ABSTRACT

OBJECTIVES: To characterize hepatitis C testing in Massachusetts and guide stakeholders in addressing the needs of people living with hepatitis C.

METHODS: All persons with a positive laboratory report for anti-hepatitis C virus (HCV) antibody, between 2014 and 2016, were included in the testing cascade. Outcomes were HCV tests received after a positive anti-HCV antibody test: nucleic acid test or genotype test. Logistic regression analyses were performed to determine factors associated with progression through the HCV testing cascade.

RESULTS: Among those reported anti-HCV antibody positive, a total of 13,194 (61%) cases had a subsequent RNA-based test, and 79% (10,374/13,194) were confirmed with current, active HCV infection. For confirmed HCV cases, 44% (4,557/10,374) had a genotype identified. The median time from an antibody-positive test to a RNA-based test was 29 days (interquartile range [IQR] = 7-151). Differences in moving through the testing cascade were observed by birth cohort and race/ethnicity.

CONCLUSIONS: Improved surveillance capture of demographic information is needed to help public health agencies ensure equity in HCV diagnosis and linkage to care.

KEYWORDS: hepatitis C, surveillance, testing cascade

Background

Hepatitis C virus (HCV) infection is estimated to contribute a higher mortality burden than 60 other nationally notifiable infectious diseases reported in the United States combined.1 Hepatitis C virus is also the leading cause of liver failure and end-stage liver disease, and is a major reason for liver transplant in the United States.2 In addition to the disease burden of chronic infection, acute HCV infections associated with the opioid epidemic have been rising nationally and in Massachusetts.3,4 Despite the high mortality and morbidity burden, the population impact of effective, curative treatment for HCV infection has not been fully characterized due to under-ascertainment of screening and retention in care. Few jurisdictions have measured the prevalence of HCV infection or screening and treatment rates. There is a lack of direct evidence that HCV testing interventions positively affect outcomes at the population level.5-7 Cost and prescribing patterns are barriers to treatment,8,9 and gaps in surveillance data impaire accurate assessment of testing, treatment, and cure rates for HCV infection by public health agencies.10

Construction of an HCV testing cascade that quantifies screening and confirmatory testing can help public health agencies ensure equity in diagnosis and linkage to HCV care at the population level. Current Centers for Disease Control and Prevention (CDC) guidelines recommend that HCV testing should be initiated with an anti-HCV antibody test and, if reactive, should be followed with an HCV RNA test,11 and genotype determination is recommended to guide treatment decisions.12 An HCV testing cascade can establish benchmarks and serve as a proxy for access to care and treatment.13 Our study provides a state-level estimate of the number of HCV-infected persons who have progressed through the recommended testing series. The goal is to characterize hepatitis C testing in Massachusetts and guide stakeholders in addressing the needs of people living with hepatitis C.

Methods

Data sources

All HCV infections have been reportable in Massachusetts since 1992, and state regulations mandate reporting of laboratory evidence of HCV infection from all clinical laboratories providing testing services in Massachusetts. We reviewed data on 21,766 Massachusetts residents who were first reported to the state HCV surveillance system with a positive anti-HCV antibody test between 2014 and 2016. During the study period,
laboratory results were received directly from clinical laborato-
ries through an electronic laboratory reporting (ELR) system. Machusetts uses an integrated web-based surveillance and 
case management system, the Massachusetts Virtual 
Epidemiologic Network (MAVEN), for more than 90 report-
able infectious diseases.14 All disease “events” are entered in real 
time, classification is standardized in accordance with CDC 
case definitions, and quality control and quality assurance are 
performed on an ongoing basis.

Data analysis
All persons with a positive laboratory report for anti-HCV 
antibody between 2014 and 2016 were included in the analy-

es. Outcomes were HCV tests received after a positive anti-
HCV antibody test: nucleic acid test (NAT) or genotype test 
(GT). The proportion of patients achieving each step in the 
testing cascade was calculated as a conditional proportion of 
the previous step (denominator–numerator linkage).

Correlates examined included sex, birth cohort (before 
1945, between 1945 and 1964, between 1965 and 1979, after 
1980), and race/ethnicity. Wilcoxon non-parametric tests were 
used to compare differences in the median time, in days, from 
an anti-HCV antibody test to an RNA test. Descriptive analy-
ses of frequency distributions were performed for all variables. 
Bivariate and multivariable logistic regression analyses were 
performed to determine factors associated with progression 
through the HCV testing cascade. Multivariable models con-
trolled for the following factors: sex, birth cohort, and race/
ethnicity. All analyses were conducted using SAS version 9.3 
(SAS Institute Inc., Cary, NC, USA).

Ethical considerations
This analysis used de-identified data collected for routine dis-

eease surveillance, not considered human subjects research, and 
was not subject to institutional review board (IRB) review.

Results
From 2014 to 2016, a total of 21 766 Massachusetts residents 
were newly reported with an anti-HCV antibody positive test 
(see Figure 1). At the time of screening, 41% were between the 
ages of 25 and 39 years (with 48% of the total cohort born dur-
ing or after 1980), 58% were men, and 48% were non-Hispanic 
white (see Table 1). Twenty-six percent of reported cases were 
born between 1945 and 1964 (“baby boomers”). 

Among those reported anti-HCV antibody positive, a total of 
13 194 (61%) cases had a subsequent RNA-based test, and 
79% (10 374/13 194) were confirmed with current, active HCV 
infection. For confirmed HCV cases, 44% (4557/10 374) had a 
genotype identified (see Figure 2).

In bivariate analyses, the following factors were associated 
with performance of RNA-based testing after a positive 
anti-HCV antibody test: born prior to 1980 and Asian

**Figure 1.** Massachusetts Hepatitis C Testing Cascade, 2014–2016. 
EIA indicates enzyme immunoassay; HCV, hepatitis C virus.
Among cases with active infection, the following factors were associated with a GT: birth between 1945 and 1964 (baby boomer) and Hispanic ethnicity. No differences were observed by sex.

In the multivariable model for performance of an RNA-based test after a positive anti-HCV antibody test, cases born prior to 1980 were more likely to have a test done compared with those born during or after 1980, those born before 1945 (adjusted odds ratio [aOR] = 1.20, 95% CI = 1.12-1.20). Asian ethnicity was associated with a higher likelihood of testing (ref: non-Hispanic white; aOR = 1.46, 95% CI = 1.33-1.60). Cases who were non-Hispanic black (ref: non-Hispanic white; aOR = 0.92, 95% CI = 0.87-0.97), Hispanic (aOR = 0.88, 95% CI = 0.83-0.92), and other or unknown race/ethnicity (aOR = 0.77, 95% CI = 0.75-0.79) were less likely to have an RNA test performed (see Table 2).

The median time from an antibody-positive test to a RNA-based test was 29 days (interquartile range [IQR] = 7-151). Thirty-five percent (4654/13 194) of people who tested anti-HCV antibody positive received reflex/same day confirmatory RNA-based testing. Among people who did not receive reflex confirmatory testing, older cohort (before 1945, 14 days, and between 1945 and 1964, 21 days) and Asian ethnicity (19 days) were associated with shorter median delay between screening and confirmatory testing. People born during or after 1980 (40 days) had the longest median time between tests (see Table 3).

Among cases with confirmed, current HCV infection, older cohorts, born before 1945 (ref: born after 1980; aOR = 1.18, 95% CI = 1.01-1.39) and between 1945 and 1964 (aOR = 1.13, 95% CI = 1.06-1.19) and Hispanic ethnicity (ref: non-Hispanic white; aOR = 1.15, 95% CI: 1.05–1.26) were associated with a greater likelihood to have a GT performed. People of other or unknown race/ethnicity (aOR = 0.85, 95% CI = 0.81-0.90) were less likely to have a GT after confirmed HCV infection (see Table 2).

### Discussion

Differences in moving through the testing cascade were observed by birth cohort and race/ethnicity. The higher likelihood of RNA-based and genotype testing among cases born prior to 1980 may reflect the success of targeted testing policies and increased provider awareness regarding HCV prevalence in respect to older cohorts, specifically people born between 1945 and 1964, who may have better access to healthcare. We are encouraged that our data show progression through recommended testing for care and treatment among this group. In contrast persons born in 1980 or later had a lower likelihood of RNA-based testing than other birth cohorts. Persons born in 1980 or later also had a lower likelihood of genotype testing after confirmed infection, possibly representing diminished likelihood of treatment at a time when genotype was required for selection of a treatment regimen. In Massachusetts, the rate of newly diagnosed HCV infections has been highest in those 15 to 29 years of age and the rate of new infections within this group continues to increase among an ongoing epidemic of opioid use disorder and related injection drug use. As young people who inject drugs are at high risk for HCV acquisition, continued efforts for prevention and screening must be accompanied by ensuring progression through testing to curative treatment to reduce ongoing transmission and burden of infection. Recent studies have suggested that expanding HCV screening recommendations in the United States to

### Table 1. Anti-hepatitis C virus antibody (HCV Ab+) laboratory results reported to the Massachusetts Department of Public Health, 2014-2016.

|                  | N   | HCV AB+ % |
|------------------|-----|-----------|
| **Sex**          |     |           |
| Women            | 8537| 39.2      |
| Men              | 12638| 58.1     |
| Missing          | 591 | 2.7       |
| **Age category** |     |           |
| 0-14 years       | 75  | 0.3       |
| 15-24 years      | 3098| 14.2      |
| 25-39 years      | 9003| 41.4      |
| 40-54 years      | 4873| 22.4      |
| 55+ years        | 4662| 21.4      |
| Missing          | 55  | 0.3       |
| **Birth cohort** |     |           |
| Before 1945      | 600 | 2.8       |
| Between 1945 and 1964 (Baby Boomers) | 5764 | 26.5 |
| Between 1965 and 1979 | 4984 | 22.9 |
| After 1980       | 10 350 | 47.6   |
| Missing          | 68  | 0.3       |
| **Race/ethnicity** |     |           |
| Asian            | 351 | 1.6       |
| Non-Hispanic black | 1097 | 5.0   |
| Non-Hispanic white | 10 441 | 48.0 |
| Hispanic         | 1517| 7.0       |
| *Other/Unknown*  | 8360| 38.4      |

Data were extracted June 2017 and are subject to change. *Other includes American Indian (<0.5%), Alaskan Native (<0.5%), Native Hawaiian Pacific Islander (<0.5%), and Other not defined/disclosed (>98%).

Asian ethnicity was associated with a higher likelihood of testing (ref: non-Hispanic white; aOR = 1.46, 95% CI = 1.33-1.60). Cases who were non-Hispanic black (ref: non-Hispanic white; aOR = 0.92, 95% CI = 0.87-0.97), Hispanic (aOR = 0.88, 95% CI = 0.83-0.92), and other or unknown race/ethnicity (aOR = 0.77, 95% CI = 0.75-0.79) were less likely to have an RNA test performed (see Table 2).
capture additional age groups could provide a more accurate assessment of HCV prevalence and be cost-effective.\textsuperscript{16} Our findings suggest that when this risk group—younger birth cohorts—test anti-HCV antibody positive, barriers to further testing required for treatment evaluation may exist.

Our analysis found disparities in HCV RNA-based testing by race/ethnicity, as black and Hispanic anti-HCV antibody positive individuals were less likely to receive confirmatory testing when compared with non-Hispanic white cases. In contrast, Asian ethnicity was associated with a higher likelihood of receiving a confirmatory test. Among cases with confirmed HCV infection (HCV RNA positive), Hispanic ethnicity was associated with a higher likelihood of receiving genotype testing. These reported differences may be associated with socioeconomic status but over 96% of Massachusetts residents have access to health insurance under a law passed in 2006 mandating health coverage.\textsuperscript{17,18} Further investigation is needed to better understand the associations between race/ethnicity and HCV testing, especially as 38% of those anti-HCV antibody were reported to be of other or unknown race/ethnicity. Improved capture of demographic information by surveillance systems is needed to help public health agencies ensure equity in identification and linkage to HCV care at the population level.

We found that the median time from a screening test to an RNA-based test was 29 days but delays in infection confirmation were higher among people born after 1980. In addition, for the 39% (8572/21766) who screened antibody positive, an RNA-based test was never reported. Our data indicate that a large proportion of HCV infections may not be confirmed by RNA-based testing, and among those confirmed, testing may not be performed in a time frame encouraging entry into care and treatment and favoring reduced disease transmission.\textsuperscript{16,19,20}

Effective surveillance is critical for success in evaluating and promoting hepatitis C elimination. The Massachusetts HCV testing cascade is a tool for monitoring the effectiveness of hepatitis C screening and confirmation. Our study provides a population-based, state-level report of the number of reported HCV-infected persons who received RNA-based and genotype testing in Massachusetts from 2014 to 2016. We included cases reported after 2014, when reporting was most standardized, and ELR data, including negative HCV laboratory results, were virtually complete. Our data are representative of all people tested.
Table 2. ORs for performance of RNA-based test and GT among anti-hepatitis C antibody positive individuals reported to the Massachusetts Department of Public Health, 2014-2016.

|                  | RNA TEST, N = 13,194 |                      | GT TEST, N = 4,557 |                      |
|------------------|----------------------|----------------------|--------------------|----------------------|
|                  | UNADJUSTED OR (95% CI) | ADJUSTED OR (95% CI) | UNADJUSTED OR (95% CI) | ADJUSTED OR (95% CI) |
| Sex              |                      |                      |                    |                      |
| Women            | 1.02 (0.99–1.04)     | 1.03 (1.00–1.07)     | 0.99 (0.94–1.03)    | 1.00 (0.95–1.05)     |
| Men              | REF                  | REF                  | REF                | REF                  |
| Birth cohort     |                      |                      |                    |                      |
| Before 1945      | 1.21 (1.12–1.32)     | 1.20 (1.10–1.30)     | 1.16 (0.99–1.37)    | 1.18 (1.01–1.39)     |
| Between 1945 and 1964 (Baby Boomers) | 1.45 (1.41–1.50) | 1.46 (1.42–1.51) | 1.13 (1.07–1.20) | 1.13 (1.06–1.19) |
| Between 1965 and 1979 | 1.14 (1.10–1.18) | 1.16 (1.12–1.20) | 1.04 (0.98–1.10) | 1.03 (0.97–1.09) |
| After 1980       | REF                  | REF                  | REF                | REF                  |
| Race/ethnicity   |                      |                      |                    |                      |
| Asian            | 1.58 (1.44–1.73)     | 1.46 (1.33–1.60)     | 0.93 (0.78–1.11)    | 0.89 (0.75–1.07)     |
| Non-Hispanic black | 1.00 (0.95–1.06) | 0.92 (0.87–0.97) | 1.05 (0.95–1.16) | 1.01 (0.91–1.12) |
| Hispanic         | 0.89 (0.85–0.94)     | 0.88 (0.83–0.92)     | 1.16 (1.06–1.26)    | 1.15 (1.05–1.26)     |
| Other/Unknown    | 0.77 (0.74–0.79)     | 0.77 (0.75–0.79)     | 0.86 (0.81–0.90)    | 0.85 (0.81–0.90)     |
| Non-Hispanic white | REF                  | REF                  | REF                | REF                  |

Data were extracted June 2017 and are subject to change. Abbreviations: CI, confidence interval; GT, genotype test; OR, odds ratio.

Table 3. Duration (in days) between positive anti-HCV antibody test and an RNA-based test, excludes 4,654 of 13,194 (35%) of people who received reflex/same day nucleic acid tests.

|                  | ALL | MEDIAN (IQR) | P VALUE |
|------------------|-----|--------------|---------|
|                  | 29 (7-151) |  |  |
| Sex              |     |              |         |
| Women            | 28 (7–137) | .0651 |  |
| Men              | 30 (8–159) |  |  |
| Birth cohort     |     |              |         |
| Before 1945      | 14 (5–67) | <.0001 |  |
| Between 1945 and 1964 (Baby Boomers) | 21 (7–85) |  |  |
| Between 1965 and 1979 | 30 (7–155) |  |  |
| After 1980       | 40 (8–198) |  |  |
| Race/ethnicity   |     |              |         |
| Asian            | 19 (7–78) | <.05 |  |
| Non-Hispanic Black | 36 (9–135) | |  |
| Non-Hispanic White | 29 (7–166) |  |  |
| Hispanic         | 37 (10–164) | |  |
| Other/Unknown    | 28 (7–139) | |  |

Data were extracted June 2017 and are subject to change. Abbreviations: HCV, hepatitis C virus, IQR, interquartile range.

through commercial and hospital laboratories in Massachusetts, including people who are incarcerated or experiencing homelessness. This cascade is a first step toward using laboratory data to better evaluate linkage to care, care retention, access to therapies, adherence to treatment, and rate of cure though further validations are needed to best define these outcomes.

Our study has a number of limitations. The Massachusetts Department of Public Health HCV surveillance system is primarily based on laboratory reporting; therefore, we were unable to confirm if residents received out-of-state testing or moved out of the area prior or subsequent to an anti-HCV antibody positive test in Massachusetts. However, 13% (1097/8572) of individuals without an RNA-based test were repeat anti-HCV antibody testers during the study period. These cases were reported with 2 or more positive anti-HCV antibody tests 6 to 12 weeks after the initial positive screening. More than half (57%) of these repeat testers were born after 1980 highlighting a need for outreach and confirmatory testing services in this population. In addition, restrictions to direct-acting antivirals for hepatitis C were not removed from MassHealth/Medicaid until August 2016. It is unknown how restrictions on access to treatment would have affected tests ordered by providers. Finally, our findings regarding race/ethnicity should be interpreted with caution due to the number of cases with missing or unascertained status.

In the era of direct-acting antivirals for hepatitis C, ongoing evaluation of screening, testing, and treatment of HCV-infected people is needed to assist in meeting state and national goals for
reduction of HCV infection, and ultimately, elimination. The National Viral Hepatitis Action Plan for 2017-2020 has identified the limited availability of data as one of the most critical gaps in understanding and responding to HCV infection. There is a need for increased and improved quality of regional, state, and local HCV surveillance data to define scope, address disparities in care, and support prevention efforts and resource allocation. Our study establishes a baseline for HCV testing practices in Massachusetts over a 3-year period. Improved surveillance capture of demographic and risk history information is needed to help public health agencies ensure equity in HCV diagnosis and linkage to HCV care at the population level. We recommend further research into specific barriers for moving through the testing cascade.

Acknowledgements
The authors thank Susan Soliva for assistance in data acquisition and cleaning.

Author Contributions
QTV drafted the main portions of the manuscript, merged data sources, analyzed and interpreted the data. SO, DC, KC, AD and RMK contributed to the design of the study and verified the analytical methods. SO, DC, and RMK were responsible for the original conception of the study. All authors reviewed and approved the final manuscript.

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