Review Article

Assessing the Effectiveness of Strategies in US Birth Cohort Screening for Hepatitis C Infection

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Abstract

Chronic hepatitis C infection in the USA is a highly morbid condition and current guidelines recommend one-time screening among the birth cohort (1945-1965). Understanding strategies to optimize screening can help inform future hepatitis C virus (HCV) screening guidelines. A focused literature search was performed using PubMed and manual abstract review from major hepatology conferences over the past 2 years. The search strategy involved using Medical Subject Headings terms for hepatitis C, screening, birth cohort, baby boomers, and 1945-1965. The review was limited to data from the USA. A total of 327 articles were identified and 36 abstracts were included, with studies published between 2012-2019. Strategies including clinician education, electronic medical record alerts, reflex HCV RNA testing, point-of-care testing, multisite (outpatient, inpatient, emergency department, endoscopy suite) initiatives, direct patient solicitation, and utilization of non-physician providers have increased HCV screening rates. However, broad implementation remains less than optimal. Barriers include lack of patient acceptance to screening and engagement in the HCV care cascade. The Veterans Affairs Healthcare System has achieved higher birth cohort screening rates through an integrated approach requiring high-level engagement by leadership and institutional commitment. Multiple strategies for increasing birth cohort screening have been successful, but overall rates of HCV screening remain low. These strategies can inform public health efforts to implement emerging national recommendations for expansion of HCV screening to all U.S. adults age 18 or older.

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Keywords: Hepatitis C; Epidemiology; HCV antibody; Screening; Birth cohort; Baby boomers; Care cascade; Electronic medical records.

Abbreviations: Ab, antibody; BPAs, best practice alerts; CDC, Center for Disease Control; DAAs, direct acting antivirals; ED, emergency department; EMR, electronic medical record; HCV, hepatitis C virus; NHANES, National Health and Nutrition Examination Survey; POCT, point-of-care testing; RDT, rapid detecting test; USPSTF, USA Preventative Services Task Force; VHA, Veterans Health Administration.

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Introduction

Chronic hepatitis C virus (HCV) infection is one of the most common indications for liver transplantation and the leading cause of hepatocellular carcinoma in the USA, accounting for approximately 19,000 deaths annually and substantial healthcare costs.[1] An estimated 4.1 million individuals in the USA are HCV antibody (Ab)-positive, indicative of past or current infection. Among those, approximately 2.4 million individuals have ongoing chronic HCV infection with positive HCV RNA.[2] The baby boomer "birth cohort" of individuals born 1945-1965 comprise approximately 75% of HCV infections in the USA despite representing only 27% of the general population.[3] One study in 2012 retrospectively applied birth cohort to previously risk-based HCV screening using the National Health and Nutrition Examination Survey (NHANES) database and determined that optimal application of risk-based guidelines would identify 82% of chronic HCV cases (number needed to screen 14.6) compared to birth-cohort screening, which would identify 76% of chronic HCV cases (number needed to screen 28.7).[4]

The Center for Disease Control (CDC) and the USA Preventative Services Task Force (USPSTF) issued recommendations in 2012[3,5] and 2013[6,7] recommending one-time universal screening in all individuals born between 1945-1965, irrespective of symptoms or risk factors. Cost effectiveness studies have confirmed birth cohort screening to be cost saving for billions in test and treat models.[5] However, recent studies indicate that HCV testing in the birth cohort minimally increased from 12.3% to 17.3% between 2013 and 2017.[8] One unique population, veterans being cared for at the Veteran Affairs Healthcare System, achieved more successful screening through automated clinical reminders through the electronic medical record (EMR) and also increased awareness among primary care providers through national directives. One study reported 79.5% of veterans born between 1945-1965 had been tested for the HCV Ab.[9]

Given the high cost and mortality associated with HCV, coupled with the presence of effective treatment options with direct-acting antivirals (DAAs), identification of patients with HCV is of paramount importance to public health efforts to achieve HCV elimination. The success of the World Health Organization campaign for global elimination of HCV infection by 2030[10,11] will depend on optimization of the HCV care cascade from screening/identification to linkage to treatment,[12] and the associated funding required to support hepatitis programs.[13]

This review summarizes existing strategies for increasing the screening or testing of HCV infection within the birth cohort (1945-1965). Although there have been substantial efforts on HCV microelimination in several global regions, this article focuses primarily on evidence from the USA. Understanding existing strategies for optimization of 1945-1965 birth cohort screening may help inform future guidelines for public health interventions focused on HCV screening, particularly in the context of the burgeoning opioid epidemic.

Methods

A focused literature search was performed using PubMed, with a combination of search terms, including screen, test, hepatitis C virus, HCV, hepatitis C, birth cohort, 1945-1965, and baby boomer, in August 2019. Manual abstract review was performed (C.T.) for major hepatology conferences, including The Liver Meeting 2017-2018 of the American Association for the Study of Liver Diseases, Digestive Diseases Week 2017-2019, and The International Liver Congress of the European Association for the Study of the Liver 2017-2019. The review was limited to USA data, with the exception of reports from six countries (Argentina, Chile, Finland, France, Greece, and Japan)[14] with similar recommendations for birth cohort screening or one-time screening for all ages. There was no time restriction imposed on the search strategy of original manuscripts.

Results

A total of 327 full text papers were identified by the database search and an additional 38 abstracts per manual review from major conferences. After individual assessment of abstracts, 36 were included in the review. Study characteristics and outcomes are summarized below (Table 1). All papers were published 2012-2019 but one study from 2012 was excluded due to assessment prior to implementation of CDC birth cohort recommendations.[15]

Current state of hepatitis C screening in the USA

The current recommendations of the CDC and USPTF regarding HCV screening are summarized as follows:

CDC (August 17, 2012): In addition to testing adults of all ages at risk for HCV infection, the CDC recommends:

- All adults born during 1945–1965 receive one-time testing for the HCV.
- Testing should begin with anti-HCV. If the anti-HCV test is positive, or reactive, then a nucleic acid test should follow.
- All persons identified with current HCV infection should receive a brief alcohol screening and intervention, as clinically indicated, followed by referral to appropriate care and treatment services.[5]

USPSTF (June 25, 2013) recommends:

- Screening for HCV infection in persons at high risk for infection.
- One-time screening for HCV infection in adults born between 1945 and 1965.

These recommendations were in line with recommendations of the Institute of Medicine and the USA Department of Health and Human Services Action Plan for the Prevention, Care and Treatment of Viral Hepatitis.[16] Subsequent studies confirmed the cost-effectiveness of birth cohort testing based on health economic models, which projected that an additional 808,580 cases of chronic HCV infection cases would be identified at a cost of $2874 per case, and that even with a test-and-treat strategy using historical DAA plus pegylated interferon/ribavirin, quality adjusted life-years increased by $532,000, with an incremental cost-effectiveness ratio of $35,700 per quality adjusted life-years saved.[17]

Despite implementation of these recommendations in 2012-2013, a recent review suggested that there was only a modest increase in HCV screening within the birth cohort in the USA, estimated to have risen from 12.3% in 2013 to 17.3% in 2017.[8] Further analysis of this dataset identified the primary care clinic as the setting in which prioritization of testing should occur, permitting unscreened or untested eligible patients access to follow-up care within the outpatient clinic.[18] This information underlines the need for more innovative screening strategies to be implemented which involve a combination of patient and provider education, harnessing the electronic health record automated alerts in the inpatient, outpatient, emergency departments, endoscopy, and colonoscopy suites, as well as a patient-centered medical home approach[19] utilizing non-physician providers to assist in improving screening, reflex testing, and linkage of care to the HCV care cascade.

Innovative strategies for screening

EMR alerts

The advent of the EMR or electronic health record has created a platform in which screening can become more streamlined with patient care in both the outpatient and inpatient settings. Additionally, several states, including New York, Connecticut, Massachusetts, California, and Colorado, have established laws mandating that baby boomers be offered screening with a one-time HCV Ab test. In New York state, laboratory data confirmed a 51% increase in the number of specimens collected for HCV testing among birth cohort individuals between 2013 and 2014, and New York Medicaid data revealed a 52% increase in average monthly testing for HCV Ab from 2012 to 2014[20] despite exclusion of HCV testing requirement in the emergency department (ED) setting.[21]

Furthermore, while EMR appears to be a cornerstone for automated alerts, given the simplicity of identifying screening candidates based solely on date of birth, additional strategies to augment EMR-based testing have resulted in significant increases in screening rates, including one study employing targeted education of resident physicians which found an increase from 62% at baseline to 81% at 6 months post-intervention.[22] Similar increases in screening rates employing education plus EMR reminders in a resident physician context resulted in up to a 3-fold increase in HCV testing rates.[23–24]

Outpatient

Primary care and outpatient specialty clinics are the cornerstone of population-based screening and the focus of most EMR alert-based interventions. Multiple studies have reported increases in HCV screening rates after implementation of EMR alerts[25–31] in multiple quality improvement interventions, including those incorporating formal Plan, Do, Study, Act cycles; although, the magnitude of increase has ranged

Table 1. Characteristics and outcomes from HCV screening strategies among birth cohort individuals

Study	Type	Design	Population	Setting	Sample size	Outcomes
EMR alerts						
Outpatient						
Jones (2017)	Abstract	Retrospective chart review	Patients born between 1945-1965 not previously screened for HCV	Baylor Scott & White in Central Texas Primary Care Clinic from 2/2014-2/2015	*n*>30,000	Statistically significant increase in baby-boomer screening for hepatitis C from 1.87% prior to EMR reminder to 14.14% after initiation of the reminder
Kahn (2018)	Abstract	Retrospective chart review	Patients born between 1945-1965 not previously screened for HCV	Northshore University Health System; Implemented 7/2017	*n*=99892	HCV tested: 13.8% (13,804/99,892) Highly varied adherence to screening guidelines by PCPs
Konerman (2017)	Abstract	Retrospective cohort study	Patients born between 1945-1965 without prior diagnosis of HCV infection, no prior documented anti-HCV testing	Primary care clinics	*n*=52,5660	HCV screening increased 10-fold from 7.6% for patients with PCP visit in 6 months prior to BPA implementation to 72% over a 1-year period after implementation
Soo (2017)	Abstract	Retrospective chart review	Patients born between 1945-1965. Excluded patients with HCV on problem list or if they had their one-time HCV screen	Automatic health maintenance alert in an integrated medical group, 6/2015-6/2016	*n*=29,987	HCV screening rate increased from baseline 13.3% to 15.6% after 1 month and to 40.2% after 12 months HCV Ab-positive: 2.3% (684/29987)
Soo (2018)	Abstract	Prospective cohort	Patients born between 1945-1965. Excluded patients with HCV on problem list based on ICD9/10 code or positive anti-HCV or HCV RNA	Automatic health maintenance alert module at primary care practices in the Providence Health and Services and rates assessed monthly in five regions in the Western USA, 1/2017 - 12/2018	*n*=76288	HCV Ab-positive: 4.6% (3507/76,288); HCV screening rate increased 31.9% from 23.0% to 54.9%

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Table 1. *(continued)*

Study	Type	Design	Population	Setting	Sample size	Outcomes
Teply (2018)	Abstract	Retrospective chart review	All patients born between 1945-1965 seen at a primary care clinic within a regional healthcare system in Midwest USA	35 primary care clinics within a regional healthcare system in Midwest USA (prealert), 6/1/2016-11/30/2016; (postalert) 12/1/2016-5/31/2017	n=29,703 (pre), 29,913 (post)	Prealert HCV tested: 1.62% (482/29.703) HCV Ab-positive: 4.2% (20/482) Postalert HCV tested: 19.0% (5685/29,913) HCV Ab-positive: 1.9% (107/5685) 10-fold increase in HCV screening
Al-Hihi (2017)	Full-text	Prospective cohort- 2 PDSA cycles	All patients born between 1945-1965 seen in a primary care clinic	Multiphysician practice in the Midwest USA representing 84 faculty physicians and residents, 6/2016-3/2017, with BPA and health maintenance alerts in the EMR and education to primary care providers via single educational sessions with a hepatologist	Not reported	Baseline screening rate preintervention: 30% (1674/5541) Screening rate at 3 mo: 45% Screening rate 3 mo after concurrent education session: 55%
Federman (2017)	Full-text	Randomized control trial	Patients born during birth cohort period were subjects. However, attending physicians and medical residents were participants in the study to see how BPA affected HCV testing and incidence of HCV Ab-positive tests	10 community and hospital-based primary care practices that implemented BPA for HCV testing among birth cohort adults, 4/2013-3/2014	n=25, 620 study-eligible visits	Testing rates greater among Birth Cohort pts in intervention sites (20.2% v 1.8%, $p<0.0001$) EHR-embedded BPA markedly increased HCV screening, but the majority of eligible pts did not receive testing indicating a need for more effective methods to promote uptake
Nitsche (2018)	Full Text	Case control	Patients born between 1945-1965	7 primary care sites in Virginia Mason Healthcare System (greater Seattle area, WA), 8/1/2014-9/14/2015 with 3 sites given additional education interventions (case) not provided to the remaining 4 (control)	*n*=73,685; cases 37,783; controls 35,902	Screening rates at the following times (case vs. control), $p<0.001$ at all time points Baseline: 6.1% vs. 4.6% Time 1: 18.1% vs. 10.4% Time 2: 20.3% vs. 12.5% Time 3: 22.2% vs. 13.7% Time 4: 23.4% vs. 14.7% Time 5: 24.2% vs. 15.3% Time 6: 17.5% vs. 10.4%

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Table 1. (*continued*)

Study	Type	Design	Population	Setting	Sample size	Outcomes
Shahnazarian (2015)	Full-text	Case control	Patients born between 1945-1965	Methodist Hospital in Brooklyn, NY prelegislative mandate (12/2013) and postmandate and postEMR intervention, 5/2014-2/2015	Not reported	PreEMR alert HCV screen: 47.2% PostEMR alert HCV screen: 87.9%
Yeboah-Korang (2018)	Full-text	Case control	Patients born between 1945-1965 in the outpatient setting	Northshore University Health System, 1/2010 to 12/2015, with retrospective chart review back to 2003 to identify overall HCV testing rates (case) and then during 7/2015; BPA alert implemented 7/2017-11/2017	n=10,089 (pre); 45,188 (post)	PreEMR alert HCV screen: 0.68% (69/10,089) PostEMR alert HCV screen: 10.76% (5451/45,188) 15.8-fold increase in HCV testing rates
Inpatient						
Mehta (2017)	Abstract	Retrospective cohort	Adult admitted to inpatient medicine service born between 1945-1965	9/2014-9/2016	n=1128	HCV Ab-positive: 9.6% (108/1128) HCV-positive: 52% (56/108) HCV RNA PCR-positive : 21% HCV RNA PCR-negative: 25% HCV RNA PCR not performed during hospitalization: 54% Only 18% of seropositive had outpatient gastrointestinal follow-up
Shen (2018)	Abstract	Retrospective cohort	Patients born between 1945-1965 categorized by 3 timeframes (premandate, postmandate but prereflex RNA, postreflex RNA) and stratified by screened vs not screened	Patients admitted to New York Presbyterian Hospital- Weill Cornell; data collected in 3 times frames: 1. Premandate (1/2013-12/2013) 2. Postmandate but prereflex (1/2014-8/2015) 3. Postreflex RNA (9/2015-12/2016)	n=51657	Overall and initial screening improved pre- and postmandate from 8% to 39% and 53% to 84% (p<0.01); this did not translate into improved linkage to care Follow-up care and initiation of treatment decreased from 31% to 20% and 9% to 5%, (p<0.01)

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Table 1. (*continued*)

Study	Type	Design	Population	Setting	Sample size	Outcomes
Turner (2015)	Full-text	Prospective cohort	Patients born between 1945-1965 admitted to hospital	Safety-net hospital in South Texas from 1/2012-1/2014 with follow-up through 12/2014	*n*=6140	HCV tested: 51% (3168/6140) HCV Ab-positive: 7.6% (240/3168) HCV RNA-positive: 63% (134/214), 4.2% overall chronic HCV: 96.3% (129/134) were counseled and 80.6% (108/134) received primary care follow-up and 38.8% (52/134) received hepatology follow-up with 5 initiating anti-HCV treatment
Direct patient solicitation- phone call, mailing						
Trowell (2018)	Abstract	Prospective cohort	Patients born between 1945-1965 chosen from a population in a Baltimore city hospital	Two-pronged approach: 1. BPA created in EMR to prompt PCP to order tests for patients; 2. Letters mailed with educational material, blood test request forms for pts without prior HCV testing	*n*=15,583	BPA screened 8786/15,583 Letters screened 3645/15,583 Screened via hospital or other affiliated locations 3152/15,583 HCV Ab-positive: 2.7% (426/15,583) HCV RNA-positive: 1.3% (204/15,583) HCV positivity rates highest in 1951-1960 birth cohort
Kruger (2017)	Full Text	Prospective cohort	Project managers of each of the three sites implementing HCV screening per CDC recommendation (BEST-C sites). Filled out standardized questionnaires about their implementation experiences and qualitative analysis	Three sites implemented interventions to increase birth-cohort testing through participation in the Birth-cohort Evaluation to Advance Screening and Testing for Hepatitis C from 12/2012-3/2014	Not reported	BPA was the preferred intervention at all three sites, but site-specific challenges prevented success of the solution in two out of three sites Despite challenges in start-up of the screening in PCP settings, it was deemed feasible and likely successful given dedicated resources, buy-in, and support from hospital administration

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Table 1. (*continued*)

Study	Type	Design	Population	Setting	Sample size	Outcomes
Yartel (2018)	Full-text	Randomized control trial	Patients born between 1945-1965 not previously screened or diagnosed	Patients randomly assigned to receive one of three independent implementation strategies (repeated mailing outreach, BPA, direct patient solicitation), 12/2012-3/2014	*n*=8992 (mailing trial) *n*=14,475 (BPA trial) *n*=8873 (patient solicitation trial)	Repeated mailing-intervention was 8 times as likely to identify anti-HCV-positive (adjusted relative risk: 8.0, 95% confidence interval: 2.8-23.0; adjusted probabilities: intervention 0.27%, control 0.03%) BPA trial was 2.6 times as likely to identify anti-HCV-positive (adjusted relative risk 2.6, 95% confidence interval: 1.1-6.4; adjusted probabilities: intervention 0.29%, control 0.11%) Patient-solicitation trial was 5 times as likely to identify anti-HCV-positive (adjusted relative risk 5.3, 95% confidence interval: 2.3-12.3)
Colonoscopy						
Abu-Heija (2018)	Abstract	Retrospective chart review	Dominantly African American adults undergoing colonoscopy born between 1945-1952, subgroup analysis with university physician group or outsider provider	Urban open access colonoscopy suite, 2014	*n*=444	HCV tested: 140/444 HCV Ab-positive: 43% (60/140) HCV RNA PCR-positive: 94% (56/60) university physician group vs. non- university physician group tested: 48% vs. 15% ($p<0.05$) Lost to follow-up after first visit: 47%
Abu-Heija (2019)	Abstract	Retrospective chart review	Dominantly African American adults undergoing colonoscopy born between 1945-1958	Urban open access colonoscopy suite in 2014 or 2017	n=988	HCV tested: 40.3% (2017) vs. 31.5% (2014) ($p=0.005$); no difference based on race or gender HCV Ab-positive: 31.5% (2017) vs. 42.9% (2014) HCV RNA PCR-positive: 97% (2017) vs. 96.5%

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Table 1. (*continued*)

Study	Type	Design	Population	Setting	Sample size	Outcomes
Matin (2018)	Abstract	Prospective cohort	Veterans undergoing colonoscopy, registered nurse screen day prior and if no prior screen for HCV and born between 1945-1965, verbal consent obtained over the phone, HCV tested when intravenous line placed	Veterans Affairs facility, 7/2017-10/2017	*n*=208 (38 did not show for appointments)	HCV tested: 145/170 (85%)
Sears (2013)	Full-text	Prospective cohort	Adults aged 50-65 years-old who received a colonoscopy answered questions in a survey and blood samples were collected for hepatitis B virus and HCV	3 month period	*n*=500	HCV tested: 72% (376/500) HCV Ab-positive: 4/376 HCV RNA PCR-positive: 1/4
Endoscopy						
Hirode (2018)	Abstract	Prospective cohort	Adults undergoing outpatient endoscopy categorized into: 1) BC and at least one RF 2) BC and no RF 3) non BC with one RF	Urban safety-net hospital, 7/2015-7/2017	*n*=1752	Acceptance of test: BC-RF+ > BC+RF- > BC+RF+ Overall HCV Ab-positive: 3.4% BC+ RF+: 12.5% BC- RF+: 4.9% BC+ RF-: 1.3% -higher in US born patients
Hirode (2019)	Abstract	Observational	Outpatient endoscopy-based patient navigator model for adults undergoing endoscopy	Urban safety-net hospital, 7/2015-9/2018	*n*=3624	Eligible for HCV screening (69.2%) based on: BC: 89.8% At least 1 HCV RF: 30.4% Eligible patients tested increased from 50.8% to 77.9%
Wong (2017)	Abstract	Prospective cohort	Adults undergoing outpatient endoscopy	Underserved safety-net hospital, 7/2015-6/2016	*n*=1125	Trend towards lower HCV test acceptance among BC (odds ratio 0.39, 95% confidence interval: 0.13-1.14) High risk (including BC): 66.5% HCV test accepted: 85.4%

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Table 1. (*continued*)

Study	Type	Design	Population	Setting	Sample size	Outcomes
ED						
Hyun (2017)	Abstract	Prospective cohort	Adults born between 1945-1965 presenting to ED using streamlined EHR ordering with patient navigators contacting individuals with confirmed infection by automated certified letters and phone calls for linkage to care	ED of community hospital, 2/2016-1/2017	*n*=12,617	HCV tested: 40.2% (5069/12617) HCV Ab-positive: 3.99% (202/5069) HCV RNA PCR-positive: 1.32% (67/5069) Linkage of care rate 37.3% in 6 month period patient navigation; awareness of infection in chronically infected but not engaged in care: 38.8% (26/67)
Minhas (2019)	Abstract	Retrospective cohort	Adults born between 1945-1965 presenting to ED with testing conducted on an opt-out basis (2/2017-11/2017) then when notification was no longer required on all-comers (11/2017-1/2018) with referral to affiliated hepatology clinic	ED of urban hospital, 2/2017-1/2018	*n*=1525	HCV Ab-positive: 15.5% (237/1525) HCV RNA PCR-positive: 67.9% (161/237) Referral to hepatology: 75% (121/161)
Allison (2016)	Full-text	Cross sectional	Adults born between 1945-1965 presenting to ED were provided study information sheet and CDC information sheet in HCV testing in baby boomers, then participated in researcher-administered questionnaire, those with positive HCV Ab were referred to clinic, non-attendance resulted in telephone call	ED of a large urban academic hospital (Bellevue, WA) in a state where birth cohort is mandated by law in all non-ED healthcare settings, 10/2014-7/2015	*n*=915	Structured interview: 46.7% (427/915) HCV tested: 90.0% (383/427) HCV Ab-positive: 7.4%

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Table 1. (*continued*)

Study	Type	Design	Population	Setting	Sample size	Outcomes
Cornett (2018)	Full-text	Retrospective cohort	Adults born between 1945-1965 presenting to ED with an opt-out test order generated by the EHR seen between 11am-7pm and given handout explaining rationale with plan for contacting patients with results	ED of small urban/ suburban area tertiary care academic hospital, 6/2016-12/2016	*n*=3046	HCV tested: 96.1% (2928/ 3046) HCV Ab-positive: 6.6% (192/2928) HCV RNA PCR-positive: 43% (71/167)
Galbraith (2015)	Full-text	Cross sectional	Adults born between 1945-1965 presenting to ED with an opt-out as part of standard clinical care, therefore no informed consent was required with ED nurses screening using questionnaire embedded in the EHR with informational packet given to HCV-positive individuals and linkage to care specialist information with coordinator arrange follow-up and phone call follow-up	ED of a large academic urban hospital (UAB) in a socioeconomically disadvantaged population, 9/ 2013-11/2013	*n*=3170	Unaware of HCV status: 73.2% (2323/3170) Opted out: 12.7% (289/2323) Automated test order: 87.3% (1988/2323) HCV tested: 76.9% (1529/1988) HCV Ab-positive: 11.1% (170/1529) HCV RNA tested: 88.2% (150/170) HCV RNA PCR-positive: 68.0% (102/150)
Hsieh (2016)	Full-text	Retrospective cohort identity unlinked seroprevalence	Adults aged >17 years-old presenting to a large academic urban hospital ED with excess blood specimen	ED of a large academic urban hospital (JHU) in a socioeconomically disadvantaged population, 6/ 2013-8/2013	n=4713	HCV Ab-positive: 13.8% (652/4713) Undocumented HCV infection: 31.3% (204/652) Diagnosed by BC: 48.5% (99/204) Diagnosed by RF: 26.5% (54/204)

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Table 1. (*continued*)

Study	Type	Design	Population	Setting	Sample size	Outcomes
Lyons (2016)	Full-text	Cross sectional seroprevalence	Adults between the ages of 18-64 presenting to the ED were consented to a "study of disease of public health importance" and given compensation, risk factors assessed via health questionnaires, deidentified data	ED of urban academic hospital, 1/2008-12/2009	*n*=1034	HCV tested: 89% (924/1034) HCV Ab-positive: 14% (128/924) HCV RNA PCR-positive: 81% (103/128) Birth cohort only testing would have missed 28% (36/128) HCV Ab-positive, 25% (26/105) HCV RNA-positive Awareness of prior diagnosis: 32% (41/128)
Schechter-Perkins (2018)	Full-text	Descriptive	Individuals >13 years-old of age presenting to the ED undergoing phlebotomy for clinical purposes, non-targeted, opt-out screening with a best practice advisory alert with navigators to facilitate linkage to care for those with positive RNA	ED of urban academic hospital (BMC), 11/2016-1/2017	*n*=3936	HCV tested: 3808 HCV Ab-positive: 13.2% (504/3808) HCV RNA PCR-positive: 59.2% (292/493) Outside BC with active infection: 54% (115) Linkage to care: 76.4% (223) Appointments scheduled: 38% (102) Attended LTC visit: 22.5% (66)
White (2016)	Full-text	Retrospective cohort	Adults born between 1945-1965 or reporting any use of injection drugs who were not known to be HCV-positive to triage nursing, EMR, with opt-out testing requiring consent with physicians able to choose testing at clinical discretion (diagnostic) with informational packets sent to HCV-positive patients with referral to primary care which could then be canceled if RNA test was negative	ED of Highland Hospital-Alameda Health System, single-center urban ED, 4/2014-10/2014	*n*=26639	HCV tested: 9.7% (2581/26,639) HCV Ab-positive: 10.3% (267/2581) Screening Ab test: 79% (2028/2581) Diagnostic Ab test: 21% (553/2581) Screening HCV Ab-positive: 9.1% (185/2028) Diagnostic HCV Ab-positive: 14.8% (82/553)

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Table 1. (*continued*)

Study	Type	Design	Population	Setting	Sample size	Outcomes
Non-physician providers						
Shelgrove (2018)	Abstract	Prospective cohort	Patients born between 1945-1965 in Yuba, Sutter, Colusa Counties. Also included patients ages 18-64 years-old in Butte, Glenn, Tehama Counties. Patients with high risk factors. Followed HCV Ab testing with reflex HCV RNA testing by PCR	Ampla Health (a Federally Qualified Health Center) offering medical, dental, mental health, specialty healthcare services in Northern California, screening from 8/2017-4/2018	*n*=5481	Detected HCV Ab seropositivity in 7.5% (410/5481). 45% (183/410) RNA-positive. Overall, 3.3% RNA-positive which averages to 20 HCV diagnosed patients/month HCV Ab-positive: 7.5% (410/5481) HCV RNA-positive: 45% (183/410) HCV RNA-positive overall: 3.3% (183/5481), average of 20 HCV diagnosed patients /month RNA-positive HCV reflex testing lead to timely diagnosis and LTC Patients attending follow-up appointment: 92% (168/183)
Travis (2018)	Abstract	Retrospective chart review	Patients born between 1945-1965	Emory Midtown University Primary Care Clinic, 12/1/2015-5/1/2018. Implemented "HCV screen" on patient intake form on 12/1/2016.	*n*=10,803	HCV screening rates increased after intervention. Before intervention was 5% (232/4336). After intervention screening rates went to 18% (765/3498) in 2016-2017 and 23% (880/2969) in 2017-2018.
Dong (2017)	Full-text	Prospective cohort	Patients in California in BBBC, high risk patients with hx of IVDU, crack cocaine or methamphetamine use.	Community pharmacy-based HCV-Ab POC screening program in California in collaboration with the local public health department. 3 month pilot, 6 community pharmacists.	*n*=83	HCV-Ab rapid POC-positive: 1.2% (1/83)

Abbreviations: Ab, antibody; BBBC, baby boomer birth cohort; BC, birth cohort; BPAs, best practice alerts; BMC, Boston Medical Center; CDC, Centers for Disease Control; ED, emergency department; EHR, electronic health record; EMR, electronic medical record; HCV, hepatitis C virus; IVDU, intravenous drug use; JHU, Johns Hopkins University; LTC, linkage to care; PCP, Primary care physician; PDSA, plan, do, study, act; POC, point of care; RF, risk factor; UAB, University of Alabama-Birmingham.

widely from increases of 1.8- to 15.8-fold.[32,33] Two studies examined the impact of educational intervention for outpatient primary care providers versus EMR alerts alone, and found an increase in screening rates as high as 45% to 55% at 3 months after a single education session.[28,34] While EMR alerts represent an easily adapted, systems-based intervention to increase birth cohort screening, current studies have been limited to largely small single-center interventions in unique clinical settings, with limited information on downstream outcomes within the care cascade, including RNA confirmation, linkage to care, and HCV treatment.

One of the few multicenter studies examining outpatient screening interventions was reported by Turner *et al.*[35] who evaluated the feasibility and impact of the Reach, Effectiveness, Adoption, Implementation, Maintenance model in a state-funded program to implement birth cohort testing in five federally qualified healthcare centers and one family medicine residency program. Within a cohort of 27, 700 baby boomers born 1945-1965, 13,334 (48.1%) successfully underwent HCV Ab testing, 695 were HCV Ab-positive (5.2%), 349 were HCV RNA-positive (2.6%), 82 initiated DAA therapy, 74 completed DAA therapy, and 70 achieved a sustained virologic response (SVR). In this grant funded intervention study involving multilevel practice engagement strategies, patient navigation, standardized HCV Ab and reflex HCV RNA testing, and access to free DAA therapy via prescription assistance programs, HCV birth cohort screening increased from 0.8% to 48.1% between 2014 and 2018. This study additionally identified multiple barriers and challenges to birth screening interventions, significant site-level variability in performance, and the central importance of best practice alerts (BPAs), reflex RNA testing, access to specialty consultation via telemedicine, and role of local champions.

Inpatient

The inpatient setting provides a unique place for birth cohort screening. Multiple studies have demonstrated that inpatient screening is effective in identifying new cases of HCV but may not translate to effective linkage to care or treatment, and is limited by factors such as socioeconomic status, racial disparities, and lack of insurance.[36,37] Two studies examined the effect of the 2014 New York state HCV screening law within large academic hospitals and showed that despite a significant increase in screening rates, 8 to 39% and 53 to 84%, respectively, very few patients were linked to care or received DAA treatment, with an overall decrease in treatment initiation during the period of observation.[38] The challenges of inpatient screening may be driven by variable access to reflex RNA testing, provider-led results reporting and education, and outpatient follow-up after hospital discharge, and underscores the need for additional research to clarify evidence-based strategies to augment linkage to care.

Direct patient solicitation

Multiple strategies targeted at direct patient contact have been explored to increase screening rates, including direct mail campaigns, with letters containing educational material and blood test request forms distributed to birth cohort patients identified via EMR.[39,40] One study compared live-person recruitment through either phone call, direct mail, or electronic health record prompt at three study sites and found that all three methods were significantly limited by requirement for substantial administrative and staffing resources beyond existing clinic infrastructure. One randomized controlled trial assigned patients to one of three independent implementation strategies: repeated mailings, BPA through electronic health record, or direct phone solicitation.[41] Compared to controls, all three methods were associated with increased screening, with repeat mailings, BPA, and direct phone solicitation resulting in 8 times, 2.6 times, and 5 times control rates, respectively, suggesting that direct patient contact may represent a valuable, complementary tool to augment birth cohort screening efforts.

Colonoscopy

Patients undergoing routine colonoscopy for colorectal cancer screening overlap with patients born 1945-1965 (age 54-74 years as of 2019). This concordance of age makes point-of-care testing (POCT) in the colonoscopy suite a unique setting for HCV screening. Abu-Heija *et al.*[42,43] reported the results of a retrospective cohort study of a predominantly African American population undergoing colonoscopy in an urban open-access colonoscopy suite, and identified an increase in birth cohort HCV testing from 31% to 40.3% between 2014-2017, high rates of HCV Ab positivity (31.5 to 42.9%), and higher likelihood of screening among patients referred from university-affiliated clinicians. Another study performed in USA veterans examined the impact of a same-day HCV testing during colonoscopy which involved registered nurse pre-screening and phone consent for HCV Ab testing in birth cohort patients 1 day prior to scheduled colonoscopy, followed by laboratory draw at the time of intravenous line placement for colonoscopy; this intervention resulted in an 85% HCV Ab testing rate in this setting.[44] Other studies have reported slightly lower rates for HCV Ab testing among patients undergoing colonoscopy targeted on the basis of risk factors identified by patient survey.[45,46]

Endoscopy

Outside the specific context of colorectal cancer screening, the endoscopy suite broadly provides an opportunity for HCV screening by gastroenterologists who are uniquely positioned to offer real-time Ab testing, results reporting, patient education, and linkage to care including DAA treatment. Few studies have examined prospective interventions in the endoscopy suite incorporating both birth cohort- and risk factor-based testing. One urban safety-net hospital in California conducted a series of studies[47,48] to examine HCV screening practices in the endoscopy suite setting, and identified lower test acceptance among birth cohort versus non-birth cohort populations (odds ratio: 0.39, 95% confidence interval: 0.13-1.14, p=0.09)[48] and 82.5% versus 93.9% (p=0.004).[47] Integration of a pre-screening tool and a patient navigator tool in the outpatient endoscopy suite resulted in an overall increase in eligible patients who were tested (50.8% to 77.9%); although, the authors identified a persistent gap in HCV testing in positive risk factor groups, as well as significant challenges in achieving patient acceptance and engagement.[49]

ED

Historic studies of HCV screening in ED populations prior to implementation of birth cohort screening guidelines revealed a higher prevalence than in the general population, with rates ranging from 4% in Michigan to 18% in Baltimore.[50–55] Although our review focused specifically on patients within the 1945-1965 year-range, some studies have revealed that testing restricted to the birth cohort alone may miss identification of up to 28% of HCV Ab-positive patients seen in the ED setting.[56] Recent reports have additionally identified high levels of patient acceptance of HCV testing in the ED setting

(90% of those completed a structured interview), but sobering low rates of linkage to care following testing among Ab positive patients.[54,57] A large CDC-funded study conducted in an urban academic ED center in Alabama demonstrated similarly high patient acceptance of HCV testing (88%), high HCV Ab positivity (11%), and high HCV RNA testing of Ab positive patients (88%).[58] However, among patients confirmed with chronic HCV infection (68% RNA positive among Ab-positive group), only 54% attended a hepatology clinic appointment following discharge despite automated phone calls and a care coordinator focused on linkage to care. Another study examining HCV testing of birth cohort versus all adults in an urban ED in California revealed higher HCV Ab positivity in birth cohort versus all adults (13.7% vs. 10.3%), limited HCV RNA confirmation testing (67%), similar proportion of HCV RNA-positive patients confirmed with chronic infection (70%), and poor linkage to care, with only 24% of RNA positive individuals attending a postdischarge clinic appointment.[59] A recent study in a large urban academic ED in Boston similarly revealed high HCV Ab positivity (13.2%) and poor attendance at postdischarge clinic appointment (22.5%) among HCV RNA-positive patients.[60] These findings underscore the high yield of targeted HCV screening in the ED context, as well as the need for innovative strategies to augment linkage to care to promote more effective patient navigation.

Non-physician providers

Non-physician clinicians including nurses, care coordinators, patient navigators, pharmacists, and advanced practice providers, such as physician assistants, nurse practitioners, and advance practice registered nurses, play a central role in all aspects of HCV screening, care navigation, and treatment, and have featured prominently in nearly all interventional studies targeting birth cohort screening. However, few studies have examined the specific roles of non-physician providers. Shelgrove *et al.*[61] highlighted the importance of care coordinators and clinic managers in the context of a federally qualified healthcare centers in California, with a focus on augmenting linkage to care. Among a cohort of patients screened for HCV, 7.5% were HCV Ab-positive (410/5481), of whom 45% were HCV RNA-positive with reflex testing (183/410), and 92% (164/183) successfully attended an appointment with either a primary care physician or specialist following diagnosis of chronic HCV infection; these findings contrast sharply with the comparatively low rates of linkage to care (22.5-37.3%) reported in other studies, such as the CDC Hepatitis Testing and Linkage to Care initiative.[60,62,63]

Utilizing medical assistants to identify eligible patients for HCV screening by means of printed patient intake forms within an outpatient primary care clinic resulted in increased testing rates, from 5% up to 23%.[64] Another research group reported the novel use of clinical pharmacists to offer point-of-care HCV Ab testing to high risk and birth cohort patients seen at a community-based pharmacy.[65] It is likely that a combination of interventions using physician and non-physician providers across practice settings will be necessary to meaningfully expand HCV screening in both birth cohort and high-risk populations.

Birth cohort screening in USA veterans

The USA Veterans Health Administration (VHA) has represented a national leader in efforts to screen and manage HCV using systems-based approaches. One early retrospective cohort study from 2011 in the Atlanta Veterans Affairs Medical Center described that over half of birth cohort veterans in care had been tested for HCV, and those born in the birth cohort were 6 times more likely to have a positive HCV Ab test and 3 times more likely to have chronic HCV compared to non-birth cohort veterans.[66] A 2016 report examined HCV testing practices within the national VHA system among 4.2 million birth cohort veterans receiving care between 2000-2013, and confirmed that 51% had undergone HCV testing; significant local and regional variabilities in testing practices (7-83%) were identified, and up to 20% of birth cohort veterans with FIB-4 scores suggestive of advanced fibrosis or cirrhosis had not received HCV testing.[67]

In the context of national efforts by Veterans Affairs' leadership to adopt birth cohort HCV screening recommendations, HCV Ab testing in birth cohort veterans had increased to nearly 70% as of 2017.[67–69] The VHA has employed a multifaceted, integrated approach, including the formation of regional HCV innovation teams focused on increasing birth cohort testing, adoption of a national HCV testing electronic clinical reminder, establishing HCV testing as a regional and national VA quality performance metric, and publishing quarterly reporting of HCV birth cohort testing rates at site, regional, and national levels to enhance transparency and accountability.[68] Many of these strategies may potentially be applicable to large non-federal health systems but requires high-level engagement by leadership and institutional commitment to achieving similar levels of success.

POCT and rapid detecting tests (RDTs)

The CDC and USPSTF guidelines recommend that HCV Ab testing should be performed as a screening test of choice, and positive results should be reflexed to HCV RNA test by PCR or nucleic acid testing.[70,71] The gold standard test for anti-HCV identification has been the enzyme immunoassay, which takes several days to weeks to process a result, and has significant laboratory requirements, including high-cost equipment, trained technicians, continuous supply of electricity and high facility cost. In contrast, newer rapid point-of-care immunoassays can provide results in as little as 20-40 m. The OraQuick test represents the most widely used POCT in the USA, approved by the Federal Drug Administration in 2010, and can detect HCV Ab in saliva or blood.[72] One meta-analysis reported a pooled sensitivity of 98% (95% confidence interval: 98-100%) and specificity of 100% (95% confidence interval: 100-110%) for HCV Ab rapid diagnostic test compared to the enzyme immunoassay reference standard. Another pooled analysis of eight studies demonstrated that OraQuick ADVANCE was associated with a sensitivity of 98% compared to 88% with other oral assays.[73] RDTs are often faster than POCTs but require specialized equipment and specially trained personnel, are limited to HCV Ab detection (unable to detect HCV RNA), and associated with lower diagnostic performance than POCTs.[74] Further studies to define optimal use of POCTs and RDTs may be helpful in identifying their appropriate role in HCV screening efforts.

Future directions

Despite major advances in antiviral therapy for chronic HCV infection since 2014, persistent deficits in the HCV care cascade within the USA threaten to limit the capacity to achieve meaningful changes in the burden of chronic infection and downstream clinical outcomes, as well as ambitious targets for HCV elimination by the WHO and USA Department of Health and Human Services. Although progress has been made within each step of the cascade, including screening (HCV Ab), confirmation (HCV RNA), linkage to care, and treatment, identification of uninfected patients represents the critical rate-limiting step. Additional challenges to achieving HCV elimination include ongoing late relapse and reinfection among patients who achieve sustained virologic response.

Since implementation of new recommendations for one-time HCV Ab testing in all USA adults born 1945-1965 by the CDC and USPSTF, birth cohort screening has provided a central focus for health system, state, and national level efforts to increase the diagnosis of chronic HCV. A multi-faceted integrative approach to screening which integrates clinical education, clinical decision support, reflex HCV RNA testing, and incorporation of non-physician providers have been proven to be successful in increasing HCV screening. However, multiple studies have confirmed that overall screening rates within the USA outside the VHA remain low, despite success within individual centers and health systems. Based on the available literature, no single strategy appears to be easily applicable across clinical settings.

Our review underscores the need for the following steps: 1) patient and provider education to address a persistent deficit in knowledge, regarding both HCV risk factors as well as national screening recommendations; 2) engagement of health systems to incorporate standardized tools, such as reflex HCV RNA testing and EMR alerts to prompt clinicians to pursue HCV testing across the inpatient, emergency department, outpatient clinic, pharmacy, and endoscopy center settings; and 3) strategic use of novel diagnostic tests (e.g. POCT/RDT) and emerging technologies (e.g. text alerts) in appropriate clinical settings. Significant resources may be required to fully support the multidisciplinary programs required to meaningfully impact broader efforts for screening, linkage to care, and treatment.

Furthermore, emerging data suggest that birth cohort screening will be inadequate to identify the growing cohort of non-birth cohort adults with chronic HCV, including a rising population of young adults recently infected with HCV in the context of substance use and the opiate epidemic. Recent NHANES reports suggest an overall decrease in chronic HCV prevalence from 1.32% to 0.80% between 1999-2004 and 2011-2016; although, an estimated 1.90 million USA adults continued to have viremic HCV, of whom only 49.8% were reportedly aware of their infection.[75] An updated report which combined NHANES data with high-risk populations excluded by NHANES (prisoners, unsheltered homeless persons, active-duty military personnel, nursing home residents) estimated a prevalence of 2.4 million HCV RNA-positive persons.[2] Expansion from birth cohort to universal screening of all USA adults may identify up to an estimated 28% of HCV-infected individuals who would be missed by birth cohort[55–60] or risk factor-based screening strategies.[76] In addition, economic models have demonstrated that a universal screening strategy in USA adults is more cost effective than a birth cohort screening strategy in populations with a HCV prevalence >0.07% among non-birth cohort adults.[77] This emerging evidence of increasing HCV incidence in younger adults[78] and resulting gap in identification of HCV-infected persons have prompted reconsideration of USA HCV screening guidelines.

In 2019, several organizations have publicly called for expansion of HCV screening to a universal approach to offer one-time HCV Ab testing to all USA adults age 18-79 years or age 18 years and older, including draft statements by the USPSTF (August 2019)[79] and CDC (October 2019),[80] as well as updated language within the HCV guidance document of the Infectious Diseases Society of America and American Association for the Study of Liver Diseases (November 2019).[81] In the context of these emerging changes in national screening recommendations, significant additional research is needed to support evidence-based recommendations on population and system-level HCV screening strategies. Lessons learned from early experiences with birth cohort screening studies may help inform future research and public health efforts at implementation of future universal screening initiatives.

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Conflict of interest

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Author contributions

Study concept and design, and critical revision of the manuscript for important intellectual content (JKL), acquisition of data (CJT), analysis and interpretation of data and drafting of the manuscript (JKL and CJT).

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