 1 or more HCV NAT tests with a positive result (eg, detectable RNA or valid genotype result; see flow diagram). A person was considered "never infected" if they only had documentation of a negative HCV Ab test and were considered "resolved/cured" if they had a positive Ab result and a negative RNA result. We excluded from this analysis anyone with only a negative RNA test or only a positive Ab test. We defined "in care" as any person with a positive RNA test who within 6 months also had any of the following: ≥1 additional NATs; or ALT, AST, and platelets ordered within 90 days (routine components of a hepatic function panel, comprehensive metabolic panel, and complete blood count); or any test ordered by an infectious diseases or gastroenterology specialist. We defined a person as "evaluated for treatment" if they had a genotype test, since guidelines recommend an HCV genotype test before initiating antiviral medication [7].

We used existing noninvasive serum fibrosis markers to categorize persons by stage of liver disease [11]. AST-to-platelet ratio (APRI) was calculated as = 100*(AST/upper limit of AST)/platelet. Advanced fibrosis or cirrhosis was defined as APRI > 1.5. The FIB-4 score was calculated using the formula: $(\text{age} \times \text{AST})/(\text{platelet} \times \sqrt{(\text{ALT})})$, when all 3 test results and age were available. We only used tests that were within ±90 days of the first HCV test result for a given patient (ie, first NAT test for "currently infected," first RNA negative test for resolved/cured, first Ab negative test for never infected) to calculate APRI and FIB-4. Among persons with multiple liver function test results available within the 90-day window, we selected the one closest to the given HCV test result. After the initial description of the population using APRI, which produced similar disease staging classification for the population, we used FIB-4 in further analyses because it accounted for age as a factor. Advanced fibrosis or cirrhosis was defined as FIB-4 score >3.25; "moderate" fibrosis was FIB-4 of 1.45–3.25; and no or minimal fibrosis was <1.45 [10].

We calculated proportions of persons by infection status, stage of liver fibrosis, and cohort year of birth. We observed the proportion of persons with advanced fibrosis or cirrhosis over the 4-year period and used logistic regression models to evaluate factors associated with our proxy measures for the following 2 outcomes among persons who were NAT positive: being in care and being evaluated for treatment. All factors investigated were included in the initial multivariable model for each outcome (birth cohort, sex, payer, provider specialty, and region for both outcomes plus severity of fibrosis for being in

care) since all were found to be significant in univariate logistic models. Multivariable models were built using backward elimination; final models included variables that had a statistically significant association with the outcome plus birth cohort and sex, which were retained as possible confounders even if not significant. We conducted χ^2 testing of comparisons; however, because of the large number of observations, almost all results were statistically significant. Statements in results reflect an assessment of the magnitude of the effect. Trends in stage at diagnosis were tested using the Cochran-Armitage trend test. $P < .05$ was considered statistically significant and was used for retaining variables during multivariate model building.

RESULTS

Quest Diagnostics performed 9 785 976 HCV tests in the United States during the 4-year period. These tests represent 9 493 037 patient encounters and 5 651 742 unique persons (Figure 1). We classified 292 681 persons as currently infected, 59 965 as cured/resolved, and 5 017 307 persons as never infected. We excluded from analysis 135 663 persons with a positive Ab test only, 146 034 persons with an undetectable RNA result only, and 92 persons with HCV test name missing. Fifty-one percent of currently infected, 61% of cured/resolved, and 48% of never infected persons had age recorded and ALT, AST, and platelet results within 90 days of their first HCV test, allowing calculation of FIB-4. There were no differences in gender or age among infected persons with and without a calculable FIB-4 (data available upon request).

Burden of Liver Fibrosis

APRI results were consistent with FIB-4 results. Overall, 22% of persons with current infection, 11% of persons with resolved/cured infection, and 3% of persons never infected had advanced fibrosis or cirrhosis (APRI >1.5). As expected, the frequency of advanced fibrosis or cirrhosis based on FIB-4 (Table 1) was higher among infected than resolved/cured or never infected persons. And, among persons with current infection, those born before 1945 had the highest frequency of advanced fibrosis or cirrhosis.

The currently infected population overall was more frequently male, aged 40–59 years, and had tests paid for by private insurance (Table 2). With increasing level of fibrosis, the proportion of persons aged ≥60 years, the proportion with Medicare as the payer of their tests, and the proportion whose tests were ordered by gastroenterology specialists increased (Table 2).

Stage at First Diagnosis

Among persons newly diagnosed with HCV, the percentage with advanced fibrosis or cirrhosis was constant over the 4-year period (12% in 2010, 12% in 2011, 13% in 2012, and 12% in 2013; $P < .0001$). Similarly, among persons born during 1945–1965, the percentage with advanced fibrosis or cirrhosis was higher but constant in the 4-year period (27% in 2010, 26% in 2011, 28% in 2012, and 28% in 2013; $P < .0001$).

Currently Infected in Care

There were 158 363 persons, or 54% of all of those currently infected, who met our criteria for being in care; thus, 134 318, or 46%, were considered not to be in care. Specifically, within 6 months of the first positive RNA test, 18% had a follow-up NAT, 18% had the hepatic panel tests, and 8% had a test ordered by an infectious diseases or gastroenterology specialist. Compared with persons not in care, the following factors were more frequent among persons in care: birth year in 1945–1965 (70% vs

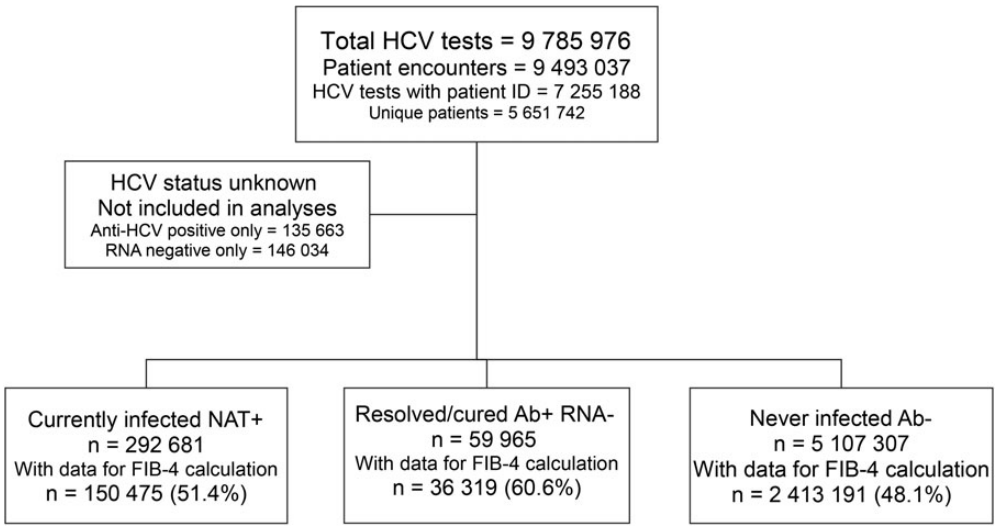

Figure 1. Definition of Hepatitis C Virus (HCV) Disease Status for Analysis, 2010–2013. Abbreviations: Ab, antibody; FIB-4, fibrosis-4; NAT, nucleic acid test.

Table 1. Burden of Liver Fibrosis Among All Persons Tested for Hepatitis C, by Infection Status and Birth Cohort, 2010–2013

Fibrosis Severity[a]	Currently Infected[b]		Resolved/Cured[c]		Never Infected[d]	
All[e]	n = 150 475	(%)	n = 36 319	(%)	n = 2 413 191	(%)
None/mild	59 933	*39.8*	26 669	*73.4*	1 950 621	*80.8*
Moderate	55 524	*36.9*	7818	*21.5*	388 218	*16.1*
Advanced /cirrhosis	35 018	*23.3*	1832	*5.0*	74 352	*3.1*
Persons born before 1945[e]						
None/mild	776	*7.4*	870	*28.5*	69 910	*30.2*
Moderate	4787	*45.9*	1710	*56.0*	129 066	*55.7*
Advanced/cirrhosis	4876	*46.7*	476	*15.6*	32 844	*14.2*
Persons born from 1945–1965[e]						
None/mild	30 474	*29.3*	13 017	*66.1*	619 693	*71.3*
Moderate	45 268	*43.5*	5477	*27.8*	215 470	*24.8*
Advanced/cirrhosis	28 271	*27.2*	1209	*6.1*	33 387	*3.8*
Persons born after 1965[e]						
None/mild	28 683	*79.6*	12 782	*94.3*	1 261 018	*96.1*
Moderate	5469	*15.2*	631	*4.7*	43 682	*3.3*
Advanced/cirrhosis	1871	*5.2*	147	*1.1*	8121	*0.6*

Abbreviation: FIB-4, fibrosis-4.

[a] Severity was defined based on FIB-4 scores: none/mild, < 1.45; moderate, 1.45–3.25; advanced/cirrhosis, > 3.25. FIB-4 score was calculated using the formula (age × aspartate aminotransferase [AST])/(platelet × $\sqrt{}$ alanine aminotransferase [ALT]). Fibrosis level based on availability of ALT/AST/platelet results within ±90-day window of first test of a given type for each category (ie, first RNA+/genotype test, first positive antibody and RNA negative test, or first negative antibody test, respectively).

[b] Currently infected included persons with either a positive hepatitis C virus (HCV)-RNA or a genotype result.

[c] Resolved/cured included persons with a positive HCV antibody result and a negative RNA result.

[d] Never infected included persons with a negative HCV antibody result.

[e] All χ^2 tests for comparisons were $P < .0001$.

65%), female (38% vs 34%), having private insurance (68% vs 50%), tested by a gastroenterologist (35% vs 2%), having advanced fibrosis or cirrhosis (21% vs 6%), and residence in the Mid- or South Atlantic regions (44% vs 36%). All factors were statistically significant in univariate analyses, and most were significant in the adjusted analysis. However, in univariate analyses, payer types of Medicaid, Medicare, and private insurance were the only factors with a crude prevalence ratio >2 for being in care. Severity of liver fibrosis was not strongly associated with being in care in either univariate or adjusted analysis (all odds ratios were 1.0–1.1).

Evaluated for Treatment

Among the 33 891 persons with detectable RNA and advanced fibrosis or cirrhosis, 50.6% had 1 or more genotype tests during the 4-year period, which was our indicator for evaluated for antiviral treatment. While the prevalence ratios from logistic regression analysis were frequently statistically significant, none of the factors we investigated had a prevalence ratio ≥2 for having a genotype test (Table 3). In univariate analyses, being born from 1945–1965 and being born after 1965 had some of the highest prevalence ratios for having a genotype test. Similarly, Medicaid as a payer; having tests ordered by a gastroenterology, infectious diseases specialist, or a physician assistant; and residence in select regions of the United States (ES Central, Pacific, South and Mid-Atlantic, and WS Central) had some of the highest prevalence ratios for being evaluated for treatment. In the adjusted model, the highest prevalence ratios were in selected regions of the United States (ES Central, Pacific, Mid and South Atlantic, and WS Central) and for persons tested by a gastroenterologist or infectious disease specialist, but none were ≥2.

DISCUSSION

We used commercial laboratory testing data to measure the burden of advanced fibrosis and cirrhosis in the US population. Results suggest that among the currently infected, 23% overall and 27% of those born from 1945–1965 had advanced fibrosis or cirrhosis. In contrast, only 3% of tested but uninfected persons had advanced fibrosis or cirrhosis. Persons with advanced fibrosis and cirrhosis are at highest risk of HCV-related complications and urgently require linkage to care. Laboratory testing data suggest that about half of infected persons with advanced fibrosis or cirrhosis were not evaluated for treatment. Given advances in treatment options [12], we expect the proportion of infected persons who are treated to increase over time. Additionally, many of the infected persons not in care were tested for HCV infection by a primary care physician. These findings indicate a need for training of primary care physicians in HCV screening, management, and referral of patients with advanced liver disease to specialists.

At the population level, measurements of advanced HCV-related liver disease are important to evaluate the impact of HCV screening recommendations and to support healthcare resources planning for persons infected. Applying the overall 23%

Table 2. Characteristics of Persons Currently Infected With Hepatitis C Virus, by Stage of Liver Fibrosis, 2010–2013[a]

	Fibrosis Severity							
	None/Mild		Moderate		Advanced/Cirrhosis			
	(FIB-4 < 1.45)		(FIB-4 1.45–3.25)		(FIB-4 > 3.25)		All Fibrosis Levels	
Characteristic	Number	%	Number	%	Number	%	Number	%
Total	59 933		55 524		35 018		150 475	
Gender								
Female	23 751	39.6	19 537	35.2	12 710	36.3	55 998	37.2
Male	36 081	60.2	35 876	64.6	22 230	63.5	94 187	62.6
Missing/unknown	101	0.2	111	0.2	78	0.2	290	0.2
Age group (y)								
≤19	820	1.4	17	0.0	5	0.0	842	0.6
20–39	19 523	32.6	2054	3.7	536	1.5	22 113	14.7
40–59	35 131	58.6	37 108	66.8	21 593	61.7	93 832	62.4
≥60	4459	7.4	16 345	29.4	12 884	36.8	33 688	22.4
Missing/unknown	0	0.0	0	0.0	0	0.0	0	0.0
Payer								
Client bill	1071	1.8	837	1.5	630	1.8	2538	1.7
Patient	508	0.8	441	0.8	281	0.8	1230	0.8
Medicare	4707	7.9	7871	14.2	6318	18.0	18 896	12.6
Medicaid	7614	12.7	5601	10.1	3785	10.8	17 000	11.3
Private insurance	45 006	75.1	39 777	71.6	23 272	66.5	108 055	71.8
Missing/unknown	1027	1.7	997	1.8	732	2.1	2756	1.8
Provider specialty								
Gastroenterology	11 593	19.3	13 701	24.7	10 623	30.3	35 917	23.9
Infectious disease	1627	2.7	1638	3.0	881	2.5	4146	2.8
Physician assistant	2754	4.6	2164	3.9	1306	3.7	6224	4.1
Primary care	21 653	36.1	19 789	35.6	11 208	32.0	52 650	35.0
Registered nurse	2800	4.7	2113	3.8	1286	3.7	6199	4.1
Other[b]	4913	8.2	3855	6.9	2516	7.2	11 284	7.5
Missing/unknown	14 593	24.3	12 264	22.1	7198	20.6	34 055	22.6
US region								
East North Central	1856	3.1	1960	3.5	1313	3.7	5129	3.4
East South Central	1307	2.2	916	1.6	560	1.6	2783	1.8
Mid-Atlantic	13 179	22.0	13 800	24.9	8061	23.0	35 040	23.3
Mountain	1398	2.3	1411	2.5	1004	2.9	3813	2.5
New England	3573	6.0	2497	4.5	1370	3.9	7440	4.9
Pacific	21 258	35.5	16 031	28.9	9754	27.9	47 043	31.3
South Atlantic	10 160	17.0	11 175	20.1	7149	20.4	28 484	18.9
West North Central	1205	2.0	1065	1.9	585	1.7	2855	1.9
West South Central	4877	8.1	5596	10.1	4382	12.5	14 855	9.9
Missing/unknown	1120	1.9	1073	1.9	840	2.4	3033	2.0

All χ^2 tests for comparisons were $P < .0001$.

Abbreviation: FIB-4, fibrosis-4.

[a] FIB-4 was calculated using the formula (age x AST)/(Platelet x $\sqrt{}$ (ALT)).

[b] Includes all other specialties with less than 5% frequency.

with advanced liver disease to the estimated 3.5 million infected persons in the population [13] suggests there may be more than 800 000 persons in the United States with urgent need of medical management [14]. Clearly, multiple barriers to treatment exist in the United States. Cost and restricted access to care may be the greatest barriers to treatment [15], despite evidence that treating infected persons early is cost effective [16]. An insufficient number of trained providers may be another barrier to managing this population's healthcare [17]. Infectious diseases specialists might improve identification of asymptomatic persons by integrating HCV screening, evaluation, and treatment with other medical services, as recommended in the American Association for the Study of Liver Disease and the Infectious Disease Society of American guidelines [7].

Our finding of the frequency of advanced liver disease falls within the values from studies of different populations. Backus

Table 3. Factors Associated With Being Evaluated for Treatment Among Persons With Advanced Fibrosis or Cirrhosis and Hepatitis C Virus Infection (n = 33 891)

Characteristic	Number and % With RNA Positive and Genotype n = 17 163		Number and % With RNA Positive Without Genotype n = 16 728		Crude PR (95% CI)	Adjusted PR (95% CI)
Birth cohort						
Born <1945	1955	*11.4*	2770	*16.6*	Ref	Ref
Born 1945–1965	14 176	*82.6*	13 172	*78.7*	1.25 (1.21–1.30)***	1.20 (1.16–1.24)***
Born >1965	1032	*6.0*	786	*4.7*	1.37 (1.30–1.45)***	1.32 (1.25–1.39)***
Missing/unknown	0	*0.0*	0	*0.0*	. . .	. . .
Sex						
Male	11 010	*64.1*	10 490	*62.7*	1.03 (1.01–1.05)**	1.01 (0.99–1.03)
Female	6126	*35.7*	6190	*37.0*	Ref	Ref
Missing/unknown	27	*0.2*	48	*0.3*	0.72 (0.53–0.98)*	0.68 (0.49–0.93)**
Payer						
Client bill	276	*1.6*	273	*1.6*	1.12 (1.02–1.22)*	1.20 (1.10–1.30)***
Patient	136	*0.8*	125	*0.8*	1.16 (1.03–1.31)*	1.13 (1.00–1.27)
Medicare	2750	*16.0*	3365	*20.1*	Ref	Ref
Medicaid	1980	*11.5*	1650	*9.9*	1.21 (1.16–1.26)***	1.17 (1.12–1.21)***
Private insurance	11 730	*68.4*	10 928	*65.3*	1.15 (1.12–1.19)***	1.09 (1.06–1.13)***
Missing/unknown	291	*1.7*	387	*2.3*	0.95 (0.87–1.05)	0.99 (0.91–1.08)
Provider specialty						
Gastroenterology	5935	*34.6*	4330	*25.9*	1.31 (1.25–1.38)***	1.32 (1.26–1.38)***
Infectious disease	480	*2.8*	382	*2.3*	1.27 (1.18–1.36)***	1.27 (1.18–1.36)***
Physician assistant	677	*3.9*	586	*3.5*	1.22 (1.14–1.30)***	1.20 (1.12–1.29)***
Primary care	5125	*29.9*	5741	*34.3*	1.07 (1.02–1.13)**	1.07 (1.02–1.13)**
Registered nurse	588	*3.4*	650	*3.9*	1.08 (1.00–1.16)*	1.07(0.99–1.15)
Other[a]	1082	*6.3*	1378	*8.2*	Ref	Ref
Missing/unknown	3276	*19.1*	3661	*21.9*	1.07 (1.02–1.13)**	1.07 (1.01–1.12)*
CDC region						
East North Central	499	*2.9*	763	*4.6*	1.04 (0.94–1.16)	1.00 (0.90–1.12)
East South Central	322	*1.9*	226	*1.4*	1.55 (1.39–1.73)***	1.47 (1.33–1.64)***
Mid-Atlantic	4042	*23.6*	3887	*23.2*	1.35 (1.24–1.46)***	1.34 (1.24–1.46)***
Mountain	360	*2.1*	590	*3.5*	Ref	Ref
New England	635	*3.7*	705	*4.2*	1.25 (1.13–1.38)***	1.18 (1.07–1.30)**
Pacific	4893	*28.4*	4419	*26.4*	1.39 (1.28–1.51)***	1.36 (1.25–1.47)***
South Atlantic	3600	*21.0*	3374	*20.2*	1.36 (1.25–1.48)***	1.31 (1.21–1.42)***
West North Central	232	*1.4*	340	*2.0*	1.07 (0.94–1.22)	1.03 (0.90–1.17)
West South Central	2282	*13.3*	1986	*11.9*	1.41 (1.29–1.54)***	1.31 (1.21–1.43)***
Missing/Unknown	298	*1.7*	438	*2.6*	1.07 (0.95–1.20)	1.06 (0.94–1.20)

FIB-4 score was calculated using the formula (age × aspartate aminotransferase)/(platelet ×$\sqrt{}$ alanine aminotransferase) and advanced fibrosis or cirrhosis was FIB-4 > 3.25.

Abbreviations: CDC, Centers for Disease Control and Prevention; CI, confidence interval; PR, prevalence ratio; Ref, reference category.

[a] Includes all other specialties, which accounted for <5% of the total.

*$P < .05$ for t test of model coefficient.

**$P < .01$ for t test of model coefficient.

***$P < .001$ for t test of model coefficient.

and colleagues found that 13% of HCV-infected US veterans had cirrhosis alone [18]. Kanwal analyzed claims data from a large insurer and found that 18% of HCV-infected persons had cirrhosis alone [19]. Udompap and colleagues analyzed data sampled from the civilian, household population and found that 16% had FIB-4 values >3.25 [20]. Finally, in a cohort of more than 10 000 persons with HCV infection in care, Holmberg found 38% had advanced fibrosis (Metavir F3) or cirrhosis (Metavir F4) [11]. Our finding that about half of those with current infection had been evaluated for treatment is only slightly lower than the observed 54% of persons in care who had treatment prescribed [8].

We found a large proportion of infected persons (46%) with no laboratory evidence of follow-up after diagnosis. Furthermore, our finding that severity of HCV-related liver fibrosis was not strongly associated with being in care is of concern. One half of persons not in care had private insurance, and 32% were tested by a primary care provider. Currently, several reflex tests are available, including anti-HCV with reflex to RNA PCR and PCR with reflex to genotype; use of these tests could

reduce these gaps. Successful treatment of HCV infection reduces the risk of complications for the individual and reduces potential transmission to others. However, regardless of whether infected persons can be treated, they should be monitored and counseled to prevent complications related to alcohol use or medication toxicity.

Region and specialist were associated with being assessed for treatment among infected persons with advanced liver disease. Most of the infected persons in our study population had private insurance or publicly funded care so that variability in treatment coverage in this group warrants further investigation.

Limitations of our study include, first, that data from laboratory testing reflect persons tested, regardless of reason for testing and therefore do not include persons who were never screened or those for whom a patient ID could not be assigned. Many may have had a clinical indication, but we are unable to determine how many. Furthermore, we included data from 1 US laboratory, and these tests might not represent all persons tested nationally or those with select testing performed elsewhere; however, this source provides a large sampling of the total number of patients tested and infected in the United States. We used APRI and FIB-4, which are not the clinical gold standard, but are gaining acceptance as epidemiologic tools. We developed laboratory-based definitions for events that would be more accurately measured using direct chart review (ie, in care, evaluated for treatment). In addition, there are limitations intrinsic to every test (ie, sensitivity/specificity of the antibody, PCR, error in ALT, AST and platelets, reliability). Misclassification of cases by infection status could occur if persons were tested for HCV Ab during the 4-year period but did not have an RNA or genotype test during the same period. Finally, we might underestimate the frequency of being in care or assessed for treatment if persons were tested for antibodies in a Quest laboratory but followed up with a NAT at a different laboratory.

Early identification of the estimated 3.5 million US persons with chronic HCV infection and the estimated 800 000 with advanced fibrosis or cirrhosis is critical for prevention of forecasted premature deaths and other complications by 2030 [21]. The findings described in this study support the CDC and USPSTF recommendations for HCV testing and appropriate referral of persons born from 1945–1965 as well as efforts to reduce barriers to care among those who are HCV infected.

Notes

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Potential conflicts of interest. A. Y. was an employee of Quest Diagnostics. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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