

Risk of HCC in NAFLD/NASH

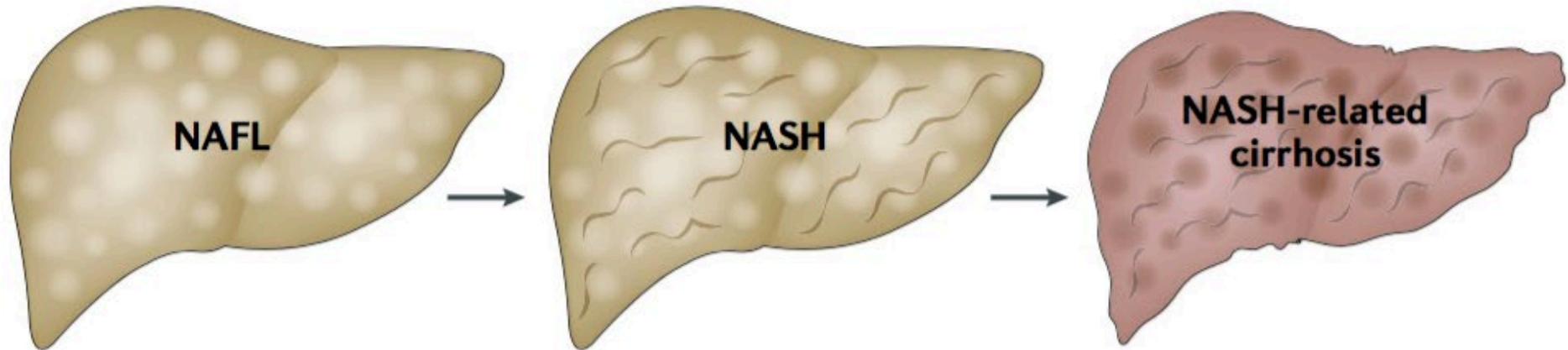
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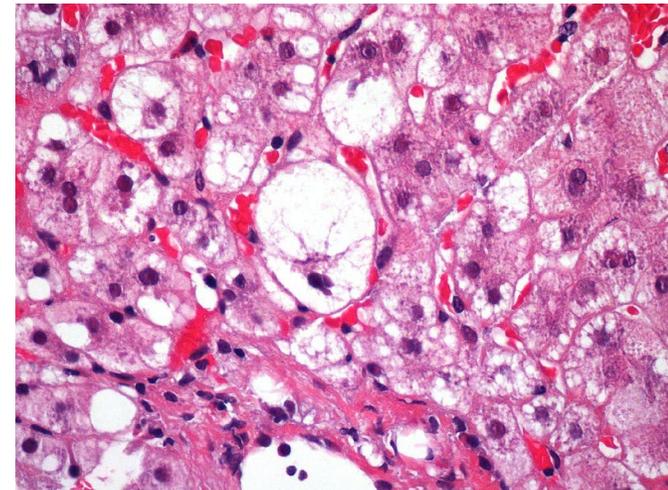
Houston, Texas

Spectrum of NAFLD

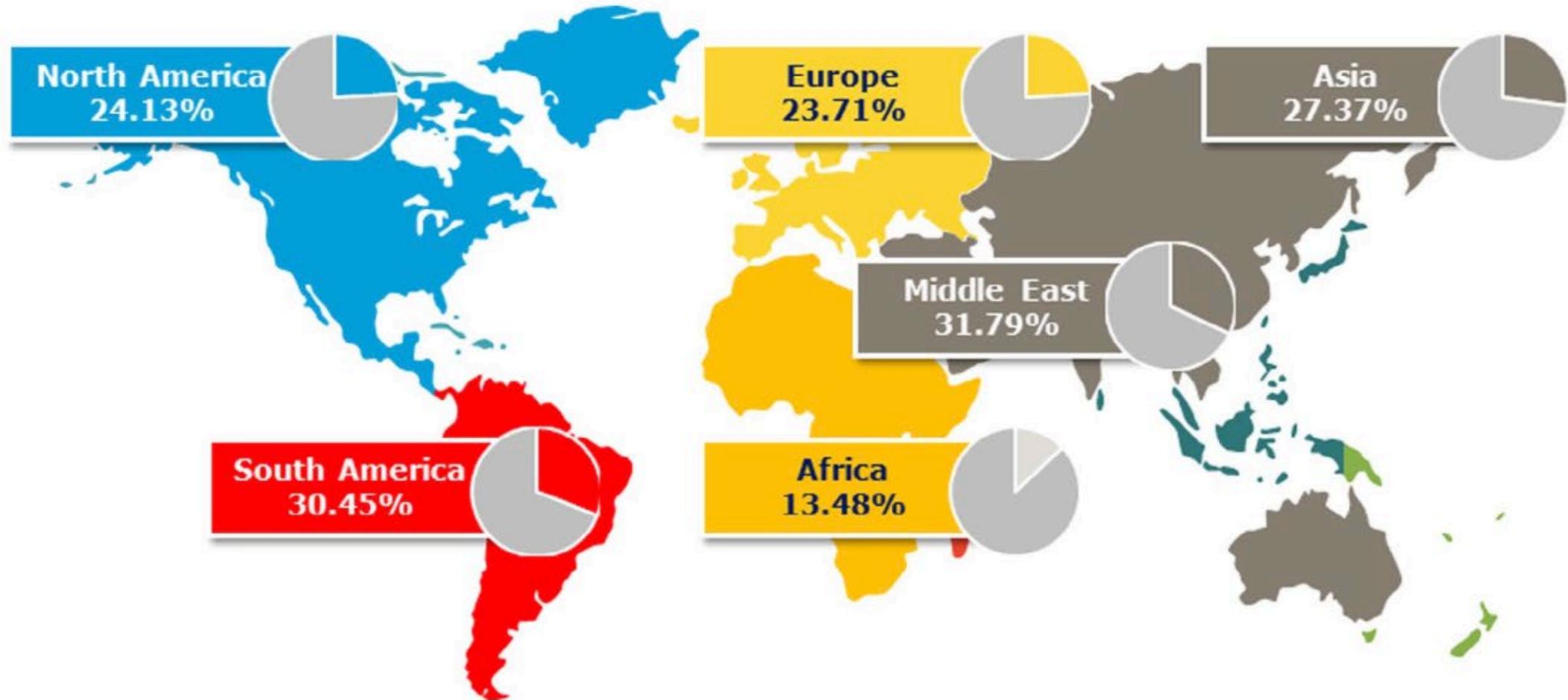


- Simple fatty liver is histologically characterized by macrovesicular steatosis with no additional pathology
- Fatty liver is generally considered benign.

- NASH is histologically advanced fatty liver. It is characterized by steatosis, inflammation, ballooning, Mallory's hyaline, and fibrosis.
- It can lead to cirrhosis and liver failure.



Prevalence of NAFLD



NAFLD is becoming one of the most important causes of liver disease, with an estimated global prevalence rate of **24%**.

Hepatology, Vol.69, No.6, 2019

Risk of Hepatocellular Cancer in Patients With Non-Alcoholic Fatty Liver Disease

Fasiha Kanwal,^{1,2,3} Jennifer R. Kramer,^{2,3} Srikar Mapakshi,^{2,3} Yamini Natarajan,¹ Maneerat Chayanupatkul,¹ Peter A. Richardson,^{2,3} Liang Li,⁴ Roxanne Desiderio,^{2,3} Aaron P. Thrift,^{1,5,6} Steven M. Asch,^{7,8} Jinna Chu,² and Hashem B. El-Serag^{1,2,3}

Gastroenterology 2018;155:1828–1837

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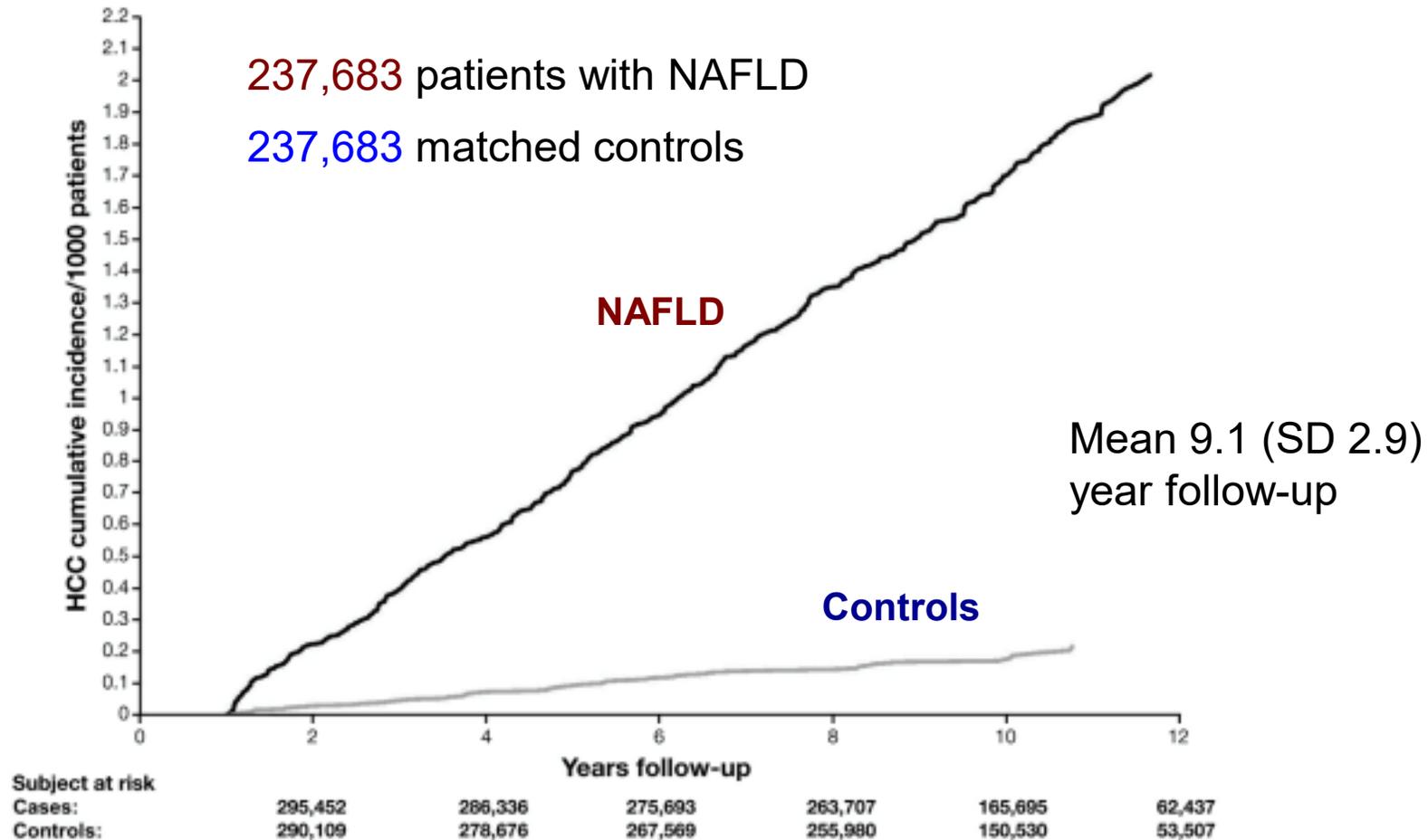
Baseline Characteristics of 237,683 NAFLD Patients

Characteristic	%
Age, mean (SD)	55.5 (13)
Race	
White	69.0
African American	11.4
Hispanic	5.4
Gender	
Men	94.5
Women	5.5

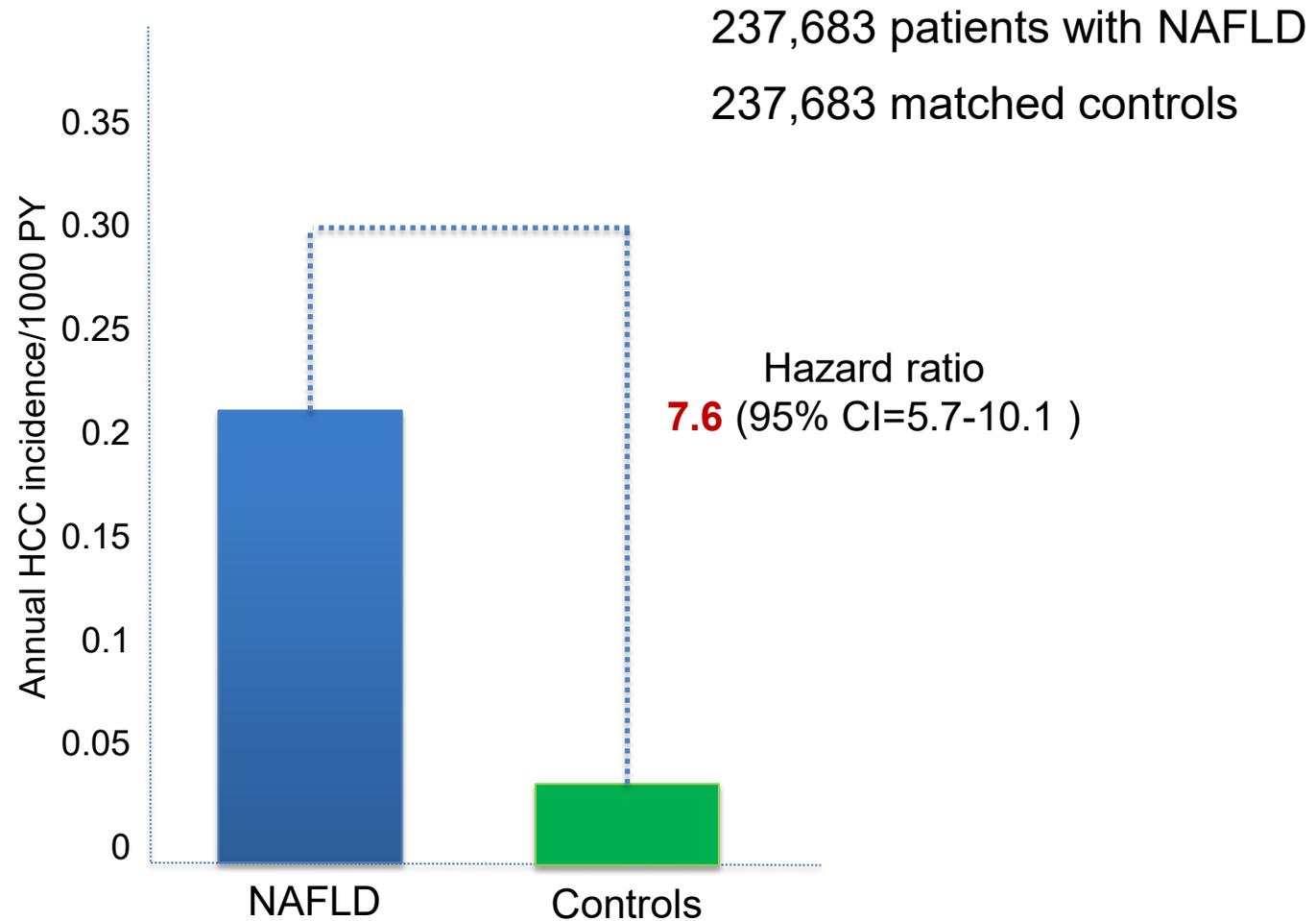
Characteristic	%
Diabetes	30.0
Hypertension	71.8
Dyslipidemia	72.0
BMI, mean (SD)	31.5 (5.6)
Coronary artery disease	21.3
Chronic obstructive lung disease	9.6
APRI, mean (SD)	0.4 (0.46)

APRI: AST to platelet ratio index

HCC in Patients with NAFLD



HCC in Patients with NAFLD



HCC in Patients with NAFLD Cirrhosis

Annual incidence rate of HCC:

0.02 per 1000 PY in controls

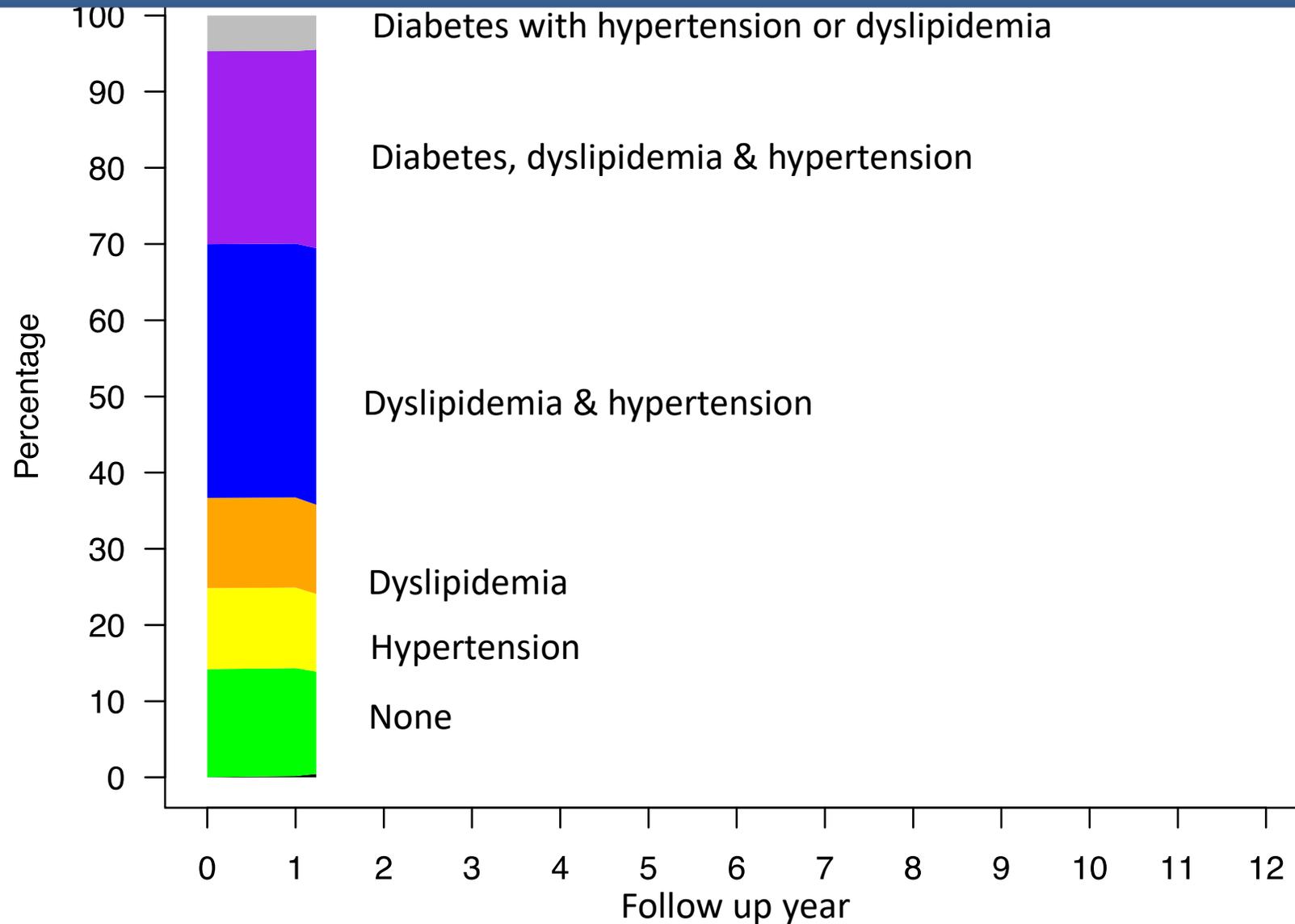
0.08 per 1000 PYs in NAFLD without cirrhosis

10.6 per 1000 PYs in NAFLD with cirrhosis

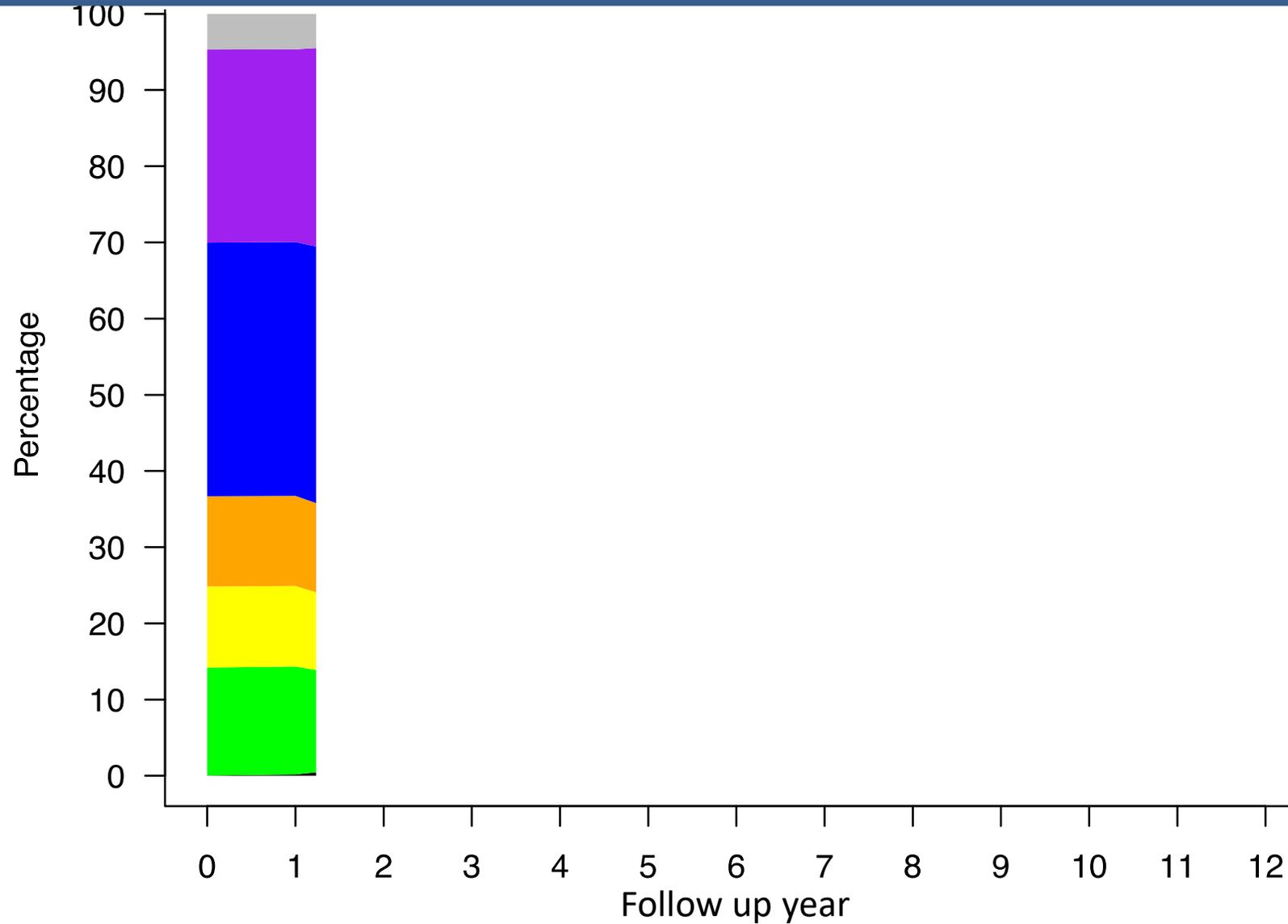
Among patients with NAFLD cirrhosis:

HCC risk ranged from **1.6** to **23.7** per 1000 PYs based on other demographic characteristics

Trends in metabolic traits in NAFLD



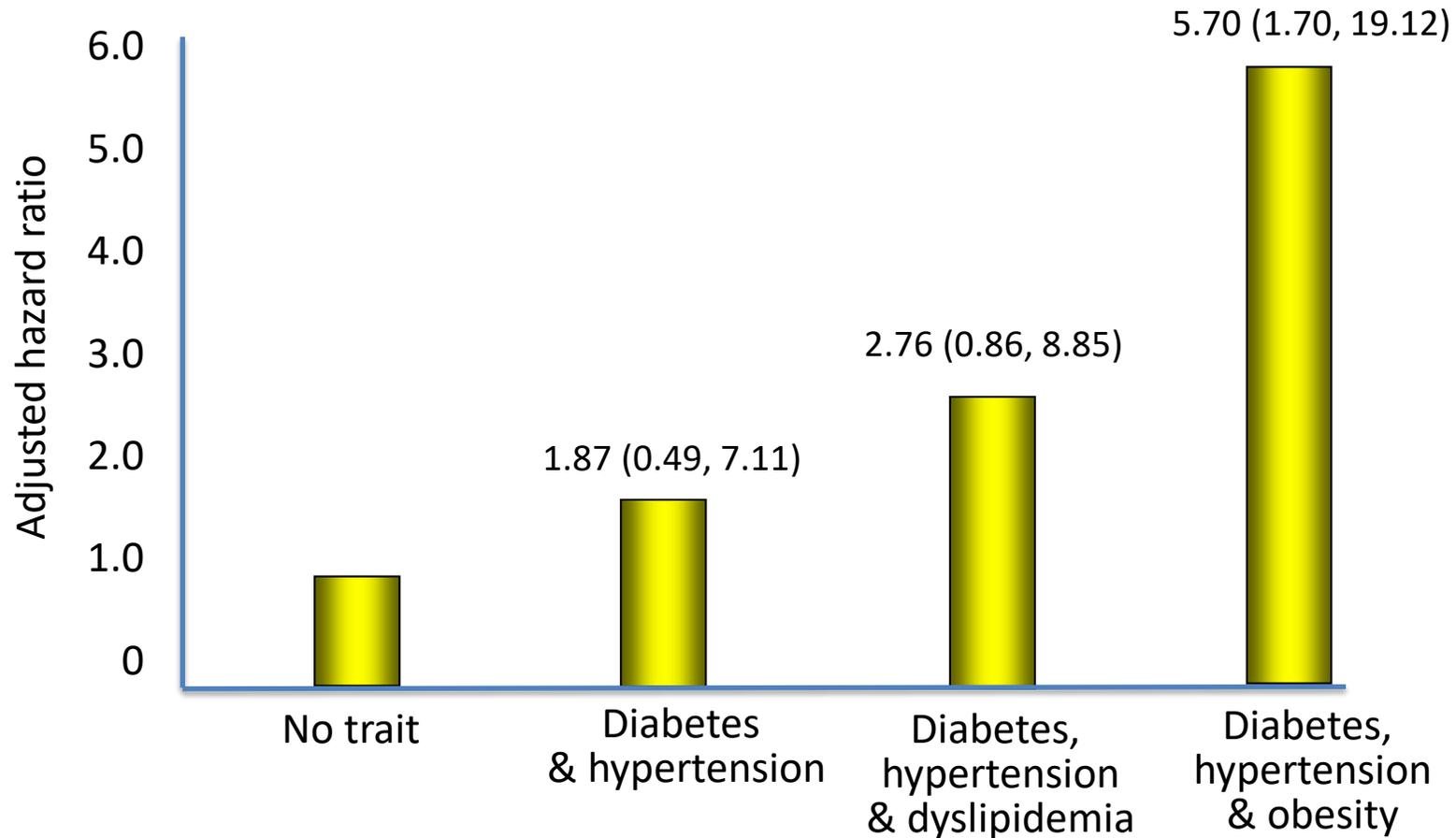
Trends in metabolic traits in NAFLD



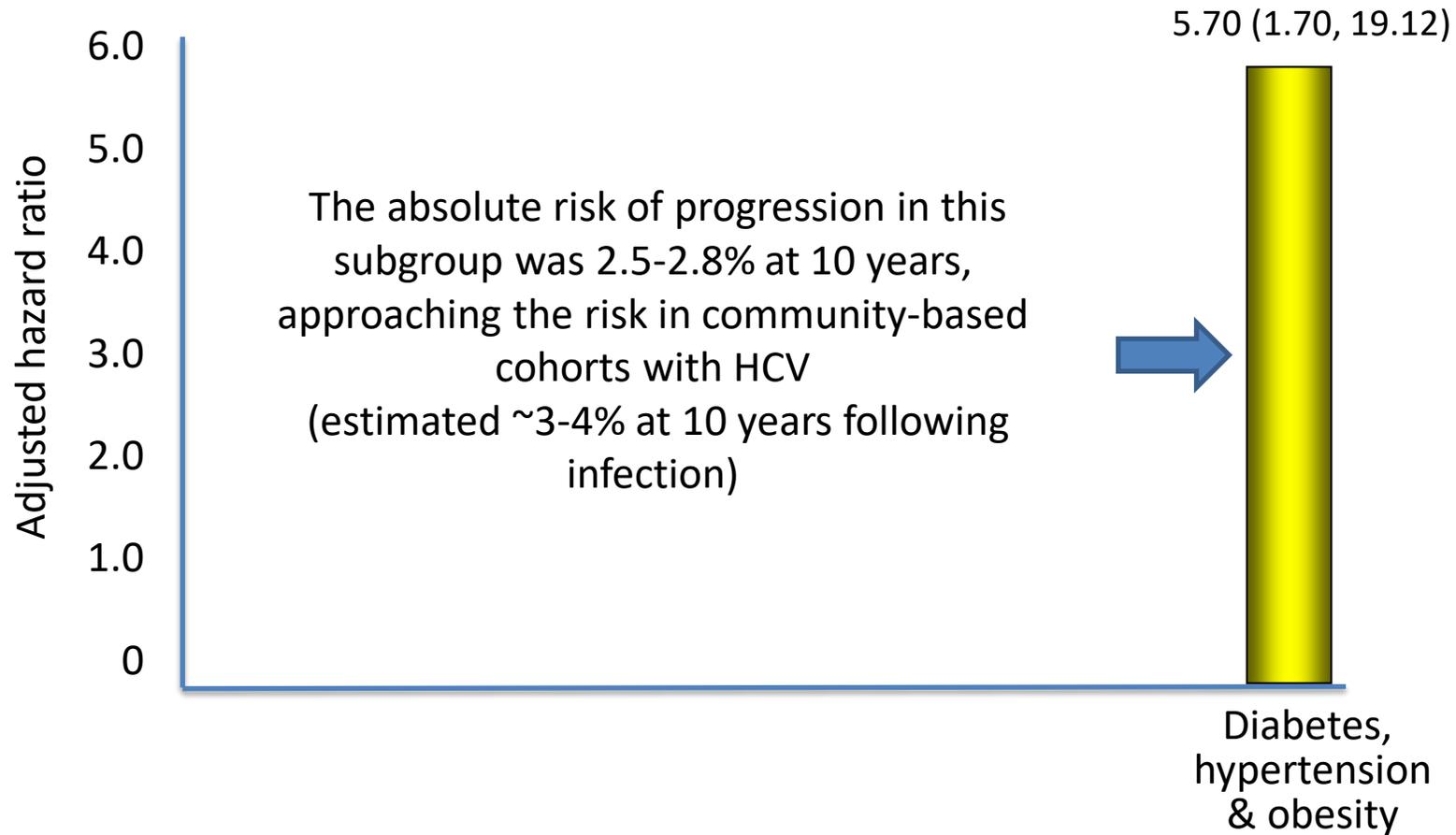
Factors associated with risk of progression to HCC in NAFLD

Characteristics	Adjusted hazard ratio (95% CI)
Age	1.07 (1.06-1.08)
Female	0.55 (0.24-1.23)
Race (ref: white)	
African Americans	0.78 (0.51-1.19)
Hispanic	1.54 (1.01-2.35)
Diabetes	2.80 (2.18-3.59)
Hypertension	1.28 (0.76-2.16)
Dyslipidemia	1.05 (0.76-1.44)
Obesity	1.44 (1.14-1.82)

Additive effect of metabolic traits on progression to HCC



Additive effect of metabolic traits on progression to HCC



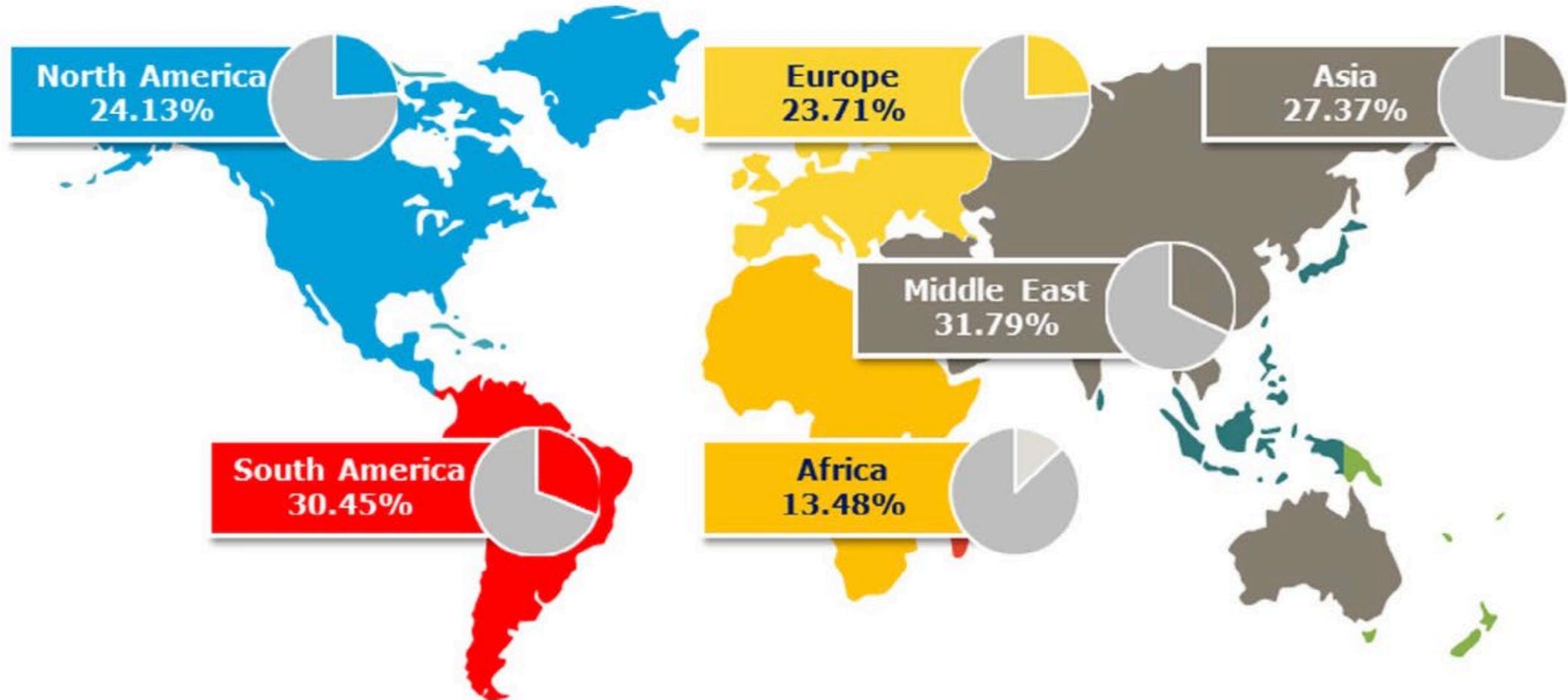
Summary - 1

- Risk of HCC was higher in NAFLD patients than that observed in general clinical population.
- The absolute risk of HCC was higher than the accepted thresholds for HCC surveillance for most patients with NAFLD cirrhosis
- Among metabolic traits, diabetes had the strongest association with HCC
- Diabetic patients with co-existing hypertension and obesity may be important targets for secondary prevention of NAFLD-related HCC

HCV vs. NAFLD

- **Relative Risk of HCC**
 - Compared to NAFLD-controls (7.6 fold)
- **Absolute Risk of HCC**
 - HCC in NAFLD
 - 0.02 per 100 at 9 years
 - HCC in NAFLD-related cirrhosis
 - 1.0 to 2.0 per 100
- **Relative Risk of HCC**
 - Compared to HCV-controls (25 fold)
- **Absolute Risk of HCC**
 - HCC in HCV
 - 1 per 100 at 30 years
 - HCC in HCV-related cirrhosis
 - 3.5 per 100 [1-7]

Prevalence of NAFLD



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Contemporary risk factors for cirrhosis in the U.S

Data from Trans-Texas HCC Consortium (THCCC)

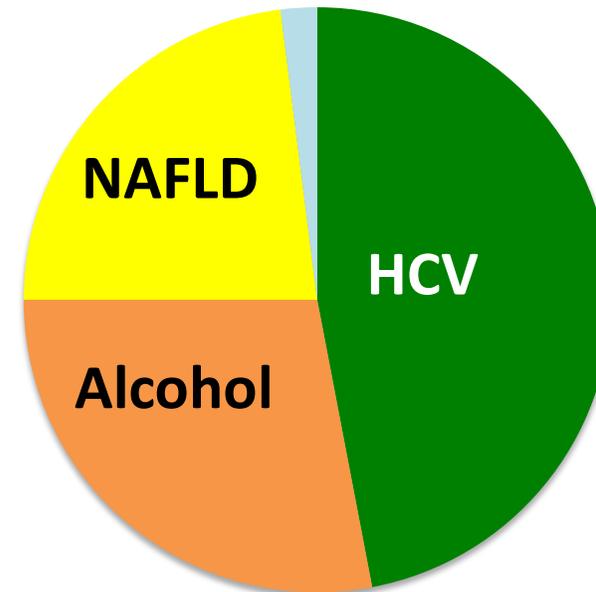
Texas Hepatocellular Carcinoma Consortium – Clinical Recruitment Sites



- Large prospective cohort of patients with cirrhosis
- Started in 5 centers (2016)
 - Extended to 7 centers (2019)

Etiology of cirrhosis

- 33.1% cured hepatitis C virus infection (HCV)
- 30.0% alcohol
- 23.3%** nonalcoholic fatty liver disease
- 16.1% active HCV
- 2.5% hepatitis B virus (HBV) infection



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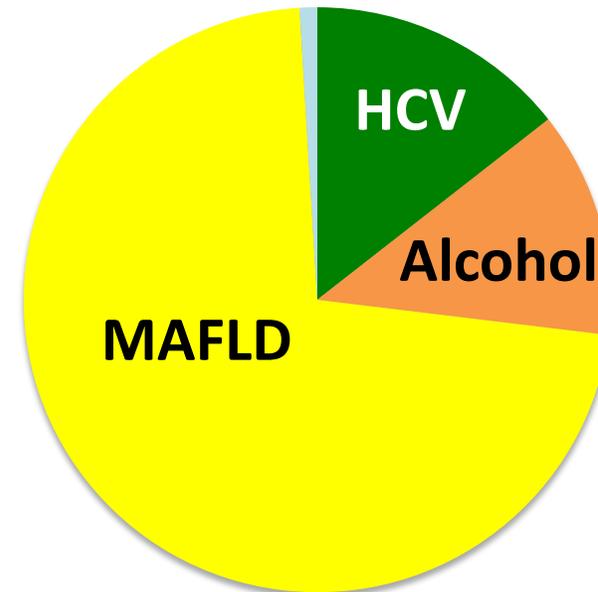


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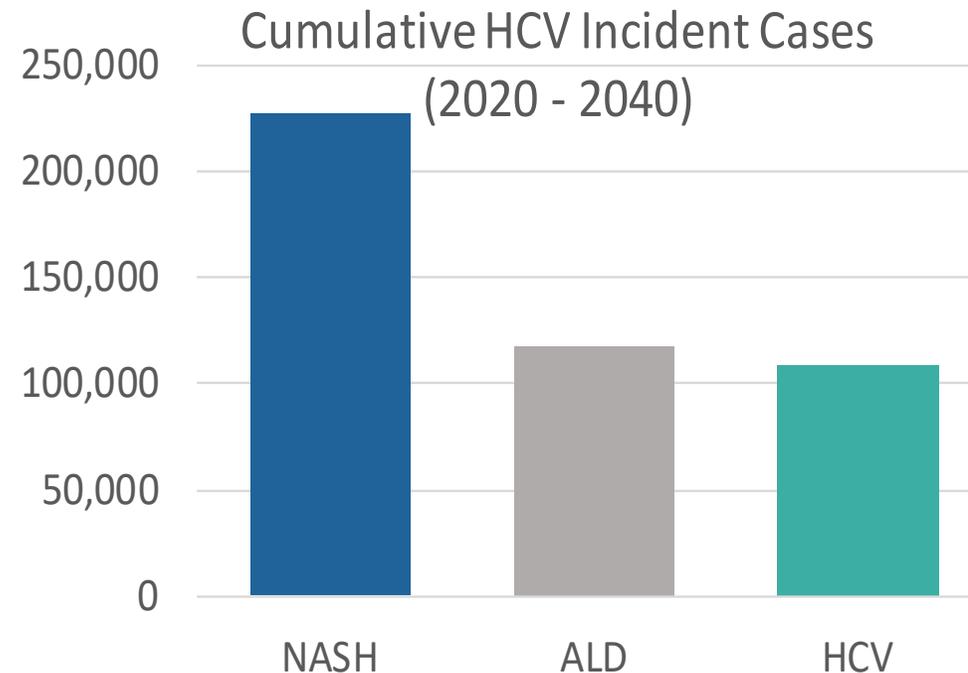
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75% has metabolic dysfunction without other active risk factors



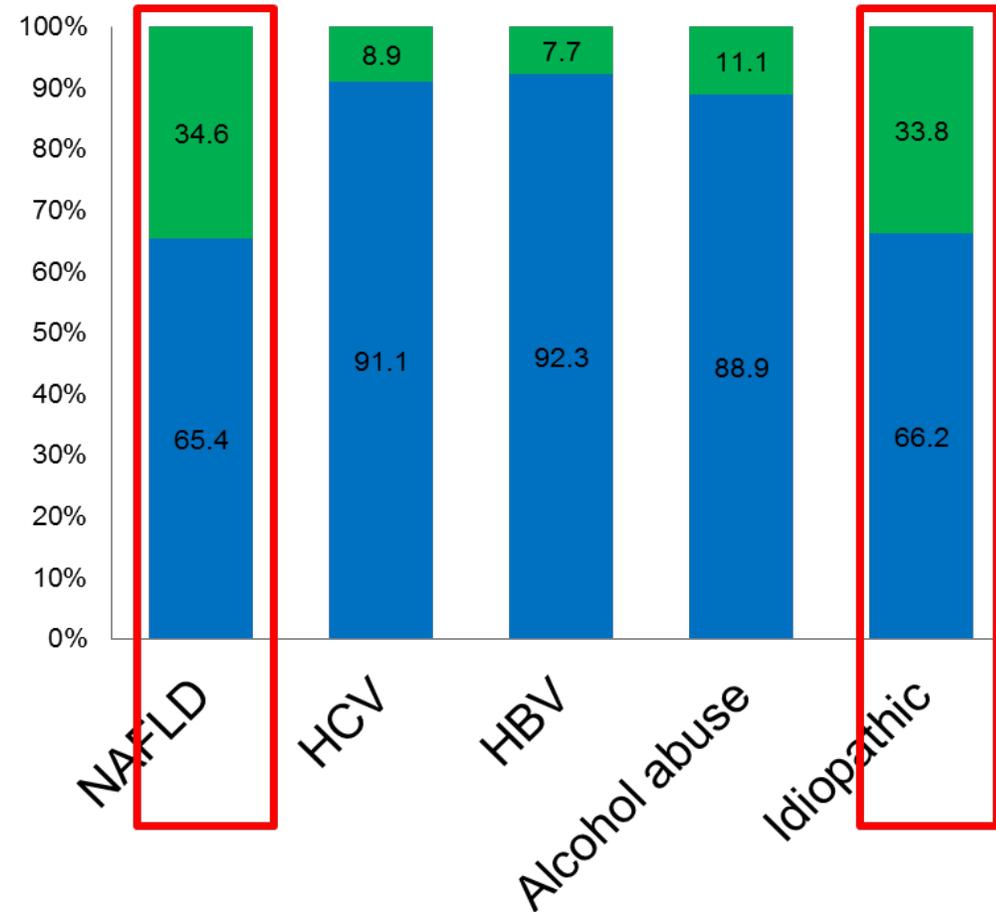
Mathematical models project that NAFLD will account for 48% of the HCC burden, **becoming the leading cause of HCC in the U.S in the next 2 decades**



- Dyson observed a 10-fold increase in MAFLD-HCC between 2000 and 2010 in Newcastle, U.K.
- A recent study estimated MAFLD will result in 135,000 HCC cases in the U.S. between 2015 and 2030

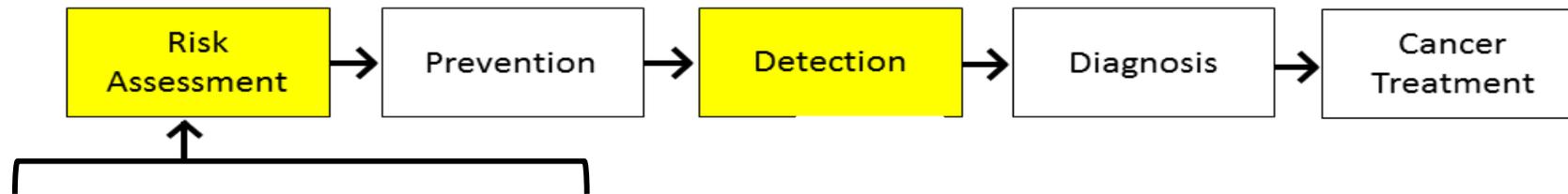
HCC can occur in the absence of cirrhosis in NAFLD

- 1500 patients with HCC seen in the VA (2005-2020)
- About 13% of patients with HCC in the VA did not have cirrhosis.
- NAFLD was the main risk factor for HCC in the absence of cirrhosis (odds ratio, 5.4, 95% CI, 3.4-8.5)



Challenges in reducing NAFLD HCC-related mortality

Quality of Cancer Care Continuum (QCCC)



90%
patients with
NAFLD and
fibrosis are
undiagnosed

Systematic **risk assessment** of patients with risk factors for NAFLD to diagnose cirrhosis

0.2-2.4%
In patients
with NAFLD
cirrhosis, the
annual risk of
HCC is variable

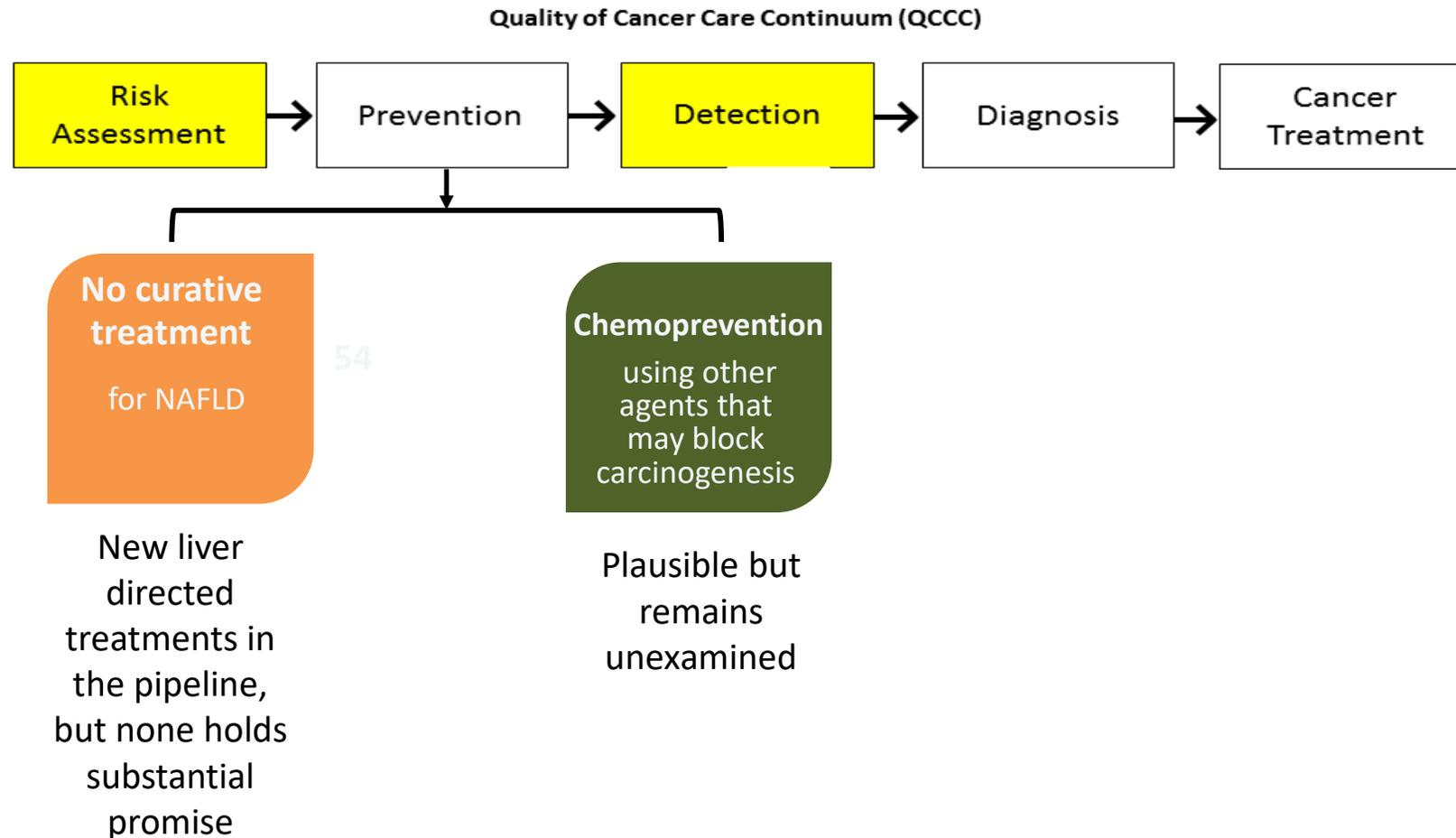
Better **risk stratification** to match prevention and early detection efforts to patients' risk of HCC

20-30%
patients with
NAFLD HCC do
not have
cirrhosis

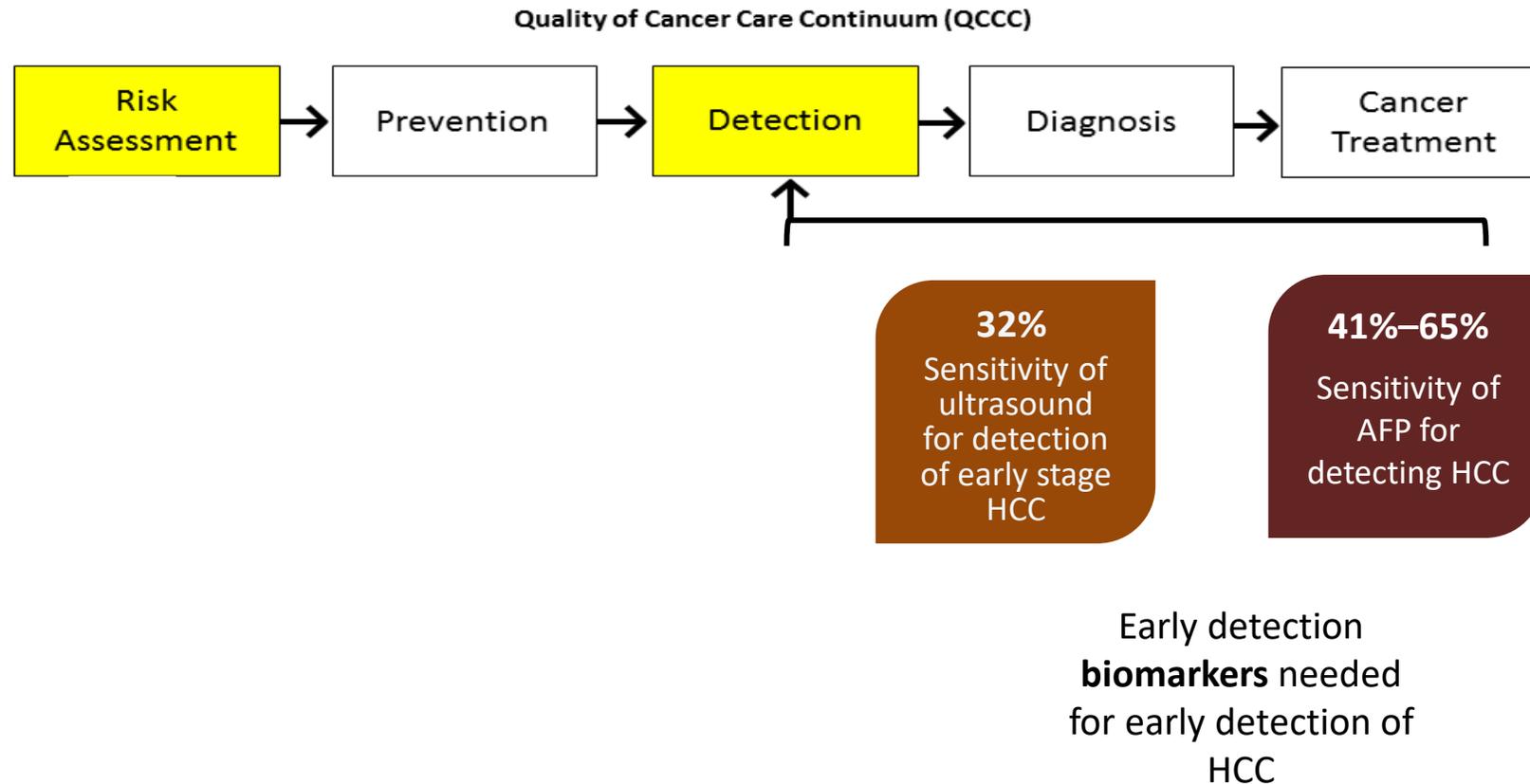
Novel **biomarkers** and tools needed for the newer groups of patients (with NAFLD)

Zaman SN, Cancer 1990;65:1607-1
Walker M, Kanwal F. APT 2016
Kanwal F, El-Serag H, Gastroenterology 2018

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Summary - 2

- NAFLD is projected to become the leading etiology of HCC in the U.S
- The absolute risk of HCC is higher than the accepted thresholds for HCC surveillance for most patients with NAFLD cirrhosis
- However, 20-30% of NAFLD-HCC develop in patients without cirrhosis. However, the absolute risk is low in the subgroup without cirrhosis
- Diabetes had the strongest association with HCC; these patients may be important targets for secondary prevention
- Several gaps exist in the NAFLD-HCC care continuum. The early steps in the continuum serve as important, high-yield targets for research

NAFLD and Risk of HCC Based on Cohort Studies

Reference	Country	NAFLD (N)	Cirrhosis %	HCC (N)	Mean follow up (yr)
Clinical					
Hui	Australia	23	100	0	7
Kojima	Japan	24	100	9	5.7
Ratziu	France	41	100	8 (3 incident)	Max 5
Yatsuji	Japan	68	100	21 (7 incident)	3.1
Ekstedt	Sweden	129	3	0	13.7
Sanyal	USA	152	100	10 (7 incident)	10
Dam-Larsen	Copenhagen	170	0	0	20
Ascha	USA	195	100	25	6.9
Bhala	Multinational	247	52	6	7.1
Soderberg	Sweden	256	7	5	8.7
Angulo	Multinational	320	51	3	8.6
Hashimoto	Japan	392	35	23 (11 incident)	3.3
Arase	Japan	1600	NR	10	8.2
Kawamura	Japan	6508	NR	16	5.6
Population based					
Adams ³⁶	USA	435	NR	2	7.6
Ong ³⁷	USA	817	NR	0	8.7