MetALD: A Tale of Two Epidemics

Alcohol-Associated Liver Disease (ALD)
vs.
Metabolic Dysfunction-Associated Steatohepatitis (MASH)

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The Road to A Healthier Liver

Common Pathways in the Pathogenesis of MASH & ALD

Overlapping mechanisms of MASH and ALD

Insulin resistance

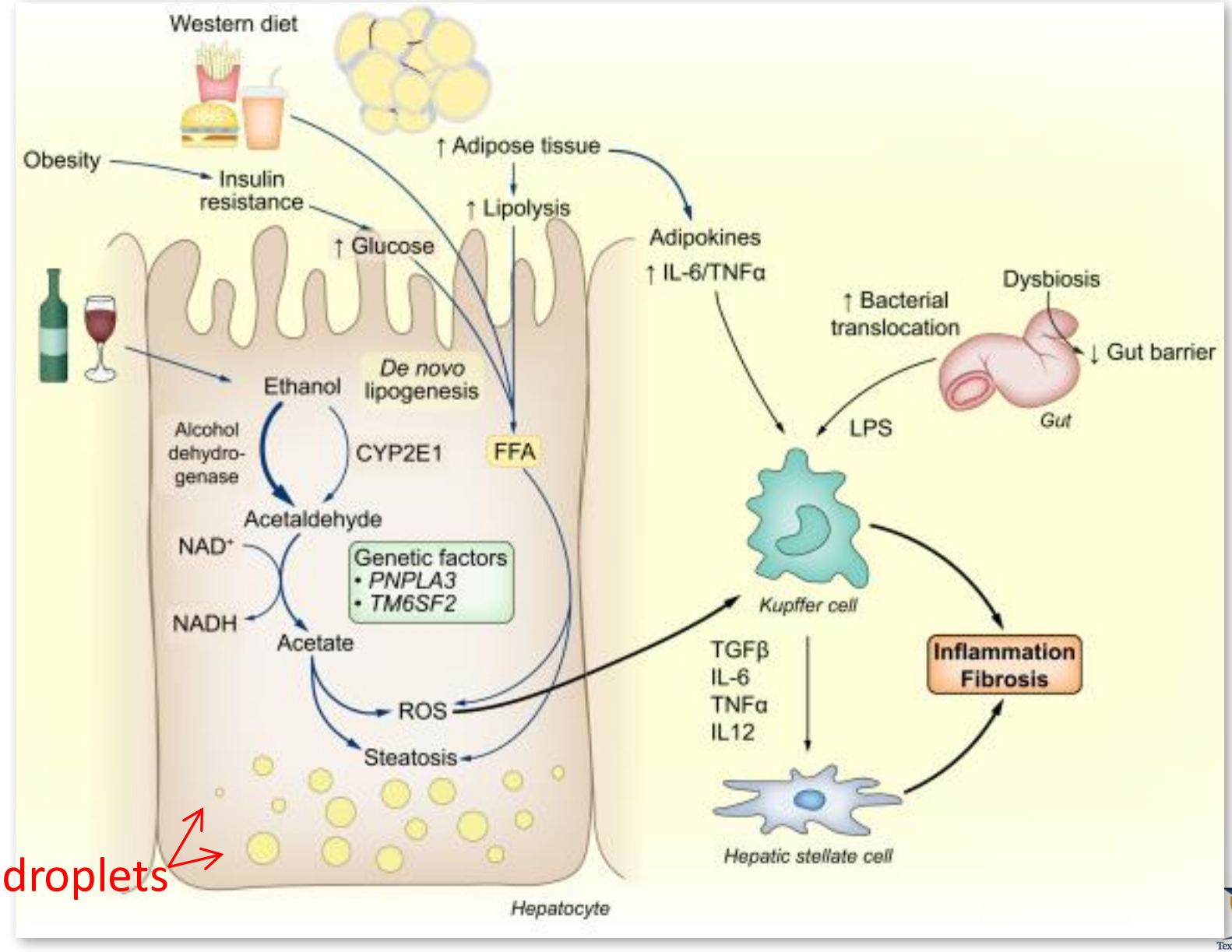
Increased peripheral lipolysis

Increased *de novo* lipogenesis

Impaired lipoprotein export from the hepatocytes

Mitochondrial dysfunction

Gut dysbiosis



Lipid droplets

Ntandja Wandji LC, et al. JHEP Rep. 2020. PMID: 32514497

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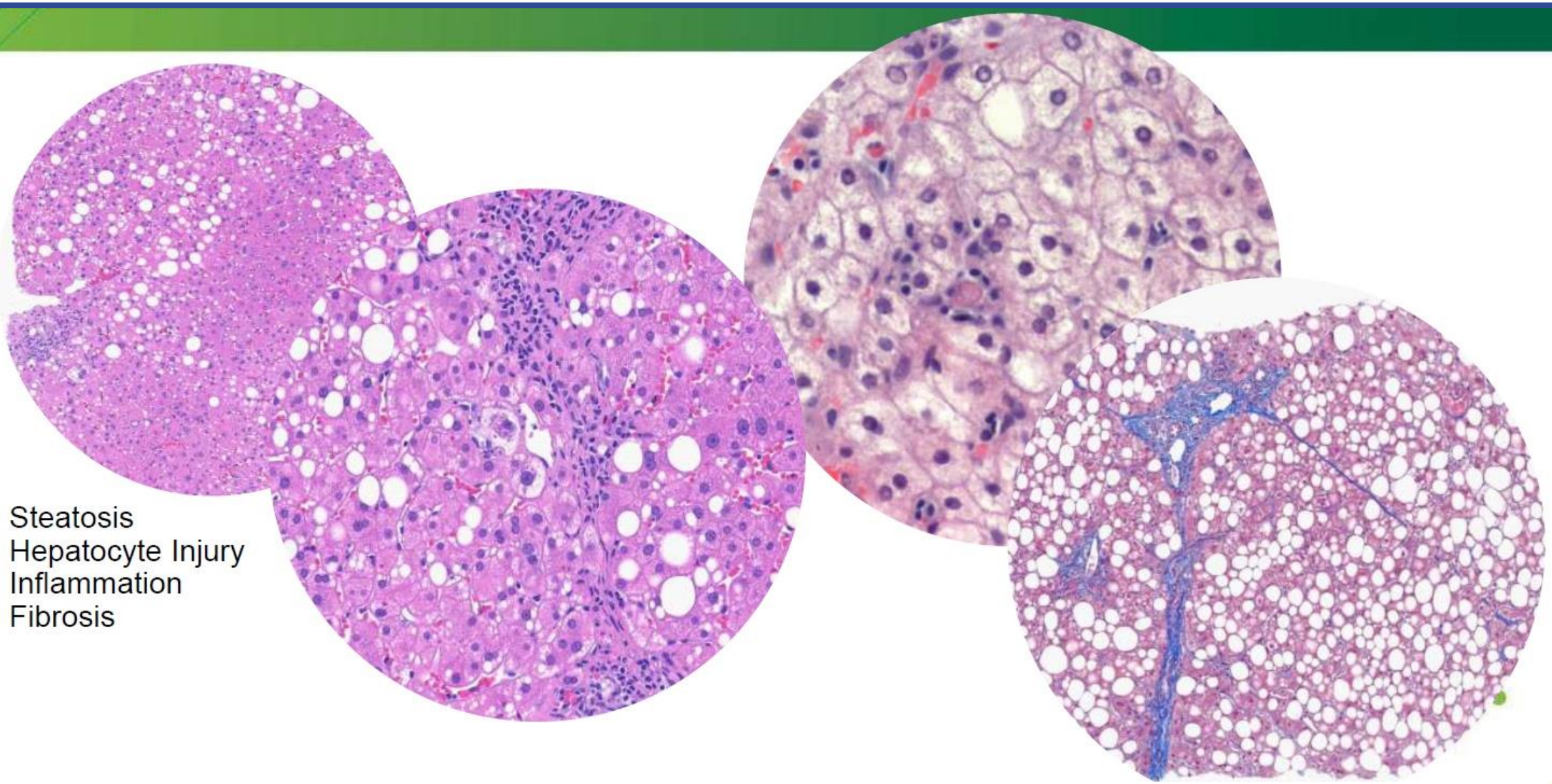
Common Histology Features in MASH and ALD



Ntandja Wandji LC, et al. JHEP Rep. 2020. PMID: 32514497

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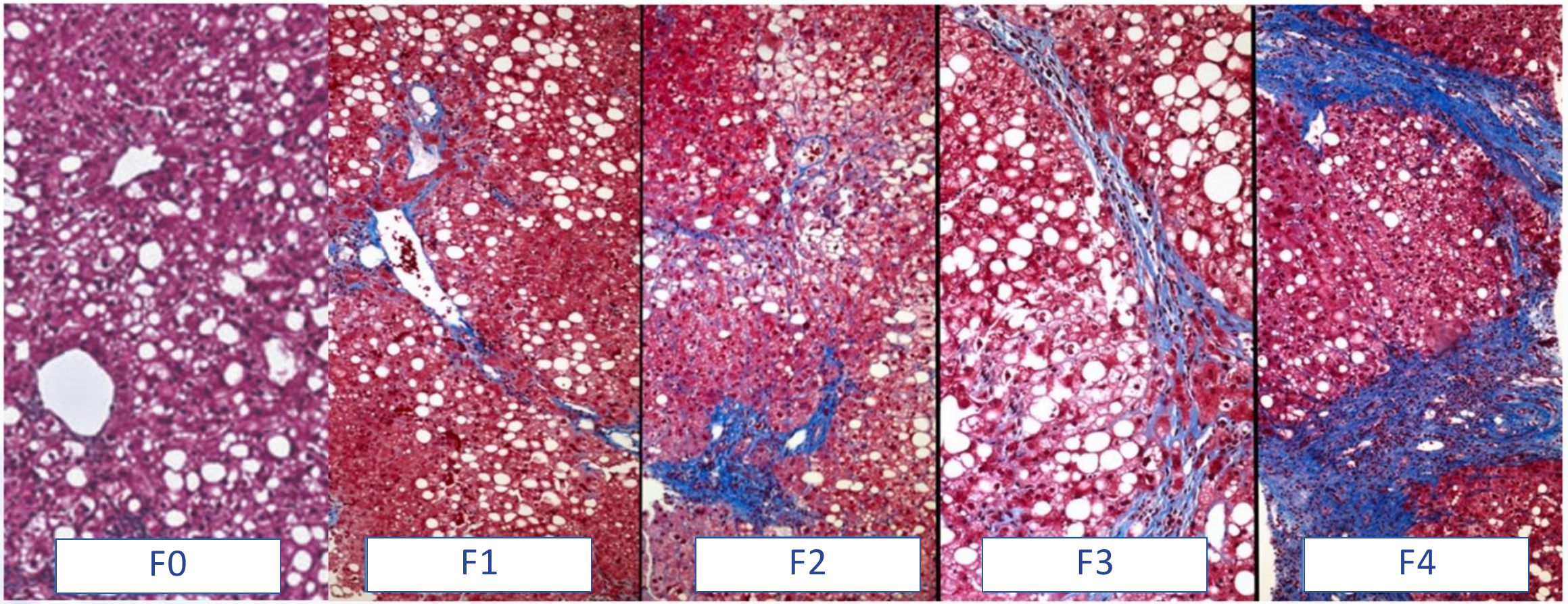
Fibrosis Progression in MASH and ALD



Estes et al., Hepatology 2018 :123-133

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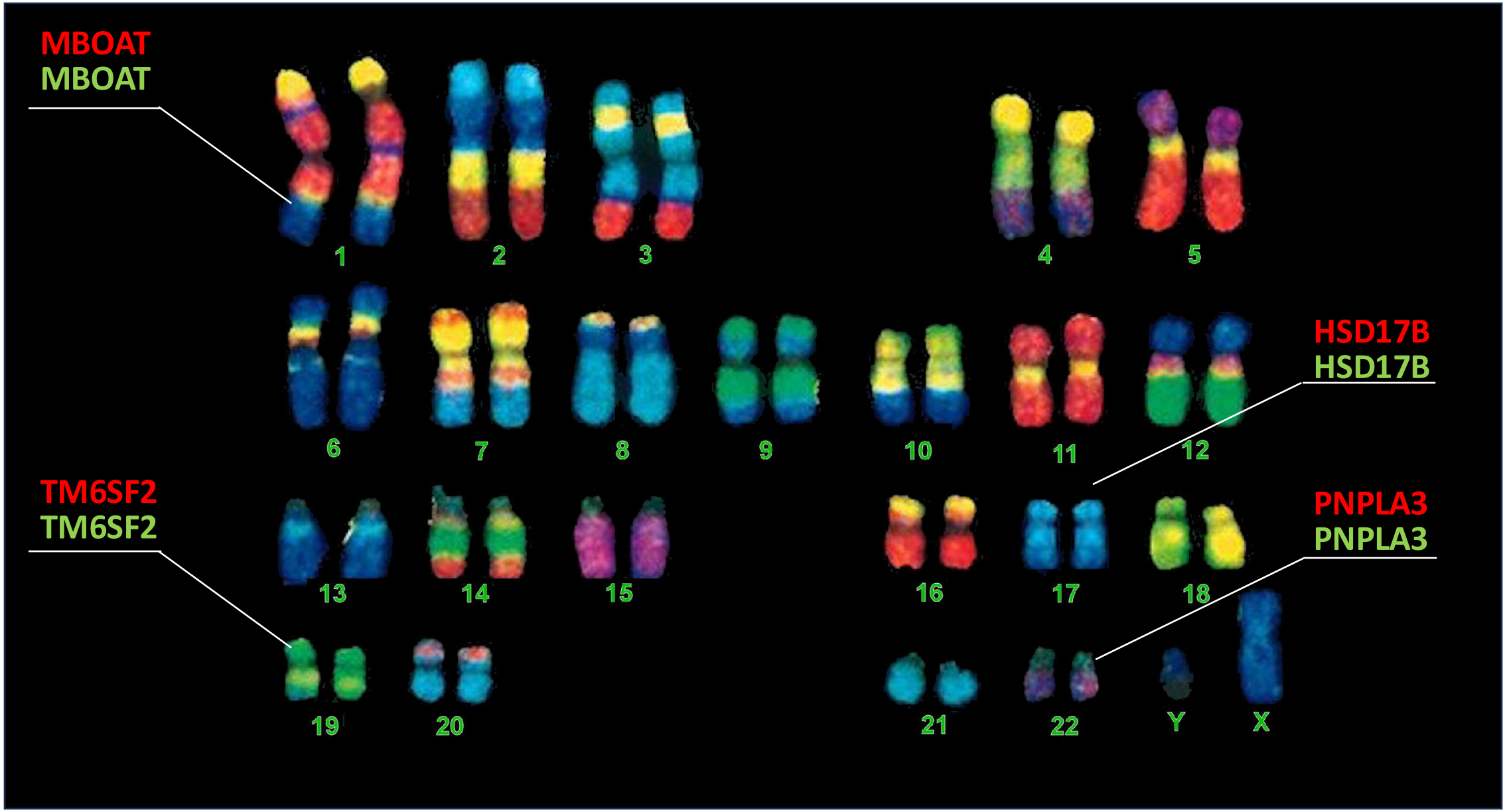
Common Genetic Determinants in MASH and ALD



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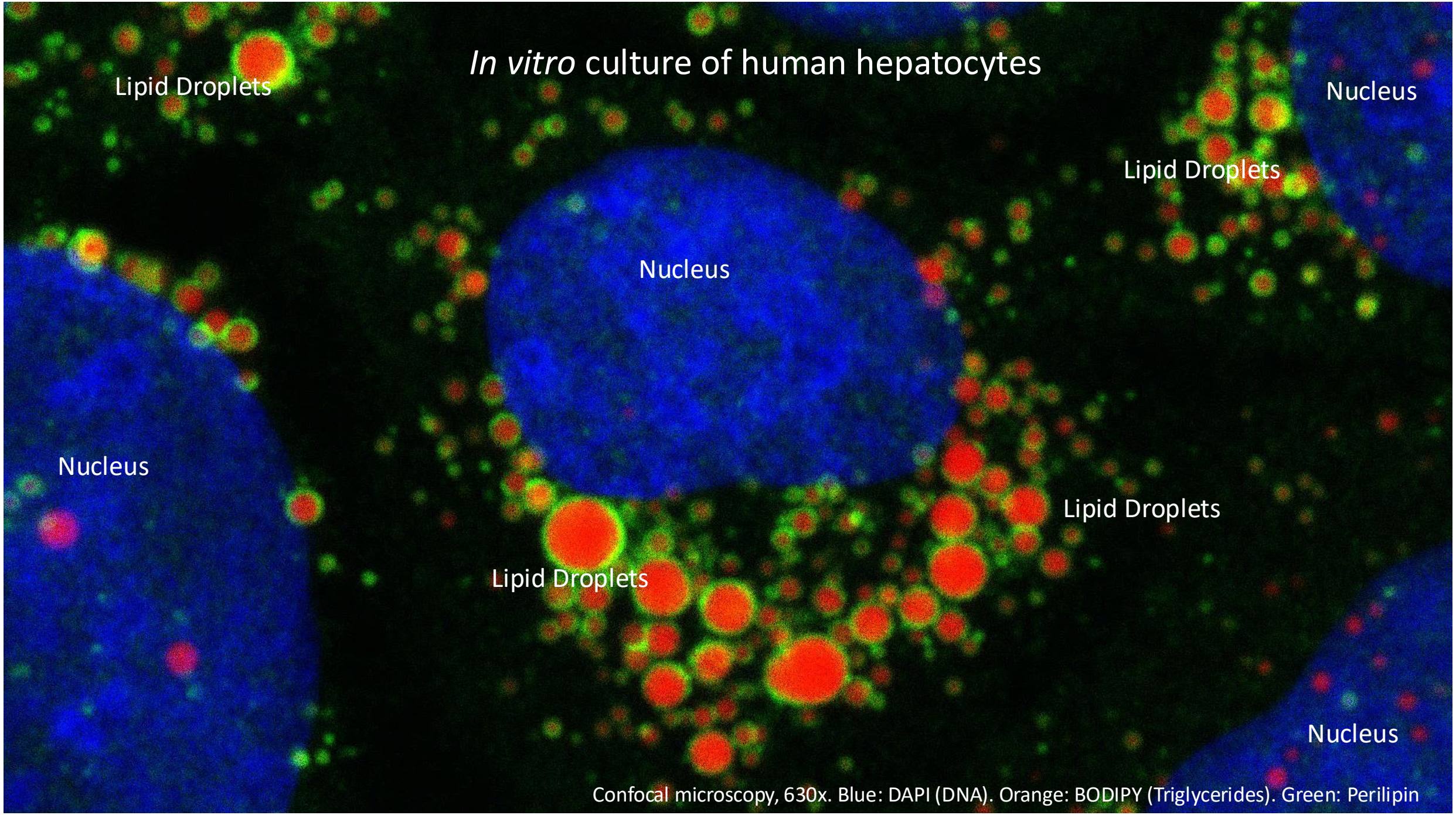
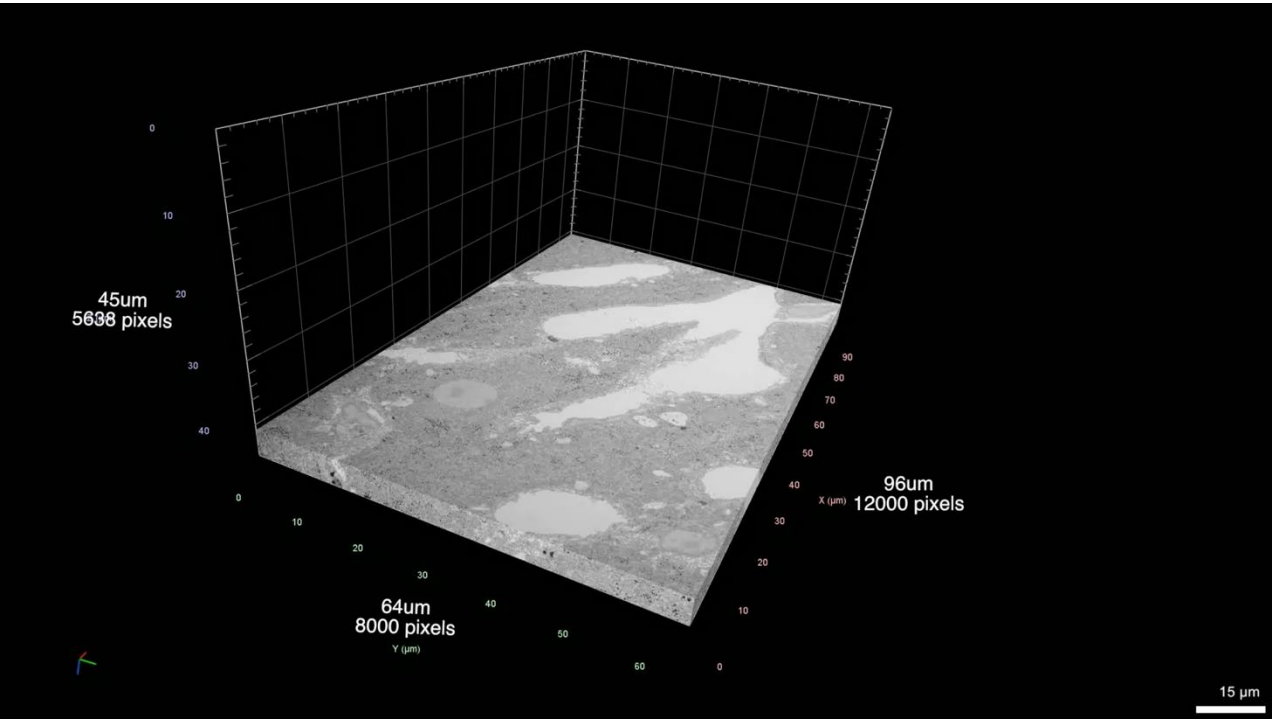
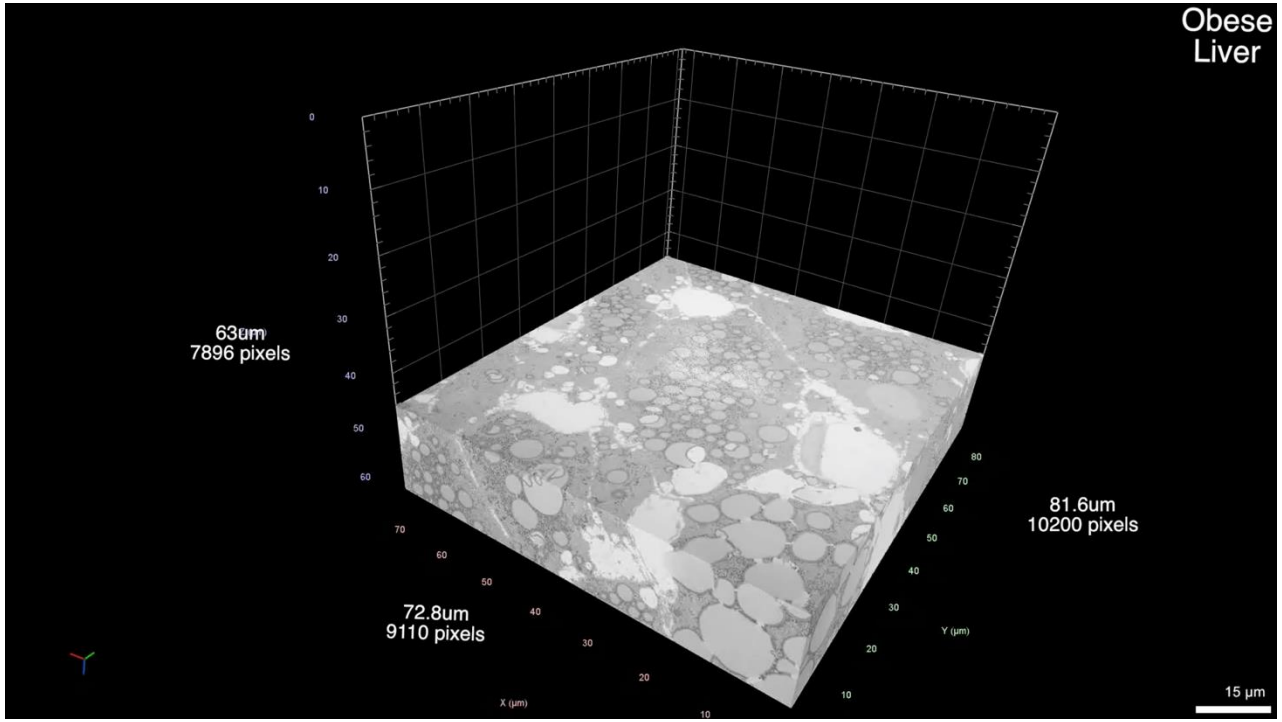

In vitro culture of human hepatocytes
Lipid Droplets
Nucleus
Lipid Droplets
Nucleus
Nucleus
Lipid Droplets
Lipid Droplets
Nucleus
Confocal microscopy, 630x. Blue: DAPI (DNA). Orange: BODIPY (Triglycerides). Green: Perilipin

Excess Fat Reshapes Hepatocyte Structure and Function

Healthy liver



Fatty liver



Parlakgul et al., Nature. 2022 Mar 9;603(7902):736–742.

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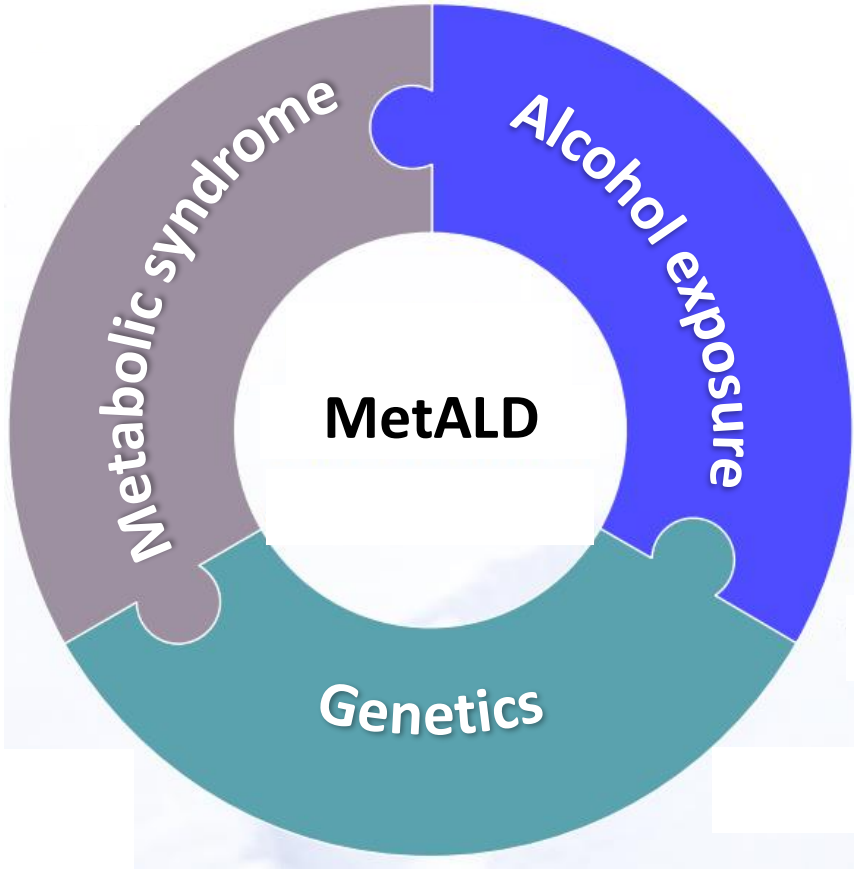
Interplay of Metabolic Risk, Alcohol, and Genetics in MetALD

1. Threshold effect of alcohol
2. Genetics x MASH interaction
3. Genetics x ALD interaction
4. Alcohol x Diabetes interaction
5. Alcohol x Metabolic Syndrome
6. Integrative model (pilot studies)



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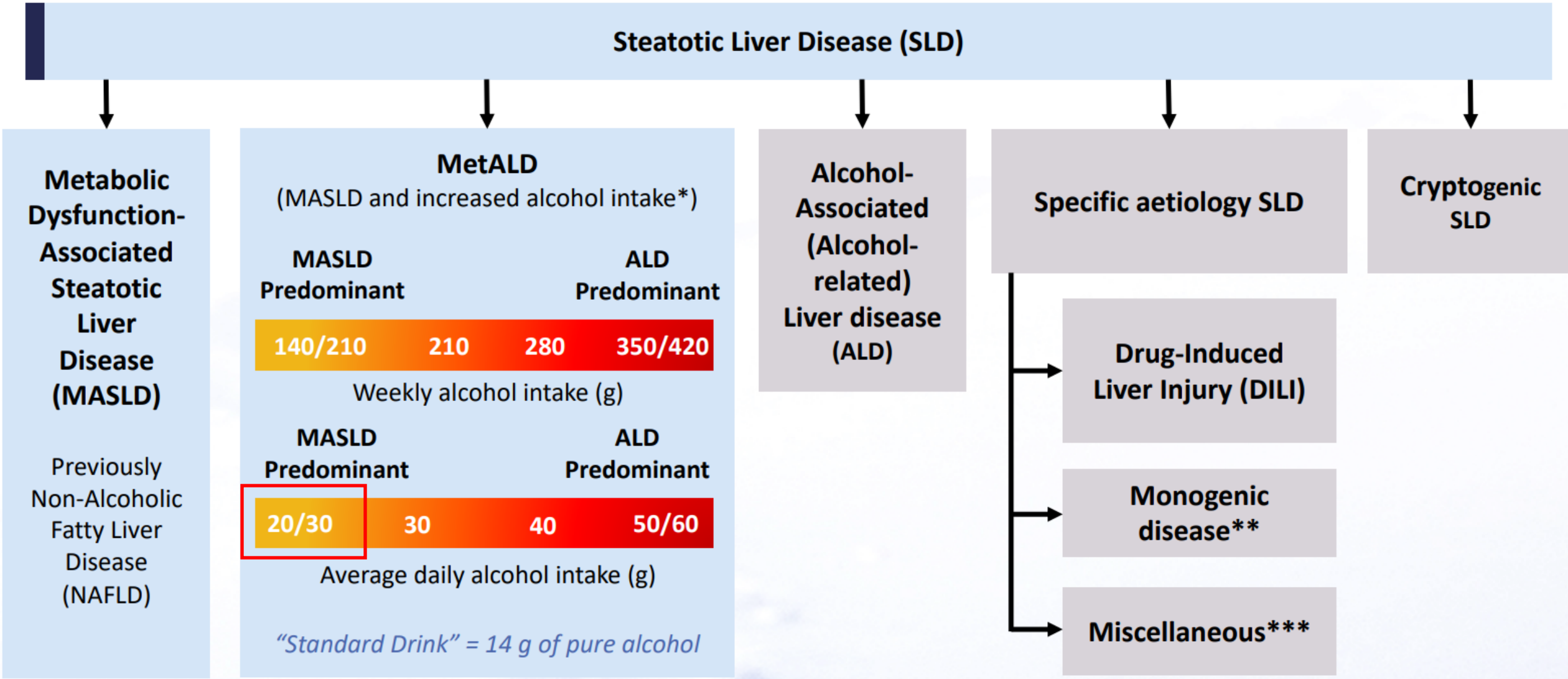
2023 Fatty Liver Disease Nomenclature



*) Average daily 20 - 50 g (1.4 – 3.6 drinks) female, 30 - 60 g (2.1 – 4.3 drinks) male
**) Lysosomal Acid Lipase Deficiency, Wilson disease, inborn errors of metabolism
***) HCV, malnutrition, celiac disease

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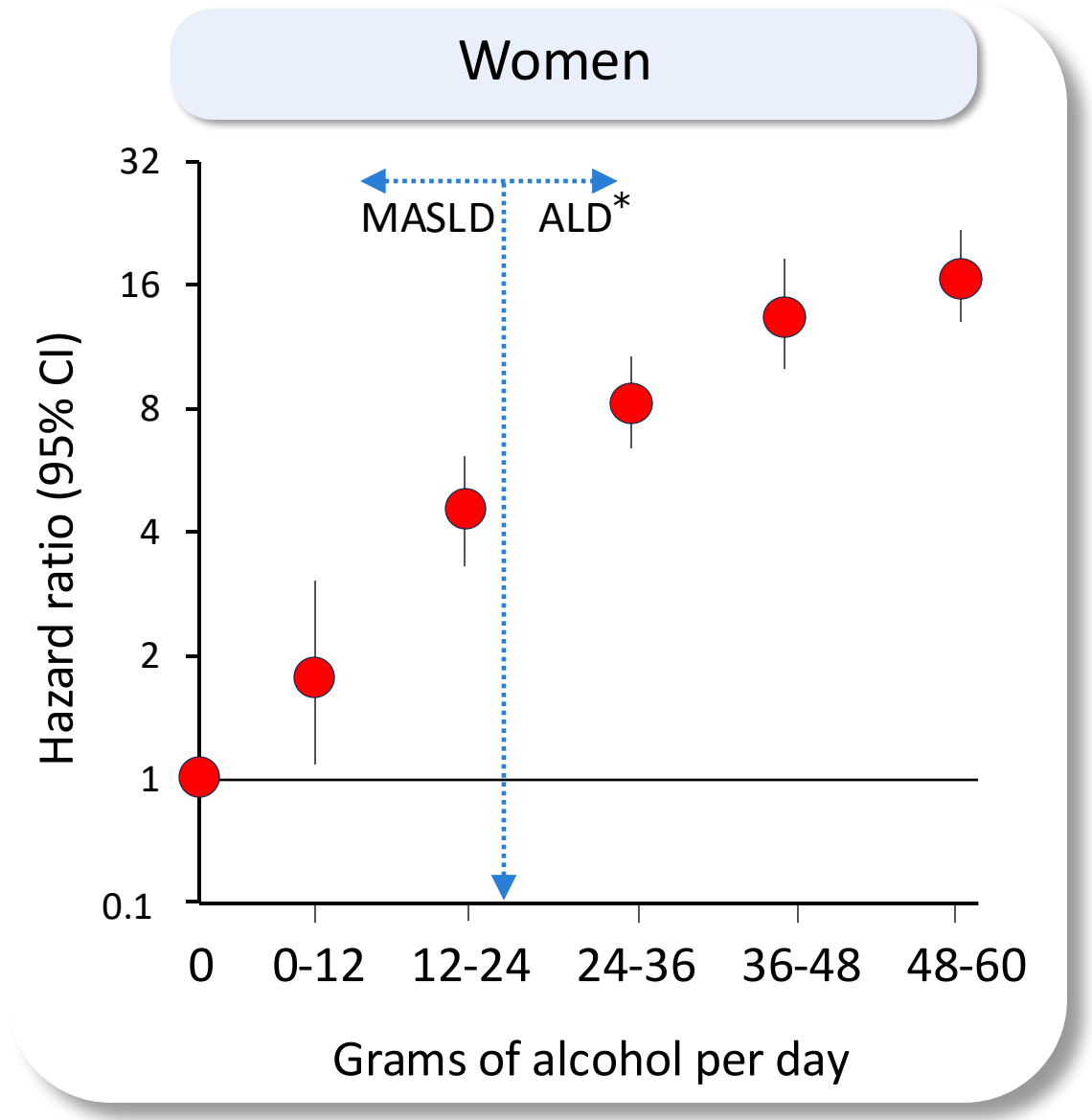
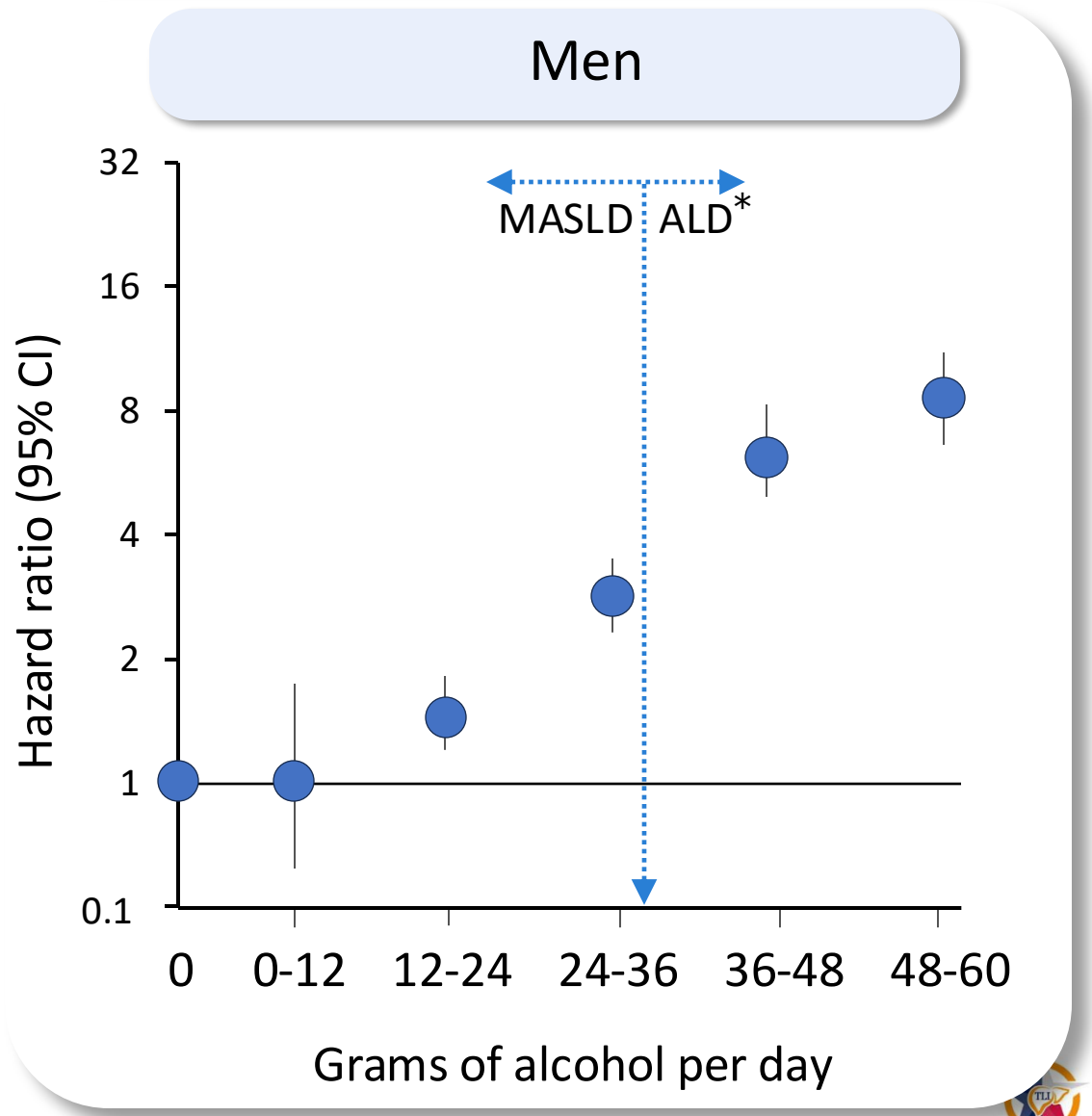
Rinella ME. Hepatology. 2023 Jun 24: PMID: 37363821

Alcohol Dose and Risk of Cirrhosis: Every Gram Matters



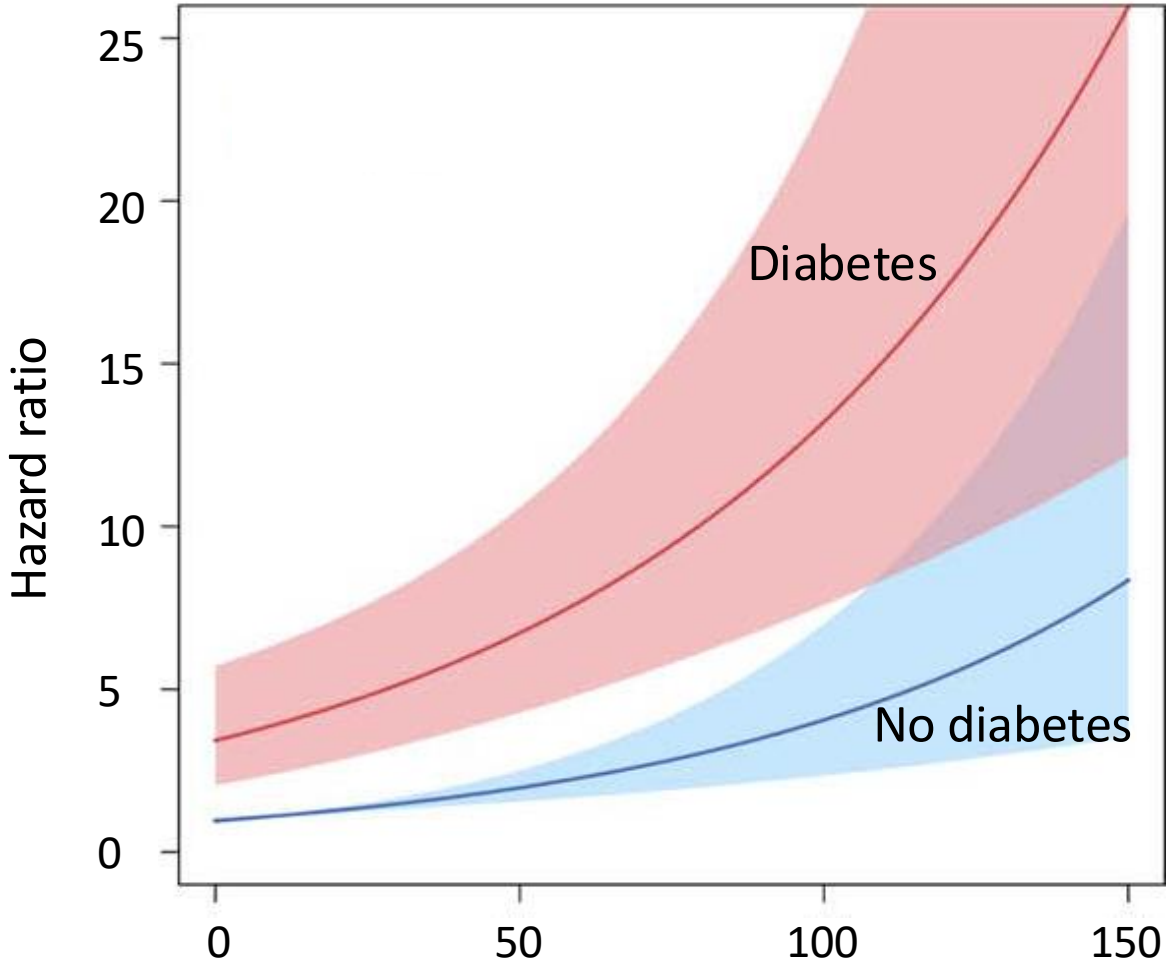


*) 2023 consensus threshold differentiating MASLD from MetALD

Rehm et al., Drug and Alcohol Review 2010;437-445

Interaction Between Alcohol and Diabetes in Fatty Liver Disease

Finnish registry study, N ~ 7000. Liver-related admissions, mortality, and liver cancer.



Aberg et al. Hepatology 2018:2141-2149

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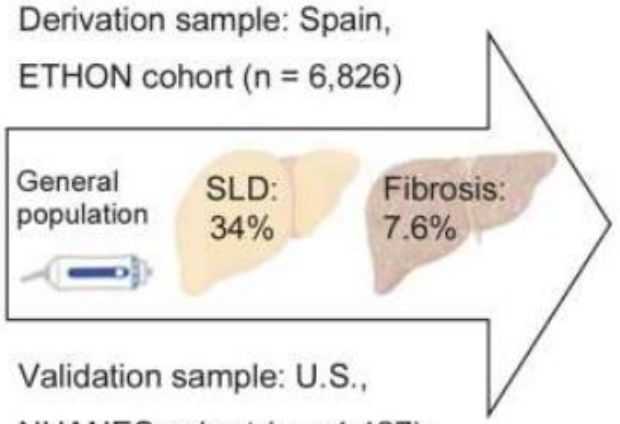
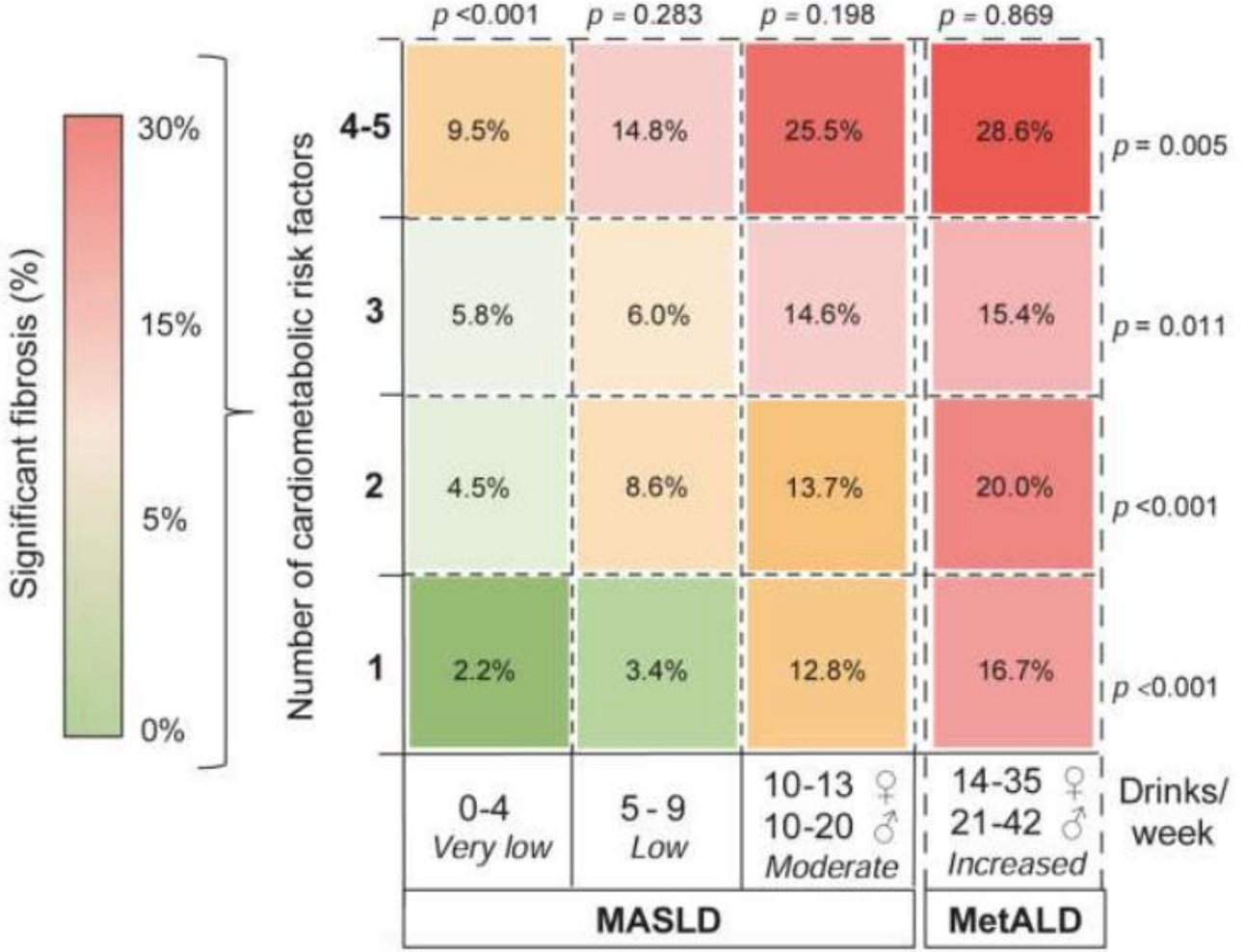
Alcohol Threshold and Speed of Progression of MetALD

MetALD

Low-to-moderate alcohol consumption is associated with **increased fibrosis** in individuals with **MASLD**



- Steatotic liver disease was defined as CAP ≥275 dB/m
- Significant fibrosis was defined as LSM ≥8.0 kPa
- Results refers to the derivation cohort
- Analysis was performed with Chi² test

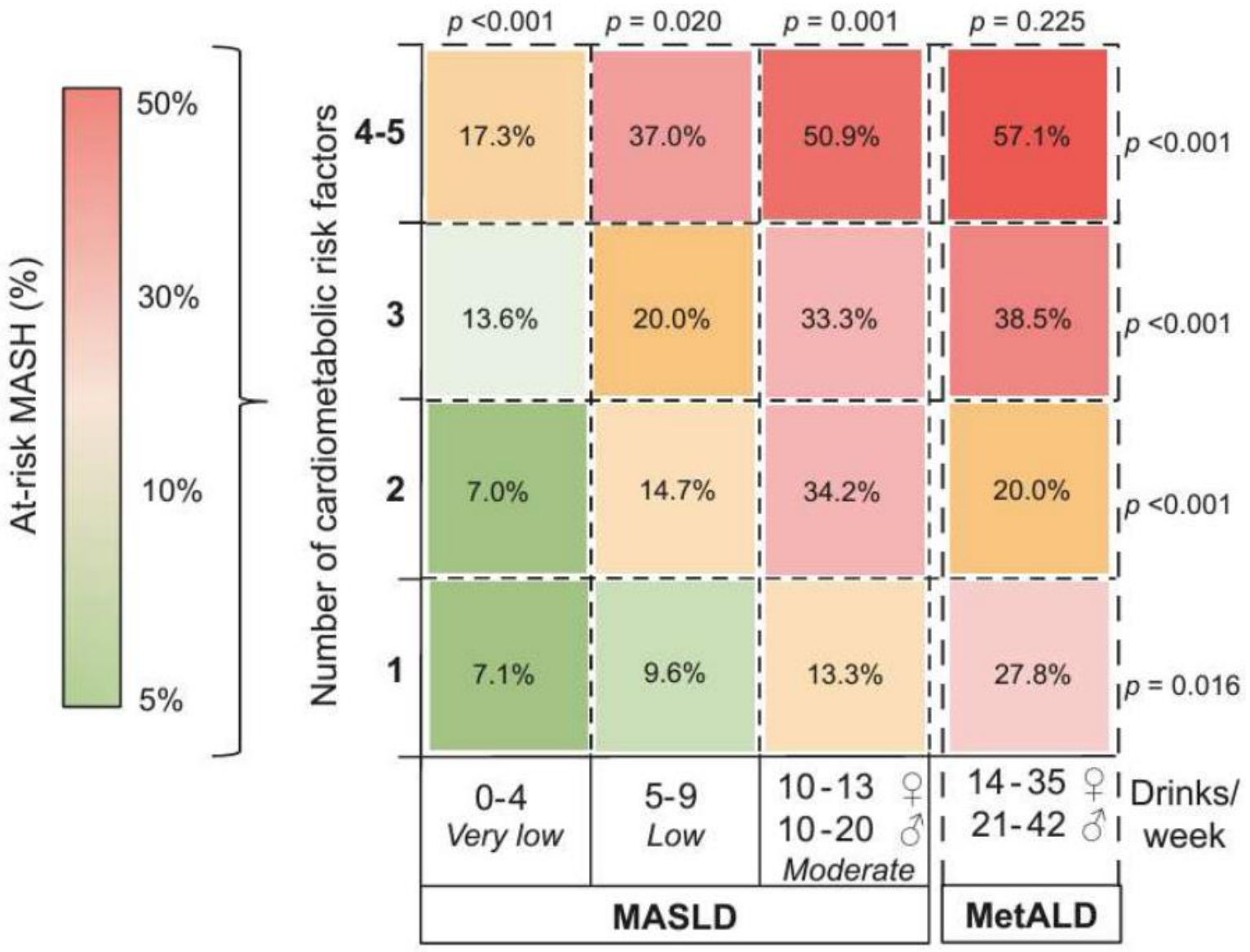


Marti-Aguado et al., J Hepatology 2024:S0168-8278

Alcohol Threshold and Speed of Progression of MetALD

MetALD

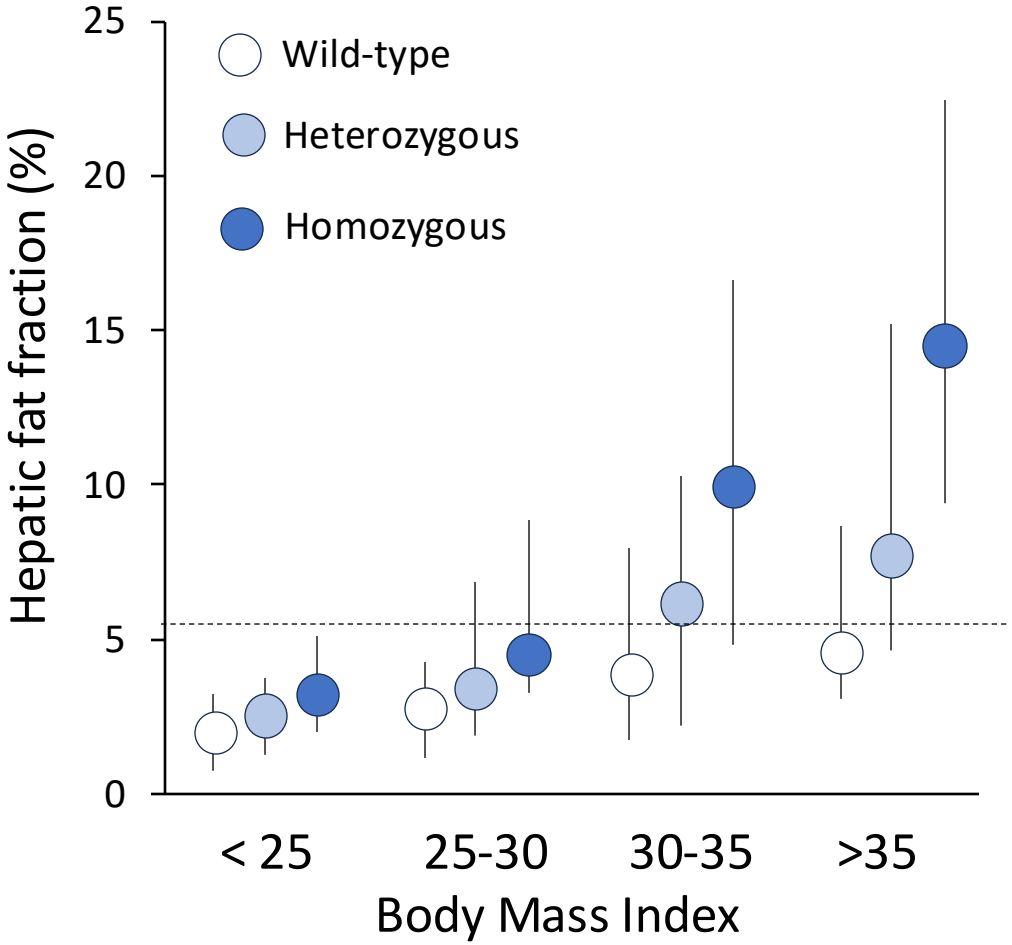
Low-to-moderate alcohol consumption is associated with **increased fibrosis** in individuals with **at-risk MASH**

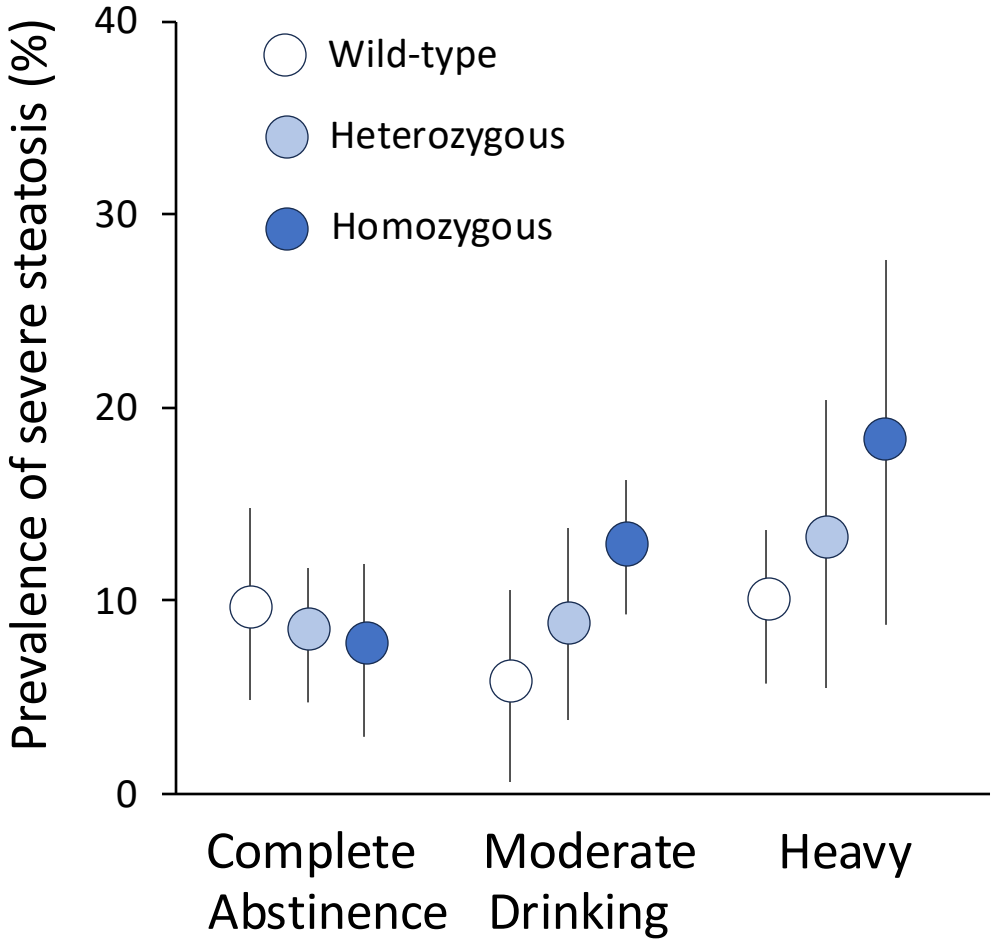


Marti-Aguado et al., J Hepatology 2024:S0168-8278

Gene-Environment Interactions in MASH and ALD

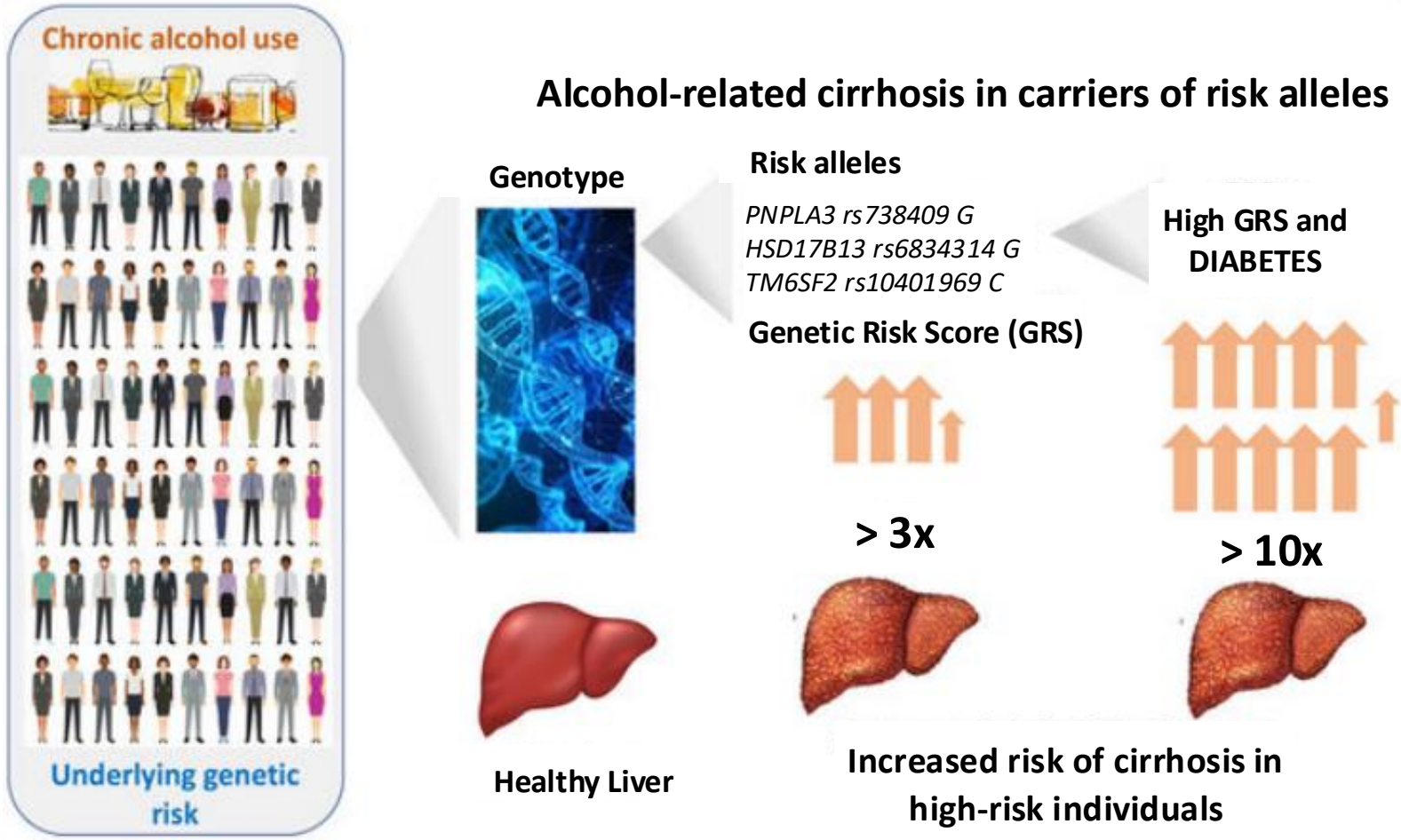
PNPLA3 I148M variant: a major genetic determinant of steatosis in Hispanic > Caucasian > African American populations





Kozlitina et al., Nat Genet. 2017 Jun;49(6):842-847; Lazo et al., CGH 2021;2606-2614

A Genetic Risk Score Predicts Development of MetALD Cirrhosis in Drinkers



Whitfield et al., *Journal of Hepatology* 2022:275-282

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A Genetic Risk Score Predicts Development of MetALD Cirrhosis in Drinkers

1. Calculate the risk score as:

(0.7839*__PNPLA3__ rs738409 G dosage) + (0.5423*__TM6SF2__ rs10401969 C dosage) – (0.4463*__HSD17B13__ rs6834314 G dosage)

2. Assign the patient to the appropriate stratum of risk, as follows:

	Score less than 0 Low risk	Score above 0.7 High risk
Relative risk if not diabetic	1 (reference)	3-fold
Relative risk if diabetic	3-fold	Over 10-fold

Patients with scores between 0 and 0.7 are at intermediate risk.

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Whitfield et al., *Journal of Hepatology* 2022:275-282

Medications for MASH: Dual Benefit on Alcohol Intake in Select Therapies

Compound	Mechanism	Effect on alcohol intake
Resmetirom	THR-beta agonist	-
Lanifibranor	Pan-PPAR agonist	-
Pegozafermin	FGF21 analogue	Suppression of alcohol consumption
Efruxifermin	FGF 21 analogue	
Semaglutide	GLP-1 agonist	
Survodutide	GLP-1 agonist	

Clinical trials design in MetALD should address outcomes from MASH and also from alcohol use disorder perspective.

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Conclusions

- ALD and MASH have overlapping pathogenesis, genetics, histology, and clinical course.
- Patients who drink in excess often have metabolic syndrome.
- Alcohol is additive with metabolic syndrome in the development and progression of fatty liver disease.
- Insulin resistance and genetic susceptibility have considerable, independent impact on progression of liver disease.
- In patients with steatotic liver disease, safe limits of alcohol use concerning liver risk do not exist.

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