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Hepatitis C Screening in Emergency Departments
The DETECT Hep C Randomized Clinical Trial

Jason Haukoos, MD, MSc; Richard E. Rothman, MD, PhD; James W. Galbraith, MD; Emily Hopkins, MSPH; Yu-Hsiang Hsieh, PhD; Carolynn Lyle, PA-C, MPH; Stephanie Gravitz, MPH; Kevin F. Kamis, MPH; Douglas A. E. White, MD; Michael S. Lyons, MD, MPH; Edward M. Gardner, MD; Alia A. Al-Tayyib, PhD; Allison L. Sabel, MD, MPH, PhD; Benjamin P. Linas, MD, MPH; Jake R. Morgan, PhD; David L. Wyles, MD; Sarah E. Rowan, MD; for the DETECT Hep C Screening Trial Investigators

IMPORTANCE Identification of individuals with hepatitis C virus (HCV) infection is a public health priority. Emergency departments (EDs) have been a focus of screening efforts, as they serve large numbers of at-risk patients who commonly do not access health care elsewhere. However, the optimal approach to HCV screening in ED settings remains unknown.

OBJECTIVE To evaluate the effectiveness of HCV screening in EDs with the hypothesis that nontargeted screening identifies more new diagnoses than targeted screening.

DESIGN, SETTING, AND PARTICIPANTS Prospective, multicenter, pragmatic randomized clinical trial performed at 3 urban EDs in Denver, Colorado; Baltimore, Maryland; and Jackson, Mississippi. Patients were 18 years or older, with exclusions for critical illness, inability to provide consent, or previously diagnosed HCV.

INTERVENTIONS As part of routine ED care, patients were randomly assigned to undergo either nontargeted screening, in which HCV testing was offered regardless of risk, or targeted screening, in which testing was offered based on risk assessment.

MAIN OUTCOMES AND MEASURES The primary outcome was newly diagnosed HCV infection (RNA detected). Secondary outcomes were repeat HCV diagnoses; HCV test offer, acceptance, and completion; HCV genotype and fibrosis staging; components of the HCV care continuum; and all-cause mortality through 18 months of follow-up. Analyses were conducted from January to March 2025 by intention-to-treat analysis, using relative risk (RR) with 95% CIs and Fisher exact tests.

RESULTS A total of 147 498 patient visits were randomized (median [IQR] age, 41 [29-57] years; 51.5% male; and 42.3% Black, 20.9% Hispanic, and 32.2% White). Of these, 73 847 patients underwent nontargeted screening, resulting in 9867 (13.4%) tested for HCV and 154 new HCV diagnoses, whereas 73 651 patients underwent targeted screening and 23 400 (31.8%) were identified to have risk factors for HCV infection, resulting in 4640 (6.3%) patients tested for HCV and 115 new HCV diagnoses. Compared with targeted HCV screening, nontargeted HCV screening identified significantly more new diagnoses of HCV infection (RR, 1.34 [95% CI, 1.05-1.70]; $P = .02$). Among patients newly diagnosed with HCV infection, small proportions from the nontargeted and targeted screening groups were linked to follow-up care (19.5% vs 24.3%, respectively), initiated direct-acting antiviral (DAA) treatment (15.6% vs 17.4%), completed DAA treatment (12.3% vs 12.2%), and attained sustained virologic response at 12 weeks (SVR12) (9.1% vs 9.6%).

CONCLUSIONS AND RELEVANCE In this multicenter randomized clinical trial, a nontargeted screening approach was superior to targeted screening for identifying new HCV infections among patients seen in 3 urban EDs. The substantial decrease in patients who went from diagnosis to SVR12 highlights an urgent need for innovative models of HCV treatment.

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Visual Abstract

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The members of the DETECT Hep C Screening Trial Investigators appear in Supplement 3.

Corresponding Author: Jason Haukoos, MD, MSc, Department of Emergency Medicine, Denver Health, 777 Bannock St, Mail Code 0108, Denver, CO 80204 (jason.haukoos@dhha.org).

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The burden of disease from hepatitis C virus (HCV) is substantial, with dramatic increases over the past decade, driven largely by the opioid epidemic.[1,2] It is estimated that up to 4 million individuals in the US are infected with HCV and, of these, approximately 800 000 remain undiagnosed.[3,4] Hepatitis C is often indolent and commonly remains asymptomatic for years. Morbidity and mortality from HCV have increased significantly in recent years, with approximately 13 000 deaths annually in the US,[5] despite the effectiveness of direct-acting antiviral (DAA) treatment[6] resulting in virologic cure for most patients who complete treatment. Once decompensated cirrhosis develops, treatment is less effective, and 5-year associated mortality exceeds 50%. As such, identification of individuals with HCV infection, and specifically at earlier stages, is a critical public health priority.[7]

Emergency departments (EDs) present an opportunity to increase HCV screening, as they serve as a medical safety net and the primary source for acute unscheduled episodic care, accounting for approximately 140 million visits annually in the US and serving large numbers of individuals who otherwise do not access health care.[8,9] Currently, the US Centers for Disease Control and Prevention (CDC), US Preventive Services Task Force (USPSTF), American Association for the Study of Liver Diseases (AASLD), and Infectious Diseases Society of America (IDSA) recommend nontargeted HCV screening for all adults at least once in their lifetime, with additional testing for those with ongoing risk (eg, injection drug use [IDU]).[10-12] Previously, the CDC and USPSTF recommended a targeted approach to HCV screening, centering on those born between 1945 and 1965 (ie, birth cohort), IDU, select medical conditions (eg, long-term hemodialysis), or recipients of transfusions or organ transplants.[13,14] Although prior research has attempted to assess the effect of various HCV screening strategies in EDs,[15,16] the optimal approach to HCV screening in this setting generally and the comparative effectiveness of nontargeted vs targeted HCV screening specifically remain unknown.

The goal of this study was to compare nontargeted and targeted HCV screening strategies when integrated into practice across multiple EDs, with the hypothesis that nontargeted screening would be superior to targeted screening for identifying new HCV infections.

Key Points

Question What is the most effective way to screen patients for hepatitis C virus (HCV) infection in emergency departments (EDs)?

Findings This multicenter randomized clinical trial included 147 498 ED patient visits. Of these, 73 847 underwent nontargeted screening, resulting in 9867 tested for HCV and 154 new diagnoses, whereas 73 651 underwent targeted HCV screening, resulting in 4640 tested for HCV and 115 new diagnoses. Compared with targeted HCV screening, nontargeted screening was associated with significantly higher numbers of new HCV diagnoses (relative risk, 1.34 [95% CI, 1.05-1.70]; $P = .02$).

Meaning Nontargeted HCV screening was superior to targeted screening for identifying HCV infection in the ED.

Methods

Study Design and Setting

We performed a multicenter, prospective, pragmatic, 2-parallel group randomized clinical trial in 3 high-volume EDs in Denver, Colorado (Denver Health Medical Center); Baltimore, Maryland (Johns Hopkins Hospital); and Jackson, Mississippi (University of Mississippi Medical Center). These sites serve large, heterogeneous, underserved populations, with a total of approximately 250 000 annual combined ED visits. The methods and rationale for this trial have been previously published.[17] The trial was designed using the PRECIS-2 framework for pragmatic trials.[18] This study is reported in accordance with CONSORT guidelines.[19,20] The Colorado Multiple Institutional Review Board (IRB) served as the central IRB for all sites and approved the study with a waiver of written informed consent due to the pragmatic nature and minimal risk of the trial. The study protocol and statistical analysis plan are included in Supplement 2.

Inclusion Criteria

Patients were eligible for inclusion if considered clinically stable by screening nurses or clinicians (eg, physicians, nurse practitioners, or physician assistants) and capable of providing consent for medical care. Enrollment occurred 24 hours per day, 7 days per week. Patients were excluded if they were (1) younger than 18 years, (2) unable to consent for care (eg, altered mentation, critical illness or injury), (3) underwent previous HCV testing as part of the trial, (4) were previously diagnosed with HCV, or (5) had an anticipated ED length of stay of less than 60 minutes based on nurse judgment.

Interventions

Randomization

Randomization occurred from November 20, 2019, through August 4, 2022, and was integrated into the electronic health record (EHR) system at each institution using a computer-generated random number algorithm developed and validated at each site prior to beginning enrollment. Real-time randomization occurred 24 hours per day, providing concealed randomization with equal probability assignment to 1 of the 2 HCV screening groups. This process triggered various EHR prompts during triage and as part of the nurses' workflow, described below.[21]

HCV Screening

All patients who met the inclusion criteria were randomized to undergo either nontargeted or targeted HCV screening. Nontargeted screening consisted of implementation of non-risk-based HCV screening, where all eligible patients were offered, regardless of risk, voluntary, rapid HCV testing by nurses as part of ED triage using a structured script and opt-out consent during medical screening. Targeted HCV screening consisted of implementation of risk-based HCV screening

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(using the following criteria: born between 1945 and 1965, IDU, intranasal drug use, tattoo or piercing in an unregulated setting, or blood transfusion or organ transplant before 1992) based on recommendations from the CDC and USPSTF at the time the study began enrollment.[13,14] Patients identified to have risk factors were offered voluntary, rapid HCV testing using a structured script and opt-out consent during medical screening.

HCV Testing

All HCV testing was voluntary and provided at no cost to patients, with consent obtained verbally as part of clinical care but separate from consent for general emergency care. All processes were fully integrated into usual ED clinical care using blood samples obtained by venipuncture for anti-HCV antibody enzyme immunoassays performed in each institution's central laboratory (OraQuick HCV Rapid Antibody Test [OraSure Technologies] at Denver Health Medical Center; Roche Elecsys Anti-HCV II [Roche Diagnostics] at Johns Hopkins Hospital; and ARCHITECT Anti-HCV assay [Abbott Laboratories] at the University of Mississippi Medical Center) and in some instances by finger stick for point-of-care anti-HCV antibody immunoassay testing (OraQuick HCV Rapid Antibody Test at Johns Hopkins Hospital). Anti-HCV immunoassays are highly sensitive (>97%) and specific (>99%), although may result in false-positive results when testing in low-prevalence populations.[22] All HCV antibody test results were returned during the ED visit. All anti-HCV antibody assays with positive results reflexed to an HCV RNA assay to identify viremia and thus active infection.[23] For patients whose test results were positive for HCV antibodies, the clinical team explained the process to obtain RNA results and provided detailed information related to outpatient follow-up for those whose test results were RNA positive.

Outcomes

The primary outcome was newly diagnosed HCV, defined as patients who had positive test results for HCV antibodies with detectable HCV RNA and without a known prior HCV diagnosis. Secondary outcomes included (1) repeat HCV diagnoses (diagnosed with HCV in the ED but then identified as having evidence of a prior HCV diagnosis); (2) HCV test offer, acceptance, and completion; (3) HCV genotype and fibrosis staging; (4) components of the HCV care continuum[24] (ie, linkage to care with an HCV clinician), DAA treatment initiation (being prescribed a DAA regimen), DAA treatment completion (having the last DAA prescription filled), and sustained virologic response 12 weeks after treatment completion (SVR12); and (5) all-cause mortality measured over an 18-month follow-up period (extended from the original 6-month planned follow-up period to accommodate the effects of the COVID-19 pandemic),[25] ending on January 31, 2024.

Data Collection

The following data were collected for all patient visits: (1) patient ED visit information (unique identifier, acuity level, mode of arrival, date and time); (2) demographics (age, gender, race and ethnicity, preferred language); (3) payer information (commercial, Medicaid, Medicare, self, or other); (4) trial eligibility; (5) details of randomization, including allocation and, if applicable, results of HCV risk factor screening; (6) whether a patient was offered, accepted, and completed HCV testing; and (7) results from HCV antibody tests and, for those whose test results were positive for HCV antibodies, results of RNA testing. Gender and race and ethnicity were collected to assess demographic distributions for patients in this trial and were classified by self-report, using categories defined by each site and collected by registration staff as part of standard emergency medical intake.

For all patients whose test results were positive for HCV antibodies, we performed comprehensive medical record review using all available records from each institution and standardized abstraction methods performed by trained research staff using REDCap.[26] We collected (1) evidence of prior HCV diagnosis; (2) evidence of prior HCV treatment; (3) HCV genotypes and fibrosis staging, if completed; (4) risk characteristics, including documentation of history of IDU classified as recent (defined as within the 3 months prior to HCV diagnosis) or ever; (5) HCV care continuum outcomes; and (6) all-cause mortality. All outcomes were collected by trained research staff while masked to study group randomization. Data from each site were transferred to Denver Health Medical Center, the data coordinating center, where they were cleaned, concatenated, and translated into native SAS format for analysis.

Statistical Analyses

Analyses were performed from January to March 2025 using intention-to-treat analysis. Given the pragmatic trial approach and minimal risk to patients, there were no interim analyses planned or performed. Continuous data are reported as medians with IQRs and categorical data as counts, proportions, or percentages with 95% CIs. Bivariate statistical tests (eg, Fisher exact tests) were used to compare variables between study groups. The primary comparison included an unadjusted relative risk (RR) with a 95% CI for newly identified HCV (primary outcome), specifically comparing nontargeted screening with targeted screening (primary hypothesis) while incorporating site as a random effect in a hierarchical log-binomial model. Secondary comparisons included unadjusted RRs with 95% CIs for secondary outcomes. Sensitivity analyses were performed, adjusting for all baseline covariates, and given the relatively small proportions of covariate missingness, both complete case analyses and with missing values coded as indicator variables were performed.[27]

Prespecified subgroup analyses included primary results by age, gender, race and ethnicity, payer, mode of arrival, acuity, and site. Analyses were further performed, stratifying by site and recent IDU. Finally, time-to-event analyses were performed using Kaplan-Meier curves with log-rank statistics and hierarchical Cox proportional hazards regression for time to linkage to care, DAA initiation, DAA treatment completion, and SVR12 during an 18-month follow-up period. Statistical significance was defined as $P < .05$ based on 2-sided statistical testing. No adjustments were made for multiple comparisons.

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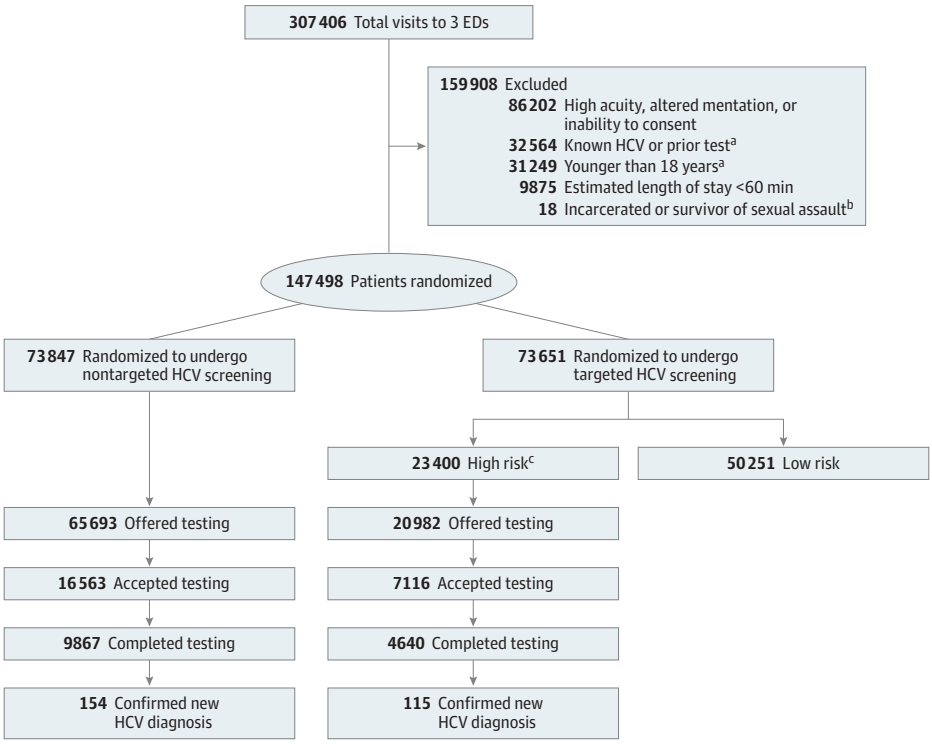
Figure 1. Participant Flow in a Trial of Hepatitis C Virus (HCV) Screening in Emergency Departments (EDs)



eFigures 1-3 in Supplement 1 describe participant flow for each site.

[a]The electronic health record was developed to automatically screen by age, known HCV, or prior positive HCV test results. Known HCV was also excluded manually by nurses during triage.

[b]Patients who are incarcerated and survivors of sexual assault were excluded from the University of Mississippi Medical Center.

[c]Defined as those born between 1945 and 1965 or with injection drug use, intranasal drug use, a tattoo or piercing in an unregulated setting, or blood transfusion or organ transplant before 1992.

The unit of analysis was the ED visit. All analyses were performed using SAS Enterprise Guide version 8.4 (SAS Institute).

Sample Size

We hypothesized a minimum 25% relative increase in new HCV diagnoses for nontargeted screening compared with targeted screening (ie, RR ≥1.25). To test this effect, we performed 1000 simulated trials using Monte Carlo methods in SAS and invoked assumptions related to proportions of test offer, acceptance, completion, and HCV prevalence, resulting in an estimated minimum of 50 000 randomized patient visits, 13 965 completed HCV tests, and 611 new HCV diagnoses across all sites to achieve a power of 80% (2-sided α = .05). Accounting for site-level clustering and using data from a prior HIV screening trial,[28] we estimated the intraclass correlation to range between 0.005 and 0.01. However, given the small number of clusters and the relatively large number of planned enrolled patients, we did not specifically modify planned enrollment based on site-level correlation.

Results

During the enrollment period, 147 498 eligible patient visits were randomized (**Figure 1**); baseline characteristics are shown in **Table 1**. Overall, the median (IQR) age was 41 (29-57) years; 51.5% were male; 42.3% were Black, 20.9% were Hispanic, 32.2% were White; and 89.4% preferred the English language. Medicaid (37.5%) was the most common payer source, followed by commercial insurance (20.3%), Medicare (18.7%), and self-pay or uninsured (16.0%). Site-specific patient flow, baseline characteristics, and comparisons of patient visits not eligible or eligible but not randomized are shown in eFigures 1-3 and eTables 1-4 in Supplement 1.

Of the 147 498 included patient visits, 73 847 (50.1%) were randomized to undergo nontargeted HCV screening, of which 65 693 (89.0%) were offered HCV testing, 16 563 (22.4%) accepted testing, and 9867 (59.6%) completed testing, resulting in 416 (4.2%) antibody-positive test results and 154 (1.6% [95% CI, 1.3%-1.8%]) with confirmed new HCV diagnoses (ie, RNA detected). Of the 73 651 (49.9%) randomized to undergo targeted HCV screening, 23 400 (31.8%) were determined to be at increased risk. Of those identified as at risk, 20 982 (89.7%) were offered HCV testing, 7116 (30.4%) accepted testing, and 4640 (65.2%) completed testing, resulting in 348 (7.5%) antibody-positive test results and 115 (2.5% [95% CI, 2.1%-3.0%]) with confirmed new HCV diagnoses (ie, RNA detected). Birth cohort and risk characteristics of patients randomized to the targeted group are shown in Table 1.

Nontargeted HCV screening led to significantly higher testing compared with targeted screening. Specifically, nontargeted HCV screening resulted in 3.1 times more individuals being offered HCV testing (89.0% vs 28.5%; difference, 60.5% [95% CI, 60.1%-60.9%]; $P < .001$). Of those who were offered testing, a higher proportion of those in the targeted screening group accepted testing (25.2% vs 33.9%; difference, 8.7% [95% CI, 8.0%-9.4%]; $P < .001$). Ultimately, nontargeted HCV screening resulted in 2.1 times more individuals completing HCV testing (13.4% vs 6.3%; difference, 7.1% [95% CI, 6.8%-7.4%]; $P < .001$).

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Table 1. Baseline Characteristics of Patients Included in the Trial[a]

Characteristic	No. (%)	
	Nontargeted HCV screening (n = 73 847)	Targeted HCV screening (n = 73 651)
Age, y		
Median (IQR)	41 (29-57)	41 (29-57)
18-29	18 564 (25.1)	18 423 (25.0)
30-39	16 229 (22.0)	16 327 (22.2)
40-49	12 324 (16.7)	12 173 (16.5)
50-59	11 386 (15.4)	11 325 (15.4)
60-69	8764 (11.9)	8673 (11.8)
70-79	4247 (5.8)	4381 (5.9)
≥80	2333 (3.2)	2349 (3.2)
Gender	n = 73 706	n = 73 498
Cisgender female	35 205 (47.8)	35 093 (47.7)
Cisgender male	38 035 (51.6)	37 921 (51.6)
Nonbinary	67 (0.1)	83 (0.1)
Transgender	301 (0.4)	308 (0.4)
Not disclosed	98 (0.1)	93 (0.1)
Race and ethnicity[b]	n = 72 721	n = 72 605
American Indian or Alaska Native	507 (0.7)	489 (0.7)
Asian	1096 (1.5)	1005 (1.4)
Hispanic	15 173 (20.9)	15 628 (21.5)
Native Hawaiian or Other Pacific Islander	72 (0.1)	92 (0.1)
Non-Hispanic Black	31 342 (43.1)	30 997 (42.7)
Non-Hispanic White	23 831 (32.8)	23 654 (32.6)
Other[b]	700 (1.0)	740 (1.0)
HCV risk factors[c]		
Birth cohort[d]	16 992 (23.0)	16 992 (23.1)
Injection or intranasal drug use	NA	5237 (7.1)
Tattoo or piercing	NA	3823 (5.2)
Transfusion or transplant	NA	638 (0.9)
>1 Risk factors	NA	2881 (3.9)
Preferred language	n = 73 597	n = 73 440
English	66 094 (89.8)	65 706 (89.5)
Spanish	5948 (8.1)	6148 (8.4)
Other[e]	1555 (2.1)	1586 (2.2)
Payer	n = 70 976	n = 70 684
Medicaid	27 794 (39.2)	27 481 (38.9)
Commercial	15 041 (21.2)	14 870 (21.0)
Medicare	13 799 (19.4)	13 763 (19.5)
Self-pay	11 726 (16.5)	11 904 (16.8)
Other[f]	2616 (3.7)	2666 (3.8)
Acuity[g]	n = 73 045	n = 72 859
Immediate (ESI 1)	7158 (9.8)	7172 (9.8)
Emergent (ESI 2)	5586 (7.6)	5650 (7.8)
Urgent (ESI 3)	42 534 (58.2)	42 457 (58.3)
Less urgent (ESI 4)	14 551 (19.9)	14 359 (19.7)
Nonurgent (ESI 5)	3216 (4.4)	3221 (4.4)
Mode of arrival	n = 73 769	n = 73 564
Self	50 811 (68.9)	50 666 (68.9)
Ambulance	21 673 (29.4)	21 550 (29.3)
Law enforcement	703 (1.0)	711 (1.0)
Medical flight or helicopter	367 (0.5)	421 (0.6)
Other[f]	214 (0.3)	216 (0.3)

Abbreviations: ESI, Emergency Severity Index; HCV, hepatitis C virus; NA, not applicable.

[a] Baseline participant characteristics stratified by site are shown in eTables 1-3 in Supplement 1, and baseline characteristics by eligibility and randomization are shown in eTable 4 in Supplement 1.

[b] Race and ethnicity were self-reported by patients using closed-response fixed categories defined by each institution and collected by registration staff as part of standard emergency medical care. Other, as in Other Pacific Islander or simply other, were prespecified formal categories used by each institution.

[c] Defined by any affirmative response to the following risk characteristics: (1) born between 1945 and 1965, (2) injection drug use or intranasal drug use, (3) tattoo or piercing in an unregulated setting, or (4) blood transfusion or organ transplant before 1992. Risk factors were not collected for patients randomized to undergo nontargeted HCV screening to remove the potential influence this might have on the performance of nontargeted screening.

[d] Born between 1945 and 1965.

[e] Other languages represent a composite incorporating 105 different preferred languages.

[f] Other was a prespecified formal category used by each institution.

[g] Acuity was classified by nurses as part of routine emergency care during medical screening using an established algorithm and consisting of the following 5 levels: ESI 1, requiring immediate life-saving intervention (eg, need for advanced life support intervention, such as epinephrine for anaphylaxis or noninvasive ventilatory support for an acute exacerbation of chronic obstructive pulmonary disease); ESI 2, a high-risk presentation (eg, active chest pain, signs of stroke, increased respiratory effort); and ESI 3, 4, and 5, based on the estimated number of different types of resources needed to determine the patient's disposition (eg, laboratory tests, radiography, computed tomography, medications, intravenous fluids, procedures, consultations) and initial vital signs.

Primary Outcome

Table 2 shows results for primary and secondary outcomes. The prevalence of new HCV diagnoses in the nontargeted and targeted screening groups were 0.21% (154/73 847) and 0.16% (115/73 651) (difference, 0.05% [95% CI, 0.01%-0.1%]), respectively. When compared with targeted HCV screening, nontargeted screening was associated with a significantly higher number of new HCV diagnoses (RR, 1.34 [95% CI, 1.05-1.70]; P = .02). This association did not change when adjusted for baseline characteristics (eTable 5 in Supplement 1).

Secondary Outcomes

Longitudinal follow-up occurred for all patients diagnosed with HCV for 18 months from the time of diagnosis. **Figure 2** and eFigure 4 in Supplement 1 show results of the HCV care continuum and mortality for those newly diagnosed with HCV. Of the 154 patients identified with newly diagnosed HCV from the

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Table 2. Trial Outcomes

Outcome	No. (%)		Unadjusted difference, % (95% CI)	Unadjusted RR (95% CI)	*P* value
	Nontargeted HCV screening (n = 73 847)	Targeted HCV screening (n = 73 651)			
Primary outcome					
New HCV diagnosis	154 (0.21)	115 (0.16)	0.05 (0.01 to 0.1)	1.34 (1.05 to 1.70)	.02
Secondary outcomes[a]					
HCV test offered	65 693 (89.0)	20 982 (28.5)	60.5 (60.1 to 60.9)	3.12 (3.09 to 3.16)	<.001
HCV test accepted	16 563 (22.4)	7116 (9.7)	12.8 (12.4 to 13.1)	2.32 (2.26 to 2.38)	<.001
HCV test completed	9867 (13.4)	4640 (6.3)	7.1 (6.8 to 7.4)	2.12 (2.05 to 2.19)	<.001
Repeat HCV diagnosis	27 (0.04)	31 (0.04)	−0.01 (−0.03 to 0.01)	0.87 (0.52 to 1.46)	.60
18-Month outcomes[b]	n = 154	n = 115			
Appointment for HCV	30 (19.5)	28 (24.3)	−4.9 (−14.9 to 5.2)	0.80 (0.51 to 1.26)	.37
DAAs, initiated	24 (15.6)	20 (17.4)	−1.8 (−10.8 to 7.2)	0.90 (0.52 to 1.54)	.74
DAAs, completed	19 (12.3)	14 (12.2)	0.2 (−7.8 to 8.1)	1.01 (0.53 to 1.93)	>.99
Sustained virologic response at 12 weeks	14 (9.1)	11 (9.6)	−0.5 (−7.5 to 6.6)	0.95 (0.45 to 2.02)	>.99
All-cause mortality	8 (5.2)	5 (4.3)	0.9 (−4.3 to 6.0)	1.19 (0.40 to 3.56)	>.99

Abbreviations: DAAs, direct-acting antivirals; HCV, hepatitis C virus; RR, relative risk.

[a] HCV genotype and fibrosis staging were prespecified secondary outcomes that were variably performed by HCV clinicians and were considered of limited clinical significance with updated HCV treatment guidelines, and thus not reported.

[b] For new HCV diagnoses only.

nontargeted group, 30 (19.5% [95% CI, 13.5%-26.6%]) successfully linked to care, whereas of the 115 patients identified with newly diagnosed HCV from the targeted group, 28 (24.3% [95% CI, 16.8%-33.2%]) successfully linked to care (difference, −4.9% [95% CI, −14.9% to 5.2%]; *P* = .37). Additionally, of the 154 patients in the nontargeted group, 24 (15.6% [95% CI, 10.2%-22.3%]) initiated DAA treatment, whereas of the 115 patients in the targeted group, 20 (17.4% [95% CI, 11.0%-25.6%]) initiated DAA treatment (difference, −1.8% [95% CI, −10.8% to 7.2%]; *P* = .74). Furthermore, of the 154 patients in the nontargeted group, 19 (12.3% [95% CI, 7.6%-18.6%]) completed DAA treatment, whereas of the 115 patients in the targeted group, 14 (12.2% [95% CI, 6.8%-19.6%]) completed DAA treatment (difference, 0.2% [95% CI, −7.8% to 8.1%]; *P* > .99). Finally, of the 154 patients in the nontargeted group, 14 (9.1% [95% CI, 5.1%-14.8%]) achieved SVR12, whereas of the 115 patients in the targeted group, 11 (9.6% [95% CI, 4.9%-16.5%]) achieved SVR12 (difference, −0.5% [95% CI, −7.5% to 6.6%]; *P* > .99). Site-specific HCV care continua for those with newly diagnosed HCV are shown in eFigures 5-7 in Supplement 1. Characteristics of those with repeat HCV diagnoses and their HCV care continua in aggregate and stratified by site are shown in eFigures 8-11 and eTable 6 in Supplement 1. Kaplan-Meier curves and Cox proportional hazards analyses for linkage to care, DAA initiation, DAA completion, and SVR12 by study group and stratified by evidence of recent IDU and site are shown in eFigures 12-15 and eTable 7 in Supplement 1.

Subgroup and Stratified Analyses

Subgroup analyses are shown in **Figure 3**. New diagnoses, demographics, risk characteristics, and outcomes stratified by site and recent IDU are shown in eTables 8-9 in Supplement 1, respectively. Of the 269 newly diagnosed patients, 112 (41.6%) had a known history of recent IDU, and among those 112 patients, 18 (16.1% [95% CI, 9.8%-24.2%]) were linked to care, 11 (9.8% [95% CI, 5.0%-16.9%]) initiated DAAs, and 6 (5.4% [95% CI, 2.0%-11.3%]) had documentation of completed DAA treatment and SVR12. When compared with those who did not have a known history of recent IDU, smaller proportions of patients who disclosed recent IDU were linked to care (16.1% vs 25.5%; difference, −9.4% [95% CI, −19.0% to 0.2%]; *P* = .06), initiated DAA treatment (9.8% vs 21.0%; difference, −11.2% [95% CI, −19.6% to −2.8%]; *P* = .01), completed DAA treatment (5.4% vs 17.2%; difference, −11.8% [95% CI, −19.1% to −4.6%]; *P* = .004), and achieved SVR12 (5.4% vs 12.1%; difference, −6.7% [95% CI, −13.3% to −0.02%]; *P* = .06).

Discussion

To our knowledge, this trial represents the largest and most comprehensive evaluation of HCV screening strategies in EDs to date and underscores the importance of understanding real-world comparative effectiveness of nontargeted to targeted opt-out HCV screening when integrated into emergency care. This is particularly important given national viral hepatitis elimination goals, which provide a framework to eliminate viral hepatitis as a public health threat in the US.[29]

This trial was performed in 3 high-volume, geographically diverse, urban EDs in the US and included full integration of HCV screening into ED processes of care, 24 hours per day, 7 days per week, while using existing clinical staff. A nontargeted screening approach was superior to a targeted screening approach for identifying patients with HCV infection,

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Figure 2. Comparisons of Emergency Department (ED) Patients With Newly Diagnosed Hepatitis C Virus (HCV) Infection Using Nontargeted (n = 154) vs Targeted (n = 115) HCV Screening

DAA indicates direct-acting antiviral; and SVR12, sustained virologic response 12 weeks following treatment completion.

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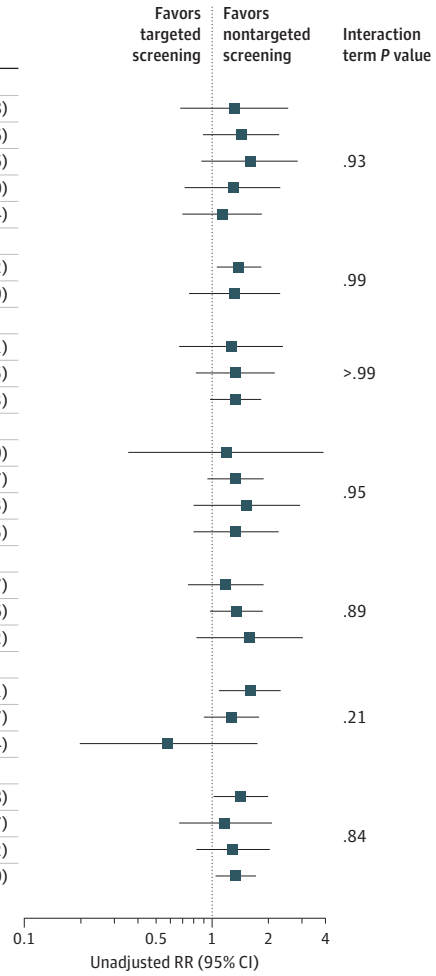
Figure 3. Subgroup Analyses for Newly Diagnosed Hepatitis C Virus (HCV)

Subgroup	No. of new HCV diagnoses/No. screened (%)		Unadjusted RR (95% CI)	Interaction term *P* value
	Nontargeted screening	Targeted screening		
Age, y				
18-29	20/154 (13.0)	15/115 (13.0)	1.32 (0.68-2.58)	
30-39	44/154 (28.6)	31/115 (27.0)	1.43 (0.90-2.26)	
40-49	29/154 (18.8)	18/115 (15.7)	1.59 (0.88-2.86)	.93
50-58	26/154 (16.9)	20/115 (17.4)	1.29 (0.72-2.30)	
≥59	35/154 (22.7)	31/115 (27.0)	1.14 (0.70-1.84)	
Gender				
Cisgender male	125/154 (81.2)	90/115 (78.3)	1.38 (1.06-1.82)	.99
Cisgender female	29/154 (18.8)	22/115 (19.1)	1.31 (0.76-2.29)	
Race and ethnicity				
Hispanic	21/154 (13.6)	17/115 (14.8)	1.27 (0.67-2.41)	
Non-Hispanic Black	39/154 (25.3)	29/115 (25.2)	1.33 (0.82-2.15)	>.99
Non-Hispanic White	93/154 (60.4)	69/115 (60.0)	1.34 (0.98-1.83)	
Payer				
Commercial	6/154 (3.9)	5/115 (4.3)	1.19 (0.36-3.89)	
Medicaid	78/154 (50.6)	58/115 (50.4)	1.33 (0.95-1.87)	.95
Medicare	23/154 (14.9)	15/115 (13.0)	1.53 (0.80-2.93)	
Self-pay	33/154 (21.4)	25/115 (21.7)	1.34 (0.80-2.25)	
Acuity[a]				
High	40/154 (26.0)	34/115 (29.6)	1.18 (0.75-1.87)	
Mid	88/154 (57.1)	65/115 (56.5)	1.35 (0.98-1.86)	.89
Low	24/154 (15.6)	15/115 (13.0)	1.58 (0.83-3.02)	
Mode of arrival				
Self	70/154 (45.5)	44/115 (38.3)	1.59 (1.09-2.31)	
Ambulance	79/154 (51.3)	62/115 (53.9)	1.27 (0.91-1.77)	.21
Other	5/154 (3.2)	9/115 (7.8)	0.58 (0.20-1.74)	
Site				
Denver	84/154 (54.5)	59/115 (51.3)	1.42 (1.02-1.98)	
Baltimore	26/154 (16.9)	22/115 (19.1)	1.17 (0.67-2.07)	.84
Jackson	44/154 (28.6)	34/115 (29.6)	1.29 (0.83-2.02)	
Overall	154/73 847 (0.21)	115/73 651 (0.16)	1.34 (1.05-1.70)	



[a]Defined as high (Emergency Severity Index [ESI] score, 1 or 2), mid (ESI score, 3), or low (ESI score, 4 or 5). RR indicates relative risk.

supporting current recommendations by the CDC, USPSTF, and AASLD-IDSA for performing non–risk-based HCV screening.[10-12] Moreover, these findings support extension of the recommendations specifically to EDs that serve as critical health care access points in the US.[9]

Several smaller observational studies have evaluated implementation of HCV screening in EDs, demonstrating the ability to identify patients with HCV.[30-32] At the time this trial was conceived, targeted screening was recommended, but we hypothesized nontargeted screening would be superior given the magnitude and changing epidemiology of HCV and the challenges of obtaining accurate risk information from patients. Shortly after the trial launched enrollment, updated national guidelines were released, recommending universal 1-time HCV testing of all adults in primary care settings.[10,11] However, understanding the effectiveness of nontargeted vs targeted HCV screening in busy, high-volume clinical settings, like EDs, remained important, and given that 2 of the 3 EDs (Denver and Jackson) had not previously performed HCV screening, it was thought that contamination of these changes would be unlikely.

Among patients randomized to undergo nontargeted HCV screening, 22% accepted testing, similar to prior findings from trials of both HCV and HIV screening in EDs.[28,33,34] Improvements in processes, including use of best practice advisories,[35] feedback,[36] automated testing algorithms,[16,37] or other patient-level interventions[38] may increase testing rates. However, even with the relatively low rates of testing, nontargeted HCV screening resulted in more than twice the number of patients completing testing compared with targeted screening. Conversely, targeted screening identified 43% of new HCV diagnoses (when considering the overall number of individuals found across both groups) while requiring only 32% of the tests, supporting the effectiveness of targeted screening. Thus, even though nontargeted screening was found to be superior to targeted screening, EDs or other high-volume clinical care settings may ultimately consider combination approaches.[39]

While many patients were identified with newly diagnosed HCV infection, clinician referral from the ED resulted in relatively small proportions of patients who were successfully linked to care (20%), initiated treatment (16%), completed treatment (12%), or attained SVR12 (9%) within 18 months. These

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findings are concerning yet similar to previously reported HCV care cascade metrics from ED populations.[24,40] Nonetheless, this points to the critical importance of improving processes for linking patients with HCV from the ED to ongoing care, especially among marginalized populations (eg, individuals who are homeless, have substance use disorders, or have comorbid psychiatric illnesses).[41,42] Although identification of patients with HCV is an important first step, novel strategies for further improving HCV care continuum metrics are needed, potentially including use of navigators[43] or conceivably initiating DAAs at the time of diagnosis in the ED. Recent introduction of point-of-care HCV RNA tests[44] and improved access to DAAs[45] may facilitate earlier diagnosis and treatment from EDs.[46] Additionally, patients who disclosed recent IDU were notably less likely to link to care or complete DAA treatment. As the current HCV epidemic is largely driven by IDU and with estimated HCV prevalence among this group exceeding 30%,[47] those who inject drugs remain a critical population for targeted interventions. Novel strategies to better engage this priority population in care are needed, including understanding barriers to care and developing approaches that align with their needs. Finally, a smaller but substantial number of patients previously diagnosed with HCV and with detectable RNA were identified during this trial, affording the opportunity to reengage those patients in care.

Limitations

This study has limitations. First, although it represents the largest pragmatic clinical trial of HCV screening in EDs to date, it included 3 academic medical centers with experience performing infectious diseases screening and thus may not be generalizable. However, given its pragmatic nature, which included real-world integration of HCV screening and linkage processes and expected variations in how screening was performed, including variations in HCV tests being offered, accepted, and completed, it is likely that results will translate to other settings. Second, this study was performed during the COVID-19 pandemic, with enrollment occurring in conjunction with the initial waves of the pandemic. This resulted in changes to ED workflow and may have changed nursing behavior related to screening implementation. However, subgroup results from Denver, where enrollment most aligned with the pandemic, were consistent with aggregated results. Additionally, HCV linkage-to-care and treatment protocols were modified in response to the COVID-19 pandemic, affecting all stages of the HCV care continuum for all sites, likely resulting in longer times for several secondary outcomes. Third, of all ED visits, 52% were excluded prior to randomization, largely due to high acuity or inability to consent. Although this proportion is relatively large, it reflects the nature of emergency care and the challenges of performing routine HCV screening in this setting. Fourth, secondary outcomes and recent IDU were determined by medical record review, which may have resulted in misclassification bias, and follow-up care outside the integrated health care systems was not captured. Fifth, this study was powered based on the primary outcome, newly diagnosed HCV, and not for HCV care continuum outcomes, thus limiting the ability to make inferences based on these secondary outcomes or specific subgroups.

Conclusions

This multicenter randomized clinical trial determined a nontargeted screening approach was superior to targeted screening for identifying new HCV infections among patients seen in 3 urban EDs. The substantial decrease in patients who went from diagnosis to SVR12 highlights an urgent need for innovative models of HCV treatment.

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Author Affiliations: Department of Emergency Medicine, Denver Health, Denver, Colorado (Haukoos, Hopkins, Lyle, Gravitz); Department of Emergency Medicine, University of Colorado School of Medicine, Aurora (Haukoos, Hopkins); Department of Epidemiology, Colorado School of Public Health, Aurora (Haukoos, Al-Tayyib); Colorado Social Emergency Medicine Collaborative, Denver (Haukoos, Hopkins); Department of Emergency Medicine, Johns Hopkins University, Baltimore, Maryland (Rothman, Hsieh); Department of Emergency Medicine, University of Mississippi Medical Center, Jackson (Galbraith); Public Health Institute at Denver Health, Denver, Colorado (Kamis, Gardner, Al-Tayyib, Rowan); Department of Emergency Medicine, Alameda Health System, Wilma Chan Highland Hospital, Oakland, California (White); Andrew Levitt Center for Social Emergency Medicine, Oakland, California (White); Department of Emergency Medicine, Ohio State University Wexner Medical Center, Columbus (Lyons); Division of Infectious Disease, Denver Health, Denver, Colorado (Gardner, Wyles, Rowan); Division of Infectious Diseases, University of Colorado School of Medicine, Aurora (Gardner, Wyles, Rowan); Department of Patient Safety & Quality, Denver Health, Denver, Colorado (Sabel); Department of Biomedical Informatics, University of Colorado School of Medicine, Aurora (Sabel); Division of Infectious Diseases, Boston University Chobanian & Avedisian School of Medicine, Boston, Massachusetts (Linas); Department of Epidemiology, Boston University School of Public Health, Boston, Massachusetts (Linas); Department of Health Law, Policy & Management, Boston University School of Public Health, Boston, Massachusetts (Morgan).

Author Contributions: Dr Haukoos and Ms Hopkins had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Haukoos, Rothman, Galbraith, Hopkins, Hsieh, White, Lyons, Gardner, Al-Tayyib, Sabel, Rowan.
Acquisition, analysis, or interpretation of data: Haukoos, Rothman, Galbraith, Hopkins, Hsieh, Lyle, Gravitz, Kamis, Al-Tayyib, Sabel, Linas, Morgan, Wyles, Rowan.
Drafting of the manuscript: Haukoos, Galbraith, Kamis, Lyons, Sabel.
Critical review of the manuscript for important intellectual content: Haukoos, Rothman, Galbraith, Hopkins, Hsieh, Lyle, Gravitz, Kamis, White, Gardner, Al-Tayyib, Sabel, Linas, Morgan, Wyles, Rowan.
Statistical analysis: Haukoos, Hopkins, Sabel, Linas, Morgan.
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Editor's Note

Leveraging the Emergency Department to Address the Hepatitis C Epidemic

Preeti N. Malani, MD, MSJ; Stephen M. Schenkel, MD, MPP

Up to 4 million individuals in the US are estimated to be infected with hepatitis C virus (HCV) and a sizable portion remain undiagnosed.[1,2] Most infections are asymptomatic, with exposure to HCV often occurring decades earlier. Hepatitis C is responsible for more than 15 000 deaths each year in the US, despite the availability of direct-acting antivirals (DAAs), which can cure more than 95% of people who complete treatment.[2] Identifying and treating individuals in the US with HCV infection, especially before cirrhosis and other complications develop, has been proposed as a national priority. In a 2023 editorial, Fleurence and Collins outlined a federal program that would use DAAs to eliminate HCV in the US.[2] They posited 3 priorities for success: improved availability of point-of-care testing to diagnose HCV infection, broad access to curative medications, and a comprehensive public health effort targeting identification and treatment of those with HCV infection. However, the best approaches to identify and subsequently treat individuals with HCV infection remain unknown.

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In this issue of *JAMA*, Haukoos and colleagues[3] report the findings of the DETECT Hep C (Determining Effective Testing in Emergency Departments and Care Coordination on Treatment Outcomes for Hepatitis C) screening trial that evaluated the effectiveness of 2 approaches to HCV screening among patients in 3 US emergency departments (EDs). As part of routine clinical care, patients were randomly assigned to undergo either nontargeted screening, in which HCV testing was offered regardless of risk, or targeted screening, in which testing was offered based on established risk factors, such as age, history of drug use, tattoos, piercings, blood transfusion, or organ transplant. The primary outcome was newly diagnosed HCV infection. Several prespecified secondary outcomes included important components of HCV care and all-cause mortality through 18 months of follow-up.

Nearly 150 000 ED visits were included and randomized. In the group assigned to undergo nontargeted screening, 9867 patients (13.4%) were tested for HCV and 154 received a new HCV diagnosis. In the group assigned to undergo targeted screening, 23 400 patients (31.8%) reported risk factors for HCV infection, resulting in 4640 patients (6.3%) tested for HCV and 115 new HCV diagnoses. The authors concluded that nontargeted HCV screening identified significantly more new diagnoses of HCV infection compared with targeted screening (relative risk, 1.34 [95% CI, 1.05-1.70]; $P = .02$), a positive result for the primary outcome.

Secondary outcomes measured at 18 months were equivalent between groups. Among patients diagnosed with HCV infection, relatively small proportions from both the nontargeted and targeted screening groups were linked to follow-up care (19.5% vs 24.3%, respectively), initiated DAA treatment (15.6% vs 17.4%), completed treatment (12.3% vs 12.2%), demonstrated sustained virologic response at 12 weeks (9.1% vs 9.6%), or died (all-cause mortality, 5.2% vs 4.3%).

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