Hepatocellular Carcinoma in Minorities

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“God, grant me the serenity to accept the things I cannot change, the courage to change the things I can, and the wisdom to know the difference”

Reinhold Niebuhr

Equity Requires Action.

“I am no longer accepting the things I cannot change. I am changing the things I cannot accept.”

Angela Davis

Objectives:

- Understand the relationship between health disparities, health equity and social determinants of health.
- Describe the current landscape of racial and ethnic disparities in hepatocellular carcinoma using an established framework.
- Understand how individual actions and community or institution-specific structural interventions could achieve widespread reduction in HCC disparities.

DEFINITIONS

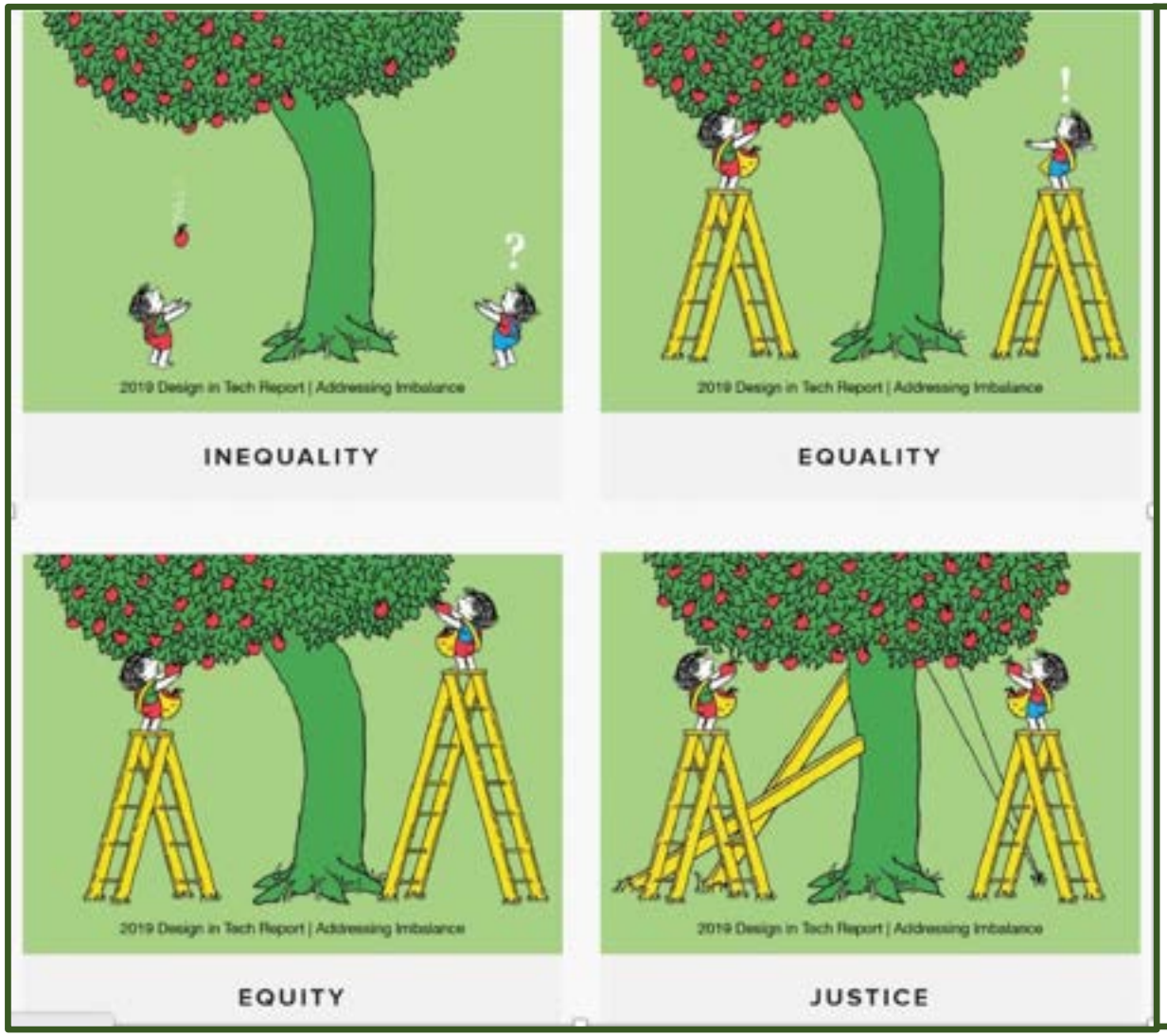
Health Disparities

*"health differences that adversely affect **disadvantaged populations**, reflected by higher disease burden, greater prevalence of risk factors, higher degree of disease-specific symptoms, and/or increased or premature mortality"*

All disparities are differences, but not all differences are disparities.

Braveman PA, E.; Orleans, T.; Proctor, D.; Plough, A. What Is Health Equity? And What Difference Does a Definition Make? Princeton, NJ, 2017.

Health Equity



"Health equity is the ethical and human rights principle that motivates us to eliminate health disparities, which are key differences in health or its key determinants (such as education, safe housing, and freedom from discrimination) that adversely affect marginalized or excluded groups.

Disparities in health and in the key determinants of health are the metric for assessing progress toward health equity."

Source: "Addressing Imbalance," by Tony Ruth for the 2019 Design in Tech Report.

Braveman PA, E.; Orleans, T.; Proctor, D.; Plough, A. What Is Health Equity? And What Difference Does a Definition Make? Princeton, NJ, 2017.

Nonalcoholic Fatty Liver Disease

Table 5. The Annual Risk of Hepatocellular Cancer in Groups of Patients With Non-Alcoholic Fatty Liver Disease Stratified by the Presence of Cirrhosis Diagnosis and/or Fibrosis-4 Score During Follow-Up

Group	Subjects	HCC cases	Total PYs of follow-up	IR (95% CI) (per 1000 PYs)
Cirrhosis diagnosis and high FIB-4 score	2,871	252	18,598	13.55 (11.93–15.33)
Cirrhosis without high FIB-4 score	1,364	45	9323	4.82 (3.52–6.46)
High FIB-4 score without cirrhosis diagnosis	34,392	101	259,942	0.39 (0.31–0.47)
Neither cirrhosis diagnosis nor high FIB-4 score	258,074	92	2,094,427	0.04 (0.04–0.05)

NOTE. FIB-4 scores were available for 95% of the cohort. Patients with no cirrhosis diagnosis and missing FIB-4 score are excluded from the table.
CI, confidence interval; HCC, hepatocellular carcinoma; IR, incidence rate; PY, person-years.

- The prevalence of NAFLD has doubled over the past two decades and is approximately 30%.

- **20% of patients with NAFLD-related HCC did not have cirrhosis**
  - Retrospective cohort study of 296,707 NAFLD patients in the VA.
  - The absolute risk of HCC in NAFLD is low 0.21/1000 person-years or 0.8% five-year and 1.7% ten-year cumulative HCC risk.
  - The absolute risk is too low in non-cirrhotic patients to recommend HCC surveillance.

- Risk was highest among oldest Hispanics.

Kanwal et al. Gastroenterology 2018; 155: 1828-1837

Operational Definitions of Race, Ethnicity, Ancestry and Social Determinants of Health

Race	Sociopolitical term related to individual and/or group identity that is linked to visible and stereotypic attributes such as skin pigmentation and hair texture, e.g. Black, White, or Asian.
Ethnicity	Categorizes individuals into cultural groups based on shared language, traditions, and foods etc.
Ancestry	Genetic ancestry, a description of the population(s) from which an individual's recent biological ancestors originated, as reflected by DNA. Genetic ancestry is estimated based on comparisons of an individual's genotype to global reference populations.
Social Determinants of Health	"nonmedical factors such as income, health insurance, education, discrimination, and the quality of the places where people live, work, learn, and play, which influence health"

1. Peterson RE et al. *Cell* 2019;179:589-603.
2. Bryc K et al. *Am J Hum Genet.* 2015;96(1):37-53. Epub
3. Braveman PA et al. What Is Health Equity? And What Difference Does a Definition Make? Princeton, NJ, 2017.

A Comparison of Two Illustrative Cases

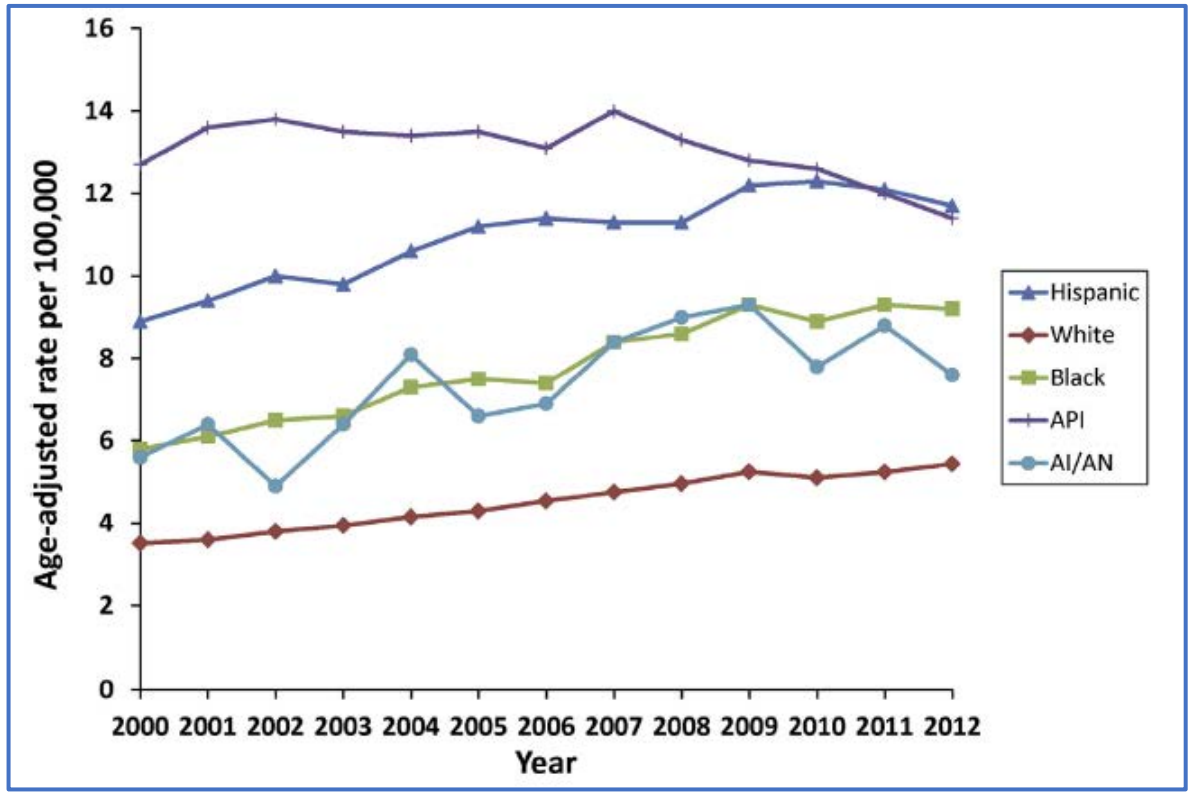
YJ

- 65 yo Black woman with HCV-related cirrhosis.
  - Achieved SVR after Harvoni in 2017
- Had LIRADS 4 lesions in 4/2021 (0.8 cm, 1 cm and 0.5 cm)
  - Biopsy recommended and negative.
- Seen in 11/2021 and CT ordered but not obtained.
- Admitted in 4/2022 with pain. Two LIRADS 5 lesions now 2 cm and 1.9 cm.
  - Recommended Y-90 and follow-up in HCC clinic.
  - Referred to Social Work

XSM

- 56 yo Cuban woman with HCV-related cirrhosis.
  - Achieved SVR but does not know details.
- Recently arrived to the US 3 months ago-had not received HCC screening.
- US and AFP ordered in 10/2022, but AFP comes back as 42,735.
- CT scan shows a 4.9 x 3.9 x 4.2 cm LIRAD 5 lesion.
  - Recommended Y-90 or TACE depending on insurance.
  - Referred to Social Work

Racial and Ethnic Disparities in HCC Incidence



White DL et al. Gastroenterology. 2017 Mar; 152(4):812-820.e5

Race/Ethnicity	Incidence (%)
American Indian/Alaskan Native	11.4
Hispanic	9.8
Asian/Pacific Islander	9.1
Non-Hispanic Black	8.1
Non-Hispanic White	4.6

McGlynn KA et al. *Hepatology*. Jan 2021;73 Suppl 1:4-13. doi:10.1002/hep.31288

Disparities in Chronic Liver Disease

HEPATITIS C

Risk, Screening and Treatment

- An estimated 2.4 million persons in the US have active HCV with notable racial differences per NHANES.
- Despite widespread use of DAAs since 2014, there are still treatment disparities: HCV patients who received care at VA facilities, Black patients had significantly lower odds of receiving DAA than Whites; OR 0.79; 95% CI 0.75-0.84.

Kanwal F et al. Clin Infect Dis 2016;63:291-9.

HEPATITIS B

Risk, Vaccination, Screening and Treatment

- In the US, approximately 1-2 million people have chronic HBV.
- REACH U.S.: 1,235 people with chronic HBV
  - 1/3 had seen a physician.
  - 1/2 of African Americans and Asians had received antivirals compared to 2/3 of Hispanics.

Hu DJ et al. Hepatology. 2013 Sep;58(3):856-62.

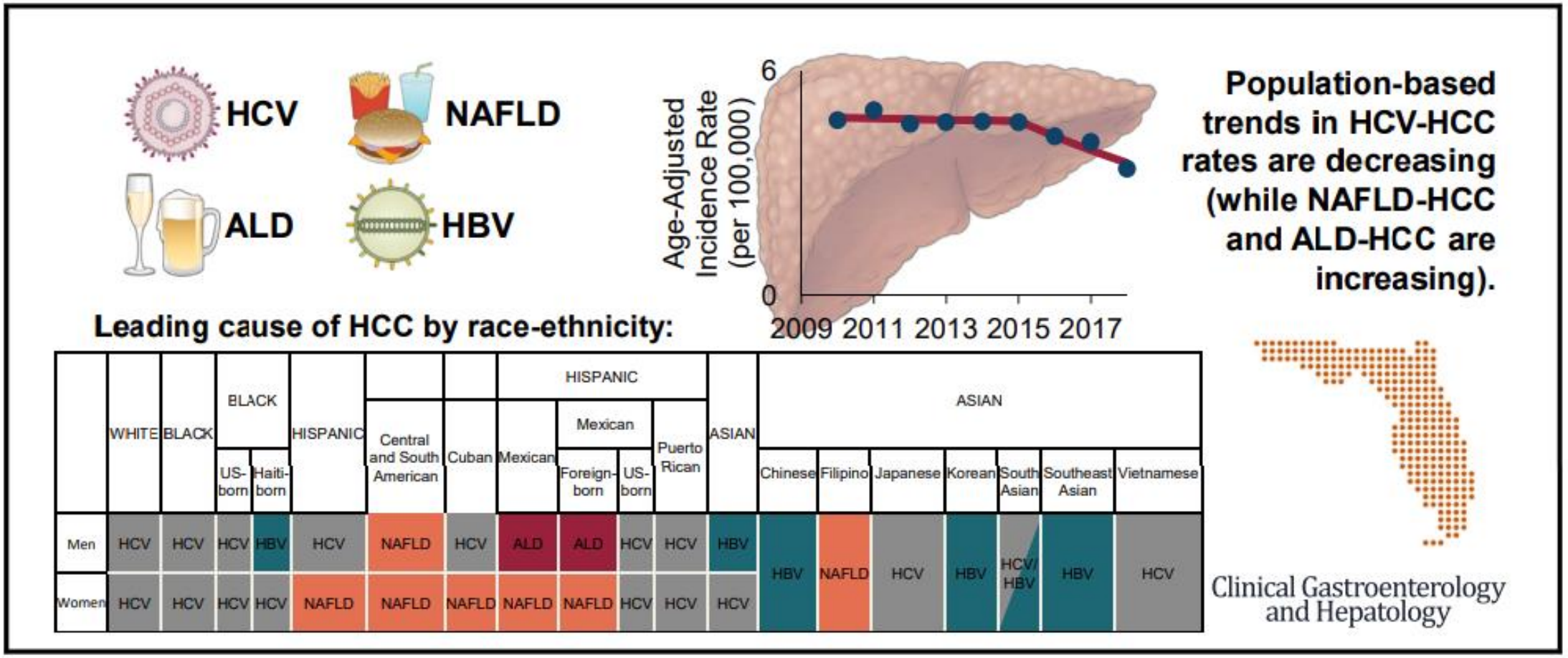
NAFLD-->MASLD

Risk, Progression and Clinical Trial Enrollment

- NAFLD and NASH disproportionately burden Hispanic populations
- Central and Mexican Americans have increased risk vs. South Americans, Dominicans, and Cubans.
- Despite this, Hispanic persons are significantly underrepresented in NAFLD clinical trials.

Patel P et al. *World J Hepatol*. 2020 Aug 27;12(8):506-518.

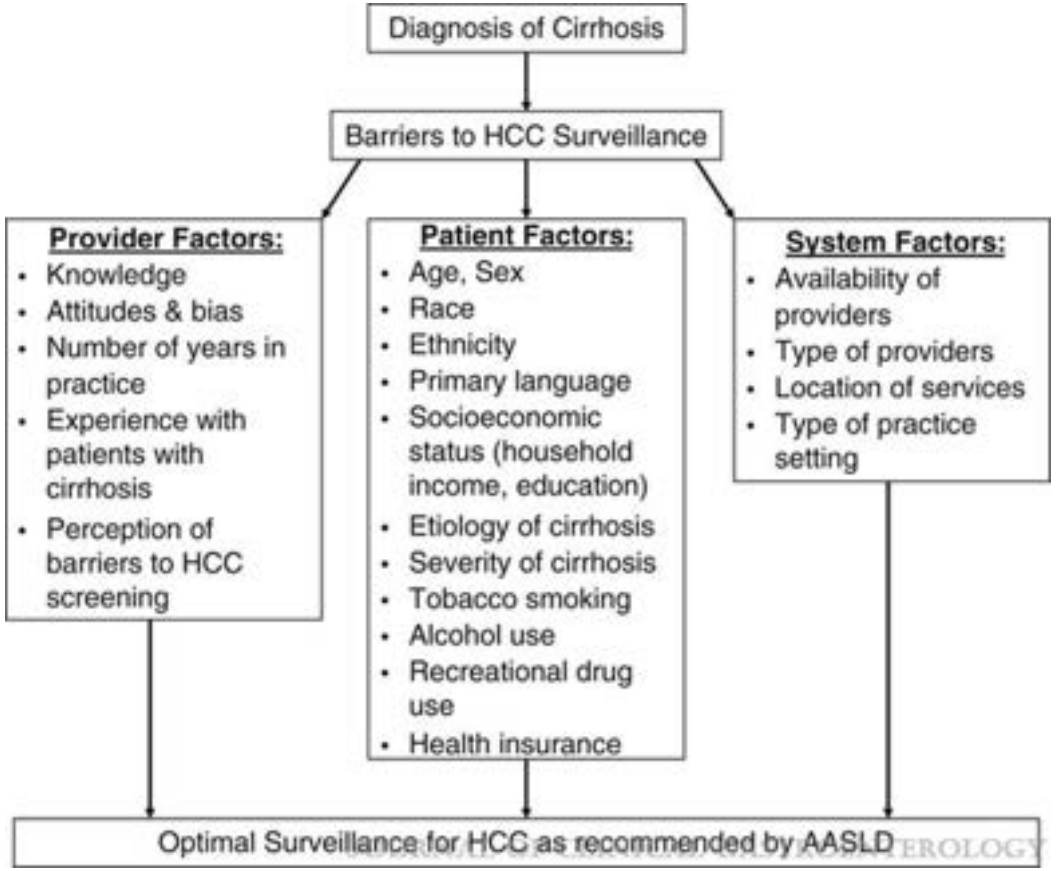
Etiology of Liver Cancer Differs by Racial Subgroup



Pinheiro PS, Jones PD et al. Clin Gastroenterol Hepatol. 2023 Sep 1:S1542-3565(23)00666-3. doi: 10.1016/j.cgh.2023.08.016. Epub ahead of print. PMID: 37678486.

Disparities in HCC Screening

Potential patient-, provider-, and health care system-specific barriers that contribute to disparities in HCC surveillance



HCC Screening rates are generally lower in Black individuals, those who are uninsured, those who live in neighborhoods with higher levels of poverty.

Ladhani S et al. *J Clin Gastroenterol*. 2020 Mar;54(3):218-226.

Population-Based Surveillance

TABLE 1 At-risk population for surveillance

Population group	Incidence of HCC
Sufficient risk to warrant surveillance	
Child-Pugh A–B cirrhosis, any etiology	≥1.0% per year
Hepatitis B	
Hepatitis C (viremic or post-SVR)	
Alcohol associated cirrhosis	
Nonalcoholic steatohepatitis	
Other etiologies	
Child-Pugh C cirrhosis, transplant candidate	
Non-cirrhotic chronic hepatitis B	≥0.2% per year
Man from endemic country[a] age >40 y	
Woman from endemic country[a] age > 50 y	
Person from Africa at earlier age[b]	
Family history of HCC	
PAGE-B score ≥ 10[c]	
Insufficient risk and in need of risk stratification models/biomarkers	
Hepatitis C and stage 3 fibrosis	< 0.2% per year
Noncirrhotic NAFLD	

Abbreviation: HCC, hepatocellular carcinoma.
[a]Endemic country as defined by AASLD hepatitis B virus guidance.
[b]Surveillance can be initiated as early as third decade of life given median age 46 years at HCC diagnosis.
[c]Other risk calculators can be considered, although PAGE-B has been validated in Western populations on antiviral therapy.

A **major barrier** to HCC screening is recognition of underlying chronic liver disease and/or cirrhosis

Singal AG et al. *Hepatology*. 2023 Dec 1;78(6):1922-1965. doi: 10.1097/HEP.0000000000000466. Epub 2023 May 22. Erratum in: Hepatology. 2023 Oct 16;: PMID: 37199193

Racial and Ethnic Disparities in HCC Stage at Presentation

Jones PD et al. Dig Dis Sci 2018;63:515-528.						
	Black (n = 135)	**White (n = 414)**	**Hispanic (n = 310)**	**Asian (n = 22)**	**Other (n = 20)**	**p-value**
Percent within Milan	30.4	54.4	46.8	40.9	55	<0.01
Rich NE et al. Clin Gastroenterol Hepatol. 2019;17:551-559 e1.						
	Black (n = 384)	**White (n = 401)**	**Hispanic (n = 332)**			
Percent within Milan	39.6	49.6	43.7			0.02
Estevez J et al. Am J Gastroenterol 2019;114:80-88.						
	Black (n = 578)	**White (n = 578)**				
Percent within Milan	34	39				0.09

Treatment Disparities are Associated with Race, Poverty, and Geography

- Black race was significantly associated with treatment delays compared to White race, odds ratio, 1.96 (95% confidence interval (CI) 1.21–3.15).

- Living in a high poverty neighborhood was also associated with delayed treatment compared to those who lived in a low poverty neighborhood, odds ratio, 1.55 (95% CI, 1.25–1.92)

- Compared to urban residents, rural and suburban residents were 12% (Odds Ratio (OR) = 0.88, 95% CI = 0.80 to 0.94; *P* < .001) and 8% (OR = 0.92, 95% CI = 0.88 to 0.95; *P* < .001) less likely to receive treatment.

1. Wagle NS et al. *Clin Gastroenterol Hepatol*. 2022 Aug 4:S1542-3565(22)00731-5.
2. Zhou K et al. *JNCI Cancer Spectr*. 2020 Nov 2;5(1):pkaa100.

Disparities in Immunotherapy

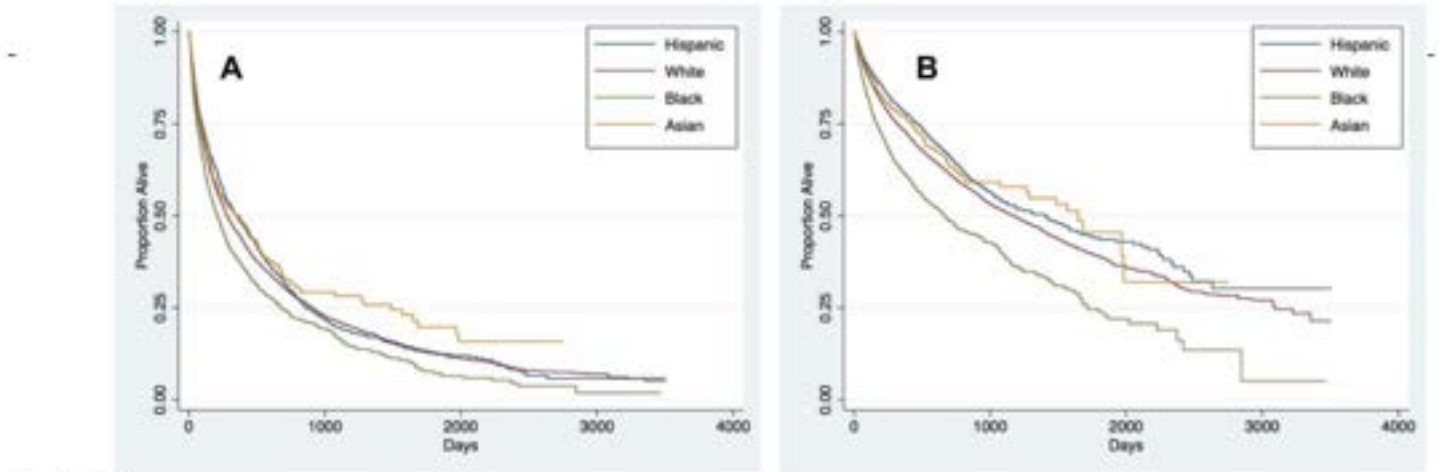
	Academic Center			Non-Academic Center		
	Adjusted Odds Ratio	95% CI	p value	Adjusted Odds Ratio	95% CI	p value
White (Ref)	1			1		
Hispanic	0.68	0.37-1.25	0.55	0.58	0.29-1.17	0.27
Black	0.97	0.59-1.58	0.99	**0.48**	**0.24-0.95**	**0.02**
Asian/Other	1.48	0.82-2.67	0.47	0.58	0.26-1.3	0.45

Association between race-ethnicity and immunotherapy by receipt, stratified by facility type

Ahn JC et al. *Hepatology*. 2022 Dec;76(6):1649-1659

Racial and Ethnic Disparities in HCC Survival

Jones PD et al. *Dig Dis Sci* 2018;63:515-528.						
	Black (n = 135)	**White (n = 414)**	**Hispanic (n = 310)**	**Asian (n = 22)**	**Other (n = 20)**	**p-value**
Median Survival, days	425	904.5	652	570	928	<0.01
Rich NE et al. *Clin Gastroenterol Hepatol.* 2019;17:551-559 e1.						
	Black (n = 384)	**White (n = 401)**	**Hispanic (n = 332)**			
Median Survival, months	10.6	16.3	14.4			
Rich NE et al. *Clin Gastroenterol Hepatol*. 2022 Feb;20(2):e267-e288.						
	Black 17.3%	**White 53%**	**Hispanic 18.4%**	**Asian 5%**		
Hazard Ratio 95% Confidence Interval	1.08 (1.05-1.12)	1 (Referent)	0.92 (0.87-0.97)	0.81 (0.73-0.88)		



Number at Risk

Hispanic	1695	159	34	4	0
White	7231	685	159	31	0
Black	1406	102	12	1	0
Asian	344	31	8	0	0

Figure 3 Kaplan–Meier curves (**A**) stratified by race/ethnicity and (**B**) stratified by race/ethnicity and adjusted for gender, age at diagnosis, insurance type, SEER Summary Tumor Stage, surgery type, and treatment status.

- Adjusted for gender, age, payer, SEER stage, surgery type, and receipt of treatment, Black patients had a 17% increased risk of death [hazard ratio (HR) 1.17, 95% confidence interval (CI) 1.07–1.29] and White patients a 9% increased risk of death [HR 1.09, 95% CI 1.02–1.17] compared to Hispanic patients.

- As a group, Hispanics lived closest to any transplant or academic cancer center, $p < 0.001$.

- Neighborhood poverty level was highest where Hispanic patients lived, $p < 0.001$.

Jones PD et al. *Hepatocellular Carcinoma* 2019(6) 167-181. https://doi.org/10.2147/JHC.S212401.

Differences in HCC Survival Within Racial and Ethnic Subgroups

- We found that Black patients from Haiti (172 days) had significantly lower survival compared to other Black patients (523 days), p 0.02.[1]

- In a sample of over 8,000 Asian individuals in the US, 5-year HCC survival was longest in Chinese patients (33.1%), and lowest in Filipino (19.9%) and Japanese patients (22%).[2]

- Among Hispanic individuals, age-standardized HCC-related mortality rates were highest in Puerto Rican persons, 6.04, compared to 3.89 in persons from Mexico, 3.87 in Non-Hispanic Whites, and 3.03 in Cuban individuals.[3]

1. Jones PD et al. *Dig Dis Sci* 2018;63:515-528.
2. Yu JR et al. *J Clin Exp Hepatol*. 2019 Mar-Apr;9(2):182-190.
3. Kim D et al. *Clin Gastroenterol Hepatol*. 2019 Jul;17(8):1607-1615.e2.

Follow-up of our Two Cases

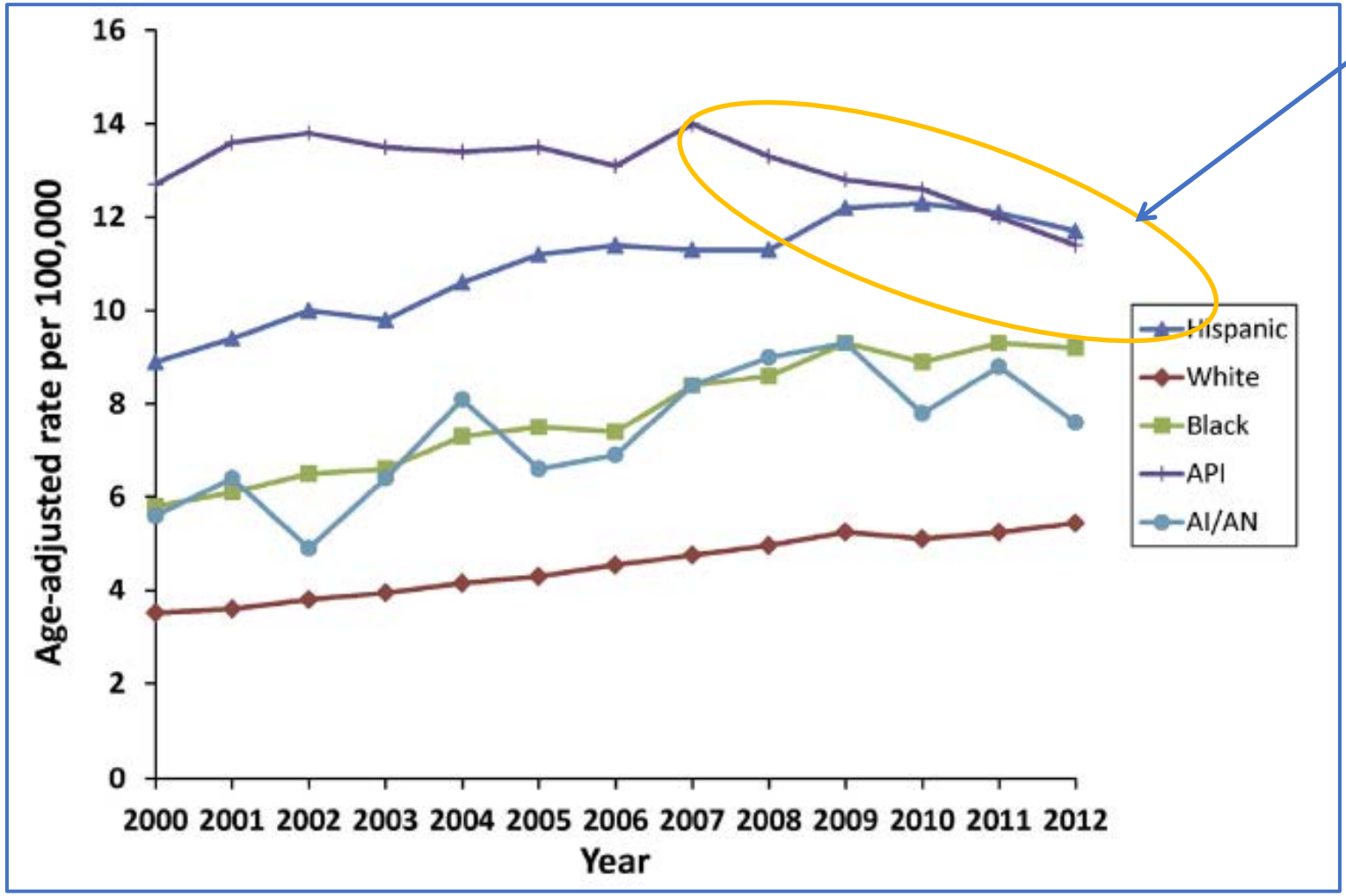
YJ

- Referral for Y-90 made in 4/2022.
  - Unclear if patient aware.
- Seen in clinic in 9/2022. Repeat CT ordered.
- Three LIRAD 5 lesions, the largest 2.9 cm and extending into the portal vein. Mild intrahepatic ductal dilation.
- Referred to IR/Rad Onc at private hospital. Visit with Rad Onc canceled as insurance is non-par. Insurance (Humana Medicare) will not cover Y-90.
  - Plan for SBRT at safety net. Marked by delays: Insurance non-par? Radiation Oncology has to waive all fees but needs administrative approvals. PCP has to escalate within network for exception. Receives SBRT in 11/2022.
- Unable to be seen by Oncology at UM. Marked delays at JMH Oncology clinic-Immunotherapy is not an option. Referred to community oncologist, told she needs a different referral.
- PCP unable to allow referral to UM.

XSM

- Referral for Y-90 made in 11/2022. Unsure if insurance will cover (Oscar-Medicaid like plan)
- Received Y-90 in 12/2022
- AFP dropped to 1,168
- Repeat Y-90 received in May of 2023.
- Referred for Transplant but after some evaluation, deemed ineligible due to lack of social support.

Result of Successful Attempts to Reduce Disparities



White DL et al. Gastroenterology. 2017 Mar; 152(4):812-820.e5

Phases of the Disparity Research Agenda

Phase 1	Phase 2	Phase 3
		
DETECTING	UNDERSTANDING	REDUCING

Kilbourne AM et al. Am J Public Health. 2006 Dec;96(12):2113-21.

Determinants of Disparities in Liver Disease Burden

National Institute on Minority Health and Health Disparities Research Framework

		Levels of Influence*			
		Individual	**Interpersonal**	**Community**	**Societal**
Domains of Influence *(Over the Lifecourse)*	**Biological**	Biological Vulnerability and Mechanisms	Caregiver–Child Interaction Family Microbiome	Community Illness Exposure Herd Immunity	Sanitation Immunization Pathogen Exposure
	Behavioral	Health Behaviors Coping Strategies	Family Functioning School/Work Functioning	Community Functioning	Policies and Laws
	Physical/Built Environment	Personal Environment	Household Environment School/Work Environment	Community Environment Community Resources	Societal Structure
	Sociocultural Environment	Sociodemographics Limited English Cultural Identity Response to Discrimination	Social Networks Family/Peer Norms Interpersonal Discrimination	Community Norms Local Structural Discrimination	Social Norms Societal Structural Discrimination
	Health Care System	Insurance Coverage Health Literacy Treatment Preferences	Patient–Clinician Relationship Medical Decision-Making	Availability of Services Safety Net Services	Quality of Care Health Care Policies
Health Outcomes		**Individual Health**	**Family/ Organizational Health**	**Community Health**	**Population Health**

National Institute on Minority Health and Health Disparities, 2018
*Health Disparity Populations: Race/Ethnicity, Low SES, Rural, Sexual and Gender Minority
Other Fundamental Characteristics: Sex and Gender, Disability, Geographic Region

Alvidrez J et al. Am J Public Health. 2019 Jan;109(S1):S16-S20.

Applying a Framework

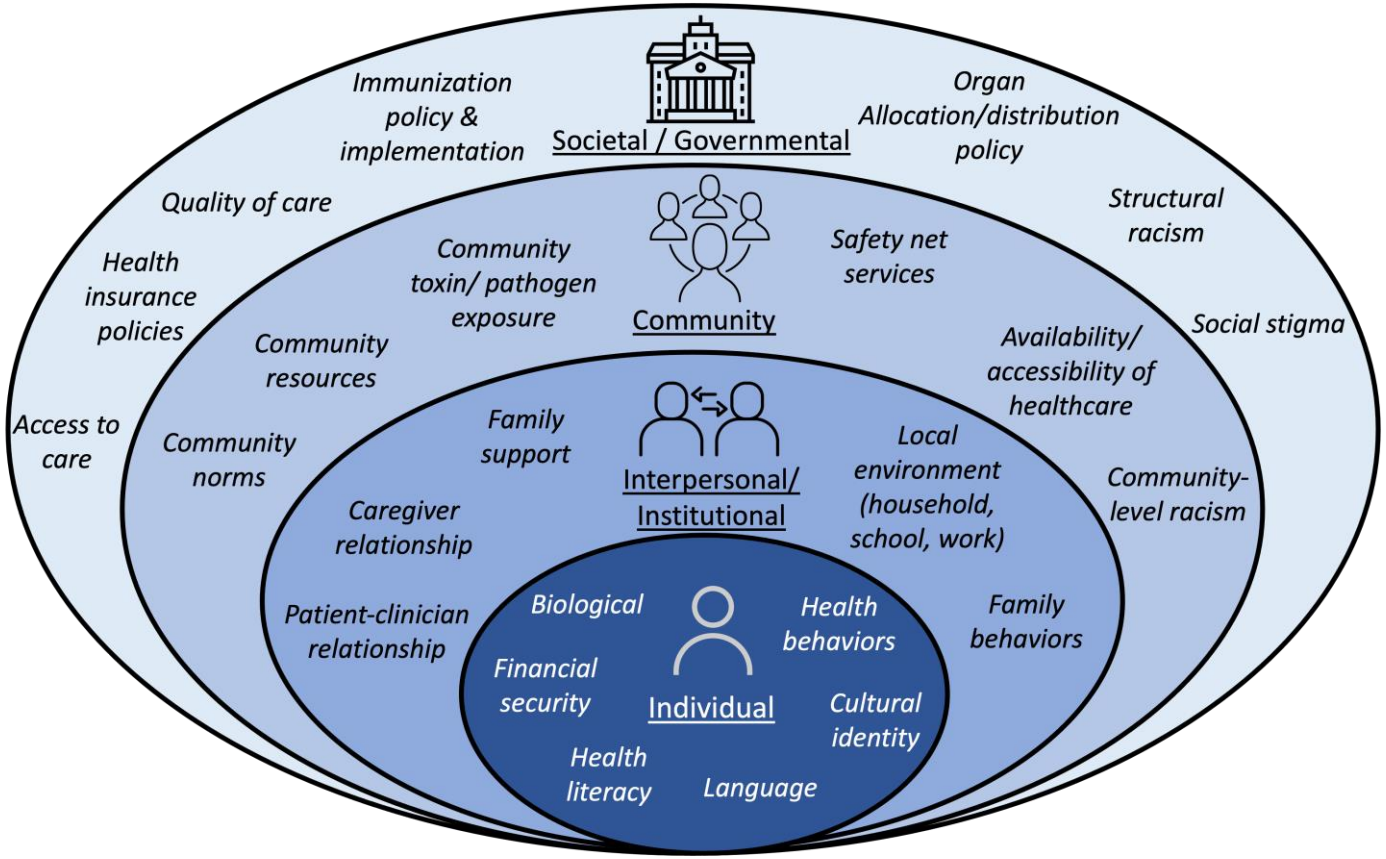


Figure 1. A research framework for investigating health disparities and inequities in patients living with chronic liver disease. Adapted from the National Institute for Minority Health and Health Disparities framework for research in disparities.

Jones PD et al. *Clin Gastroenterol Hepatol*. 2023 Apr 13:S1542-3565(23)00267-7.

Problem Statement:

The vast majority of literature describes disparities.

Phase 1

DETECTING

- Define health disparities.
- Define vulnerable populations.
- Measure disparities in vulnerable populations.
- Consider selection effects and confounding factors.

- **Pitfalls:** Most administrative and retrospective data sources provide inadequate data regarding key determinants.

Kilbourne AM et al. Am J Public Health. 2006 Dec;96(12):2113-21.

Understanding Disparities can be Overwhelming

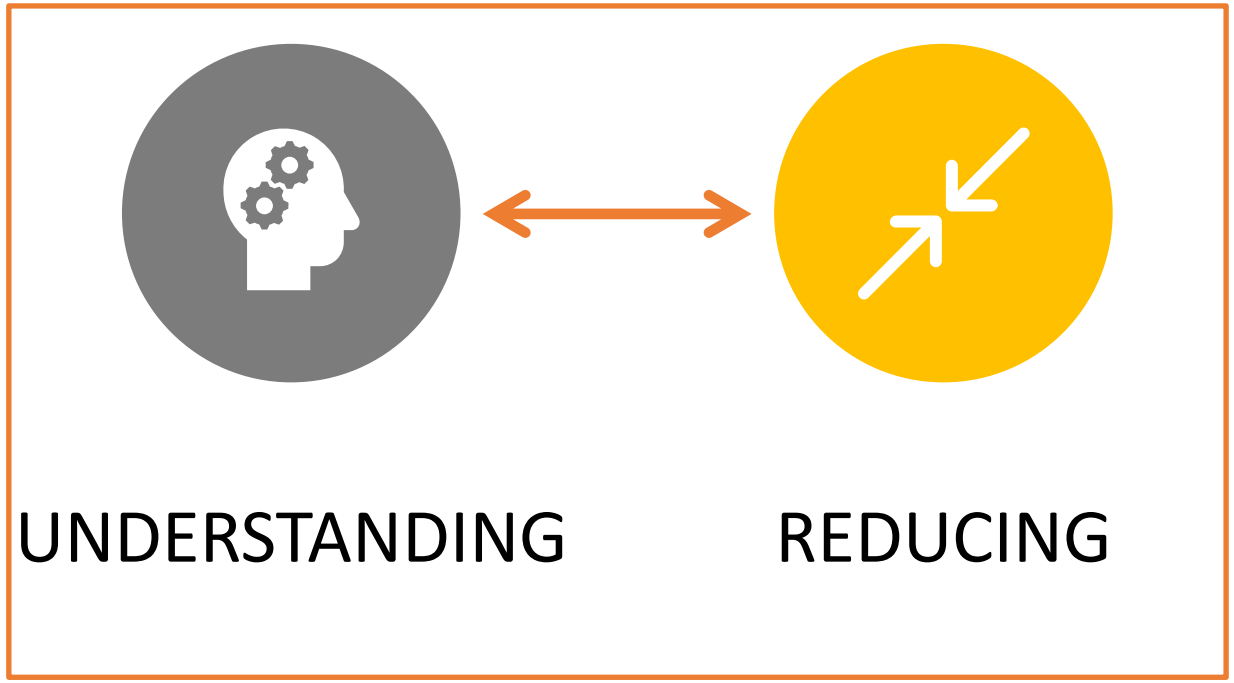
Phase 2

UNDERSTANDING

- Identifying determinants of health disparities at the following levels:
  - Patient/Individual
  - Provider
  - Clinical encounter
  - Health care system.
- This will require prospective studies and a trans-disciplinary approach

Kilbourne AM et al. Am J Public Health. 2006 Dec;96(12):2113-21.

Can we do two things at the same time?



Phases of the Disparity Research Agenda

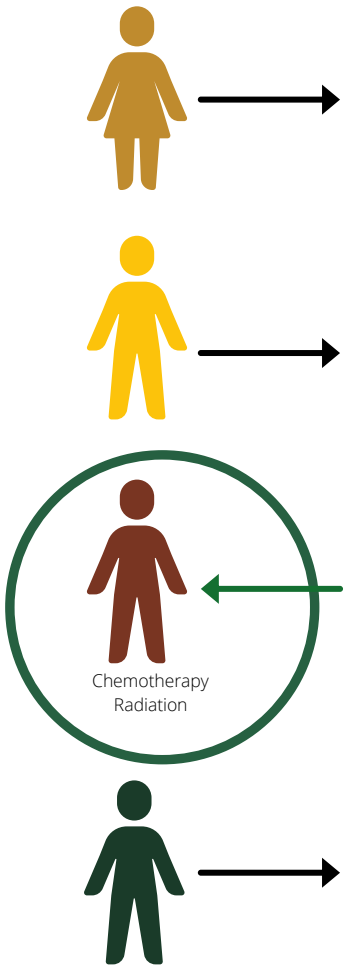
Kilbourne AM et al. Am J Public Health. 2006 Dec;96(12):2113-21.

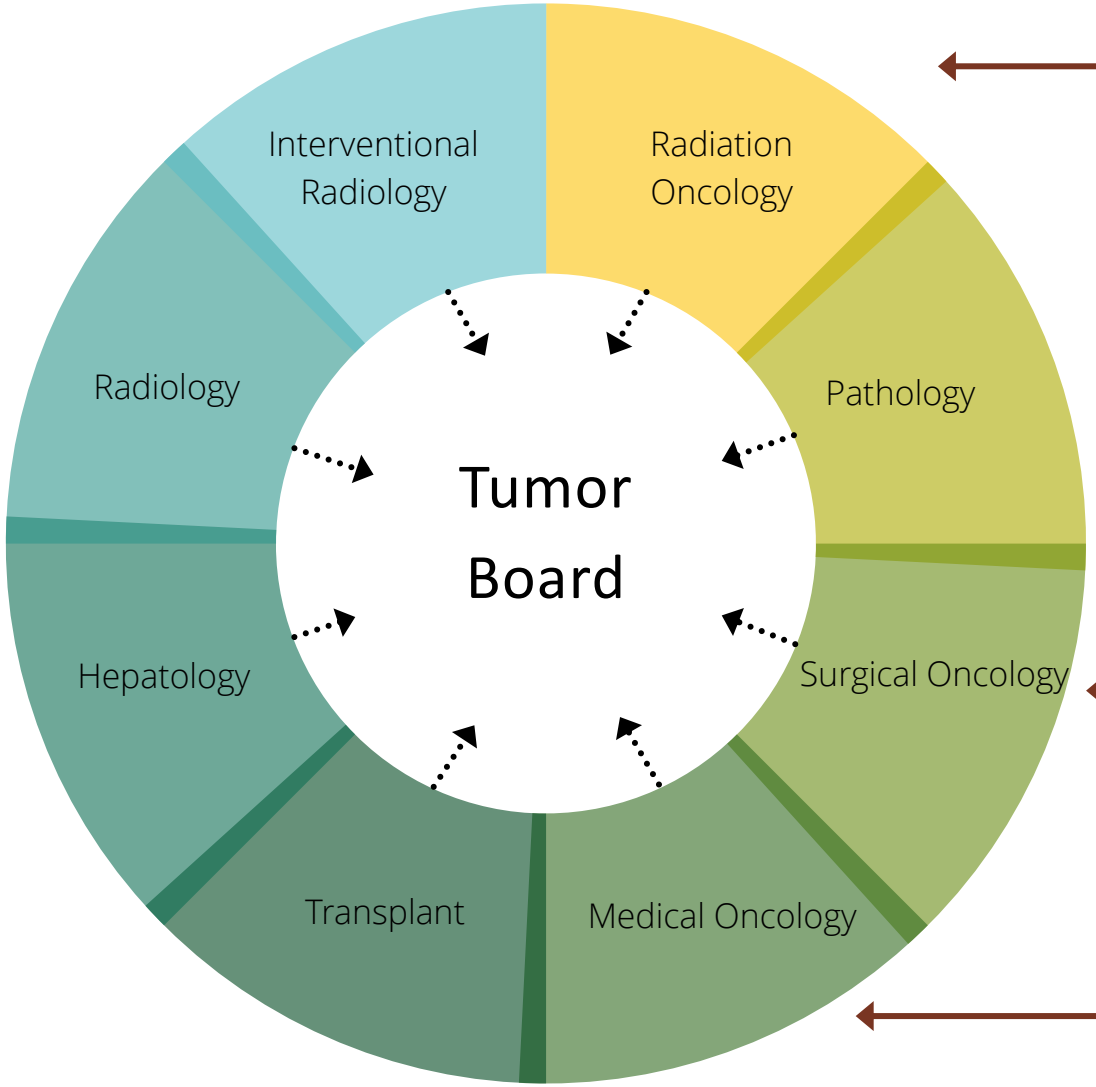
Institutional-Level Solutions

- Systematic measurement of social determinants
- Implementing a chronic disease management model improved HCC screening rates.
- Shifting to patient-centered care

Jones PD et al. *Clin Gastroenterol Hepatol*. 2023 Apr 13:S1542-3565(23)00267-7.
Wigg AJ et al. *Clin Gastroenterol Hepatol*. 2013 Jul;11(7):850-8.e1-4.

Navigation Improves Outcomes and Disparities





New Patients Only

Medical Oncology
Surgical Oncology
Radiation Oncology

Navigation beyond the first visit could attenuate and potentially eliminate treatment and survival disparities.

Conceptual Model of Targeted Navigation

Figure 4

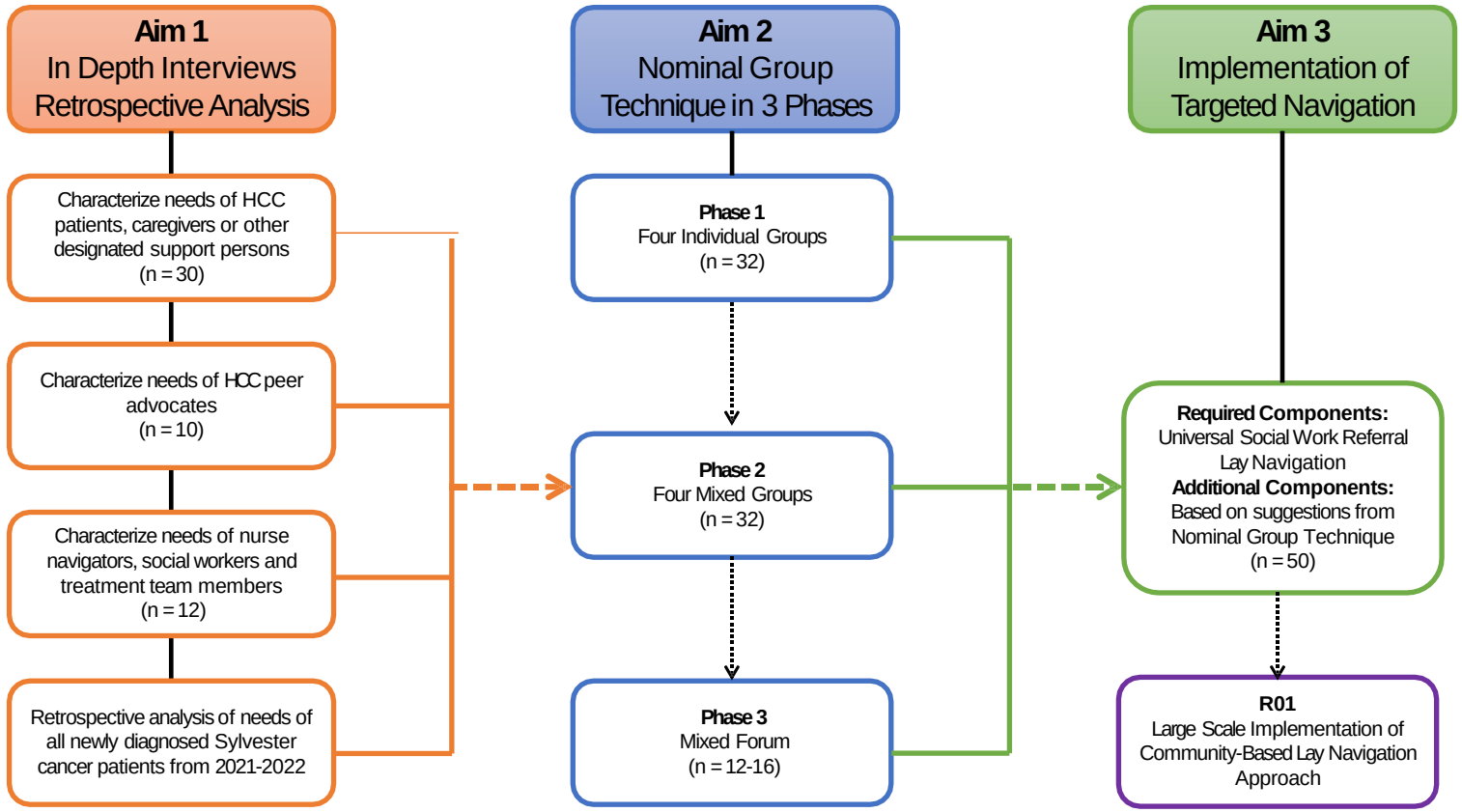


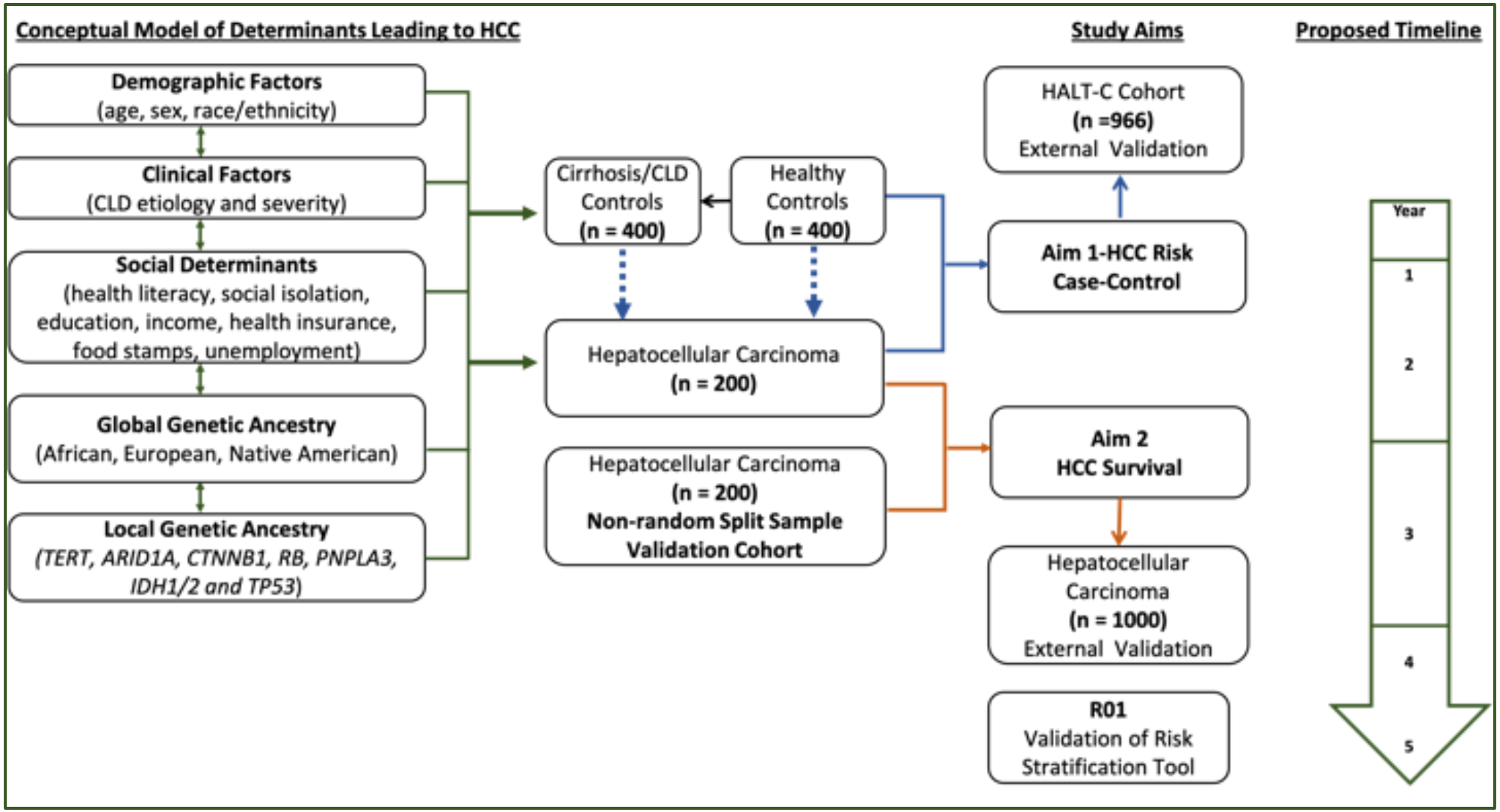
Figure 4. Conceptual Model.
In **Aim 1**, we will characterize need of hepatocellular (HCC) patients as well as caregivers or other designated support persons, e.g. clergy, friends. To gain a global perspective of the needs of HCC patients, we will also characterize the needs of 10 HCC peer advocates. This will enable us to identify similarities and differences between the HCC experience at Sylvester Comprehensive Cancer Center vs. other facilities in the United States. We will characterize the needs of social workers, nurse navigators and members of the treatment team. We will also conduct a retrospective analysis of newly diagnosed Sylvester patients using existing data. In **Aim 2**, we will employ Nominal Group Technique (NGT) to determine components of the ideal navigations program, measures of successful navigation, target population, required participants and brainstorm regarding challenges to successful implementation and potential solutions. Data from Aim 1 will be shared with the Nominal Groups in Phase 2. (Dashed orange arrow). In **Aim 3**, we will pilot our targeted navigation with 50 newly diagnosed HCC patients. The results of this study will inform a future R01 application that implements community-based lay navigation on a larger scale.

Genetics and Hepatocellular Carcinoma
Precision Medicine and Health Disparities Collaborative

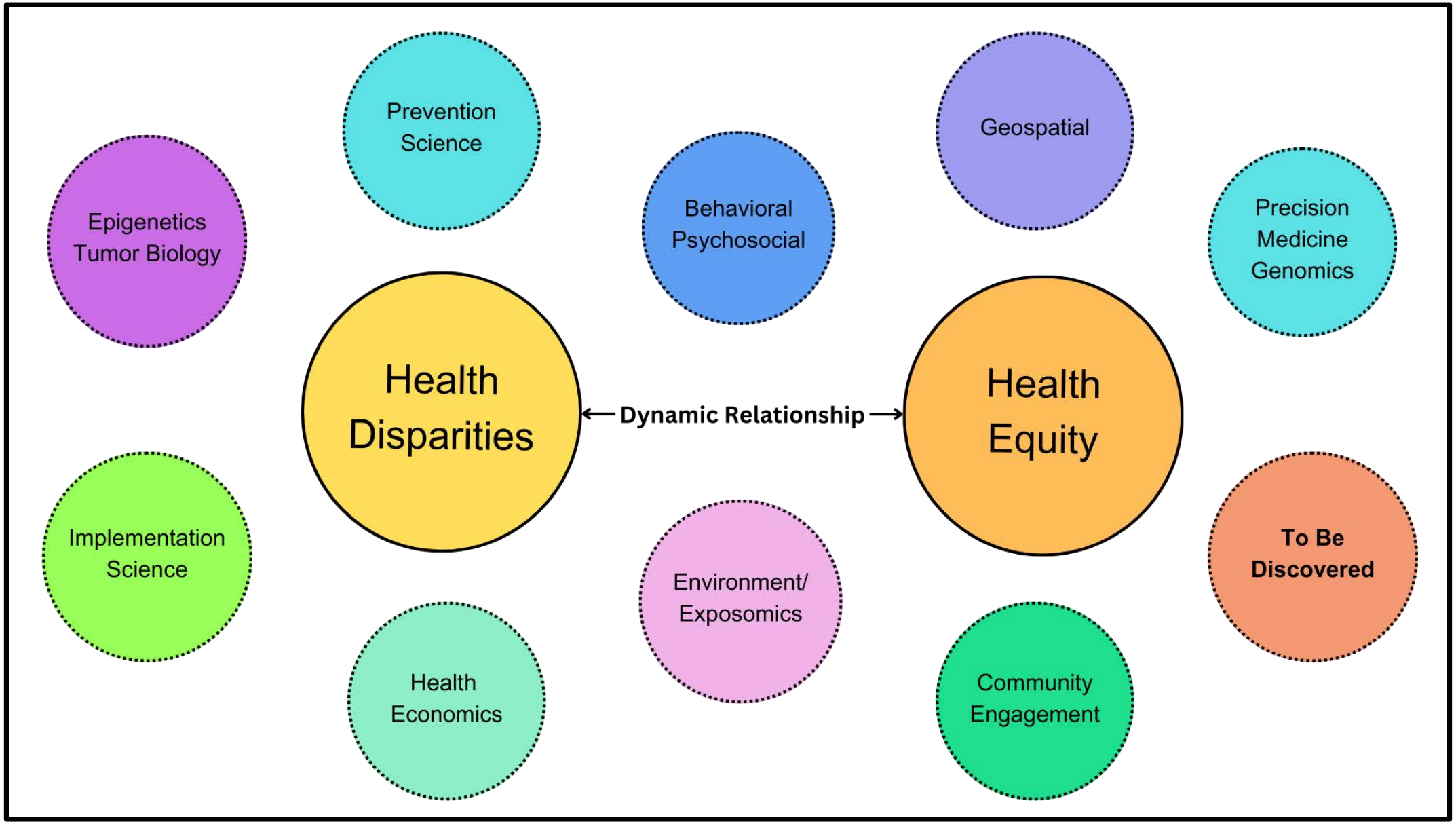
- Aim 1-To understand HCC patient perspectives on individual and system-level facilitators and barriers to biospecimen procurement and cultural attitudes about genetic testing.

- Aim 2: To obtain pilot data on global genetic ancestry and ancestral haplotypes containing commonly mutated HCC genes such as *TERT, ARID1A, CTNNB1, RB, BAP1, TP53,* and *IDH1/2* in diverse patients with HCC
  - Using ICD-10 code C22.0, we identified 649 patients.
  - Data merged with Vanderbilt Cancer Registry and 484 patients with ICD-O-3 codes for HCC. Of note, 89 do not have registry data with which to confirm HCC diagnosis.

Does Genetic Ancestry HCC Risk/Outcomes as Noted in Other Cancer Types?



Our Network is Our Net Worth



Take Home Points

- HCC has significant racial and ethnic disparities in risk, treatment and survival.
- Health Disparities ≠ Health Equity.
- Health disparities occur at the intersection of individual, interpersonal, community and institutional levels within biological, behavioral, sociocultural, physical environment and health care system domains to influence health outcomes in individuals, families, organizations, communities, and populations.
- To achieve health equity, we must detect, understand **AND ACT** on various determinants of health disparities.

Thank You

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