Hepatitis C Care Cascade Among Persons Born 1945-1965: 3 Medical Centers

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ABSTRACT

OBJECTIVES: Effective screening, diagnosis, and treatment are needed to reduce chronic hepatitis C virus (HCV) infection–associated morbidity and mortality. In order to successfully increase HCV treatment, it is necessary to identify and understand gaps in linkage of antibody-positive patients with newly identified HCV to subsequent HCV RNA testing, clinical evaluation, and treatment.

STUDY DESIGN: To estimate attainment of HCV care cascade steps among antibody-positive patients with newly identified HCV, we conducted chart reviews of patients with a new positive HCV antibody test at 3 academic medical centers participating in the Birth-Cohort Evaluation to Advance Screening and Testing of Hepatitis C (BEST-C) study.

METHODS: We tracked receipt of RNA testing, clinical evaluation, treatment initiation, and treatment completion among individuals born between 1945 and 1965 who were newly diagnosed as HCV antibody–positive between December 2012 and October 2015 at 3 BEST-C centers, predominantly from the participating medical centers' primary care practices and emergency departments.

RESULTS: Of the 130 HCV-seropositive individuals identified, 118 (91%) had an RNA or genotype test, 75 (58%) were RNA-positive, 73 (56%) were linked to care, 22 (17% overall; 29% among RNA-positive) started treatment, and 21 (16%; 28% among RNA-positive) completed treatment.

CONCLUSIONS: This analysis showed that although linkage to care was largely successful in the target birth cohort, the largest gap in the HCV care cascade was seen in initiating treatment. Greater emphasis on linking patients to clinical evaluation and treatment is necessary in order to achieve the public health benefits promised by birth-cohort testing.

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Chronic hepatitis C virus (HCV) infection is undiagnosed in 50% of those infected.[1,2] Hoping to increase HCV case identification, in 2012 the CDC recommended a 1-time HCV antibody test for persons born between 1945 and 1965, the birth cohort that contains approximately 80% of individuals with HCV antibodies.[1,2] In 2013, the US Preventive Services Task Force recommended testing for the same group.[3,4] The Birth-Cohort Evaluation to Advance Screening and Testing of Hepatitis C (BEST-C) experimental evaluation demonstrated that birth-cohort testing interventions increase HCV case identification at a reasonable cost compared with that of other testing strategies.[5,6] However, observational studies have identified persistent gaps in the subsequent cascade of treatment services that are needed to achieve a virologic cure: confirmatory testing (HCV RNA), clinical evaluation, and antiviral treatment.[7-13] One meta-analysis estimated that only 50% of the 3.5 million Americans living with chronic HCV had been tested for HCV antibodies, 27% received confirmatory RNA testing, 16% had been treated, and 9% achieved sustained virologic response (SVR), defined as undetectable viral load at 12 weeks following end of treatment (EOT).[7] A second study found that only 29% of high-risk primary care patients who tested positive for antibodies were evaluated for treatment, less than 4% started treatment, and only 2% achieved SVR.[12] The end of the BEST-C experiment, which compared testing interventions to promote birth-cohort testing with standard-of-care HCV antibody testing at 3 academic medical centers, created the opportunity to assess the rates of linkage to care in primary care and emergency departments affiliated with these centers.

Studying attainment of "care cascade" steps among patients identified at BEST-C medical centers is instructive in understanding the possible impact of future HCV testing interventions, especially in managed care settings. These settings have a long history of proactive health promotion activities, such as patient education and care coordination, that may be effective in addressing gaps in care experienced by patients with newly diagnosed HCV.

In this paper, we used electronic health records (EHRs) to examine HCV care and treatment among antibody-positive patients identified at BEST-C study centers during the study period.

TAKEAWAY POINTS

In this analysis of patients with newly diagnosed hepatitis C between December 2012 and October 2015, linkage to care was largely successful in the 1945-1965 birth cohort, but treatment initiation remained low.

- The largest gap in the hepatitis C virus care cascade was initiating treatment.
- Greater emphasis on linking patients to clinical evaluation and treatment is needed.
- Managed care is well poised to address barriers to initiating treatment.

METHODS

Study Population

Patients included in this analysis were those who tested HCV antibody–positive during the BEST-C study period (December 2012-October 2015) at any of the 3 participating healthcare systems ("centers") as an enrolled participant of the BEST-C study or as an unenrolled patient who was identified during the same study period. All evaluated patients were born between 1945 and 1965 and had no previous record of being tested for HCV in the EHR.[5,6,14] Information about BEST-C has previously been described.[5,14] This study received institutional review board approval from the University of Alabama, Henry Ford Health System, Mount Sinai Hospital, and NORC at the University of Chicago.

Measures

We defined the care cascade as consisting of the following 7 consecutive steps: (1) a positive HCV antibody test; (2) a confirmatory test, defined as a qualitative or quantitative RNA or HCV genotype test; (3) receipt of a positive RNA result or genotype; (4) clinical evaluation (either concurrently with receipt of confirmatory RNA test result or at a subsequent encounter), defined as a visit with a specialty provider (hepatologist, gastroenterologist, or infectious disease specialist) or other HCV treatment provider (primary care provider trained to treat HCV); (5) initiation of antiviral therapy as indicated in the EHR; (6) treatment completion as indicated in the EHR by a provider; and (7) EOT virologic response, defined as an undetectable viral load at treatment completion (within 2 weeks of the end of intended course of treatment). Only 1 patient received a liver biopsy. Sustained viral load 12 weeks following EOT was not available at the end of the study; we therefore do not report on this step or the final outcome of the cascade.

Data Collection and Analysis

Using a standardized abstraction form, center coordinators collected data from the EHR of each patient from the date of his or her first positive HCV antibody test from December 1, 2012, through October 31, 2015. Coordinators identified relevant laboratory orders, encounters, and pharmacy records associated with each step of the HCV care cascade and sent deidentified person-level data to the coordinating center (NORC at the University of Chicago). Because of small sample sizes, the care cascade steps were not stratified by center. Data were analyzed using Microsoft Excel 2013 and SAS version 9.4 (SAS Institute, Inc; Cary, North Carolina).

We calculated the proportion of persons who progressed along the HCV care cascade as the number of individuals who completed each step (numerator) divided by the number of individuals with a positive HCV antibody test (denominator). We also calculated the proportion of individuals completing each step (numerator) divided by the number of individuals completing the previous step. Due to problems extracting pharmacy information from their EHR systems, 1 center did not report treatment of any patients. Therefore, we also calculated the care cascade and the percent of patients initiating treatment using data from the 2 centers with accessible treatment records ("treating centers").

We estimated patients' liver disease stage at initial evaluation using their first recorded AST (aspartate aminotransferase) to Platelet Ratio Index (APRI) scores. Disease stage was categorized using the following values: 0.0 to 0.54, 0.55 to less than 1.0, 1.0 to less than 2.0, and 2.0 or greater (ranging from no liver disease at 0.0 to advanced fibrosis/cirrhosis).[15] Using χ^2 tests and Fisher's exact tests and data from the 2 treating centers, we compared differences in treatment initiation by sex, race, birth year, insurance type, APRI score categories, and HCV genotype. A P value $\leq .05$ was considered statistically significant.

RESULTS

We identified a total of 130 individuals born between 1945 and 1965 who were newly identified with an HCV-seropositive test result (**Table 1**). Among the newly identified HCV-seropositive patients, 36% were born between 1950 and 1954, 56% were black, and the majority were insured by Medicare alone (42%) or private insurance (36%). Ninety-one of the 130 antibody-positive patients participated in the BEST-C study (83 intervention arm, 8 standard-of-care testing).

Using data from all 3 centers, of the 130 HCV-seropositive patients identified, 118 (91%) received a confirmatory RNA and/or genotype test, 75 (58%) had a positive RNA or genotype test result, 73 (56%) received a clinical evaluation, 22 (17% at all centers; 26% [22/84] at the 2 treating centers) initiated treatment, and 21 (16% at all centers; 25% [21/84] at the 2 treating centers) were known to have completed treatment (**Figure 1**). All treated patients came from the 2 treating centers. When considering the treatment cascade sequence of only the 75 patients with a positive RNA or genotype result, 97% received a clinical evaluation, 29% at all centers (43% at the 2 treating centers) initiated treatment, and 28% at all centers (41% at the 2 treating centers) were known to have completed treatment by the end of the study period. When considering only the patients identified at the 2 treating centers, 26% (22/84) of antibody-positive patients, 43% (22/51) of RNA-positive patients, and 45% (22/49) of patients receiving a clinical evaluation initiated treatment (**Figure 2**). At the 2 treating centers, treatment initiation

for RNA-positive patients did not differ by sex, race, birth year, insurance type, or HCV genotype (Table 2).

Centers reported treatment or a reason for nontreatment for 73 (97%) of 75 RNA-positive patients. Twenty-two (29%) were treated; deferral of treatment was responsible for nearly half of the patients not treated, including 19 (25%) who chose to defer treatment for unknown reasons and 15 (20%) who were not treated due to physician assessment of prioritization for care (eg, in 1 case, treatment for brain cancer was prioritized over HCV treatment); and 17 patients were lost to follow-up for unknown reasons. Of the patients who initiated treatment, 1 (5%) did not complete treatment due to nonadherence (eg, not taking medication). Eleven patients were treated solely with direct-acting antivirals (DAAs), 9 (41%) with ledipasvir/sofosbuvir, and 2 (9%) with ombitasvir, paritaprevir, and ritonavir tablets plus dasabuvir (Table 3). RNA viral load test results were available for 14 of 21 (67%) patients who completed treatment; all 14 patients achieved an undetectable viral load at EOT.

APRI scores were available for 39 of the 75 HCV RNA–positive patients, of whom 24 (62%) had an APRI score of less than 0.55, 10 (26%) had an APRI score of 0.55 to less than 1.0, 2 (5%) had an APRI score of 1.0 to less than 2.0, and 3 (8%) had an APRI score of 2.0 or greater (Table 2; lower APRI scores indicate less advanced disease progression and the higher the value [>2.0], the greater the likelihood of cirrhosis). Rates of treatment initiation did not significantly differ by APRI score category at the 2 treating centers ($P = .30$) (Table 2). Of the 22 patients who initiated treatment, APRI scores were available for 21 (95%). Of these patients, 15 (71%) had an APRI score of less than 0.55, 4 (19%) had an APRI score of 0.55 to less than 1.0, and 2 (10%) had an APRI score of 2.0 or greater. Two patients with a known APRI score of 1.0 to less than 2.0 (suggesting advanced fibrosis) were not treated; 1 patient had a treatment contraindication (currently using alcohol in the period prior to interferon-free treatments) and 1 patient deferred treatment. The patient with a known APRI score of 2.0 or greater who was not treated was lost to follow-up (not shown).

TABLE 1. Characteristics of Hepatitis C Antibody–Positive Patients Born 1945-1965 (N = 130): 3 Medical Centers, December 2012-October 2015

Characteristic	n	%[a]
Sex		
Female	65	50.0
Male	65	50.0
Birth year		
<1950	28	21.5
1950-1954	47	36.2
1955-1959	38	29.2
≥1960	17	13.1
Race		
White	29	22.3
Black	73	56.2
Other/unknown	28	21.5
Primary insurance		
No insurance	4	3.1
Medicare	54	41.5
Medicaid	21	16.2
Dual (Medicaid and Medicare)	1	0.8
Private	47	36.2
Unknown	3	2.3
Center		
1	64	49.2
2	20	15.4
3	46	35.4

[a]Some columns may not add up to 100% due to rounding.

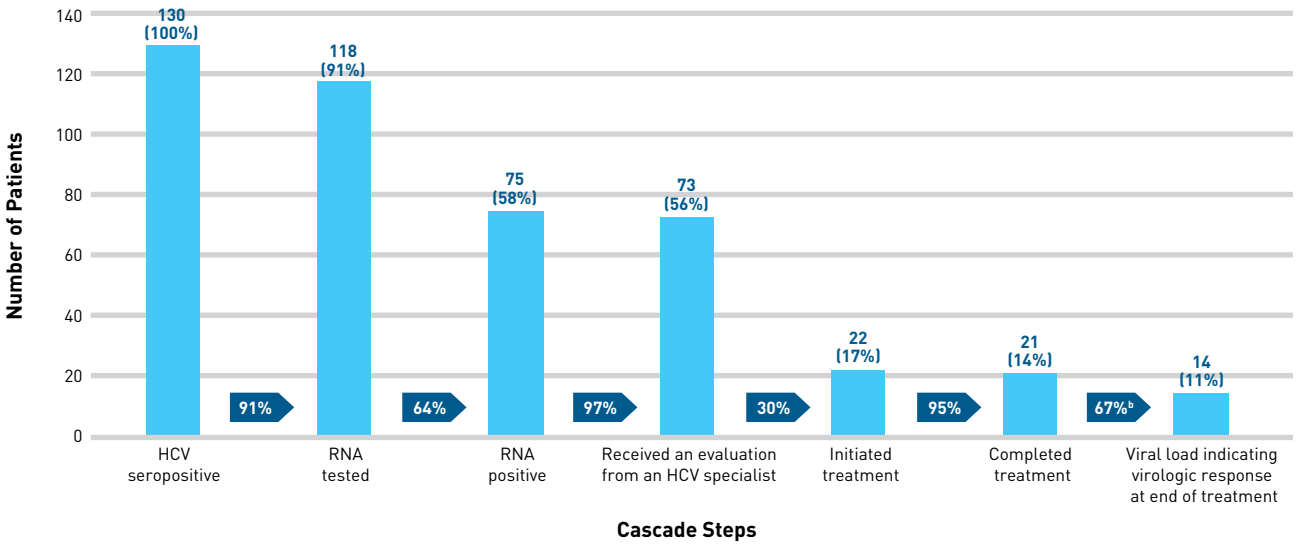
DISCUSSION

Our research followed 130 newly identified HCV-seropositive patients to assess their progression through the HCV care cascade in 3 US health centers. We found that successful HCV case identification did not automatically lead to treatment initiation. At the 2 treating centers, only 45% of patients who had a clinical evaluation initiated treatment; however, treatment initiation rates following an intervention were higher than those observed in many other settings. Centers were largely successful in ensuring confirmatory RNA testing for patients who tested seropositive (91%) and in linking RNA-positive patients to clinical evaluation for treatment (97%). Ideally, all seropositive patients should receive confirmatory RNA testing; additionally, same-day HCV RNA testing and HCV RNA reflex testing, in which the same blood sample used for HCV antibody testing is used for the RNA test, may help address persistent RNA testing gaps.[16,17]

We also observed that a lower proportion of patients who received RNA testing were RNA-positive (64%) than observed in national estimates (75%),[2] possibly because these national estimates arose from a different HCV testing protocol. Further, a positive HCV antibody test and an RNA-negative test can occur when there is natural clearance of the HCV virus, antibody cross-reactivity, or comorbid immune disorders.[18,19] Due to lack of data, we were not able to determine if any of these factors led to a greater than expected number of negative RNA results following positive HCV antibody results. Another potential explanation for the lower than expected percentage of RNA-positive results is that chronic HCV infection is associated with an increased mortality risk. Therefore, it is likely that a larger proportion of people who were RNA-positive had already died, leaving a comparatively higher proportion of those who had spontaneously cleared HCV (ie, survival bias).

In our study, a high proportion of patients who had chronic HCV were clinically evaluated (97% of RNA-positive patients and 56% of antibody-positive). This proportion is higher than the 29% of antibody-positive patients reported in a recent study examining a cohort of persons born between 1945 and 1965 conducted at 3 large

FIGURE 1. Care Cascade Among HCV Antibody–Positive Patients Born From 1945-1965 at 3 Academic Medical Centers, December 2012-October 2015[a]

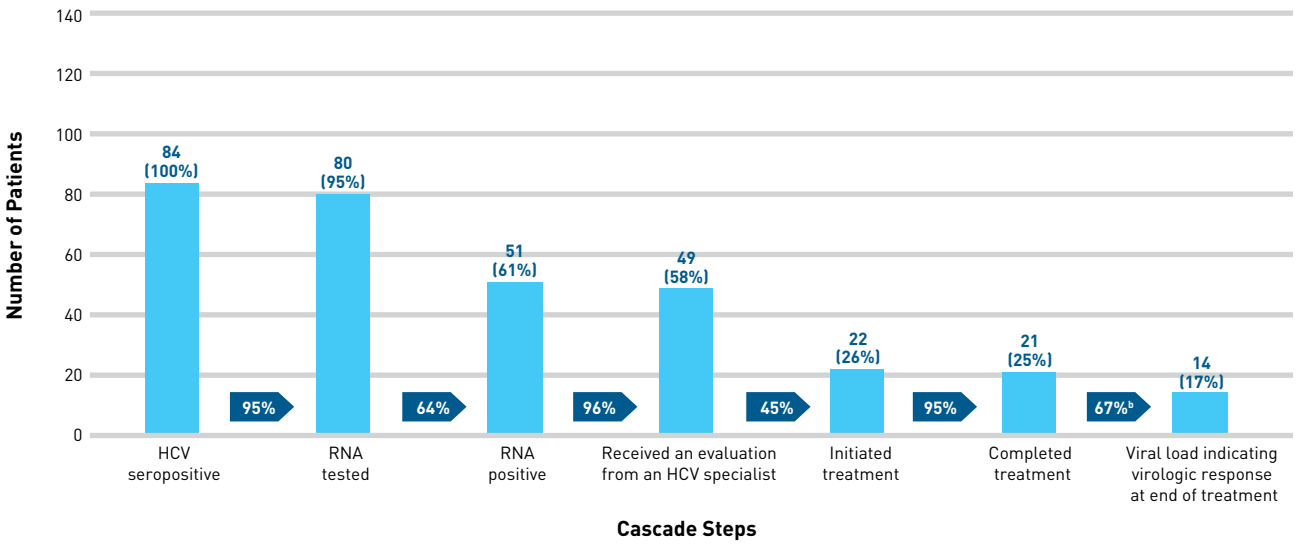


HCV indicates hepatitis C virus.

[a]The proportions of patients in each step of the HCV care cascade from the patients who were HCV antibody–positive are shown in parentheses above each bar. The proportions of patients in each step of the HCV care cascade from the patients in the preceding step are shown in the arrows between each bar.

[b]Only 14 patients completing treatment had viral load data available and all 14 patients showed a virologic response at the end of treatment.

FIGURE 2. Care Cascade Among HCV Antibody–Positive Patients Born From 1945-1965 at 2 Treating Academic Medical Centers, December 2012-October 2015[a]



HCV indicates hepatitis C virus.

[a]The proportions of patients in each step of the HCV care cascade from the patients who were HCV antibody–positive are shown in parentheses above each bar. The proportions of patients in each step of the HCV care cascade from the patients in the preceding step are shown in the arrows between each bar.

[b]Only 14 patients completing treatment had viral load data available and all 14 patients showed a virologic response at the end of treatment.

TABLE 2. Treatment Initiation and Characteristics of Hepatitis C RNA–Positive Patients Born 1945-1965 (n = 51): 2 Medical Centers, December 2012-October 2015

Characteristic	n	% Initiating Treatment[a] (n = 22)	% Not Initiating Treatment[a] (n = 29)	χ^2 or Fisher's Test Statistic	*P*
Sex				1.4	.24
Female	30	50.0	50.0		
Male	21	33.3	66.7		
Birth year				<0.01	.41
<1950	11	54.6	45.4		
1950-1954	18	27.8	72.2		
1955-1959	17	47.1	52.9		
≥1960	5	60.0	40.0		
Race				0.72	.70
White	15	46.7	53.3		
Black	22	36.4	63.6		
Other/unknown	12	50.0	50.0		
Primary insurance				0.01	.59
No insurance	3	0.0	100.0		
Medicare	19	47.3	52.6		
Medicaid	13	46.2	53.8		
Dual (Medicaid and Medicare)	0	0.0	0.0		
Private	16	43.8	56.3		
Unknown	0	0.0	0.0		
APRI score				0.01	.30
<0.55	24	62.5	37.5		
0.55-<1.0	10	40.0	60.0		
1.0-<2.0	2	0.0	100.0		
≥2.0	3	66.7	33.3		
Genotype				0.07	.13
1	33	45.5	54.6		
2	9	78.8	22.2		

APRI indicates AST (aspartate aminotransferase) to Platelet Ratio Index.
[a]Some rows may not add up to 100% due to rounding.

TABLE 3. Treatment Regimen and Virologic Response for Hepatitis C RNA–Positive Patients Born 1945-1965 (n = 75): 3 Medical Centers, December 2012-October 2015

Treatment Status	n	%[a]
RNA-positive patients	75	100
Not treated/unknown if treated due to EHR problems	53	71
Reason for not initiating treatment		
Deferred treatment, patient decision	19	25
Did not return/lost to follow-up	17	23
Deferred treatment, physician decision	15	20
No reason reported	2	3
Initiated treatment	22	29
Type of treatment		
Ledipasvir/sofosbuvir	9	41
Sofosbuvir, ribavirin, and pegylated interferon	6	27
Sofosbuvir and ribavirin	5	23
Ombitasvir, paritaprevir, and ritonavir tablets plus dasabuvir	2	9
Discontinued treatment	1	5
Completed treatment	21	95
Viral load indicating virologic response at end of treatment	14	67
Viral load results not available at end of treatment	7	23

EHR indicates electronic health record.
[a]Some rows may not add up to 100% due to rounding.

urban primary care clinics affiliated with a teaching hospital in the Bronx, New York.[12] Unfortunately, despite high rates of clinical evaluation in our study, the overall proportion of newly identified antibody-positive patients who initiated treatment (17%) was similar to previously reported findings (7%-21% treated), although this rate was higher (26%) in the 2 treating centers.[9,11-13,20]

Several important factors may have contributed to the low rate of treatment initiation we observed. First, due to the timing of the study, many patients may have deferred treatment until new, all-oral, interferon-free, single-tablet regimens were approved for use beginning in October 2014.[21,22] These regimens have greater effectiveness, with fewer adverse effects and a shorter treatment duration, than the interferon-based treatment available to most patients during 2013.[23] Even after the approval of interferon-free treatment, lack of insurance coverage for these treatments may have led to the low percentage of patients initiating treatment.[24,25] Managed care is well situated to address concerns about coverage for interferon-free HCV treatments. Second, a large proportion of HCV-infected patients in this study (65.4%) were born between 1950 and 1959, thus either just entering eligibility for Medicare or not yet eligible for Medicare, which may have limited insurance coverage for treatment.

Another potential barrier to receiving HCV treatment may be current alcohol or illicit drug use. Certain state Medicaid programs require abstinence from illicit drug use and alcohol in order for a patient to be eligible for reimbursement for DAA HCV therapy.[17,26,27] The center not reporting treatment of any patients had Medicaid restrictions that required patients to abstain from drug and alcohol use and abuse and also required fibrosis scores indicating advanced disease before treatment with interferon-free therapies[25]; patients with mild disease were monitored. Of the 2 treating centers, 1 center did not have requirements to abstain from drugs and alcohol but did have restrictions that required severe fibrosis before DAA treatment access.[25] The state requirements of the other center were unknown.[25]

Medicaid restrictions may result in providers regarding active substance use as a barrier to HCV therapy.[26] A recent study found that although type of insurance was not associated with HCV screening, HCV treatment rates were significantly lower for HCV-positive Medicaid patients than for HCV-positive Medicare and commercially

insured patients.[28] Although 20% of RNA-positive patients in our study were not treated due to physician prioritization for care, such as a competing comorbidity, most of these patients also reported current alcohol use. It is not possible to discern how alcohol use factored into decisions related to treatment.[29]

Treatment initiation was the largest and most important gap identified by our study. Treatment can curb morbidity and mortality due to advanced liver fibrosis or cirrhosis by preserving remaining liver function and reducing risk for liver cancer and hepatic decompensation.[30] Interventional efforts may increase rates of treatment initiation. Seventeen patients were lost to follow-up after testing RNA-positive for unknown reasons. Some of these patients may have benefited from interventions to recontact them in an attempt to schedule and provide HCV care and treatment where appropriate. Other individuals may have deferred treatment due to a lack of insurance coverage. Efforts to assure coverage of DAAs by all health insurers and lower the co-pays and deductibles associated with that treatment could reduce an important barrier to treatment for some patients.[31,32] Given the availability of well-tolerated all-oral treatments, virtually all patients are able to benefit from treatment, which reduces HCV-associated morbidity and mortality.

There is an ongoing need for evidence of how patients progress through the HCV care cascade within different health systems at different time points to understand where there are gaps in the cascade. This need will continue until the problem of access to HCV treatment can be resolved. This study demonstrates that when focused interventions are put in place to increase HCV testing, there is an improvement in the completion of specific steps of the care cascade, including RNA testing and linkage and referral to HCV care. However, in our study, treatment initiation remained low, so other interventions may be needed to overcome barriers to treatment initiation. Researchers of future studies may wish to examine barriers to treatment initiation among patients with HCV who completed clinical evaluation, how treatment access is affected by different payment models,[33] and how specific interventions may decrease barriers to treatment initiation.

Limitations

This study is limited by at least the following factors. First, the number of chronic HCV infections identified in this cohort was small and represents a convenience sample drawn from 3 health centers in the United States, which limits the generalizability of the analysis. Cascade data were not stratified by center because of the small sample size. Patients identified by the BEST-C intervention may have received clinical evaluations at a higher rate due to higher vigilance among the study investigators, although similarly high vigilance might be expected following any organized interventional effort. Second, follow-up time for included patients varied based on their HCV-positive test date. Patients testing HCV-seropositive later in the study period would have less follow-up time than patients testing HCV-seropositive earlier in the study period (although all patients were observed for at least 1 year). Third, APRI scores at diagnosis and at the time of treatment were unavailable for many patients, which limited the power of our study to detect differences in APRI scores for patients who initiated treatment compared with patients who did not. Fourth, 1 center was not able to obtain data on patient treatment from its EHR system. However, this did not limit the clinical evaluation of HCV RNA–positive patients and the majority of patients were evaluated at this center. Many restrictions on coverage for DAAs that were common in 2014-2015 were subsequently lifted or relaxed in 2016-2017. Patients included in our data may have been treated after data collection ended. Fifth, only EOT viral load data, as opposed to SVR data, were available for patients who completed treatment. Finally, at any given step of the care cascade, patients could have received care at a different center, which could lead to an underestimate of treatment rates and treatment outcomes.

CONCLUSIONS

Although the BEST-C study was designed to test BEST-C testing interventions to increase HCV testing, it also offered the opportunity to assess linkage to care in real-world settings; these observational data demonstrated that although linkage to care was highly successful (97% evaluated by an HCV specialist), initiation of treatment continues to be a challenge among persons born between 1945 and 1965. Reflex testing, interventions to reduce loss to follow-up, and minimizing restrictions on treatment imposed by third-party payers are potential ways to help overcome barriers to HCV RNA testing and treatment initiation for patients with HCV infection. Managed care is well positioned to help address these barriers to treatment initiation. ■

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Author Disclosures: Dr Brady is currently employed by GlaxoSmithKline, but this work is unrelated to her work there and was conducted prior to her employment. Dr Nerenz is employed by an integrated healthcare system that provides screening and treatment services for hepatitis C and receives payments and incurs costs for those services. Dr Brown is a member of advisory boards discussing hepatitis C for Merck, Gilead, and AbbVie; has received grants from Merck, Gilead, AbbVie, Novartis, and Allergan; and has completed multicenter studies on hepatitis C with funding from Merck, Gilead, and AbbVie (all grant funding was to institution). Dr Rein receives grants from Gilead and Merck. The remaining authors report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

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