Alcohol as an Accelerator of MASH

Distinct Triggers, Shared Outcomes

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The Road to A Healthier Liver

Key Takeaways

1. **ALD and MASH are not separate diseases**
   They synergize through shared biology, accelerating fibrosis and clinical progression.

2. **Lipid flux—not fat itself—is the central driver**
   Genetics, alcohol, and metabolic stress converge on impaired hepatocyte lipid handling.

3. **Alcohol remains the dominant modifiable risk factor**
   Abstinence has the greatest impact on progression, recompensation, and survival.

4. **Emerging therapies target both biology and behavior**
   GLP-1–based and FGF21 therapies address food intake, alcohol craving, and metabolic pathways.

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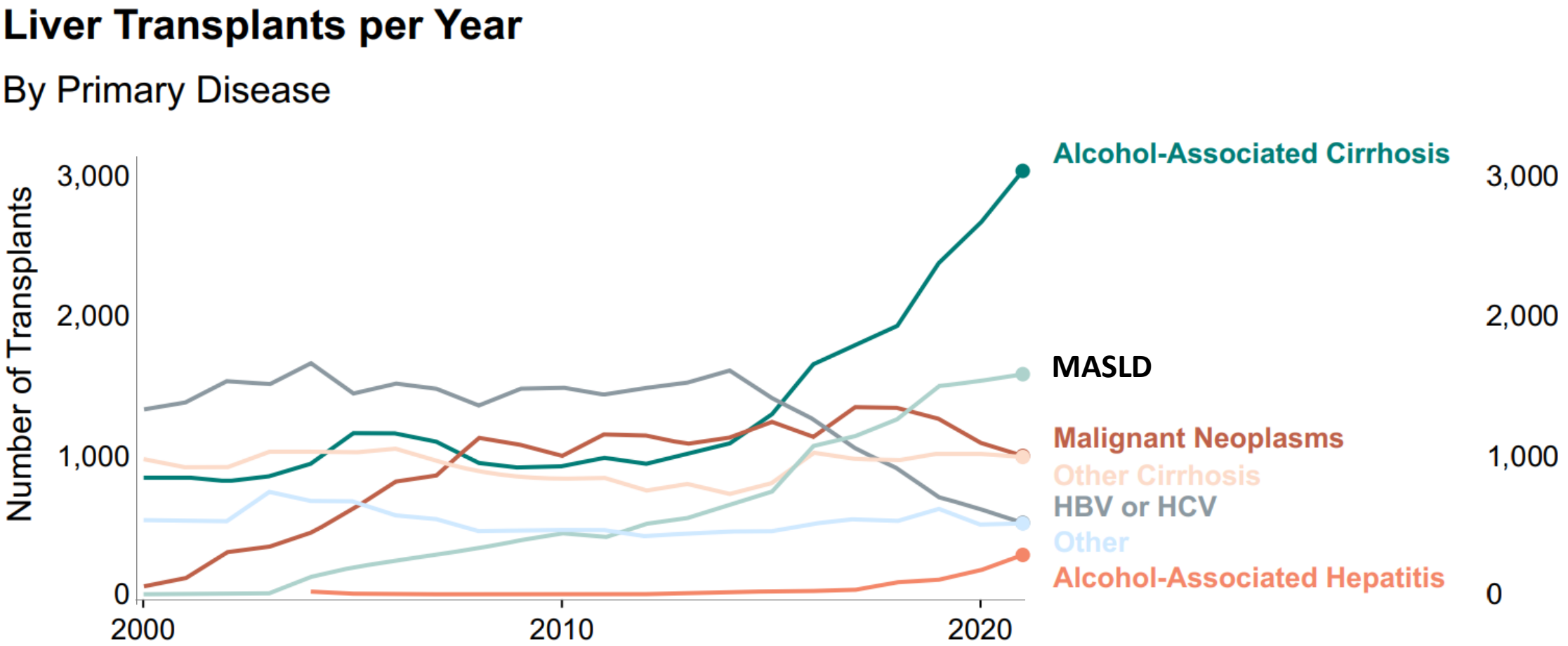
The New Transplant Reality: Alcohol and Metabolic Liver Disease



Vock et al., Liver Transpl. 2025 Jan 1;31(1):32-44.

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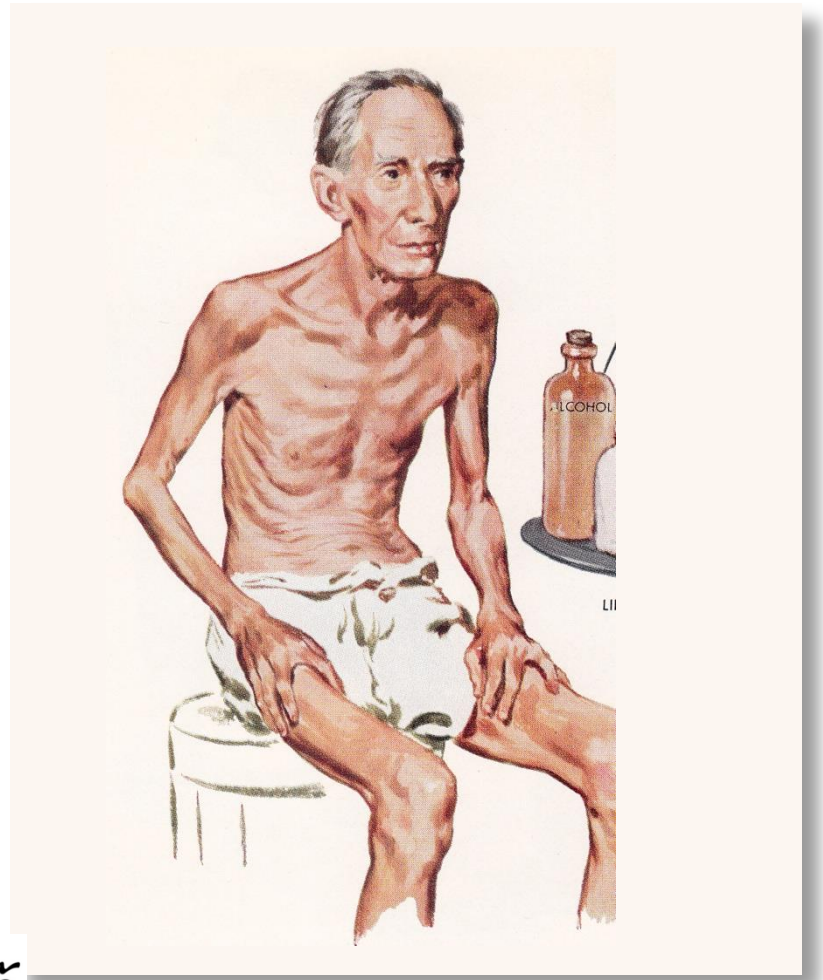
Fatty Liver: Evolving Concept of a Disease Spectrum

Alcohol

- **Synergism**

MASH



F. Netter M.D.

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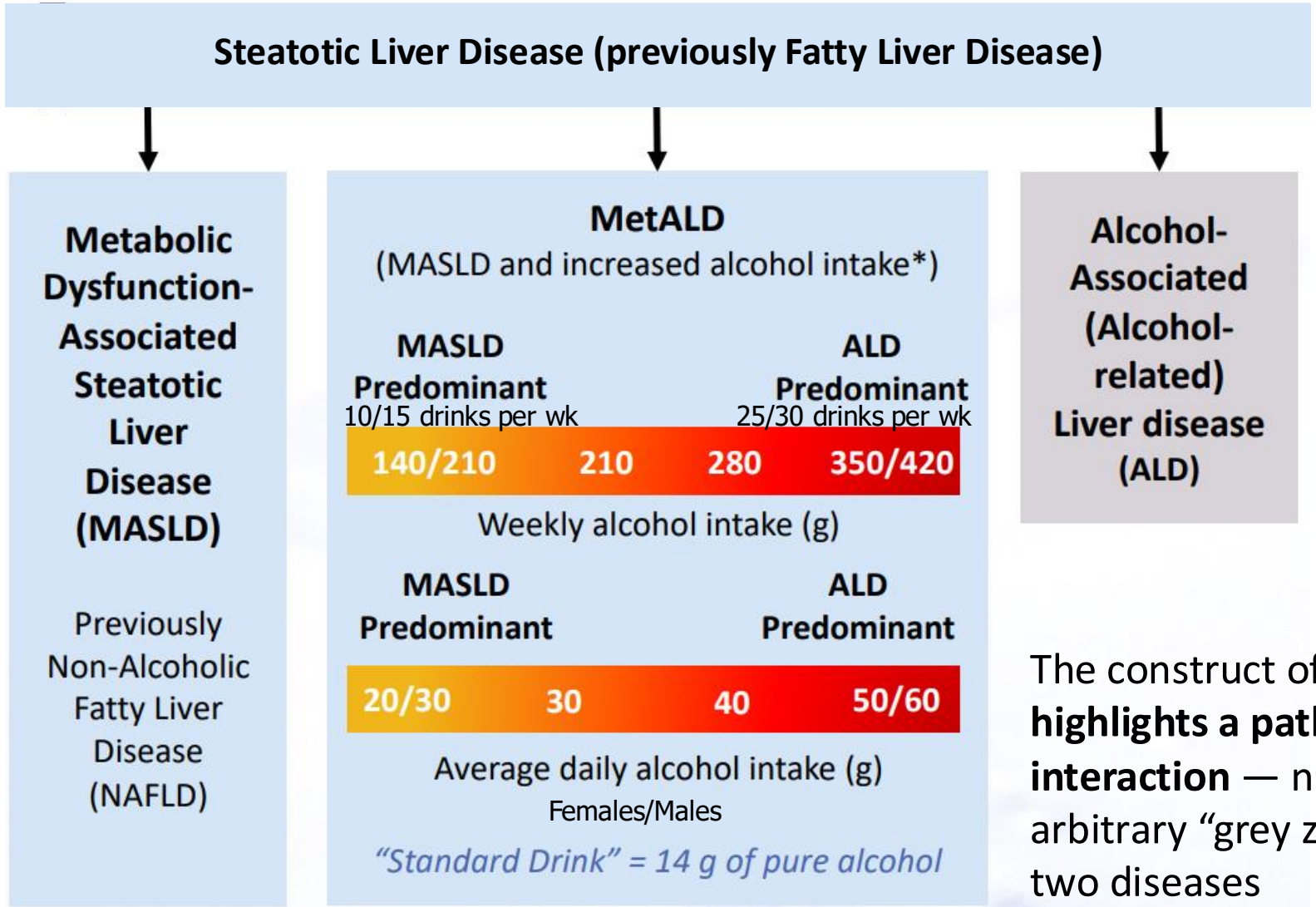
2023 Fatty Liver Disease Nomenclature – Cognitive Fallacies



The construct of *MetALD* **highlights a pathophysiologic interaction** — not just an arbitrary "grey zone" between two diseases

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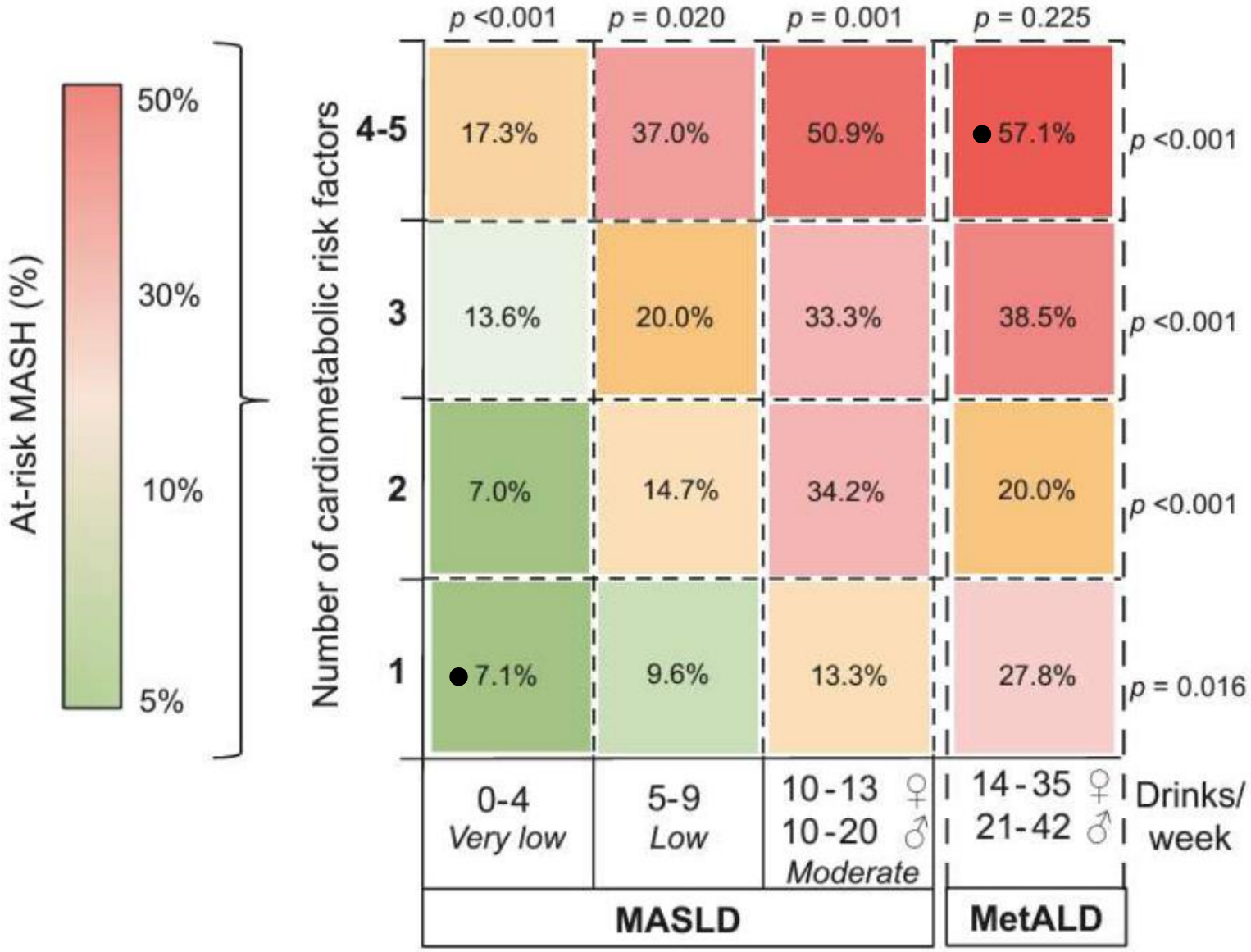
Rinella et al., Hepatology. 2023 Dec 1;78(6):1966-1986.

Synergism in MetALD: Alcohol and Metabolic Risk are Mutual Amplifiers



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

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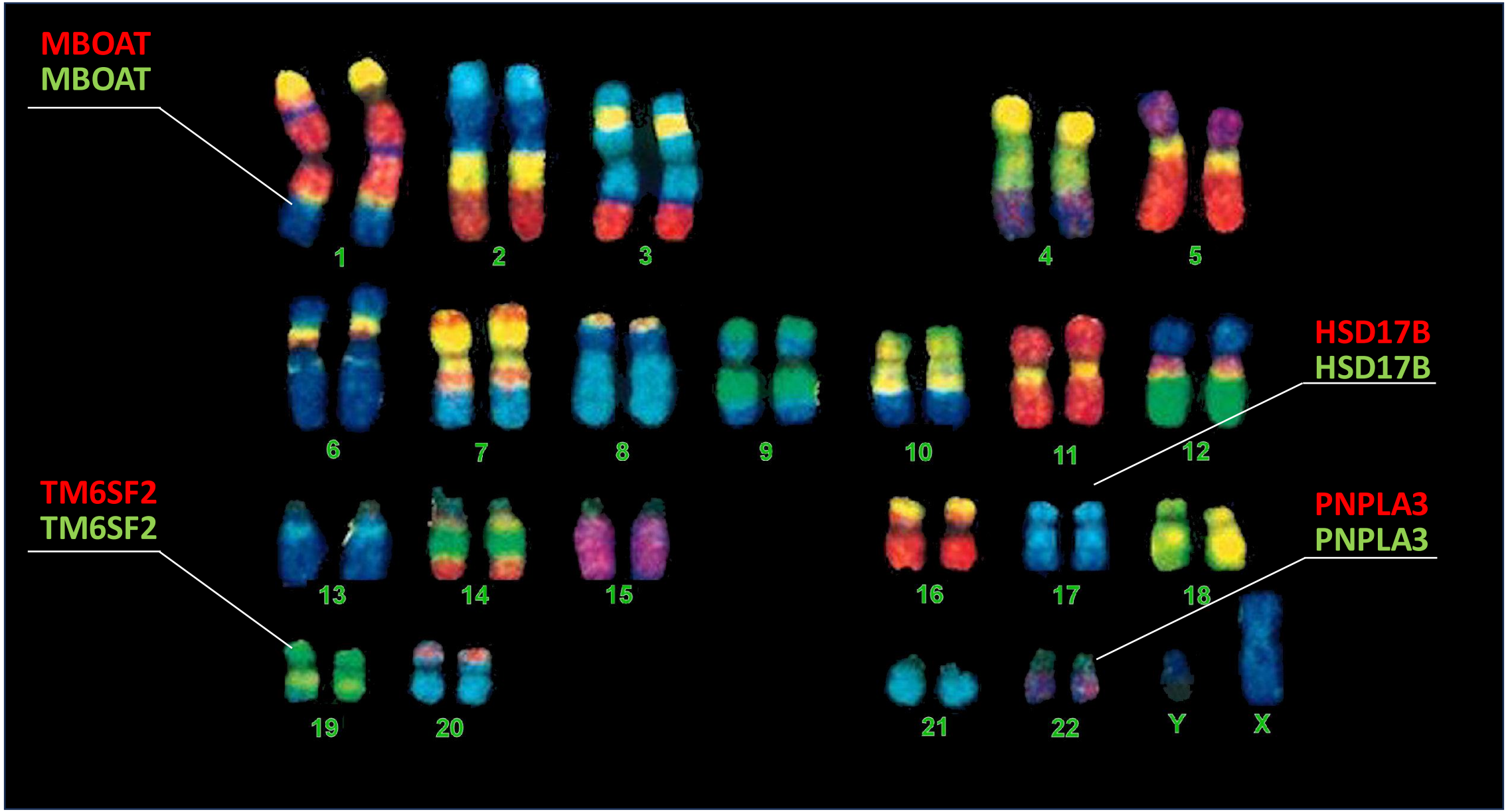
Identical Genetic Determinants in ALD and MASH



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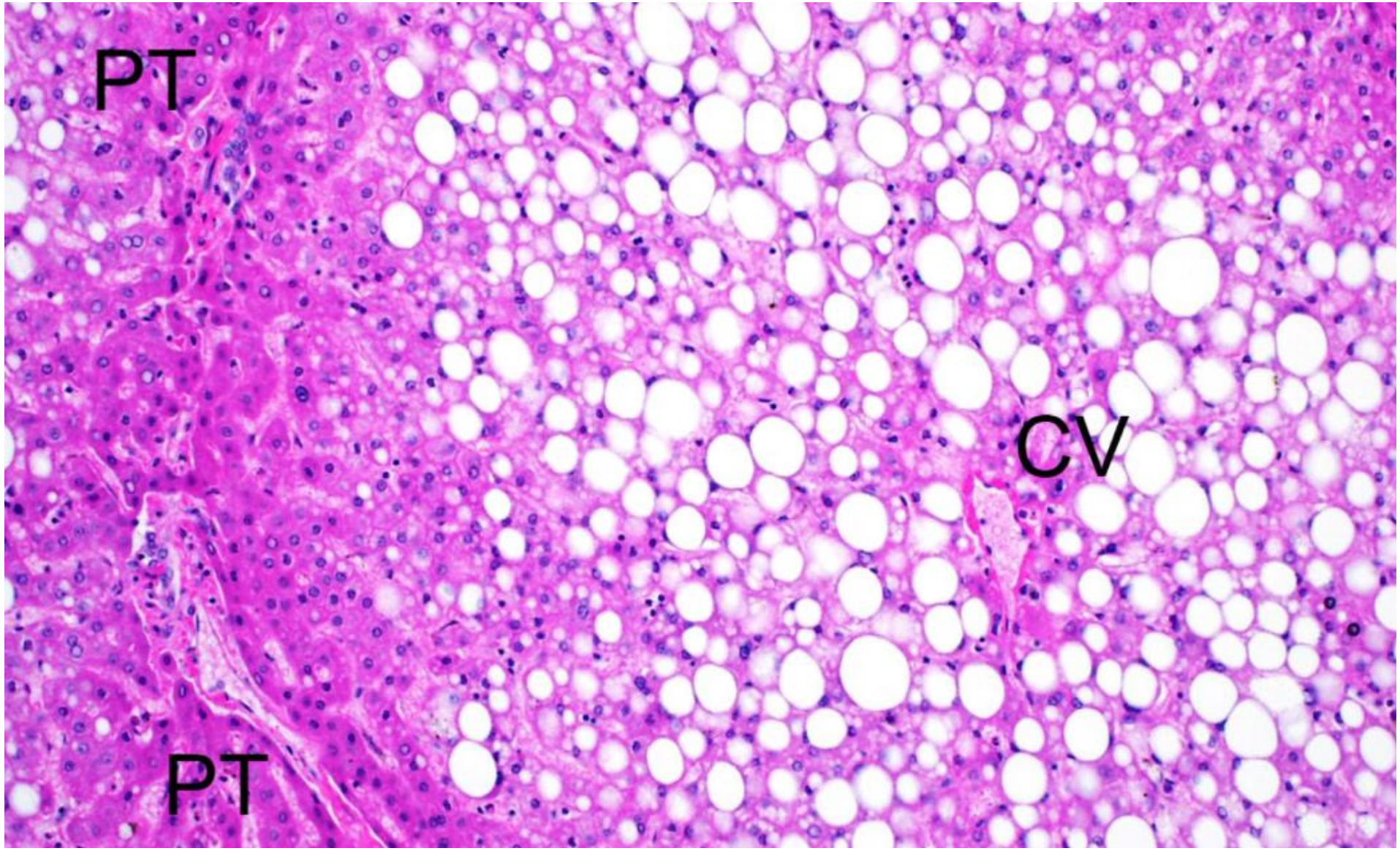
What Genetics Taught Us: Hepatocyte Lipid Handling in ALD/MASH



Liver biopsy; H&E, magnification 100x

PT, portal tract; CV, central vein

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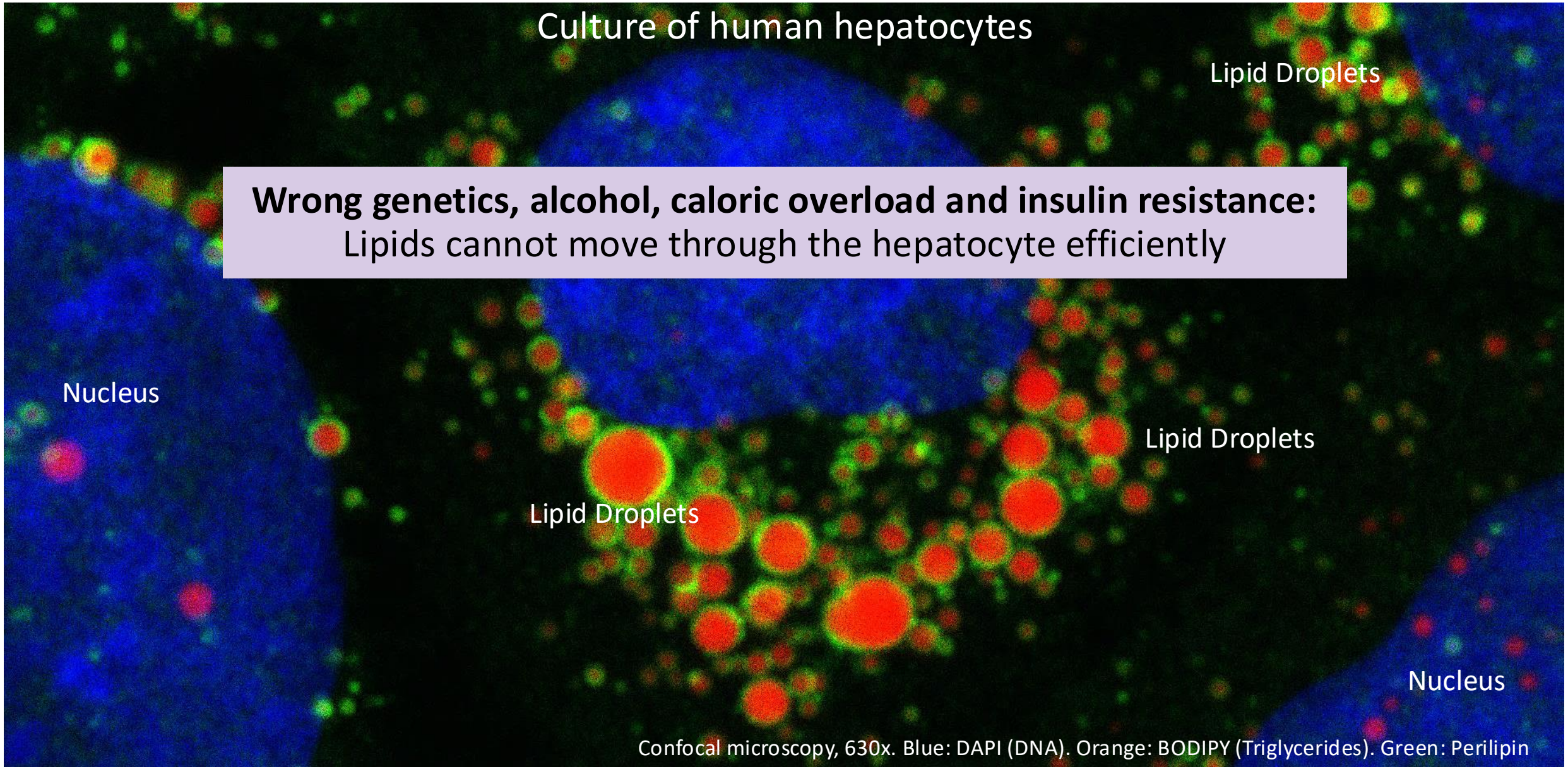
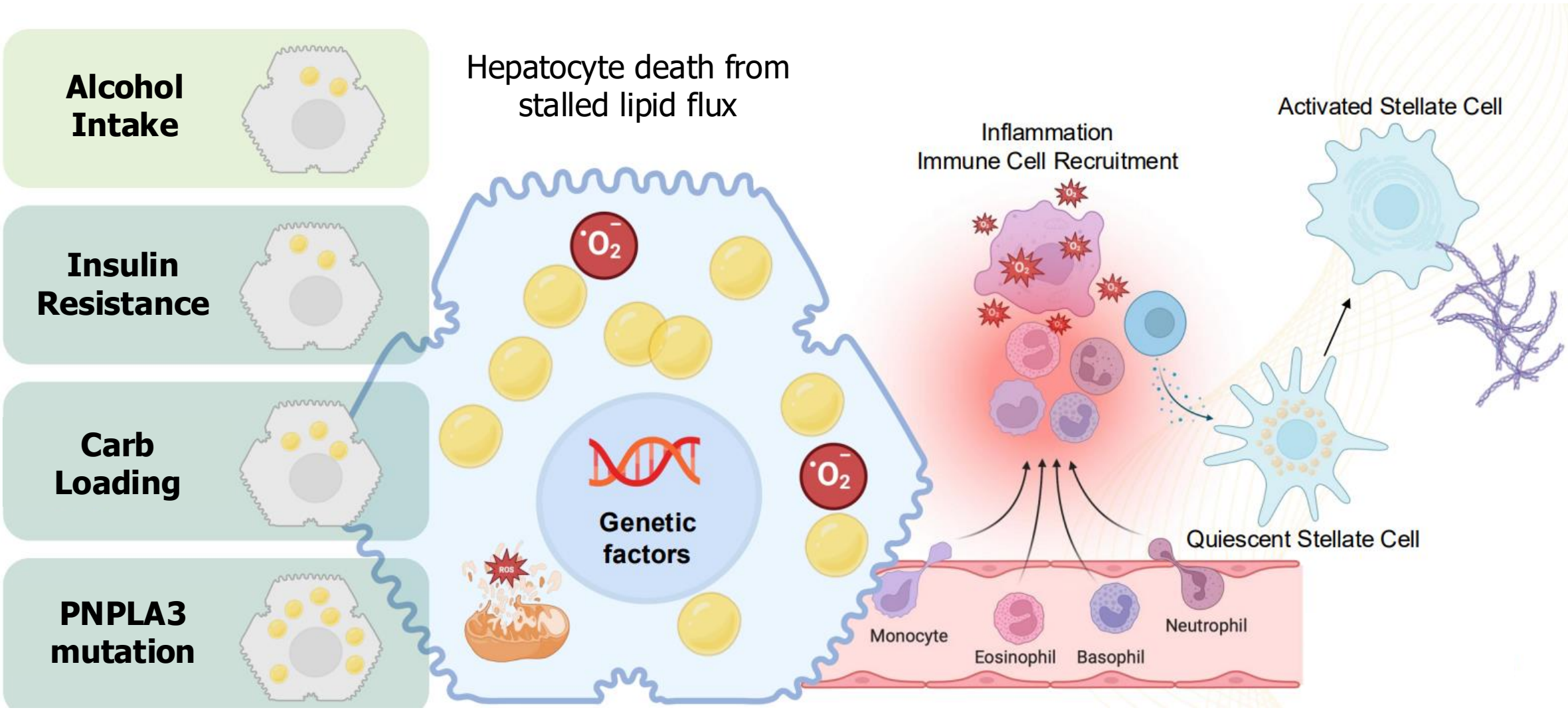
The Hepatic Lipid Flux Mechanism



If Lipid Flux Stalls: Common Pathobiology of MASH & ALD



Ntandja-Wandji LC, JHEP Rep. 2020 May 22;2(3):100101.

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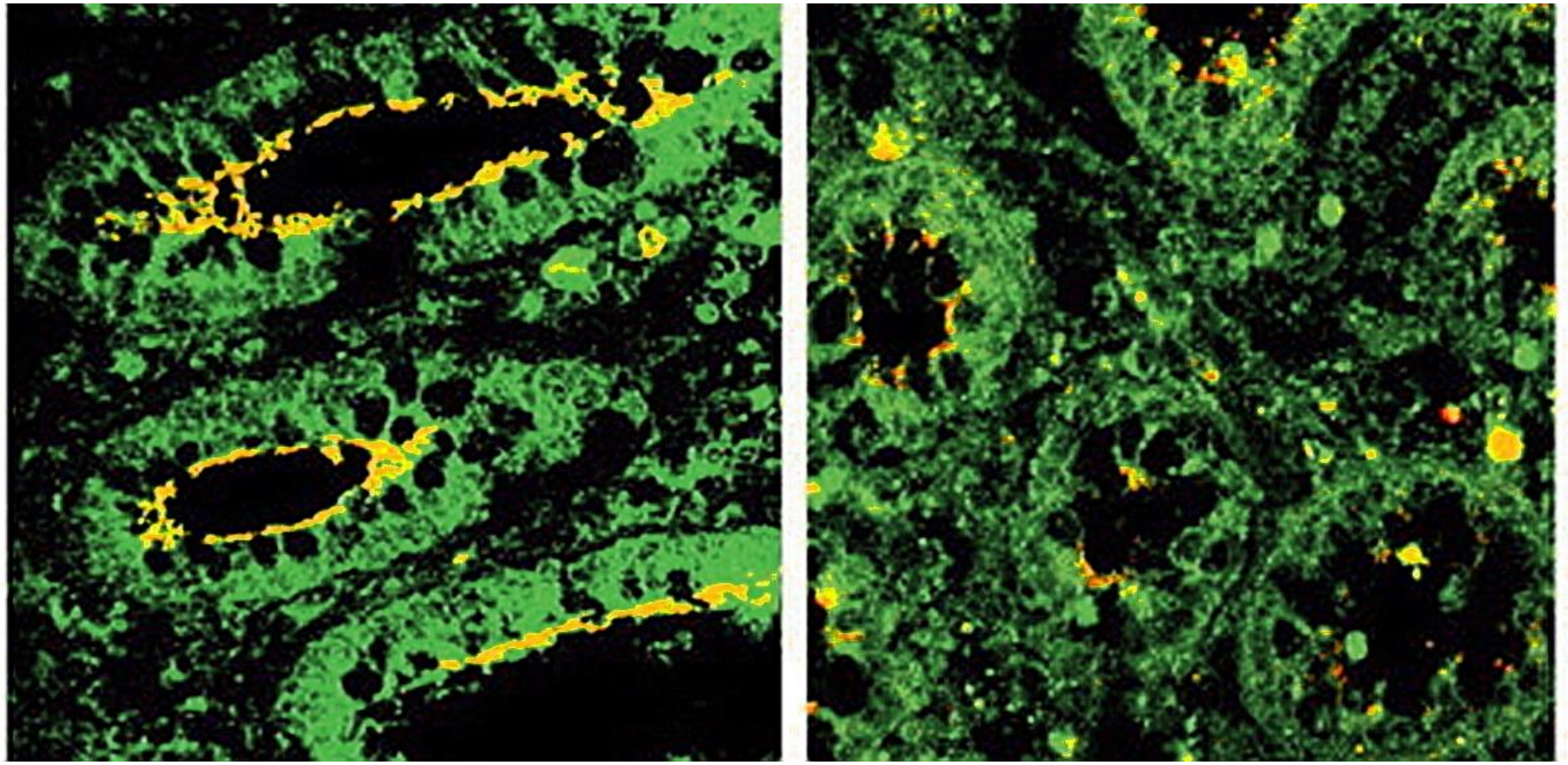
Disrupted Intestinal Barrier ("Leaky Gut") in ALD

Human colonic mucosal biopsies

Control **Alcohol**



Yellow: ZO-1 (marker of tight junctions). Green: intestinal cells.
Confocal microscopy.

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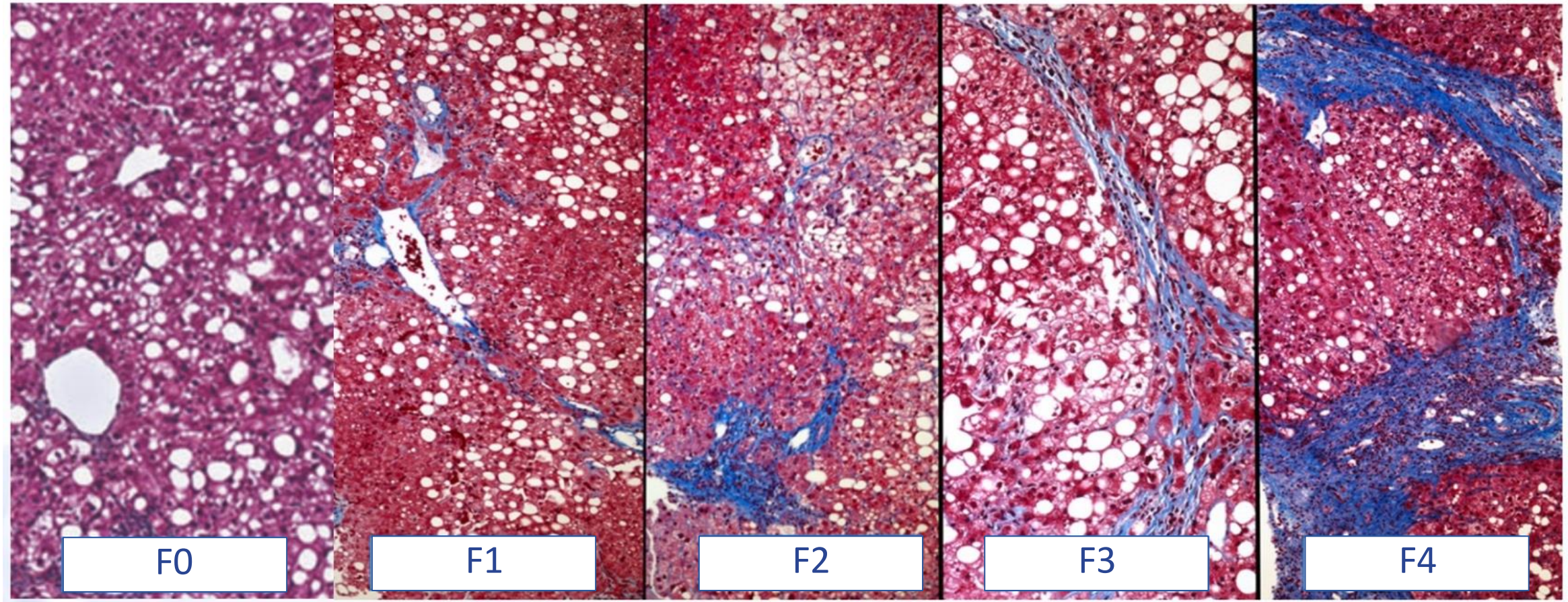
Basuroy S et al. Am J Physiol Gastrointest Liver Physiol 2005;289:G367-G375

Fibrosis Progression in MASH and ALD



Estes et al., Hepatology 2018:123-133

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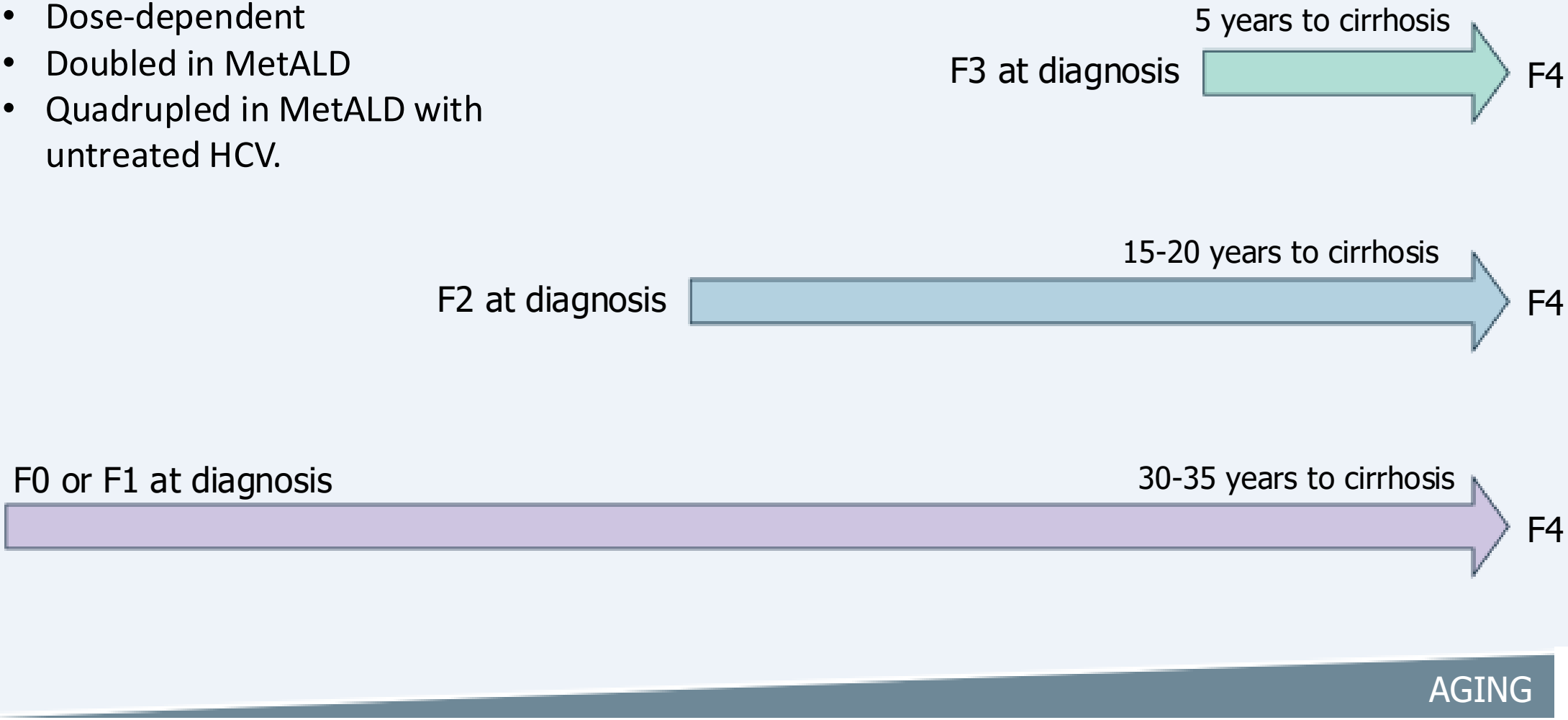
Natural History of ALD or MASH: Fibrosis Stage, and Disease Trajectory

The rate of fibrosis progression is:

- Dose-dependent
- Doubled in MetALD
- Quadrupled in MetALD with untreated HCV.



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Foundational Interventions are Necessary – But not Sufficient

LIFESTYLE & WEIGHT LOSS

- **Weight loss ≥7–10%**
  MASH resolution → fibrosis regression
- **Mediterranean-style diet**; avoid sugar-sweetened drinks, refined carbs
- **≥150 min/week activity**

ALCOHOL COUNSELING

- **High priority**
  Even light/moderate alcohol + metabolic risk = ↑ fibrosis
- **No safe threshold** in MASLD
- **Binge pattern especially harmful**
  Oxidative stress, hepatocellular injury
- **Early counseling** to prevent progression to MetALD

No therapy rivals abstinence in altering outcomes* in ALD and MetALD.

*) progression, recompensation, survival

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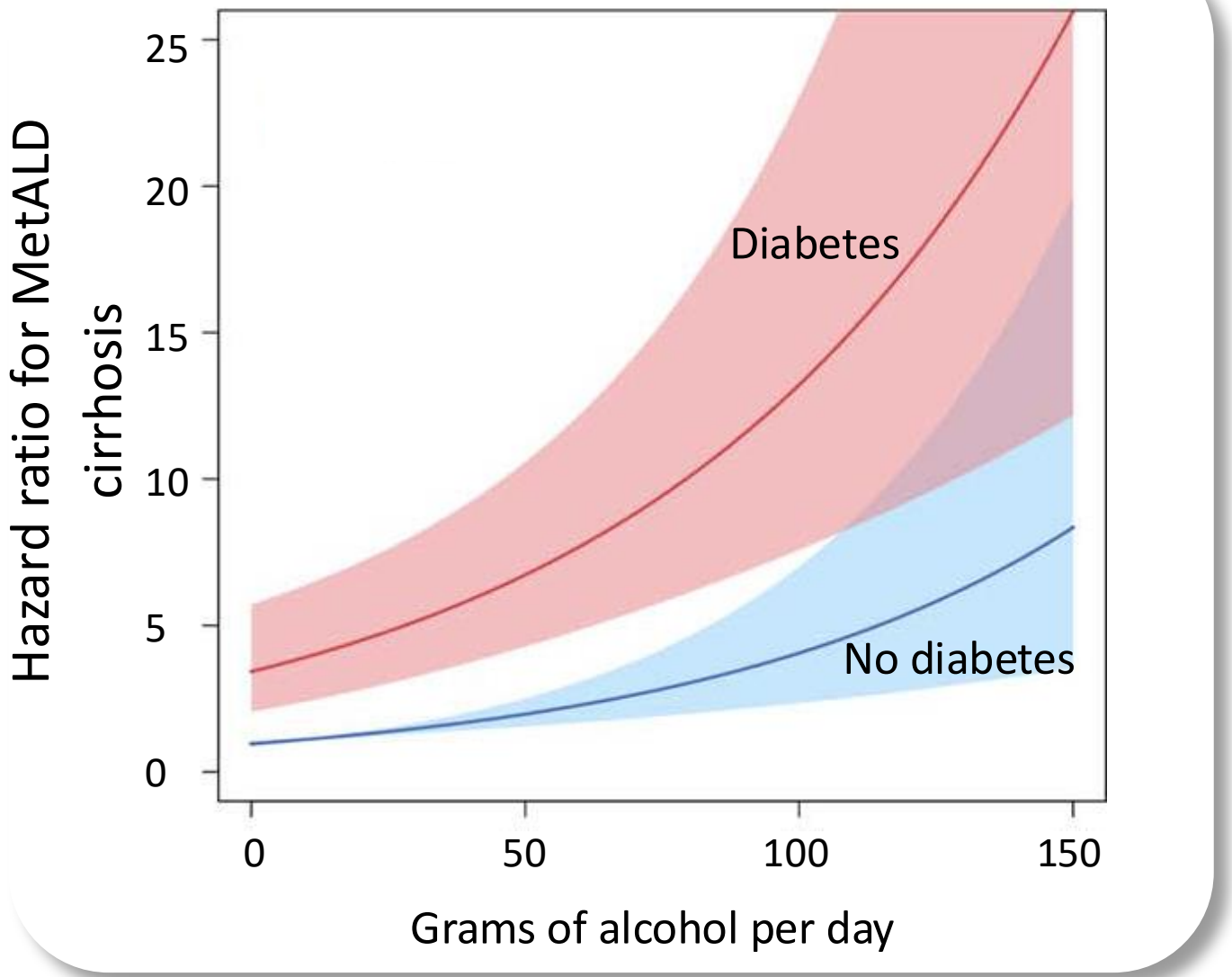
Interaction Between Alcohol and Diabetes in Fatty Liver Disease

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



Aberg et al. Hepatology 2018:2141-2149

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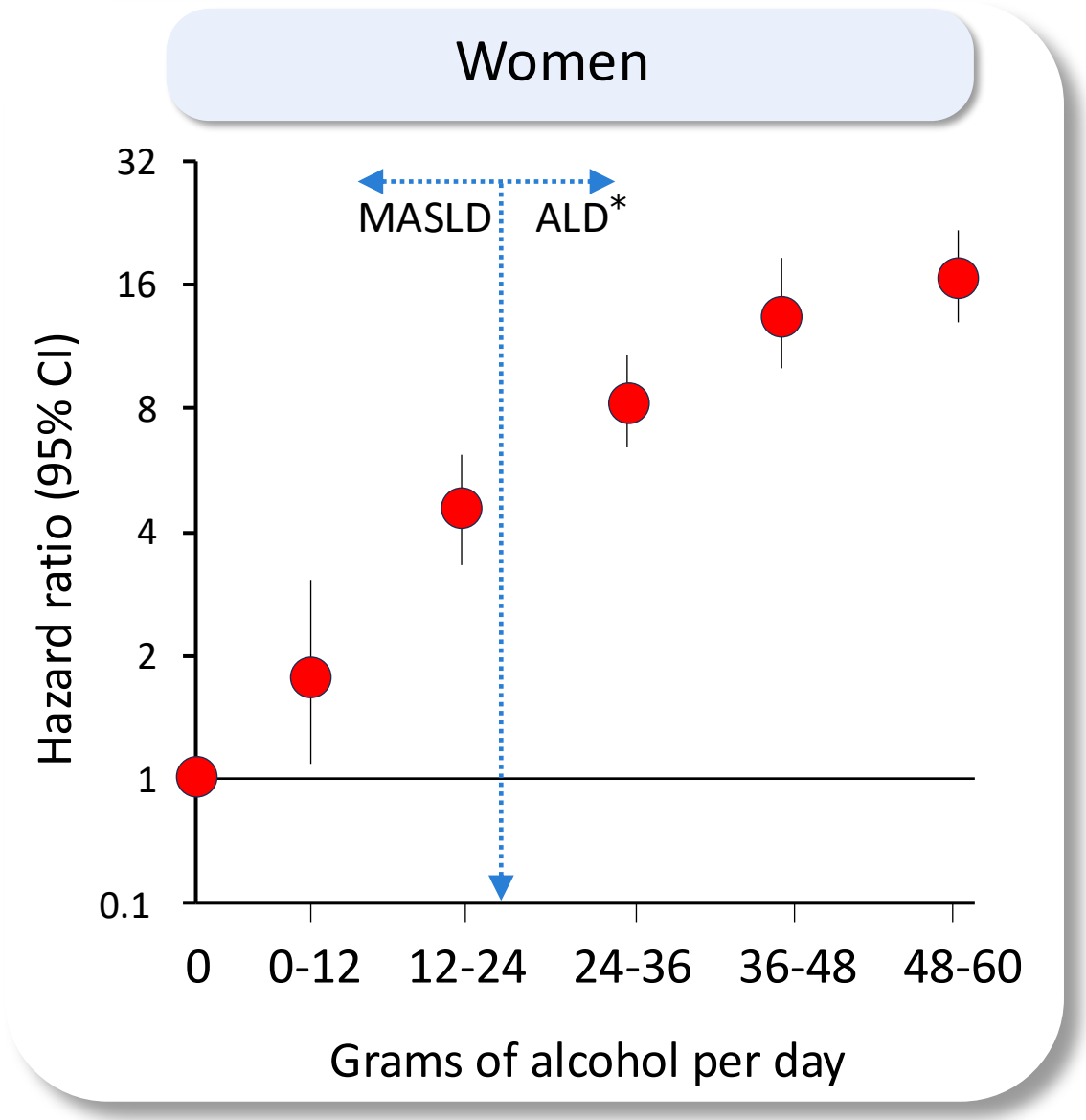
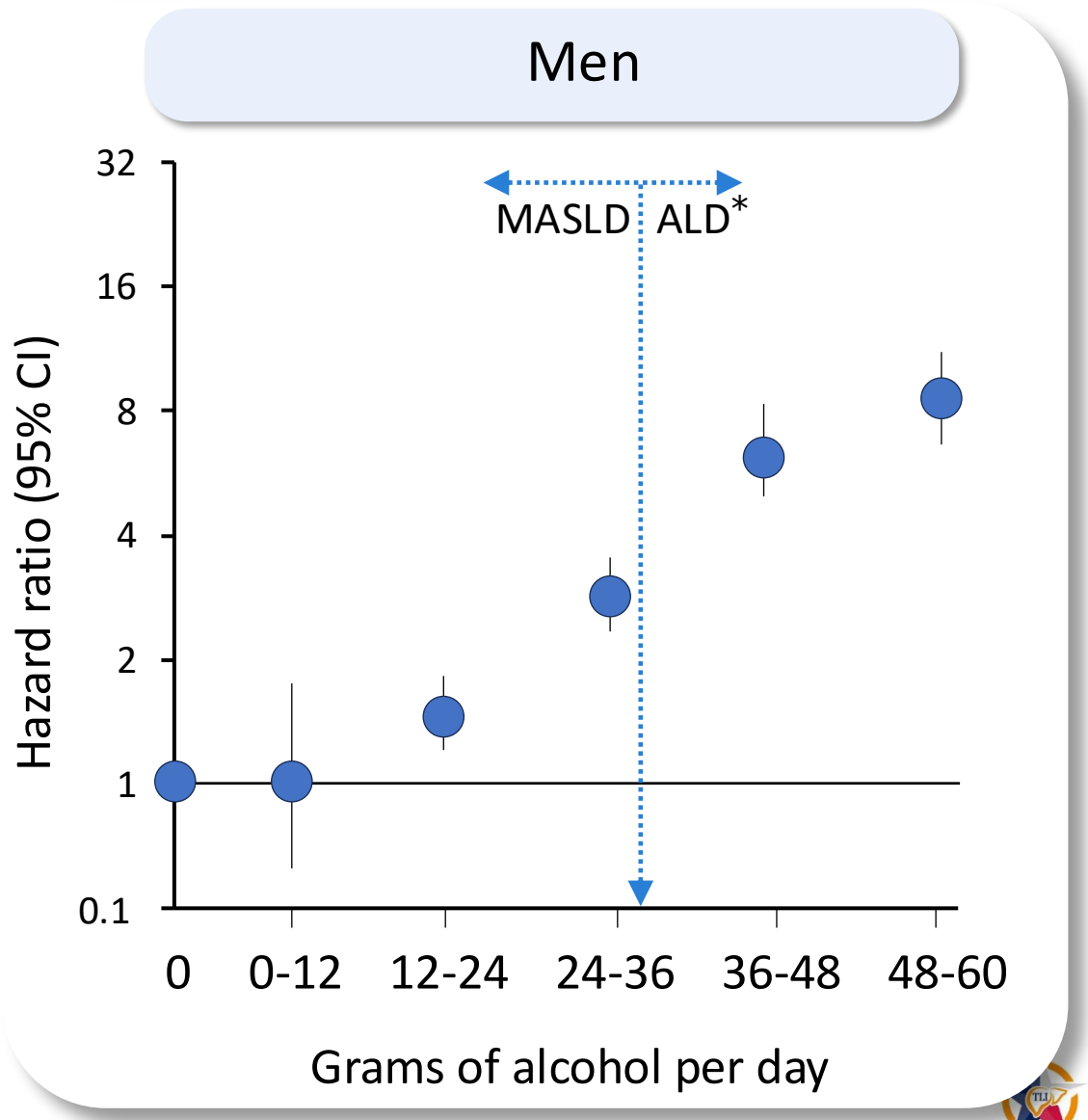
Alcohol Dose and Risk of Cirrhosis: Every Gram Matters





*) 2023 consensus threshold differentiating MASLD from MetALD

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

Biologic Targets of Fatty Liver Disease Therapeutics

Three principal targets: Alcohol craving, Food noise, Lipid Flux and Fibrosis

CNS effects (food noise, reward mechanisms):	*FGF21 and GLP-1 agonists*
Out-of-control lipid flux and insulin resistance:	*FGF21 and GLP-1 agonists*
Gut motility:	*GLP-1 agonists*
Direct antifibrotic effects:	*FGF21 agonists*
Intrahepatic fat burner:	*Resmetirom*

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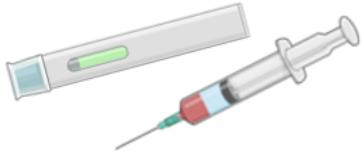
Current Landscape of Fatty Liver Disease Therapeutics

Oral

Class	Drug Name	Phase
THR-β Agonist	Resmetirom FDA	3
	VK2809	2
	TERN-501	2
PPARs	Lanifibranor (pan-PPAR)	3
	Chiglitizar (pan-PPAR)	2
	Seladelpar (PPAR-δ)	2
	Saroglitizar (PPAR-α/γ)	2
DGAT 2 inhibitor	Ervogastat	2
Acetyl-Co A Carboxylase Inhibitor	Clesacostat	2



Injectable

Class	Drug Name	Phase
Incretins Reduced alcohol craving	Semaglutide (GLP-1) FDA	3
	Survodutide (GLP-1/GCG)	3
	Tirzepatide (GLP-1/GIP) Off-label	2
	Pemvidutide (GLP-1/GCG)	2
	Efinopegdutide (GLP-1/GCG)	2
	Retatrutide (GLP-1/GIP/GCG	2
	Efocipegtrutide (GLP-1/GIP/GCG)	2
FGF-21 Reduced alcohol craving	Efruxifermin	3
	Pegozafermin	3
	Efimosfermin alfa	2
Galactin-3 inhibitor	Belapectin	2b/3

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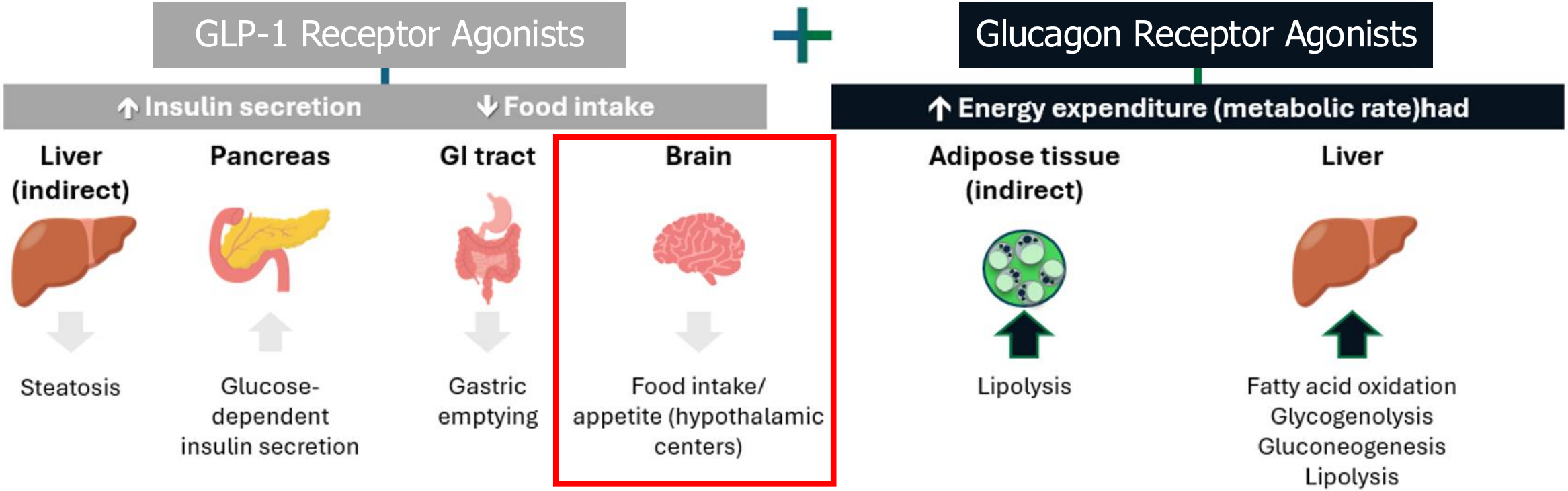
GLP-1 Agonists Act Beyond the Liver



Administration of dual GLP-1/glucagon receptor agonists resulted in superior weight loss, lower glucose levels and reduced food intake compared with pure GLP-1 receptor agonists alone.

Del Prato S et al. *Obes Rev*. 2022; 23:e13372.

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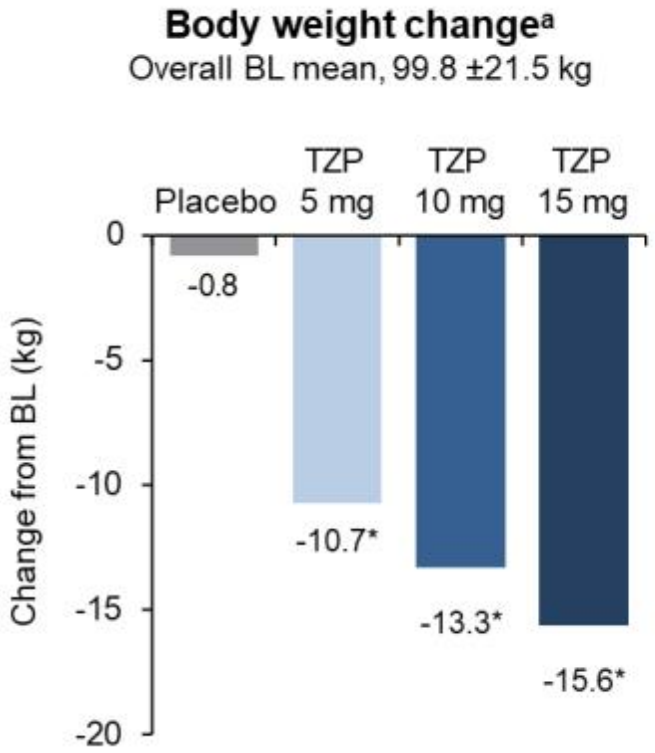
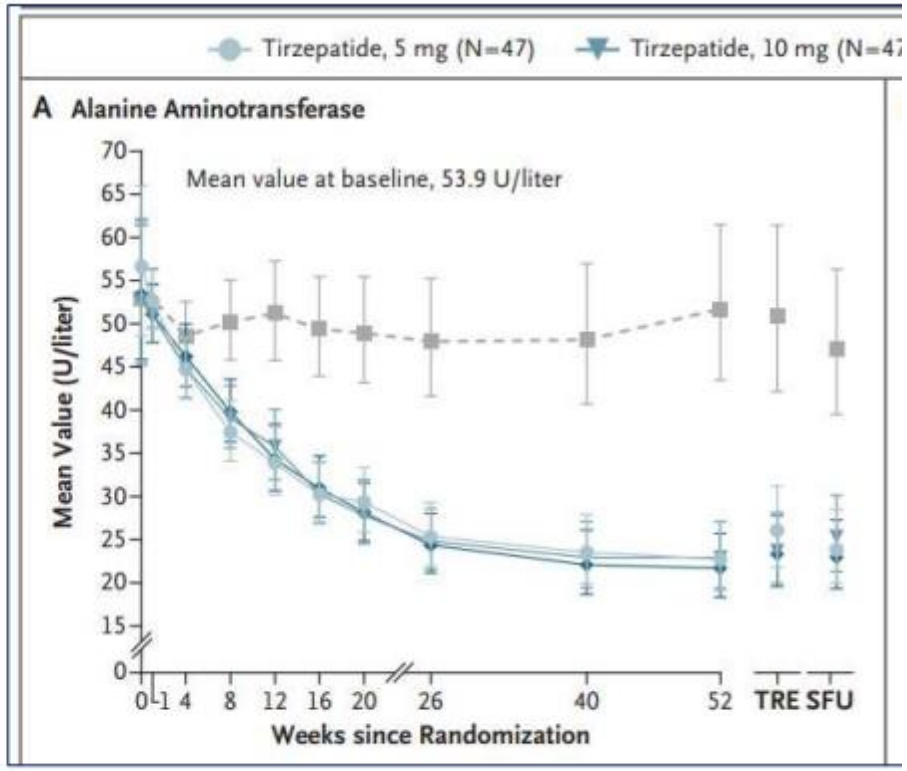
Tirzepatide, a dual GIP and GLP-1 agonist, in MASH F2-3
Body weight and liver enzymes





Loomba et al., NEJM 2024;391:299-310

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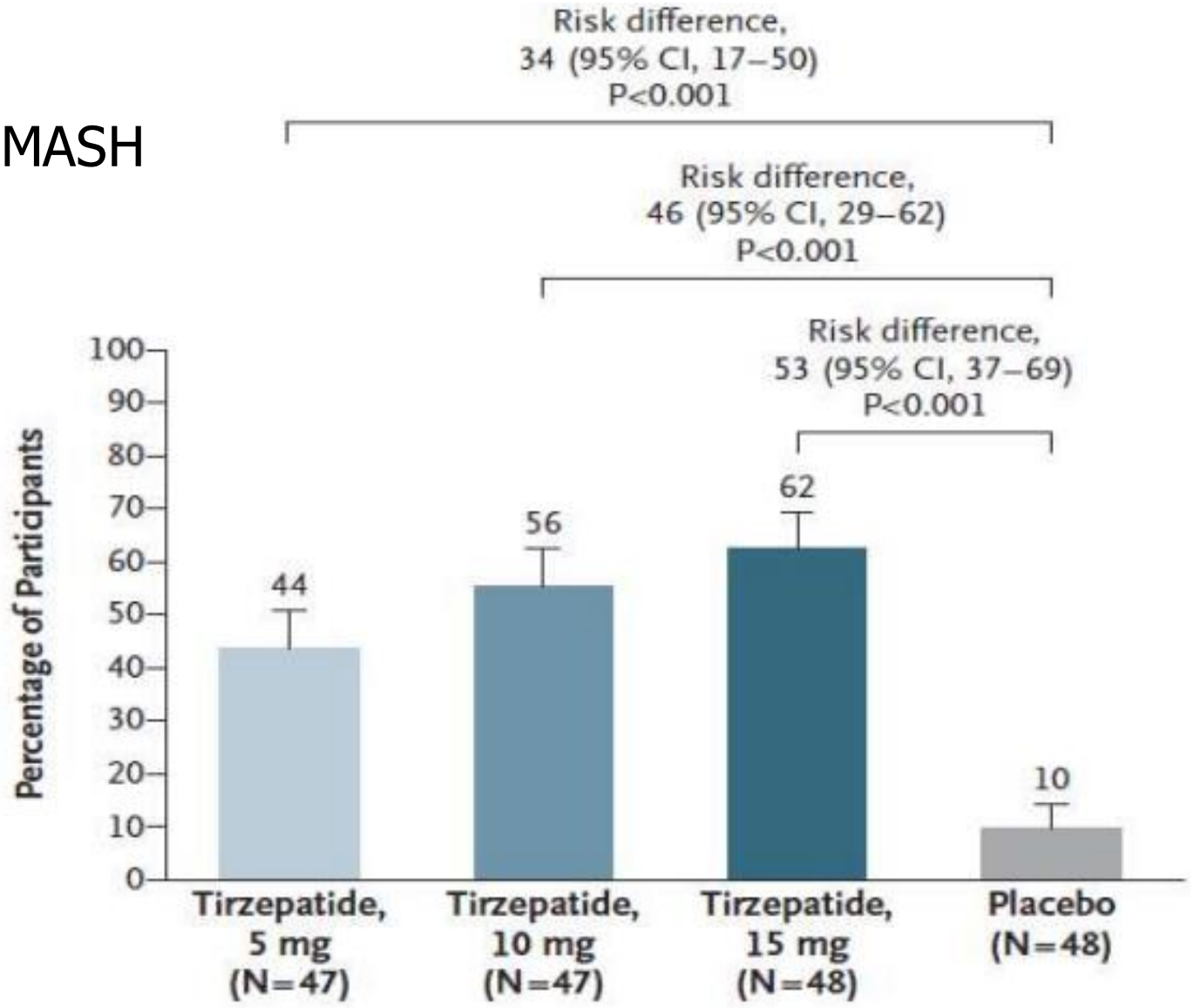
Tirzepatide, a dual GIP and GLP-1 agonist, in MASH F2-3

Resolution of MASH



Loomba et al., NEJM 2024;391:299-310

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Tirzepatide and Semaglutide Reduce Alcohol Cravings

153 patients with obesity and concurrent alcohol use.
Analysis of 68000 social media posts before and after the initiation of semaglutide or tirzepatide

Quddos et al., Sci Rep 2023;13:20998

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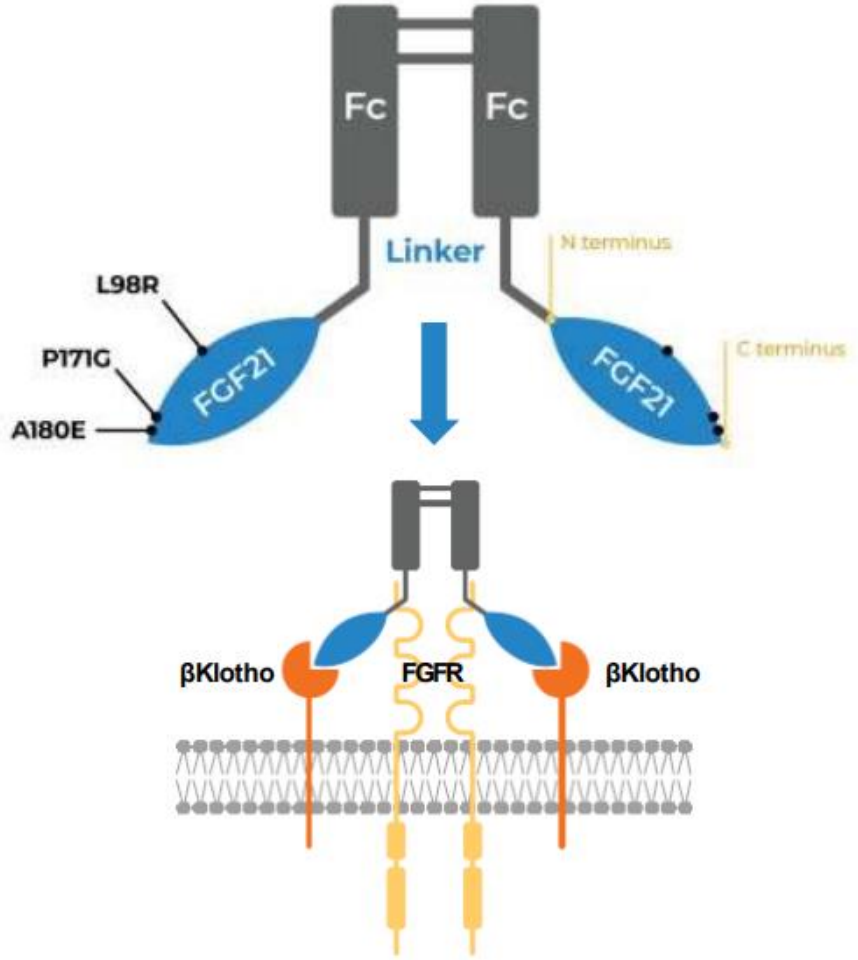
Pegozafermin is an Engineered Bivalent FGF21 Analog



- Akero proprietary Fc-FGF21, Point mutations
- Increases half-life from < **2 hours** to **~3 days**
- **High affinity** for β-Klotho
- Better translation to **human** pharmacology
- **Balanced potency** at FGFR1c, 2c, 3c
- **Inactive** at FGFR4

Stanislaus (2017) *Endocrinology*; Lee (2018) *Nature*; Kharitonenkov (2007) *Endocrinology*.

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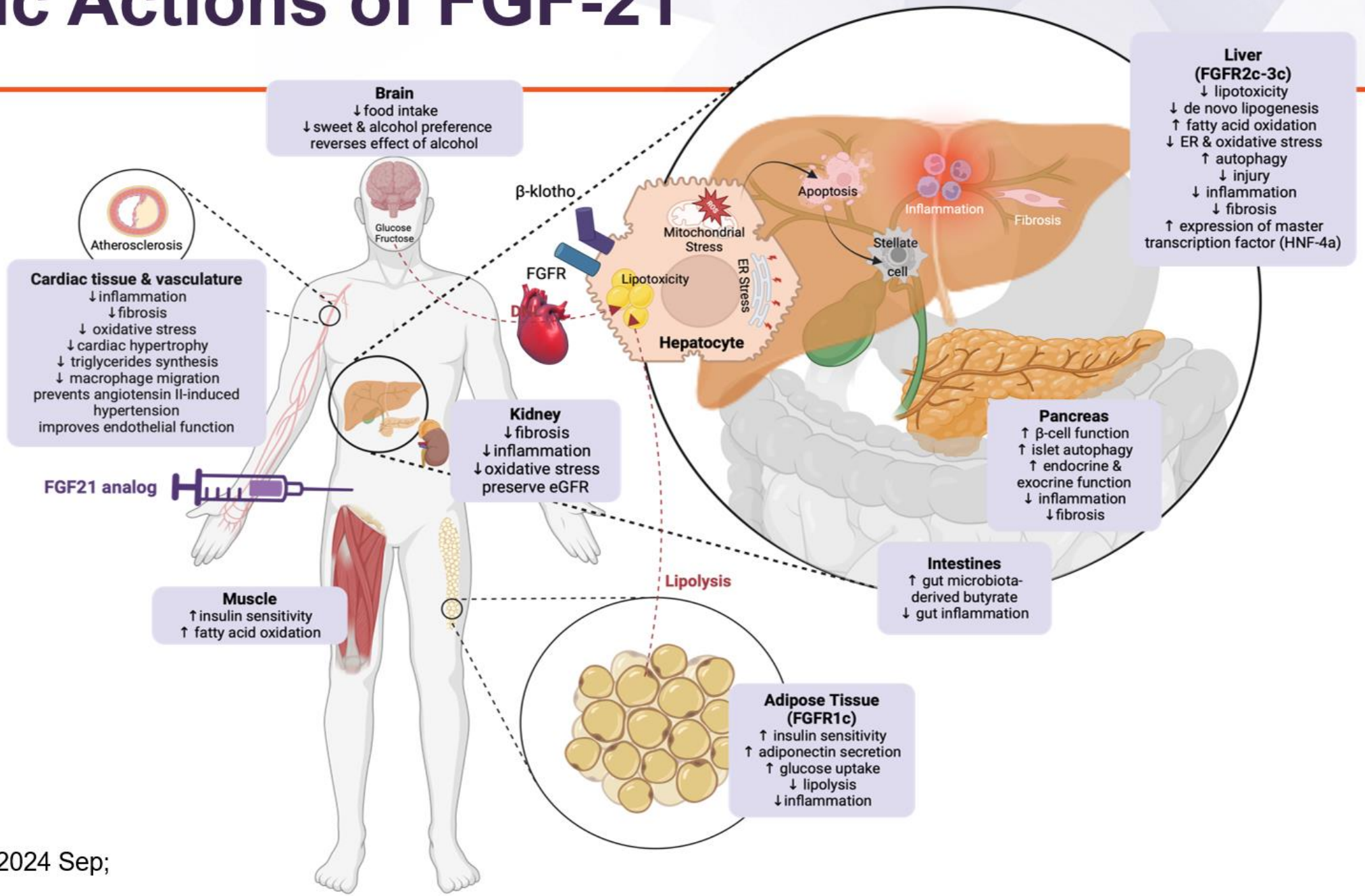
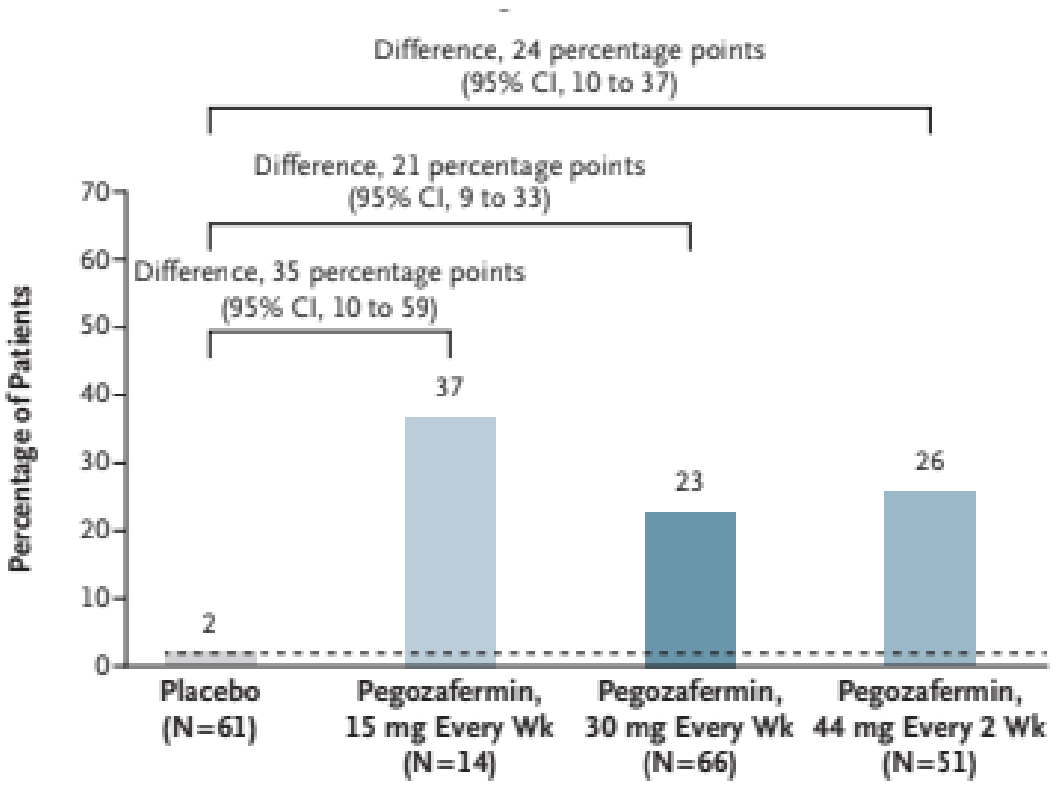
Pleiotropic Actions of FGF-21



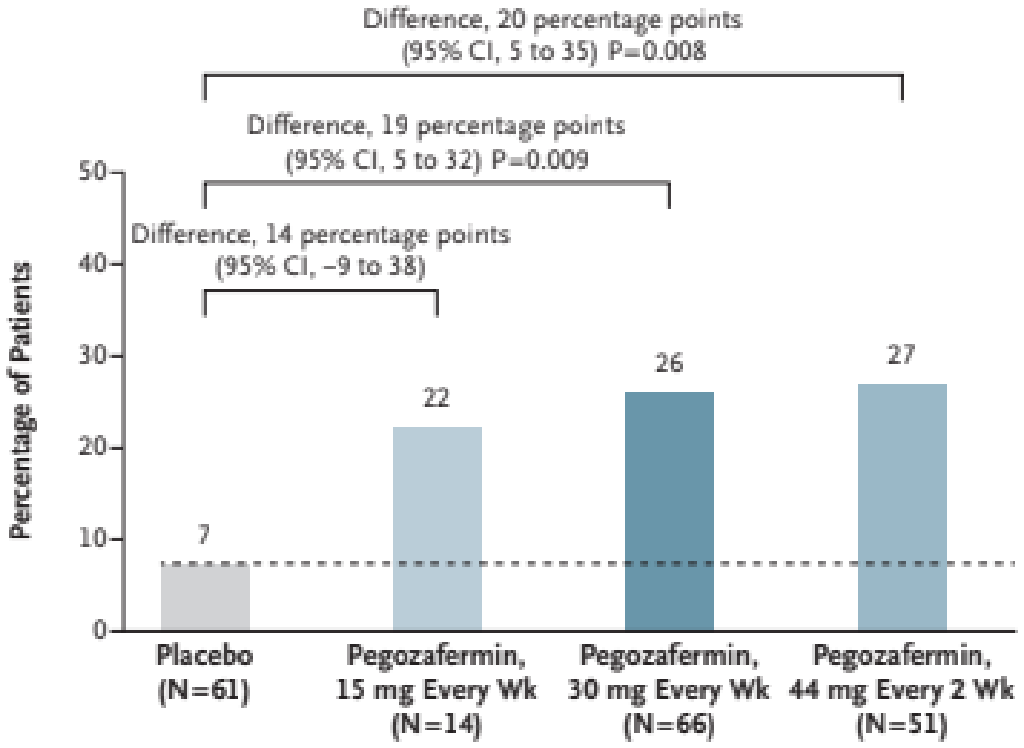
Harrison SA et al. *J Hepatol.* 2024 Sep; 81(3):562-576.

ENLIVEN Phase 2b Extension Study: Pegozafermin for the Treatment With Fibrosis – Results at 48 Weeks

MASH Resolution



Fibrosis Improvement by ≥1 stage



Loomba et al., NEJM 2023;389(11):998-1008

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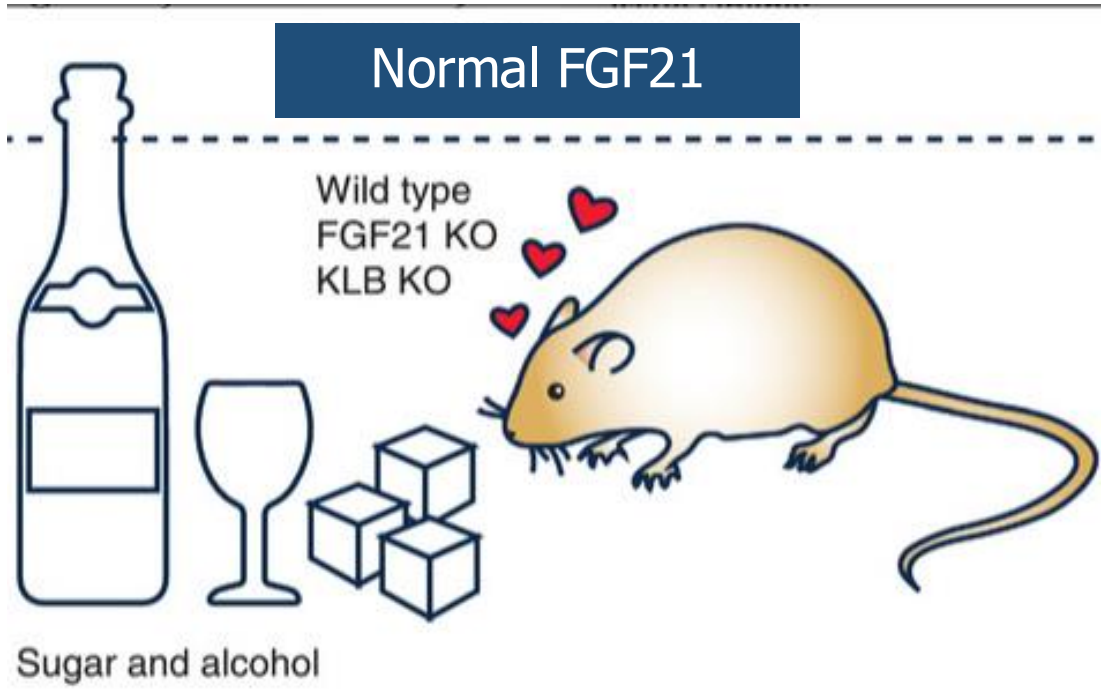
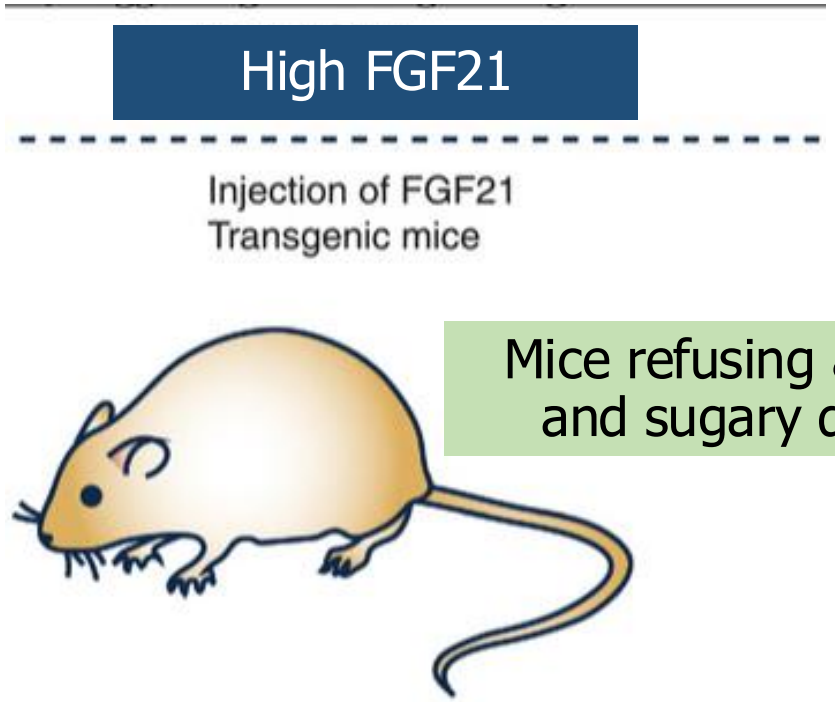
Injected FGF21 Converts Alcohol Preference to Aversion





Mice refusing alcohol and sugary drinks

Hepatocytes make FGF21 in response to fasting and protein restriction. FGF21 signals to the hypothalamus and reward circuits to change dietary preferences from empty calories (sugars, alcohols) to protein-rich diet.

FGF21 tells your brain: ”Enough candy and fermented sugars (i.e. alcohol), your body needs real materials now”

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Kliewer et al., Cell Metab. 2016 Feb 9;23(2):344-9.

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