

AWARD NUMBER: W81XWH-19-1-0690

TITLE: Risk of Hepatocellular Cancer After Virological Cure with Direct Acting Antiviral Agents in Individuals with Hepatitis C

PRINCIPAL INVESTIGATOR: Jagpreet Chhatwal, PhD

CONTRACTING ORGANIZATION: Massachusetts General Hospital, Boston, MA

REPORT DATE: October 2021

TYPE OF REPORT: Annual Report

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE October 2021		2. REPORT TYPE Annual Report		3. DATES COVERED 01Sep2020-31Aug2021	
4. TITLE AND SUBTITLE Risk of Hepatocellular Cancer After Virological Cure with Direct Acting Antiviral Agents in Individuals with Hepatitis C				5a. CONTRACT NUMBER W81XWH-19-1-0690	
				5b. GRANT NUMBER PR181562	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Jagpreet Chhatwal, PhD and Fasiha Kanwal, MD, MSHS E-Mail: jagchhatwal@mgch.harvard.edu and Kanwal@bcm.edu				5d. PROJECT NUMBER 0011335789-0001	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Massachusetts General Hospital Department of Radiology 101 Merrimac Street Boston, MA 02114				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Development Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Purpose: The overarching goal of this project is to reduce HCC-related morbidity and mortality in persons with chronic hepatitis C (CHC) who have been virologically cured by direct acting antivirals (DAAs). Aims: 1) Examine determinants of HCC in virologically cured patients and develop a risk prediction model for HCC; 2) Conduct a virtual clinical trial using a mathematical model of the natural history of HCC to evaluate benefits vs harms of HCC surveillance; 3) Develop an online HCC Simulator. Design: Using cause-specific Cox proportional hazard models for competing risks, we will identify risk factors in a retrospective cohort study of >100,000 patients with DAA-induced SVR. For dynamic risk prediction of HCC, we will use the landmark Cox model. We will use a mathematical model to simulate a virtual trial comparing long-term effectiveness of no surveillance vs routine surveillance. Finally, we will develop an interactive decision support tool. Progress: The project is on target to be completed by 09/30/2022. Findings: We identified a range of predictors for HCC in virologically cured patients with CHC. We also found that the nature of predictor variables changed over time. Metabolic traits predicted HCC; however, viral factors (HCV genotype) were no longer predictive at 24 months after cure. A Mathematical model of the natural history of HCC in DAA-cured CHC patients was developed that led the team to conclude that the burden of HCC will shift from viremic to virologically cured CHC patients, and to older populations in the next decade. These findings are reported in a meeting abstract that will be presented during the Liver Meeting 2021 and a manuscript that was accepted by JAMA Network Open.					
15. SUBJECT TERMS: Hepatocellular carcinoma; Chronic hepatitis C (CHC); Direct-acting antivirals (DAAs); Sustained viral response (SVR); Risk stratification; Protective factors; Risk factors; Risk prediction models; Benefits and harms; Decision support tool; Simulator tool; Cancer surveillance					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	53	19b. TELEPHONE NUMBER (include area code)

TABLE OF CONTENTS

	<u>Page</u>
1. Introduction	4
2. Keywords	4
3. Accomplishments	4-10
4. Impact	10
5. Changes/Problems	10
6. Products	11
7. Participants & Other Collaborating Organizations	12-37
8. Special Reporting Requirements	37
9. Appendices	38-53

1.INTRODUCTION: Hepatocellular carcinoma (HCC) is the fastest growing cause of cancer deaths in Americans. HCC incidence has increased 3-fold between 1975–2009 and the trend is still upwards. Despite moderate advances in treatment, most HCC patients present with advanced stage and have low survival (5-year <15%). Chronic hepatitis C (CHC) infection is the leading cause of HCC. The direct-acting antiviral (DAA) treatments offer cure from chronic infection. However, the subsequent risk of HCC persists in patients with CHC after virological cure. In fact, virologically-cured CHC is one of the most important emerging risk factors for HCC. While patients with advanced HCC have a median survival of less than 1 year, patients with early HCC who receive potentially curative therapy achieve 5-year survival rates near 70%. Early diagnosis, therefore, is critical to improved survival. However, the long-term harms and benefits of routine HCC surveillance in virologically cured CHC patients have not been evaluated. Furthermore, instead of using a one-size-fits-all approach, surveillance recommendations based on individualized risk factors could be more efficient — such an approach could detect HCC in early stages in high-risk patients and spare many non-HCC patients who do not need surveillance. The goals of this study are to: (1) identify the most salient protective and risk factors, and combine these factors in predictive models that differentiate high from low risk patients; (2) provide data on long-term benefits and harms of HCC surveillance tailored to individualized risk factors; and (3) develop a first publicly available decision support tool, HCC Simulator, for individualized surveillance recommendations.

2.KEYWORDS:

Hepatocellular carcinoma

Chronic hepatitis C

Direct-acting antivirals

Sustained viral response

Risk stratification

Protective factors

Risk factors

Risk prediction models

Benefits and harms

Decision support tool

Simulator tool

Cancer surveillance

3.ACCOMPLISHMENTS:

◦**What were the major goals of the project?**

The Statement of Work includes the following major goals:

Specific Aim 1 (Kanwal Lead): To examine determinants of HCC in virologically cured patients and develop a risk prediction model for HCC in these patients

Major Task 1: Examine determinants of HCC in patients virologically cured with direct acting antiviral (DAA) agents

Subtask 1: Data acquisition from VA Corporate Data Warehouse, data cleaning, variable creation, and cohort identification (Target date 2/28/2020) – 100% complete

Subtask 2: EMR chart abstractions to confirm HCC (Target date 2/28/2020) – 100% complete

Subtask 3: Data analysis of HCC predictors (Target date 4/30/2020) – 100% complete

Major Task 2: Develop & optimize HCC risk prediction model

Subtask 1: Model fitting/Variable selection (Target date 06/30/20) – 100% complete

Subtask 2: Risk stratification (Target date 07/31/20) – 100% complete

Subtask 3: Subgroup sensitivity analysis (Target date 08/31/20) – completed 03/31/2021

Specific Aim 2 (Chhatwal Lead, Kanwal Team Participating): To evaluate the benefits vs harms of HCC surveillance in virologically cured patients

Major Task 3: Develop a mathematical model simulating the natural history of HCC that incorporates risk estimates and key factors identified in Aim 1

Subtask 1: Model description – Develop a simulation model (individual-level state-transition model) of the natural history of HCC in virologically cured hepatitis C patients (Target date 08/31/20) – 100% complete

Subtask 2: Add modules to the simulation model: surveillance and diagnosis, treatment options based on the BCLC stage at diagnosis (Target date 11/30/2020) – 100% complete

Subtask 3: Liver transplantation - Extend simLT module to simulate the life course of HCC patients on the UNOS waiting list and after the transplant; we will also incorporate HCC recurrence (Target date 11/30/2020) – Delayed. 50% complete. Expected to be complete 03/31/2022.

Subtask 4: Costs and quality of life – Using published studies, estimate costs associated with the mathematical model's (simHCC's) states (Target date 12/31/2020) – 100% complete

Major Task 4: Use simHCC to compare long-term effectiveness of no surveillance versus routine surveillance

Subtask 1: Generate a set of outcomes for surveillance vs no surveillance strategies for each risk group (Target date 01/31/21) – 100% complete

Subtask 2: Conduct probabilistic sensitivity analysis (Target date 02/28/21) – 100% complete

Subtask 3: Conduct value of information analysis (Target date 04/30/21) – 100% complete

Specific Aim 3 (Chhatwal Lead, Kanwal Team Participating): To develop HCC Simulator, an online interactive tool for physicians and patients that provides the short- and long-term value of HCC surveillance in different risk groups

Major Task 5: Create a large dataset of hypothetical virologically cured patients

Subtask 1: Using simHCC model, simulate the life course of 1 million patients having different profiles (Target date 05/31/21) – 100% complete

Subtask 2: Generate a set of graphical outcomes for each patient profile with and without HCC surveillance (Target date 06/30/21) – 100% complete

Major Task 6: Create an online tool, HCC Simulator

Subtask 1: Create an online platform using RShiny (Target date 09/30/21) – Delayed. 30% complete. Expected to be complete 03/31/2022.

Subtask 2: Create a homepage for HCC Simulator (Target date 10/31/21) – Delayed. 0% complete. Expected to be complete 06/30/2022.

Subtask 3: Make the HCC Simulator available on the internet (Target date 11/30/21) – 0% complete

Major Task 7: Conduct a feasibility to assess the usability of the HCC Simulator in a clinical setting

Subtask 1 (Chhatwal & Kanwal Teams Combined): Develop focus group and patient interview guides (Target date 12/31/21) – 0% complete

Subtask 2: Provider and patient recruitment for focus groups and individual patient interviews (Kanwal Team); Conduct focus groups and individual patient interviews (Chhatwal Team Lead; Kanwal Team Supporting) (target date 03/31/22) – 0% complete

Team A (Fasiha Kanwal Team): Dr. Kanwal's team will recruit all providers and patients for focus group sessions and individual patient interviews and will record the sessions and interviews.

Recruit, consent, and enroll 30 patients/human subjects for participating in 6 focus groups

Recruit, consent and enroll 20 providers for individual interviews

Team B (Chhatwal Team): Dr. Chhatwal's team will conduct the focus groups and individual patient interviews

Subtask 3 (Kanwal Team): Transcription services (Target date 04/30/22) – 0% complete

Subtask 4: Coding and analysis of transcripts (Target date 05/31/22) – 0% complete

Team A (Kanwal Team): Dr. Kanwal's team will review coding and analysis results

Team B (Chhatwal Team): Dr. Chhatwal's team will code and analyze transcripts

Major Task 8: Incorporate results from focus group and individual patient feedback into the HCC Simulator

Subtask 1: Re-design relevant components of the HCC Simulator based on the feedback (Target date 07/31/22) – 0% complete

Team A (Kanwal Team): Dr. Kanwal's team will review results

Team B (Chhatwal Team): Dr. Chhatwal's team will modify the HCC Simulator

Subtask 2: Launch the HCC Simulator (Target date 08/31/22) – 0% complete

Team A (Kanwal Team): Dr. Kanwal's team will serve as in a supporting/consulting role

Team B (Chhatwal Team): Dr. Chhatwal's team will launch the HCC Simulator

Major Task 9: Manuscripts and dissemination of results

Subtask 1: Organize a Webinar on use of the HCC Simulator (Target date 08/31/22) – 0% complete

Team A (Kanwal Team): Dr. Kanwal's team will participate in the development of the Webinar contents

Team B (Chhatwal Team): Dr. Chhatwal's team take the lead to organize a Webinar on its use

Subtask 2: Report project results through manuscripts in peer-reviewed journals (Target date 09/30/22) – 30% complete

1. Predictors of HCC in CHC patients with virologically induced cure – article submitted
2. Risk prediction model to identify patients at high risk for HCC after DAA induced virological cure – manuscript in progress
3. Cost-effectiveness of personalized HCC surveillance in virologically cured CHC patients – article submitted
4. When to stop HCC surveillance after virological cure with CHC
5. What's the HCC incidence risk threshold above which surveillance is cost-effective? – published
6. A brief report on HCC Simulator

Both Team A and Team B will participate collaboratively and equally in manuscript writing

◦ **What was accomplished under these goals?** The following was accomplished under these goals:

Specific Aim 1: To examine determinants of HCC in virologically cured patients and develop a risk prediction model for HCC in these patients.

The major activities undertaken by the Kanwal Team in Year 2 included ongoing data cleaning, variable creation, and data analysis of HCC predictors, model building and results.

We included patients 18 years or older who achieved sustained virological response (SVR) with DAA treatment in any of the 129 VHA hospitals. We defined DAA treatment as ≥ 1 filled prescription of sofosbuvir, simeprevir, ledipasvir, combination of paritaprevir/ritonavir, ombitasvir and dasabuvir, and daclatasvir between 1/1/2014-12/31/2018 and followed up for HCC through 12/31/2019. We used the date of first filled prescription as treatment initiation and the last date covered by the final prescription as treatment completion date. We classified patients as having achieved SVR if all HCV RNA tests were negative after end of DAA treatment, with one HCV RNA test recorded at least 12 weeks after treatment completion. Because our objective is to examine the risk of incident HCC in patients virologically cured of HCV, we excluded patients who failed to achieve SVR. We also excluded patients with evidence of HCC prior to or during DAA treatment course.

The study **outcome** was new cases of HCC after the date of completing DAA. HCC was defined based on 2 or more instances of ICD-9 (155.0) or ICD-10 codes (C22.0, C22.8, C22.9, D01.5) in CDW or any instance of HCC recorded in the CCR. We also reviewed electronic medical records of cases that had ICD codes but not included in CCR.

Predictor variables. These include age, gender, race/ethnicity, socioeconomic status, marital status, place of residence (rural vs. urban), cirrhosis, HCV genotype, previous HCV treatment status, HIV, diabetes, hypertension, dyslipidemia, body mass index (BMI), alcohol use, other medical comorbidity, HIV, hepatitis B status, and healthcare utilization. We also derived 11 laboratory variables including values of bilirubin, AST, ALT, international normalized ratio, platelet tests, white cell count, hemoglobin, lymphocytes, neutrophils, creatinine, and sodium values. All variables were longitudinal and time updating over time.

Statistical analysis. We used cause-specific Cox proportional hazard models for competing risks constructed at 3 landmark times (baseline, 1- and 2- years after SVR) to examine the associations between demographics, clinical, and behavioral factors measured at these landmark times and the subsequent HCC risk, stratified by cirrhosis/advanced fibrosis status. We classified patients as having cirrhosis or advanced fibrosis if they had a diagnosis code for cirrhosis or ≥ 1 FIB-4 values > 3.25 prior to each landmark time. In patients with multiple FIB-4 values in the 12-month period, we used the values closest to each landmark time.

We constructed 6 separate models (3 separate landmark times for patients with and without cirrhosis/advanced fibrosis). The prediction at a landmark time was based on the regression model at that time. The outcome was the time from the landmark to HCC. At each landmark, the data only included the at-risk patients at that time (e.g., those who are alive without HCC).

Our predictor variables included time-independent (such as demographics) and time-dependent (such as FIB-4 and biomarkers of liver injury and inflammation) defined at each landmark time. For continuous measures (e.g., age, BMI, ALT, AST, etc.), we assessed both categorical and continuous values in the models to determine the best performing measure. The predictors also incorporated longitudinal information of a patient up to the landmark time, including change in FIB-4 category (defined as remained stable at low risk, increased from low to high risk, declined from high to low risk, or remained stable at high risk) as well as changes in serum albumin, sodium, bilirubin, creatinine, and hemoglobin between index and each landmark time. For model parsimony and interpretability, we only considered two-way interactions that are frequently observed in the cohort or suggested by literature (e.g., two-way interactions between key laboratory tests including serum albumin, hemoglobin, bilirubin, and creatinine).

There were a small amount of missing data in the predictors at all three landmark times. We used multiple imputation to create 5 imputed datasets and then combined the results using multiple imputation formula. The imputed values were generated from the FCS (fully conditional specification) method of SAS PROC MI. Skewed biomarkers were log-transformed to make the data closer to multivariate normality. Each imputed dataset went through a model building process with backward selection (entry p-value = 0.10; retaining p-value = 0.05). The final model included all predictors selected from at least one imputation dataset.

Specific objectives: Our specific objectives were to acquire data from VA Corporate Data Warehouse and complete data cleaning, variable creation, and cohort identification; abstract EMR to confirm HCC; analyze

data to identify predictors of HCC risk; develop and optimize HCC prediction models and perform subgroup analyses. We have completed these objectives.

Significant results: We have identified 98,612 patients who initiated DAA during 1/1/2014-12/31/2018 and achieved SVR; 2298 patients developed HCC and 7903 patients died until 12/31/2019. Mean age was 61.6 years old (sd=7.5); 96.4% were male; 38.5% were Black and 51.2% were white.

The cumulative incidence rates of HCC at 1, 2, and 3 years were 0.6%, 1.4% and 2.1%, respectively. In 31, 543 patients with cirrhosis or advanced fibrosis at baseline, cumulative incidence of HCC was 1.5%, 3.3%, and 5.0% at 1, 2 and 3 years, respectively. In contrast, HCC risk was considerably lower in 67,069 patients without cirrhosis or advanced fibrosis (p-value for comparison between cirrhosis <0.0001).

In the baseline model, among 31, 543 patients with cirrhosis or advanced fibrosis, the risk of HCC was lower in women (adjusted HR =0.55, 95% CI = 0.38-0.79) and African American patients (adjusted HR = 0.80, 95% CI = 0.71-0.90). Alcohol use (adjusted HR = 1.14, 95% CI = 0.99-1.31) and HCV genotype 3 were associated with a higher risk of HCC (adjusted HR = 1.45, 95% CI = 1.22-1.73). Patients with a previous history of non-response to DAA (adjusted HR = 1.29, 95% CI = 1.17-1.43) and those with longer duration since cirrhosis diagnosis had higher HCC risk (compared with new diagnosis of cirrhosis within previous 12 months, adjusted HRs were 1.38, 95% CI = 1.07-1.77, 1.60, 95% CI = 1.32-1.94, 1.72, 95% CI = 1.44-2.05 for patients diagnosed with cirrhosis within 1 to 2 years, 2 to 5 years and longer than 5 years). Baseline serum bilirubin, albumin, and presence of varices were also associated with HCC risk. Similarly, HCC risk increased with higher FIB-4 values. Specifically, HCC risk was 2.2-fold higher (adjusted HR= 2.2, 95% CI, 1.82-2.67) in cirrhosis patients who also had FIB-4 >3.25 than those with value <1.45, although few patients with cirrhosis had FIB-4 scores <1.45. Patients without any history of smoking had 21% lower risk for HCC than current smokers (adjusted HR = 0.79, 95% CI = 0.67-0.93). Patient who smoked but quit also experienced a reduction in HCC risk (adjusted HR =0.86, 95% CI = 0.77-0.96). None of the pre-specified interaction terms were significant in the adjusted models.

Most of the associations remained at 12- and 24-month landmark times, with few notable exceptions. Changes in serum albumin and FIB-4 values between baseline and landmark times were strongly associated with subsequent risk of HCC. For example, one unit increase in serum albumin between baseline and 1 year landmark time was associated with a 21% reduction in HCC risk. This effect was independent of the baseline albumin value. Compared to patients with persistently high FIB-4, the risk of HCC was 47% lower in patients who had persistently low FIB-4 scores (HR compared to patients with high FIB-4 at the time of virological cure that subsequently fell to <1.45 at 2 years (HR = 0.63, 95% CI = 0.50-0.79). Race, HCV genotype, and bilirubin were no longer predictive of HCC risk at 24-month landmark time, whereas change in hemoglobin from baseline became associated with risk of HCC.

Among patients without cirrhosis or advanced fibrosis, at baseline, patients with hypertension and diabetes had 2.0 to 1.5-fold higher risk of HCC than their counterparts. After controlling for diabetes and hypertension, there was no difference in the risk of HCC between patients with BMI 25-30 or those with BMI higher than 30. Risk of HCC was higher in patients with BMI <25, with the highest risk in patients with BMI <18.5. Baseline serum albumin and Fib-4 were associated with HCC risk. Patients with baseline FIB-4 between 1.45 and 3.25 had 2.2-fold higher risk of HCC than those with low FIB-4 <1.45 (HR=2.22, 95% CI = 1.85-2.68). Similarly, prior treatment failure and HCV genotype 3 were associated with HCC risk in patients without cirrhosis or advanced fibrosis. Only metabolic traits (diabetes, hypertension) and change in FIB-4 remained associated with HCC risk at all landmark times. At 2-year landmark time, patients with hypertension and diabetes had 1.8 to 1.4-fold higher risk of HCC than their counterparts. Patients who had an increase in FIB-4 from <3.25 at index to >3.25 at 2-year landmark time had 2-fold increase in HCC risk.

The AUCs for the models in patients with and without cirrhosis were 0.72 (95% CI, 0.70-0.74) and .0.68 (95% CI, 0.66-0.70), respectively.

Specific Aim 2: To evaluate the benefits vs harms of HCC surveillance in virologically cured patients

For Specific Aim 2, **the major activities** undertaken by the Chhatwal Team, with participation from the Kanwal Team, in Year 2 included developing a mathematical model simulating the natural history of HCC to evaluate the benefits and harms of routine HCC screening in virologically cured patients. We included the following new modules in year 2: surveillance and diagnosis; treatment options based on the BCLC stage at diagnosis; costs associated with HCC surveillance, hepatitis C sequelae, liver transplant and other HCC treatments. We also extracted quality of life associated with all health states in the model. Using this extended model, we conducted three studies.

Study 1

We evaluated the cost effectiveness of HCC surveillance in hepatitis C cured patients. Primary outcomes included life expectancy, quality-adjusted life years (QALYs), total costs, and incremental cost-effectiveness ratio (ICER) of each of the simulated surveillance strategies.

Preliminary results: In virologically-cured patients with cirrhosis, the ICER of biannual surveillance remained below \$100,000/QALY (range: \$85,000-\$98,100) when surveillance was stopped at age 65, rising above \$100,000 if surveillance continued beyond 65. For every 1000 patients, surveillance detected 260 HCCs in 'very early'/early stage, and 120 in intermediate/advanced stage. In contrast, no surveillance detected 92 HCCs in 'very early'/early stage, and 274 in intermediate/advanced stage. Compared to no surveillance, HCC surveillance provided QALY gains of 47 per 1000 patients. In virologically-cured patients with advanced fibrosis, the ICER of biannual surveillance remained above \$100,000 irrespective of the stopping age.

Conclusion: Biannual surveillance for HCC in virologically-cured hepatitis C patients with cirrhosis is cost-effective until the age of 65.

Study 2

The AASLD guidance recommends biannual surveillance for hepatocellular carcinoma (HCC) in hepatitis C virus (HCV) infected individuals with cirrhosis if HCC incidence is above 1.5 per 100 person-years (PY). However, the incidence threshold for surveillance in cirrhosis individuals who achieved virological cure with direct-acting antivirals is unknown. Using our microsimulation model, we also estimated the HCC incidence above which routine HCC surveillance is cost-effective in this growing population of individuals with virologically cured HCV.

Preliminary results: In 50-year-old virologically cured individuals with HCV cirrhosis, the incremental cost-effectiveness ratio (ICER) of biannual surveillance (up to age 75) vs. no surveillance was \$100,000-per-QALY at HCC incidence of 0.7 per 100-PY. At this HCC incidence, routine HCC surveillance vs no surveillance would result in additional 2,650 life years gained and 1400 QALYs per 100,000 persons undergoing surveillance. Using the WTP threshold of \$50,000-per-QALY (old willingness-to-pay), HCC surveillance could be cost effective at an annual HCC incidence of 2.0 per 100 PY.

Conclusion: Our study provides an important update on HCC incidence threshold above which routine HCC surveillance is cost-effective is individuals with HCV cirrhosis who achieved cure with DAAs. At the accepted WTP thresholds, HCC surveillance could be cost-effective if the annual incidence rate of HCC exceeds 0.7%, which is much lower than the previous 1.5% incidence used to guide HCC surveillance decisions.

Study 3

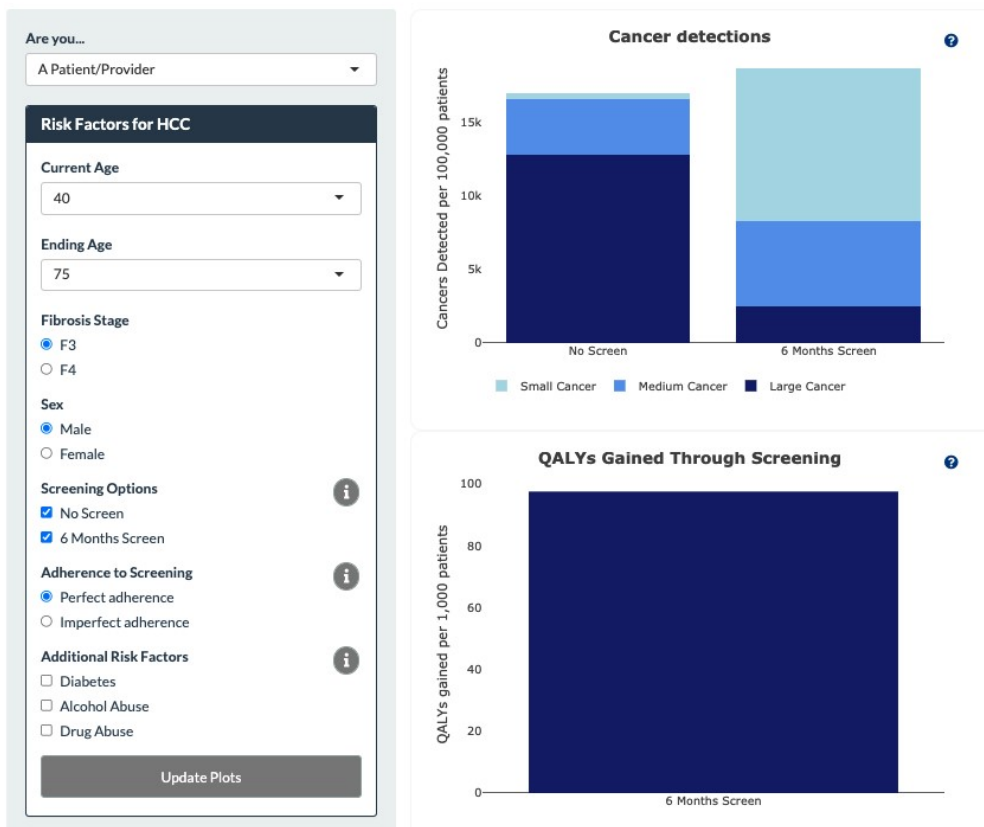
We also conducted probabilistic sensitivity analysis and value of information analysis to evaluate the impact of uncertainty of HCC surveillance recommendations. Preliminary results are being analyzed and will be finalized in soon for submission to a journal.

Specific Aim 3: To develop HCC Simulator, an online interactive tool for physicians and patients that provides the short- and long-term value of HCC surveillance in different risk groups

For Specific Aim 3, the **major activities** undertaken by the Chhatwal Team, with participation from the Kanwal Team, in Year 2 included the following.

Using the mathematical model, we simulated the life course of hypothetical patients with different risk profiles and stored them in a database. The dataset included cause of death (liver-related, or non-liver-related), development of HCC overtime, and likelihood of detection of HCC with or without surveillance.

We used the above database to create an online, interactive framework, which allows users to enter specific patient profiles and generate model-predicted long-term outcomes in graphical format. We use RShiny, an R package to develop an interactive online interface of the HCC Simulator. Figure shows the beta version of the HCC Simulator outcomes that is under development.



◦**What opportunities for training and professional development has the project provided?**

Nothing to Report

◦**How were the results disseminated to communities of interest?**

Nothing to Report

◦**What do you plan to do during the next reporting period to accomplish the goals?**

In Year 3, Dr. Kanwal's team will further refine and optimize the HCC risk prediction model.

In Year 3, Dr. Chhatwal's group will further evaluate a subgroup of patients with advanced fibrosis who could benefit from routine HCC surveillance. We will evaluate the optimal time to start and stop surveillance in different subgroups identified in Aim 1.

Dr. Chhatwal's team will use the hypothetical database to create an online, interactive framework, which will allow users to enter specific patient profiles and generate model-predicted long-term outcomes in graphical format. They will use RShiny, an R package to develop an interactive online interface of the HCC Simulator.

Both teams will work together to conduct user-centered design assessments of the HCC Simulator with patients and feasibility testing with patients and providers to assess usability of the HCC Simulator in clinical settings. As part of a user-centered design process, we will initially elicit patients' perceptions on the design and understandability of HCC Simulator as a decision support tool using focus groups. Themes arising from the focus groups will inform the design of a live prototype of the HCC Simulator. The team will then conduct individual, Think-Aloud interviews with patient and providers to elicit usability of the HCC Simulator. Themes from patient and provider interviews will inform refinements to the final design as needed, before wide-spread dissemination. The team plans to build this tool with the goal of expanding the use of the program beyond specialists (e.g., hepatologists and gastroenterologists) and patients at risk of developing HCC.

4.IMPACT: Nothing to Report.

5.CHANGES/PROBLEMS:

◦Changes in approach and reasons for change

Nothing to Report.

◦Actual or anticipated problems or delays and actions or plans to resolve them

Chhatwal Team – Because of COVID-19 and family emergency, Dr. Chhatwal's availability was limited for about 6 weeks. The team experienced delays in development of a liver transplant module in the simulation model of HCC surveillance (Task 3.3). To move forward, the team used prior liver transplant work, without incorporating recurrence of HCC post liver transplant and treatment. The team will finish task 3.3 in Year 3.

Kanwal Team – The team experienced delays due to the COVID-19 emergency. Despite extraordinary efforts by the VA to expand network capabilities to accommodate the sudden and dramatic increase in the number of employees working remotely from home, all team members regularly experienced connection problems and slow response time on all platforms (VINCI, VA secure servers, Outlook Email, Skype, etc.). Mondays after IT system and program changes over the weekend were especially difficult. Working remotely has also lengthened the hiring process. The team is poised to begin Major Task 7 and is in the process of hiring an additional research coordinator who will be dedicated to facilitating the HCC simulator feasibility assessment process in collaboration with the Chhatwal team. The team expects to complete the project requirements by the end of year 3.

◦Changes that had a significant impact on expenditures

Chhatwal Team – Nothing to report. No change in the scope of work is planned.

Kanwal Team – Longer hiring lead-times due to the COVID-19 emergency caused a delay in hiring an additional research coordinator who will be responsible for Task 7 feasibility assessment process. We request permission to carry forward unused funds to Year 3 to cover the cost of this coordinator's salary. No change in the scope of work is planned.

◦Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to Report.

6.PRODUCTS:

◦Publications, conference papers, and presentations

Chen Q, Ayer T, Adey MG, Wang X, Kanwal F, Chhatwal J. Assessment of Incidence of and Surveillance Burden for Hepatocellular Carcinoma Among Patients With Hepatitis C in the Era of Direct-Acting Antiviral Agents. JAMA Netw Open. 2020;3(11):e2021173. Published 2020 Nov 2.
doi:10.1001/jamanetworkopen.2020.21173. Acknowledgement of Federal support reported.

Kramer JR, Cao Y, Li L, Smith D, Chhatwal J, El-Serag HB, Kanwal F. Longitudinal associations between risk factors and subsequent risk of hepatocellular cancer in patients with hepatitis C virus infection and virological cure. Submitted.

Mueller PP, Chen Q, Ayer T, Nemutlu G, Bethea ED, Peters MLB, Lee B, Nanjua NZ, Kanwal F, Chhatwal J. Duration and Cost-effectiveness of Hepatocellular Carcinoma Surveillance in Hepatitis C Patients After Viral Eradication. Under Review - Journal of Hepatology.

Risk prediction model to identify patients at high risk for HCC after DAA induced virological cure – manuscript in progress

■Books or other non-periodical, one-time publications.

Nothing to report.

■Other publications, conference papers, and presentations.

Kramer JR, Cao Y, Li L, Smith D, Chhatwal J, El-Serag HB, Kanwal F. Longitudinal associations between risk factors and subsequent risk of hepatocellular cancer in patients with hepatitis C virus infection and virological cure. Abstract accepted for the 2021 AASLD The Liver Meeting, November 12-15th. Anaheim, CA.

Chhatwal J, Hajjar A, Mueller PP, Nemutlu G, Peters MLB, Kanwal F. Hepatocellular Carcinoma Incidence Threshold for Routine Surveillance is Much Lower in Hepatitis C Cirrhosis Individuals Who Achieve Virological Cure. Abstract accepted for the 2021 AASLD The Liver Meeting, November 12-15th. Anaheim, CA. Also accepted for inclusion in the Best of The Liver Meeting's summary slide deck in the Health Services and Public Health Research category.

◦**Website(s) or other Internet site(s)**

Nothing to report.

◦**Technologies or techniques**

Nothing to report.

◦**Inventions, patent applications, and/or licenses**

Nothing to report.

◦**Other Products**

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

◦**What individuals have worked on the project?**

Name: Fasiha Kanwal, MD, MSHS

Project Role: Principal Investigator

Researcher Identifier (e.g. ORCID ID): <https://orcid.org/0000-0001-6715-3966>

Nearest person month worked: 2

Contribution to Project: As the Principal Investigator, Dr. Kanwal oversees all aspects of the project and has primary responsibility for supervising Aim 1 activities: 1) Data acquisition, data cleaning, variable creation, cohort identification, 2) EMR chart abstractions to confirm HCC, 3) data analysis of HCC predictors, 4) develop and optimize HCC risk prediction model.

Funding Support:

Name: Jennifer R. Kramer, PhD

Project Role: co-Investigator

Researcher Identifier (e.g. ORCID ID): <https://orcid.org/0000-0003-2953-4949>

Nearest person month worked: 2

Contribution to Project: Dr. Kramer is leading the Data Analysis Team based at the VA (Aim 1 to examine determinants of HCC in virologically cured patients and develop a risk prediction model for HCC in these patients). She works closely with the PI, the biostatistician, and the data analyst on data acquisition, and operationalizing study variables. She supervises chart abstractors, oversees data analysis, and interprets results.

Funding Support:

Name: Roxanne Desiderio, BS

Project Role: Research Assistant

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 6

Contribution to Project: Ms. Desiderio conducted electronic medical record (EMR) chart reviews and assisted with administrative tasks, such as meeting scheduling, reporting, and maintaining regulatory documentation.

Funding Support:

Name: Yumei Cao, MS

Project Role: Data Analyst

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 12

Contribution to Project: Ms. Cao is the data analyst for Aim 1 of the project, responsible for the build and upkeep of the study databases, quality control measures, and conducting statistical analyses with the guidance of Drs. Kramer, Richardson, and Kanwal. She performed the programming required to identify the cohort, define the study variables, and construct analytic datasets. Ms. Cao provided weekly summary reports on the state of data analysis at the weekly project meeting headed by Dr. Kanwal (PI).

Funding Support:

Name: Donna Smith, MEd

Project Role: Project Coordinator

Researcher Identifier (e.g. ORCID ID): <https://orcid.org/0000-0003-1906-666X>

Nearest person month worked: 3

Contribution to Project: Ms. Smith is responsible for all administrative and regulatory tasks of the project, including IRB protocol approvals, renewals, and amendments; organizing project team meetings; maintaining study binders; and managing the budget. She coordinates data acquisition requests and data use agreement renewal updates. She will work closely with the core research investigators to coordinate writing and editing of progress reports and will assist with the development and publication of dissemination products.

Funding Support:

Name: Chris Williams, BS

Project Role: IT Manager

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 1

Contribution to Project: Mr. Williams is responsible for performing computer server maintenance and upgrades. He provides support and training for study personnel on project-related software programs. He ensures that data privacy standards are maintained and processes Data Use Agreements and PKI for study personnel. These functions are critical part of our data-management security plan to ensure compliance and the safety of all encrypted veteran data.

Funding Support:

Name: Jagpreet Chhatwal, PhD

Project Role: Principal investigator

Researcher Identifier (e.g. ORCID ID): <https://orcid.org/0000-0001-8741-4430>

Nearest person month worked: 2

Contribution to Project: As the Principal Investigator, Dr. Chhatwal has primary responsibility for supervising Aim 2 activities: development of the mathematical model to simulate the natural history of HCC in hepatitis C cured patients, literature review, validation and analysis of the proposed model.

Funding Support:

Name: Ali Hjaar, PhD

Project Role: Postdoc

Researcher Identifier (e.g. ORCID ID): <https://orcid.org/0000-0003-4654-9798>

Nearest person month worked: 6

Contribution to Project: Dr. Hjaar is a postdoctoral fellow who developed the natural history model of hepatitis C and HCC using a programming language. He also assisted with estimation model inputs and analysis of outcomes.

Funding Support:

Name: Neeti Kulkarni

Project Role: Programmer

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 1

Contribution to Project: Ms. Kulkarni is a research analyst responsible for developing an online tool to inform HCC screening for patients and providers. She also assisted with estimation of model inputs and analysis of outcomes.

Funding Support:

Name: Mary Ann Ladd, BS

Project Role: Data Manager

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 1

Contribution to Project: Ms. Ladd is the Systems Manager of the MGH Institute for Technology Assessment. She was responsible for overseeing the integration and day-to-day management of computer systems at the Institute for Technology Assessment, and for facilitating electronic communications among collaborators. She worked with the other team members to facilitate data extraction and storage, and ensure that all study data are secure, adequately stored and backed up.

Funding Support:

Name: Peter Mueller, PhD

Project Role: Research Scientist

Researcher Identifier (e.g. ORCID ID): <https://orcid.org/0000-0002-5334-0362>

Nearest person month worked: 3

Contribution to Project: Dr. Mueller is a research scientist who assisted with the development of the natural history model of hepatitis C and HCC using a programming language, setup of the computer server for computational runs for the model. He also assisted with the analysis of outcomes.

Funding Support:

◦Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

PREVIOUS, CURRENT, AND PENDING SUPPORT (PCPS)

KANWAL, FASIHA

PREVIOUS

Title: RSG-17-022-01 A Personalized Surveillance Program for Hepatocellular Carcinoma

Role on project: co-PI (Lead PI: Chhatwal)

AIMS: 1) Develop an effective and cost-effective surveillance program in hepatitis C patients who have – and have not – been cured of their infection, by incorporating individual's risk factors including age, sex, genotype and biomarkers; 2) Evaluate personalized HCC surveillance in patients with HBV, NASH, and ALD stratified by their risk factors; 3) Project the impact of personalized HCC surveillance on population-level cancer control, and identify future research priorities that will reduce HCC mortality and burden.

Time Commitment (Level of Effort): 0.2 calendar months

Supporting Agency: American Cancer Society

Name and address of funding agency's Grant's Officer:

Elvan Daniels

Extramural Grants Department

American Cancer Society

250 Williams Street

Atlanta, GA 30303-1002

E-mail: ellie.daniels@cancer.org

Phone:

Performance Period: 07/2017-06/2021

Level of funding:

Brief description of project's goals: The goal of this proposal is to reduce the burden of hepatocellular carcinoma by identifying effective surveillance programs that improve early detection.

% Overlap: None

CURRENT

Title: NIDDK P30 DK 56338-10/15 Center for Gastrointestinal Development, Infection and Injury

Role on project: Co-director (Overall PI: El-Serag)

AIMS: 1) To serve clinical and basic science investigators in digestive diseases with comprehensive study design consultation and support; 2) To assist DDC investigators in all aspects of the acquisition of clinical specimens required for their research in digestive diseases; 3) To support comprehensive data analyses and interpretation of basic, translation, clinical and epidemiological studies.

Time Commitment (Level of Effort): 0.6 calendar months

Supporting Agency: NIH/National Institute of Diabetes and Digestive and Kidney Diseases

Name and address of funding agency's Grant's Officer:

Peter J Perrin

Program Official

Division of Digestive Diseases and Nutrition, NIDDK, NIH

6707 Democracy Blvd., Room 6015

Bethesda, MD 20892-5450

Email: Peter.Perrin@nih.hhs.gov

Phone:

Fax: 301 480-8300

Performance Period: 12/1999-02/2023

Level of funding:

Brief description of project's goals: This Center supports four scientific cores, conferences and a pilot project program to facilitate on-going Digestive Disease research of center members, promote interactions and translational research between basic and clinical areas, develop new projects, nurture new investigators, and provide GI educational activities.

% Overlap: None

Title: HSR&D Project # IIR 16-075 (Application # 1 I01 HX002204-01A2) Patient Centered Care for Individuals with Advanced Liver Disease

Role on project: MPI

AIMS: 1) To develop risk stratification models of advanced liver disease (AdvLD) prognosis; 2) To describe patients' experiences and goals of AdvLD care; 3) To identify clinicians' perceptions of opportunities and barriers to patient-centered AdvLD care.

Time Commitment (Level of Effort): 4.2 calendar months

Supporting Agency: VA HSR&D

Name and address of funding agency's Grant's Officer:

Cathie Plouzek, PhD, PMP

Health Services Research and Development (10P9H)

Office of Research and Development, VA Central Office

Department of Veterans Affairs

810 Vermont Avenue NW

Washington, DC 20420

Phone:

E-mail: cathie.plouzek@va.gov

Performance Period: 05/2018-04/2021 (NCE 05/2021-04/2022)

Level of funding:

Brief description of project's goals: The main goal of the project is to develop a patient-centered care model for advanced liver disease, including risk-prediction models and clinician-patient collaborative treatment planning guides that focus on addressing patient unmet needs and expectations about illness course and care preferences for curative, supportive, and palliative care. The study findings will have direct impacts on current advanced liver disease care, as well as provide evidence for developing innovative care models for other serious chronic illnesses.

% Overlap: None

Title: 1 U01 CA230997-01 Risk Stratification for and Early Detection of Liver Cancer

Role on project: PI

AIMS: 1) Develop and test novel personalized risk stratification indices for predicting future HCC development in cirrhosis from diverse etiologies; 2) Develop and evaluate an algorithm combining existing HCC blood based biomarkers (AFP, AFPL3, DCP), their longitudinal changes and host features (e.g., cirrhosis etiology) to improve early HCC detection; 3) Evaluate novel plasma-based methylation markers for cell-free DNA (MDMs) as an independent surveillance biomarker for early HCC detection. Using the PRoBE design, we will test 12 individuals MDMs identified in Phase 2 study.

Time Commitment (Level of Effort): 2.4 calendar months

Supporting Agency: NIH Consortium on Translational Research in Early Detection of Liver Cancer: Translational Research Centers (U01)

Name and address of funding agency's Grant's Officer:

Viviana Knowles
National Cancer Institute
Office of Grants Administration
9609 Medical Center Drive
West Tower, 2nd floor
Rockville MD 20850
Phone (240) 276-6300
viviana.knowles@nih.gov

Tel.

Performance Period: 09/2018-08/2023

Level of funding:

Brief description of project's goals: The overarching goal of our Translational Research Center (TRC) is to reduce the mortality of hepatocellular cancer (HCC) by developing personalized indices that combine novel and existing biomarkers with clinical, behavioral and genetic data to improve clinical risk stratification and increase early detection of HCC.

% Overlap: None

Title: PR181562 Risk of hepatocellular cancer after virological cure with direct acting antiviral agents in individuals with hepatitis C (subject grant)

Role on project: MPI

AIMS: 1) To examine determinants of HCC in virologically cured patients and develop a risk prediction model for HCC in these patients; 2) To evaluate benefits versus harms of HCC surveillance in virologically cured patients; 3) To develop HCC Simulator, an online interactive tool for physicians and patients that provides the short- and long-term value of HCC surveillance in different risk groups.

Time Commitment (Level of Effort): 2.4 calendar months

Supporting Agency: Department of Defense Office of Congressionally Directed medical Research Programs (CDMRP)

Name and address of funding agency's Grant's Officer:

Claudio Ortiz, Ph.D.
Science Officer, Goldbelt Frontier
Congressionally Directed Medical Research Programs (CDMRP)
US Army Medical Research Materiel Command (USAMRMC)
1077 Patchel Street
Fort. Detrick, MD 21702-5024
PH:
Email: claudio.d.ortiz.ctr@mail.mil

Performance Period: 07/2019-06/2022

Level of funding:

Brief description of project's goals: The goal of this study is to examine the risk and determinants of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C (CHC) virologically cured with new direct acting antiviral agent (DAA) regimens and to identify cost-effective strategies for early detection of HCC in those patients.

% Overlap: None

Title: Cirrhosis Quality Collaborative

Role on project: co-PI (Corresponding co-PI: Volk)

AIMS: Phase 1: Design phase and network development. Aim 1a: Design a collaborative chronic care network that involves stakeholders at all levels in the design process. Aim 1b: Engage clinician, patient and policy stakeholders to refine a parsimonious set of quality measures – including patient-reported outcomes (PRO's). Phase 2: Software build and network pilot. Aim 2a: Work with ArborMetrix to build the data registry. Aim 2b: Prospectively collect data on the set of quality measures across 10 sites, to identify variation in process, outcome, and patient reported measures of cirrhosis care. Aim 2c: Pilot test a rapid-cycle quality improvement project on a single focused target.

Time Commitment (Level of Effort): 0.6 calendar months

Supporting Agency: American Association for the Study of Liver Diseases

Name and address of funding agency's Grant's Officer:

Julie Deal

Interim CEO, American Association for the Study of Liver Diseases

1001 N. Fairfax Street, #400

Alexandria, VA 22314

Phone:

Performance Period: 09/2018-08/2023

Level of funding:

Brief description of project's goals: This is the first large-scale quality improvement project targeting patients with advanced and chronic liver diseases. It will pilot test a collaborative chronic care network, including necessary technology infrastructure.

% Overlap: None

Title: CPRIT RP200633 Reducing disparities in the risk of hepatocellular cancer

Role on project: MPI

AIMS: 1) Examine the role of individual, inter-personal and community level factors in explaining racial/ethnic disparities in cirrhosis progression to HCC (prevention); 2) Examine the role of individual, inter-personal and community level factors in explaining racial/ethnic disparities in HCC tumor stage at diagnosis (early detection); 3) Identify specific targets for future interventions to reduce racial/ethnic HCC disparities.

Time Commitment (Level of Effort): 1.5 calendar months

Supporting Agency: Cancer Prevention & Research Institute of Texas (CPRIT)

Name and address of funding agency's Grant's Officer:

General CPRIT Contact Information:

Email: cprit@cprit.state.tx.us

Cancer Prevention and Research Institute of Texas

1701 North Congress Avenue, Suite 6-127

Austin, TX 78701

Phone:

Fax: 512-475-2563

Performance Period: 08/2020-08/2025

Level of funding:

Brief description of project's goals: The primary objective of this study is to identify in a large racial/ethnically and socioeconomically diverse cohort of patients with cirrhosis the multi-level factors that explain racial and ethnic disparities in HCC risk/incidence and tumor stage at diagnosis, as well as a set of potentially actionable (identifiable, preventable or treatable) determinants of HCC disparities in Texas.

% Overlap: None

Title: 1R01CA256977 Multi-level Evaluation of Racial/Ethnic and Socioeconomic Disparities in Liver Disease Outcomes (New)

Role on project: MPI

AIMS: 1) Examine the contribution of individual-, interpersonal-, and community-level factors to racial/ethnic and socioeconomic disparities in cirrhosis progression to hepatic decompensation, including HCC; 2) Identify individual-, interpersonal-, and community-level determinants of racial/ethnic and socioeconomic disparities in liver-related hospitalization; 3) Characterize the contribution of individual-, interpersonal-, and community-level factors to racial/ethnic and socioeconomic disparities in overall survival of patients with cirrhosis.

Time Commitment (Level of Effort): 1.8 calendar months

Supporting Agency: National Institutes of Health

Name and address of funding agency's Grant's Officer:

Rina Das, PhD
National Institute on Minority Health and Health Disparities (NIMHD (<https://www.nimhd.nih.gov/>))
Telephone:
Email: dasr2@mail.nih.gov (<mailto:dasr2@mail.nih.gov>)
Performance Period: 03/2021-02/2026

Level of funding:

Brief description of project's goals: To conduct a comprehensive evaluation of multilevel factors hypothesized to play important roles in causing racial/ethnic and SES disparities in three key measures of cirrhosis prognosis: a) hepatic decompensation, including HCC, b) liver-related hospitalization, and c) overall survival.

% Overlap: None

PENDING

None.

OVERLAP

There is no overlap between current projects and this application. If the pending R01 application "Multi-level Evaluation of Racial/Ethnic and Socioeconomic Disparities in Liver Disease Outcomes" is funded, we will adjust the scope and effort from the R01 project to avoid overlap with the pending CPRIT grant.

PREVIOUS, CURRENT, AND PENDING SUPPORT (PCPS)

KRAMER, JENNIFER R., MPH, PhD

PREVIOUS

Title: R01 CA206479-01 Identifying Novel Pharmacologic Risk factors for Common Malignancies in Individuals with Well-controlled HIV Infection

Role on project: Co-Investigator

AIMS: 1) a) To measure the effect of the duration of specific classes of cART medications on the risk of each of the 8 NADCs of interest in a cohort of veterans with well-controlled HIV, adjusting for known risk factors for each type of cancer, and b) to assess the extent of cancer risk that is mediated by metabolic disorders; 2) a) To measure the effect of duration of specific classes of common medications used to treat metabolic disorders known to impact cancer risk, utilized by HIV-infected individuals (e.g., statins, metformin, betablockers and ACE-Inhibitors) on the risk of developing the 8 NADCs of interest in a cohort of veterans with well-controlled HIV-infection; and b) to assess the extent that the observed cancer risk association from these common metabolic disorder-related medication is primarily mediated through their impacts on metabolic disorder control.

Time Commitment (Level of Effort): 2.4 calendar months

Supporting Agency: National Institutes of Health; National Cancer Institute

Name and address of funding agency's Grant Officer:

Viviana Knowles
National Cancer Institute
Office of Grants Administration
9609 Medical Center Drive
West Tower, 2nd floor
Rockville MD 20850
Phone

viviana.knowles@nih.gov

Tel.

Performance Period: 06/2016-05/2021 (NCE)

Level of funding;

Brief description of project's goals: This proposal aims to examine the effect of novel pharmacological agents on cancer risk in individuals with well-controlled HIV infection using the VA Corporate Data Warehouse.

% Overlap: None

Title: EPID-001-16S: Sex hormones and HCV-related liver disease progression

Role on project: Co-Investigator

AIMS: 1) To evaluate the association between baseline levels of circulating major sex hormones, including precursors, metabolites, and carrier proteins, and risk of liver disease progression to incident cirrhosis, decompensation, and/or HCC; 2) To evaluate the association between use of androgen altering medications including the anti-androgen finasteride or supplemental testosterone (T) and risk of HCV-related liver disease progression.

Time Commitment (Level of Effort): 0.6 calendar months

Supporting Agency: VA HSR&D

Name and address of funding agency's Grant Officer:

Sara Clark

Department of Veterans Affairs

Office 10P9B

1100 First St. NE

Washington, DC 20002

sara.clark@va.gov

Tel.

Performance Period: 07/2017-06/2021

Level of funding;

Brief description of project's goals: The goals of this proposal are to examine circulating sex hormone levels at baseline and risk of hepatitis C-related liver disease progression in males and to examine use of sex hormone modifying medications on risk of hepatitis C-related liver disease progression.

% Overlap: None

Title: 1 I01 BX004183-01A1 Million Veteran Program (MVP); Subaward – Immunogenetic determinants of HPV-related head and neck cancer in Veterans

Role on project: Co-Investigator

AIMS: 1) To utilize clinical data to phenotype four study cohorts within the MVP: cancer-free controls, HPVOPC, OPC, and non-OPC HNSCC patients; 2) To perform parallel integrative analysis of the association between polymorphism of immune genes and HPVOPC, OPC, and non-OPC HNSCC.

Time Commitment (Level of Effort): 0.6 calendar months

Supporting Agency: VA HSR&D

Name and address of funding agency's Grant Officer:

Jennifer Moser

Department of Veterans Affairs (VACO 10X2)

1100 First Street NE

Washington, DC 20002

Jennifer.moser@va.gov

Tel.

Performance Period: 07/2019-06/2021

Level of funding;

Brief description of project's goals: To determine the clinical predictors, and genotypic variation in immune-related genes is associated with risk of OPC, an HPV-related cancer among Veterans.

% Overlap: None

CURRENT

Title: 1R01CA260689-01 (PQ3) Addressing Cancer Treatment Disparities for Persons with HIV

Role on project: Co-Investigator

Aims: Aim 1: To evaluate differences in the timing of cancer treatment initiation between PWH and matched uninfected patients, and risk factors for delayed treatment in PWH. Aim 2: To evaluate disparities in short-term SAEs and cancer treatment.

Time Commitment (Level of Effort): 1.4 calendar months

Supporting Agency: NIH/NCI

Name and address of funding agency's Grant Officer:

Geraldina Dominguez

National Cancer Institute
National Institutes of Health
31 Center Drive, Room 3A33
Bethesda, MD, USA 20852-2440
Telephone:

Email: domingug@mail.nih.gov

Performance Period: 06/15/2021 – 05/31/2022

Level of Funding: (subcontract total DC)

Brief Description of project's goals: This project will address critical knowledge gaps for the four most common NADCs in PWH treated with CRT/RT (anal, head and neck, lung, or prostate cancer).

% Overlap: None

Title: HSR&D Project # IIR 16-075 (Application # 1 I01 HX002204-01A2) Patient Centered Care for Individuals with Advanced Liver Disease

Role on project: Co-Investigator

AIMS: 1) To develop risk stratification models of advanced liver disease (AdvLD) prognosis; 2) To describe patients' experiences and goals of AdvLD care; 3) To identify clinicians' perceptions of opportunities and barriers to patient-centered AdvLD care.

Time Commitment (Level of Effort): 0.6 calendar months

Supporting Agency: VA HSR&D

Name and address of funding agency's Grant Officer:

Cathie Plouzek, PhD, PMP
Health Services Research and Development (10P9H)
Office of Research and Development, VA Central Office
Department of Veterans Affairs
810 Vermont Avenue NW
Washington, DC 20420
Phone: (202) 443-5753
Cell:

E-mail: cathie.plouzek@va.gov

Performance Period: 05/2018-04/2021 (NCE 05/2021-04/2022)

Level of funding;

Brief description of project's goals: The main goal of the project is to develop a patient-centered care model for advanced liver disease, including risk-prediction models and clinician-patient collaborative treatment planning guides that focus on addressing patient unmet needs and expectations about illness course and care preferences for curative, supportive, and palliative care. The study findings will have direct impacts on current advanced liver disease care, as well as provide evidence for developing innovative care models for other serious chronic illnesses.

% Overlap: None

Title: VA IIR 16-025 Less is More: Improving Antimicrobial Stewardship for Asymptomatic Bacteriuria

Role on project: Co-Investigator

AIMS: 1) Conduct formative assessments of context, barriers and facilitators at each of the four VA medical sites to inform intervention implementation; 2) Evaluate implementation of a scalable version of the Kicking CAUTI intervention in four geographically distinct VA medical centers, including acute and long-term care settings, with four contemporaneous controls; 3) Assess the financial implications of the intervention through a budget impact analysis

Time Commitment (Level of Effort): 0.6 calendar months

Supporting Agency: VA HSR&D

Name and address of funding agency's Grant Officer:

Cathie Plouzek, PhD, PMP
Health Services Research and Development (10P9H)
Office of Research and Development, VA Central Office
Department of Veterans Affairs
810 Vermont Avenue NW
Washington, DC 20420
Phone:

E-mail: cathie.plouzek@va.gov

Performance Period: 02/2018-09/2021

Level of funding;

Brief description of project's goals: The main goal of this project is to implement the Kicking UTI intervention across four VA sites nationally. Kicking UTI is an intervention to improve management of Asymptomatic Bacteriuria in Veterans in hospitals and long-term care, to protect Veterans from the harms of unnecessary antibiotic use. It was designed and validated in a previous study.

% Overlap: None

Title: 5R01CA212008-02 Harms of Hepatocellular Carcinoma Screening in Patients with Cirrhosis

Role on project: Co-Investigator

AIMS: 1) Assess the effect of HCC screening on a) physical harms due to follow-up tests, b) financial harms, and c) overdiagnosis in patients with severe liver dysfunction or comorbid illness, through electronic medical record data, manual chart review, and validated survey measures; 2) Assess the effect of HCC screening on screening-related psychosocial harms, e.g. cancer-specific worry, situational anxiety, mood disturbances, and decisional regret, through longitudinal validated measures and qualitative interviews; 3) Create and disseminate a balance sheet of benefits and harms to inform patients, nurses, providers, healthcare organizations, payers, and policymakers about the value of HCC screening in patients with cirrhosis.

Time Commitment (Level of Effort): 0.6 calendar months

Supporting Agency: National Cancer Institute

Name and address of funding agency's Grant Officer:

Crystal Wolfrey
Chief Grants Management Officer
National Cancer Institute
Office of Grants Administration
9609 Medical Center Drive
West Tower, 2nd floor
Rockville MD 20850
wolfreyc@mail.nih.gov,

Performance Period: 08/2017-07/2022

Level of funding;

Brief description of project's goals: The purpose of this study is to investigate the harms that may be associated with screening for HCC in patients with cirrhosis recruited from 4 medical centers in Texas.

% Overlap: None

Title: PR181562 Risk of hepatocellular cancer after virological cure with direct acting antiviral agents in individuals with hepatitis C (subject grant)

Role on project: Co-Investigator

AIMS: 1) To examine determinants of HCC in virologically cured patients and develop a risk prediction model for HCC in these patients; 2) To evaluate benefits versus harms of HCC surveillance in virologically cured patients; 3) To develop HCC Simulator, an online interactive tool for physicians and patients that provides the short- and long-term value of HCC surveillance in different risk groups.

Time Commitment (Level of Effort): 2.4 calendar months

Supporting Agency: Department of Defense Office of Congressionally Directed medical Research Programs (CDMRP)

Name and address of funding agency's Grant's Officer:

Claudio Ortiz, Ph.D.
Science Officer, Goldbelt Frontier
Congressionally Directed Medical Research Programs (CDMRP)
US Army Medical Research Materiel Command (USAMRMC)
1077 Patchel Street
Fort. Detrick, MD 21702-5024

Email: claudio.d.ortiz.ctr@mail.mil

Performance Period: 07/2019-06/2022

Level of funding;

Brief description of project's goals: The goal of this study is to examine the risk and determinants of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C (CHC) virologically cured with new direct acting antiviral agent (DAA) regimens and to identify cost-effective strategies for early detection of HCC in those patients.

% Overlap: None

Title: CPRIT RP200633 Reducing disparities in the risk of hepatocellular cancer (New)

Role on project: co-Investigator

AIMS: 1) Examine the role of individual, inter-personal and community level factors in explaining racial/ethnic disparities in cirrhosis progression to HCC (prevention); 2) Examine the role of individual, inter-personal and community level factors in explaining racial/ethnic disparities in HCC tumor stage at diagnosis (early detection); 3) Identify specific targets for future interventions to reduce racial/ethnic HCC disparities.

Time Commitment (Level of Effort): 1.5 calendar months

Supporting Agency: Cancer Prevention & Research Institute of Texas (CPRIT)

Name and address of funding agency's Grant's Officer:

General CPRIT Contact Information:

Email: cprit@cprit.state.tx.us

Cancer Prevention and Research Institute of Texas

1701 North Congress Avenue, Suite 6-127

Austin, TX 78701

Fax: 512-475-2563

Performance Period: 08/2020-08/2025

Level of funding:

Brief description of project's goals: The primary objective of this study is to identify in a large racial/ethnically and socioeconomically diverse cohort of patients with cirrhosis the multi-level factors that explain racial and ethnic disparities in HCC risk/incidence and tumor stage at diagnosis, as well as a set of potentially actionable (identifiable, preventable or treatable) determinants of HCC disparities in Texas.

% Overlap: None

Title: 1R01CA256977 Multi-level Evaluation of Racial/Ethnic and Socioeconomic Disparities in Liver Disease Outcomes (New)

Role on project: co-Investigator

AIMS: 1) Examine the contribution of individual-, interpersonal-, and community-level factors to racial/ethnic and socioeconomic disparities in cirrhosis progression to hepatic decompensation, including HCC; 2) Identify individual-, interpersonal-, and community-level determinants of racial/ethnic and socioeconomic disparities in liver-related hospitalization; 3) Characterize the contribution of individual-, interpersonal-, and community-level factors to racial/ethnic and socioeconomic disparities in overall survival of patients with cirrhosis.

Time Commitment (Level of Effort): 1.8 calendar months

Supporting Agency: National Institutes of Health

Name and address of funding agency's Grant's Officer:

Rina Das, PhD

National Institute on Minority Health and Health Disparities (NIMHD (<https://www.nimhd.nih.gov/>))

Email: dasr2@mail.nih.gov (mailto:dasr2@mail.nih.gov)

Performance Period: 03/2021-02/2026

Level of funding:

Brief description of project's goals: To conduct a comprehensive evaluation of multilevel factors hypothesized to play important roles in causing racial/ethnic and SES disparities in three key measures of cirrhosis prognosis: a) hepatic decompensation, including HCC, b) liver-related hospitalization, and c) overall survival.

% Overlap: None

PENDING

OVERLAP

None

PREVIOUS, CURRENT, AND PENDING SUPPORT (PCPS)

AANAND D. NAIK, M.D.

PREVIOUS

None.

CURRENT

Title: HSR&D Project # IIR 16-075 (Application # 1 I01 HX002204-01A2) Patient Centered Care for Individuals with Advanced Liver Disease

Role on project: Co-PI (MPI: Naik & Kanwal)

AIMS: 1) To develop risk stratification models of advanced liver disease (AdvLD) prognosis; 2) To describe patients' experiences and goals of AdvLD care; 3) To identify clinicians' perceptions of opportunities and barriers to patient-centered AdvLD care.

Time Commitment (Level of Effort): 0.6 calendar months

Supporting Agency: VA HSR&D Research Line

Name and address of funding agency's Grant's Officer:

Cathie Plouzek, PhD, PMP

Health Services Research and Development (10P9H)

Office of Research and Development, VA Central Office

Department of Veterans Affairs

810 Vermont Avenue NW

Washington, DC 20420

E-mail: cathie.plouzek@va.gov

Performance Period: 05/2018-04/2021 (NCE 05/2021-04/2022)

Level of funding: (total)

Brief description of project's goals: Study will develop prognostic models for advanced liver disease predicting mortality, complications, and hospitalizations as well as a mixed methods qualitative exploration of patients, caregivers, and health professionals' values, goals, and expectations of care and outcomes in the setting of advanced liver disease.

% Overlap: None.

Title: Southeast Texas Geriatric Workforce Enhancement Program (SETx-GWEP)

Role on project: PI

AIMS: Establish an interprofessional geriatrics education and training consortium to engage primary care providers and the full spectrum of healthcare and community health professionals in a highly targeted integrated geriatrics and primary care training model to improve health outcomes for older adults.

Time Commitment (Level of Effort): 1.20 calendar months

Supporting Agency: Health Resources and Services Administration

Name and address of funding agency's Grant's Officer:

Nina Tumosa

Program Contact

553 Bragg Hill Rd

Fairlee, VT, 05045-4405

Email: ntumosa@hrsa.gov

Performance Period: 07/01/2019-06/30/2024

Level of funding:

Brief description of project's goals:

Collaborators will develop and deliver programming for the SETx-GWEP to advance a healthcare workforce that provides optimal, value-conscious care to older adults and their families that maximizes patient and family engagement and improves healthcare processes and outcome for older adults.

% Overlap: None.

Title: Patient Priorities Care: Dissemination and Scaling Phase for Patients with Heart Failure

Role on project: Co-Investigator (PI: Tinetti)

AIMS: Building on the pilot work of the original Patient Priorities Care pilot project, the aims of the Houston site will support project dissemination and scaling. Dr. Naik and the BCM team will work to prepare technical assistance, products, and training that enables adoption of Patient Priorities Care. They will participate in training of expert faculty as well as provide consultation to practices and clinicians implementing Patient Priorities Care.

Time Commitment (Level of Effort): 1.2 calendar months

Supporting Agency: John A. Hartford Foundation

Name and address of funding agency's Grant's Officer:

Mark Barreiro, MS

Senior Grants Officer

The John A. Hartford Foundation

55 E. 59th Street

16th Floor

New York, NY 10022-1713

E-mail: mark.barreiro@johnhartford.org

Performance Period: 11/2018-10/2022

Level of funding: sub-award

Brief description of project's goals:

Develop and pilot test a model of patient goals directed care to guide integration of primary and specialty care services in a certified patient centered medical home.

% Overlap: None.

Title: VA Quality Scholars Program: Coordinating Center for the VA Quality Scholars Program

Role on project: Program Director

AIMS: 1) To iteratively enhance the existing VAQS curriculum in partnership with VAQS senior scholars. 2) To facilitate recruitment, performance, and placement of interprofessional clinicians who will be the next generation of quality scholars. 3) To link fellows with senior scholars across VAQS sites and the spectrum of VA quality and patient safety programs.

Time Commitment (Level of Effort): 0.6 calendar months

Supporting Agency: VA Office of Academic Affiliations

Name and address of funding agency's Grant's Officer:

Bonnie S. Graham, MBA

Director, San Francisco VA Health Care System

4150 Clement St.,

San Francisco, CA 94121

E-mail: bonnie.graham@va.gov

Performance Period: 07/2014-09/2023

Level of funding: (annually)

Brief description of project's goals:

The VA's premier training program for post-doctoral physicians and doctoral-trained nurses in quality improvement and patient safety across eight national VA centers. The Coordinating Center delivers a national curriculum, conducts program evaluation, manages a week-long Summer Institute, and assists with program recruitment, marketing, and internet communications

% Overlap: None.

Title: VA Advanced Fellowships in HSR: Advanced Fellowships Program in Health Services Research (MD/PhD Post-doctoral Fellowships Program)

Role on project: Program Director

AIMS: Program Goal 1: To produce interprofessional team scientists who embrace an HSR identity and contribute to improvements in healthcare outcomes and services in VA. Program Goal 2: To develop a pipeline of interprofessional team scientists by recruiting, mentoring and developing social, organizational and behavioral scientists through formative post-doctoral training in HSR. Program Goal 3: To integrate clinical and operations partners into fellows' mentoring teams and cultivate implementation and partnership research training as a cardinal element of our Education and Training mission.

Time Commitment (Level of Effort): 2.4 calendar months

Supporting Agency: VA Office of Academic Affiliations/HSR&D Service

Name and address of funding agency's Grant's Officer:

Science Officer: Karen Sanders, MD

Deputy Chief Academic Affiliations Officer

Veterans Health Administration

Department of Veterans Affairs

810 Vermont Ave NW

Washington, DC 20420

E-Mail: karen.sanders@va.gov

Performance Period: 02/2015-09/2022

Level of funding:

Brief description of project's goals:

Direct the overall health services research fellowships for advance MD and PhD post-doctoral fellows. This program has been continuously funded since 2004 (successful renewal in 2015).

% Overlap: None.

Title: Big-Data Scientist Training Enhancement

Role on project: Program Director

AIMS: Objective 1: All BD-PCOR Fellows participate in a Core Curriculum. Objective 2: BD-PCOR Fellows participate in an interprofessional mentoring program. Objective 3: BD-PCOR fellows conduct mentored research leading to scholarly products. Objective 4: BD-PCOR Fellows work with their mentors to identify relevant didactic learning opportunities.

Time Commitment (Level of Effort): 0.6 calendar months

Supporting Agency: VA OAA/National Cancer Institute

Name and address of funding agency's Grant's Officer:

Deborah Ludke, MHA

Administrative Officer, Advanced Fellowships and Professional Development

Long Beach VA Medical Center (11/111)

5901 East Seventh Street

Long Beach, CA 90822

E-mail: Deborah.ludke@va.gov

Performance Period: 10/2015-09/2022

Level of funding: annual

Brief description of project's goals:

Houston BD-STEP program goal is to provide mentored-training for quantitative scientists from engineering, natural sciences, and computing in large dataset analytical models using VA healthcare data infrastructure.

% Overlap: None.

Title: Project # PR181562: Risk of hepatocellular cancer after virological cure with direct acting antiviral agents in individuals with hepatitis C (subject grant)

Role on project: Co-Investigator (PI: Kanwal; Co-PI: Chhatwal)

AIMS: 1) To examine determinants of HCC in virologically cured patients and develop a risk prediction model for HCC in these patients; 2) To evaluate benefits versus harms of HCC surveillance in virologically cured patients; 3) To develop HCC Simulator, an online interactive tool for physicians and patients that provides the short- and long-term value of HCC surveillance in different risk groups.

Time Commitment (Level of Effort): 0.6 calendar months

Supporting Agency: Department of Defense Office of Congressionally Directed medical Research Programs (CDMRP)

Name and address of funding agency's Grant's Officer:

Claudio Ortiz, Ph.D.
Science Officer, Goldbelt Frontier
Congressionally Directed Medical Research Programs (CDMRP)
US Army Medical Research Materiel Command (USAMRMC)
1077 Patchel Street
Fort. Detrick, MD 21702-5024

Email: claudio.d.ortiz.ctr@mail.mil

Performance Period: 07/2019-06/2022

Level of funding:

Brief description of project's goals:

The goal of this study is to examine the risk and determinants of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C (CHC) virologically cured with new direct acting antiviral agent (DAA) regimens and to identify cost-effective strategies for early detection of HCC in those patients.

% Overlap: None.

Title: Effect of Patient Priorities Care Implementation in Older Veterans with Multiple Chronic Conditions

Role on project: Principal Investigator

AIMS: 1) Using our primary care-research partnership, we will conduct a formative assessment of PPC implementation for Veterans with MCC and develop implementation tools; 2) Evaluate the effectiveness of PPC in a randomized controlled study at two VA primary care centers; 3) Conduct a summative assessment of implementation outcomes of PPC in VA primary care.

Time Commitment (Level of Effort): 3.0 calendar months

Supporting Agency: VA HSR&D Research Line

Name and address of funding agency's Grant's Officer:

Cathie Plouzek, PhD, PMP
Health Services Research and Development (10P9H)
Office of Research and Development, VA Central Office
Department of Veterans Affairs
810 Vermont Avenue NW
Washington, DC 20420

E-mail: cathie.plouzek@va.gov

Performance Period: 07/01/2021-06/30/2025

Level of funding:

Brief description of project's goals:

The goal of this study is to determine if the PPC approach can reduce treatment burden and increase care that is better aligned with patient priorities compared to usual care. The study also identifies barriers and promoters to providing the PPC model in routine VA care.%

Overlap: None.

PENDING

None.

OVERLAP

There is no overlap between current projects and this application.

PREVIOUS/ CURRENT/ PENDING SUPPORT

LI, LIANG

PREVIOUS

Title/Grant Number: Comparative Effectiveness Research on Cancer in Texas (CERCIT) 2.0: Data Core / RP160674

Effort: 0.96 Calendar Months, 8% Effort (all years of participation)

Supporting Agency: Cancer Prevention & Research Institute of Texas Subaward via UTMB

Grants Officer: Patricia Moore, cpnit@cpnit.state.tx.us

Performance Period: 6/1/2016-8/30/2021

Funding Amount:

Project Goals: To create a statewide resource for outcomes and comparative effectiveness research in cancer for Texas. PID4721

Specific Aims: Aim 1: Create Data Resource of linked cancer and claims data for Texas residents. Aim 2: Use data resource to examine the entire trajectory of cancer care in Texas. Aim 3: Train the next generation of cancer outcomes and comparative effectiveness investigators in Texas. Aim 4: Disseminate Findings.

Overlap: None

Title/Grant Number: Eliminating tobacco-related disparities among African Americans/5R01MD010362-04

Effort: 1.3 Calendar Months, 10.83% Effort (all years of participation)

Supporting Agency: NIH/NHMD Subaward via Utah University

Grants Officer: Xinzhi Zhang, zhangx12@mail.nih.gov

Performance Period: 08/28/2017-01/31/2021

Funding Amount:

Project Goals: To examine the influence of demographics and social history, bio-behavioral and psychosocial predispositions, contextual and environmental factors, and acute individual and contextual precipitants on smoking lapse and abstinence. PID 5129

Specific Aims: Effort complete as of 1/31/2019.
Aim 1: Influence of demographics and social history, bio-behavioral/psychosocial predispositions, contextual and environmental influences, and acute precipitants on smoking lapses among AA smokers.
Aim 2: Influence of demographics and social history, bio-behavioral/psychosocial predispositions, contextual and environmental influences, and acute precipitants on early and long-term abstinence from smoking among AA smoker.

Overlap: None

CURRENT

Title/Grant Number: Cancer Center Support Grant (CCSG) - Biostatistics Resource Group (BRG) / 5P30CA016672 45 (New)

Effort: 1.2 Calendar Months, 10% Effort (Cyclical project, effort varies in all years of participation)

Supporting Agency: NIH/NCI

Grants Officer: Shafik, Hasnaa, shafikh@mail.nih.gov

Performance Period: 8/28/1996-6/30/2024

Funding Amount:

Project Goals: To enhance the scientific excellence of research at MD Anderson through outstanding statistical designs and methods, including the proper and efficient use of standard and cutting-edge methods. PID858033

Specific Aims:	1) To provide biostatistical collaboration, consultation, and quantitative resources to clinical, laboratory, behavioral, and prevention scientists at MD Anderson Cancer Center; and to develop innovative statistical methods with application to cancer research, prevention, early detection, and patient care; and to create accompanying software programs. 2) To contribute to research rigor and reproducibility at the institution by serving on regulatory boards, by reviewing research protocols, and by enhancing the reproducibility procedures used by statistical analysts. 3) To provide formal educational programs and training in biostatistics for graduate students and postdoctoral fellows; to provide informal training and continuing education to statistical analysts; and to provide educational outreach to MD Anderson researchers.
Overlap:	None
Title/Grant Number:	Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer: Coordinating and Data Management Center (CSCPDP-CDMC) / 5U01DK108328-07
Effort:	2.4 Calendar Months, 20% Effort (all years of participation)
Supporting Agency:	NIH/NCI
Grants Officer:	Aynur Unalp-Arida, aynur.unalp-arida@nih.gov,
Performance Period:	9/28/2015-6/30/2025
Funding Amount:	
Project Goals:	To provide network coordination and collaborative activities, will provide scientific leadership in study design, statistical support, and computational analyses, and will provide data management and protocol development and execution. PID11706
Specific Aims:	Aim 1: Support Operation and Coordination of CPDPC. Aim 2: Continue the Accrual and Follow up of Patients in CPDPC-approved Studies. Aim 3: Support the Infrastructure for Biomarker Development, Prevention Studies, and Therapeutic Trials. Aim 4: Design and Support New Studies as Selected by the Steering Committee.
Overlap:	This is a continuation of the funded project. No overlap. Project will not commence until 9/1/2020, then new cycle start date will have effective date of July 1, 2020
Title/Grant Number:	Multi-Site Development & Evaluation of a Quantitative 3D Hyperpolarized C-13 MRI Clinical Prostate Cancer Exam / 5R01CA211150-05
Effort:	0.24 Calendar Months, 2% Effort (all years of participation)
Supporting Agency:	NIH/NCI
Grants Officer:	Huiming Zhang, zhanghui@mail.nih.gov,
Performance Period:	03/1/2017-02/28/2022
Funding Amount:	
Project Goals:	Demonstrating new and improved imaging methods that enhance image quality, and consequently, improve sensitivity and specificity of minimally invasive metabolic imaging strategies (1% effort eff 9.1.18, 2% in year 3). PID5247
Specific Aims:	Aim 1: Establish a method for external validation of HP MRI measurements. Aim 2: Implement highly optimized preclinical dynamic HP MRS and MRI protocols and a robust constrained reconstruction algorithm for quantifying tumor metabolism using HP [1-13C]-pyruvate. Aim 3: Develop a data-driven HP MRI protocol and establish imaging characteristics in patients with head and neck cancers.
Overlap:	None

Title/Grant Number: Socioeconomic status, stress, and smoking cessation / 5R01CA190329-06
 Effort: 0.12 Calendar Months, 1% Effort (all years of participation)
 Supporting Agency: NIH/NCI Subaward via University of Utah
 Grants Officer: Xinzhi Zhang, zhangx12@mail.nih.gov
 Performance Period: 7/1/2017-06/30/2022
 Funding Amount:
 Project Goals: To examine the influence of socioeconomic status and social history, contextual and environmental influences, bio-behavioral/psychosocial predispositions, and acute momentary precipitants on stress, smoking lapse, and abstinence PID5135 (under NCE - pending execution of amendment 9.23.2021).
 Specific Aims: Aim 1: Delineates the key hypothesized pathway linking SES to stress to smoking lapse/abstinence.
 Aim 2: Delineates the key hypothesized links of environment/context and bio-behavioral/psychosocial predispositions with SES, smoking lapse/abstinence, and stress.
 Aim 3: Examines the dynamic relationships of acute precipitants and stress, and their influence on lapse/abstinence.
 Overlap: None

Title/Grant Number: Estimating the Cost Trajectories and Projecting the Cost of Cancer Care in the United States: Methodology and Application / 5R01CA225646-03
 Effort: 3 Calendar Months, 25% Effort (all years of participation)
 Supporting Agency: NIH/NCI
 Grants Officer: Martinson Owusu, , owusumo@mail.nih.gov
 Performance Period: 7/5/2018-6/30/2023
 Funding Amount:
 Project Goals: To develop novel methodology and apply the methodology to estimate and project the future cost of cancer care in the US. PID6729
 Specific Aims: Aim 1: To develop new statistical methods to model the longitudinal incident costs of cancer patients.
 Aim 2: To improve the net costing approach by developing innovative propensity score methods for the selection of non-cancer controls.
 Aim 3: To project the cancer care costs in the United States for the next 10 years.
 Aim 4: To facilitate the reproducibility and application of the methods developed from this project by developing and disseminating user-friendly software programs.
 Overlap: None

Title/Grant Number: Magnetic resonance Imaging as a Non-Invasive Method for Assessment of Pancreatic fibrosis (MINIMAP): a pilot study/5R01DK116963-03
 Effort: 0.12 Calendar Months, 1% Effort (all years of participation)
 Supporting Agency: NIH/NIDDK via subaward from Indiana University
 Grants Officer: Chelsie Bousum, cbousum@iu.edu
 Performance Period: 09/20/2018-06/30/2022
 Funding Amount:
 Project Goals: To evaluate non-invasive methods to detect and quantify pancreatic fibrosis. PID7394. FP00004518 (Under no cost extension)
 Specific Aims: The objective of this protocol is to perform statistical analysis of de-identified data for the MINIMAP study.
 Overlap: None

Title/Grant Number: Dynamic Prediction of Renal Failure Using Longitudinal Prognostic Information among Patients with Chronic Kidney Disease and Kidney Transplant / 5R01DK118079-03
 Effort: 3 Calendar Months, 25% Effort (all years of participation)
 Supporting Agency: NIH/NIDDK

Grants Officer:	Kevin C. Abbott, Kevin.abbott@nih.gov
Performance Period:	04/1/2019-03/31/2024
Funding Amount:	
Project Goals:	To develop novel DP methods for kidney/graft failure with adjustment for the competing risk by death, external validation and re-calibration, and creating software for routine use in clinical practice. PID7824
Specific Aims:	Aim 1: Develop novel statistical methodology for dynamic prediction. Aim 2: Develop and externally validate dynamic kidney failure prediction models for (a) patients with CKD and (b) KTx recipients. Aim 3: Develop and disseminate web-based dynamic prediction model software for clinical practice.
Overlap:	None
Title/Grant Number:	Phase 1/2 Trial of Indomethacin in Chronic Pancreatitis (The PAIR Trial) / 5R21DK117212-02
Effort:	0.12 Calendar Months, 1% Effort (all years of participation)
Supporting Agency:	NIH/NIDDK Subaward via Mayo Clinic-Rochester
Grants Officer:	Jose Serrano, (serranoj@extra.niddk.nih.gov
Performance Period:	7/12/2019-3/31/2022
Funding Amount:	
Project Goals:	To investigate the pancreatic effects of IN in humans, and to correlate changes in a pancreatitis biomarker with changes in clinical symptoms of CP. PID11646 / FP00005110 (Under no cost extension)
Specific Aims:	Aim 1: the primary analysis will be a linear random intercept model that incorporates PJ PGE2 data from both baseline and day 28 from all randomized patients Aim 2: we will use multivariate analysis of variance model (MANOVA) with repeated measures. The multivariate outcomes include patient-related outcomes (BPI and PROMIS-10 scores) and PJ PGE2 concentrations between baseline and day 28.
Overlap:	None
Title/Grant Number:	Risk Of Hepatocellular Cancer After Virological Cure With Direct Acting Antiviral Agents In Individuals With Hepatitis C / W81XWH-19-1-0689
Effort:	0.24 Calendar Months, 2% Effort (effort varied in prior years of participation)
Supporting Agency:	DOD via subaward Baylor College of Medicine
Grants Officer:	Baylor College of Medicine, subaward@bcm.edu
Performance Period:	9/1/2019-8/31/2022
Funding Amount:	
Project Goals:	To examine the determinants of hepatocellular carcinoma (HCC) in patients diagnosed with chronic hepatitis C (CHC) who have been virologically cured with the new direct acting antiviral (DAA) regimens. PID11158 / FP00008073
Specific Aims:	Aim 1: To examine determinants of HCC in virologically cured patients and develop a risk prediction model for HCC in these patients. Aim 2: To evaluate benefits versus harms of HCC surveillance in virologically cured patients. Aim 3: To develop an HCC Simulator, an online interactive tool for physicians and patients that provides the short- and long-term value of HCC surveillance in different risk groups.
Overlap:	None

Title/Grant Number: A novel natural history study of medullary thyroid carcinoma: Incorporating the patient perspective to inform advanced disease management / 5R01FD006650-03

Effort: 1.2 Calendar Months, 10 % Effort (all years of participation)

Supporting Agency: NIH/FDA

Grants Officer: Daniel Lukash, daniel.lukash@fda.hhs.gov, 240-402-7596

Performance Period: 9/1/2019-7/31/2023

Funding Amount:

Project Goals: To understand the pathway to progressive disease, integrating for the first time patients perspectives. PID8226

Specific Aims: Aim 1: To fully characterize the disease longitudinally from both the clinical and patient perspectives to understand the significance of each in association with outcome.
Aim 2: To derive a treatment algorithm (decision aid) for utilization of MTC drug therapy in which the patient's unique set of values are considered
Aim 3: To determine if current and novel biomarkers can be used to enhancedecision making in the treatment of advanced disease

Overlap: None

Title/Grant Number: Improving Risk Prediction for Li-Fraumeni Syndrome: A Practical Tool for Clinical Health Care Providers / RP200383 **New**

Effort: 0.12 Calendar Months, 1% Effort (all years of participation)

Supporting Agency: Cancer Prevention & Research Institute of Texas (CPRIT)

Grants Officer: CPRIT Helpdesk
E-mail: Help@CPRITGrants.org

Performance Period: 8/31/2020- 8/30/2023

Funding Amount:

Project Goals: Improving the clinical management of individuals with a family history of early-onset cancers by developing a user friendly genetic counseling application to assess carrier probability and lifetime risk of developing cancers in individuals with TP53mutations. PID11859

Specific Aims: Goal 1. Validation of TP53 prediction (carrier status and cancer occurrence) usingfamily data from MDACC Clinical Cancer Genetics Program.
Goal 2. LFSPRO dissemination into clinical genetic counseling practice.

Overlap: None

Title/Grant Number: Mechanism-based Approach to Pain in Chronic Pancreatitis (MAP-CP) / 5R21DK122293-02 **New**

Effort: 0.6 Calendar Months, 5% Effort (all years of participation)

Supporting Agency: University of Pittsburgh

Grants Officer: Not available

Performance Period: 9/14/2020-5/31/2022

Funding Amount:

Project Goals: To use data and serum collected by the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer as part of the PROCEED study toinvestigate the subtypes of pain in Chronic Pancreatitis and identify potential biomarkers. FP00006539_Res1 PID12612

Specific Aims: This study is designed to test the hypothesis that patient-derived information can be used to identify pain phenotypes that inform management of chronic pancreatitis-related pain. Aim 1 is to determine if distinct biomarker profiles can discriminate pain phenotypes. We will measure expression of selected targets in sera and compare across chronic pancreatitis patients stratified by pain characteristic (intensity, temporality, and interference) as well as pain mechanism (nociceptive versus neuropathic). Aim 2 is designed to evaluate whether temporal changes in pain phenotype are associated with the natural course of disease and/or treatment such as opioid use.

Overlap: None

Title/Grant Number: Multimodal Imaging and Therapy of Ovarian Cancer / 1R01CA255753-01A1 **New**

Effort: 0.6 Calendar Months, 5% Effort (all years of participation)

Supporting Agency: NIH/NCI

Grants Officer: Christopher Hatch, Ch29v@nih.gov

Performance Period: 7/1/2021-6/30/2026

Funding Amount:

Project Goals: To create a new paradigm for approaching ovarian cancer that enables presurgical planning, surgical resection, and tumor photodestruction after a single nanoparticle injection. FP00010097_Res1 (Awarded - Pending Set-up)

Specific Aims: Aim 1 Test the hypothesis that ovarian tumor delivery can be augmented by targeting DM-Dual-Gd to proven targets or novel imaging target CDCP1. Aim 2 Test the hypothesis that ovarian tumor detection can be improved using the NIR II window compared to the NIR I window. Aim 3 Test the hypothesis that DM-Dual-Gd-based nanoparticles enable photodestruction of ovarian tumors. Aim 4 Test the hypothesis that pre-surgical NIR imaging employing DM-Dual-Gd can improve survival of models of intraperitoneal ovarian cancer.

Overlap: None

Title/Grant Number: Data Management and Analysis Core for Comparative Effectiveness Research on Cancer in Texas / RP210130 **New**

Effort: 1.2 Calendar Months, 10% Effort (all years of participation)

Supporting Agency: University of Texas Medical Branch

Grants Officer: Patty Moore, Phone: Email: research@cpr.it.texas.gov

Performance Period: 8/31/2021-8/30/2026

Funding Amount:

Project Goals: The Data Management and Analysis Core will become the hub for cancer comparative effectiveness research in Texas. FP00012865 (pending contract negotiation)

Specific Aims: 1) Support data management and analysis; 2) Expand our TCR linkage to nationally representative survey data, and 3) Recruit and train new CER investigators from at least 8 Texas academic and research institutions with a large number of underrepresented investigators.

Overlap: None

PENDING

Title/Grant Number: A Pilot Clinical Trial of Paricalcitol for Chronic Pancreatitis / #TBA

Effort: 0.6 Calendar Months, 5% Effort (all years of participation)

Supporting Agency: Subaward via Cedars-Sinai Medical Center
 Grants Officer: Not available
 Performance Period: 4/1/2022-3/31/2025
 Funding Amount:
 Project Goals: The objective of the study is to examine the feasibility of testing the effect of a potent vitamin D analogue, paricalcitol, on health-related quality of life (HRQoL) and potentially delay disease progression in patients with Chronic Pancreatitis (CP). FP00014083

Specific Aims: 1. Conduct a randomized double-blind, placebo-controlled pilot trial of paricalcitol to evaluate the feasibility of performing subsequent efficacy focused trials. Feasibility will be met if the of patients who enroll and complete the 12-month study is $\geq 75\%$ of planned. There will be a 21-month recruitment period and a one-year treatment period.
 2. Monitor health-related quality of life (HRQoL) measures; and imaging biomarkers and liquid biomarkers to identify measures/biomarkers that have the potential to measure responses to the treatment in subsequent efficacy focused trials.

Overlap: None

Title/Grant Number: PREVENTION OF HEPATOCELLULAR CARCINOMA RELATED TO METABOLIC SYNDROME / #TBA

Effort: 0.6 Calendar Months, 5% Effort (all years of participation)

Supporting Agency: Subaward via Baylor College of Medicine
 Grants Officer: Yujing Liu, Ph.D.
 Deputy Director, Division of Receipt and Referral
 Center for Scientific Review
 National Institutes of Health
 6700B Rockledge Dr. Room 4518
 Bethesda, MD 20892
 E-Mail: liuyujin@mail.nih.gov

Performance Period: 4/1/2022-3/31/2027
 Funding Amount:
 Specific Aims: Hepatocellular carcinoma (HCC) is the most rapidly increasing cause of cancer deaths among Americans. Most HCC cases arise in patients with liver cirrhosis. Recently, the etiology of cirrhosis and HCC in the United States has changed dramatically, with a marked decrease in chronic hepatitis C (HCV) and hepatitis B (HBV) and an epidemic increase in metabolic (dysfunction)-associated fatty liver disease (MAFLD). MAFLD affect 20–30% of adults in the US where it is projected to become the leading cause of HCC in the next two decades. In the absence of curative treatments for MAFLD or its underlying metabolic disorders (e.g., diabetes, obesity), there is an urgent need to develop effective strategies to reduce HCC burden in the growing MAFLD population. However, the best approach to prevent MAFLD-HCC remains unclear due to major gaps in knowledge:
 There are large individual variations in HCC risk, and the features (e.g., demographic, clinical, biochemical, genetic factors) that define subgroups of MAFLD patients at high HCC risk are unclear. The lack of well-defined, high-risk groups for HCC is the main roadblock for implementing and studying any preventive measures in MAFLD.

- Two preventive strategies hold substantial promise, but their role in reducing HCC-related morbidity and mortality in MAFLD remains unknown.
- Several agents may be effective for HCC chemoprevention, but they are unexamined in MAFLD. Treatments that target biological pathways in HCC and that are used to treat underlying metabolic dysfunction (e.g., metformin, statins, glitazones) are rational HCC chemopreventive strategies. However, no studies have examined the benefit or harms of these medications in MAFLD.

- The cost-effectiveness of HCC surveillance in MAFLD is unclear. HCC surveillance (e.g., liver imaging every 6 months) is recommended by practice guidelines for high-risk patients with HCV, HBV, or alcoholic liver disease. However, extrapolation from these conditions to MAFLD is not possible due to differences in prevalence, magnitude of HCC risk, and presence of co-existing comorbidities.

Overlap: None

In-Kind: None

Overlap: None

OTHER SUPPORT

JAGPREET CHHATWAL

CURRENT SUPPORT

NSF 16-601 (Chhatwal)	08/15/2017 – 07/31/2022 (NCE)	1.35 calendar months
National Science Foundation	total costs	

Collaborative Research: Smart intervention strategies for Hepatitis C elimination

Goals: In this project, we will estimate the true disease burden of hepatitis C at the state and national level, identify effective control strategies using infectious disease modeling and optimal control theory, and develop decision support tools for practical use by stakeholders.

Role: Principal Investigator

Overlap with proposed project: None.

Research Scholar Grant (Chhatwal)	07/01/2017 – 06/30/2022 (NCE)	2.28 calendar months
American Cancer Society	total costs	

A personalized surveillance program for hepatocellular carcinoma

Goals: The goal of this proposal is to reduce the burden of hepatocellular carcinoma by identifying effective surveillance programs that improve early detection.

Role: Principal Investigator

Overlap with proposed project: None.

R01 (Samir)	03/01/2019 – 02/28/2023	0.75 calendar months
National Institutes of Health	total costs	

Development of a Machine Learning Model to Integrate Clinical, Laboratory, Sonographic, and Elastographic Data for Noninvasive Liver Tissue Characterization in NAFLD

Goals: We have developed a set of general-purpose shear wave elastography (SWE) liver image analysis algorithms, termed SWE-Assist. We propose (1) to customize and refine SWE-Assist to create a new high-risk NASH-specific SWE image diagnosis toolkit, termed hrNASH-Det, and (2) to integrate hrNASH-Det with clinical, and laboratory data to create an accurate, non-invasive hrNASH diagnostic tool.

Role: Co-Investigator

Overlap with proposed project: None.

R01 (Deshmukh)	04/01/2019 – 03/31/2023	0.39 calendar months
National Institutes of Health	total costs	

Optimizing Age-based Anal Cancer Screening among People Living with HIV using Decision Analytic Modeling

Goals: The goal of the proposed research is to identify optimal (effective and cost-effective) age-specific anal cancer screening algorithms considering HSIL management using a Simulation Model of Anal Cancer.

Role: Co-Investigator

Overlap with proposed project: None.

(THIS AWARD)

W81XWH1910690 (Chhatwal)

09/01/2019 – 08/31/2022

1.83 calendar months

Department of Defense

total costs

Risk of hepatocellular cancer after virologic cure with direct acting antiviral agents in individuals with hepatitis C

Goals: The overall goal of this study is to examine the determinants of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C virologically cured with the new direct-acting antiviral regimens and to evaluate benefits versus harms of HCC surveillance in those patients.

Role: Co-Principal Investigator

Overlap with proposed project: None.

UM1DA049394 (Williams)

04/01/2019 – 03/31/2023

2.67 calendar months

National Institutes of Health

total costs

HEALing Communities Study: Developing and Testing an Integrated Approach to Address the Opioid Crisis (Data Coordinating Center)

Goals: We aim to evaluate the cost-effectiveness and budget impact of interventions that can reduce opioid-related deaths in HEALing Communities Study and other jurisdictions.

Role: Co-Investigator

Overlap with proposed project: None.

R37 CA231957 (Lubitz)

National Institutes of Health

07/01/2019 – 06/30/2024

1.38 calendar months

Thyroid Nodule Treatment Optimization: A Personalized Approach

Goals: The objective of this proposed research is to harness a comprehensive computer model to simulate individuals with benign and malignant nodules in the U.S. population to identify optimal personalized treatment approaches.

Role: Co-Investigator

Overlap with proposed project: None.

NSF 18-541 (Gopalappa)

01/01/2020 – 12/31/2023

0.18 calendar months

National Science Foundation

total costs

Simulation and Decision-Analysis Algorithms for Integrated Modeling of Diseases: A healthy lives for all approach

Goals: The goal of the proposed research is to develop an integrated multi-disease modeling framework to inform public health strategy plans such as HealthPeople2020 that address social determinants, reduce disparities and aims for healthy lives for all.

Role: Principal Investigator

Overlap with proposed project: None.

Contract (Chhatwal)

03/01/2020 – 12/31/2021 (NCE) 0.46 calendar months

Task Force for Global Health

total costs

Hepatitis C Elimination Simulator: An Interactive Global Analysis and Planning Tool for Hepatitis C Elimination

Goals: To help countries identify effective and affordable policies to diagnose and treat HCV, we are developing an interactive online tool, the Hep C Elimination Simulator that will provide country-level information on the HCV epidemic, model the impact of various diagnostic and treatment strategies on HCV disease burden, estimate the budget impact of different interventions, and track the treatment cascade and progress towards elimination.

Role: Principal Investigator

Overlap with proposed project: None.

2035361 (Chhatwal) 07/01/2020 – 06/30/2022 (NCE) 0.45 calendar months
National Science Foundation total costs
Mitigation and Suppression of Coronavirus Pandemic with Data-driven RAPID Decisions Using COVID-19 Simulator
Goals: To evaluate and identify effective mitigation strategies using COVID-19 Simulator at the county level in the US by considering testing rates in the absence and presence of COVID-19 pharmaceutical interventions.
Role: Principal Investigator
Overlap with proposed project: None.

NEW

(Chhatwal) 04/05/2021 – 01/31/2022 0.12 calendar months Johns
Hopkins University total costs
Simulation modeling to end the COVID pandemic
Goals: (1) Estimate the timing of lifting of restrictions (by different phases) in each state considering different vaccine uptake rates. (2) Evaluate the effect of emerging SARS-CoV-2 variants on the timing of herd immunity in each state. (3) Improve general accessibility and user experience for COVID-19 Simulator by improving conducting user interface design research.
Role: Principal Investigator
Overlap with proposed project: None.

(Loomba) 05/20/2020 – 04/30/2023 0.12 calendar months
University of California, San Diego total costs
Non-invasive screening of diabetics for advanced fibrosis due to NAFLD
Goals: This project will enable us to determine the circumstances under which NAFLD screening is efficient and cost-effective and identify optimal screening strategies for individuals based on age, sex, obesity, and other risk factors.
Role: Co-Investigator
Overlap with proposed project: None.

Completed Since Last Report

(Chhatwal) 01/31/2018 – 12/31/2020 0.12 calendar months
Foundation for Innovative New Diagnostics total costs
Cost-effective analysis of Simplified diagnostic algorithms for Hepatitis C
Goals: The objective is to evaluate the long-term effectiveness and cost-effectiveness of different HCV diagnostic algorithms that FIND will implement as part of the demonstration research projects in India, Georgia, Myanmar, Vietnam, Cameroon, and Malaysia.
Role: Principal Investigator
Overlap with proposed project: None.

(Chhatwal) 07/01/2020 – 02/28/2021 0.16 calendar months
Johns Hopkins University total costs
Informing State-level COVID-19 Testing and Contact Tracing using the COVID-19 Simulator
Goals: To address several time-sensitive policy decisions at the state and national level, we recently developed and launched an interactive COVID-19 policy simulation model. We propose to extend the COVID-19 Simulator to: (1) Estimate the underlying antibody prevalence of COVID-19 and active COVID-19 cases in each state, and (2) Evaluate minimum testing and contract tracing needed to mitigate the spread of COVID-19 at different phases of reopening in each state.
Role: Principal Investigator
Overlap with proposed project: None.

Pending Support

(Chhatwal) 08/15/2022 – 02/14/2024 1.0 calendar months

National Science Foundation

total costs

PIPP phase I: ALERT – Adaptive Learning Enterprise for Responding in a Timely way to Pandemics.

Goals: To identify and address three grand challenges pertinent to the Predictive Intelligence for Pandemic Prevention (PIPP) initiative that fall under the preemergence stage, the localized emergence stage, and the pandemic emergence stage.

Role: Principal Investigator

Overlap with proposed project: None.

(El-Serag)

04/01/2022 – 03/31/2027

2.4 calendar months

National Institutes of Health

total costs

Prevention of Hepatocellular Carcinoma Related to Metabolic Syndrome

Goals: The goal of our proposed research is to examine the risk and determinants of hepatocellular cancer in patients with nonalcoholic fatty liver disease (NAFLD) and metabolic syndrome.

Role: Co-Investigator

Overlap with proposed project: None.

◦**What other organizations were involved as partners?**

MD Anderson Cancer Center (Houston, TX) provided the following types of support:

- In-kind support (partner makes software, computers, equipment, etc., available to project staff)
- Facilities (project staff use the partner's facilities for project activities)

8.SPECIAL REPORTING REQUIREMENTS

◦**COLLABORATIVE AWARDS:**

The Initiating PI and the Collaborating/Partnering PI are submitting separate reports.

◦**QUAD CHARTS:**

Nothing to report.

9.APPENDICES:

Nothing to report.



Assessment of Incidence of and Surveillance Burden for Hepatocellular Carcinoma Among Patients With Hepatitis C in the Era of Direct-Acting Antiviral Agents

Qiushi Chen, PhD; Turgay Ayer, PhD; Madeline G. Adey, MPH; Xiaojie Wang, MS; Fasiha Kanwal, MD, MSHS; Jagpreet Chhatwal, PhD

Abstract

IMPORTANCE In the US, hepatocellular carcinoma (HCC), primarily associated with hepatitis C virus (HCV) infection, is the fastest rising cause of cancer-related death. Wider use of highly effective direct-acting antiviral agents (DAAs) substantially reduces the burden of chronic HCV infection, but the subsequent impacts with HCV-associated HCC remain unknown.

OBJECTIVE To assess projected changes in the incidence rate of and surveillance burden for HCC in the era of DAA treatment for HCV.

DESIGN, SETTING, AND PARTICIPANTS This decision analytical model study was performed from January 2019 to February 2020, using an individual-level state-transition simulation model to simulate disease progression, screening, and different waves of antiviral treatments for HCV in the US from 2012 to 2040.

INTERVENTIONS Current clinical management for chronic HCV infection.

MAIN OUTCOMES AND MEASURES Model outcomes were projected temporal trends and age distribution of incident HCC cases and candidates for HCC surveillance among patients with viremia and patients with virologically cured HCV.

RESULTS The simulation model projected that the annual incidence of HCC among patients with viremia and patients with virologically cured HCV will continue increasing to 24 000 (95% uncertainty interval [UI], 18 000-31 000) cases until 2021. In patients with virologically cured HCV, incident HCC cases are projected to increase from 1000 (95% UI, 500-2100) in 2012 to the peak of 7000 (95% UI, 5000-9600) in 2031 with a subsequent decrease to 6000 (95% UI, 4300-8300) by 2040. The proportion of incident HCC cases that occur in individuals with virologically cured HCV is estimated to increase from 5.3% in 2012 to 45.8% in 2040. The number of candidates for HCC surveillance in the population with virologically cured HCV is projected to increase from 106 000 (95% UI, 70 000-178 000) in 2012 to the peak of 649 000 (95% UI, 512 000-824 000) in 2030 and decrease to 539 000 (95% UI, 421 000-687 000) by 2040, while the proportion of all candidates for surveillance who are virologically cured is estimated to increase from 8.5% to 64.6% during the same period. The average age of HCC incidence and surveillance candidates is estimated to increase from 55 in 2012 to 72 and 71, respectively, by 2040.

CONCLUSIONS AND RELEVANCE The results of this study suggest that the burden of HCC will shift from patients with viremia to patients with virologically cured HCV, and to older populations. Appropriate management may be warranted for early detection of HCC in patients who may no longer be receiving specialty care for liver conditions.

JAMA Network Open. 2020;3(11):e2021173. doi:10.1001/jamanetworkopen.2020.21173

Open Access. This is an open access article distributed under the terms of the CC-BY License.

Key Points

Question What are the projected changes in incidence of and surveillance burden for hepatocellular carcinoma (HCC) among populations with hepatitis C virus (HCV) in the era of direct-acting antiviral agents (DAAs)?

Findings In this decision-analytical model, the incidence of HCC associated with HCV and candidates for HCC surveillance were projected to increase before starting to decrease in the era of DAAs. The burden of HCC associated with HCV was projected to shift from patients with viremia to individuals with virologically cured HCV and to older individuals.

Meaning Results of this study suggest that routine HCC surveillance is needed for early detection of HCC in individuals with virologically cured hepatitis C who may no longer be receiving specialty care of liver diseases.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Introduction

Hepatocellular carcinoma (HCC) is the fastest rising cause of cancer-related mortality in the US.^{1,2} The incidence of HCC has increased over the last 2 decades owing to the hepatitis C virus (HCV) epidemic.³ Most HCC cases are diagnosed in advanced stages, with a median survival less than 1 year.⁴ Regular surveillance for HCC may help improve early cancer detection rates when curative treatment can be applied and is recommended in patients with HCV-associated cirrhosis.⁵⁻⁷

The availability of direct-acting antiviral agents (DAAs) for HCV treatment has substantially altered the landscape of HCV. Though new DAA regimens can result in a virological cure (ie, sustained virological response [SVR]) in more than 90% of patients with HCV,⁸ many patients remain at risk of developing HCC after virological cure.^{9,10} Current clinical guidelines recommend that patients with virologically cured HCV with cirrhosis (or advanced fibrosis) to undergo routine HCC surveillance every 6 months.^{11,12}

Though the incidence rate of HCC in patients with virologically cured HCV is lower than that in patients with viremia, the absolute number of patients with virologically cured HCV requiring routine HCC surveillance is estimated to increase in the next decade.¹³ Patients with virologically cured HCV may experience improvement in liver function and hence live longer and could undergo surveillance for several years. In contrast, most patients with virologically cured HCV, despite being at risk for HCC, may not undergo routine HCC surveillance because of the perceived lower risk. Previous studies have reported that HCC surveillance rates are much lower in patients receiving primary care vs patients receiving specialty care.^{14,15} Thus, identifying HCC cases through surveillance in this cohort could be more challenging than that in other individuals at risk.

Estimating the burden of HCC surveillance in the cohorts of patients with virologically cured HCV may help guide primary and specialty care providers. The objective of this study was to evaluate the burden of HCC surveillance in the era of new HCV antiviral treatments by projecting the number and the characteristics of new HCC incident cases and candidates for routine HCC surveillance.

Methods

We used a previously developed mathematical model, Hepatitis C Disease Burden Simulation model (HEP-SIM),^{8,16} to simulate the population with HCV who would be considered candidates for HCC surveillance in the era of DAAs in the US. The HEP-SIM is an individual-level state-transition model that simulates the changing landscape of HCV by replicating disease progression, screening for HCV, different waves of antiviral treatments for HCV, and insurance coverage from 2001 to 2040. The model was previously validated with results of the National Health and Nutrition Examination Survey (NHANES) 2003-2010,¹⁷ reports from the Centers for Disease Control and Prevention,¹⁸ and natural history results from a long-term follow-up study of patients with advanced fibrosis.¹⁹ In this study, we projected temporal trends in HCC incidence and the changing characteristics of the number of patients with HCV (patients with viremia and patients with virologically cured HCV) who will be candidates for routine HCC surveillance in the era of DAAs. All data used in this analysis were publicly available and this study thus did not require approval from an institutional review board. This study followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guideline for decision analytical model studies. We describe the major model components; further model details can be found elsewhere.¹⁶

Population Characteristics and Natural History

The population in the HEP-SIM model represented patients with HCV in the US. The population included the NHANES population and the non-NHANES population, including incarcerated (in prisons), homeless, active-duty military, and nursing home populations. Patient HCV genotypes, liver disease states, awareness rate, and age distribution were estimated from published studies and other sources (eTable 1 and eTable 2 in the [Supplement](#)). New incidence of HCV infections was based on

the Centers for Disease Control and Prevention–reported estimates for the years 2006 to 2015 (eTable 3 in the [Supplement](#)), and we assumed that the annual incidence would change at the average rate observed during 2006 to 2015 until 2026 and then become constant.

We simulated the natural history of HCV, which was defined by different stages of liver disease, with chronic HCV infection defined using METAVIR fibrosis scores (F0, no fibrosis; F1, portal fibrosis without septa; F3, numerous septa without fibrosis; and F4, cirrhosis), decompensated cirrhosis, HCC, liver transplant, and liver-related death. Rates of fibrosis progression and decompensation were estimated from published metaregression analysis and observational studies²⁰⁻²² (eTable 4 in the [Supplement](#)). Patients with decompensated cirrhosis or with HCC had higher mortality rates²³ and were eligible to for liver transplant.²⁴⁻²⁶

Screening and Treatment for Patients With HCV in the DAA Era

To accurately represent the HCV disease burden that would subsequently affect the burden of HCC, we simulated the clinical management of HCV, ie, screening and treatment, from 2001 to 2040. In each year, patients with HCV could be diagnosed through usual care, which included risk-based screening (eTable 5 in the [Supplement](#)). Since 2013, we implemented one-time birth-cohort screening for individuals born between 1945 and 1965 among the NHANES, nursing home, and homeless populations in addition to the diagnosis through usual care. From 2020 to projections to 2040, we included one-time universal screening of all adults between aged 18 to 79 years, following the updated screening recommendation by the US Preventive Services Task Force.²⁷ For universal screening, we assumed the screening rate of 9% per year, which is the rate observed in the one-time birth-cohort screening policy.^{28,29}

For HCV treatment, we modeled multiple waves of antiviral treatments available in the US during different periods.¹⁶ The market share of different types of treatment regimens for each HCV genotype was estimated using commercial claims from research organizations (QuintilesIMS and Ipsos) (eTable 6 in the [Supplement](#)). Treatment efficacy measured as SVR rate was dependent on the regimen type, individual HCV genotype, presence of cirrhosis, and failure of previous treatment if any, which were estimated based on data from multiple clinical trials and real-world studies (eTable 7 in the [Supplement](#)). For all populations except individuals who were incarcerated or homeless, the number of patients receiving treatment in each year was estimated based on published data and drug sales until 2016 (eTable 8 in the [Supplement](#)). In the individuals who were incarcerated and homeless, treatment uptake was 1% per year from 2010 to 2016 and 5% per year starting in 2017.³⁰ Our model did not consider treatment for patients with decompensated cirrhosis. With limited treatment capacity, priorities were given to patients with bridging fibrosis (F3) or compensated cirrhosis. Patients whose previous treatment failed may be eligible for retreatment, depending on his previous regimen, new available regimen, and presence of cirrhosis (eTable 7 in the [Supplement](#)).¹⁶

HCC Incidence

Patients with HCV having bridging fibrosis (F3), compensated, and decompensated cirrhosis were at risks of developing HCC.^{9,10,22} The HCC risk in patients with virologically cured HCV was lower than in patients with viremia (eTable 4 in the [Supplement](#)).⁹ Patients with compensated cirrhosis could progress to decompensated cirrhosis even after achieving virological cure of HCV and they remained at risk of developing HCC.³¹ We assumed a lower risk of HCC in patients with decompensated cirrhosis with virologically cured HCV than in those with viremia based on a prospective cohort study.³²

Subpopulations

We considered different subpopulations in the HEP-SIM model (eTable 9 in the [Supplement](#)) based primarily on their health insurance status. We assumed that for the NHANES and nursing home populations, all patients aged 65 years and older were covered by Medicare, and patients aged less than 65 years were covered by private (49.8%), Medicaid (9.2%), or other public insurance (14.3%),

or were uninsured (26.7%) based on NHANES data.^{13,28,33} For the population of individuals who were homeless, the insurance distribution was estimated from a 2012 study (3.2% privately insured, 31.5% Medicaid, 65.3% uninsured).³⁴ We incorporated insurance expansion during the period from 2014 to 2017 owing to the implementation of the Affordable Care Act (eTable 10 in the [Supplement](#)). We also include patients who were incarcerated as a separate population because this population represents a substantial group of viremic infections that were not accounted for in NHANES data.³⁵

Model Outcomes

Our primary model outcome was the number of patients who developed HCC and the number of patients who were candidates for routine HCC surveillance from 2012 to 2040. Candidates for HCC surveillance were defined as patients with F3 fibrosis stage, or compensated cirrhosis, with or without virological cure. In addition, we assumed that 15% (range, 5%-25%) of patients with compensated cirrhosis (eligible for liver transplant) were candidates for HCC surveillance.^{36,37} We further stratified the number of candidates for HCC surveillance by viremia status (ie, with viremia or virologically cured HCV), cirrhosis, and subpopulation category. We also projected the age distribution of HCC incident cases and surveillance candidates for each year. To account for model uncertainty in parameters, we conducted probabilistic sensitivity analysis by sampling model inputs from the recommended statistical distributions³⁸ (eTable 11 in the [Supplement](#)). We evaluated model outputs for sampled parameters by 2000 iterations and presented the 95% uncertainty intervals (UIs) for model outcomes. The simulation model was developed in C++ programming language and all statistical analysis was performed in R version 3.6.0 (R Project for Statistical Computing).

Results

HCC Incidence

This decision analytical model study was conducted from January 2019 to February 2020. In 2012, the annual incidence of HCC among patients with HCV (with viremia and virologically cured HCV) was 18 000 (95% UI, 11 000-32 000). The annual incidence of HCV-associated HCC is projected to increase to 24 000 (95% UI, 18 000-31 000) cases in 2021 and decrease to 13 000 (95% UI, 11 000-16 000) cases by 2040 (**Figure 1**). In 2012, 1000 (95% UI, 500-2100) new HCC cases (5.3% of all new cases) developed in patients with virologically cured HCV; this number is projected to peak at 7000 (95% UI, 5000-9600) new cases (35.0% of all new cases) in 2031 and then decrease to 6000 (95% UI, 4300-8300) new cases (45.8% of all new cases) by 2040. Most of the HCC cases would develop in patients with cirrhosis. The number of new HCC cases among patients with cirrhosis who achieved virological cure increased substantially from 700 (95% UI, 300-1700) in 2012 to 4500 (95% UI, 3000-6700) in 2040 (eFigure 1 in the [Supplement](#)).

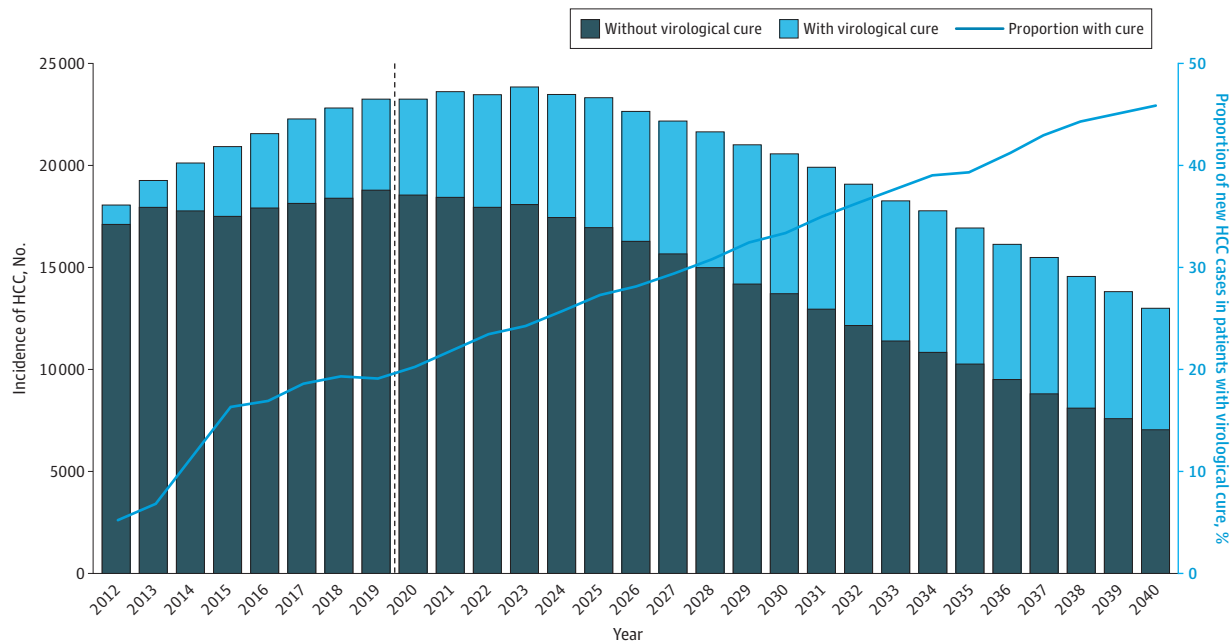
We estimated that between 2012 and 2040, the cumulative incidence of HCV-associated HCC would be 583 000 cases (95% UI, 458 000 cases to 738 000 cases), and 27.1% (95% UI, 20.3%-34.7%) of these cases would develop among patients with virologically cured HCV. The 95% UIs for the annual HCC incidence by virologically cured status in each year are presented in eFigure 2 in the [Supplement](#).

HCC Surveillance Candidates

Our model projected that in 2012, a total of 1.24 million (95% UI, 0.96 million-1.71 million) patients with HCV (with viremia and virologically cured HCV) were at risk of developing HCC and would be candidates for routine HCC surveillance in the US. The number of candidates eligible for HCC surveillance is estimated to increase to 1.49 million (95% UI, 1.23 million to 1.85 million) in 2020 and then gradually decrease to 0.83 million (95% UI, 0.66 million to 1.04 million) by the end of 2040 (**Figure 2**). In 2012, 106 000 (95% UI, 70 000-178 000) surveillance candidates were those who had achieved virological cure; this number is projected to peak at 649 000 (95% UI, 512 000-824 000) in 2030 and then decrease to 539 000 (95% UI, 421 000-687 000) individuals

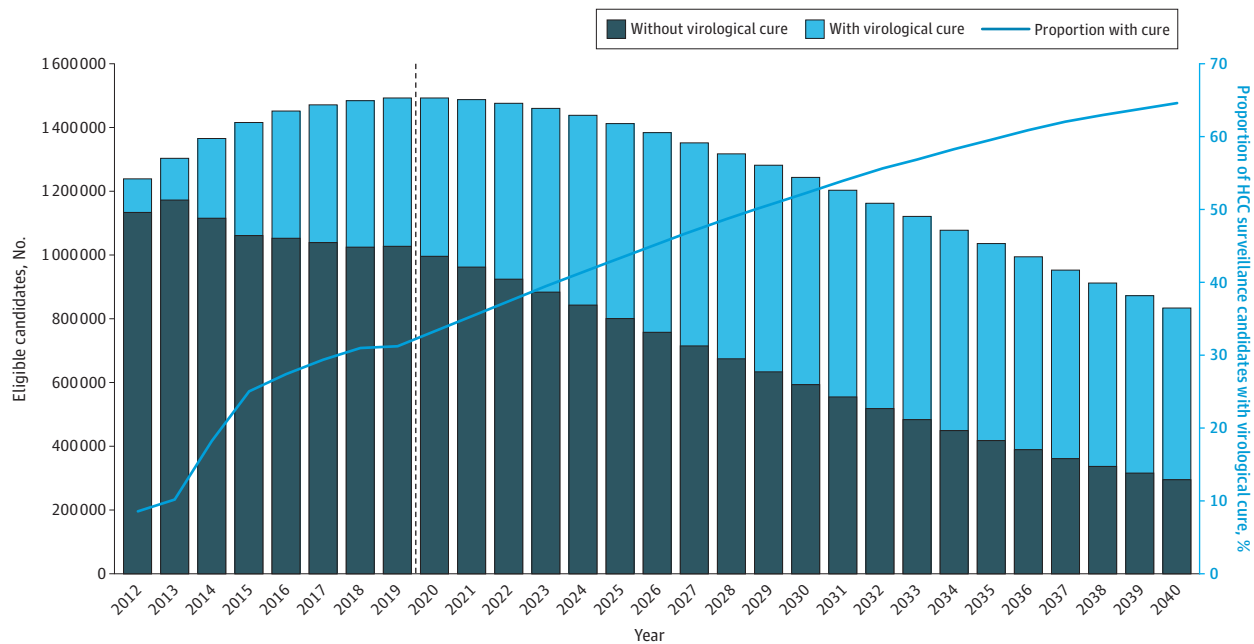
by 2040. However, the proportion of all HCC surveillance candidates who are virologically cured is estimated to increase from 8.5% in 2012 to 64.6% in 2040. We also projected that the proportion of surveillance candidates with cirrhosis (compensated and decompensated) is estimated to increase from 42.8% in 2012 to 49.6% in 2040, and that the proportion of patients with cirrhosis among

Figure 1. Projection of Annual Hepatocellular Carcinoma (HCC) Incidence by Cure Status From 2012 to 2040



The dashed line represents the starting year of the universal hepatitis C virus screening in US adults.

Figure 2. Projection of Number of Candidates for Hepatocellular Carcinoma (HCC) Surveillance by Cure Status From 2012 to 2040



The dashed line represents the starting year of the universal hepatitis C virus screening in US adults.

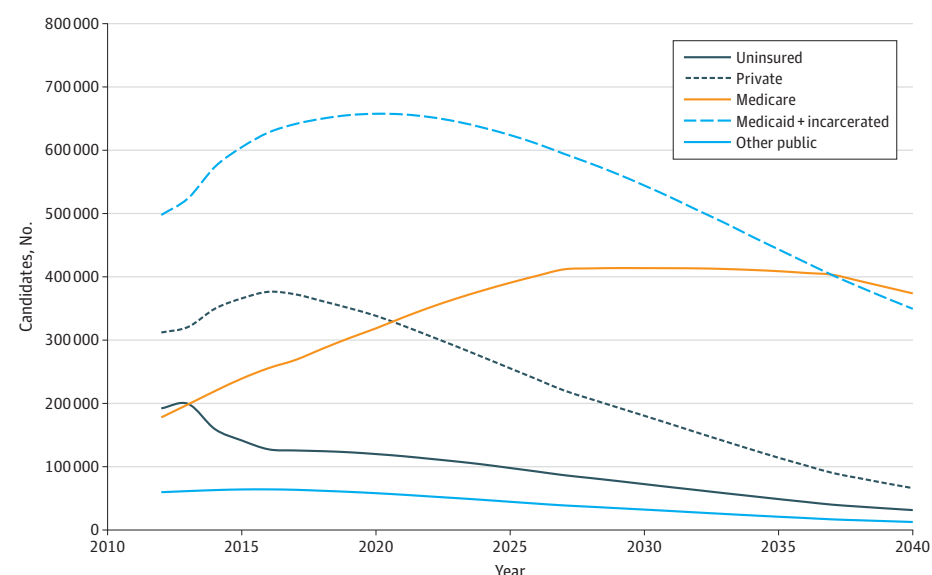
patients with virologically cured HCV is estimated to increase from 34.5% to 43.5% in the same time period (eFigure 3 in the [Supplement](#)).

We further analyzed HCC surveillance candidates by subpopulation (**Figure 3**). In 2012, 312 000 (95% UI, 225 000-443 000) patients (25.2%) who were candidates for HCC surveillance were covered by private insurance, 178 000 (95% UI, 111 000-274 000) patients (14.4%) by Medicare, 498 000 (95% UI, 390 000-679 000) patients (40.2%) and by state-administered programs (including Medicaid and the population incarcerated in state prisons), 60 000 (95% UI, 44 000-85 000) patients (4.8%) by other public insurance, and 192 000 (95% UI, 144 000-265 000) patients (15.5%) were uninsured. The number of HCC surveillance candidates increased in the privately insured pool to 376 000 (95% UI, 277 000-509 000) patients (25.9%) by 2016 and decreased in the uninsured pool to 127 000 (95% UI, 96 000-168 000) patients (8.8%) because of the implementation of the Affordable Care Act in 2014. The number of HCC surveillance candidates covered by Medicare increased further because of the aging population of patients with HCV (with viremia and virologically cured HCV) and is expected to surpass the number of candidates who are privately insured from 2021 to 2040 (Figure 3). Among all payers, the state-administered programs (Medicaid and state prisons) is estimated to have the highest burden of HCC surveillance: the number of HCC surveillance candidates incarcerated in state prisons or covered by Medicaid is projected to peak at 658 000 (95% UI, 557 000-786 000) in 2020 and decrease to 349 000 (95% UI, 280 000-427 000) by the end of 2040.

Aging of HCC Population

The average age of HCC incidence is projected to increase from 55 in 2012 and to 72 in 2040 (eFigure 4 in the [Supplement](#)). The proportion of incident HCC cases older than age of 65 years is projected to increase from 16.4% in 2012 to 76.5% in 2040 (**Figure 4**). Similarly, the average age of surveillance candidates is projected to increase from 55 years in 2012 to 71 years in 2040. The proportion of surveillance candidates aged 65 years and older is projected to increase from 16.1% in 2012 to 73.8% in 2040.

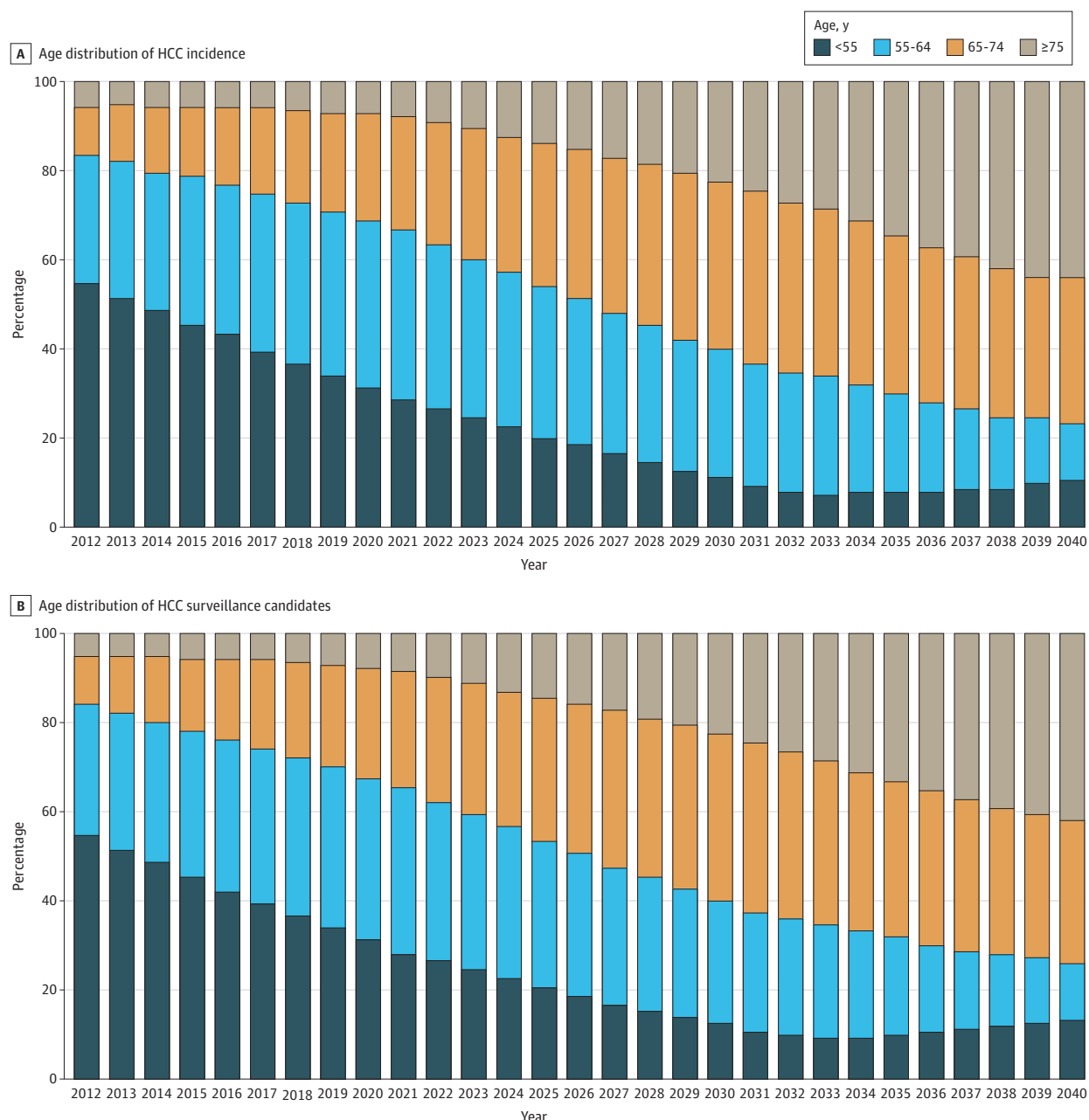
Figure 3. Number of Candidates for Hepatocellular Carcinoma Surveillance by Insurance Subgroup From 2012 to 2040



Discussion

The incidence of HCC has increased over the last 2 decades primarily because of the chronic HCV.³ With the availability and wider use of new DAAs for HCV treatment, the burden of HCC and routine HCC surveillance attributable to HCV could change in the era of DAAs. In this modeling study, we found that the incidence of HCC is estimated to continue to increase until 2021. Between 2012 and 2040, 583 000 patients with HCV (with viremia and virologically cured HCV) were estimated to develop HCC, and 27% of those cases would be among patients with virologically cured HCV. The number of candidates eligible for HCC surveillance is estimated to increase from 1.24 million in 2012 to 1.49 million in 2020, while the burden of surveillance is expected to shift from patients with viremia to individuals who achieved virological cure. In 2012, 9% of all candidates for HCV

Figure 4. Age Distribution of HCC Incidence and HCC Surveillance Candidates From 2012 to 2040



surveillance were virologically cured, which is projected to increase to 65% by 2040. The average age of HCC incidence and surveillance candidates is also projected to shift from 55 years in 2012 to more than 70 years in 2040.

Our study provides insights on the trends in HCC in the DAA era. Some studies³⁹⁻⁴¹ conducted statistical analysis based on cancer registry data predominately in the pre-DAA era. The forecasted incidence was based on historical trends without factoring in the changes in the management of HCV.^{39,42} Thus those findings may not be applicable to the DAA era. While other studies that used DAA-era data reported that the burden of HCC will decrease in the era of DAAs,^{8,13,43} those studies excluded patients with HCV who were incarcerated, homeless, and residing in nursing homes, and were active-duty military personnel. Our study accounted for such populations with less access to screening and treatment for HCV than the general population, and we found that the overall HCC incidence in the population with HCV will continue to increase until 2021 despite the recent availability of highly effective DAAs.

Our study also provides information on the shifting burden of surveillance for HCC and the need to emphasize the clinical treatment for patients with virologically cured HCV. Despite virological cure, patients with advanced fibrosis or cirrhosis will remain at risk of developing HCC. Therefore, as the number of patients with virologically cured HCV increases, the new cases of HCC from this cohort will increase. In addition, the burden of surveillance for HCC will shift from patients with viremia to patients with virologically cured HCV. These changes may have substantial practical implications for the continuum of care. Most of the patients with virologically cured HCV will transition from receiving care from liver specialists to receiving care from primary care physicians. However, most people do not receive regular surveillance in primary care settings⁴⁴ and the knowledge of HCC surveillance in primary care settings remains low.⁴⁵ Therefore, it is vital to emphasize that biannual HCC surveillance is warranted for these patients in primary care settings.

The optimal clinical management of patients with virologically cured HCV remains unclear. While the HCC management guidelines by the European Association for the Study of the Liver recommends routine HCC surveillance in patients with virologically cured HCV having advanced fibrosis and cirrhosis,⁷ the guideline by the American Association for the Study of Liver Diseases recommends routine HCC surveillance only in individuals with cirrhosis without specifying the status of virological cure.⁶

The optimal surveillance strategy in patients with virologically cured HCV will rely on more evidence and studies in the following 3 aspects. First, long-term data are needed for a better understanding of the risk of HCC after DAA-induced virological cure in patients with HCV. It is unclear how much of the current knowledge of the HCC risk among patients with virologically cured HCV from an interferon-based regimen could be used to inform surveillance policies in the era of DAAs. Some studies suggest that patients with HCV cured by DAA regimens could have higher HCC risks than those with HCV cured by interferon-based regimens,^{9,10,46} but the increase was not found to be significant after adjusting for confounders,⁴⁷ and the difference was not found to be conclusive.⁴⁸ In addition, compared with the available data in the interferon-based treatment era, the observations in DAA era are subject to shorter follow-up time and present an older at-risk population.

Second, health economic data are needed to identify cost-effective HCC surveillance policies for patients with virologically cured HCV. The primary reason for not recommending routine surveillance in patients with virologically cured HCV with advanced fibrosis may be that biannual surveillance using ultrasonography and α_1 -fetoprotein testing for the lifetime was not found to be cost-effective in this cohort.^{49,50} Instead of a general surveillance, further research is warranted to identify risk-based surveillance in these patients that could provide a good use of limited resources.⁵⁰ In addition, the optimal age for stopping surveillance is unknown. It is plausible that patients with virologically cured HCV may not need HCC surveillance throughout their remaining lifetime.

Third, tailoring surveillance policies to individual-level factors may be a useful approach, especially as emerging molecular biomarkers show their value in the prediction of HCC risks in addition to current clinical risk factors.⁵¹ Comprehensive risk prediction models can be developed by

integrating multilevel risk factors to further refine the risk predictions.⁵² A tailored surveillance strategy could differentiate the patients at high risk who can benefit more from surveillance compared with the others, and thus further improve the cost-effectiveness and efficiency of medical resource use.^{53,54}

Like any modeling study, our model projection results are subject to inherent uncertainty that arises from the uncertainties in model parameter estimates and model assumptions. Some model parameters and assumptions cannot capture all possible disease variability and diverse real-world clinical practice. Therefore, instead of presenting the prediction of outcomes, our model projection results provide insights on the overall trends of the HCC incidence and surveillance burden, which has also been shown to be robust in the presence of model uncertainty from our sensitivity analysis.

Limitations

This study has limitations. First, we did not explicitly model HCC diagnosis process, which depends on incidence, underlying surveillance strategies, and testing accuracy. We considered HCC as an aggregate health state and used aggregate-level parameters for the population to characterize the overall burden of HCC. Further details would be necessary for analyzing the outcomes of particular HCC surveillance and treatment strategies. Second, our analysis was limited to HCV-associated HCC and did not account for other emerging risk factors such as metabolic disorder (eg, diabetes, nonalcoholic fatty liver disease), hepatitis B, and alcohol consumption. Management of HCC in these other populations at increased risk is becoming increasingly important but would require modeling of different disease factors, which is beyond the scope of this study. In addition, our model did not account for fibrosis regression following successful DAA treatment. Based on recent studies that suggested stable HCC risks following SVR in patients including those with improved noninvasive markers for fibrosis,^{55,56} we assumed that patients would still be candidates for HCC surveillance even if they had fibrosis regression. However, it is possible that the risk of HCC could decrease with fibrosis regression as time from SVR accrues; therefore, our study may have overestimated the burden of HCC surveillance.

Conclusions

This decision analytical model study suggests that the new cases of HCC associated with HCV will continue to increase even in the era of DAAs. We also found that the risk of HCC as well as the burden of HCC surveillance is projected to shift from patients with active HCV to those who had achieved virological cure. Routine HCC surveillance in patients with virologically cured HCV who remain at risk of HCC may help reduce the burden of HCC in the era of new antiviral agents.

ARTICLE INFORMATION

Accepted for Publication: August 8, 2020.

Published: November 18, 2020. doi:10.1001/jamanetworkopen.2020.21173

Open Access: This is an open access article distributed under the terms of the [CC-BY License](#). © 2020 Chen Q et al. JAMA Network Open.

Corresponding Author: Jagpreet Chhatwal, PhD, Massachusetts General Hospital Institute for Technology Assessment, 101 Merrimac St, 10th Floor, Boston, MA 02114 (jagchhatwal@mgh.harvard.edu).

Author Affiliations: Institute for Technology Assessment, Massachusetts General Hospital, Harvard Medical School, Boston (Chen, Adeo, Chhatwal); Harold and Inge Marcus Department of Industrial and Manufacturing Engineering, Pennsylvania State University, University Park (Chen); H. Milton Stewart School of Industrial and Systems Engineering, Georgia Institute of Technology, Atlanta (Ayer, Wang); Department of Medicine, Baylor College of Medicine, Houston, Texas (Kanwal); Houston Veterans Affairs Health Services Research and Development Center of Excellence, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas (Kanwal).

Author Contributions: Dr Chhatwal had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Chen, Ayer, Kanwal, Chhatwal.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Chen, Ayer, Adey, Kanwal, Chhatwal.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Chen.

Obtained funding: Ayer, Kanwal, Chhatwal.

Administrative, technical, or material support: Ayer, Adey, Kanwal, Chhatwal.

Supervision: Ayer, Kanwal, Chhatwal.

Conflict of Interest Disclosures: Dr Ayer reported receiving personal fees from Merck and Value Analytics Labs outside the submitted work. Dr Kanwal reported receiving grants from Veterans Health Administration during the conduct of the study. Dr Chhatwal reported receiving grants and personal fees from Merck and Gilead, personal fees from Novo Nordisk and Value Analytics Labs outside the submitted work. No other disclosures were reported.

Funding/Support: This study was supported by the American Cancer Society Research Scholar Grant RSG-17-022-01-CPPB (Chhatwal), the Office of the Assistant Secretary of Defense for Health Affairs under awards W81XWH-19-10689 (Kanwal) and W81XWH-19-10690 (Chhatwal), and the National Cancer Institute grant U01 CA230997 (Kanwal).

Role of the Funder/Sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66(1):7-30. doi:10.3322/caac.21332
2. Ryerson AB, Ehemann CR, Altekruse SF, et al. Annual Report to the Nation on the Status of Cancer, 1975-2012, featuring the increasing incidence of liver cancer. *Cancer*. 2016;122(9):1312-1337. doi:10.1002/cncr.29936
3. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology*. 2012;142(6):1264-1273.e1. doi:10.1053/j.gastro.2011.12.061
4. Artinyan A, Mailey B, Sanchez-Luege N, et al. Race, ethnicity, and socioeconomic status influence the survival of patients with hepatocellular carcinoma in the United States. *Cancer*. 2010;116(5):1367-1377. doi:10.1002/cncr.24817
5. Volkow ND, Wargo EM. Overdose prevention through medical treatment of opioid use disorders. *Ann Intern Med*. 2018;169(3):190-192. doi:10.7326/M18-1397
6. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011;53(3):1020-1022. doi:10.1002/hep.24199
7. European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2012;56(4):908-943. doi:10.1016/j.jhep.2011.12.001
8. Kabiri M, Jazwinski AB, Roberts MS, Schaefer AJ, Chhatwal J. The changing burden of hepatitis C virus infection in the United States: model-based predictions. *Ann Intern Med*. 2014;161(3):170-180. doi:10.7326/M14-0095
9. Kanwal F, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB. Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. *Gastroenterology*. 2017;153(4):996-1005.e1. doi:10.1053/j.gastro.2017.06.012
10. Janjua NZ, Chong M, Kuo M, et al. Long-term effect of sustained virological response on hepatocellular carcinoma in patients with hepatitis C in Canada. *J Hepatol*. 2017;66(3):504-513. doi:10.1016/j.jhep.2016.10.028
11. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2018. *J Hepatol*. 2018; 69(2):461-511. doi:10.1016/j.jhep.2018.03.026
12. AASLD-IDS. Monitoring patients who are starting HCV treatment, are on treatment, or have completed therapy: recommendations for testing, managing, and treating hepatitis C. Accessed January 1, 2019. <https://www.hcvguidelines.org/evaluate/monitoring>
13. Chhatwal J, Wang X, Ayer T, et al. Hepatitis C disease burden in the United States in the era of oral direct-acting antivirals. *Hepatology*. 2016;64(5):1442-1450. doi:10.1002/hep.28571

14. Davila JA, Henderson L, Kramer JR, et al. Utilization of surveillance for hepatocellular carcinoma among hepatitis C virus-infected veterans in the United States. *Ann Intern Med*. 2011;154(2):85-93. doi:10.7326/0003-4819-154-2-201101180-00006
15. Singal AG, Tiro J, Li X, Adams-Huet B, Chubak J. Hepatocellular carcinoma surveillance among patients with cirrhosis in a population-based integrated health care delivery system. *J Clin Gastroenterol*. 2017;51(7):650-655. doi:10.1097/MCG.0000000000000708
16. Chhatwal J, Chen Q, Bethea ED, Hur C, Spaulding AC, Kanwal F. The impact of direct-acting anti-virals on the hepatitis C care cascade: identifying progress and gaps towards hepatitis C elimination in the United States. *Aliment Pharmacol Ther*. 2019;50(1):66-74. doi:10.1111/apt.15291
17. Denniston MM, Jiles RB, Drobeniuc J, et al. Chronic hepatitis C virus infection in the United States, national health and nutrition examination survey 2003 to 2010. *Ann Intern Med*. 2014;160(5):293-300. doi:10.7326/M13-1133
18. Centers for Disease Control and Prevention. Surveillance for viral hepatitis – United States, 2011. Accessed November 20, 2013. <https://www.cdc.gov/HEPATITIS/Statistics/index.htm>
19. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA*. 2012;308(24):2584-2593. doi:10.1001/jama.2012.144878
20. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology*. 2008;48(2):418-431. doi:10.1002/hep.22375
21. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology*. 1997;112(2):463-472. doi:10.1053/gast.1997.v112.pm9024300
22. Planas R, Ballesté B, Alvarez MA, et al. Natural history of decompensated hepatitis C virus-related cirrhosis: a study of 200 patients. *J Hepatol*. 2004;40(5):823-830. doi:10.1016/j.jhep.2004.01.005
23. Wolfe RA, Roys EC, Merion RM. Trends in organ donation and transplantation in the United States, 1999-2008. *Am J Transplant*. 2010;10(4, pt 2):961-972. doi:10.1111/j.1600-6143.2010.03021.x
24. Thuluvath PJ, Guidinger MK, Fung JJ, Johnson LB, Rayhill SC, Pelletier SJ. Liver transplantation in the United States, 1999-2008. *Am J Transplant*. 2010;10(4, pt 2):1003-1019. doi:10.1111/j.1600-6143.2010.03037.x
25. Chhatwal J, Ferrante SA, Brass C, et al. Cost-effectiveness of boceprevir in patients previously treated for chronic hepatitis C genotype 1 infection in the United States. *Value Health*. 2013;16(6):973-986. doi:10.1016/j.jval.2013.07.006
26. Lang K, Danchenko N, Gondek K, Shah S, Thompson D. The burden of illness associated with hepatocellular carcinoma in the United States. *J Hepatol*. 2009;50(1):89-99. doi:10.1016/j.jhep.2008.07.029
27. US Preventive Services Task Force. Draft recommendation statement: hepatitis C virus infection in adolescents and adults: screening. Accessed September 30, 2019. <https://www.uspreventiveservicestaskforce.org/Page/Document/draft-recommendation-statement/hepatitis-c-screening1>
28. Denniston MM, Kleven RM, McQuillan GM, Jiles RB. Awareness of infection, knowledge of hepatitis C, and medical follow-up among individuals testing positive for hepatitis C: National Health and Nutrition Examination Survey 2001-2008. *Hepatology*. 2012;55(6):1652-1661. doi:10.1002/hep.25556
29. Hep C State Policy Simulator. Accessed July 30, 2020. <https://www.hepcsimulator.org/>
30. HepCorrections. Estimates of treatment uptake among incarcerated population. Accessed October 30, 2019. <http://www.hepcorrections.org/>
31. Cardoso AC, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. *J Hepatol*. 2010;52(5):652-657. doi:10.1016/j.jhep.2009.12.028
32. Romano A, Angeli P, Piovesan S, et al. Newly diagnosed hepatocellular carcinoma in patients with advanced hepatitis C treated with DAAs: A prospective population study. *J Hepatol*. 2018;69(2):345-352. doi:10.1016/j.jhep.2018.03.009
33. Stepanova M, Kanwal F, El-Serag HB, Younossi ZM. Insurance status and treatment candidacy of hepatitis C patients: analysis of population-based data from the United States. *Hepatology*. 2011;53(3):737-745. doi:10.1002/hep.24131
34. Kates J. *Medicaid Coverage and Care for the Homeless Population: Key Lessons to Consider for the 2014 Medicaid Expansion*. Henry J. Kaiser Family Foundation; 2012.
35. Hofmeister MG, Rosenthal EM, Barker LK, et al. Estimating prevalence of hepatitis C virus infection in the United States, 2013-2016. *Hepatology*. 2019;69(3):1020-1031. doi:10.1002/hep.30297

36. Jesse MT, Abouljoud M, Goldstein ED, et al. Racial disparities in patient selection for liver transplantation: an ongoing challenge. *Clin Transplant*. 2019;33(11):e13714. doi:10.1111/ctr.13714
37. Mazumder NR, Celaj S, Atiemo K, et al. Liver-related mortality is similar among men and women with cirrhosis. *J Hepatol*. 2020;S0168-8278(20)30235-X. doi:10.1016/j.jhep.2020.04.022
38. Briggs A, Claxton C, Sculpher M. *Decision Modelling for Health Economic Evaluation*. 1st ed: Oxford University Press; 2006.
39. Han SS, Kelly SP, Li Y, et al. Changing landscape of liver cancer in California: a glimpse into the future of liver cancer in the United States. *J Natl Cancer Inst*. 2019;111(6):550-556. doi:10.1093/jnci/djy180
40. Pham C, Fong TL, Zhang J, Liu L. Striking racial/ethnic disparities in liver cancer incidence rates and temporal trends in California, 1988-2012. *J Natl Cancer Inst*. 2018;110(11):1259-1269. doi:10.1093/jnci/djy051
41. White DL, Thrift AP, Kanwal F, Davila J, El-Serag HB. Incidence of hepatocellular carcinoma in all 50 United States, from 2000 through 2012. *Gastroenterology*. 2017;152(4):812-820.e5. doi:10.1053/j.gastro.2016.11.020
42. Singal AG, Murphy CC. Hepatocellular carcinoma: a roadmap to reduce incidence and future burden. *J Natl Cancer Inst*. 2019;111(6):527-528. doi:10.1093/jnci/djy184
43. Razavi H, Elkhoury AC, Elbasha E, et al. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. *Hepatology*. 2013;57(6):2164-2170. doi:10.1002/hep.26218
44. Davila JA, Morgan RO, Richardson PA, Du XL, McGlynn KA, El-Serag HB. Use of surveillance for hepatocellular carcinoma among patients with cirrhosis in the United States. *Hepatology*. 2010;52(1):132-141. doi:10.1002/hep.23615
45. McGowan CE, Edwards TP, Luong MU, Hayashi PH. Suboptimal surveillance for and knowledge of hepatocellular carcinoma among primary care providers. *Clin Gastroenterol Hepatol*. 2015;13(4):799-804. doi:10.1016/j.cgh.2014.07.056
46. Kozbial K, Moser S, Schwarzer R, et al. Unexpected high incidence of hepatocellular carcinoma in cirrhotic patients with sustained virologic response following interferon-free direct-acting antiviral treatment. *J Hepatol*. 2016;65(4):856-858. doi:10.1016/j.jhep.2016.06.009
47. Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. *J Hepatol*. 2017;S0168-8278(17)32273-0. Published online September 5, 2017. doi:10.1016/j.jhep.2017.08.030
48. Waziry R, Hajarizadeh B, Grebely J, et al. Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: a systematic review, meta-analyses, and meta-regression. *J Hepatol*. 2017;67(6):1204-1212. doi:10.1016/j.jhep.2017.07.025
49. Farhang Zangneh H, Wong WWL, Sander B, et al. Cost effectiveness of hepatocellular carcinoma surveillance after a sustained virologic response to therapy in patients with hepatitis C virus infection and advanced fibrosis. *Clin Gastroenterol Hepatol*. 2019;17(9):1840-1849.e16. doi:10.1016/j.cgh.2018.12.018
50. Singal AG, Ioannou GN. For whom is hepatocellular carcinoma surveillance after sustained virologic response cost-effective? *Clin Gastroenterol Hepatol*. 2019;17(9):1732-1735. doi:10.1016/j.cgh.2019.02.020
51. Yang JD, Patel T. Early detection of hepatocellular carcinoma: expanding the utility of circulating tumor markers. *Hepatology*. 2019;69(5):1855-1857. doi:10.1002/hep.30468
52. Fujiwara N, Friedman SL, Goossens N, Hoshida Y. Risk factors and prevention of hepatocellular carcinoma in the era of precision medicine. *J Hepatol*. 2018;68(3):526-549. doi:10.1016/j.jhep.2017.09.016
53. Goossens N, Bian CB, Hoshida Y. Tailored algorithms for hepatocellular carcinoma surveillance: Is one-size-fits-all strategy outdated? *Curr Hepatol Rep*. 2017;16(1):64-71. doi:10.1007/s11901-017-0336-z
54. Kanwal F, Singal AG. Surveillance for hepatocellular carcinoma: current best practice and future direction. *Gastroenterology*. 2019;157(1):54-64. doi:10.1053/j.gastro.2019.02.049
55. Kanwal F, Kramer JR, Asch SM, Cao Y, Li L, El-Serag HB. Long-term risk of hepatocellular carcinoma in HCV patients treated with direct acting antiviral agents. *Hepatology*. 2020;71(1):44-55. doi:10.1002/hep.30823
56. Rich NE, Yang JD, Perumalswami PV, et al. Provider attitudes and practice patterns for direct-acting antiviral therapy for patients with hepatocellular carcinoma. *Clin Gastroenterol Hepatol*. 2020;18(4):974-983. doi:10.1016/j.cgh.2019.07.042

SUPPLEMENT.

eTable 1. Population Characteristics of Hepatitis C Patients in the United States

eTable 2. Age Distribution of Initial Population Infected With Hepatitis C

eTable 3. Annual Hepatitis C Incidence for Years 2001 to 2040

eTable 4. State Transition Probabilities Used in HEP-SIM

eTable 5. Screening Type and Annual Rate by Subpopulation

eTable 6. Market Share of NS5A Inhibitors (Versus Non-NS5A Inhibitors) Inhibitors by Year of Treatment

eTable 7. SVR Rates by Treatment, Genotype, Treatment History, and Fibrosis States

eTable 8. Treatment Uptake Rate by Subpopulation

eTable 9. Insurance Status of Hepatitis C Patients Under Age 65

eTable 10. Insurance Changes According to the Affordable Care Act

eTable 11. Sampling Distribution for Model Parameters in Probabilistic Sensitivity Analyses

eFigure 1. Annual HCC Incidence by Cirrhosis Status and SVR Status

eFigure 2. Probabilistic Sensitivity Analysis Results for the Number of HCC Incidence and Surveillance Candidates by Cure Status

eFigure 3. Number of Candidates for HCC Surveillance by Fibrosis Stage, 2012-2040

eFigure 4. The Average Age of HCC Incidence During 2012-2040 in DAA Era

eReferences

Longitudinal associations between risk factors and subsequent risk of hepatocellular cancer in patients with hepatitis C virus infection and virological cure.

Jennifer R. Kramer, Yumei Cao, Liang Li, Donna Smith, Jagpreet Chhatwal, Hashem El-Serag, Fasiha Kanwal

Background: The risk of hepatocellular carcinoma (HCC) persists in patients with HCV after virological cure. We sought to determine if risk factors for HCC change as time from treatment elapses.

Methods: We utilized the Veterans Affairs data to examine a cohort of patients with HCV who achieved sustained viral response (SVR) from DAAs from 1/1/2014 to 12/31/2018, and followed until HCC diagnosis, death, or 12/31/2019. We utilized cause-specific Cox proportional hazard models constructed at 3 landmark times (baseline, 12 and 24 months after SVR) to examine the associations between demographic (age, race, sex, marital status), clinical (cirrhosis complications, duration of cirrhosis, FIB-4, albumin, sodium, bilirubin, creatinine, sodium, hemoglobin, obesity, hypertension and dyslipidemia), and behavioral factors (alcohol abuse, smoking) measured at these landmark times and the subsequent HCC risk, stratified by cirrhosis status.

Results: We identified 98,612 patients with virologic cure [38.5% Black, mean age 61 yrs]. Almost 32% had cirrhosis at time of SVR. Incident HCC developed in 2,298 patients. Among patients without cirrhosis, the annual incidence rates of HCC was 0.21% and 0.27% in year 1 and 2, respectively. The corresponding estimates were 1.6% and 1.9% in patients with cirrhosis. The association between risk factors and subsequent HCC changed over the landmark time and varied substantially with cirrhosis status. In patients **without cirrhosis**, metabolic traits (diabetes and hypertension) and increase in FIB-4 were strongly associated with HCC risk at all landmark times. In patients **with cirrhosis**, demographic factors (risk lower in females and blacks), viral factors (risk higher in HCV genotype 3), and cirrhosis related factors (risk higher with longer cirrhosis duration, presence of varices, higher bilirubin, and lower albumin) predicted HCC risk at 12 months. Change in serum albumin and FIB-4 scores between baseline and 12-month landmark times also predicted HCC risk. Race, HCV genotype, and bilirubin were no longer predictive of HCC risk at 24-month landmark time, whereas change in hemoglobin from baseline became associated with risk of HCC.

Conclusions: In a cohort of patients with virologically cured HCV infection, risk factors for HCC were different in patients with and without cirrhosis. In patients with cirrhosis, they were mostly disease severity related, whereas metabolic traits were important in patients without cirrhosis. These data could inform HCC surveillance decisions in patients with cured HCV.

Table: Select risk factors from adjusted models for HCC at 12-months post SVR in patients with HCV infection stratified by cirrhosis status

Risk Factor	Patients without cirrhosis HR (95% CI)	Patients with cirrhosis HR (95% CI)
Change in FIB-4 (ref: stays low)		
Low at baseline (≤ 3.25) to high (> 3.25) at 12 mo.	2.36 (1.46-3.79)	1.45 (1.12-1.86)
High at baseline and stays high at 12 mo.	N/A	1.73 (1.50-2.00)
Diabetes	1.42 (1.16-1.75)	N/A
Hypertension	2.13 (1.47-3.07)	N/A
Cirrhosis duration > 60 months	N/A	1.71 (1.39-2.11)
Varices	N/A	1.58 (1.38-1.80)
Bilirubin	N/A	1.25 (1.11-1.41)
Change in albumin	N/A	0.79 (0.67-0.95)

Table: Select risk factors from adjusted models for HCC at 12-months post SVR in patients with HCV infection stratified by cirrhosis status

Risk Factor	Patients without cirrhosis HR (95% CI)	Patients with cirrhosis HR (95% CI)
Change in FIB-4 (ref: stays low)		
Low at baseline (≤ 3.25) to high (> 3.25) at 12 mo.	2.36 (1.46-3.79)	1.45 (1.12-1.86)
High at baseline and stays high at 12 mo.	N/A	1.73 (1.50-2.00)
Diabetes	1.42 (1.16-1.75)	N/A
Hypertension	2.13 (1.47-3.07)	N/A
Cirrhosis duration > 60 months	N/A	1.71 (1.39-2.11)
Varices	N/A	1.58 (1.38-1.80)
Bilirubin	N/A	1.25 (1.11-1.41)
Change in albumin	N/A	0.79 (0.67-0.95)

Abstract accepted for the 2021 AASLD The Liver Meeting, November 12-15th. Anaheim, CA. Also accepted for inclusion in the Best of The Liver Meeting's summary slide deck in the Health Services and Public Health Research category.

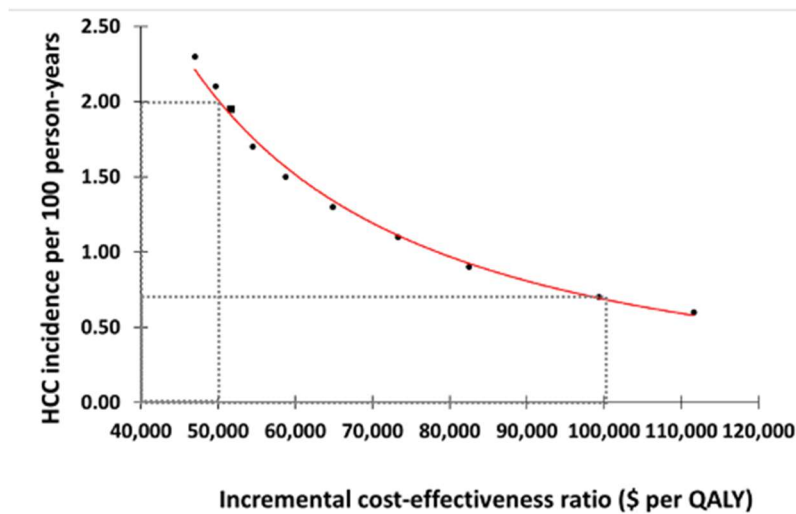
Hepatocellular Carcinoma Incidence Threshold for Routine Surveillance is Much Lower in Hepatitis C Cirrhosis Individuals Who Achieve Virological Cure

Jagpreet Chhatwal, Ali Hajjar, Peter P Mueller, Gizem Nemutlu, Mary Linton B Peters, Fasiha Kanwal

Background: The AASLD guidance recommends biannual surveillance for hepatocellular carcinoma (HCC) in hepatitis C virus (HCV) infected individuals with cirrhosis if HCC incidence is above 1.5 per 100 person-years (PY). However, the incidence threshold for surveillance in cirrhosis individuals who achieved virological cure with direct-acting antivirals is unknown. Our objective was to estimate the HCC incidence above which routine HCC surveillance is cost-effective in this growing population of individuals with virologically cured HCV.

Methods: We developed a microsimulation model of the natural history of HCC in individuals with HCV and cirrhosis who achieved virological cure with oral direct-acting antivirals (DAAs). We used published data on the natural history of HCV, competing risk post HCV cure, HCC tumor progression, real-world HCC surveillance adherence, contemporary HCC treatment options and associated costs, and utilities of different health states. We estimated the HCC incidence above which biannual HCC surveillance using ultrasound and alpha-fetoprotein would be deemed cost-effective using willingness-to-pay (WTP) thresholds of \$100,000 per quality-adjusted life year (QALY), as recommended by the 2nd US Panel on Cost-effectiveness.

Results: In 50-year-old virologically cured individuals with HCV cirrhosis, the incremental cost-effectiveness ratio (ICER) of biannual surveillance (up to age 75) vs. no surveillance was \$100,000-per-QALY at HCC incidence of 0.7 per 100-PY (Figure). At this HCC incidence, routine HCC surveillance vs no surveillance would result in additional 2,650 life years gained and 1400 QALYs per 100,000 persons undergoing surveillance. Using the WTP threshold of \$50,000-per-QALY (old willingness-to-pay), HCC surveillance could be cost effective at an annual HCC incidence of 2.0 per 100 PY.



Conclusion: Our study provides an important update on HCC incidence threshold above which routine HCC surveillance is cost-effective in individuals with HCV cirrhosis who achieved cure with DAAs. At the accepted WTP thresholds, HCC surveillance could be cost-effective if the annual incidence rate of HCC exceeds 0.7%, which is much lower than the previous 1.5% incidence used to guide HCC surveillance decisions.