Phases of Biomarker Validation: HEDS and THCCC cohorts

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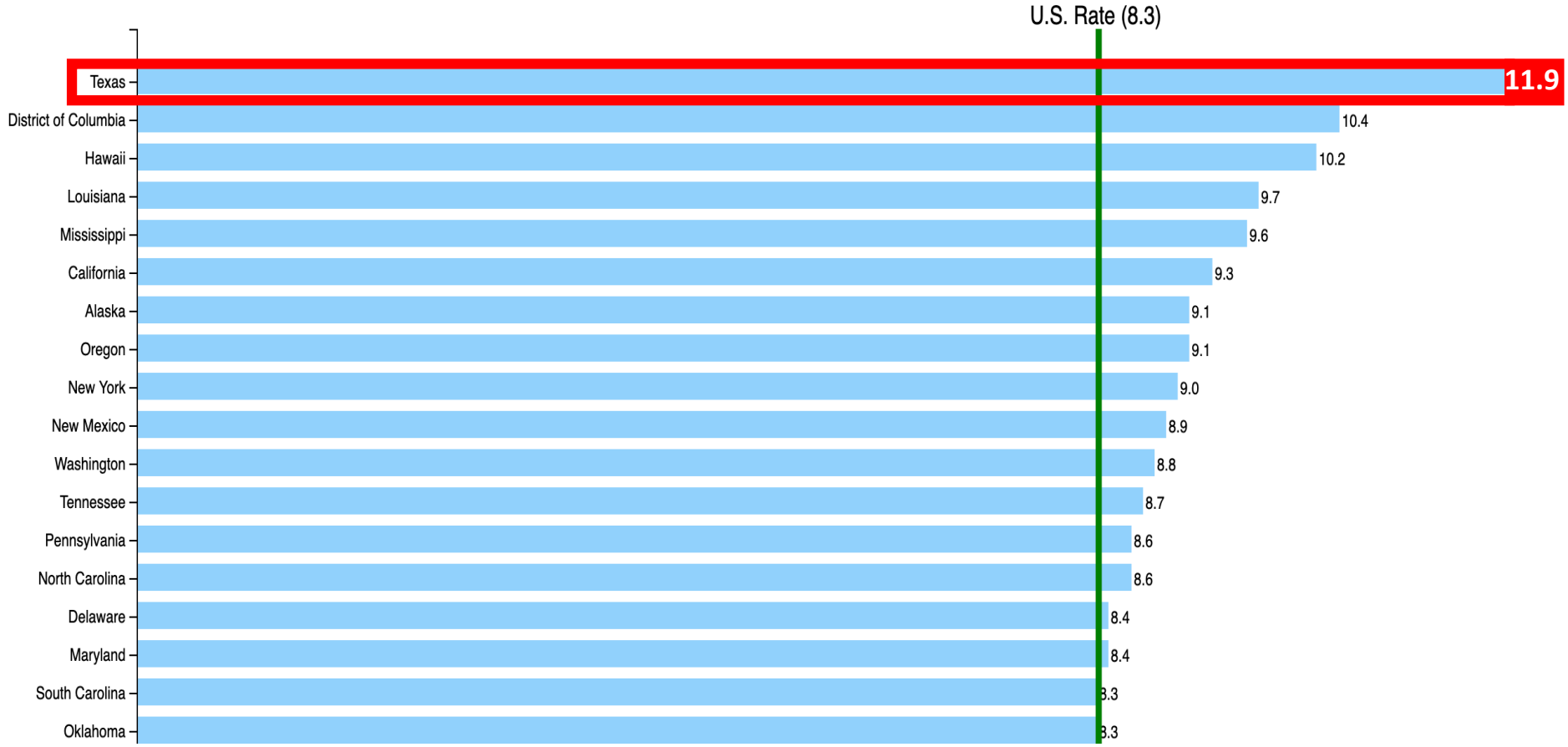
Topics

- Early Detection
- Phases of Biomarker Validation
- HEDS and THCCC cohorts

Liver Cancer Incidence Rates in USA: 2017



U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2019 submission data (1999-2017)

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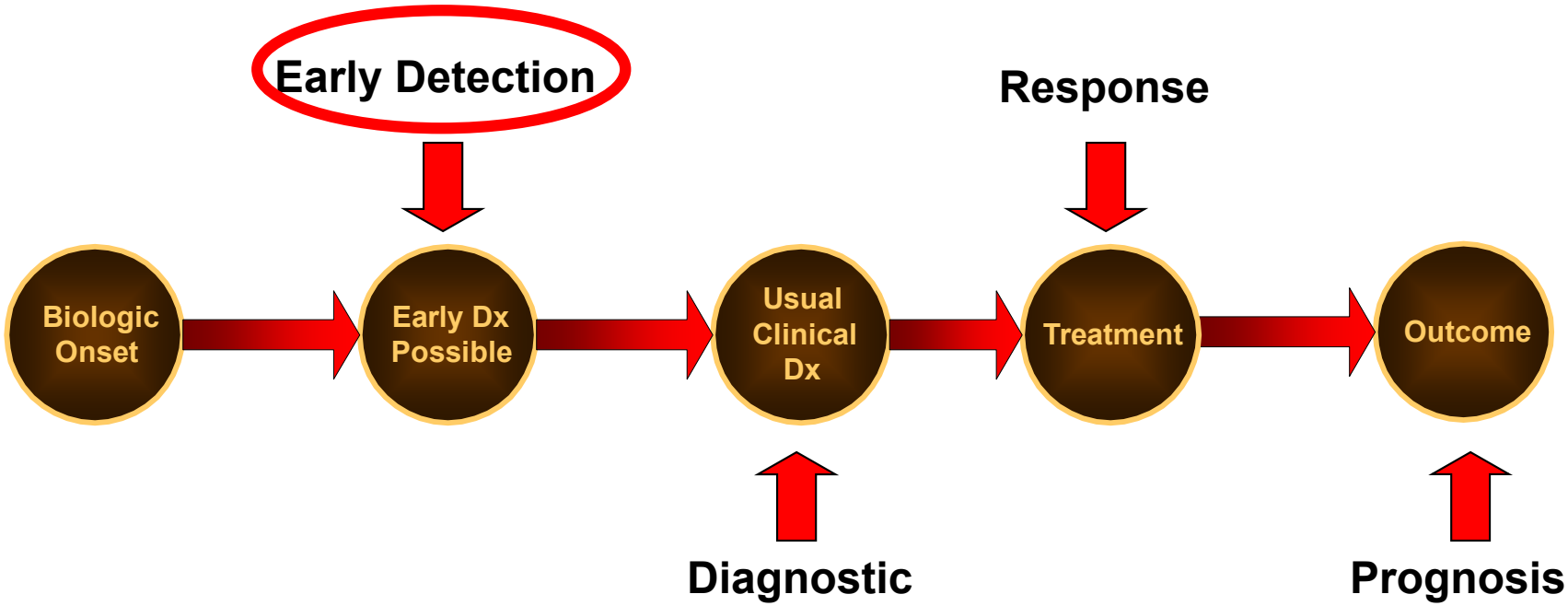
Disease Processes in Cancer



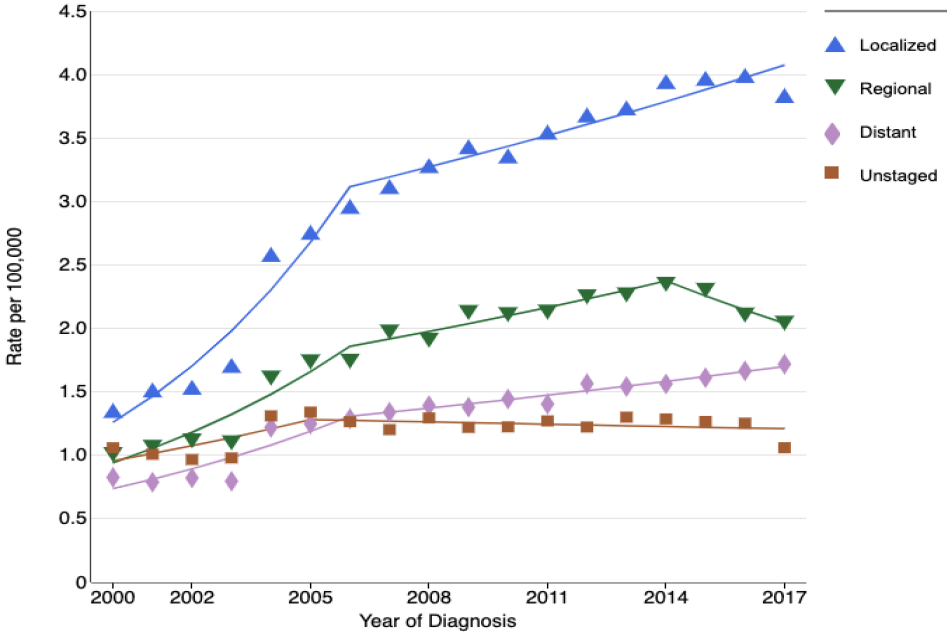
Etiology of Liver Disease in Liver Cancer

- High prevalence of NAFLD in Hispanics[1]
- Obesity, DM and metabolic syndrome[2]
- HCV infection is highly variable among Hispanics[3]
- National Epidemiologic Survey on Alcohol and Related Conditions, Hispanics had the greatest prevalence of heavy drinking (31.6%) compared to other race/ethnic minorities[4]

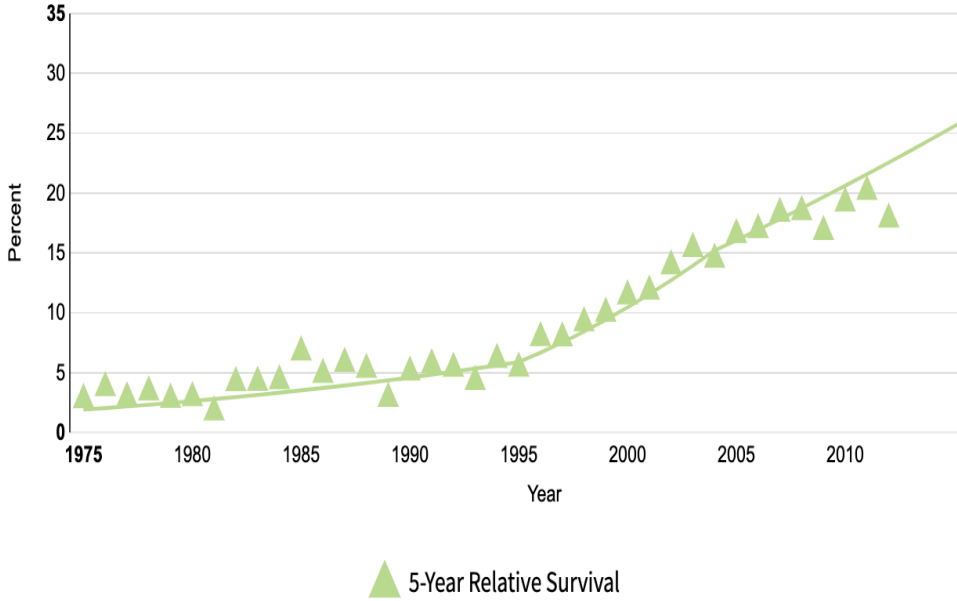
Kallwitz, et al. 2015. Clin. Gastroenterol. Hepatol. 13:569-576
Kanwal, et al. 2018. Gastroenterology. 155:1828
Hall, et al. 2018. BMC Infect. Dis. 18:224
Dawson, et al. 2015. Drug Alcohol Dep. 148:56

Age-Adjusted Incidence Rates by Liver Cancer Staging and 5-Yr Survival

Incidence per Staging

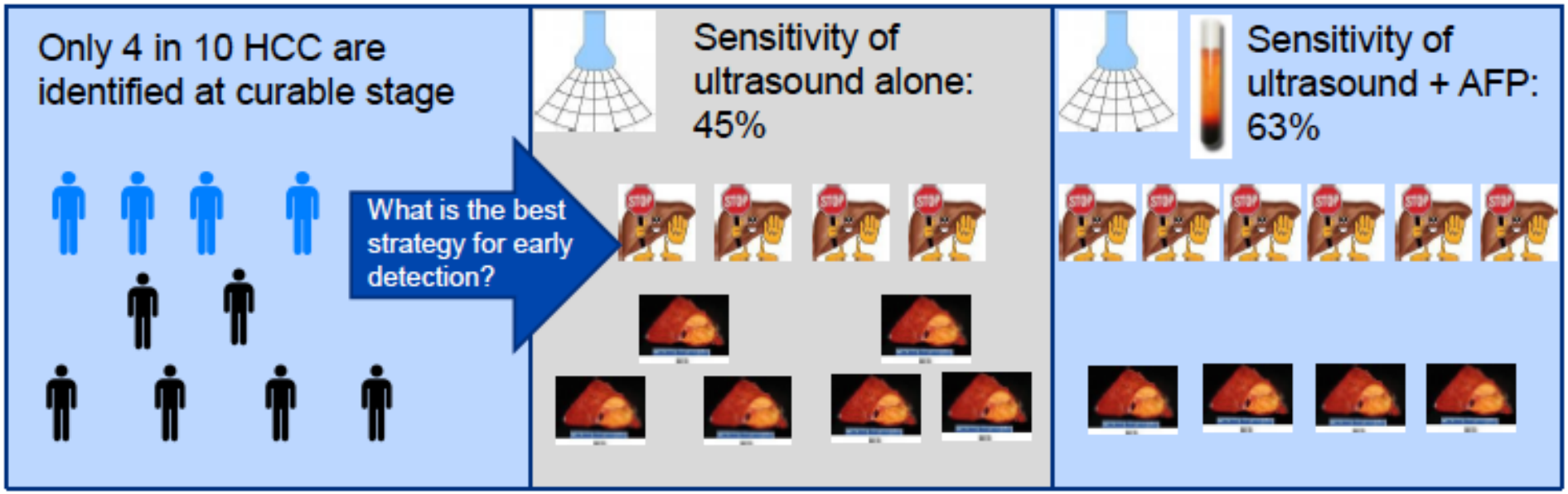


5-yr Survival



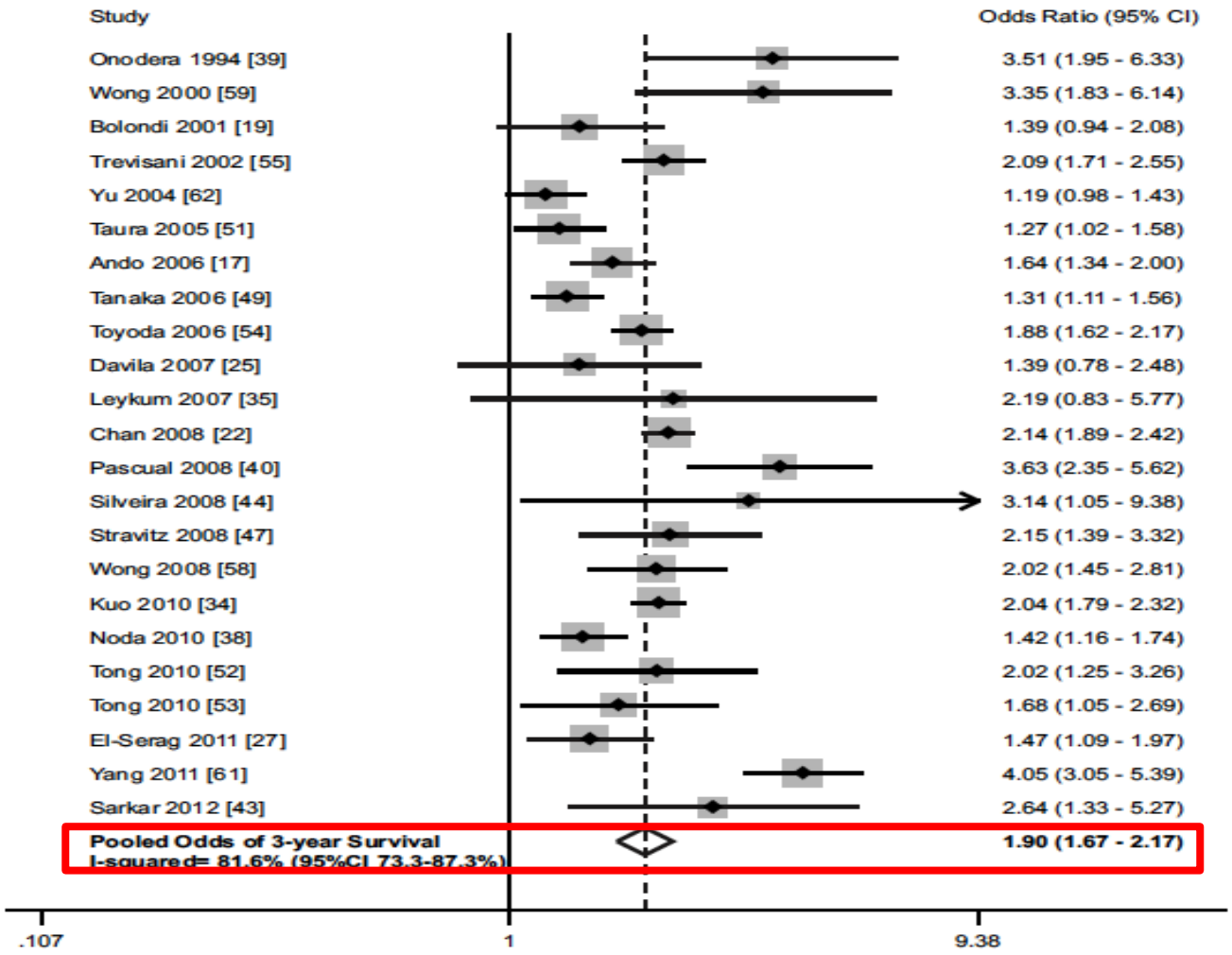
https://seer.cancer.gov/statfacts/html/livibd.html

Current Surveillance for HCC: US and AFP



Tzarzeva K, et al. Gastroenterology 2018

HCC Surveillance Improves Survival



Singal AS, et al. Plos One 2014.

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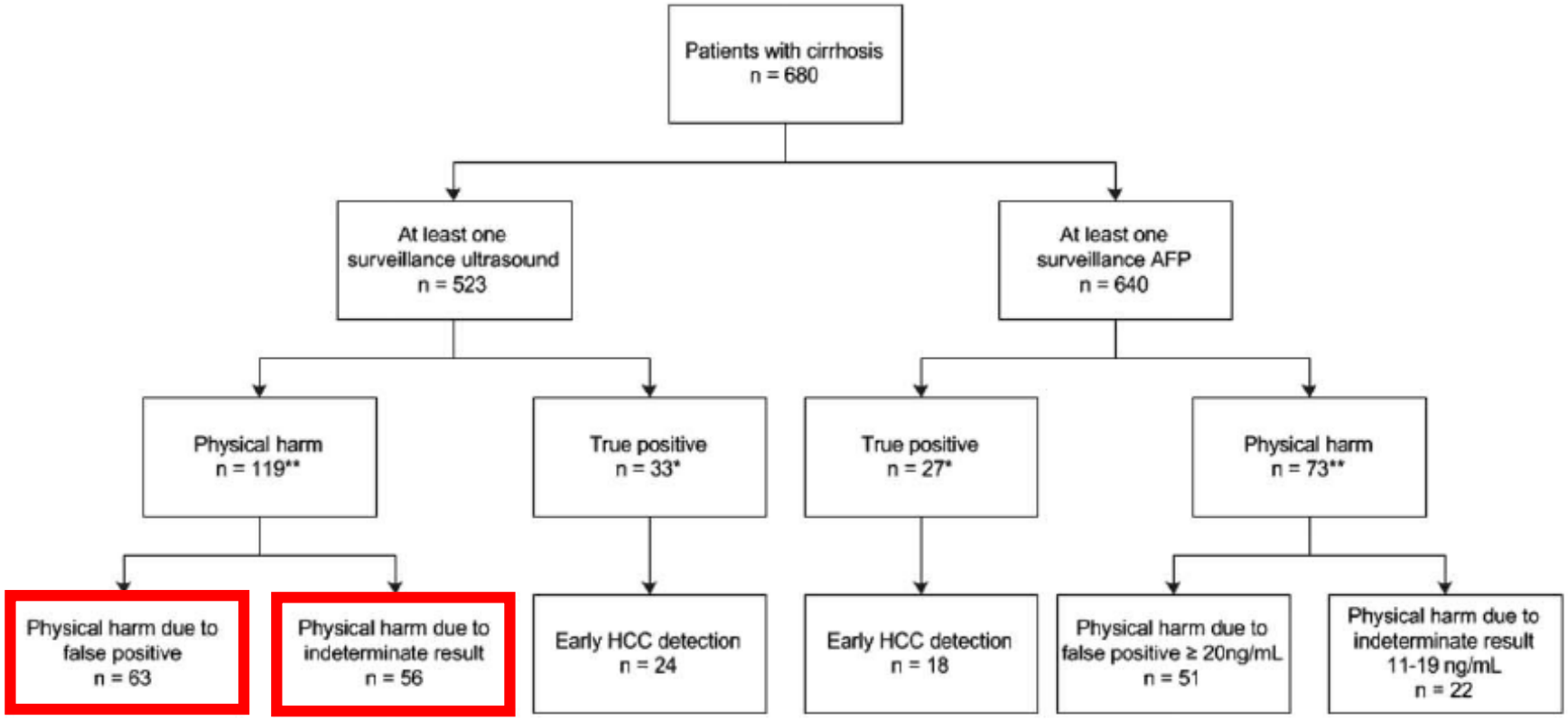
Harms of HCC Surveillance



* 12 HCC detected by both ultrasound and AFP
** 7 patients with physical harm due to false positive ultrasound and AFP

Atiq O, et al. Hepatology 2017

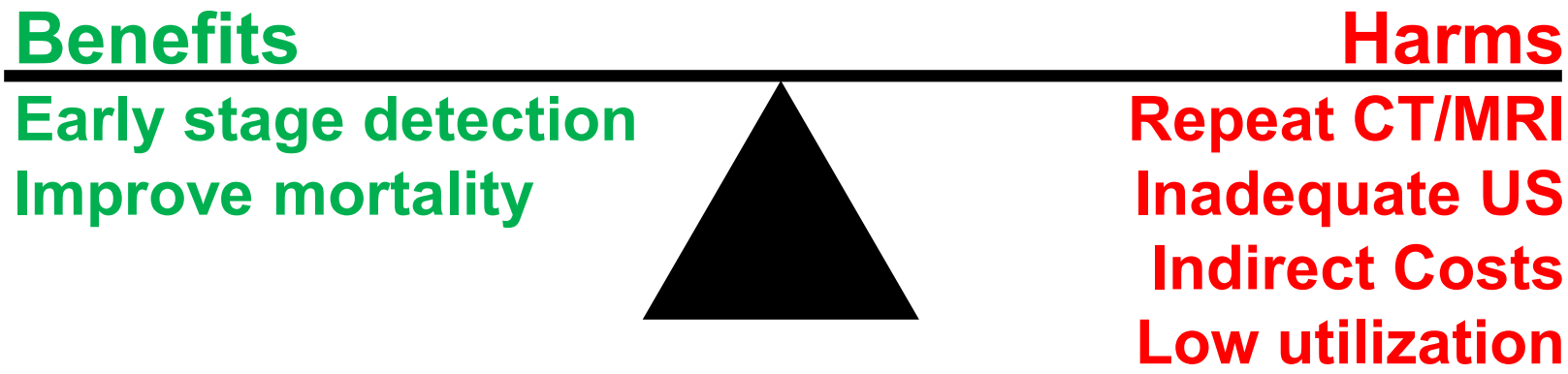
US Quality in HCC Surveillance

Variable	Adjusted odds ratio (95% CI)
Child Pugh B/C	1.65 (1.06 – 2.57)
BMI category	
Normal	Reference
Obese	2.60 (1.36 – 4.97)
Morbidly obese	8.86 (4.02 – 19.5)
Cirrhosis etiology	
Hepatitis C	Reference
Hepatitis B	2.02 (0.67 – 6.10)
Alcohol-related	1.84 (1.09 – 3.09)
NASH-related	2.48 (1.30 – 4.75)

~ 20% of US were classified as inadequate

Simmons et al. Aliment Pharm Ther 2017

HCC Surveillance



Phases of Development of Biomarkers in Cancer

Phase 1: Preclinical exploratory studies (***pilot***)

Phase 2: Clinical Assay Development for Clinical Disease (***case-control***)

Phase 3: Retrospective Longitudinal Study (***detect preclinical disease***)

Phase 4: Prospective Screening Studies (***biomarker determining early diagnosis***)

Phase 5: Cancer Control Studies (***RCT***)

Phases of HCC Biomarker Development

Phases	Outcomes	Biomarkers Types
1	Exploratory TPR and FPR	Blood, Urine
2	Clinical Assay TPR and FPR	Blood, Urine
3	Pre-clinical HCC	Blood, Urine, Imaging
4	HCC Detection rates	Blood, Urine, Imaging
5	Decrease in HCC mortality	Blood, Urine, Imaging

DCP Study: Phase 2 Biomarker Study

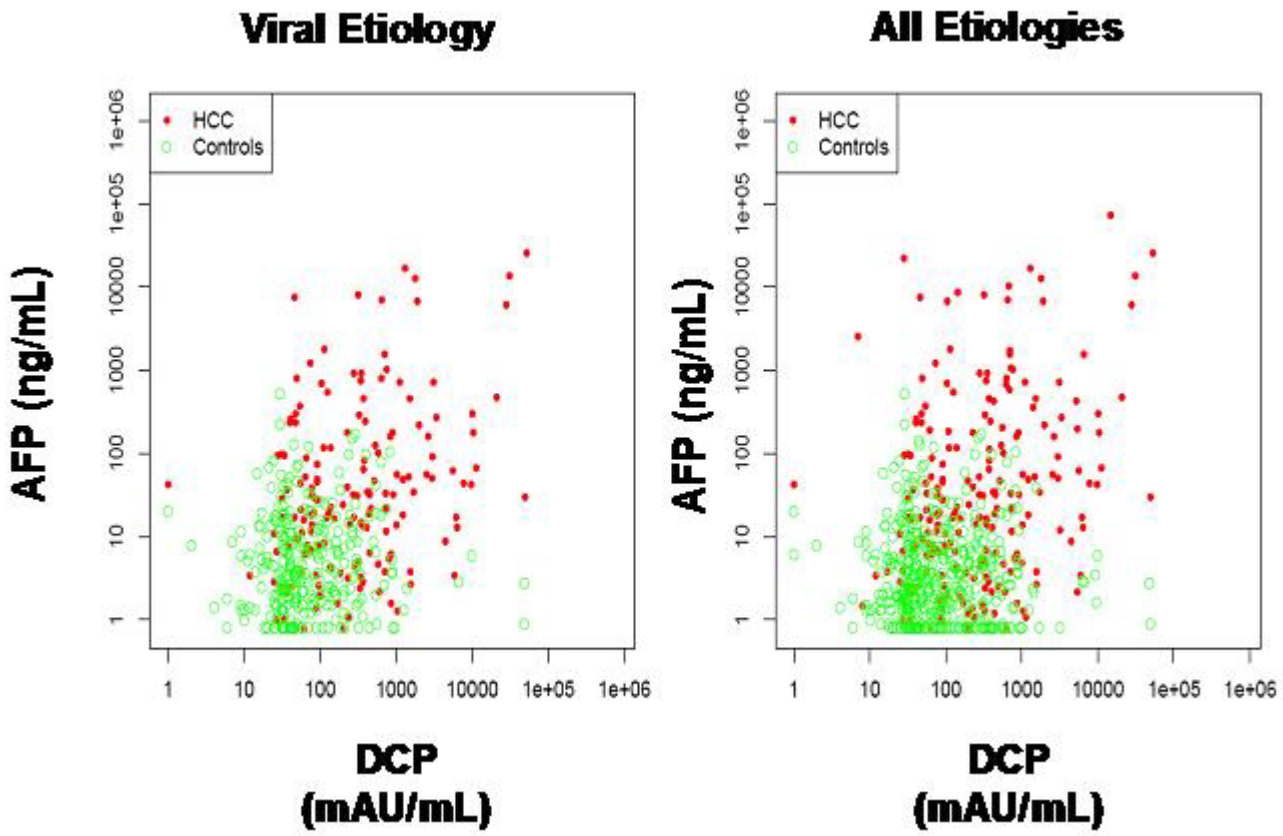
Variable	Cirrhosis controls (n = 417)	Early HCC (n = 208)	Late HCC (n = 211)	*P* value[a]
Age, mean (SD), *y*	55 (8.8)	60 (9.9)	61 (10.3)	<.0001
Sex (M:F), %	69.5:30.5	72.5:27.5	86.8:13.2	<.0001
Race, %				<.0001
W	80	57	71.4	
AA	4.1	14	6.3	
As	7.3	19.5	19.9	
Other	8.5	9.5	2.4	
Ethnicity, %				
Hispanic	12.7	15	5.2	.003
Etiology, %				
Viral:Nonviral	65:35	74:26	61:39	.003
HCV	60	58	45	.001
HBV	5	16	16	
Alcohol	12	11	9	
Cryptogenic	13	5	18	
Others	10	10	12	
Child–Pugh class, %				.0001
A	55.9	70.4	66.5	
B	44.1	27.7	29.2	
C	0	1.9	4.2	
Maximum tumor diameter, mean (SD), *cm*	NA	2.9 (1.0)	7.0 (3.8)	<.0001
No. of lesions, mean (SD)	NA	1.3 (0.6)	2.3 (1.5)	<.0001
1, %		79.2	41	<.0001
2, %		12.1	24.6	
3, %		8.7	11.4	
4, %		0	9.5	
≥5		0	13.2	
Portal vein thrombosis, %	NA	0	24.5	<.0001
Metastasis, %	NA	0	13.2	<.0001
BCLC stage n (%)	NA			
Very early (0)		77 (37)	0	<.0001
Early (A)		131 (63)	0	
Intermediate (B)		0	130 (62)	
Advanced (C)		0	81 (38)	
Terminal (D)		0	0	

Marrero JA, et al. GASTROENTEROLOGY 2009;137:110–118

Cutoffs for each marker Controls vs. Early Stage HCC

	Cutpoint (95%CI)	Sensitivity (%)	Specificity (%)
DCP mAU/mL	202 (61-331)	56	77
AFP-L3 %	0.6 (0.6-1.9)	37	93
Total AFP ng/mL	10.9 (5.7-18.4)	66	82

Complement of AFP and DCP Controls vs. Early HCC



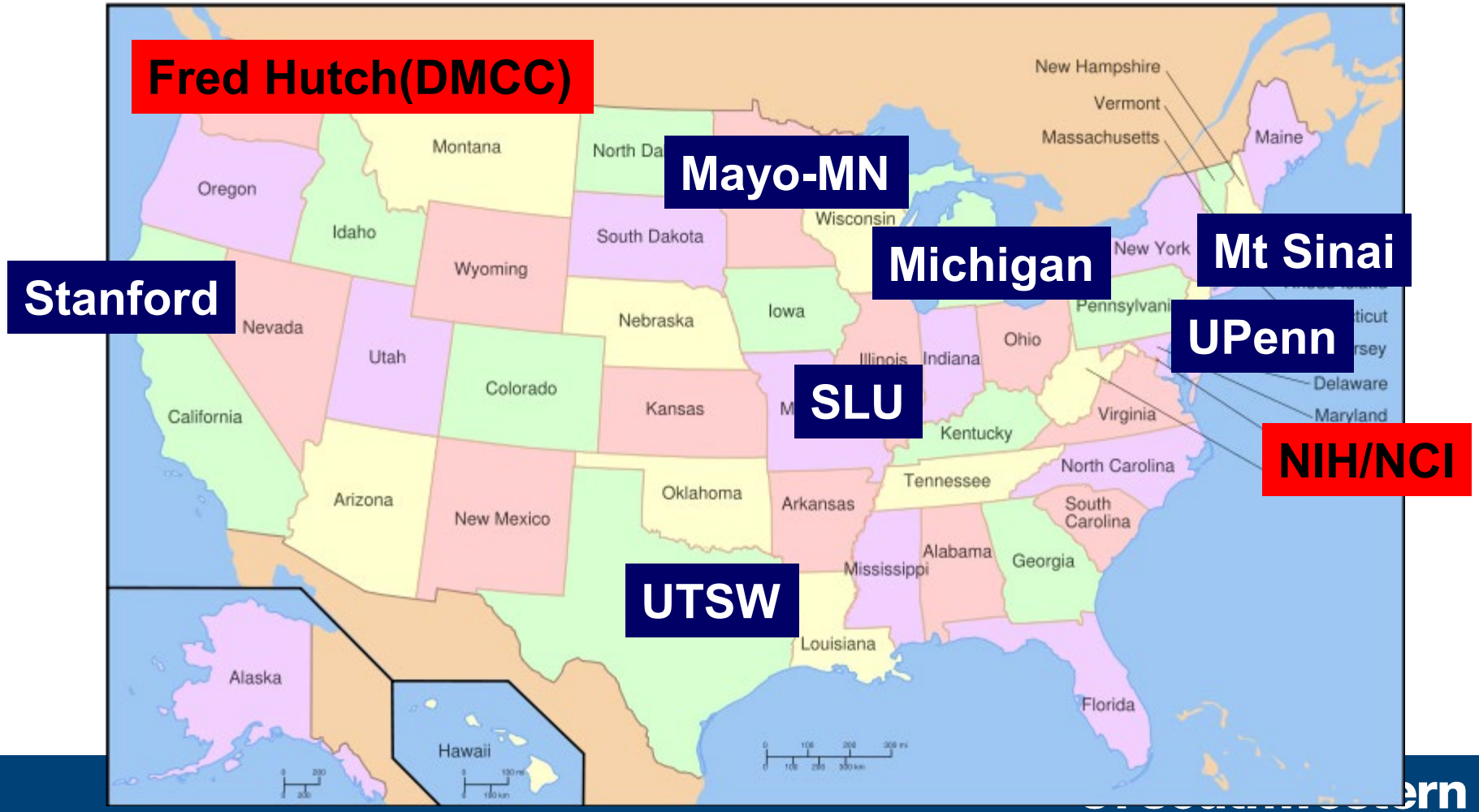
Marrero JA, et al. GASTROENTEROLOGY 2009;137:110–118

AFP, DCP: HALT C Trial

Test	Sensitivity (%)	Specificity (%)
DCP ≥ 40 mAU/ml		
0	74	86
-6	63	88
-12	43	94
AFP ≥ 20 ng/ml		
0	61	81
-6	57	76
-12	47	75
DCP ± AFP		
0	91	74
-6	86	69
-12	73	71

Lok AS, et al. Gastroenterology 2010

Hepatocellular carcinoma Early Detection Strategy (HEDS) Study



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Risk Factors that Predict HCC in the HEDS Study

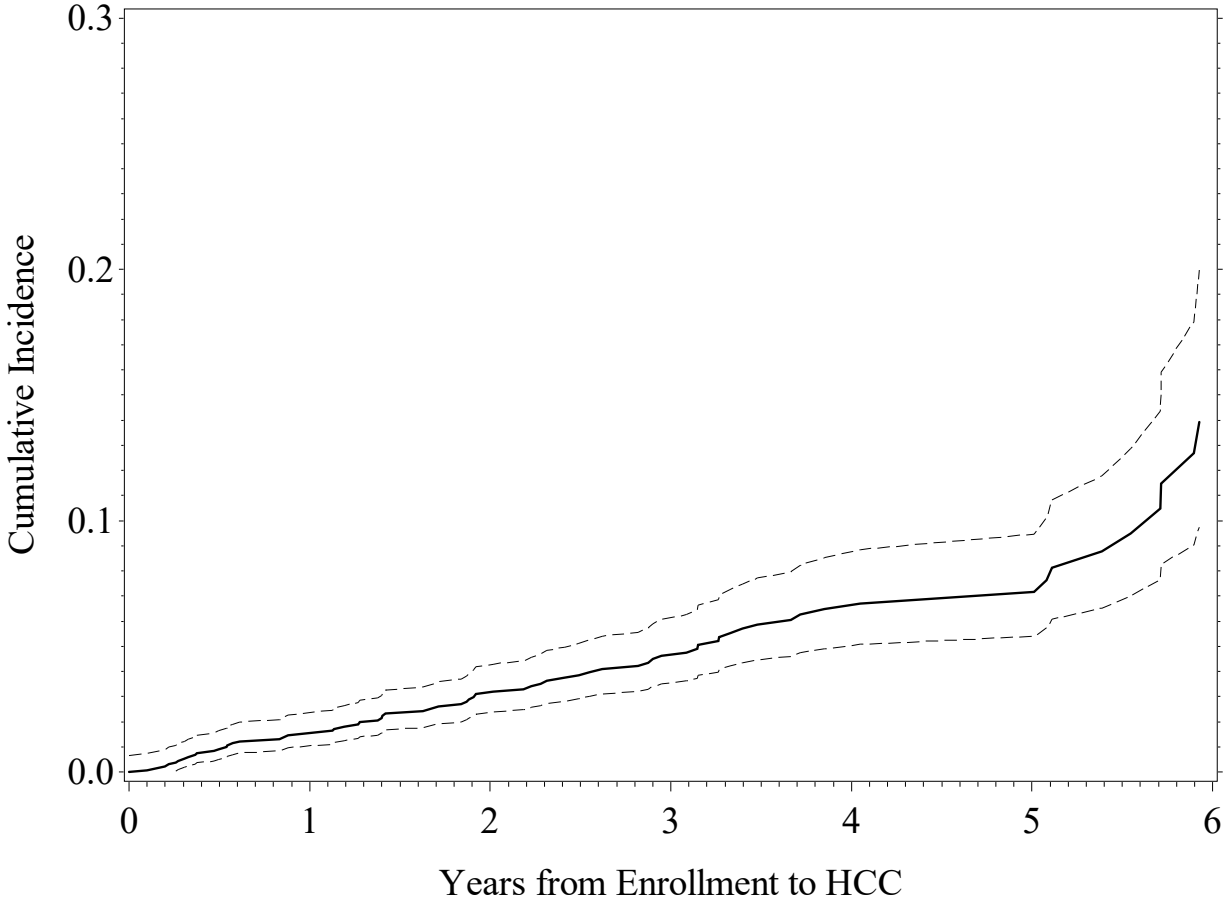
- 1,559 patients enrolled with a median follow up of 3.4 years
- Men 53%; median BMI 30.1; 79% NHW
- HCV 42%; NAFLD 21.6% ; Alcohol 20.8%
- 87 incidence HCC; incidence rate 2.7% per 1,000 person-years

Risk Factors that Predict HCC in the HEDS Study

Predictor	Complete Data Models			
	Sig. Predictors From Full Set†	Stepwise Selection	Forward Selection	Backward Elimination
Female	0.36 (0.21, 0.63)	0.34 (0.20, 0.59)	0.33 (0.20, 0.57)	0.34 (0.20, 0.59)
Age (per 5 year change)	1.22 (1.05, 1.41)	1.18 (1.02, 1.36)	1.18 (1.03, 1.37)	1.18 (1.02, 1.36)
Log(BMI)	**4.30 (1.38, 13.5)**	**4.34 (1.43, 13.1)**	**3.90 (1.27, 11.9)**	**4.34 (1.43, 13.1)**
Log(AFP)	1.45 (1.06, 2.00)	1.60 (1.22, 2.12)	1.59 (1.20, 2.10)	1.60 (1.22, 2.12)
Albumin	NS	0.57 (0.38, 0.86)	0.58 (0.39, 0.88)	0.57 (0.38, 0.86)
Family Hist. of HCC or Liver Disease	NS	—	1.67 (0.99 2.82)	—
Esophageal Varices	NS	1.80 (1.10, 2.96)	1.72 (1.04, 2.84)	1.80 (1.10, 2.96)

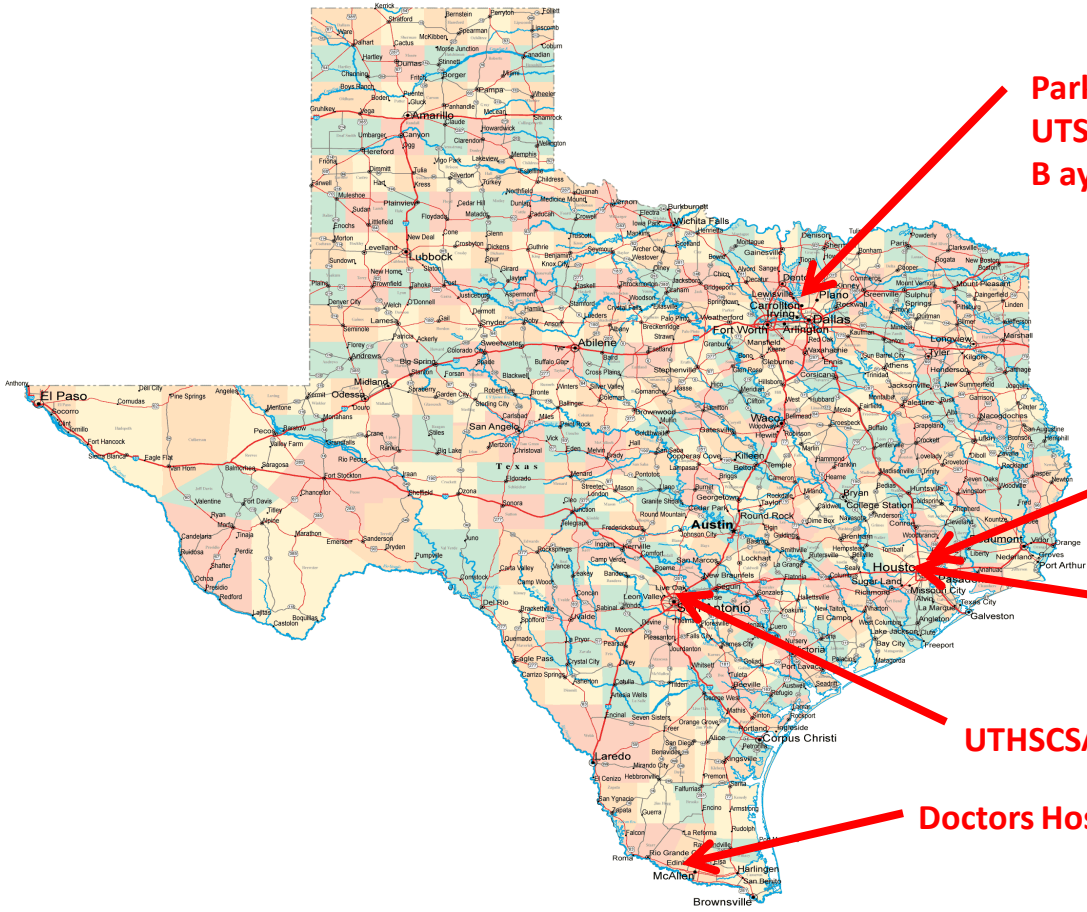
Reddy R, et al. AASLD 2020 Abstract 1057

Cumulative Incidence of HCC: competing risk model



Years from study entry	Probability
1	0.015 (0.009, 0.023)
3	0.046 (0.035, 0.060)
5	0.067 (0.054, 0. 084)

The Texas Hepatocellular Carcinoma Consortium (THCCC)



Parkland
UTSW Clements Univ Hospital
B aylor University MC

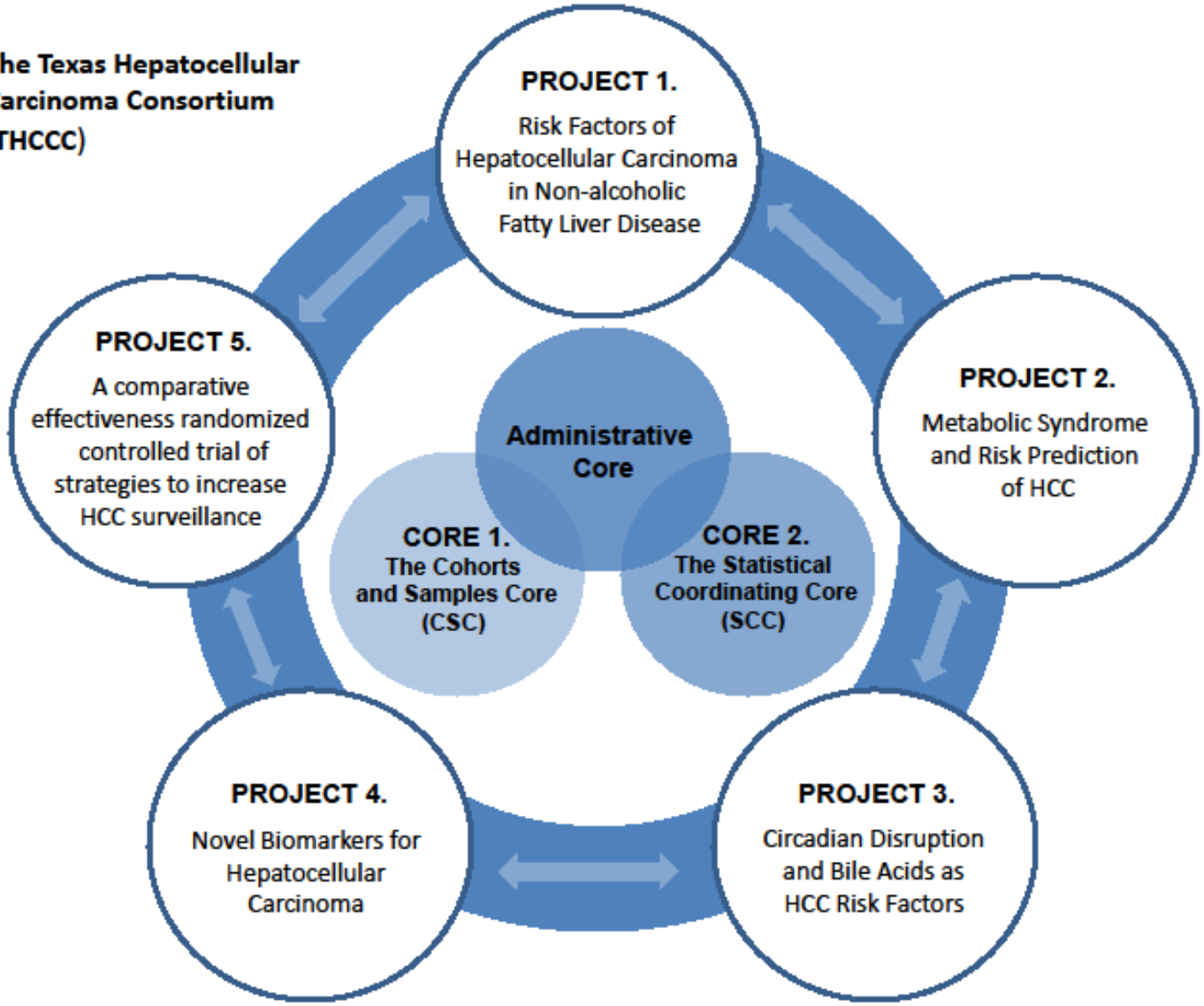
MDACC

Baylor-St Lukes Hospital
Houston VAH
Baylor College Med

UTHSCSA/Texas Liver Ins

Doctors Hospital

The Texas Hepatocellular Carcinoma Consortium (THCCC)



The Texas Hepatocellular Carcinoma Consortium (THCCC): data collection

Data forms/source	Event interval	Submission schedule
Recruitment data	Baseline	At the time of initial subject contact
Informed consent data and source	Baseline	Within 14 d after subject registration
Eligibility data	Baseline	At the time of registration
Baseline data and source	Baseline	Within 14 d after subject registration
Follow-up data	Every 6 mo for years 1–5	Within 14 d after each assessment
Post-HCC follow-up data	1 yr after diagnosis	Within 14 d after each assessment
Histologic diagnosis data/source (pathology report)	When applicable	Within 14 d after becoming aware of the diagnosis
Adverse event data	When applicable	Within 5 d after becoming aware of the event
Off-study data/source	Off study	Within 14 d after off-study date

HCC, hepatocellular carcinoma

Feng Z, et al. Am J Gastroenterol 2019;114

THCCC Data

- Incidence rate of 1.9%

Table 1. Data from 2,403 patients enrolled from the THCCC	
BMI, mean (SD)	31.1 (7.0)
Diabetes	1043 (43.4%)
Overweight or obesity	1928 (80.2%)
Diabetes, overweight or obesity	2041 (84.9%)
Diabetes or obesity	1605 (66.8%)
HCV Active	371 (15.4%)
HBV	51 (2.1%)
NAFLD/NASH	647 (26.9%)
Current Heavy Drinkers, Male	114 (4.7%)
Current Heavy Drinkers, Female	24 (0.99%)
Dyslipidemia	811 (33.7%)
Diabetes, obesity, overweight, or dyslipidemia	2097 (87.3%)

Phase 3 Validation Studies

HEDS

- GALAD
- Glycotest
- Longitudinal AFP
- Risk Stratification molecular signature

THCCC

- GALAD
- Exact Sciences
- Longitudinal AFP
- Metabolic syndrome
- Risk Stratification molecular signature

Summary

- The THCCC and HEDS are unique cohorts that will allow to study new paradigms in early detection, risk assessment and prevention therapies