NASH Core Curriculum: NASH Pathogenesis

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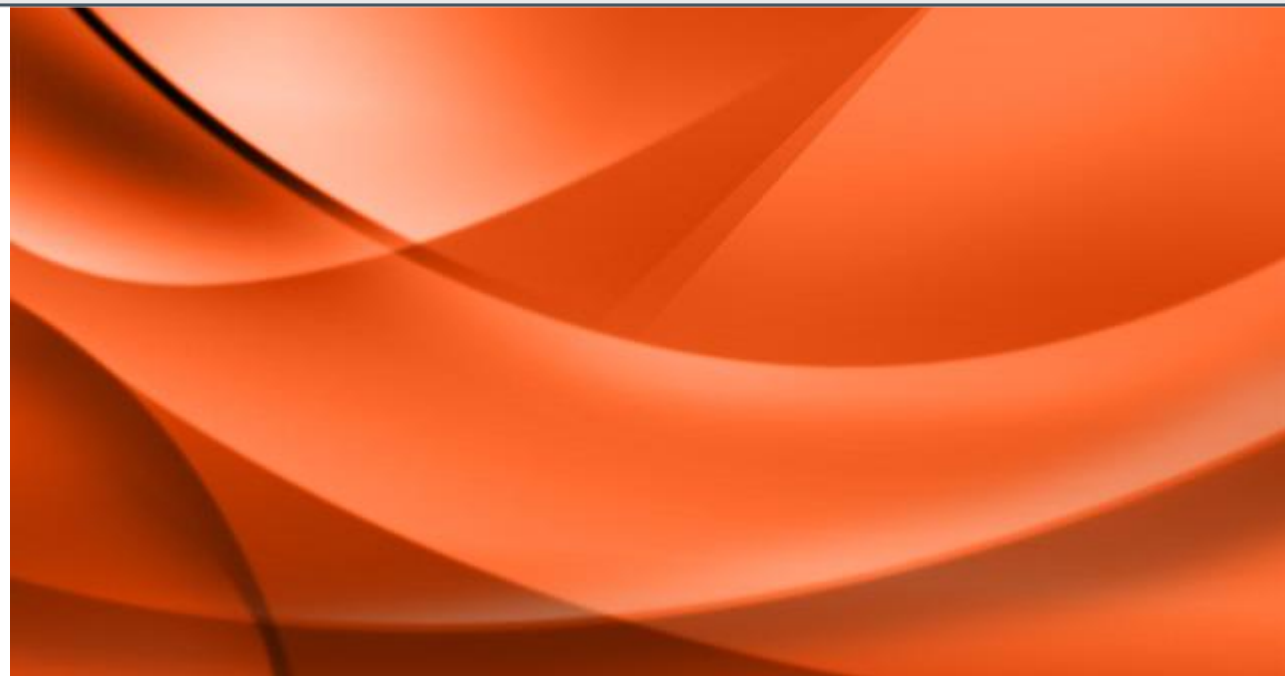

Faculty and Disclosures

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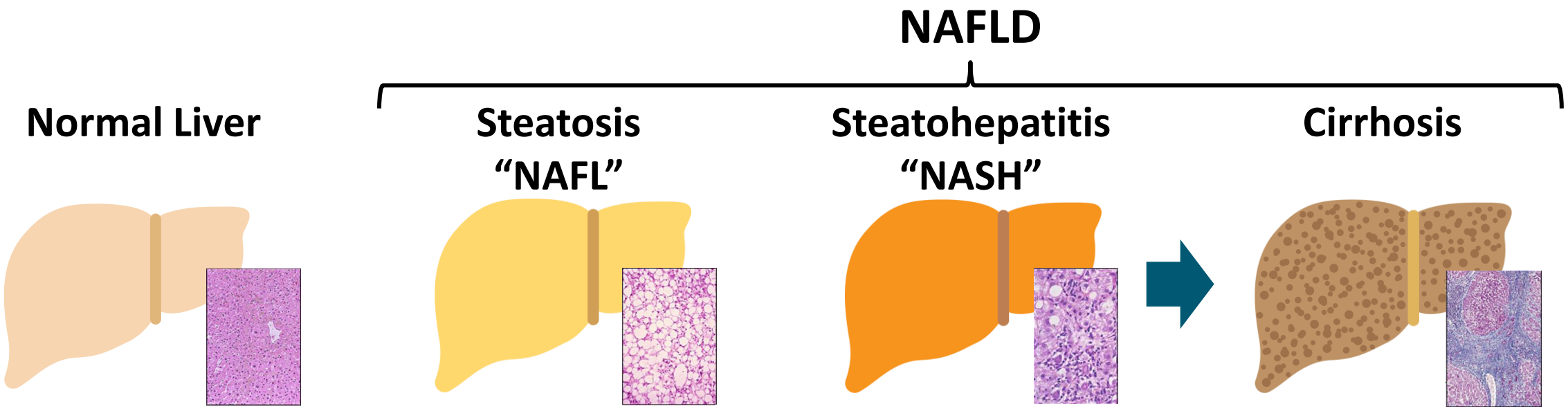
Agenda

- What is NASH?
- What Is the Relationship Between NASH and Other Metabolic Disturbances?
- Is NASH Reversible?

What Is NASH?

The NAFLD Continuum



Worldwide prevalence:	25%[1]	3% to 5%[1]	1% to 2% at risk*

*Based on analysis of NHANES data estimating 1.74% prevalence of NASH with advanced fibrosis[2]

1. Younossi. J Hepatol. 2019;70:351. 2. Kabbany. Am J Hepatol. 2017;112:581.

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Metabolic Associated Fatty Liver Disease (MAFLD)

Proposed Definition[1]

- Diagnosis based on presence of **hepatic steatosis** plus at least 1 of:
  - **Obesity, T2D, metabolic disease**
- Not a diagnosis of exclusion
- Acknowledges metabolic basis of disease

Considerations[2]

- Ambiguity about definition of "metabolic disease"
- Better nomenclature will be based on **specific underlying causes,** not associations
- Consensus needed among *all* stakeholders:
  - Academic, pharma, regulatory, patient advocacy groups, payers, policy makers

1. Eslam. J Hepatol. 2020;73:202. 2. Younossi. Hepatology. 2020;[Epub].

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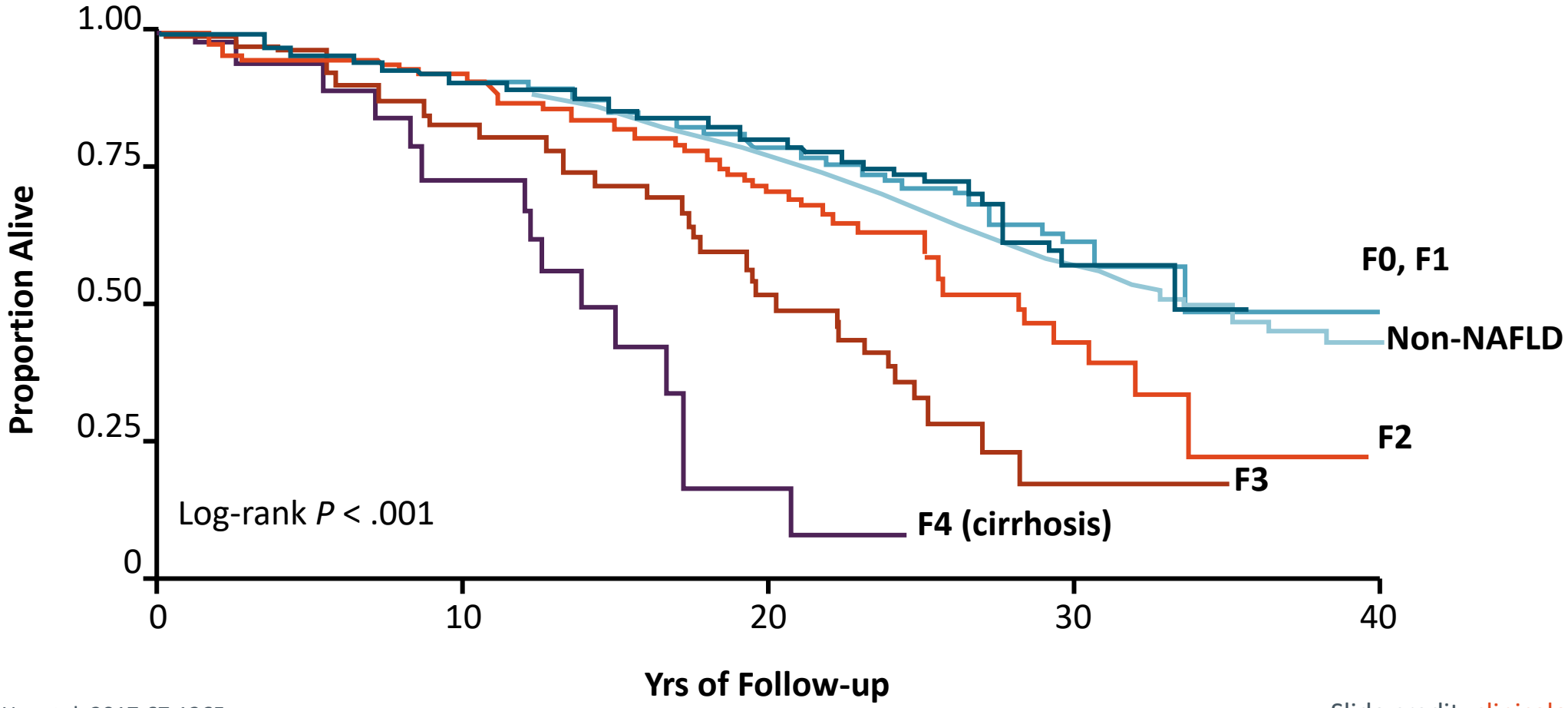
Liver Fibrosis Is a Risk for Adverse Outcomes

- Retrospective survival analysis of 646 NAFLD patients and matched controls



Hagström. J Hepatol. 2017;67:1265.

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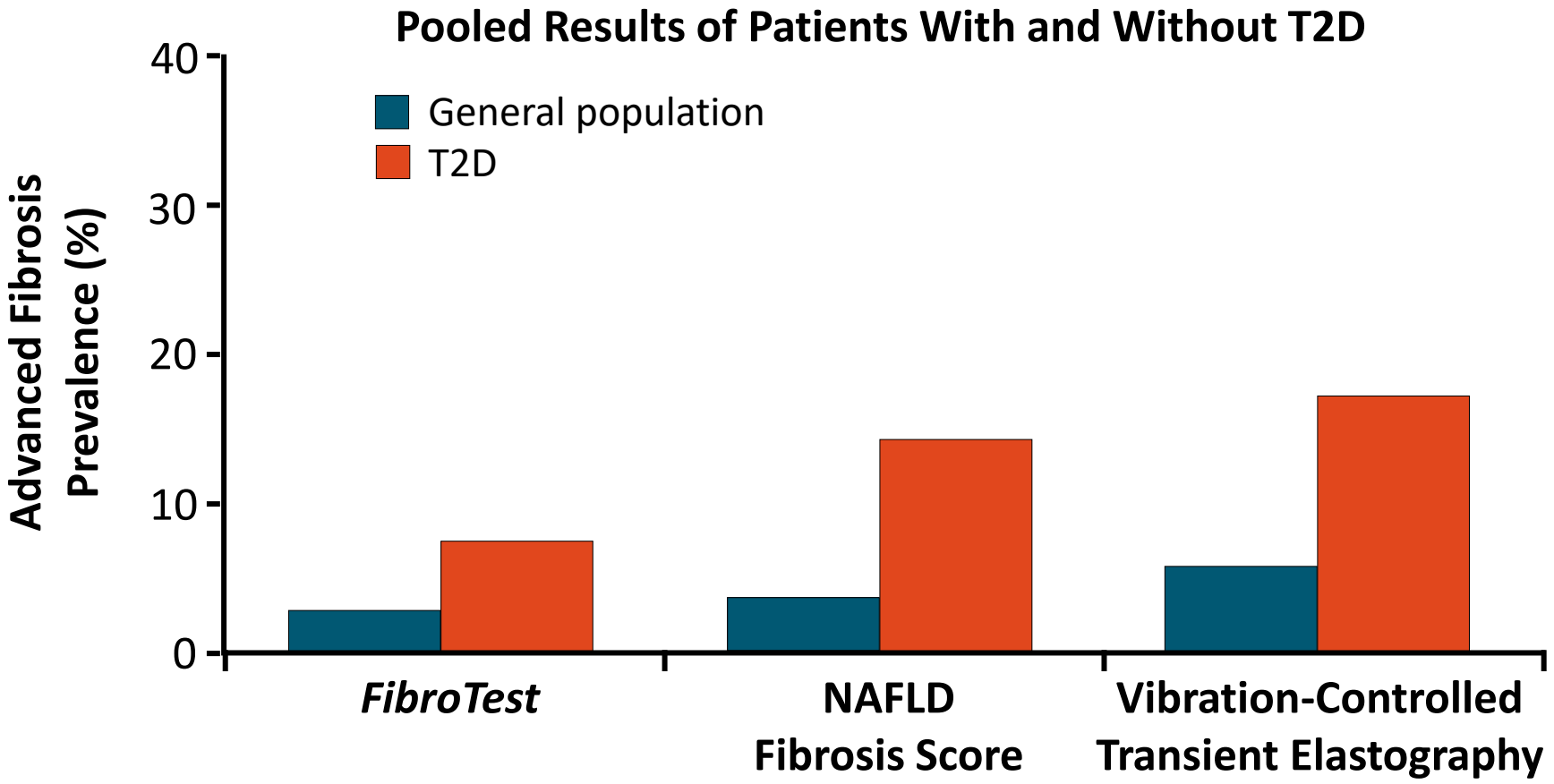
T2D as a Risk for Advanced Fibrosis (by Diagnostic Approach)

- Meta-analysis (N = 3229)



Bril. Diabetes Care. 2017;40:419.

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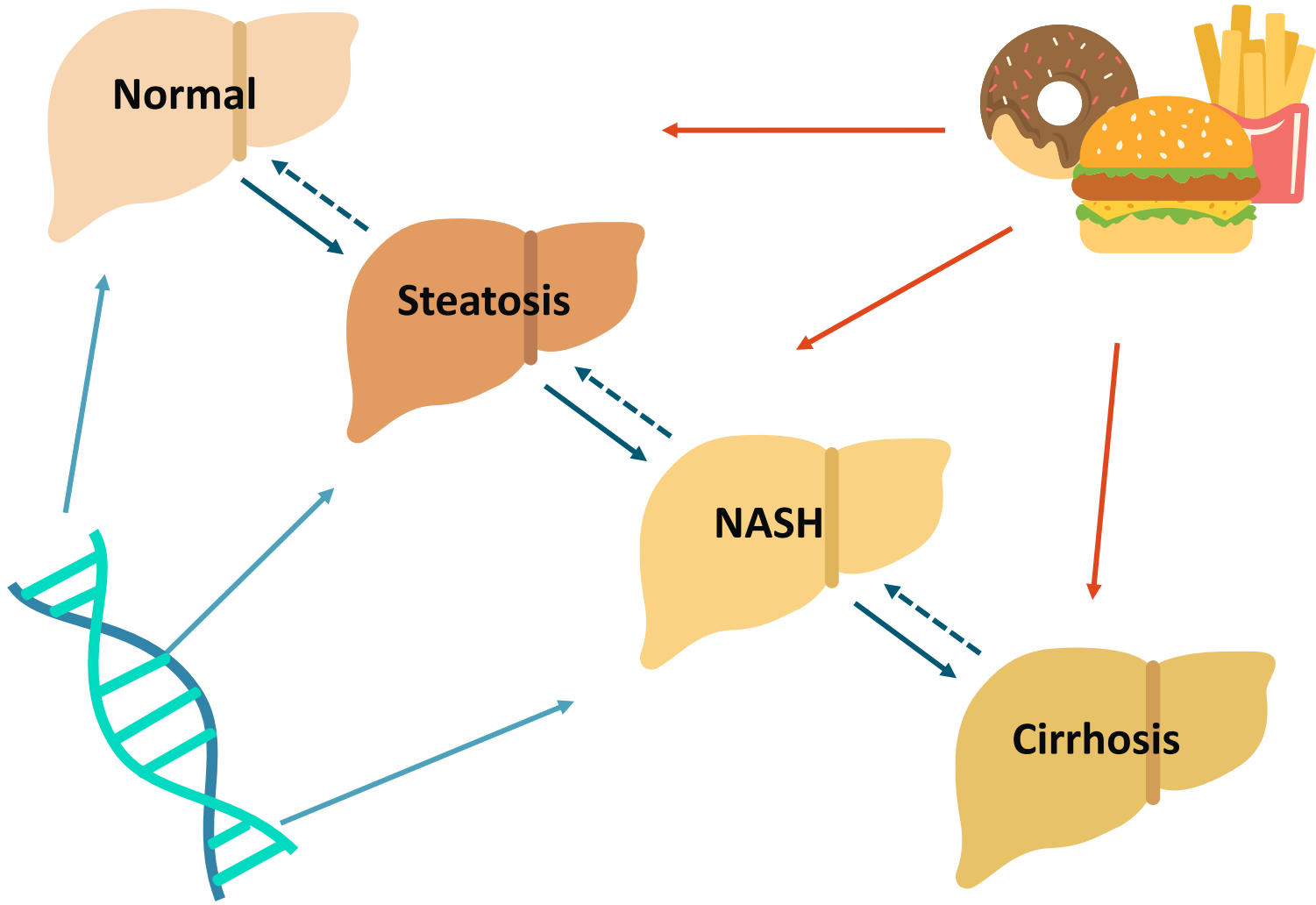
NAFLD as a Complex Disease Trait: Genetic and Environmental Modifiers



Genes
PNPLA3
TM6SF2
GCKR
SOD2
MBOAT7

Environment
Sedentary lifestyle
Snacking, fast food
Saturated fats
Trans fats
Processed red meat

Epigenetics
Gut microbiome

Cotter. Gastroenterology. 2020;158:1851. Krawczyk. Gastroenterology. 2020;158:1865.

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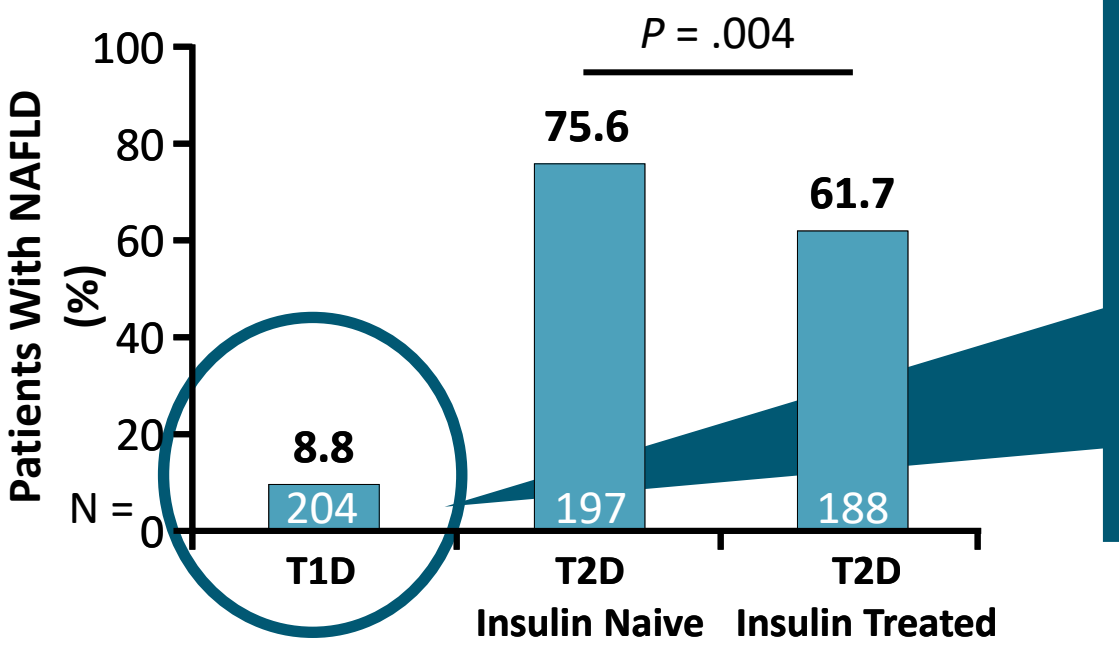
What Is the Relationship Between NASH and Other Metabolic Disturbances?

T2D as a Risk for NAFLD

- Data from 4 phase III trials of peg-lispro (IMAGINE-1/2/3/5 studies combined, ALT ≤ 2.5 ULN)
- NAFLD defined as ≥ 6% liver fat by MRI (MRI done in a subset of study patients)
  - NAFLD **correlated** with insulin use
  - NAFLD **did not correlate** with A1C



	Liver Fat < 6% (n = 186)	Liver Fat ≥ 6% (n = 18)
Liver fat, %	2.3	11.8
BMI, kg/m^2	26.4	28.1
Insulin dose, U	52	71
HTN, %	28	78
ALT, U/L	20.4	25.6

Cusi. Diabetes Obes Metab. 2017;19:1630.

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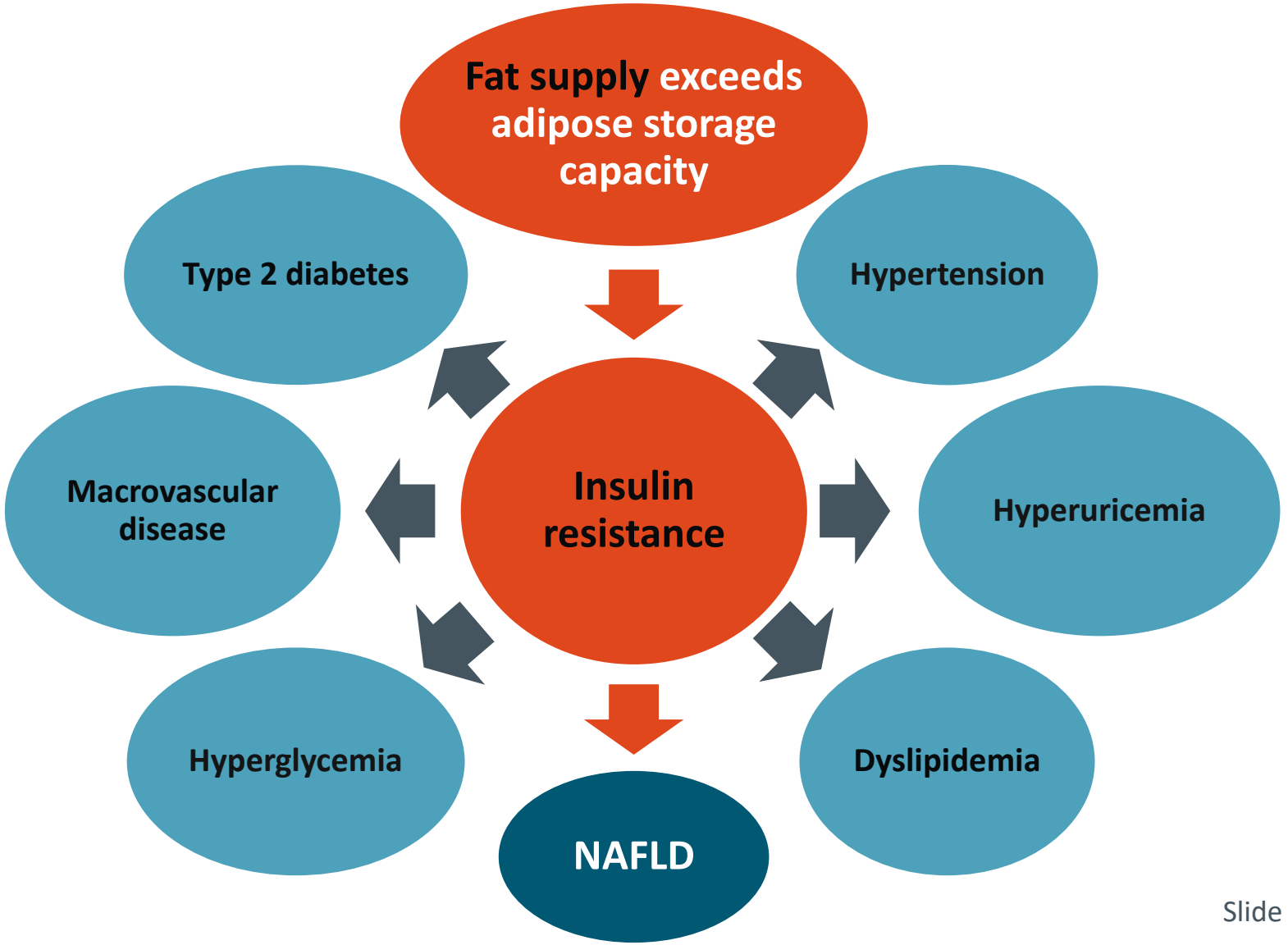
Obesity and Insulin Resistance as Pathogenic Drivers



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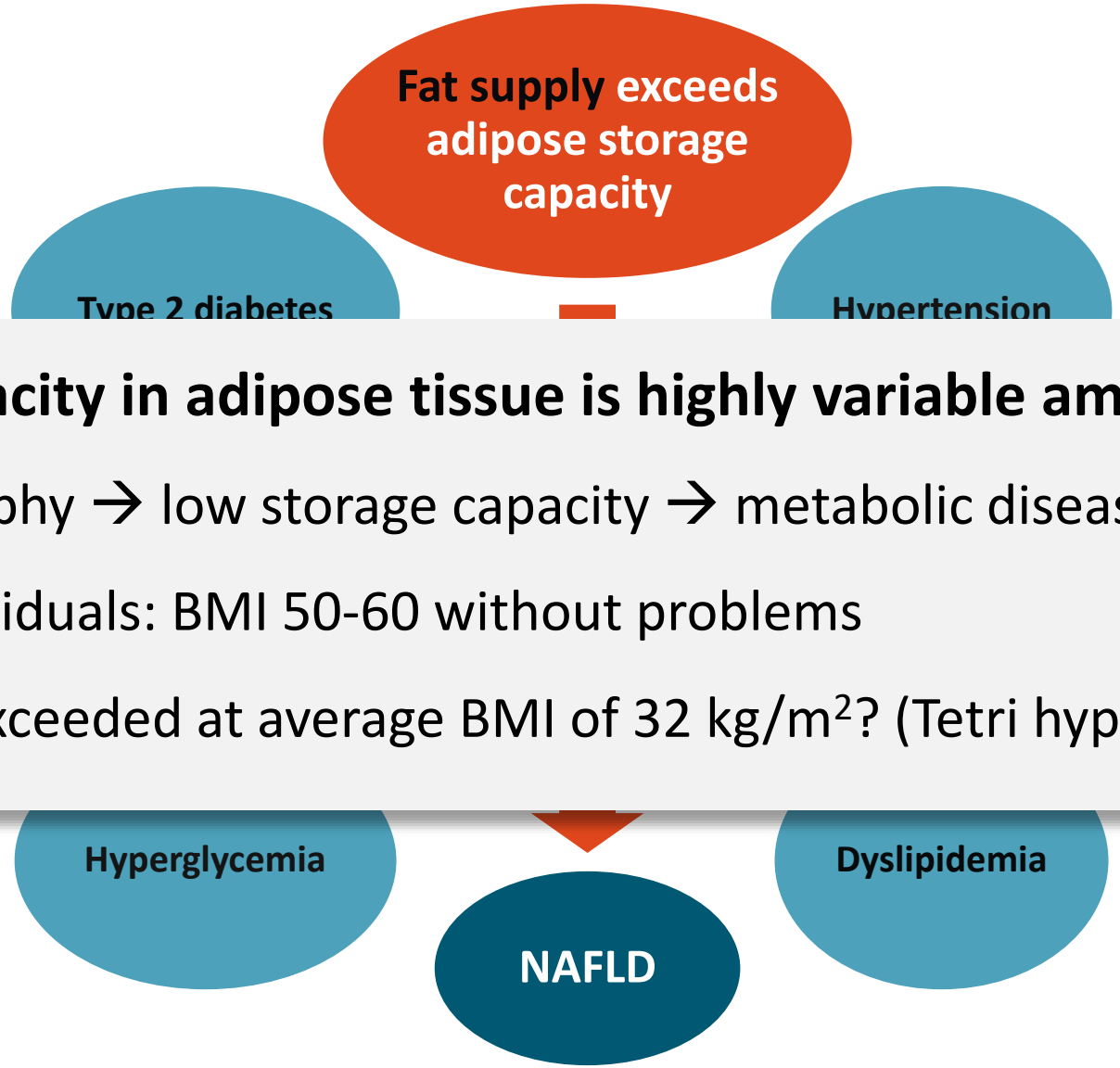
Obesity and Insulin Resistance as Pathogenic Drivers



Storage capacity in adipose tissue is highly variable among individuals

- Lipodystrophy → low storage capacity → metabolic disease with normal BMI
- Some individuals: BMI 50-60 without problems
- Capacity exceeded at average BMI of 32 kg/m^2? (Tetri hypothesis)

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What About "Lean" NASH?

- Definitely occurs
  - Role of lifestyle modification?
    - Improvement in Asian individuals with BMI < 25 kg/m^2 [1]
    - Prevalence depends on definition of "lean"
  - BMI < 25 kg/m^2 but abdominal adiposity?[2]
  - BMI < 23 kg/m^2 in Asian individuals
- *PNPLA3* I148M allele likely plays a major role in lean NAFLD[3]

1. Wong. J Hepatol. 2018;69:1349. 2. Younossi. Medicine. 2012;91:319. 3. Younes. Semin Liver Dis. 2019;39:86.

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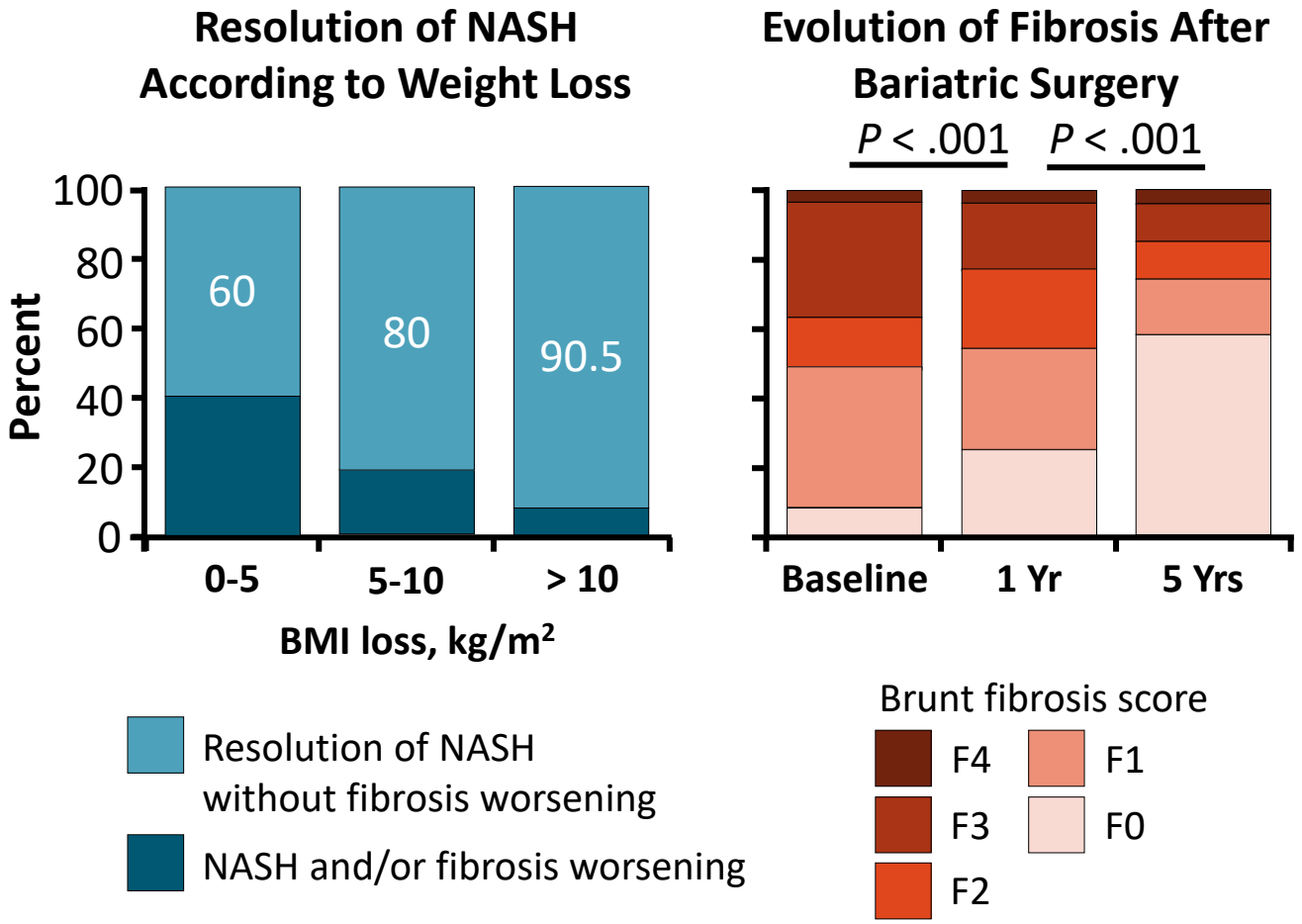
Is NASH Reversible?

Is NASH Reversible?

- French single-center study of **bariatric surgery** in severely obese patients with biopsy-confirmed NASH (N = 180)
- At 5 yrs post surgery, 64 of 94 patients (84%) had NASH resolution with no worsening of fibrosis
  - NASH improvement correlated with weight loss



Lassailly. Gastroenterology. 2020;159:1290.

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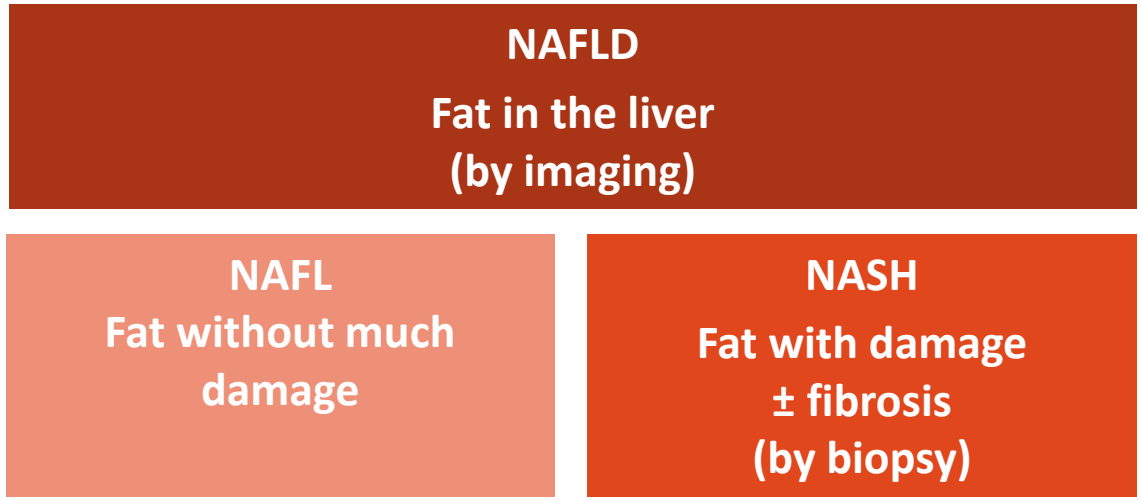
Summary



- Degree of **fibrosis** determines outcomes
- **T2D** is associated with more fibrosis

Pathogenesis and Progression

- NAFLD probably doesn't cause **IR, T2D, CVD,** etc—it is just another manifestation of the same **underlying process of adipose overload**
- NAFLD is reversible with weight loss; early fibrosis is too

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