NAFLD vs MASLD: What is the difference and when should we be concerned?

Eric Lawitz, MD

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Let’s Focus on the Known Nomenclature….

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Definition of NAFLD and NASH

- Non-Alcoholic Fatty Liver Disease (NAFLD)
  - Overarching term that includes all disease grades and stages and refers to a population in which
  - Presence of hepatic steatosis ≥5% AND
  - No secondary causes AND
  - Alcohol consumption
    - <21 standard drinks on average per week in men
    - <14 standard drinks on average per week in women
    - Considered the reasonable threshold for significant alcohol consumption when evaluating patients with suspected NAFLD.
- Non-Alcoholic Steatohepatitis (NASH)
  - Progressive type of NAFLD additionally characterized by the presence of inflammation and cellular injury (ballooning)
  - Patients with at least stage 2 fibrosis (F2) are considered “at-risk” NASH (higher risk for liver-related events)

Rinella M et al., *Hepatology* 77(5): 1797-1835, May 2023. DOI: 10.1097/HEP.0000000000000323

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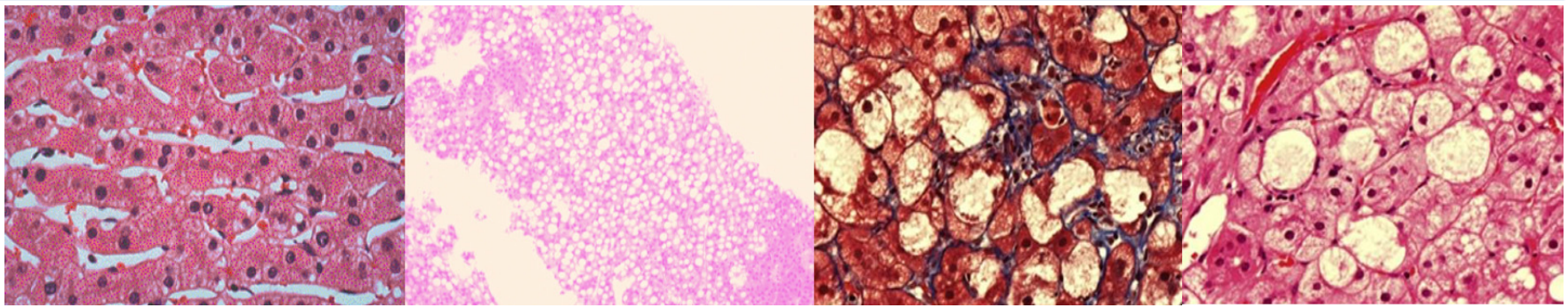
NAFLD Encompasses the Entire Spectrum of Fatty Liver Disease

NAFLD

Disease of hepatic fat accumulation, absent alcohol consumption, hereditary disorders, or steatogenic medication use



Normal

NAFL

- >5% hepatic steatosis
- No evidence of hepatocyte injury (ballooning) or fibrosis

NASH

- Progressive type of NAFLD
- >5% hepatic steatosis ± inflammation with hepatocyte injury (ballooning) ± fibrosis

NASH Cirrhosis

Cirrhosis + current or previous histological evidence of steatosis

Chalasani N et al. *Hepatology*. 2018;67(1):328-357.

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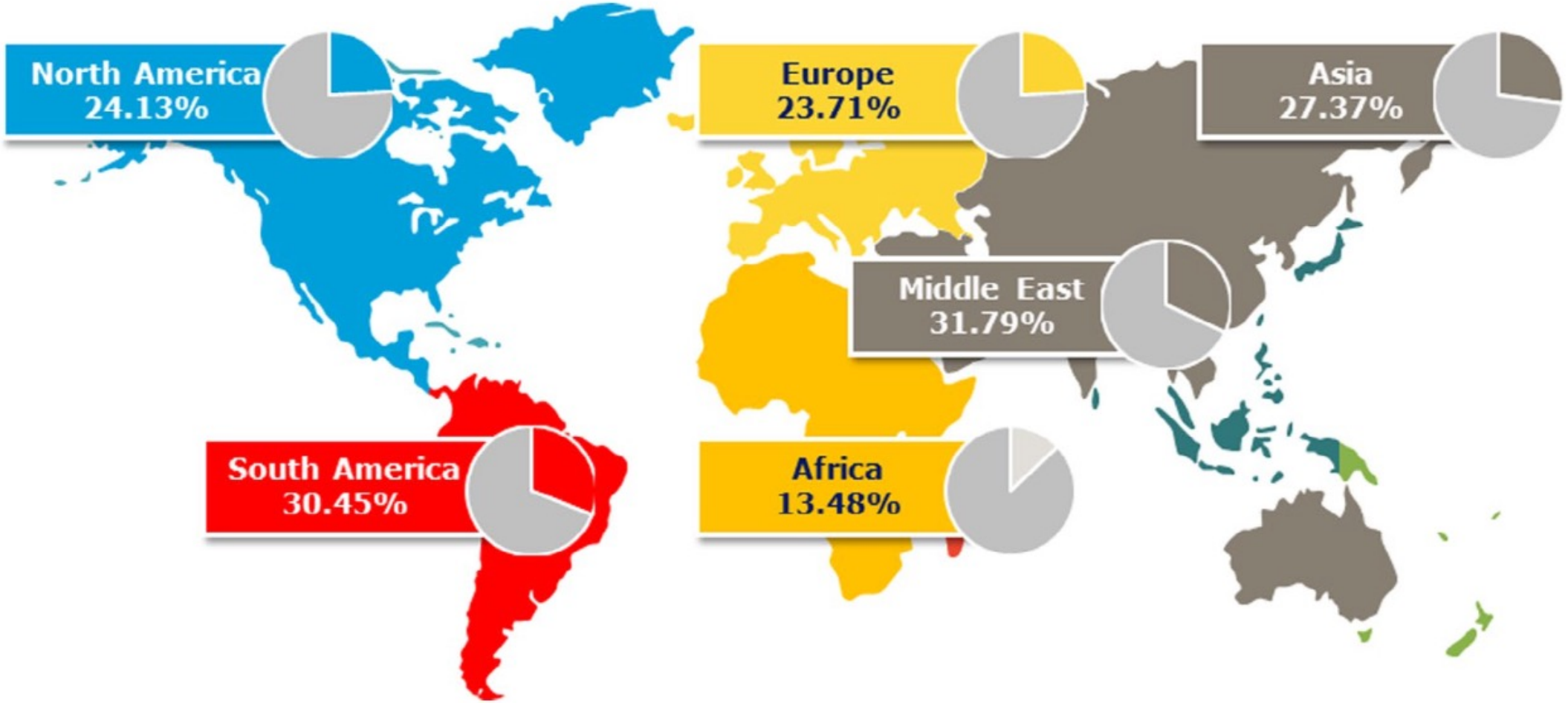
NAFLD Prevalence Worldwide



Hepatology, Vol.69, No.6, 2019

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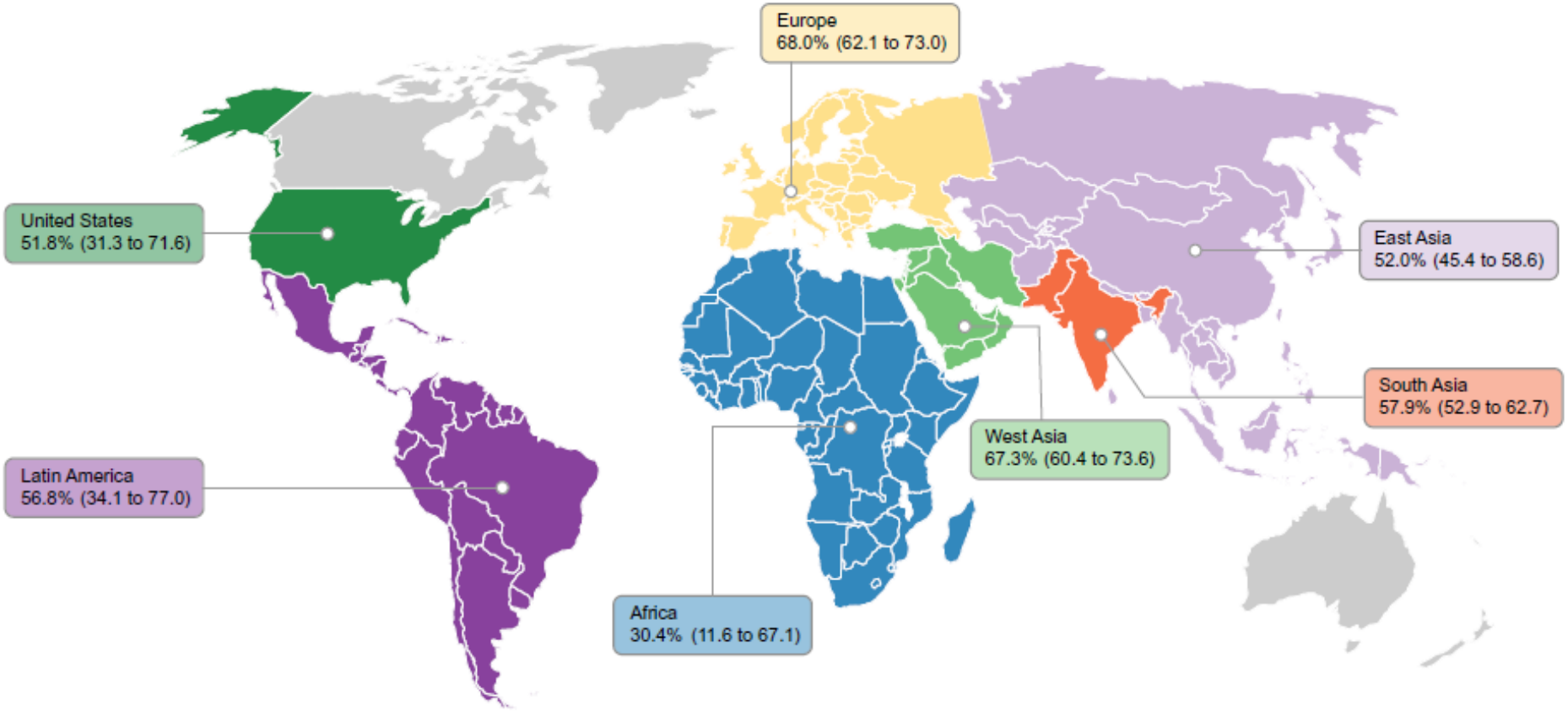
NAFLD and NASH Prevalence in Patients With T2DM



- 55.5% have NAFLD
- 37.3% have NASH
- 17.0% have advanced fibrosis

Younossi ZM et al. *J Hepatol*. 2019;71:793.

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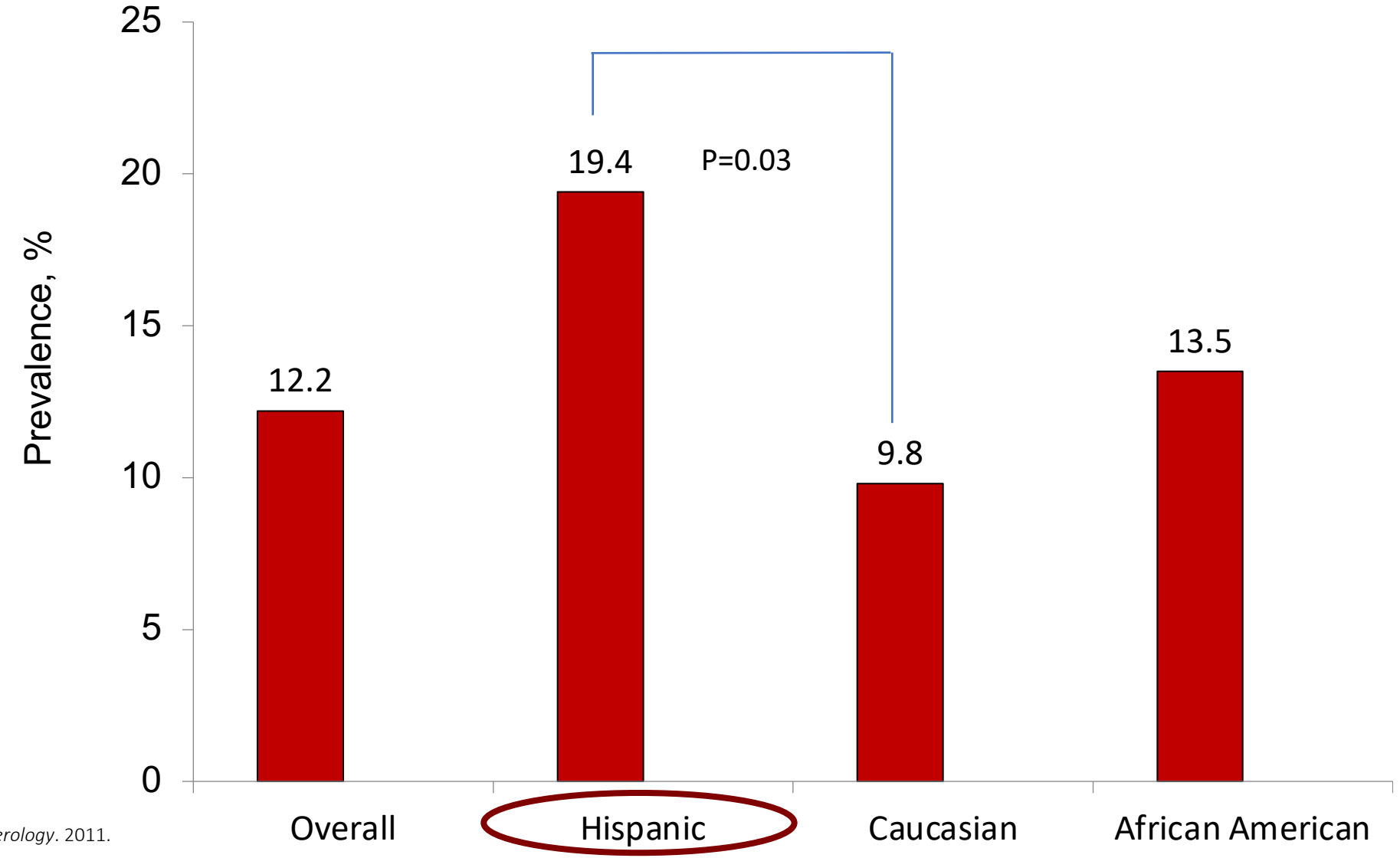
Disparities in NAFLD Prevalence



Williams et al. *Gastroenterology*. 2011.

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Identification of Patients at Risk for NASH

RISK FACTORS for NASH

- Age >50
- BMI >30
- Elevated liver enzymes
- Type 2 diabetes
- Hypertension
- Dyslipidemia
- Metabolic syndrome
- Fatty liver on ultrasound
- Previous Fibroscan >8 kPa, CAP >280

Highest risk profile:
Post-menopausal, obese, diabetic, Hispanic, female

Fibrosis stage is the **strongest** predictor of mortality

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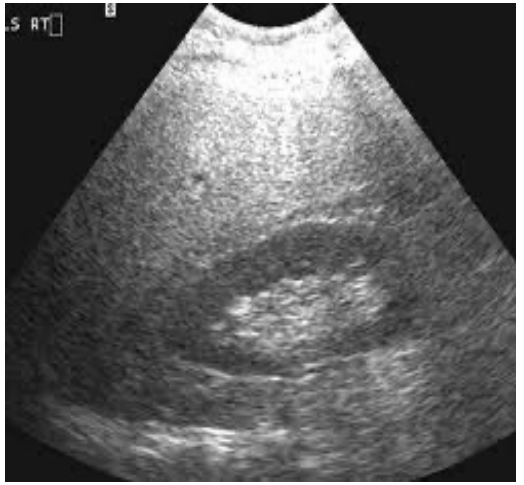
Incidental Discovery of NAFLD/NASH in Primary Care

- Vague right upper quadrant pain
- Hepatomegaly on exam
- Little (<20 gm/day) to no alcohol use
- “Bright” liver on ultrasound
- “Seronegative” chronic hepatitis (ALT>AST)
  - Viral serologies (HBsAb, HCV Ab)
  - Iron profile
  - Autoimmune markers (ANA, ASMA, AMA)
  - Ceruloplasmin
  - Alpha-1 antitrypsin
- Metabolic syndrome (3 or more features)
- *Caveat:* Recognition of elevated liver enzymes (normal F< 20 U/L; M< 30 U/L)



Clark JM, *Am J. Gastro* 2003

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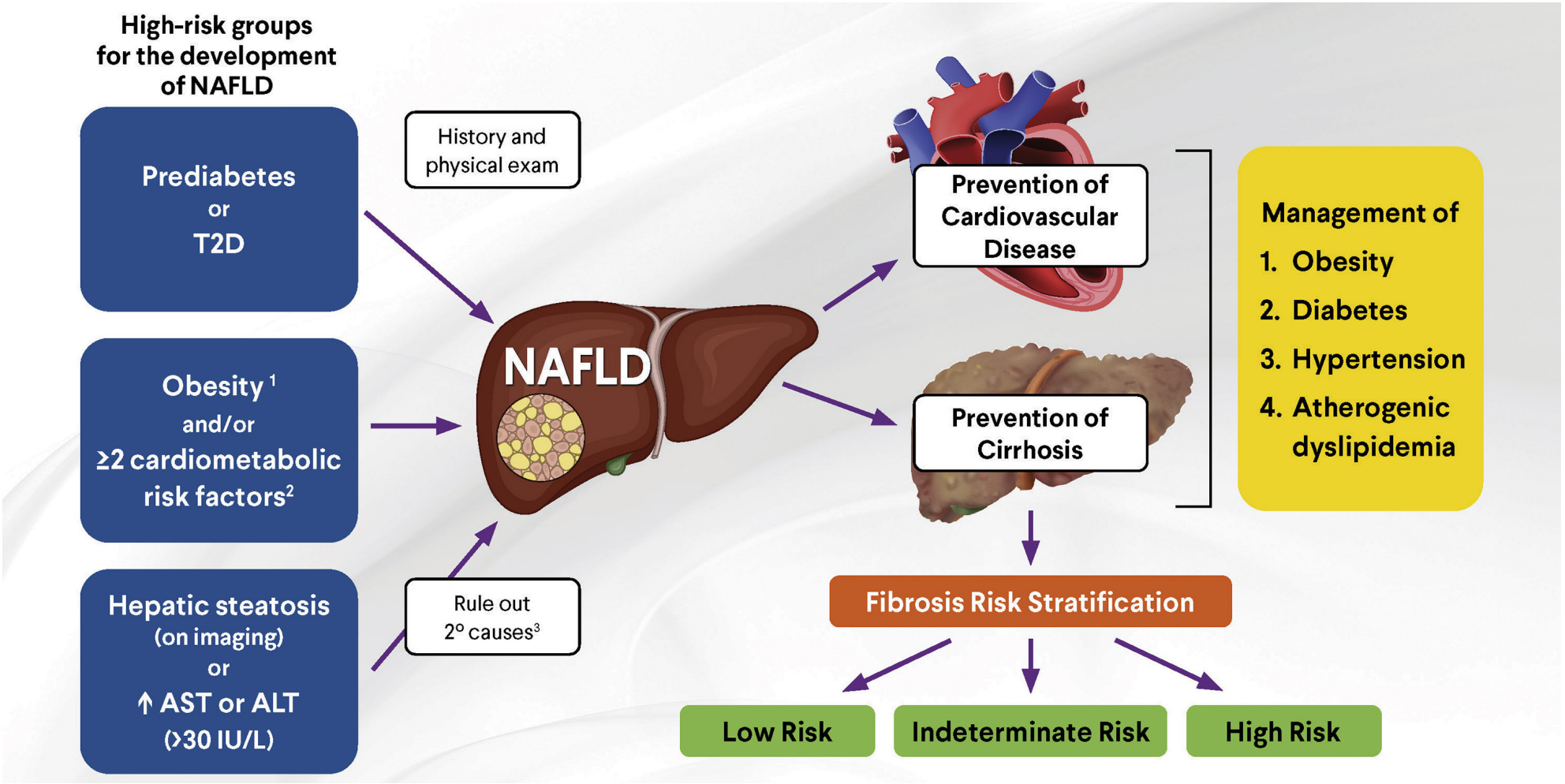
Management Algorithm for NAFLD – Overview



Cusi K et al. American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings. *Endocr Pract* 2022.

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PCP Challenge

- NAFLD patients have high rates of morbidity and mortality
  - Primarily unrelated to liver disease
- Liver perspective: 70-75% are F0-2 and at very low risk for long-term liver complications
  - Need to identify the 20-25% with advanced fibrosis (≥F3) and 1-3% already cirrhotic
- Bigger perspective: Addressing metabolic risk factors, obesity, T2DM → improve global health

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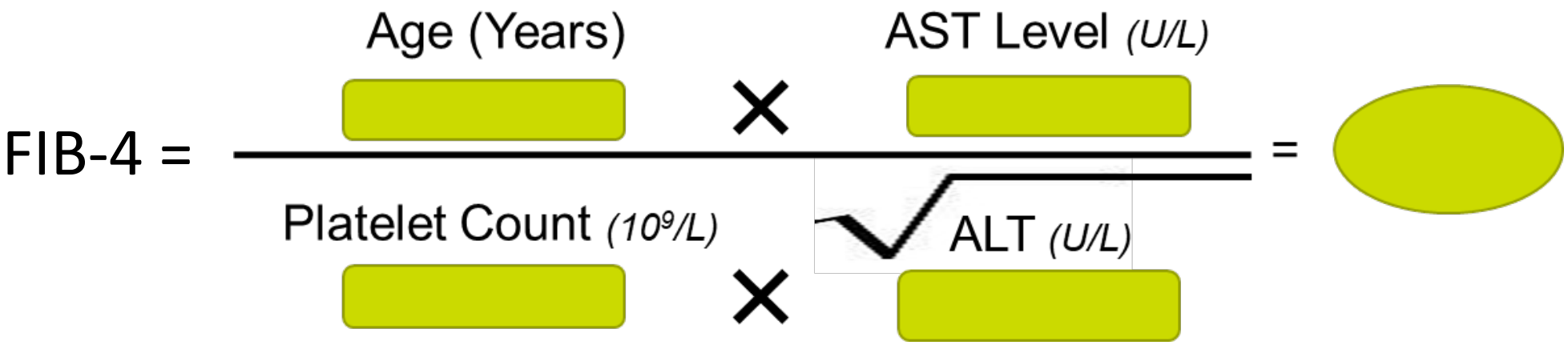
Step 1: Calculate FIB-4

- Based on age, platelet count, alanine aminotransferase (ALT) level and aspartate aminotransferase (AST) level
- Simple score that uses readily available patient data



Calculator available at: https://www.mdcalc.com

LabCorp will calculate as well (Test 403604; CPT 84450; 84460; 85049)

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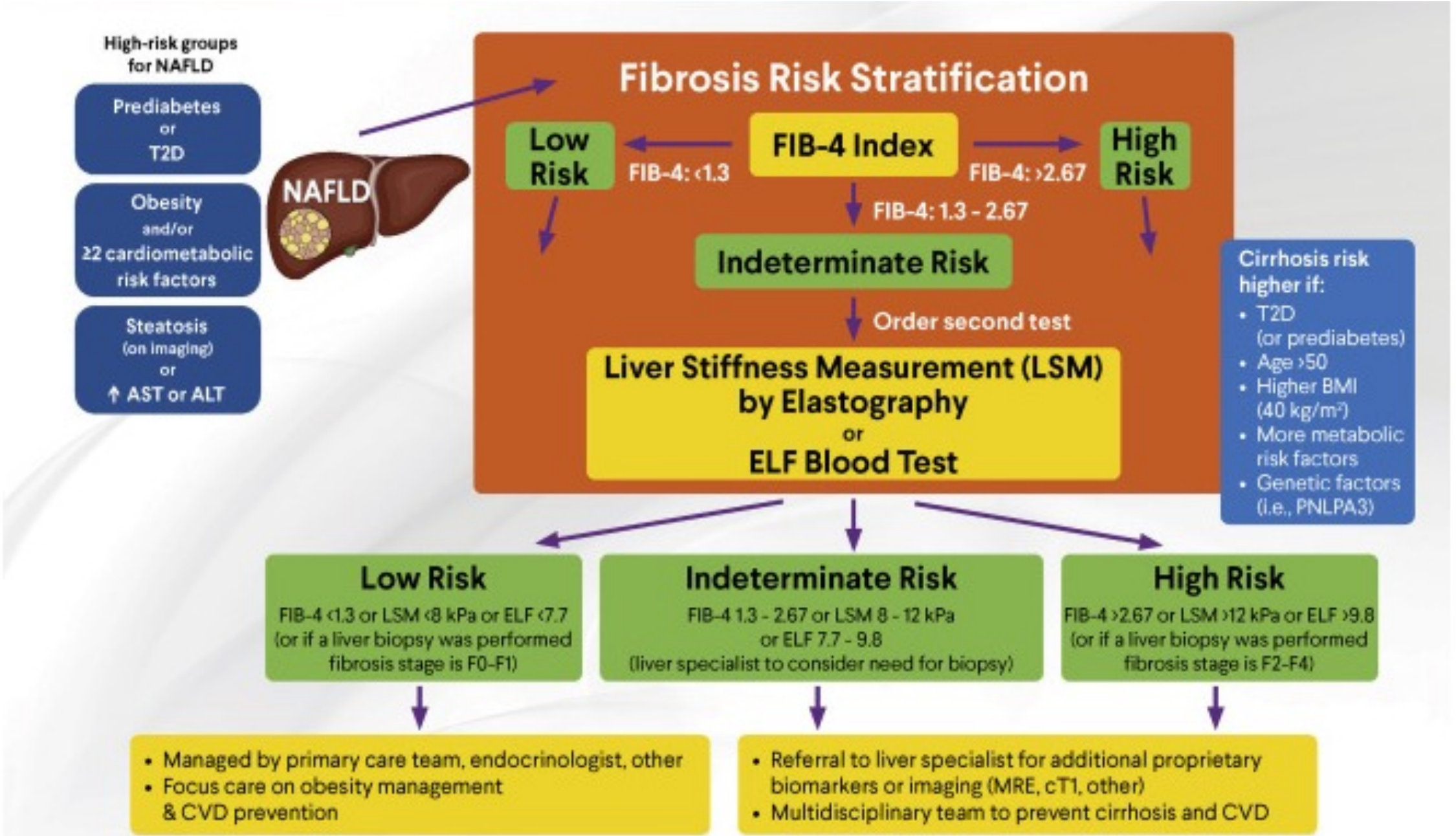

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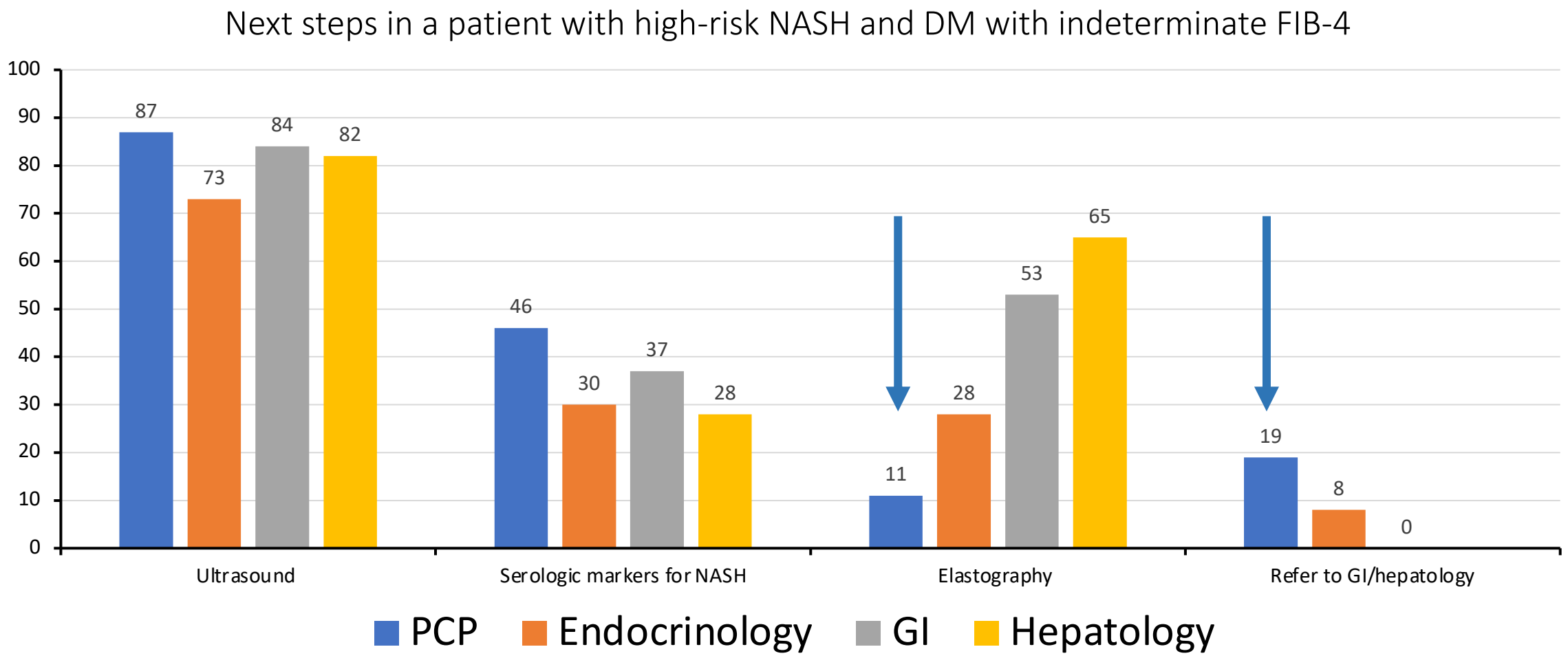
Elastography/Referral is Underused in Primary Care



Porayko MK et al. Differences in NAFLD/NASH Management by Provider Specialty: Opportunities for Optimizing Multidisciplinary Care. *J Multidiscip Healthc*. 2022.

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Goals of NASH Management (in ≥F3)

- Improve metabolic abnormalities
- Prevent/arrest/reverse liver fibrosis
- Prevent advanced liver disease, liver failure, liver cancer and related outcomes (only ≥ F3 patients at risk)
- Reduce cardiovascular complications

Chalasani N, et al. *Hepatology*. 2018;67:328-35.

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Current Management of NAFLD

- Patient education
- Intense lifestyle modification
- Medications focused on weight loss
- Consider referral to bariatric surgery
- Consider clinical trials

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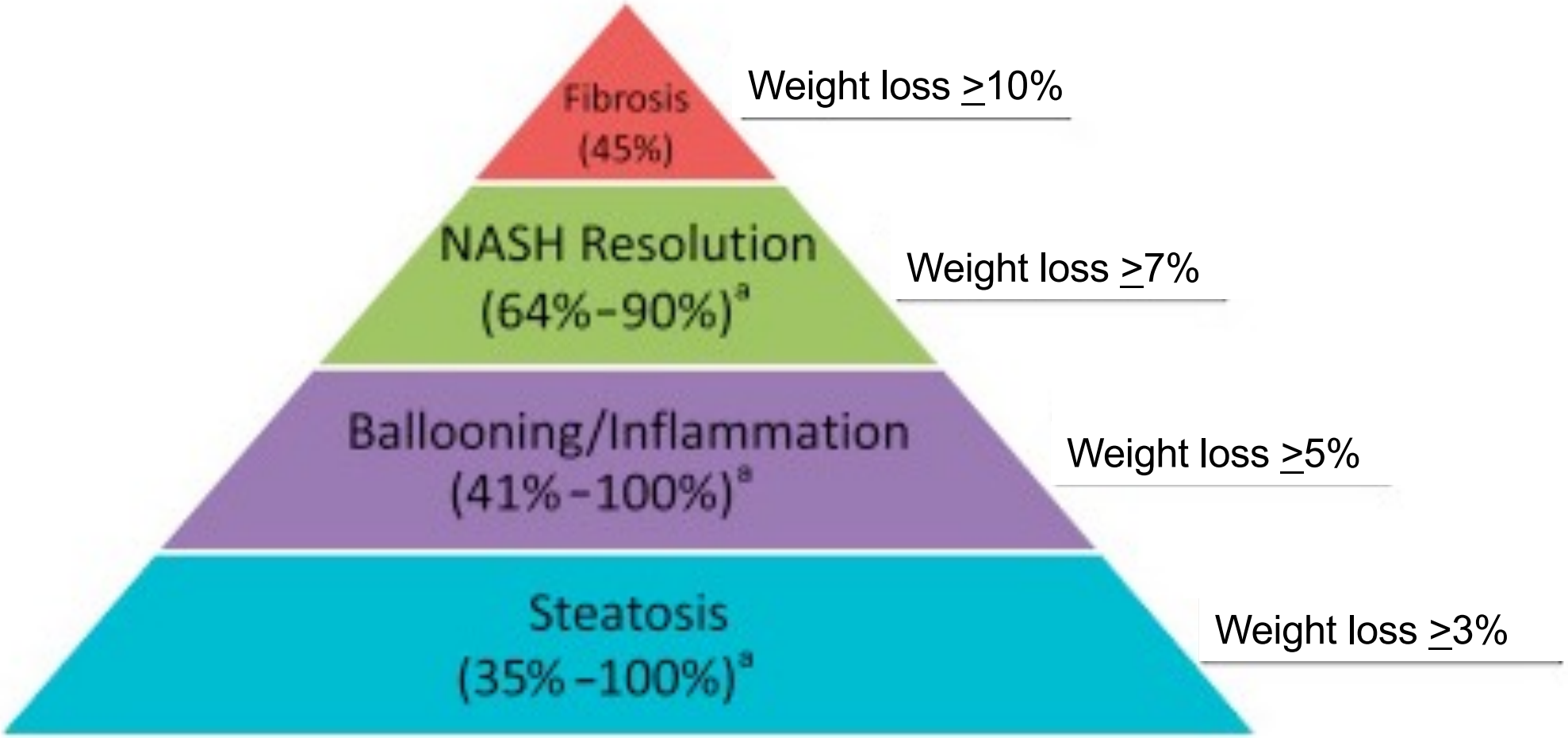
Weight loss is recommended



Hannah WN, et al. *Clin Liver Dis*. 2016;20(2):339-50., Sheka AC, et al. *JAMA*. 2020;323(12):1175-1183., Promrat K, et al. *Hepatology* 2010;51:121-129.

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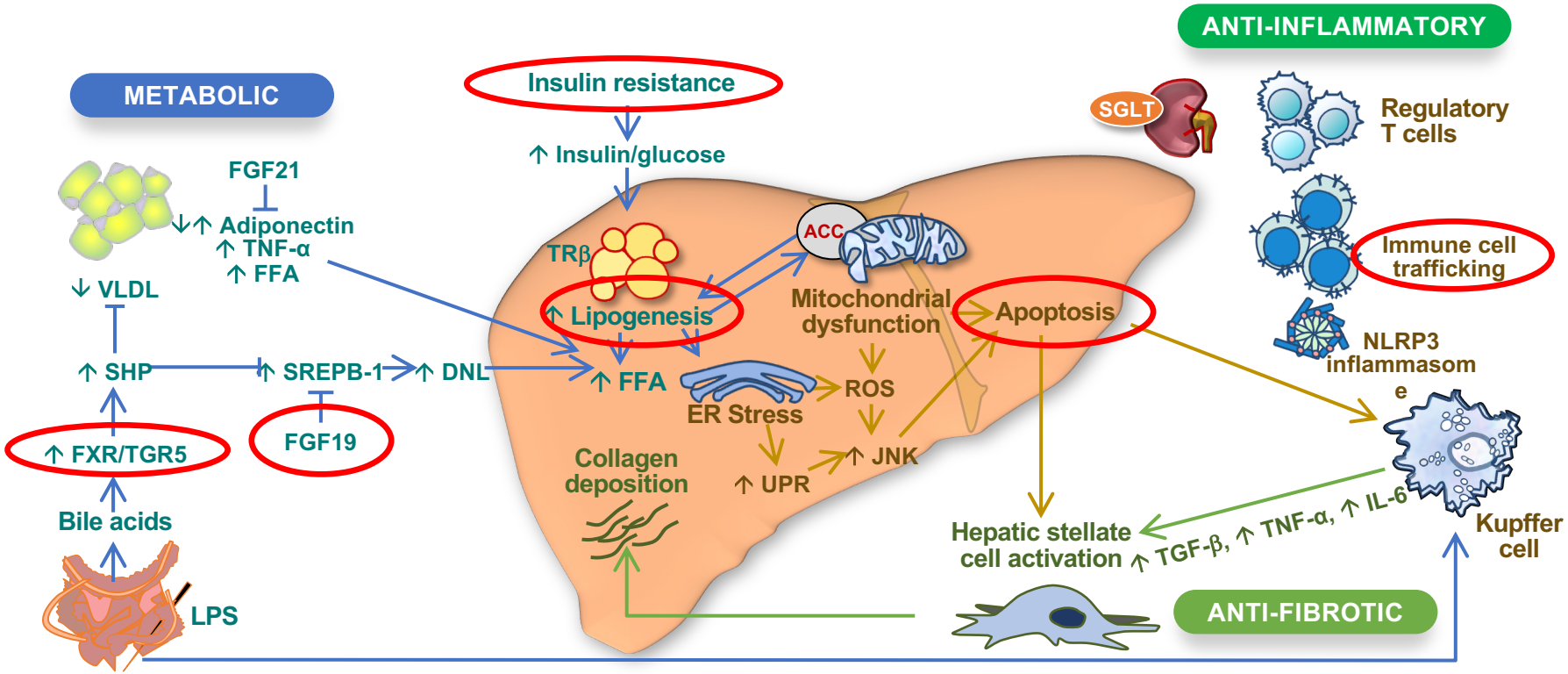
Targets for NASH and Related Fibrosis



ACC, acetyl-CoA carboxylase; AOC, amine oxidase, copper containing; ASK, apoptosis signal-regulating kinase; CCR, CC chemokine receptor; DNL, de novo lipogenesis; ER, endoplasmic reticulum; FFA, free fatty acids; FGF, fibroblast growth factor; FXR, farnesoid X receptor; IL, interleukin; JNK, Jun N-terminal kinases; LPS, lipopolysaccharide; NLRP3, nucleotide-binding oligomerization domain and leucine rich repeat and pyrin domain containing protein 3; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SCD, stearoyl CoA desaturase; SGLT, sodium-glucose linked transporter; SHP, small heterodimer partner; SREBP, sterol regulatory element binding proteins; TGF, transforming growth factor; TGR5, G protein-coupled bile acid receptor 1; TLR, toll like receptor; TNF, tumor necrosis factor; TR, thyroid receptor; UPR, unfolded protein response VLDL, very low density lipoprotein.

Adapted from Konerman MA et al. *J Hepatol*. 2018;68:362–375.

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Managing NAFLD in Primary Care

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Guidance Statements: Primary Care

- General population-based screening for NAFLD is not advised.
- All patients with hepatic steatosis or suspected NAFLD based on presence of obesity and metabolic risk factors should undergo primary risk assessment (FIB-4).
- High-risk individuals (e.g., T2DM, medically complicated obesity, family hx of cirrhosis, >moderate alcohol consumption) should be screened for advanced fibrosis.
- Patients with pre-DM, T2DM or 2 metabolic risk factors (or imaging evidence of steatosis) should have FIB-4 repeated every 1-2 years.

Note: AST and ALT are frequently normal in patients with advanced NASH and should not be used in isolation to exclude the presence of NASH with significant fibrosis.

Rinella M et al., *Hepatology* 77(5): 1797-1835, May 2023. DOI: 10.1097/HEP.0000000000000323

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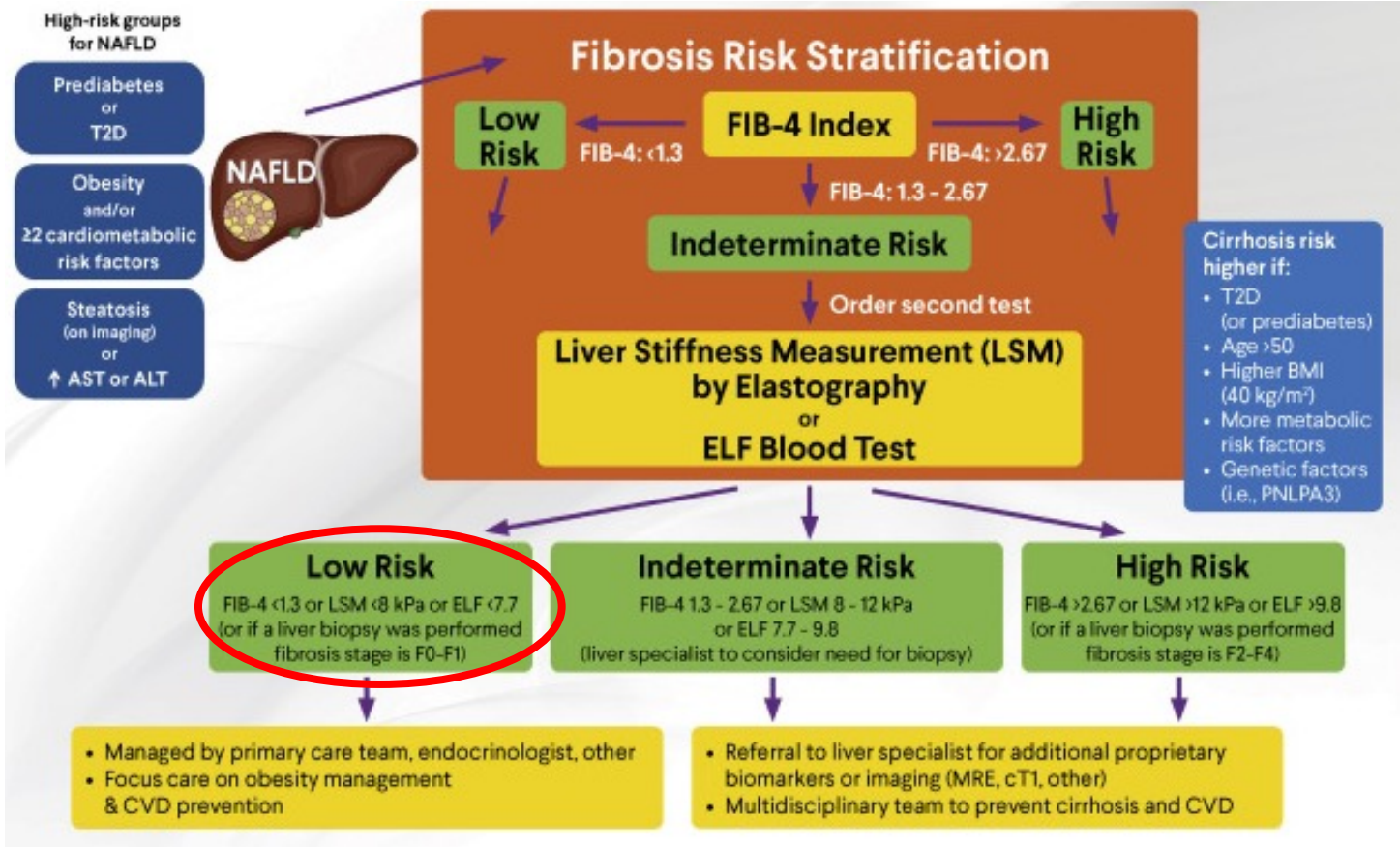
Low Risk: Continue Management Under Primary Care

- Manage any features of metabolic syndrome, diabetes, hypertension, dyslipidemia → referral for specialty care as appropriate.
- Prescribe dietary intervention and physical activity. Aim for 5-10% baseline weight loss.
- Continue regular follow-up (at least yearly) to encourage continued lifestyle change and monitor goals.
- Monitor anthropometrics, glucose control, liver biochemistry annually → referral as appropriate.



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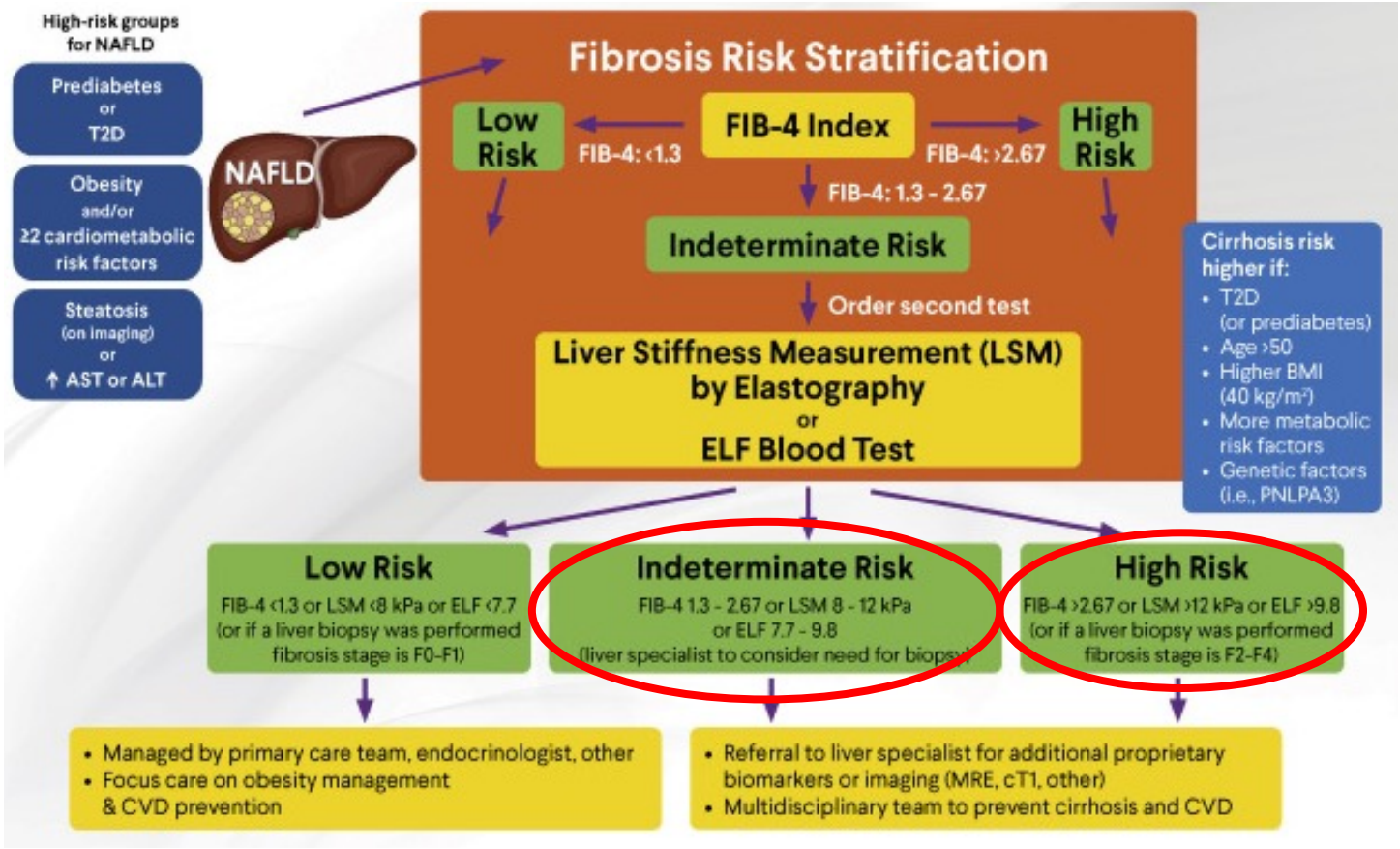
Intermediate/High Risk: Liver Specialist Involvement

- Patients with suspected advanced NASH or discordant NITs: Refer to liver specialist.
- Patients with NASH cirrhosis require
  - Surveillance for HCC (ultrasound and AFP Q6 months)
  - Surveillance for esophageal varices
  - Monitoring for decompensation



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Conclusion

- Weight loss remains effective but underutilized.
- Critical to risk stratify patients to identify advanced fibrosis.
- Low risk patients need to focus on cardiovascular risk reduction and stay under PCP management.
- Intermediate/High risk patients need to be referred to liver specialists for further workup and management.

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And Now the New Nomenclature…

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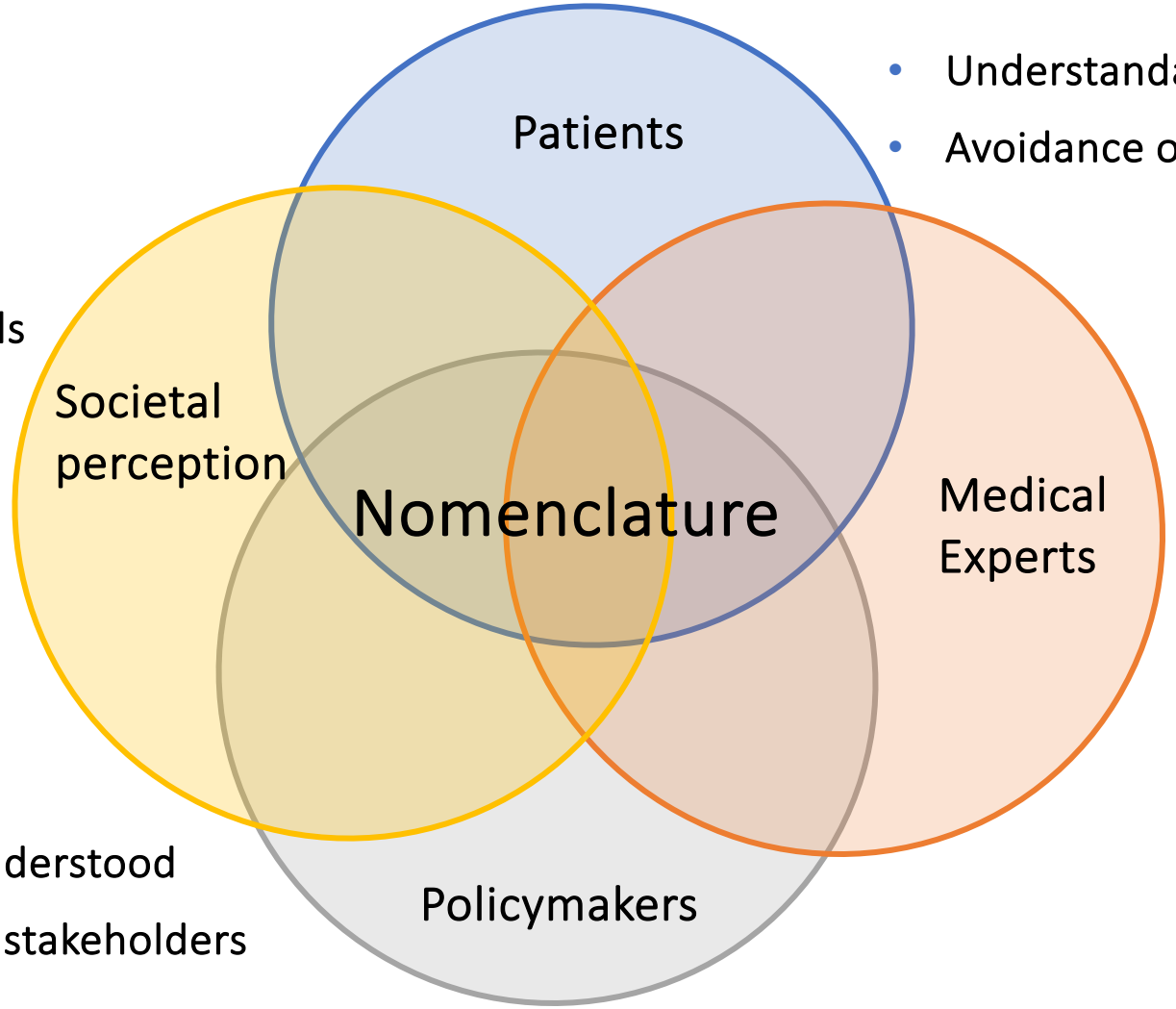
Why the Change?: WHO Guidance



- Understandable
- Avoidance of stigma

- Cannot marginalize groups or individuals

- Accuracy and precision
- Clear defining characteristics

- Disease impact understood
- Awareness across stakeholders
- Clinical care pathway

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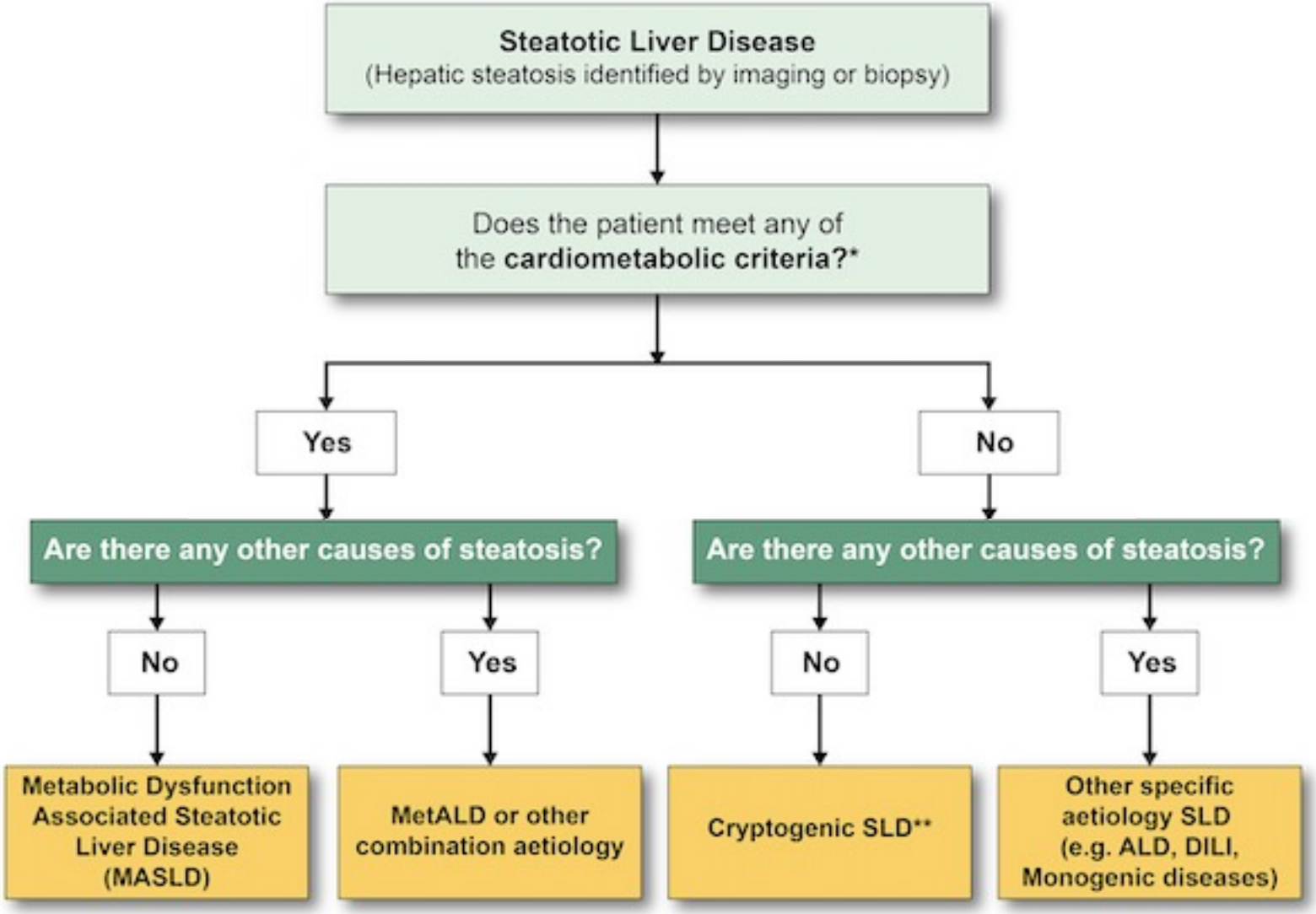

Adult Criteria

At least 1 out of 5:

- ☐ BMI ≥ 25 kg/m² [23 Asia] **OR** WC > 94 cm (M) 80 cm (F) **OR** ethnicity adjusted
- ☐ Fasting serum glucose ≥ 5.6 mmol/L [100 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol/L [≥140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** type 2 diabetes **OR** treatment for type 2 diabetes
- ☐ Blood pressure ≥ 130/85 mmHg **OR** specific antihypertensive drug treatment
- ☐ Plasma triglycerides ≥ 1.70 mmol/L [150 mg/dL] **OR** lipid lowering treatment
- ☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [40 mg/dL] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) **OR** lipid lowering treatment

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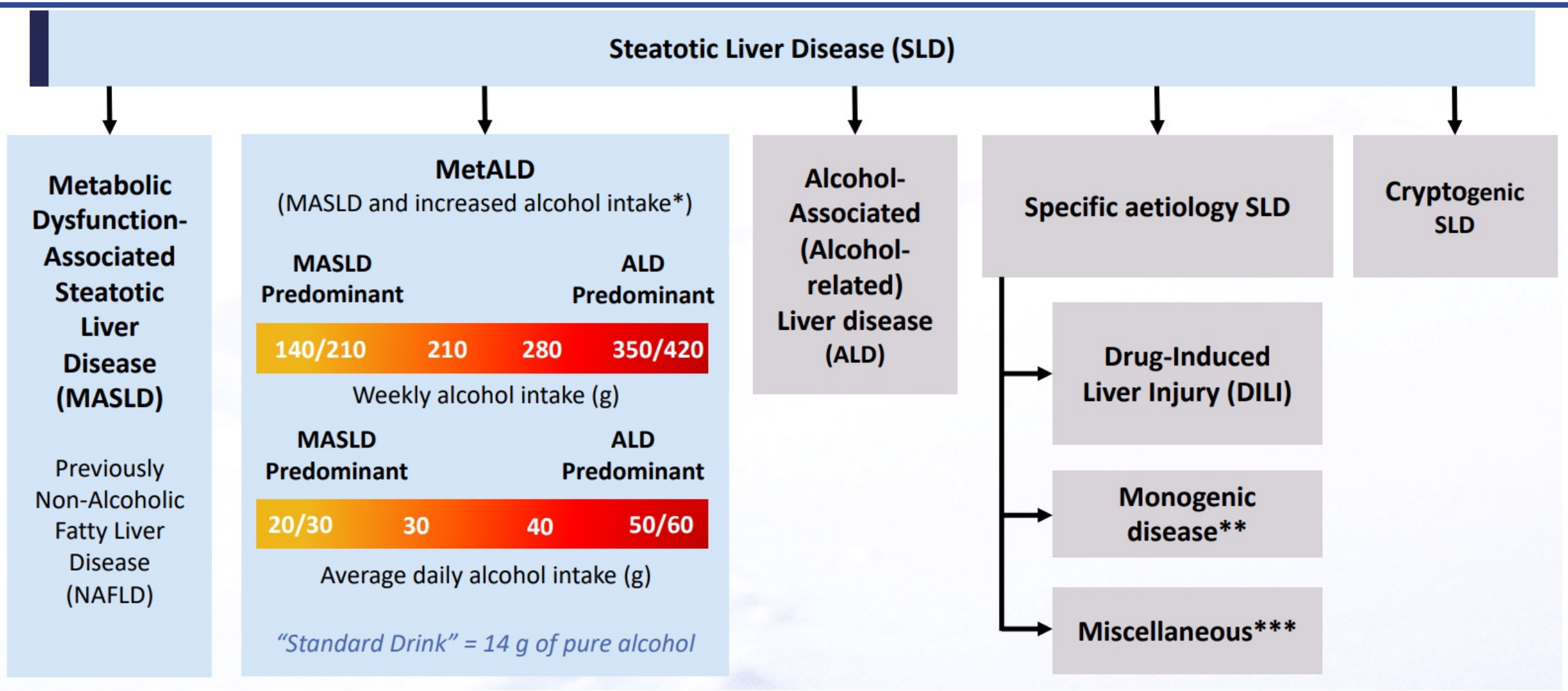
Rinella ME. *Hepatology*. 2023 Jun 24: PMID: 37363821

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

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

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