

Paris MASH Meeting 2025

September 11 & 12

11th EDITION



PARIS
MASH
MEETING

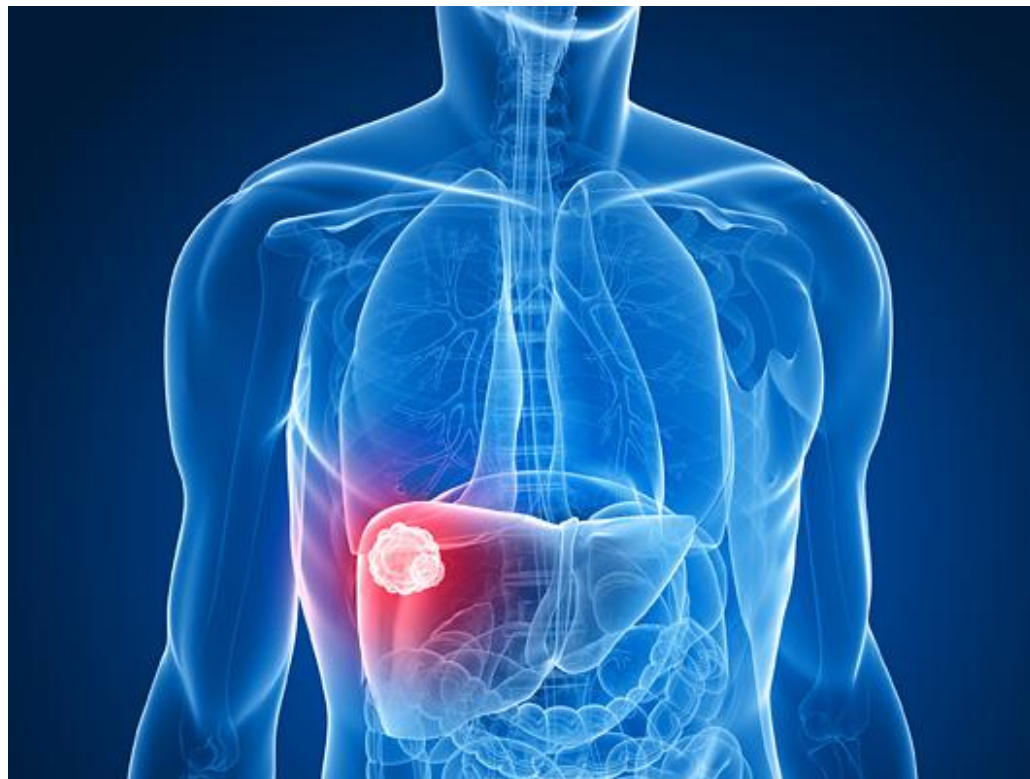


Mechanistic implications of MASLD as etiology of HCC on checkpoint inhibitor therapies

Peter R. Galle

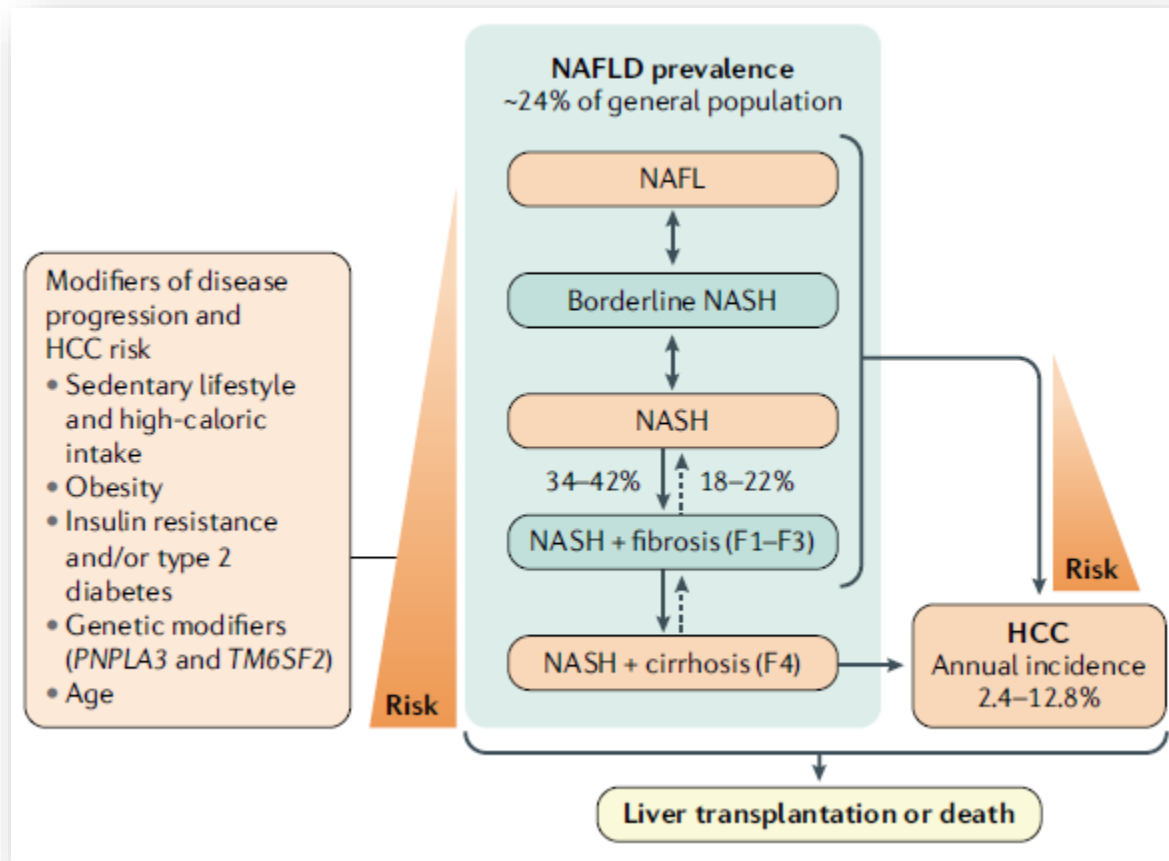
Disclosures

- Bayer
- BMS
- MSD
- AstraZeneca
- SIRTEX
- Merck
- Lilly
- Blueprint
- Adaptimmune
- Eisai
- Roche
- Ipsen
- Gilead

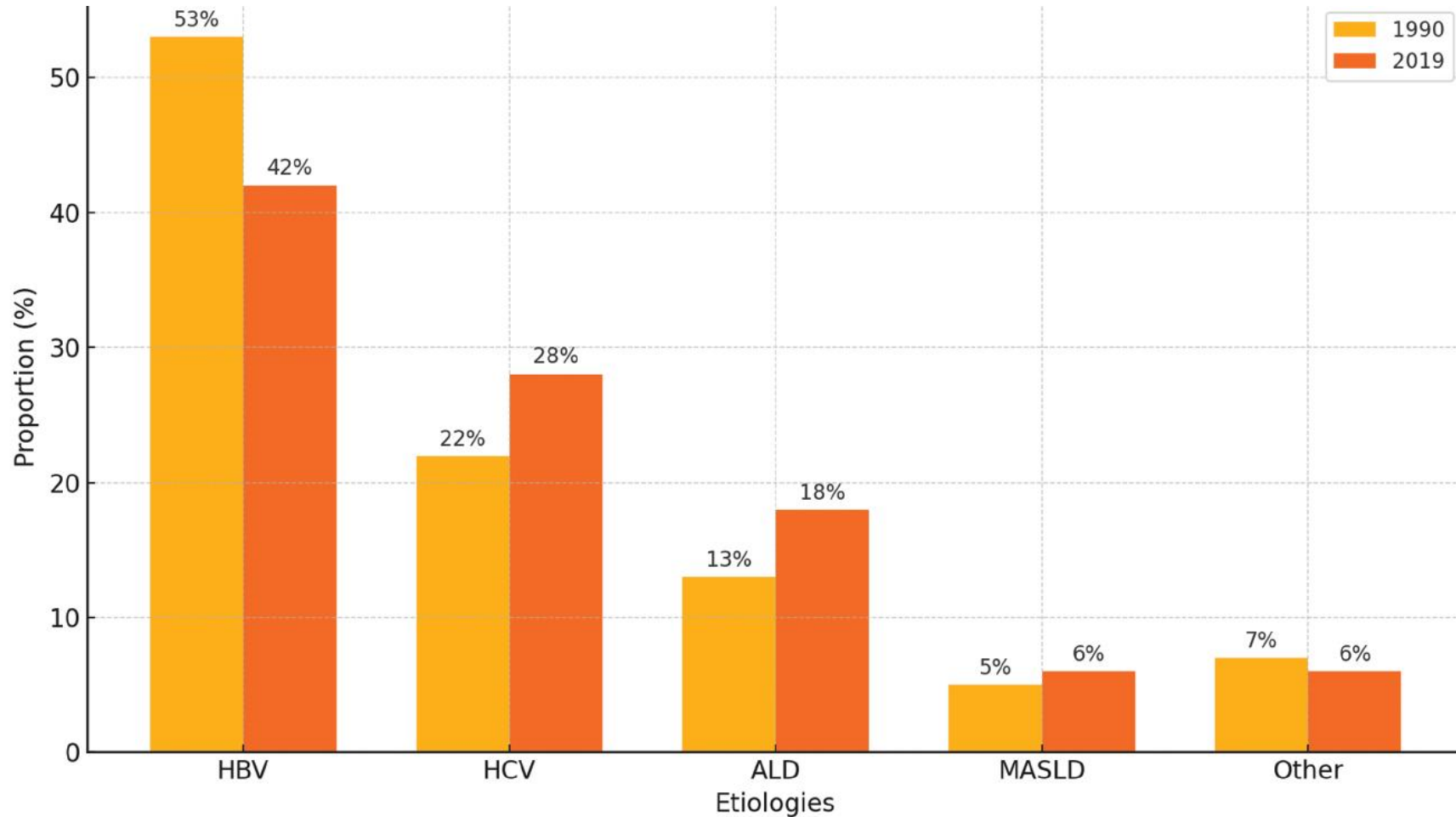


The NAFLD – NASH – HCC sequence

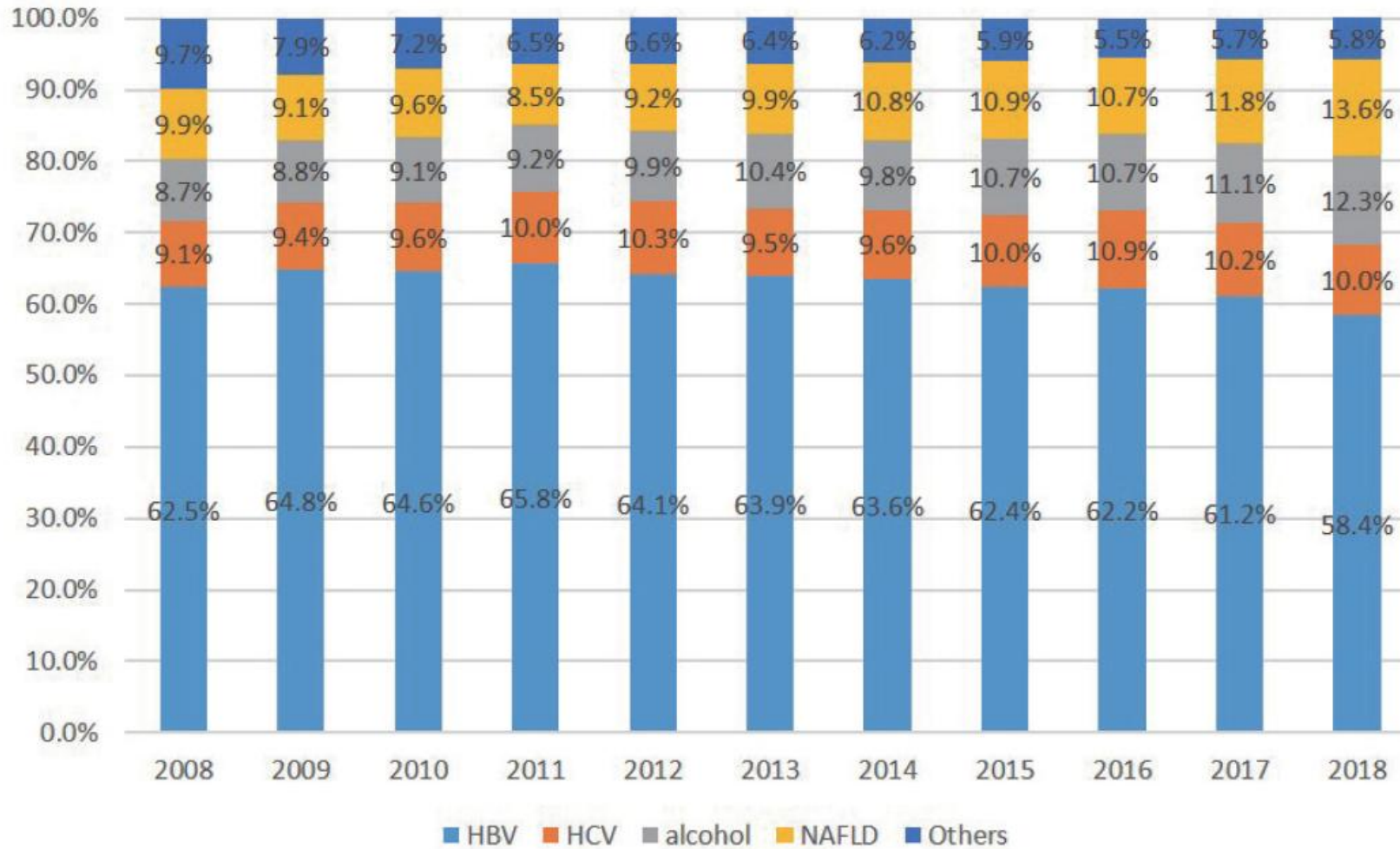
The MASLD – MASH – HCC sequence



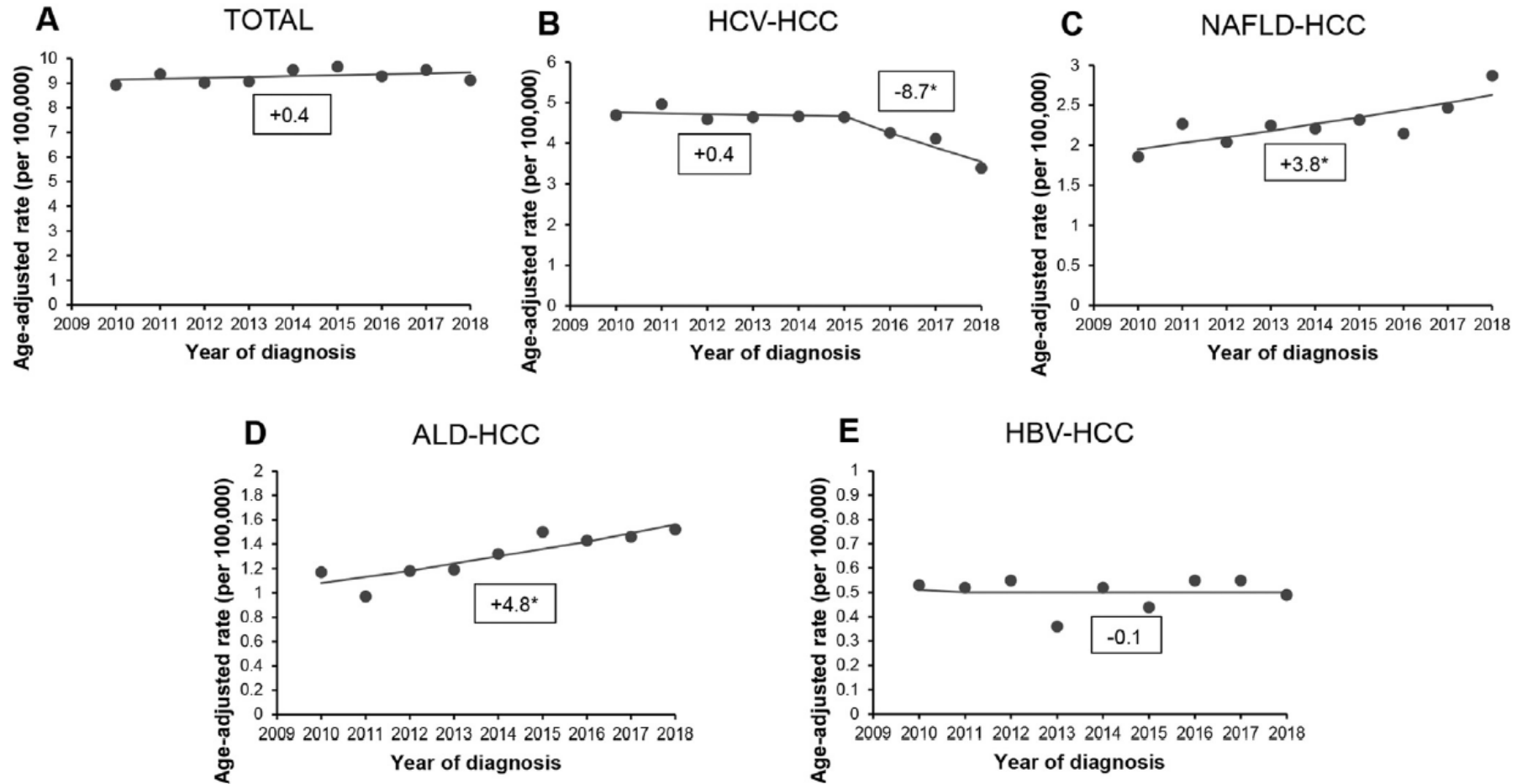
The proportion of HCC etiologies globally, between 1990 and 2019



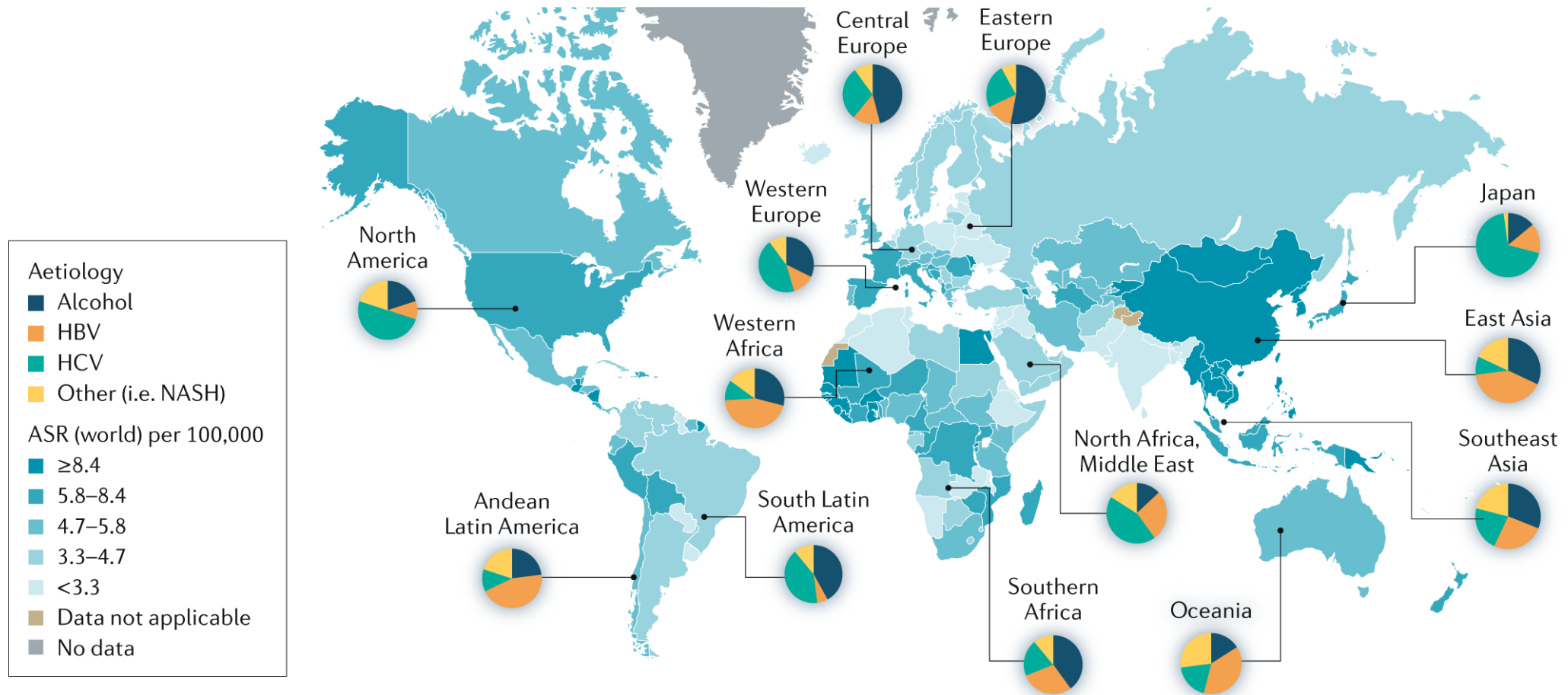
Distribution of HCC etiologies demonstrating increase of NAFLD between 2008 and 2018 in South Korea



Trends in HCC AAIRs for all race/ethnicities combined in men in Florida 2010–2018



Increasing MASH-HCC incidence



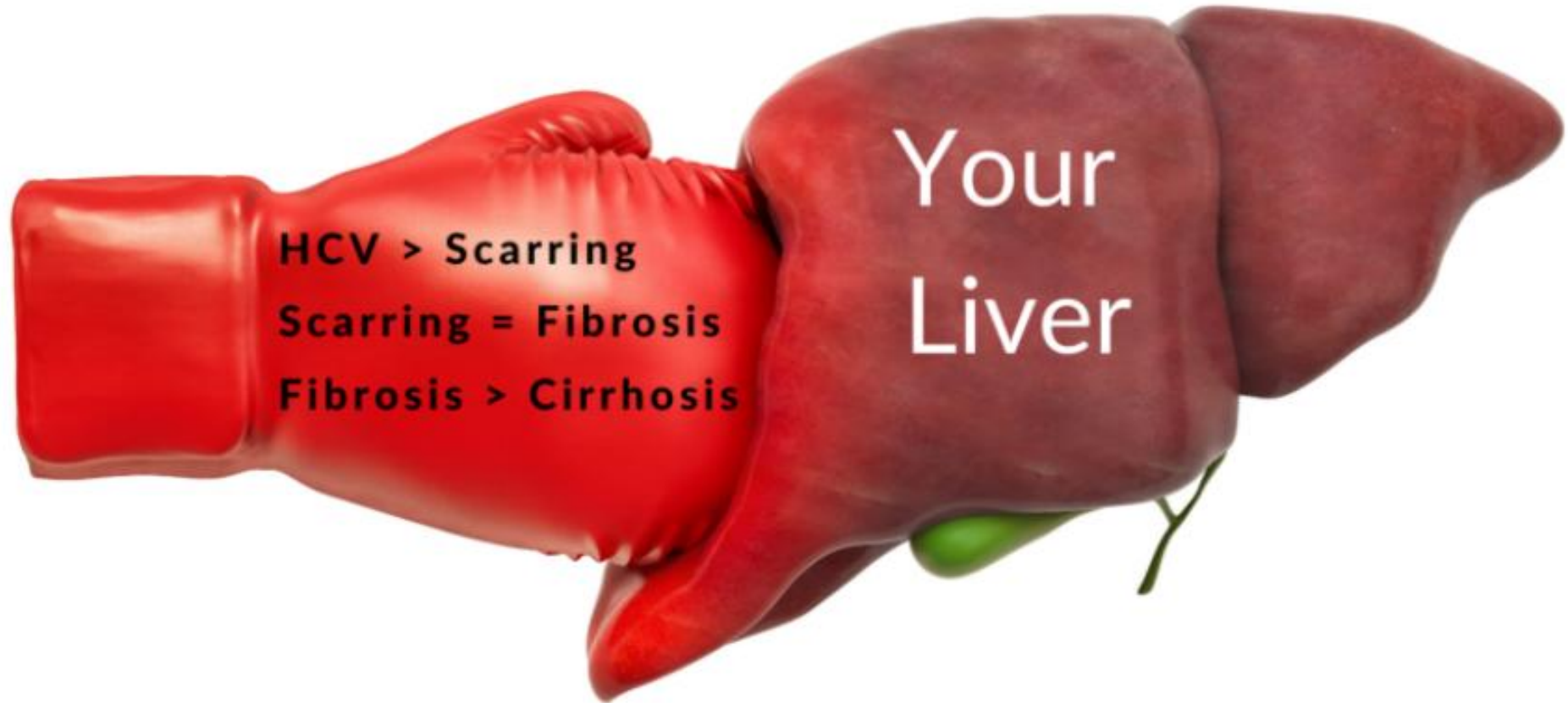
Prediction: Most frequent etiology in developed countries from 2030 onwards

HCC as a leading cause of death

Table 2. Liver cancer age-adjusted^a mortality rates per 100,000 by detailed race/ethnicity in California, Florida, New York (2012-2016).

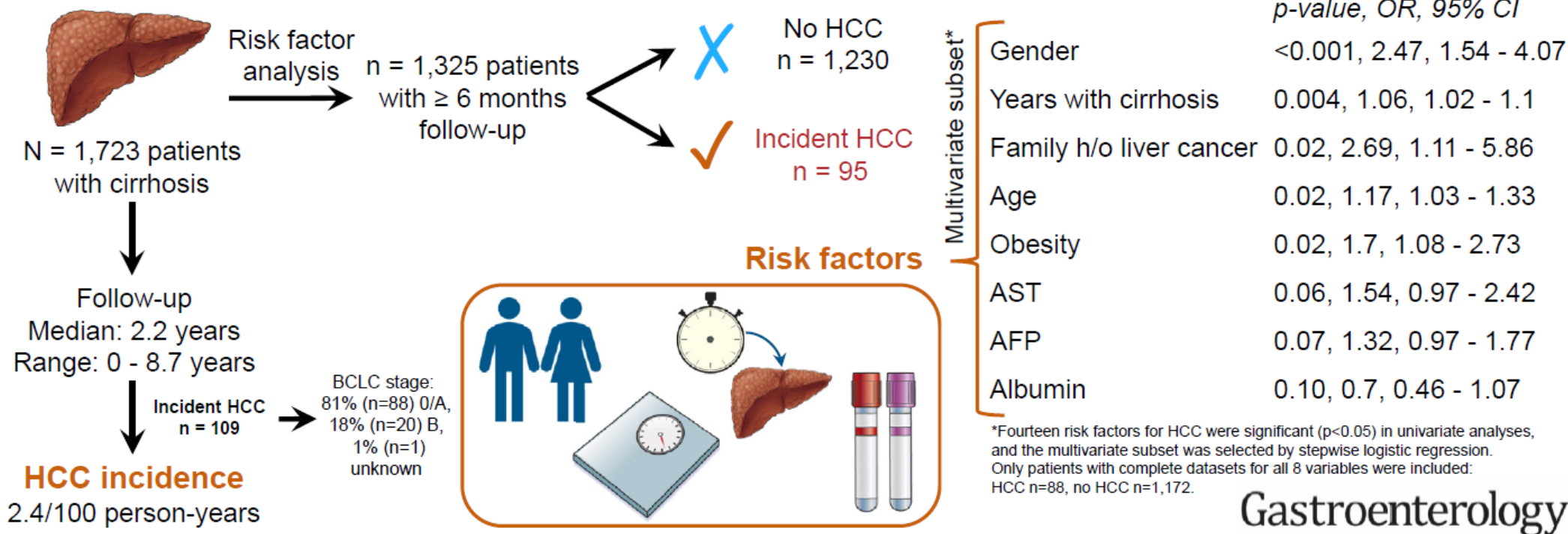
	AAMR ^b by State			Pooled 3 States				Cause of cancer death rank
	California	Florida	New York	Total AAMR ^b	1945-1965 birth cohort AAMR ^b	Older ^c cohort AAMR ^b	1945-1965 birth cohort AAMR/Total AAMR ^b	
Male								
All-populations-combined ^d	11.3	9.1	9.2	10.6	5.0	5.2	47%	5
White	8.6	9.0	7.5	8.5	4.2	4.0	50%	5
Black ^e	13.8	10.3	12.5	12.1	6.7	4.8	55%	4
African American	14.0	11.7	13.0	12.9	7.7	4.9	59%	4
Afro-Caribbean		6.8	7.0	6.6	2.3	3.4	35%	6
Hispanic ^f	14.9	9.1	13.0	13.0	5.9	6.7	46%	4
Mexican	15.6	13.5	10.2	15.4	7.0	8.0	46%	2
Mexican American	23.1	24.2		23.0	11.9	10.4	52%	1
Mexican Immigrant	11.0			10.9	4.3	6.3	39%	4
Puerto Rican		16.2	20.6	17.6	9.6	7.6	54%	2
Cuban		6.4		6.6	2.9	3.5	44%	5
South/Central American	13.5	9.1	9.2	10.9	3.6	7.0	33%	4
Dominican			8.5	7.9	3.3	4.5	42%	4

What knocks out our Liver?



Incidence and Risk Factors for Hepatocellular Carcinoma in Cirrhosis

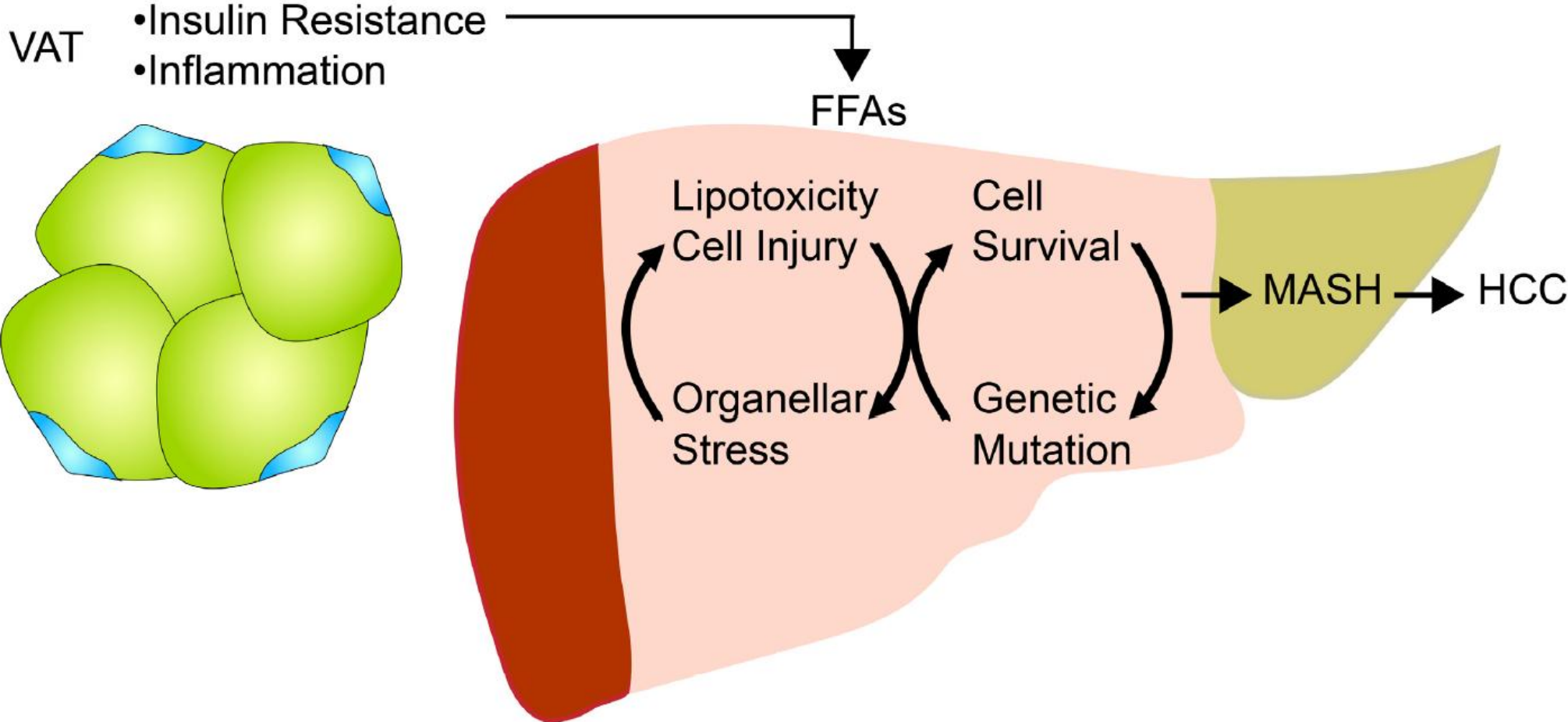
Incidence and Risk Factors for Hepatocellular Carcinoma in Cirrhosis: the Multi-center Hepatocellular Carcinoma Early Detection Strategy (HEDS) Study



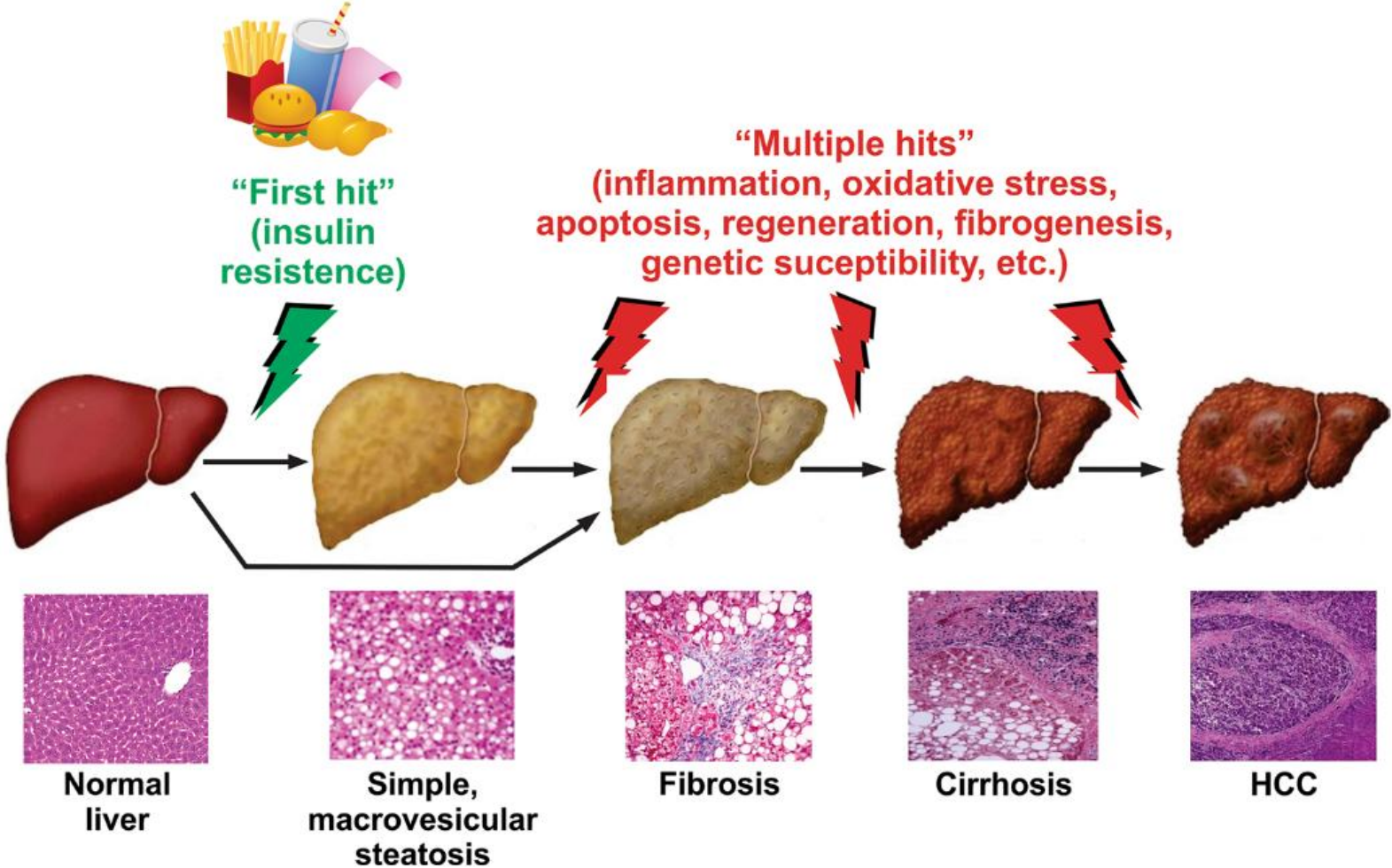
Gastroenterology

Are all HCCs created equal?

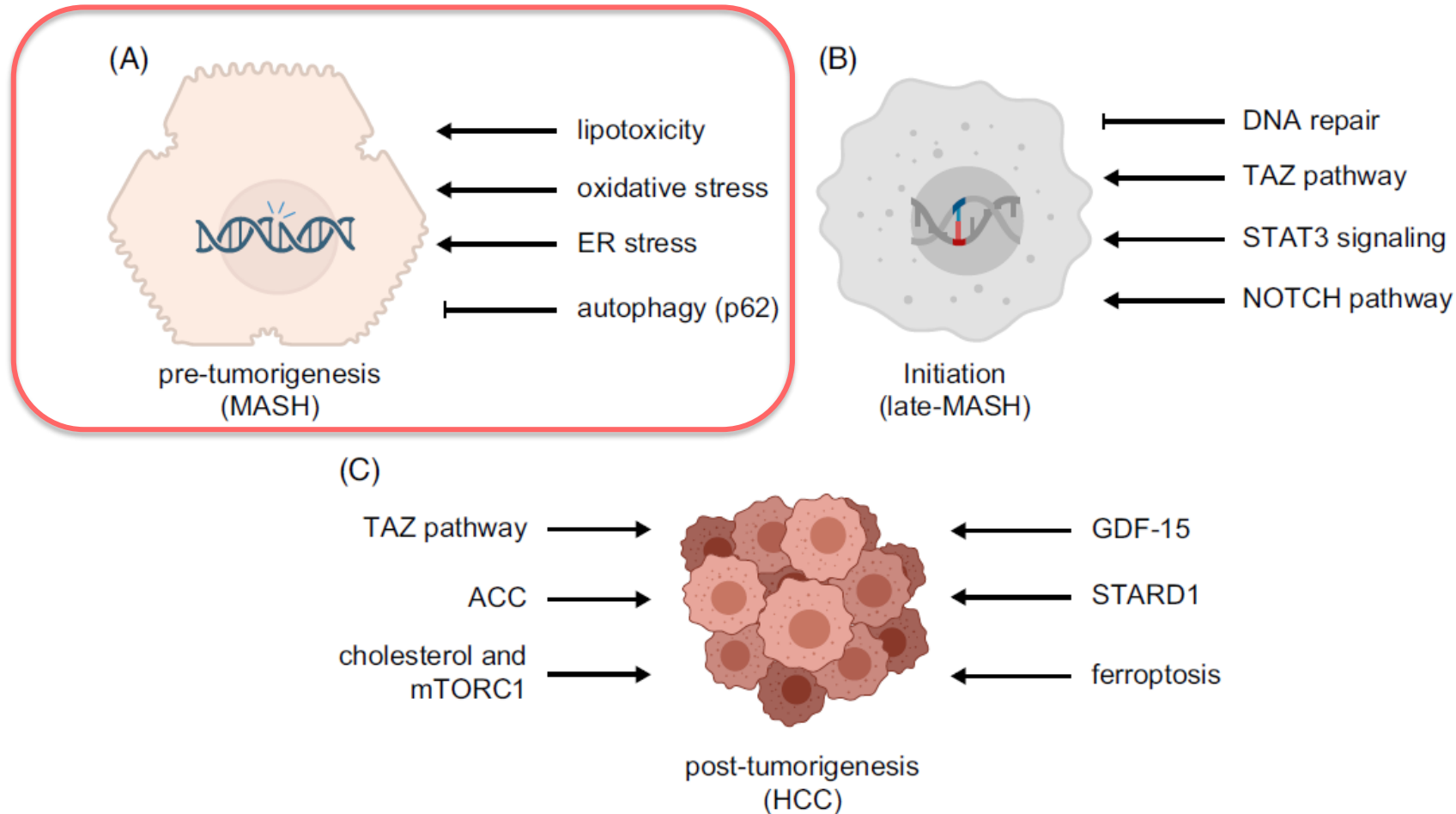
Pathophysiological course of MASH-derived HCC



Multiple-hit theory of clinical progression of NAFLD



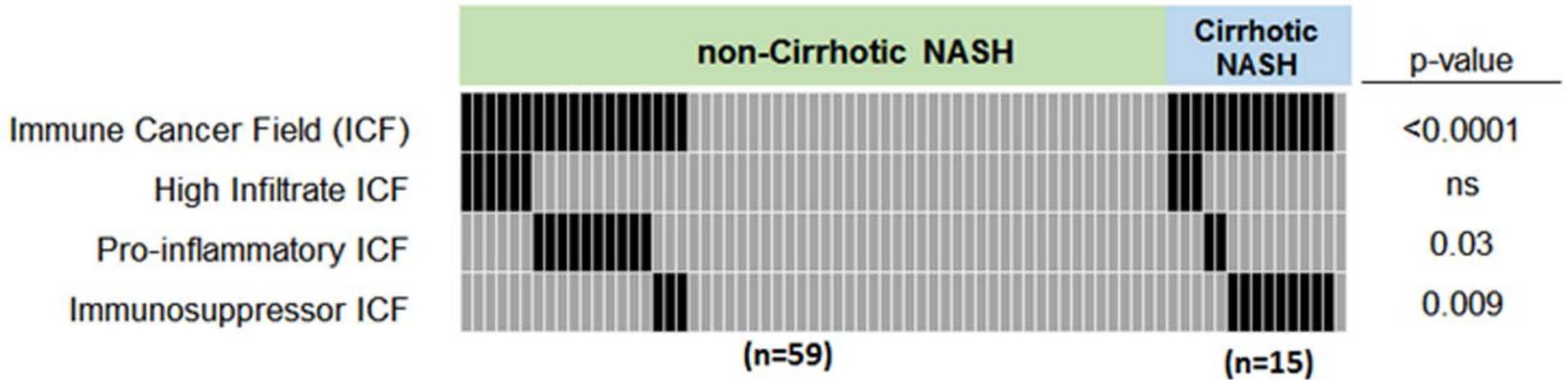
Molecular Mechanisms in MASLD and MASLD-related HCC



Pre-tumorigenesis (MASH): SNPs associated with NAFLD/NASH-related HCC

Gene	Variant	Normal protein function and variant mechanism	NAFLD/NASH OR (95% CI)	NAFLD/NASH-related HCC OR (95% CI)
<i>PNPLA3</i> (refs. ^{15,102,108,109})	rs738409 c.444C>G p.I148M	WT: regulates lipid droplets in hepatocytes Variant: protein ubiquitination is impaired, resulting in the accumulation of hepatic lipid droplets that promote hepatic steatosis	OR for the G allele in patients with NASH 2.05 (1.86–2.27) versus healthy controls	OR for the G allele in patients with NAFLD-related HCC 2.26 (1.23–4.14) versus patients with NAFLD alone
<i>TM6SF2</i> (refs. ^{102,103,110,111})	rs58542926 c.449C>T p.E167K	WT: regulates liver fat metabolism Variant: associated with upregulation of cholesterol and fatty acid biosynthesis pathways	OR for the T allele in patients with NASH 1.61 (1.34–1.92) versus healthy controls	OR for the T allele in patients with NAFLD-related HCC 1.92 (1.31–2.81) versus patients with NAFLD alone
<i>MBOAT7</i> (refs. ^{104,105,112})	rs641738 C>T p.G17E	WT: participates in the regulation of triglyceride metabolism Variant: associated with increased hepatic triglyceride content and steatosis development	OR for the T allele 1.18 (1.00–1.40) versus C allele in patients with NASH	OR for the T allele in NAFLD-related HCC 2.10 (1.33–3.31) versus patients with NAFLD alone
<i>GCKR</i> ^{106,107,113}	rs1260326 c.1337C>T p.P446L	WT: regulates glucokinase activity Variant: modulates insulin resistance and inflammatory markers on interaction with plasma n-3 PUFAs	OR for the T allele in patients with NASH 1.55 (1.10–2.17) versus healthy controls	OR for the T allele in patients with NASH-related HCC 1.84 (1.23–2.75) versus general population

Cirrhotic NASH showed a significantly higher prevalence of an immunosuppressive pro-carcinogenic cancer field



immunosuppressive ICF subtype:
activation of stroma and transforming growth factor (TGF) β

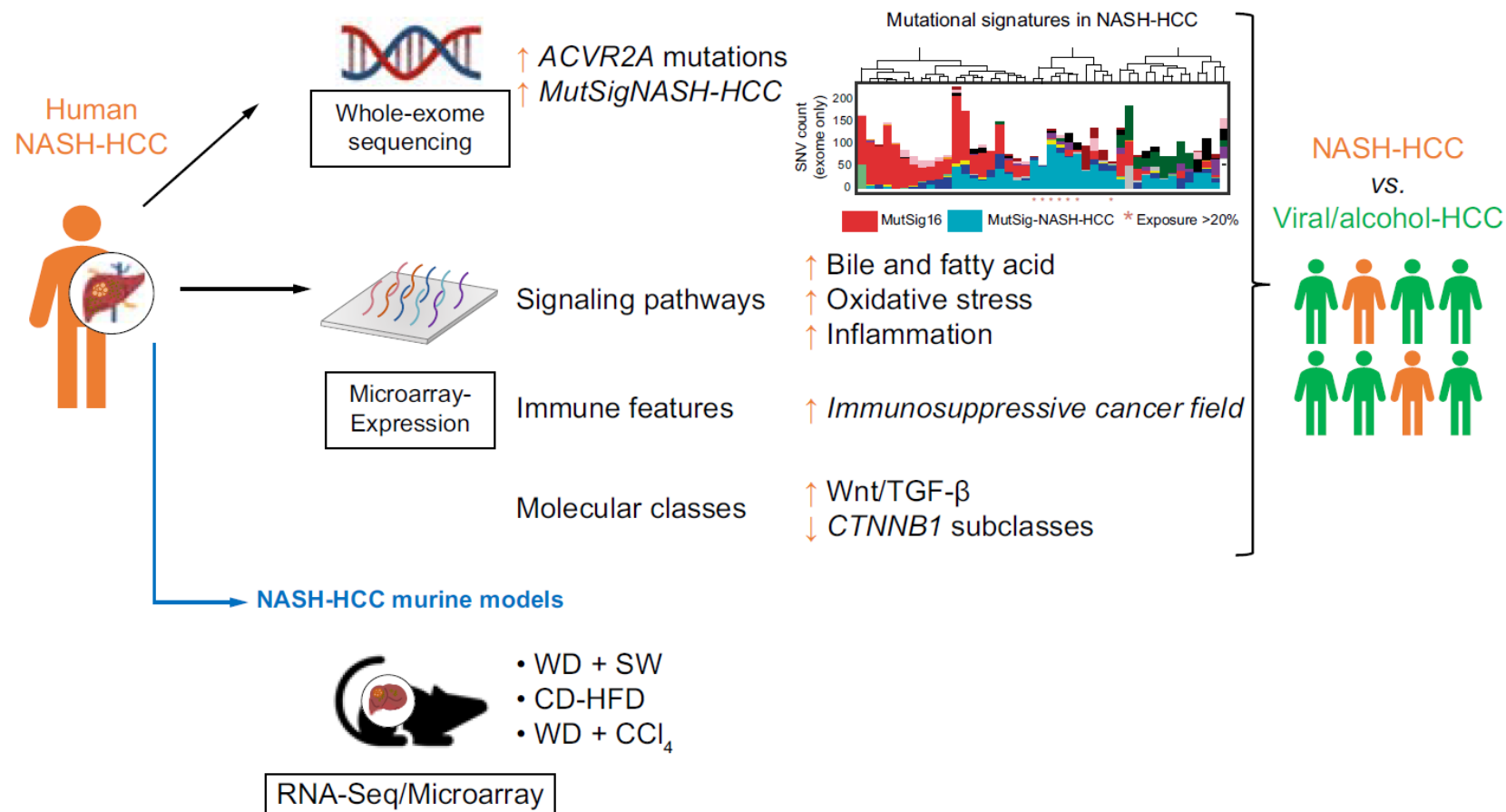
Genetic predisposition for HCC in MASLD/MASH patients

Reference	Score	Outcome	AUROC	Sensitivity	Specificity
Donati et al.	HCC risk score: Age, sex, obesity, T2DM, severe fibrosis, number of risk alleles (PNPLA3 I148M, TM6SF2 E167K, and MBOAT7 rs641738 C > T risk variants)	Prediction of HCC	0.96 ± 0.04	96%	89%
Bianco et al.	PRS-HFC: PNPLA3, TM6SF2, MBOAT7 and GCKR risk alleles	Prediction of HCC	0.61	43%	80%
	PRS-5: PRS adjusted for the rs72013567 HSD17B13 variant	Prediction of HCC	0.65	43%	79%
Pennisi et al.	GEMS score: Sex, age, diabetes, HDL, albumin, PLT and PNPLA3, TM6SF2, HSD17B13 genotype	Prediction of liver-related events	0.87	Not available	Not available

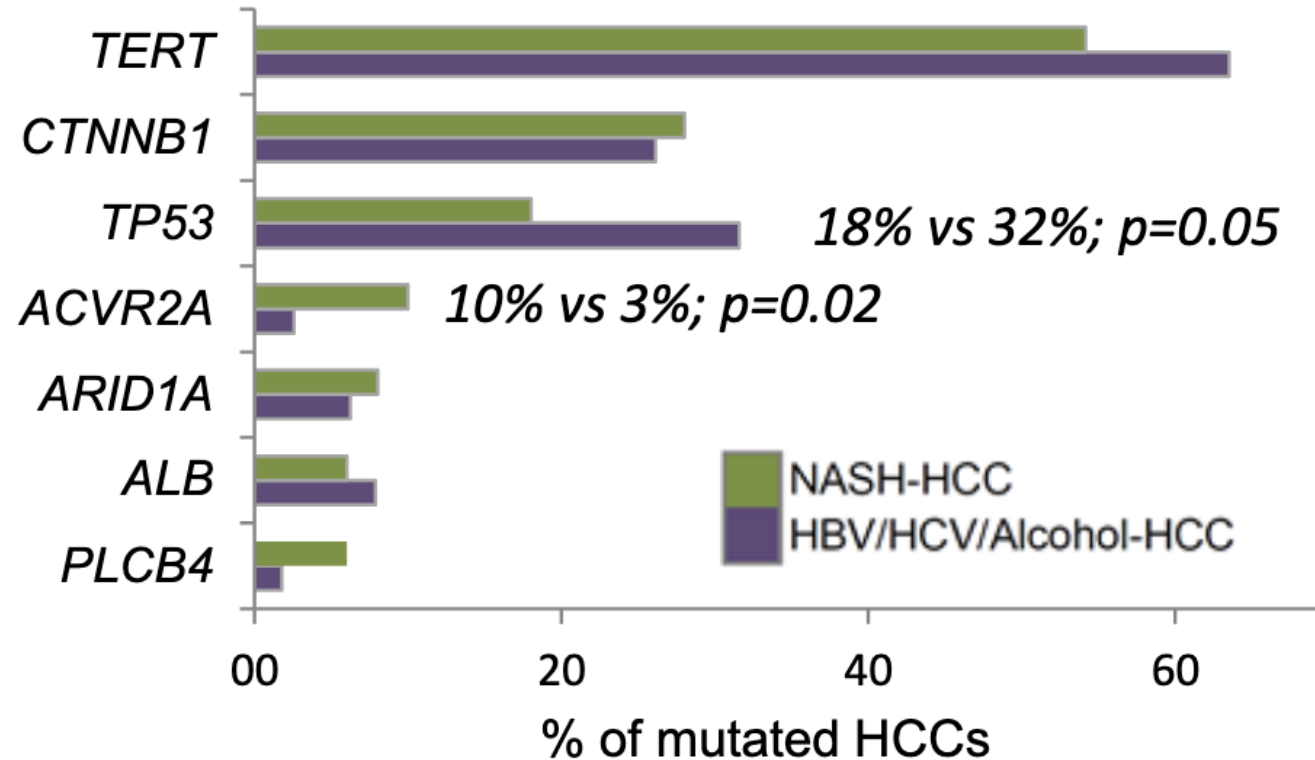
No clinical relevance so far!

Initiation (late MASH/HCC):

Molecular characterisation of hepatocellular carcinoma in patients with non-alcoholic steatohepatitis



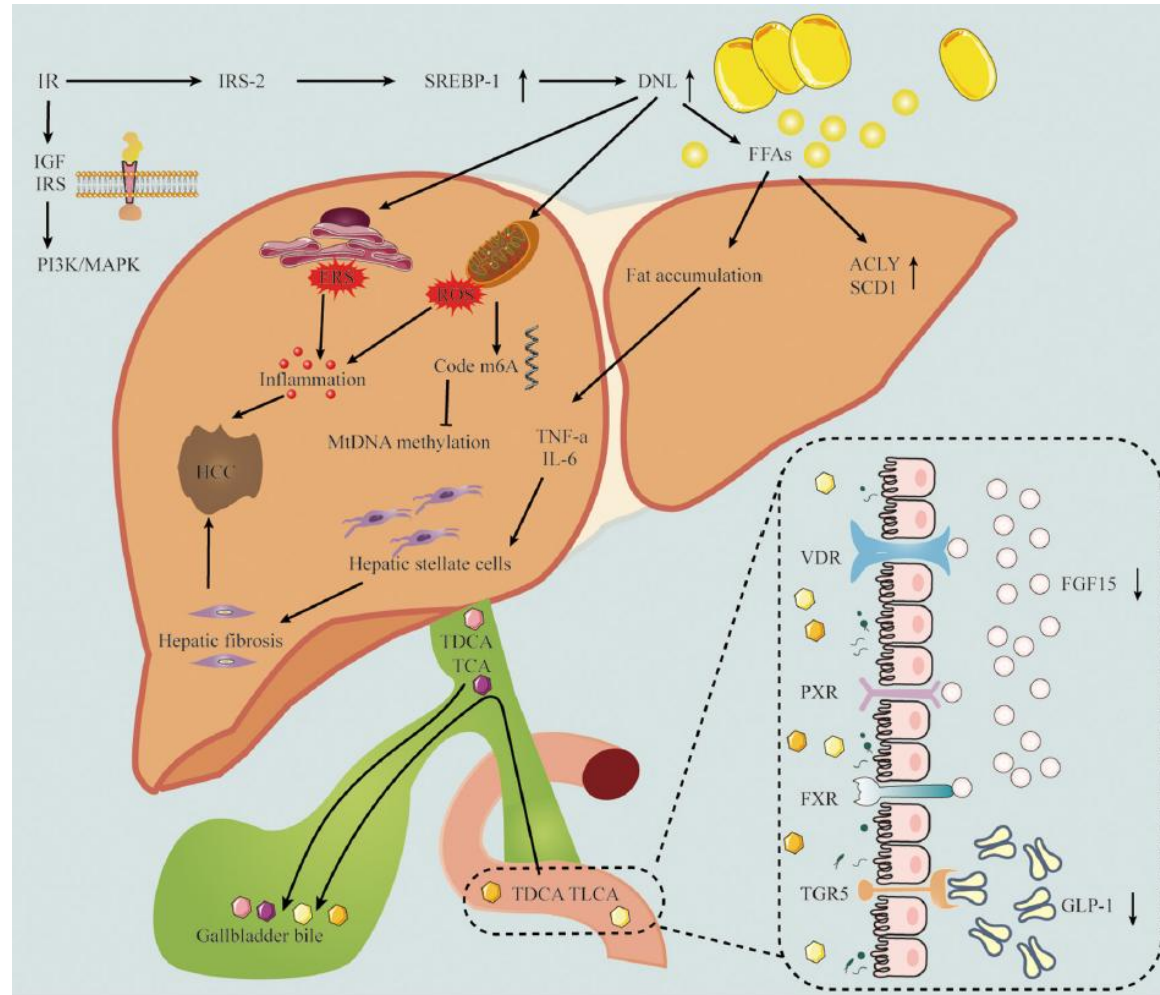
Mutations in MASH-HCC



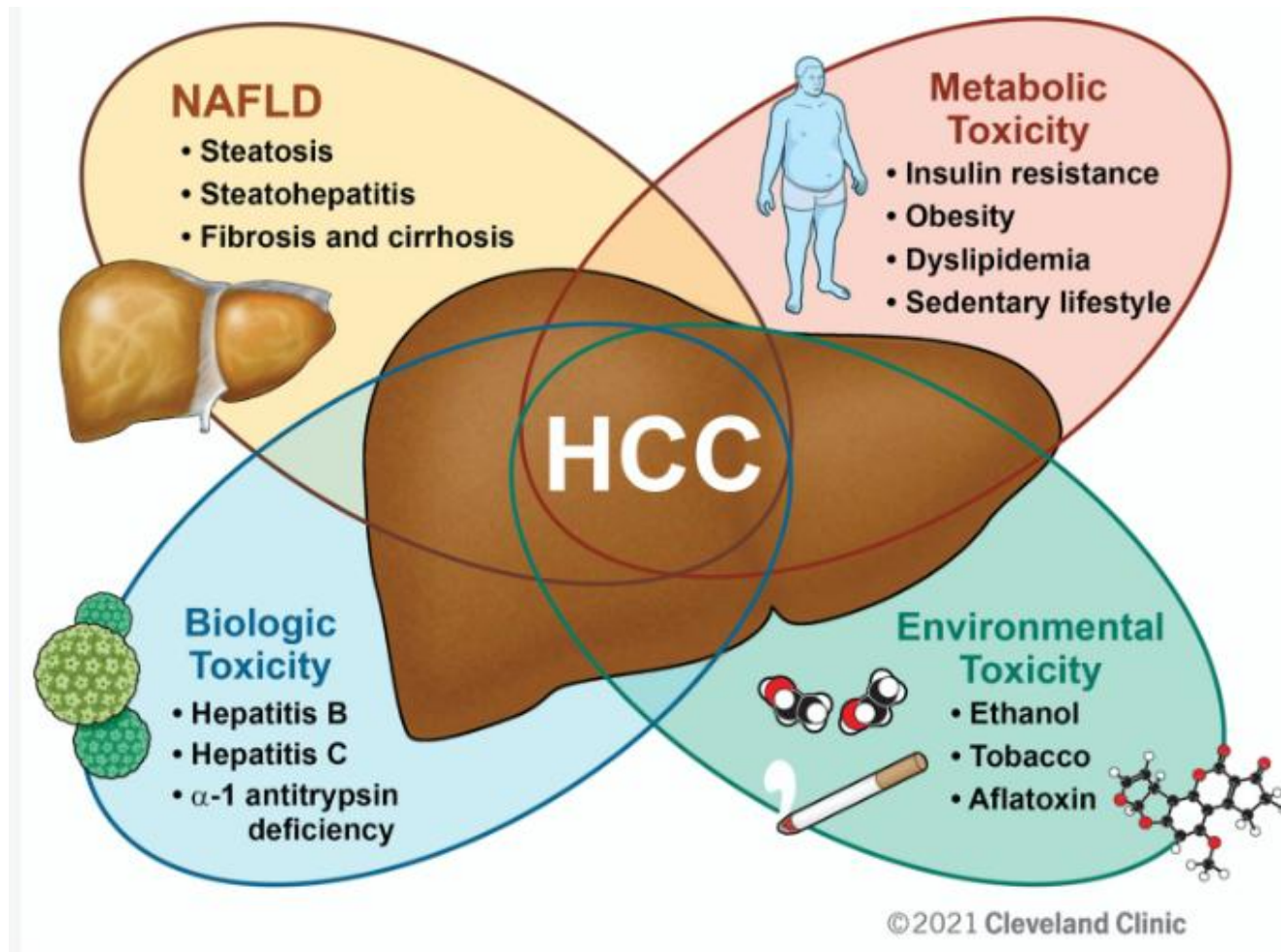
- TERT, CTNNB1, TP53 and ACVR2A mutations most frequent
- ACVR2A-mutations significantly more frequent

More complexity added ...

The pathogenesis of MASLD-related HCC involves the Gut



HCC as the culmination of a complex multifactorial process with metabolic syndrome and NAFLD playing key roles

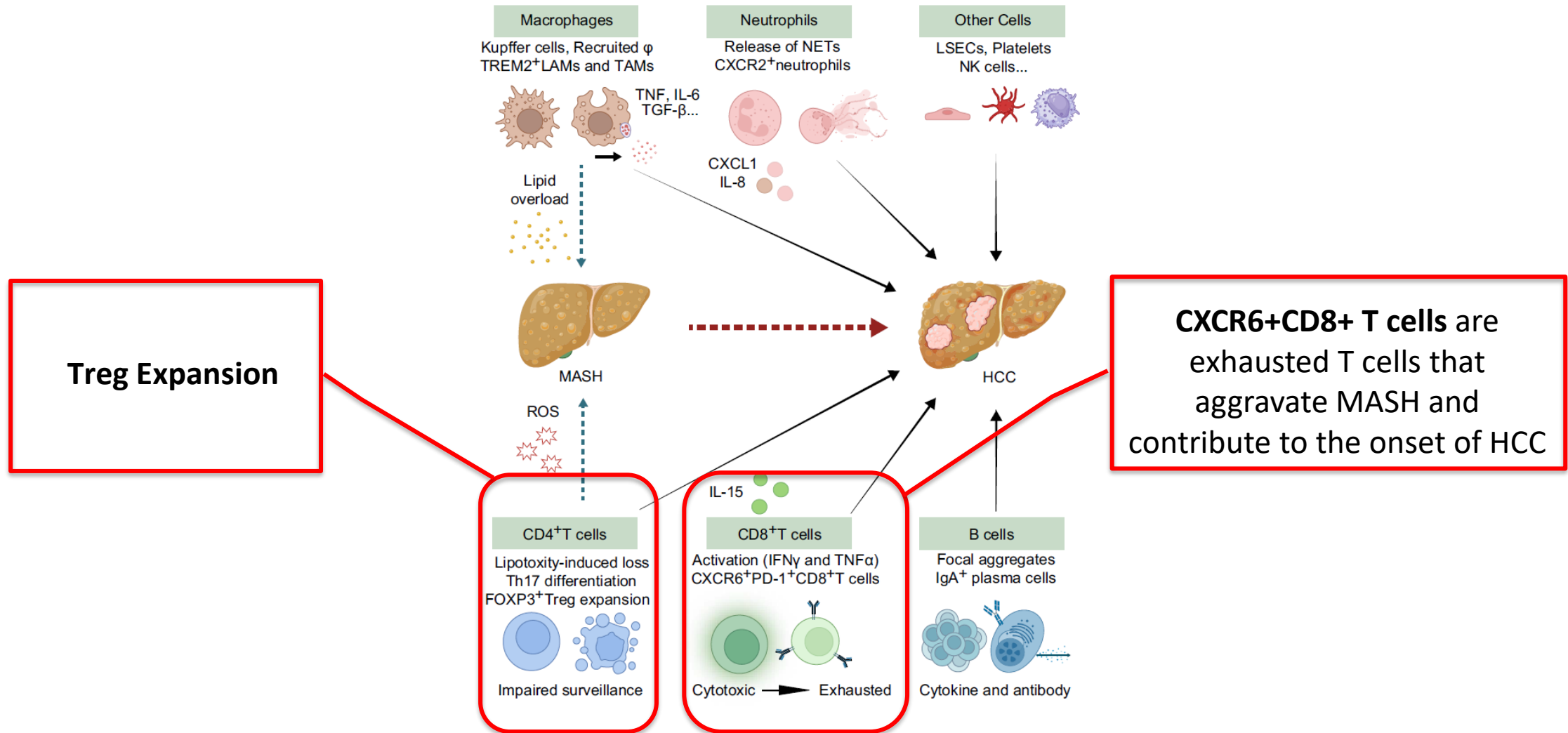


Time for TIME

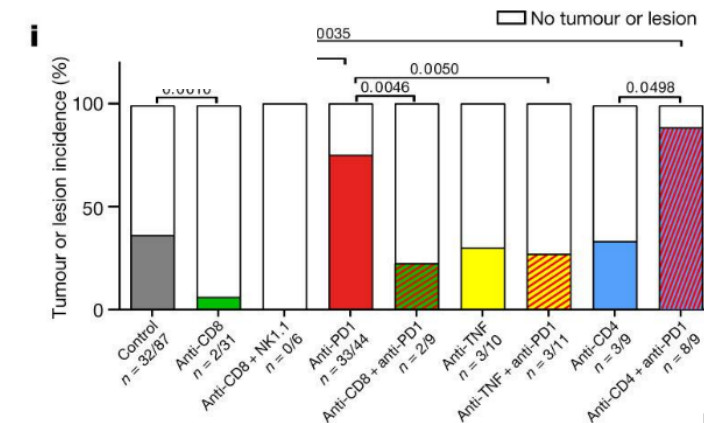
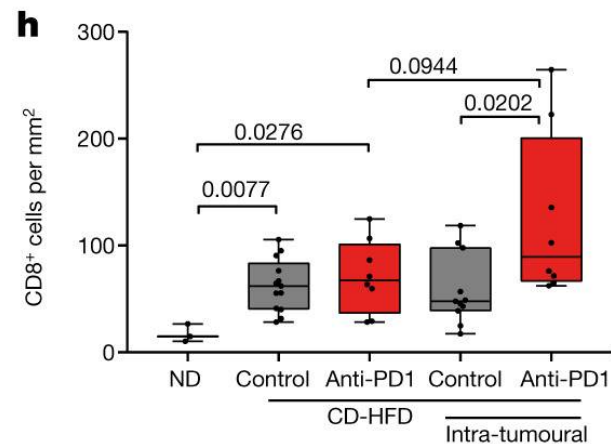
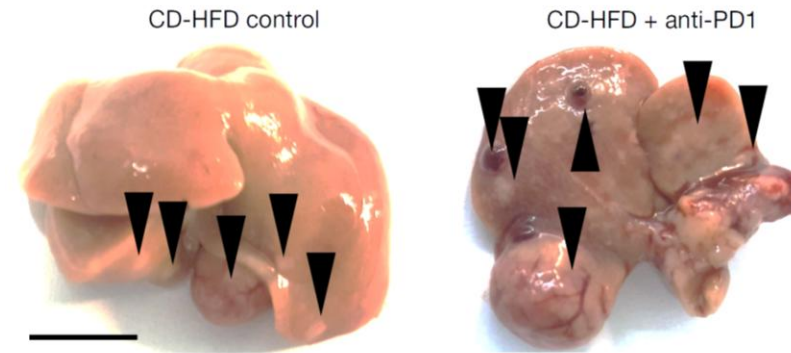
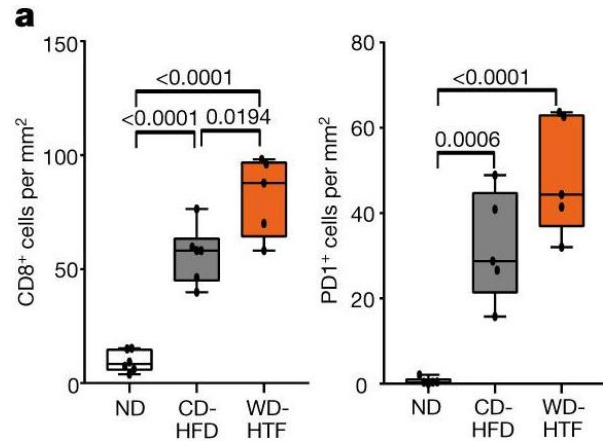
Tumor Immune Micro Environment

Tumor Microenvironment:

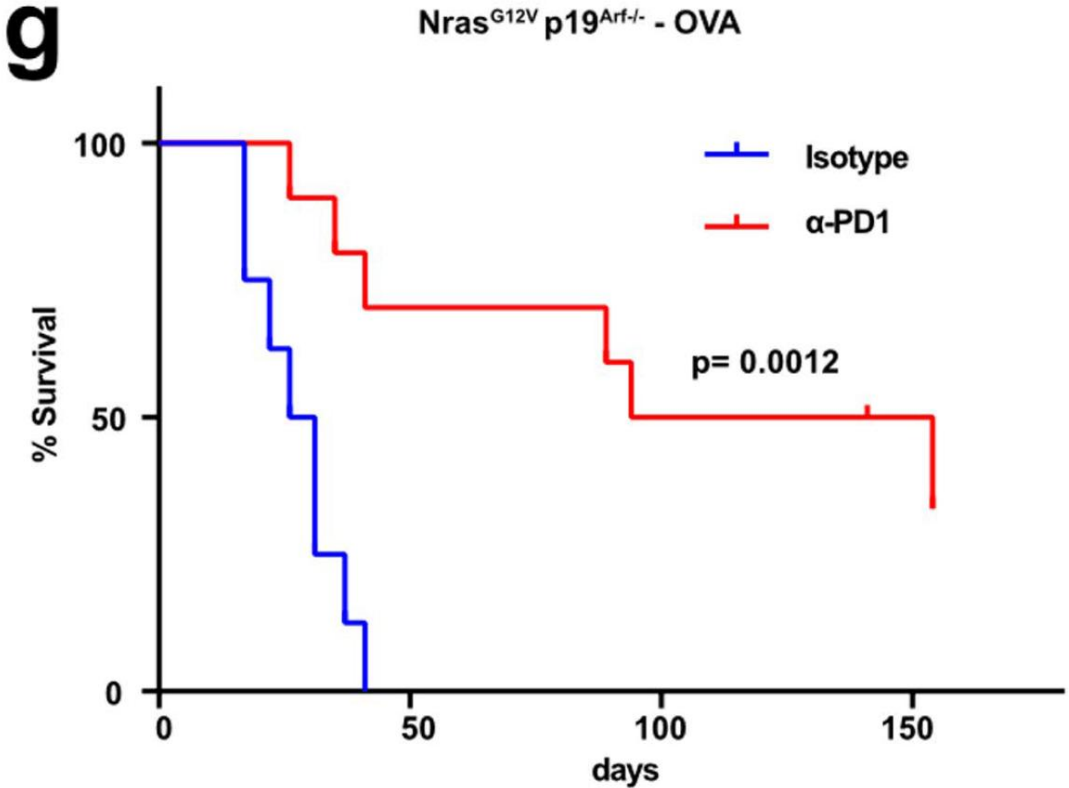
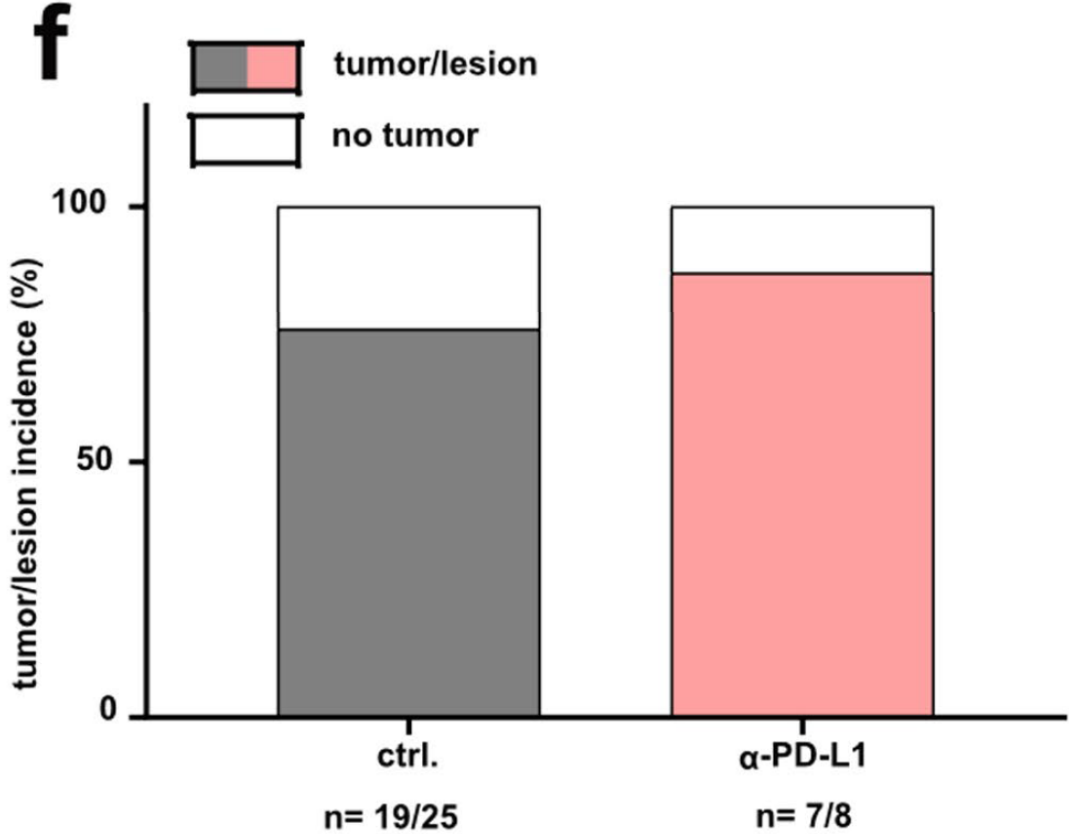
Immune cells involved in the pathogenesis of MASH-HCC



NASH progression is associated with increased, activated CD8⁺PD1⁺ T cells

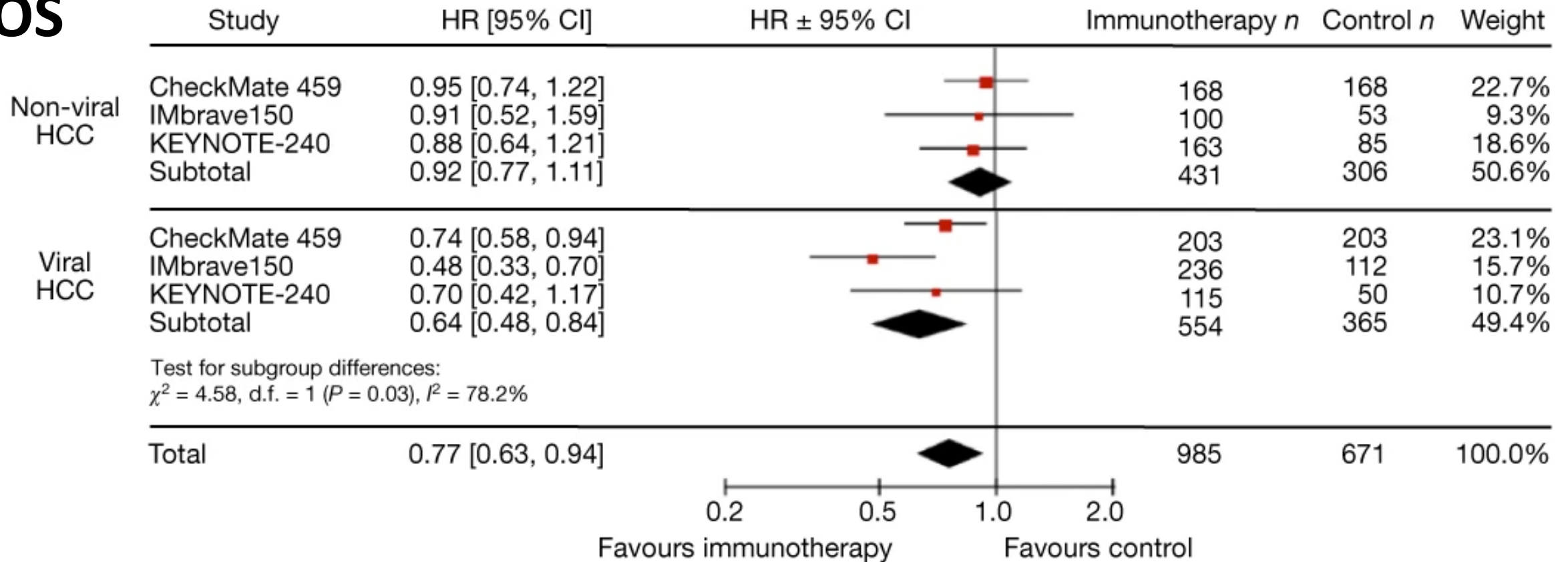


Anti-PD-L1 treatment does not achieve anti-tumour effects in NASH-induced tumours



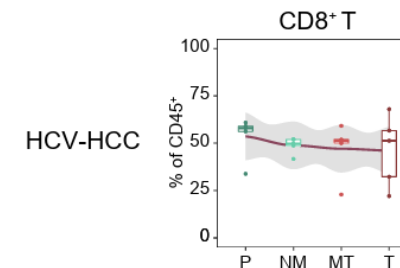
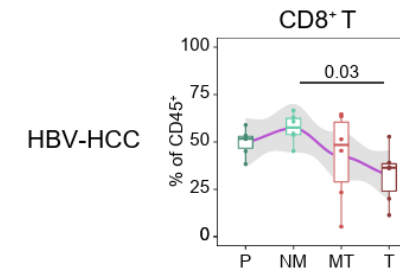
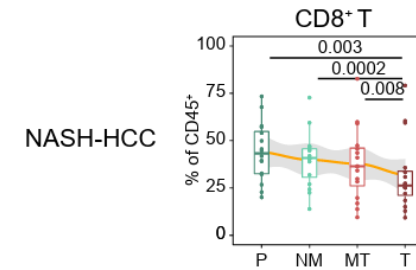
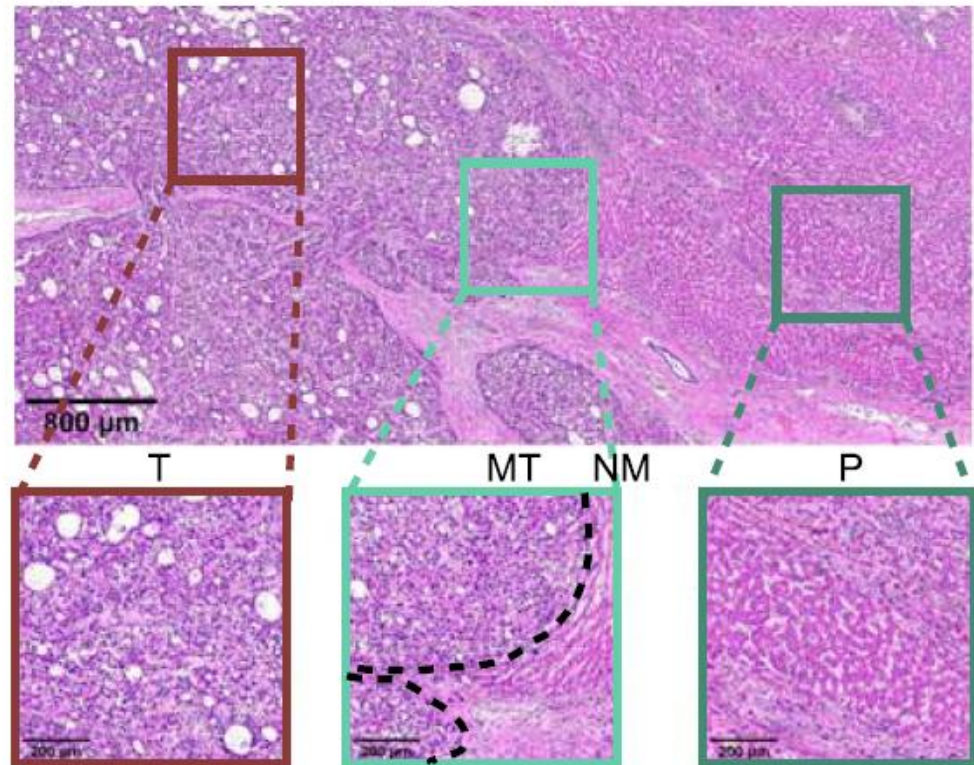
Does NASH affect efficacy of immunotherapy?

OS

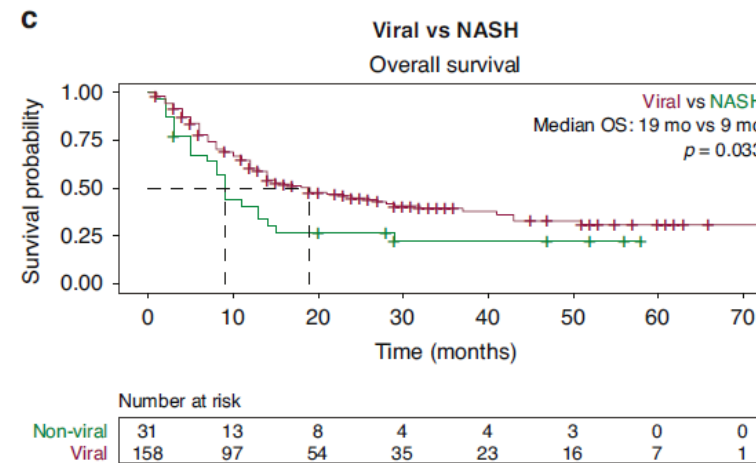
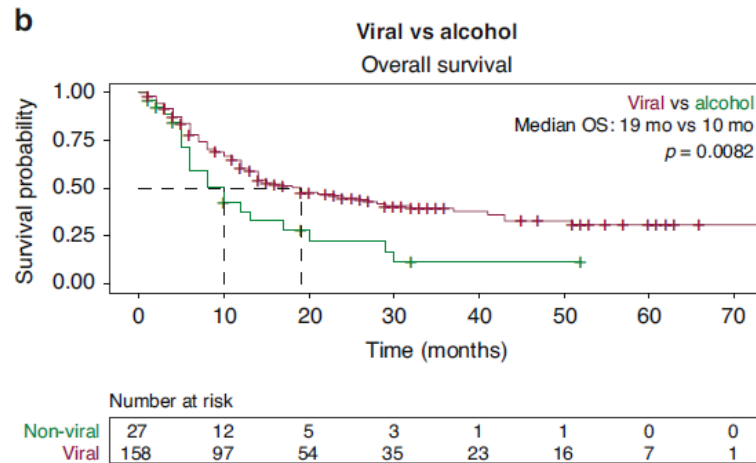
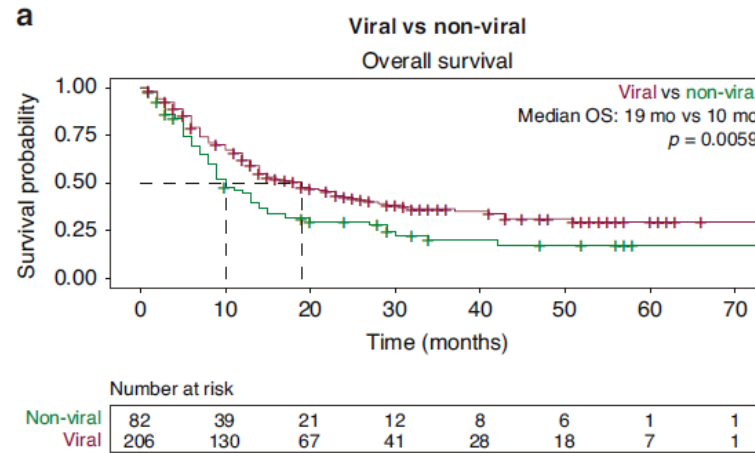


Spatial proteomics of immune microenvironment in non-alcoholic steatohepatitis-associated HCC

H&E of patient 12



Retrospective study on 1L ICI (Nivo, Pembro, Atezo) for advanced, unresectable HCC at Mount Sinai



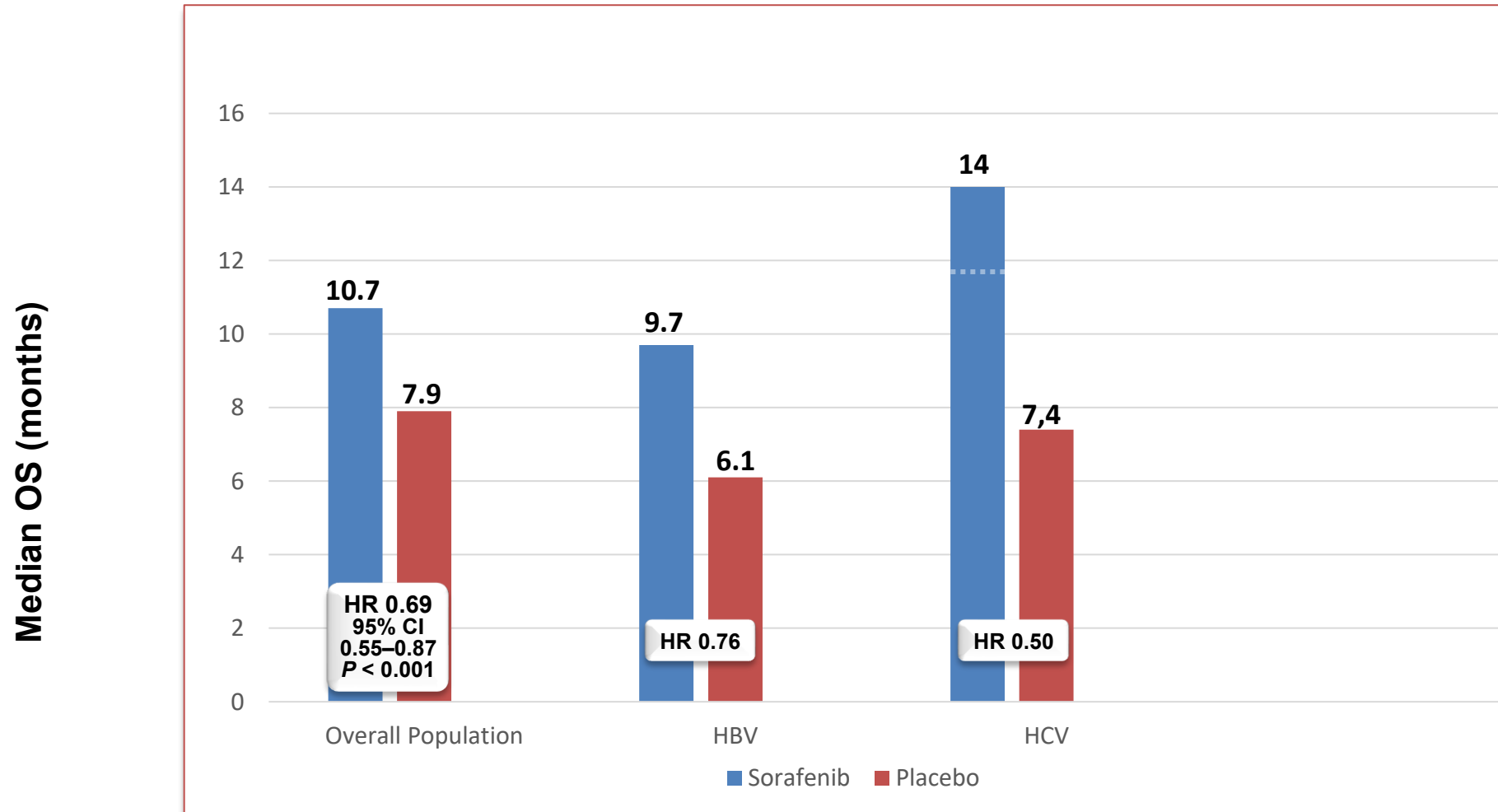
Immunotherapy for MASH HCC?

Conclusion:recent studies have revealed that **nonviral HCC**, which is primarily caused by **metabolic dysfunction–associated steatotic hepatitis (MASH)**, has a distinct and **less favorable response** to the immune checkpoint inhibitors

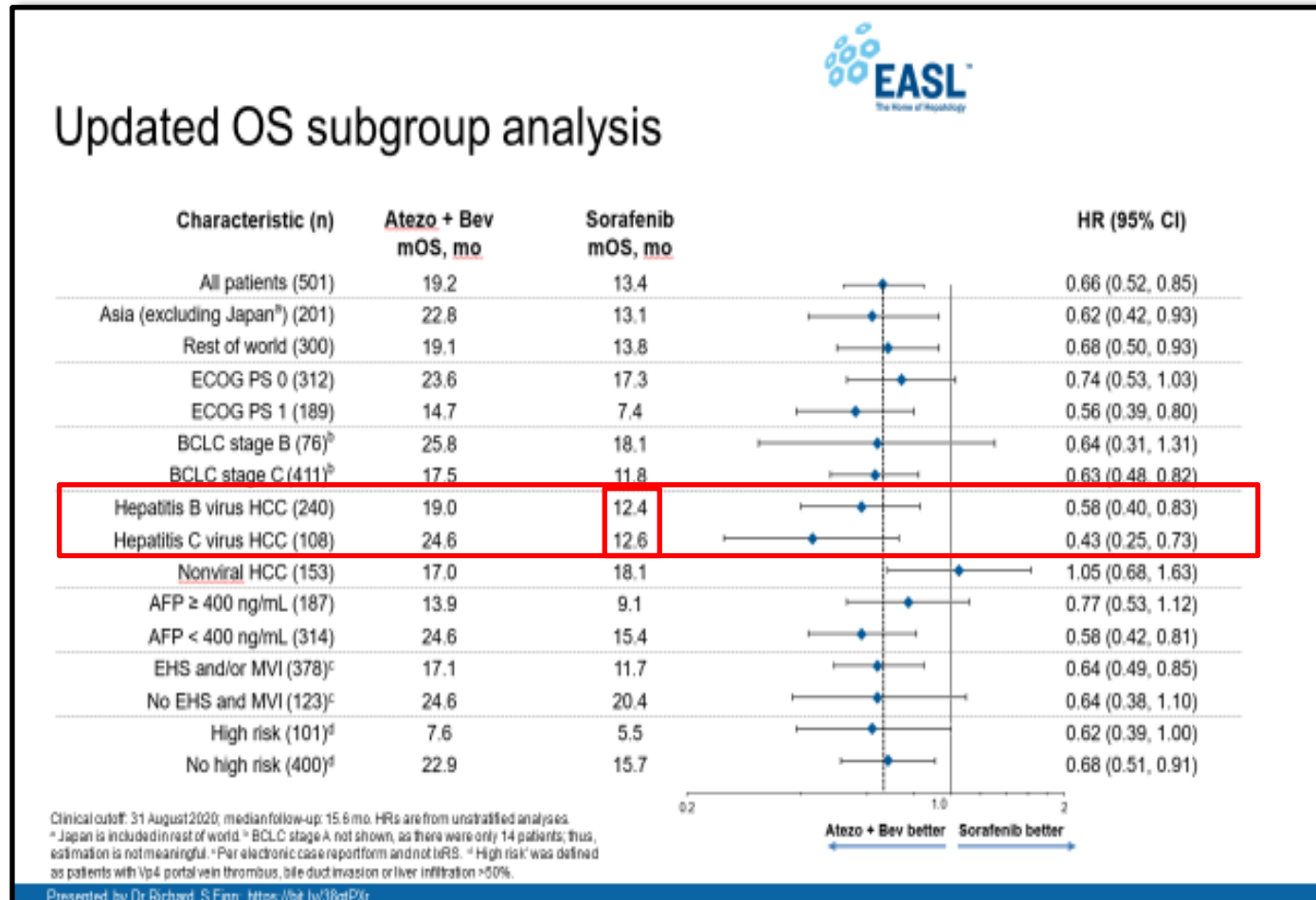
Is this assumption correct?

THE PROBLEM OF SUBGROUP ANALYSIS

SHARP – Subgroup Analysis



Updated IMbrave150 analysis: exploratory subgroups



Clinical cut-off date: 31 August 2020; median follow-up: 15.6 months

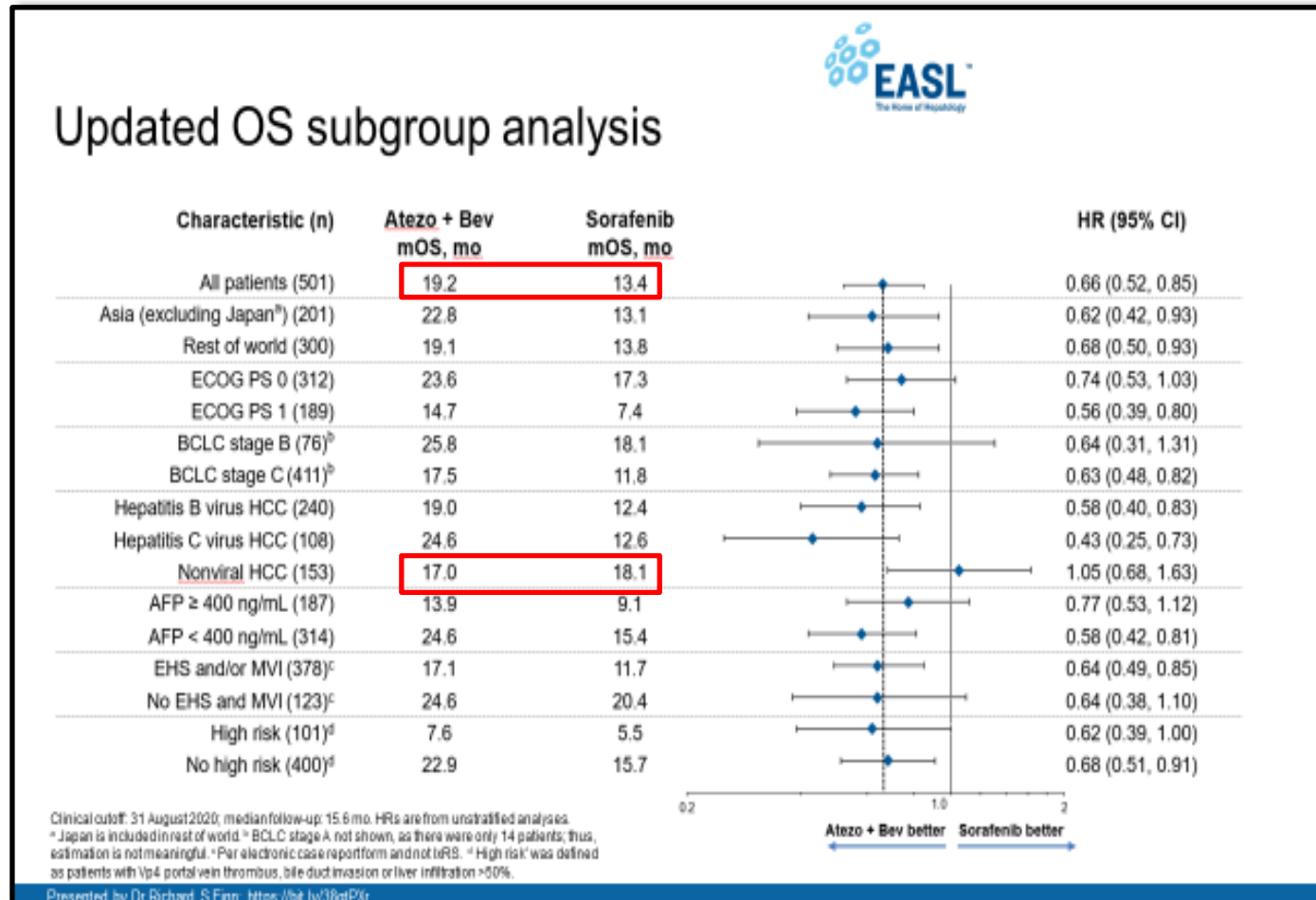
*HRs are from unstratified analyses; [†]Japan is included in RoW

[‡]BCLC stage A not shown as there were only 14 patients, thus the estimation is not meaningful

[§]Per eCRF not IxRS; [¶]High risk[†] was defined as patients with Vp4 portal vein thrombus, bile duct invasion or liver infiltration >50%

BCLC, Barcelona Clinic Liver Cancer; eCRF, electronic case report form; mo, months; mOS, median OS; mPFS, median PFS

Updated IMbrave150 analysis: exploratory subgroups



Clinical cut-off date: 31 August 2020; median follow-up: 15.6 months

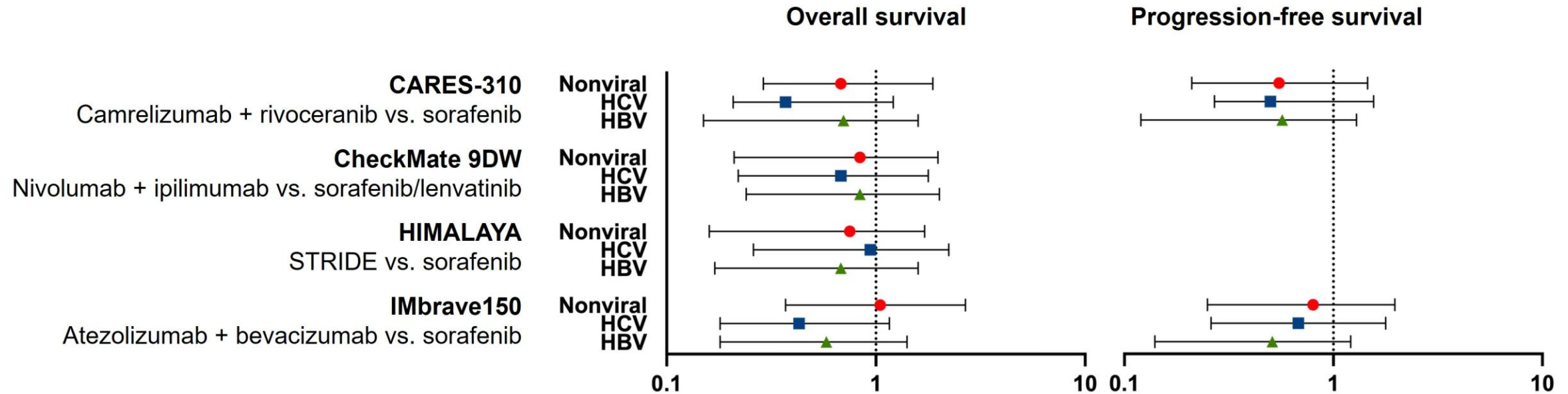
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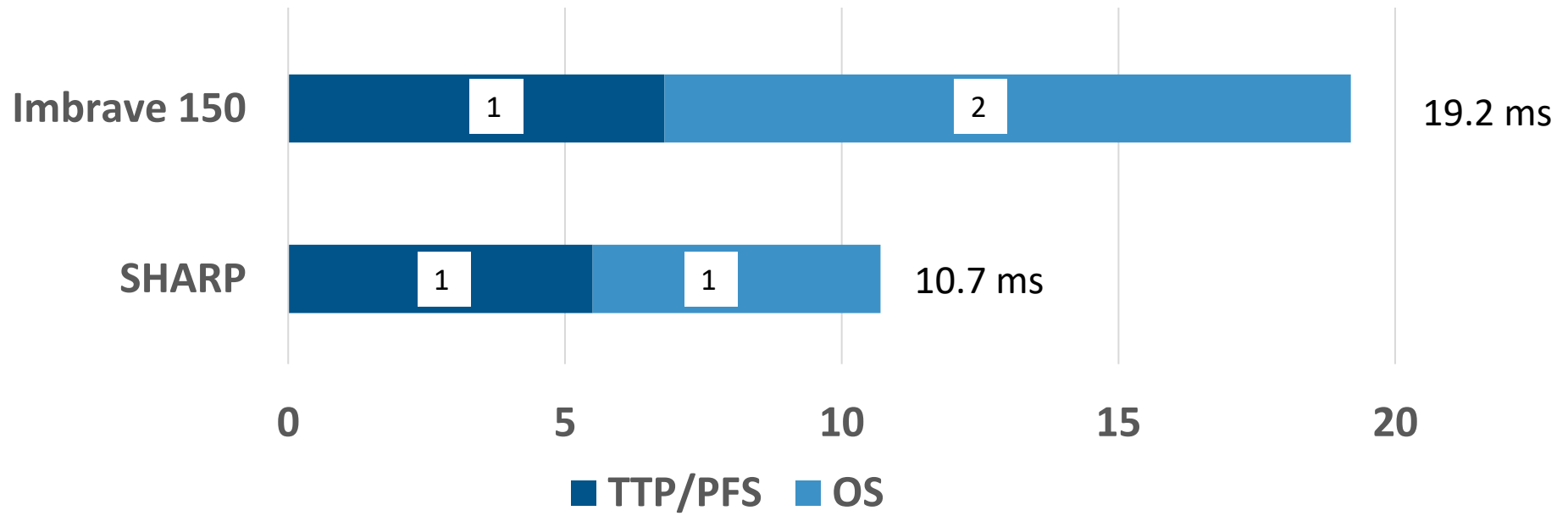
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BCLC, Barcelona Clinic Liver Cancer; eCRF, electronic case report form; mo, months; mOS, median OS; mPFS, median PFS

Recent phase III trials support efficacy of ICI in Non-viral HCC



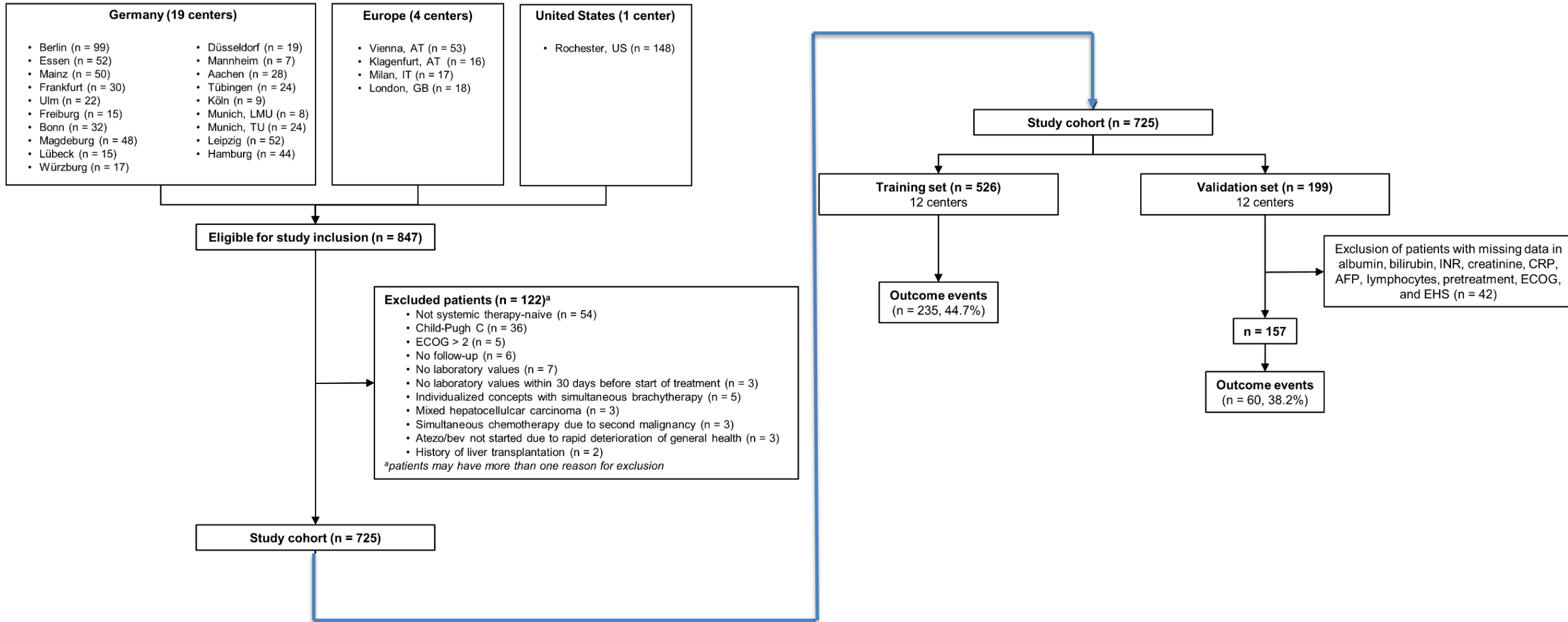
Post-Progression Survival 2007 - 2019



Problems with Post-hoc Subgroup Analyses

- Imbalances in the prognostic factors (AFP, tumor burden, EHS, MVI, etc)
- Post progression treatment affects OS
- Confounding impact of liver function during and post treatment
- Ill defined subgroups: non-viral etiology (NASH vs alcohol)

Multicentric retrospective analysis of atezolizumab + bevacizumab in real-world setting



Etiology of HCC has little informational value for prognosis in Atezo/Bev treated HCCs

Etiology

Unknown/no liver disease	91 (17.3%)
HBV	55 (10.5%)
HCV	93 (17.7%)
Harmful alcohol use	128 (24.3%)
MASLD	89 (16.9%)

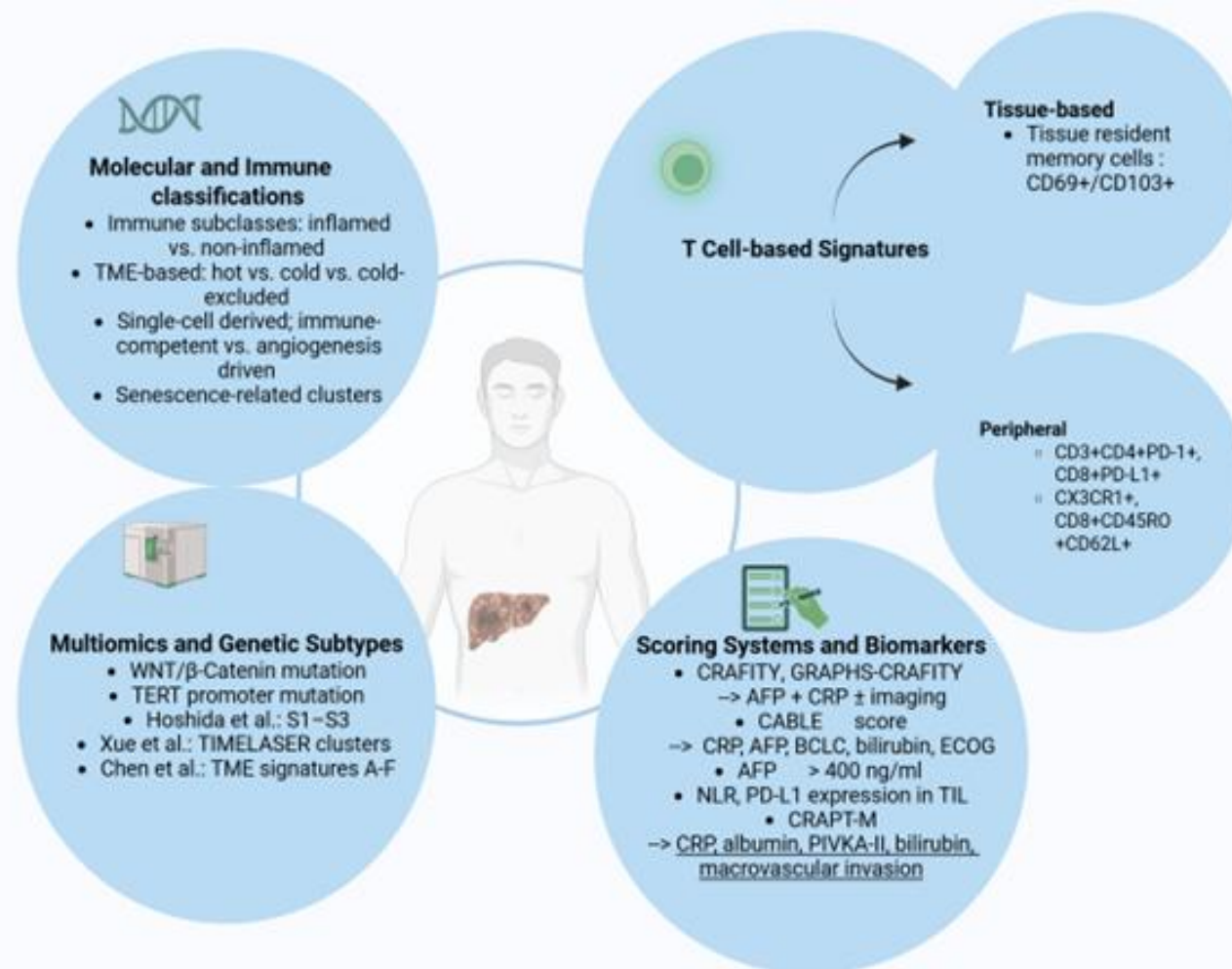
- Univariable Cox proportional hazards models
- Not statistically significant

Variable	Explained Deviance	Chi ² -Test (p-value)
Age (years)	2.77%	0.4
Gender (male vs female)	2.20%	0.2
Etiology		
9 categories ^a	3.03%	0.2
Nonviral vs viral vs mixed etiology	1.93%	0.8
NAFLD/NASH vs others	1.93%	0.3
Cirrhosis (yes vs no)	2.48%	0.041
Pretreatment (yes vs no)	2.65%	<0.001
ECOG	5.65%	<0.001
BCLC	3.92%	<0.001
Child-Pugh stage	6.42%	<0.001
EHS (yes vs no)	2.48%	0.002
MVI (yes vs no)	3.39%	<0.001
AFP, log ₁₀ (ng/ml)	3.45%	<0.001
Albumin (g/dl)	9.30%	<0.001
Bilirubin, log ₁₀ (mg/dl)	6.61%	<0.001
Creatinine, log ₁₀ (mg/dl)	2.56%	0.002
CRP, log ₁₀ (mg/l)	7.58%	<0.001
INR, log ₁₀	3.39%	<0.001
Platelets, log ₁₀ (/nl)	2.66%	0.007
Neutrophils (/nl)	3.48%	<0.001
Lymphocytes (/nl)	5.70%	<0.001
Monocytes (/nl)	2.19%	<0.001

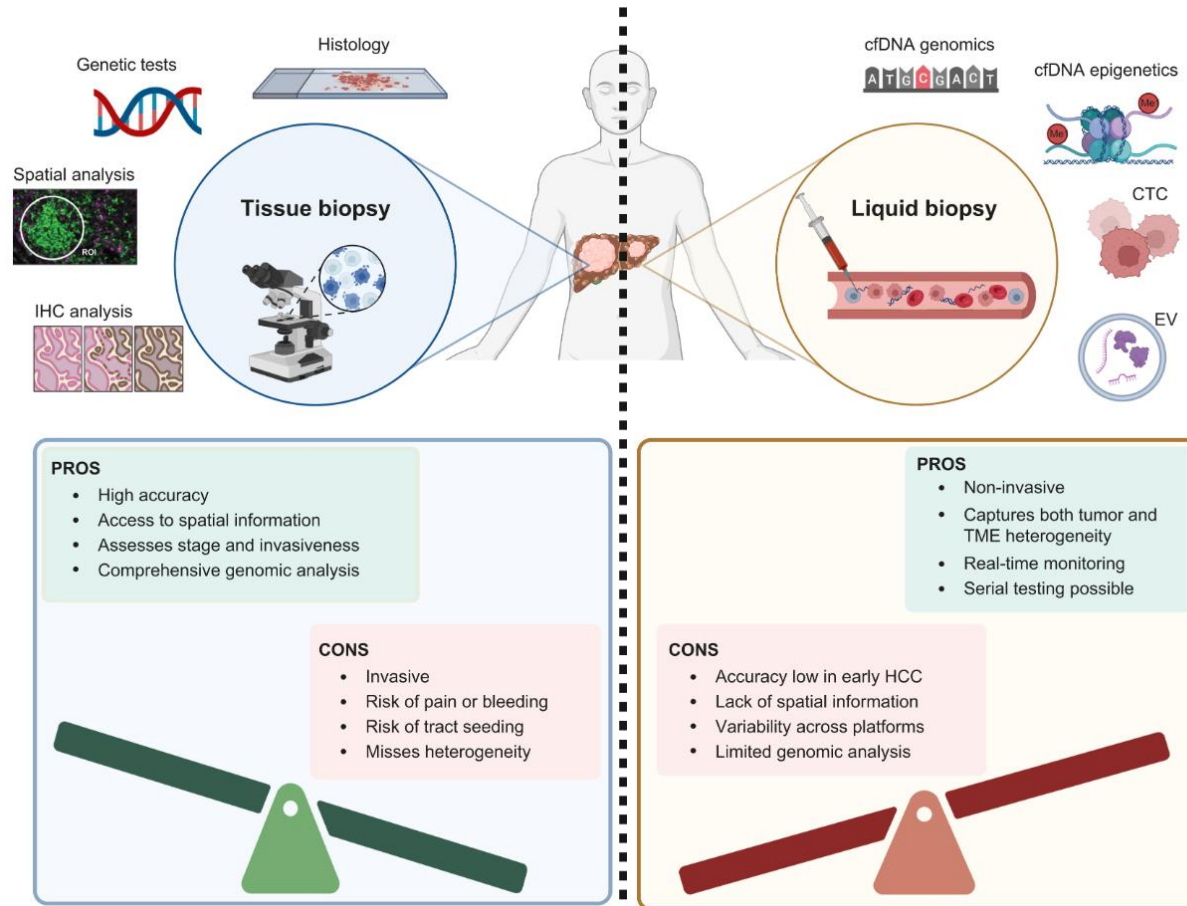
Conclusion

- **Preclinical** data suggested limited anti-tumor surveillance and limited efficacy in immunotherapy-treated MASH-HCC
- Initial subgroup analyses from **clinical trials** suggested limited anti-tumor efficacy in immunotherapy-treated HCC
- **Subsequent clinical trials** show anti-tumor efficacy in immunotherapy-treated MASH-HCC (HIMALAYA, CARES-310, CM9DW)
- Prospective data are lacking

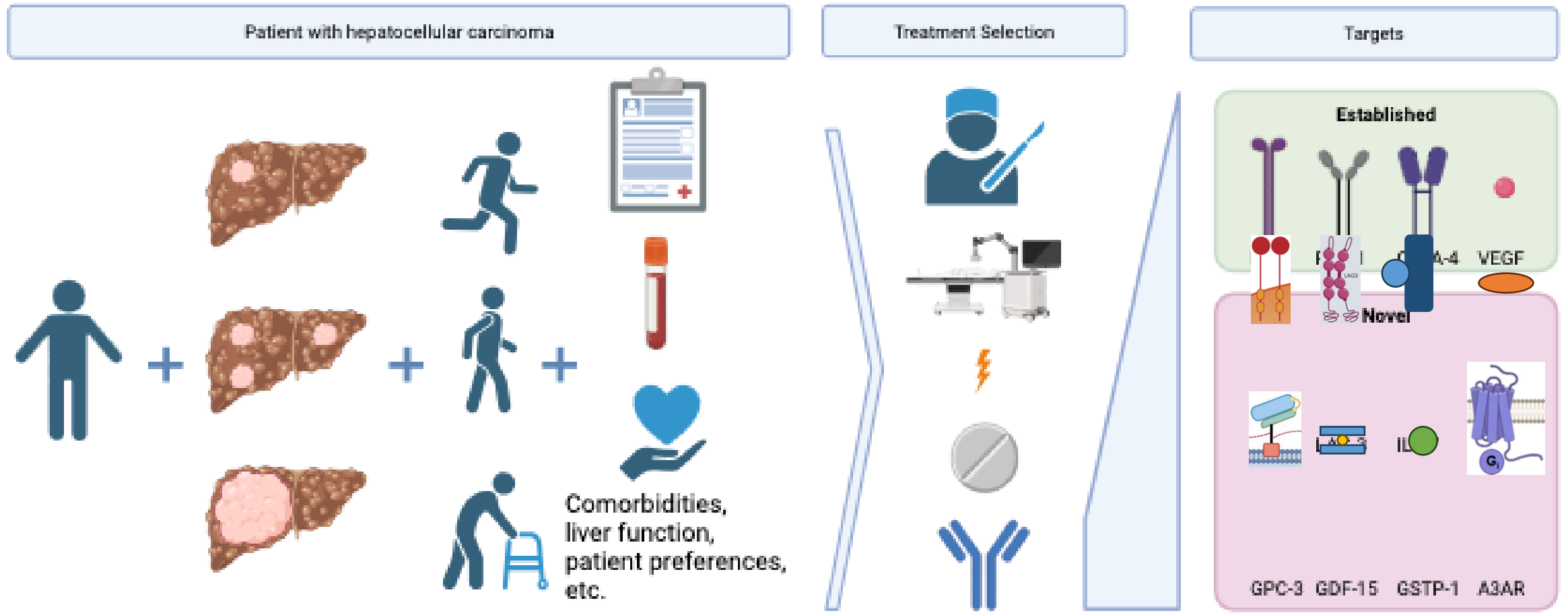
Integrated landscape of subclassification and biomarker strategies supporting treatment personalization in advanced HCC



An old debate: to biopsy or not to biopsy in HCC



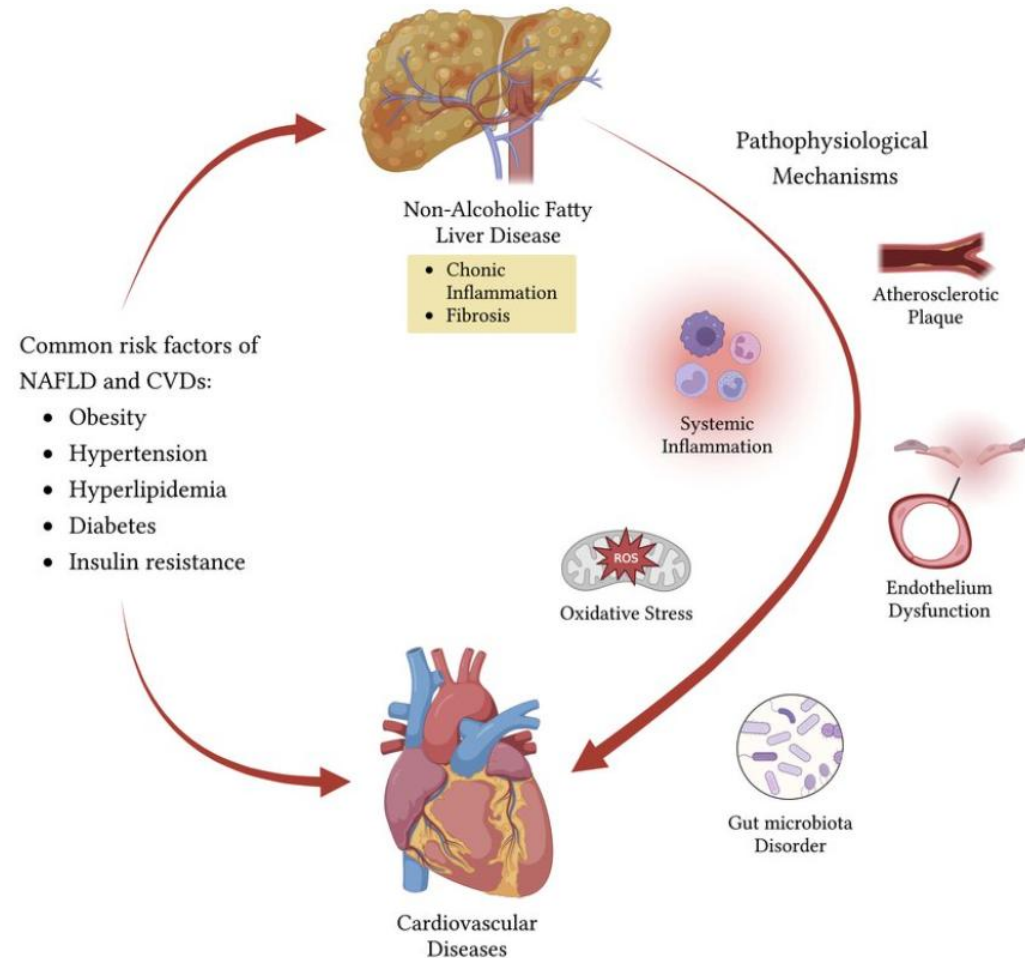
Precision medicine in HCC: Patient- and disease-related factors plus established and novel immunotherapeutic targets



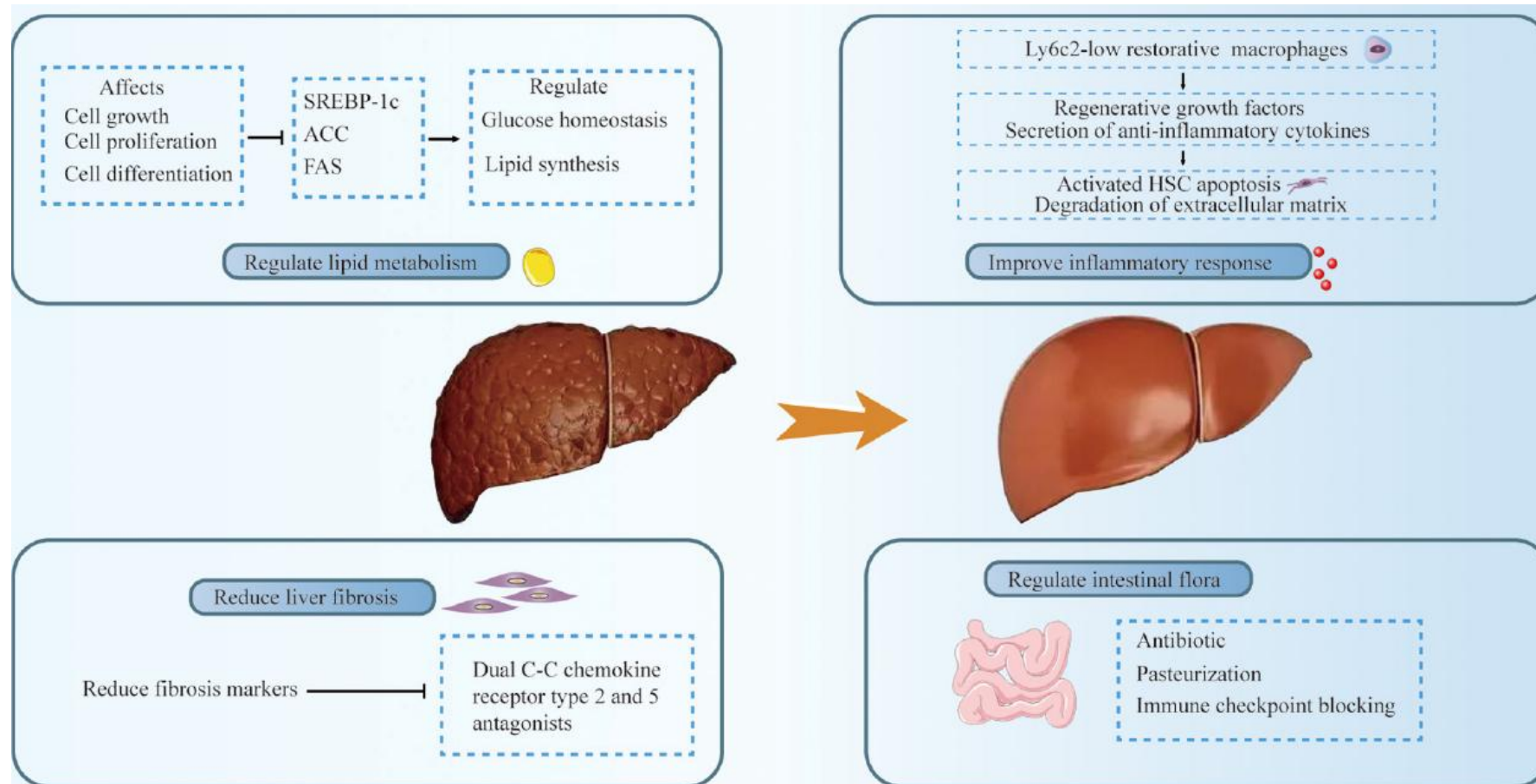
It's more than the tumor, stupid!



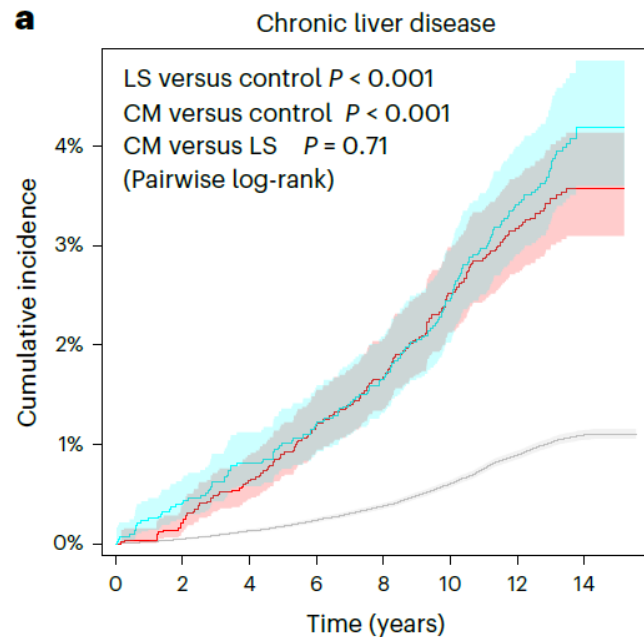
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Treatment of MASLD-related HCC goes beyond anti-tumor Therapy



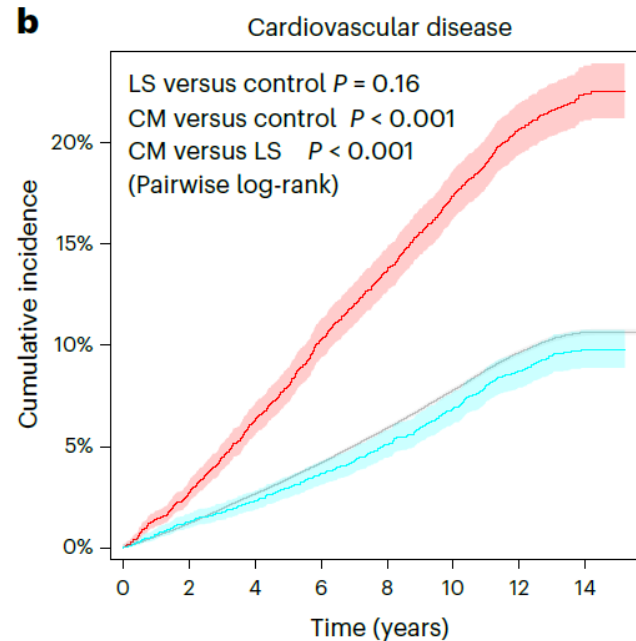
Data-driven cluster analysis identifies distinct types of MASLD



— Cardiometabolic cluster ($N = 5,231$)
 Adjusted HR: 4.04 (3.50–4.66), $P < 0.001$
 Nonadjusted HR: 3.64 (3.13–4.24), $P < 0.001$

— Liver-specific cluster ($N = 4,366$)
 Adjusted HR: 4.52 (3.88–5.26), $P < 0.001$
 Nonadjusted HR: 3.80 (3.25–4.44), $P < 0.001$

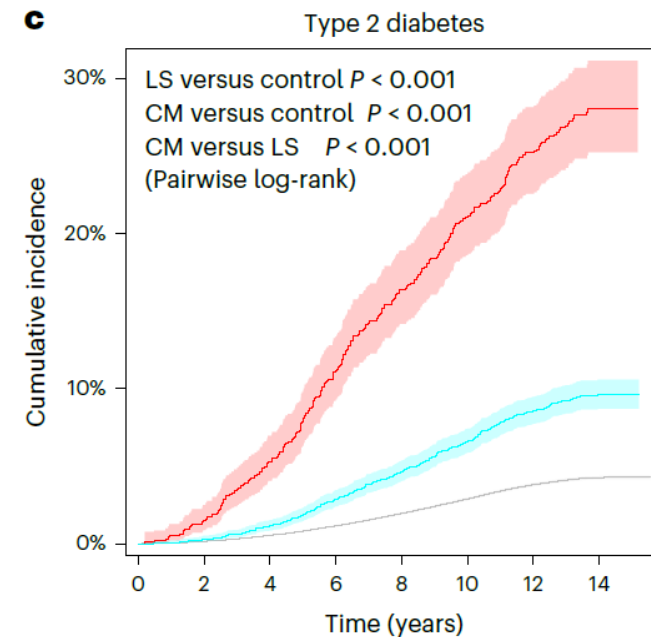
— Control cluster ($N = 203,583$)
 (Reference)



— Cardiometabolic cluster (3,999)
 Adjusted HR: 1.80 (1.68–1.93), $P < 0.001$
 Nonadjusted HR: 2.31 (2.16–2.47), $P < 0.001$

— Liver-specific cluster ($N = 4,137$)
 Adjusted HR: 1.18 (1.07–1.31), $P = 0.054$
 Nonadjusted HR: 0.91 (0.82–1.00), $P < 0.001$

— Control cluster (187,603)
 (reference)



— Cardiometabolic cluster ($N = 942$)
 Adjusted HR: 6.82 (6.01–7.73), $P < 0.001$
 Nonadjusted HR: 7.81 (6.89–8.84), $P < 0.001$

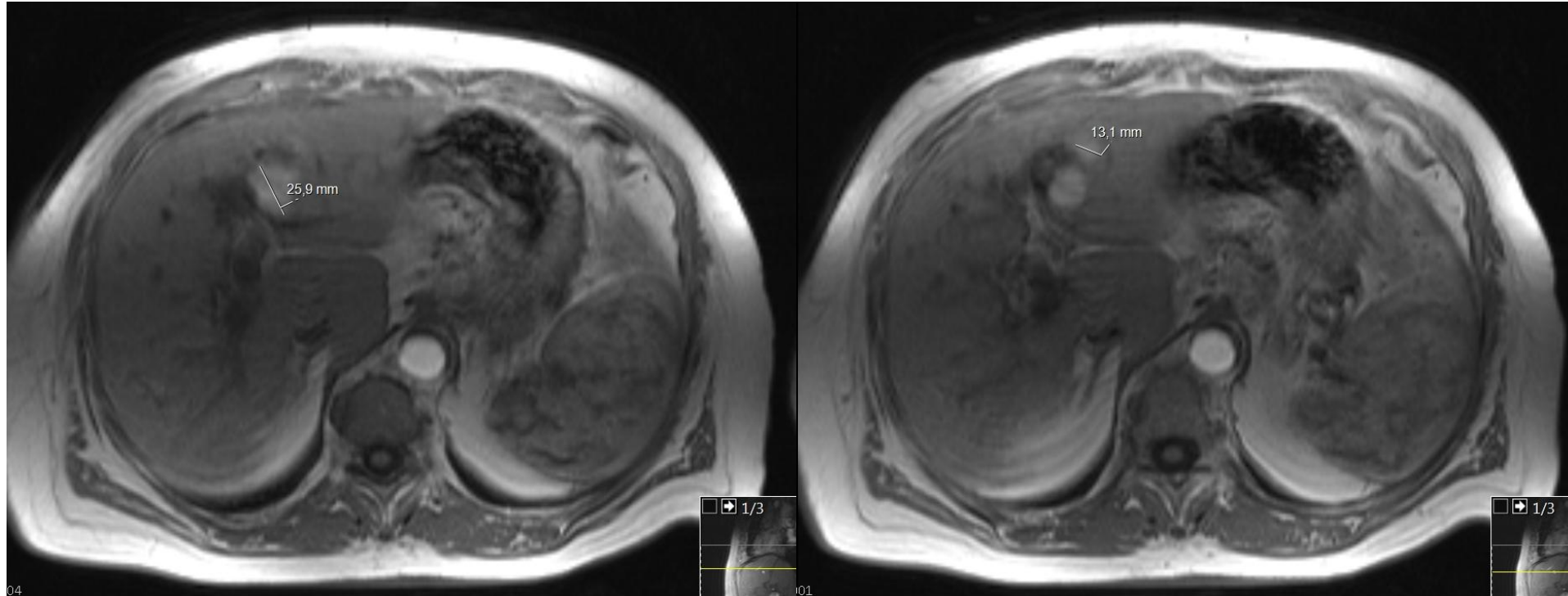
— Liver-specific cluster ($N = 4,017$)
 Adjusted HR: 2.91 (2.62–3.23), $P < 0.001$
 Nonadjusted HR: 2.3 (2.07–2.55), $P < 0.001$

— Control cluster ($N = 191,832$)
 (reference)

Case

- 64 year old female patient
- 169 cm, 95 kg (BMI: 33.3)
- Type 2 diabetes (insulin-dependent)
- Known NASH-associated liver cirrhosis Child-Pugh A
 - GPT 29, GOT 39, AP 147, GGT 398, Bilirubin 1.30, protein 76, albumin 32, INR 1.2
 - No ascites
 - No hepatic encephalopathy
- Takes part in the HCC surveillance program at our clinic
- Increase in AFP-levels: 8 → 65 ng/ml

Suspected HCC on the CT scan

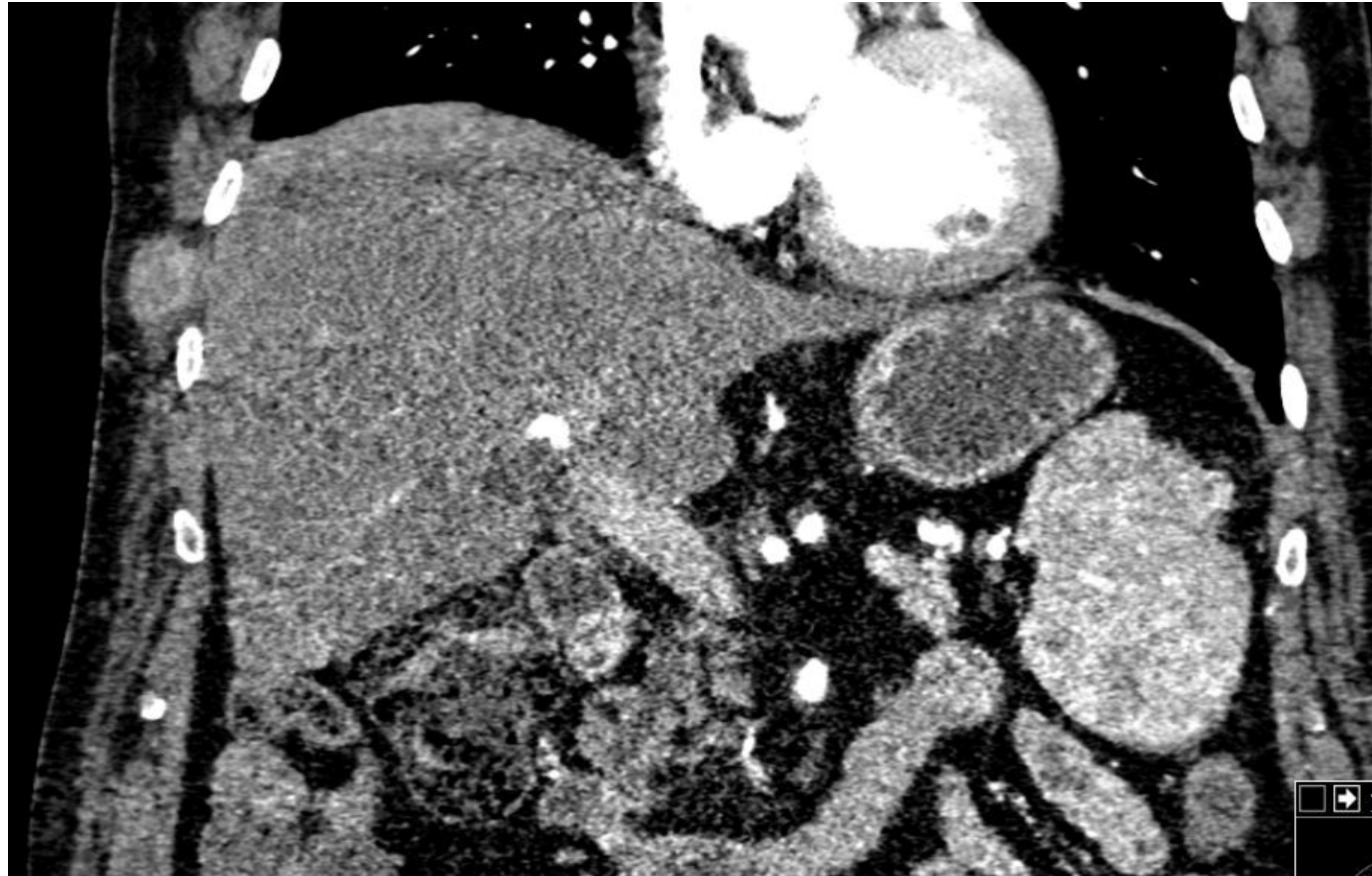


- Two hypervascularized lesions suspicious of HCC
- Ultrasound guided biopsy: Moderately differentiated HCC
- The patient underwent resection of segments 2 & 3 (pT2, pN0, M0, G2, R0)

Case continued

- Subsequent HCC recurrence
- 2 TACE sessions as a bridge to transplant
- 18 months after diagnosis, she underwent a liver transplantation
- Slow recovery after transplantation, complicated by an abscess in the parotid gland (microbial diagnostics: MRSA)

Needle tract seeding metastasis



- 3 years after transplantation, the CT scan shows a mass in the right 7th intercostal space
- Surgical resection: Soft tissue metastasis of the known HCC

Case continued

- Liver biopsy 5 years after transplantation:
 - 20 % macrovesicular & 30 % microvesicular steatosis
 - Fibrosis stage F2
 - Recurrent NASH
- The further course:
 - Peripheral artery disease of both legs
 - Chronic kidney failure
 - Atrial fibrillation
 - Chronic heart failure with repeated decompensation
 - **No further HCC recurrence**
 - **Death from metabolic long-term complications >11 years after HCC diagnosis**

Thank you!

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