Updates in HCC Epidemiology and Care Cascade Recommendations

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Objectives

- Describe disparities in chronic liver disease management that contribute to poor HCC outcomes
- Review recent updates in HCC epidemiology with a focus on highlighting disparities
- Review the CLDF HCC Care Cascade Decision Support Tool to improve management of patients with HCC

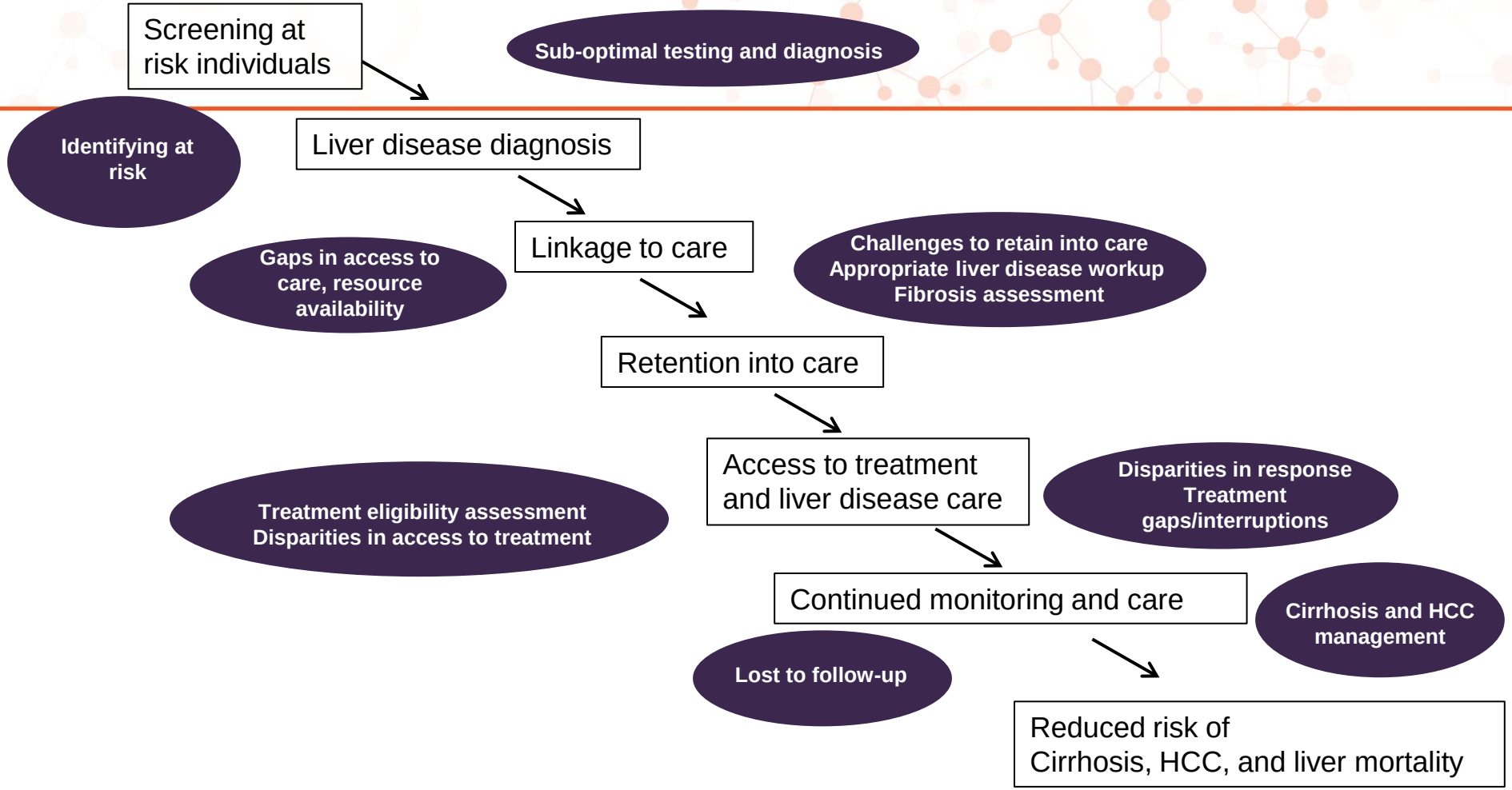
Burden of Liver Disease

- Globally, liver disease accounts for ~2 million deaths per year
  - ~1 million due to cirrhosis-related complications
  - ~1 million due to viral hepatitis and liver cancer
  - Cirrhosis and liver cancer account for 3.5% of all deaths worldwide
  - Liver cancer is third leading cause of cancer-related deaths
- In the U.S., liver disease and cirrhosis account for ~52k deaths per year
  - 12th leading cause of death in the US
  - HCC is ~5th leading cause of cancer deaths in the US (~31k deaths estimated in 2022)
  - HCC 5-year overall survival < 30%, due to delays in timely diagnosis and treatment

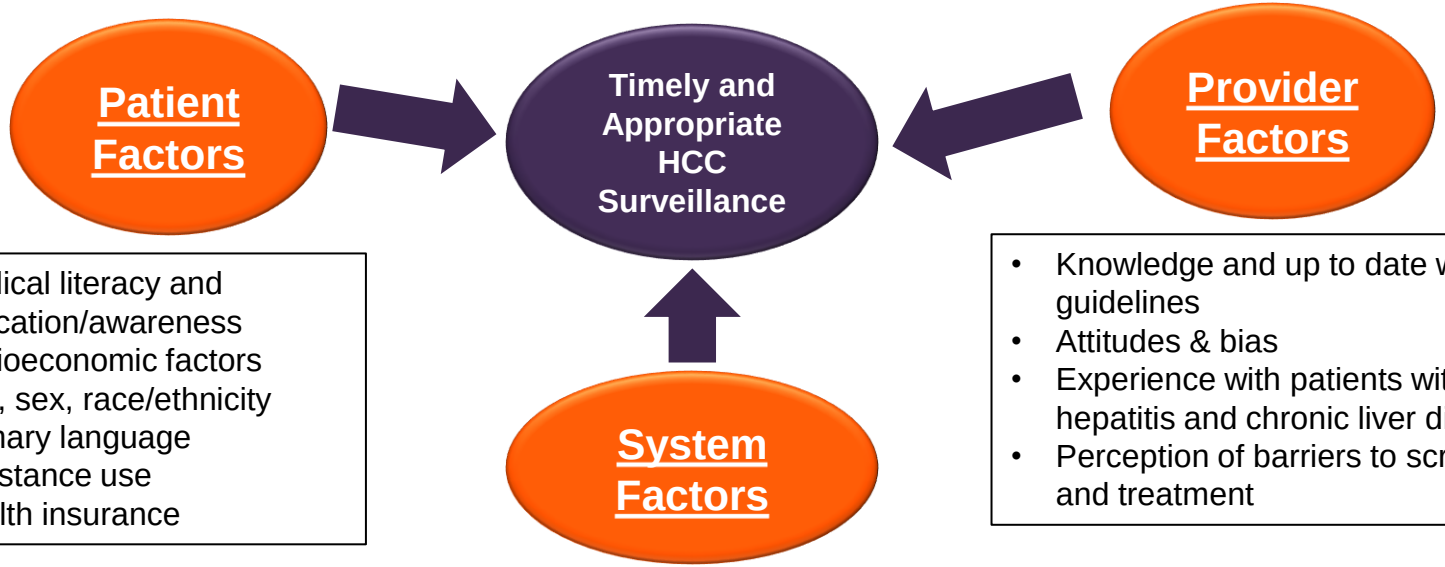
NCHS, CDC data 2022; WHO data; NCI SEER; Asrani et al. *J Hepatol*. 2019;70:151-71.

Understanding Gaps and Disparities Can Guide Targeted Interventions

- Poor clinical outcomes are preventable
  - Identify and address modifiable factors
  - Early detection and timely access to effective therapies
  - Early intervention through education and prevention of both patients and providers
- Socio-economically disadvantaged and vulnerable populations experience the majority of healthcare disparities
  - Compounds existing inequities (e.g., insurance, education/health literacy, household income, geography/transportation, language barriers, bias/discrimination)
  - Identify “low-hanging fruit” that can have a significant impact on liver disease outcomes


Screening at risk individuals
Sub-optimal testing and diagnosis
Identifying at risk
Liver disease diagnosis
Linkage to care
Gaps in access to care, resource availability
Challenges to retain into care
Appropriate liver disease workup
Fibrosis assessment
Retention into care
Access to treatment and liver disease care
Treatment eligibility assessment
Disparities in access to treatment
Disparities in response
Treatment gaps/interruptions
Continued monitoring and care
Cirrhosis and HCC management
Lost to follow-up
Reduced risk of Cirrhosis, HCC, and liver mortality

Multi-Factorial Barriers to Effective HCC Surveillance



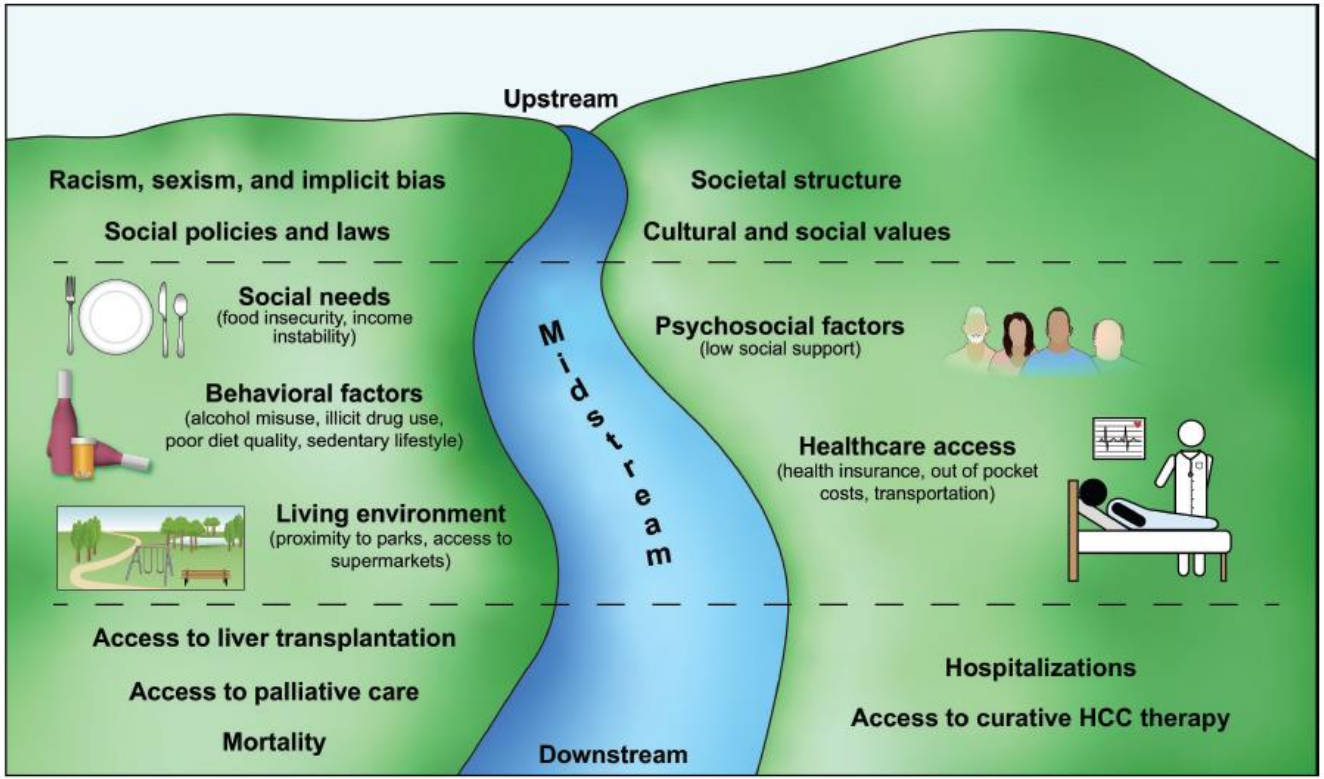
- Medical literacy and education/awareness
- Socioeconomic factors
- Age, sex, race/ethnicity
- Primary language
- Substance use
- Health insurance

- Knowledge and up to date with guidelines
- Attitudes & bias
- Experience with patients with viral hepatitis and chronic liver disease
- Perception of barriers to screening and treatment

- Availability of providers
- Type of providers (primary care vs. GI/liver)
- Location of services
- Type of practice setting
- Costs

Ladhani et al. *J Clin Gastro*. 2020.

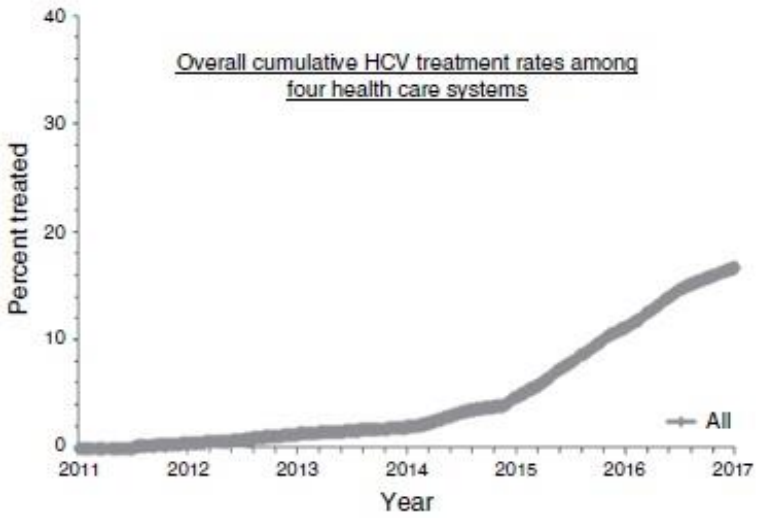
Conceptual Framework for the Contribution of Social and Structural Determinants of Health to Disparities in Liver Disease Outcomes



Kardashian et al. *Hepatology*. 2022.

Disparities in HCV Treatment Across Multi-Center Safety-Net Study

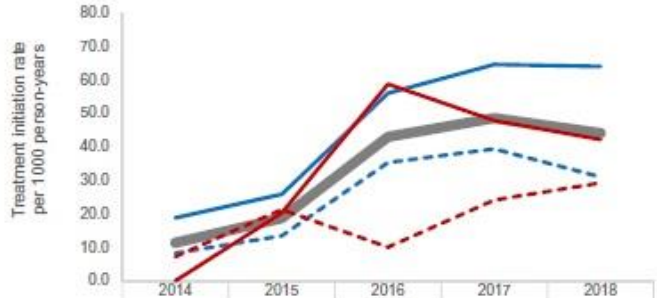
- Retrospective cohort study of 4 safety-net health system to evaluate disparities in access to HBV or HCV treatment.
- From 2011 to 2017, 29,544 chronic HCV patients were identified (60.5% male, 55.9% white, 38.4% African American, 8.8% Hispanic) and ***overall cumulative treatment was 16.9%.***
- Compared to non-Hispanic whites, significantly ***lower odds of treatment in Hispanics*** (OR 0.48, 95% CI 0.39-0.60).
- Compared to commercially insured patients, ***significantly lower odds of treatment in patients with Medicaid*** (OR 0.21, 95% CI 0.20-0.24) or none/indigent care (OR 0.19, 95% CI 0.15-0.21).



	Year						
	2011	2012	2013	2014	2015	2016	2017
Treatment rate (%)	0.5	1.4	2.0	4.8	11.1	16.4	16.9

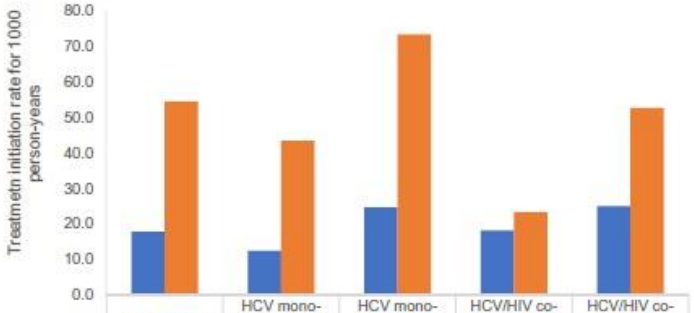
Wong et al. *Am J Gastro*. 2018; Jain et al. *Hepatology*. 2018.

- Retrospective study of Florida Medicaid claims data from 2013-2018.
- Among 14,063 newly diagnosed chronic HCV patients, DAA treatment increased following removal of fibrosis stage restriction in 2018, but ***only 8% received DAA overall***.
- Co-infection with HIV or concurrent substance use disorder was associated with ***47-59% less likely to receive HCV DAA***.
- Compared to non-Hispanic whites, African Americans also ***30% less likely to receive HCV treatment***.



	2014	2015	2016	2017	2018
All patients	11.4	18.7	43.0	48.6	44.1
HCV mono-infected with SUD	8.3	13.4	35.4	39.4	31.0
HCV mono-infected without SUD	18.8	25.9	56.1	64.7	64.1
HCV/HIV co-infected with SUD	7.2	21.3	10.0	24.2	29.2
HCV/HIV co-infected without SUD	0.0	20.3	58.8	47.9	42.2

HCV: hepatitis C virus, SUD: substance use disorders, HIV: human immunodeficiency virus
* Cochran-Armitage test was used to test trends (P<0.001).

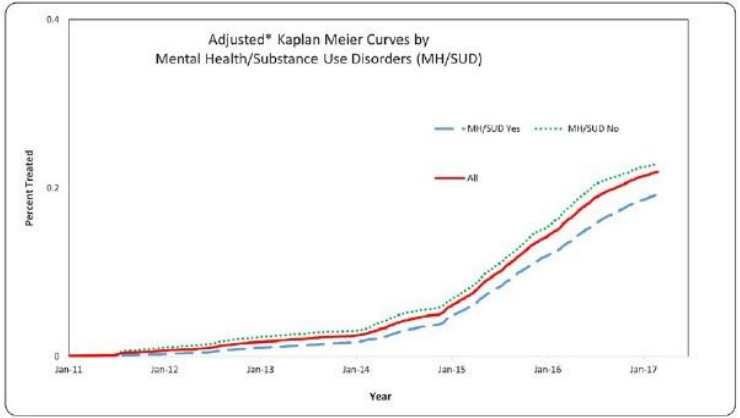


	All patients	HCV mono-infected with SUD	HCV mono-infected without SUD	HCV/HIV co-infected with SUD	HCV/HIV co-infected without SUD
Before June 1, 2016	17.9	12.5	24.7	18.3	25.0
After June 1, 2016	54.5	43.4	73.4	23.3	52.7

DAA: direct-acting antiviral, HCV: hepatitis C virus, SUD: substance use disorders, HIV: human immunodeficiency virus
Chi-square tests were used to compare treatment initiation rates before and after June 1, 2016. (all groups had significant increases within each group (P<0.01) except those with HCV/HIV with SUD (P=0.08).

Park et al. *Hepatol Comm*. 2021:5:203-16

- Multi-center safety-net cohort of 29,544 chronic HCV patients from 2011-2017
  - HCV treatment increased from 3.5% to 21.7% post DAA
  - Concurrent ***mental health or substance use disorders*** were associated with significantly lower odds of receiving HCV treatment (aOR 0.63, 95% CI 0.55-0.71)
- National VA data of ~134,000 chronic HCV patients from 2014-2020
  - Increasing rates of treatment over time, but patients with ***past or present history of alcohol use disorder*** (based on AUDIT-C) were ~25% less likely to be treated (HR 0.75, 95% CI 0.70-0.81) compared to lower risk drinking behavior

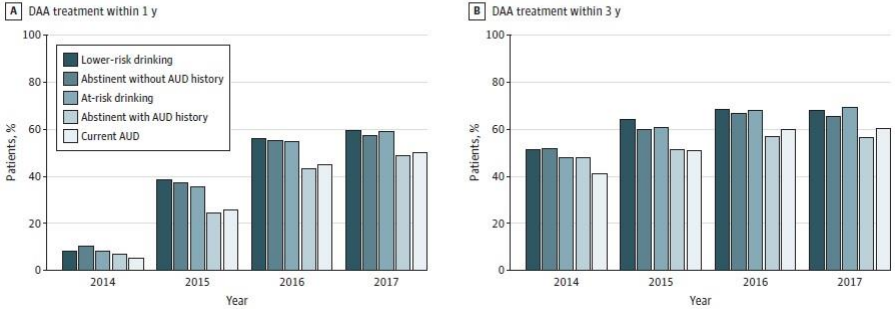


Cumulative treatment risk (%) across 7-year study: January 2011 - February 2017

MH/SUD	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
No	1.0	2.3	3.0	6.6	14.6	21.1	21.6
Yes	0.2	0.8	1.3	3.6	8.6	13.2	13.6
All	0.5	1.4	2.0	4.8	11.1	16.4	16.9

*Adjusted for age, gender, race/ethnicity, insurance status, cirrhosis

Figure. Percentage of Patients With Hepatitis C Virus Within Veterans Health Administration Birth Cohort Receiving Direct-Acting Antiviral (DAA) Treatment Within 1 and 3 Years by Alcohol Use Category and Index Year



Jain et al. *Hepatology*. 2019;69:51-63; Haque et al. *JAMA Netw Open*. 2022.

HBV Cascade of Care – Global Estimates

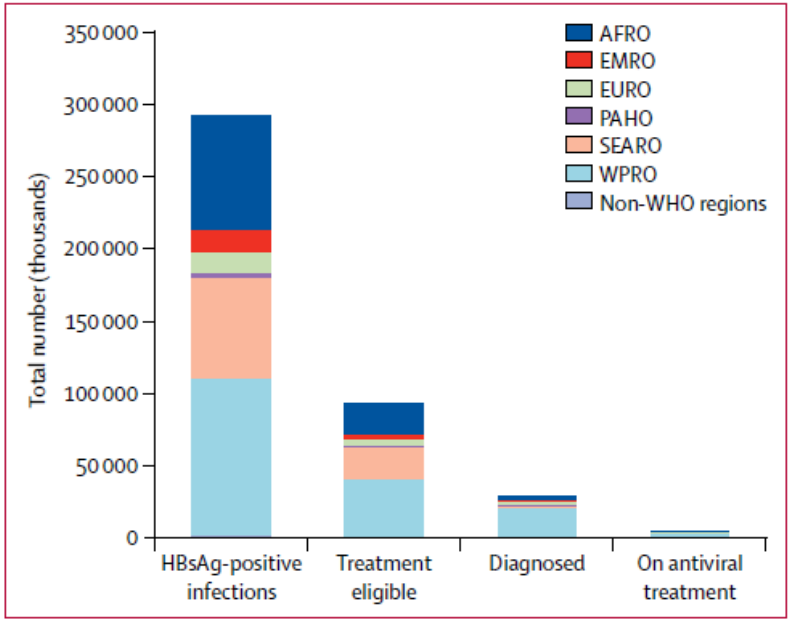


Figure 2: **Global and regional hepatitis B virus cascade of care in 2016**
AFRO=Regional Office for Africa. EMRO=Eastern Mediterranean Regional Office. EURO=Regional Office for Europe. PAHO=Pan American Health Organization. SEARO=South-East Asia Regional Office. WPRO=Western Pacific Regional Office.

Polaris collaborators. *Lancet*. 2018;3:383-403.

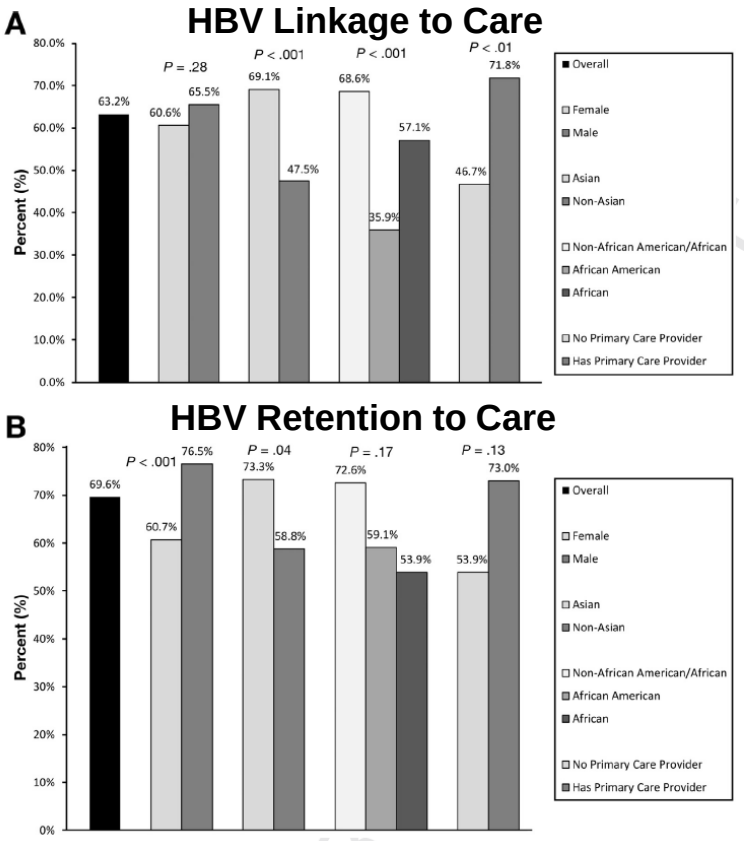
Low Rates of HBV Testing and HBV Treatment Among Minority Communities

- Racial and Ethnic Approaches to Community Health across the U.S. (REACH U.S. Cohort)
- Incorporated patients from 28 communities across 17 states to characterize risk factors and delivery of care
- 2009 – 2010 cohort utilized to assess HBV testing and care practices
- Total 53,896 patients (40.2% African American, 30.6% Hispanic, 18.5% API, 10.7% AI/AN)
- ***Overall, 39.2% reported receiving HBV testing, and among those with chronic HBV, only 33.3% reported receiving specialty care***

Hu et al. *Hepatology*. 2013; 58:856-862.

Low Rates of Linkage to Care After HBV Diagnosis Among Safety-Net Populations

- Retrospective cohort study of adults with chronic HBV at a single center safety-net health system from 2009 to 2017
- Total of 454 chronic HBV patients were included (54.2% men, 72.7% Asian, 14.4% African American, 6.3% African)
- Linkage to care = initial visit with HBV provider after HBV diagnosis
- Retention to care = two additional visits with HBV provider after initial linkage to care

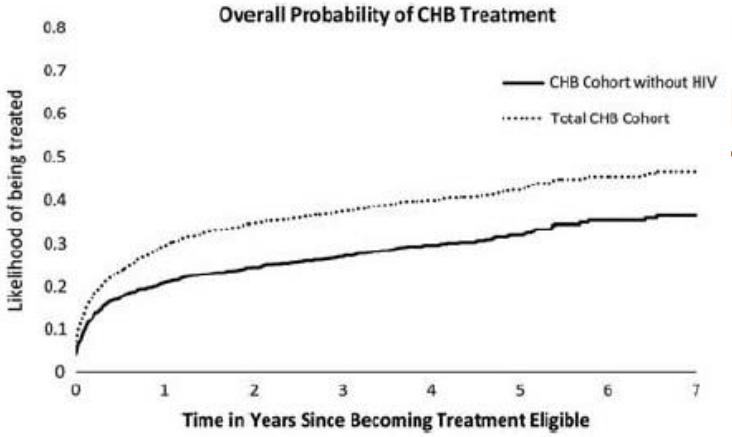


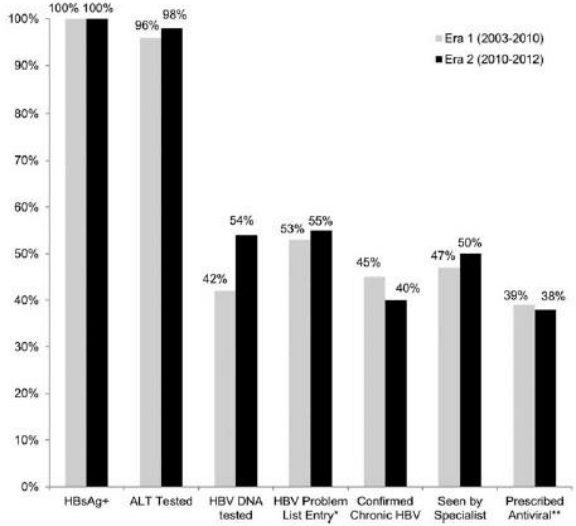
Tang et al. *Clinical Gastroenterology and Hepatology*. 2019;17:1909–1911.

Disparities in HBV Treatment

- From 2010 to 2018, 5,157 chronic HBV patients were identified (54.7% male, 35.5% non-Hispanic white, 34.6% African American, 22.3% Asian, 7.7% Hispanic).
- Among treatment eligible, ***48.4% were treated*** (37.3% in non-HIV).
- Lower treatment rates in women vs. men (OR 0.40, 95% CI 0.33-0.49) and lower treatment with older age.
- Asians and African Americans significantly more likely to be treated
- Non-English patients more likely than English patients to be treated

- VA national data of chronic HBV patients from 1999 to 2013
- 21,419 patients with HBV identified (94% male, 52% white, 41% African American, 7% API, 5% HIV co-infection)
- Overall, 44% had HBV DNA testing, and of those with confirmed chronic HBV, ***<40% received antiviral therapy.***





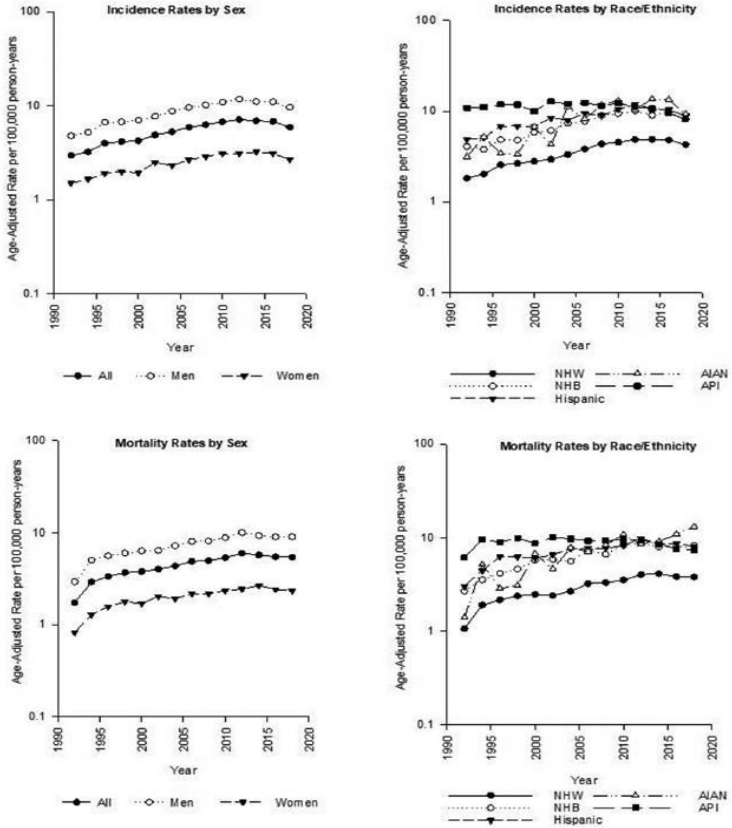
Wong et al. *J Clin Gastro*. 2021; Serper, et al. *Hepatology*. 2016:63:1774-82.

Updates in HCC Epidemiology and Trends

- Declining incidence of HCV-related HCC due to effectiveness of HCV cure regimens
- Increasing burden of NAFLD/NASH-related HCC as the large population of patients with fatty liver are aging and developing liver-related complications
- Despite improvements in HCC treatment options, overall 5-year HCC survival remains less than 30%

Racial/Ethnic Disparities in HCC Incidence and Mortality

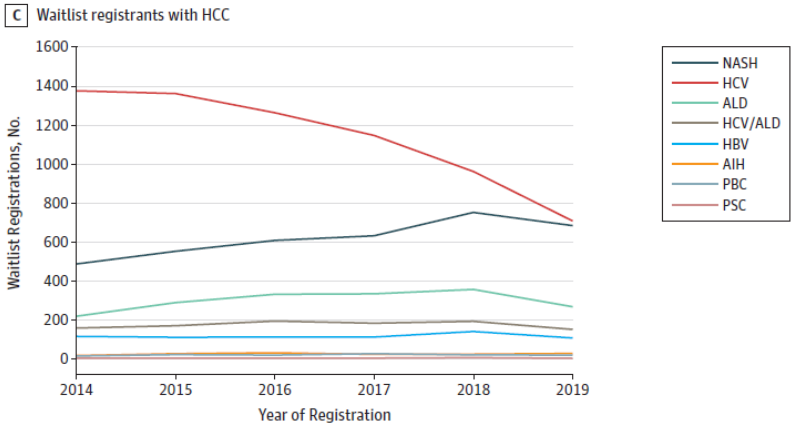
- NCI SEER data from 1992-2018 evaluating HCC incidence and mortality
- HCC incidence and mortality appears to have peaked in 2015 and have been declining since
- However, significant race/ethnicity-specific disparities were observed
- Trends may reflect improved treatment of viral hepatitis and the emergence of NASH and ALD as leading contributors to HCC incidence and mortality

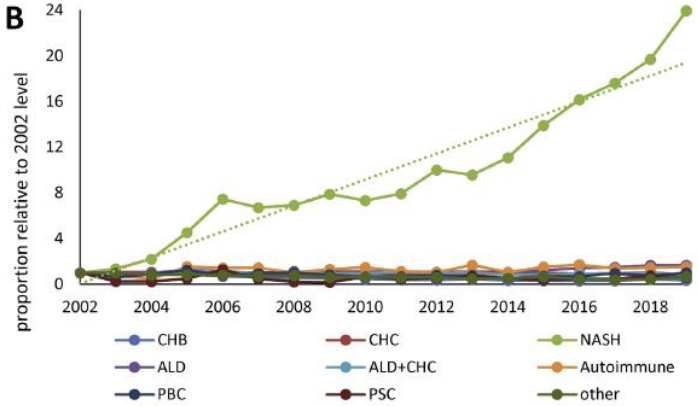


Alvarez et al. *Hepatology*. 2022.

HCC Trends on US LT Waitlist

- Declining prevalence of HCV among waitlisted patients with HCC
- Corresponding rise in NASH-related HCC to become leading indication for LT among patients with HCC
- Unlike non-HCC patients, ALD as an etiology has remained stable in HCC patients awaiting LT





Younossi et al. *CGH*. 2021; Wong et al. *JAMA Netw Open*.

Suboptimal HCC Surveillance

- Wolf, et al performed a systematic review and meta-analysis (2010-2018) of 29 studies, inclusive of 118,799 patients
  - Pooled estimate of HCC surveillance among cirrhosis patients was ***24% (18.4-30.1)***
- Data from our team and others have demonstrated that ethnic minorities, particularly African Americans and Hispanics consistently have lower rates of HCC screening compared to non-Hispanic whites
- Suboptimal screening leads to more advanced tumor state at diagnosis and fewer treatment options for ethnic minorities

TABLE 2. Race/Ethnicity-specific Variations in Stage of HCC at Diagnosis

	Distant vs. Localized HCC			Within Milan Criteria		
Variables	**OR**	**95% CI**	***P*e**	**OR**	**95% CI**	***P***
Non-Hispanic white	1.00	Reference	—	1.00	Reference	—
Hispanic	0.94	0.87-1.01	0.08	1.02	0.97-1.07	0.503
Black	1.20	1.10-1.30	< 0.001	0.80	0.75-0.85	< 0.001
Asian	0.87	0.80-0.94	< 0.001	1.00	0.95-1.06	0.86

	Total HCC		
Treatment Categories	**OR**	**95% CI**	***P***
Any treatment vs. no treatment			
Non-Hispanic white	1.00	Reference	—
Hispanic	0.61	0.57-0.65	< 0.001
Black	0.61	0.56-0.66	< 0.001
Asian	1.23	1.15-1.31	< 0.001
Curative vs. noncurative treatment			
Non-Hispanic white	1.00	Reference	—
Hispanic	0.55	0.51-0.60	< 0.001
Black	0.60	0.55-0.66	< 0.001
Asian	1.21	1.12-1.30	< 0.001

Wolf E et al. *Hepatology*. 2021; Ha et al. *Cancer*. 2016; Ha et al. *J Clin Gastro*. 2016.

Effective HCC Surveillance Is One of the Most Important Steps in the HCC Cascade of Care

- Effective HCC Surveillance leads to earlier tumor stage at diagnosis
- Tumor stage directly correlates with HCC treatment options
- More options for curative intent leads to better long-term survival
- Understanding and addressing disparities in HCC surveillance is important to reduce downstream disparities in HCC outcomes
- Complex interplay between patient, provider, and system level factors

A Digital, Interactive, Decision-Support Algorithm to Facilitate and Improve the Hepatocellular Carcinoma Care Cascade in Adults: Integrating the Barcelona Clinic Liver Cancer (BCLC) Staging System and United Network for Organ Sharing(UNOS) Down-Staging Criteria into One Tool

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HCC Care Cascade Decision-Support Algorithm

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HCC Care Cascade - Introduction

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HCC Care Cascade

HCC Care Cascade - Introduction

The CLDF HCC working group has developed a practical, point-of-care, digital tool to assist healthcare professionals in the screening and surveillance, tumor staging, and treatment of patients with HCC that is based on the following resources:

- The AASLD and EASL HCC guidance, which deliver data-supported approaches to the diagnosis, staging, and treatment of patients diagnosed with HCC (1, 2).

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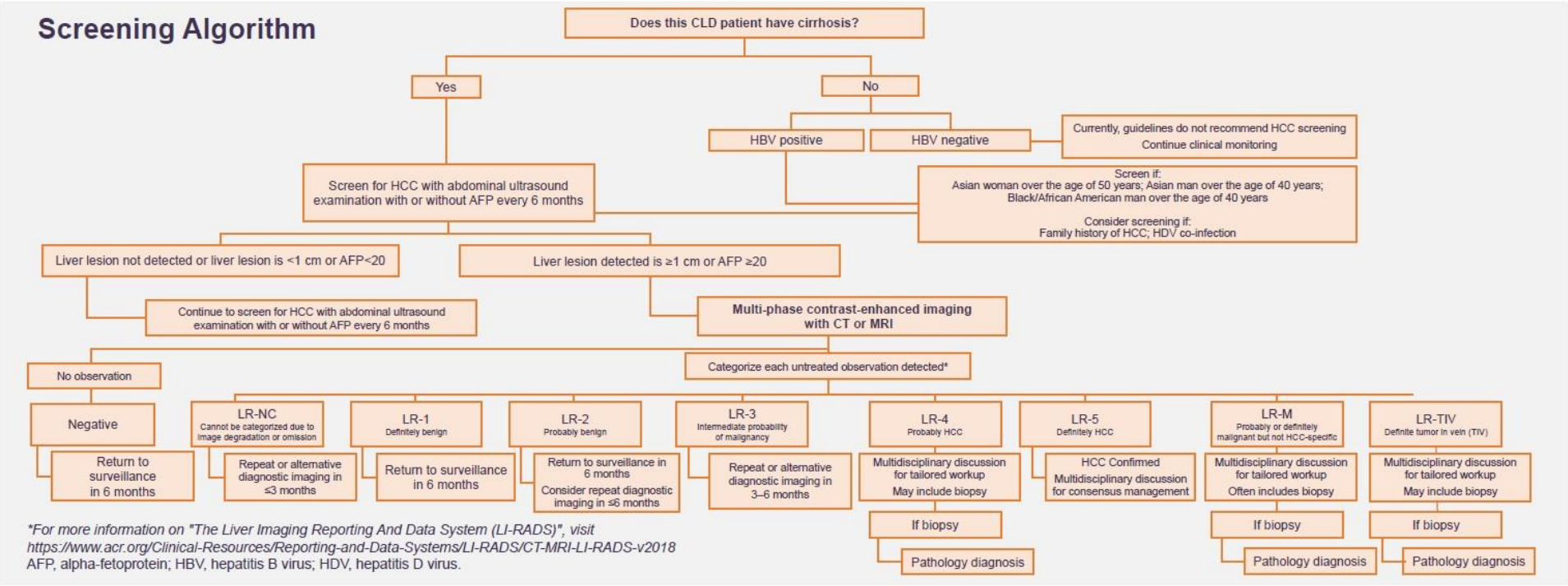

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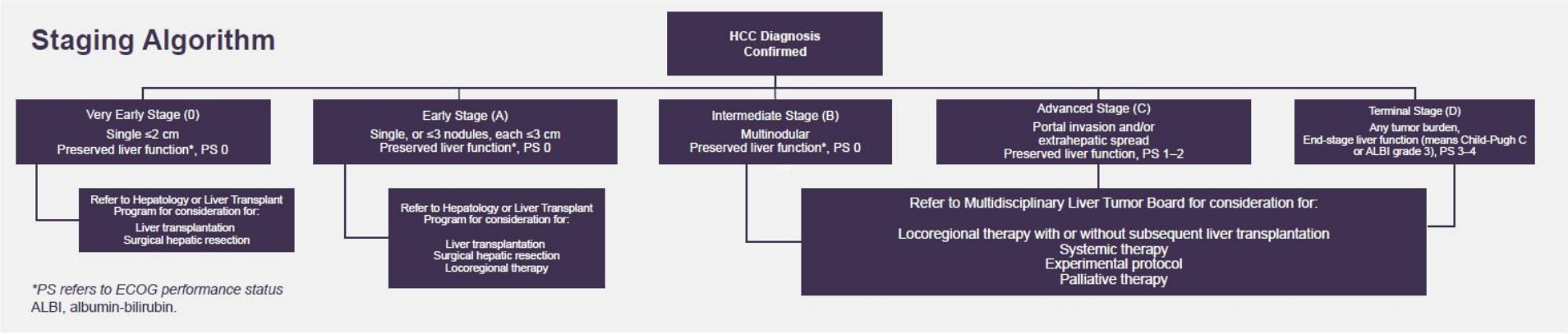

Take Home Points

- HCC remains a leading cause of cancer-related mortality in the U.S. and globally
- Disparities in timely diagnosis and treatment of chronic liver diseases contributes to continued HCC burden
- Gaps and disparities in timely HCC screening and surveillance persist
- Novel interventions are needed to improve the HCC care cascade to improve long-term HCC outcomes

Acknowledgements

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