Steatotic Liver Disease

Philip N Styne MD AGAF FACP

2026

Disclosure

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Objectives

- Define the **new nomenclature** for fatty liver disease
- Identify the **risk factors** for fatty liver disease
- List the **risk factors for advanced** fatty liver disease
- Identify the **non-invasive tests** available to assess advanced disease
- **Lifestyle** treatment
- List the **medication** to treat the appropriate patients

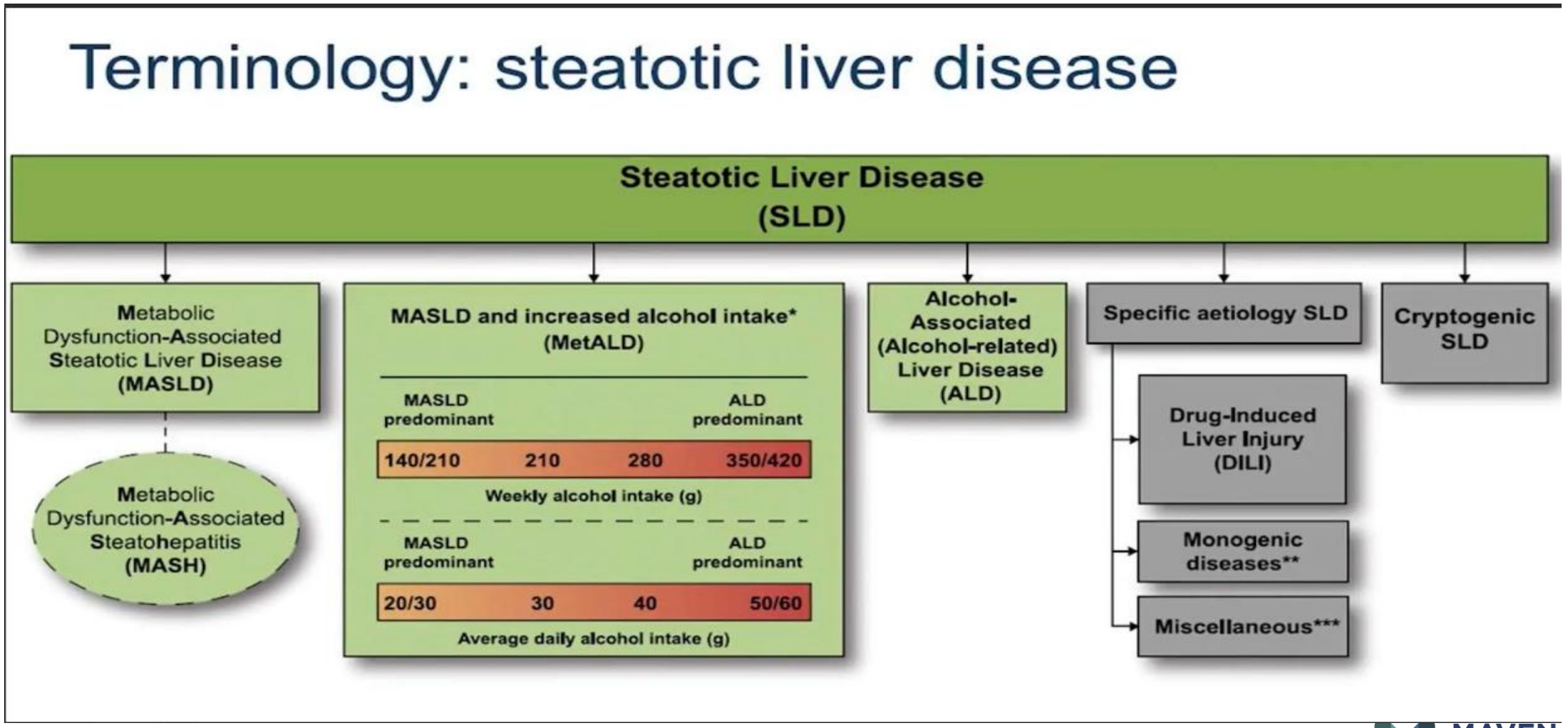
Definitions

- Steatotic Liver Disease – greater than 5% fat on liver biopsy– replaces fatty liver
- MASLD – Metabolic dysfunction Associated Steatotic Liver Disease – replaces NAFLD
- MetALD -- Metabolic dysfunction and Alcohol associated Liver Disease – adds a new category

Definitions

- MASH – Metabolic dysfunction Associated Steatohepatitis – replaces NASH
  - the fat and its associated metabolic abnormalities produce inflammation and fibrosis that can lead to cirrhosis

Definitions



WHO Gets MASLD

MASLD Risk Factors

Diet & lifestyle

Metabolic disorders

Diabetes
Obesity
Dyslipidemia

Polycystic ovarian syndrome
Obstructive sleep apnea

Age & sex

Genetics

PNPLA3
TM6SF2
MBOAT7
HSD17B13

Jancovic P et al. *BJOG: An International Journal of Obstetrics and Gynecology*. 2023.

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Metabolic Risk Factors

- Glucose fasting ≥ 100 mg/dl
- HDL cholesterol < 40 mg/dl
- Triglycerides ≥ 150 mg/dl
- Obesity waist _BMI ≥ 30 , waist ≥ 38 M 32 F
- HTN ≥ 130/90

Genetics

- PNPLA3 paptatin-like phospholipase domain-containing protein 3
  - PNPLA3-1148M variant increases risk of MASLD and alcoholic liver disease
- TM6SF2 transmembrane 6 superfamily member 2
- MBOAT7 membrane-bound O-acyltransferase domain-containing protein 7

Drugs Associated with SLD

- Amiodarone
- Tamoxifen
- Glucocorticoids
- Methotrexate

Alcohol Use Definitions

- Moderate -- MetALD
  - 20—50 g/d (140-350 g/w) F
  - 30– 60 g/d (210-420 g/w) M
- Heavy -- ALD
  - >50 g/d F
  - >60 g/d (210-420 g/w) M

12 oz beer = 5 oz wine = 1.5 oz whiskey = 14 g

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Who to Screen for Fibrosis

- **First-degree relatives** of patients with **cirrhosis**
- Individuals with **obesity** and one or more obesity related **comorbidities**
- Individuals with moderate of greater **alcohol** consumption (20-50g/d F, 30-60g/d M)
- Patients with **type 2 diabetes mellitus**
- Patients with 2 or more **metabolic risk factors** without diabetes

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Assessments

- History– Meds, toxins, alcohol, co-morbidities
- Family history – as we see the genetics
- Physical exam-- BMI, Waist circumference
- Lab- CMP – AST, ALT, Alk Phos, CBC
- Lab score-- FIB-4, ELF, FibroSure
- Scans-- US, CT, MR, Elastography

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Initial Lab Workup

- ALT/AST
- Alk Phos, bili
- Albumin
- CBC
- PT/INR
- Fasting glucose HgbA1c
- Total and HDL cholesterol and triglycerides

Lab Workup for Differential

- Hep BsAg, Hep BcAb total-- if either + Hep B DNA -1/1000 chronic **B**
- Hep C Ab if + Hep C RNA -8/1000 chronic **C**
- Iron, TIBC, ferritin -1/300 **hemachromatosis**
- AMA, ANA, ASMAb if high AST/ALT, Alk Phos or Hx auto-immune disease -1/10,000 **AIH**
- Ceruloplasmin -1/30-100,000 **Wisons**
- **AIAT** -1/3500
- **Celiac** panel -1/500
- PETH **Alcohol** use

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FIB--4

- < 1.3 – low risk
- < 1.3 -- if T2D and or ≥2 metabolic risks screen q2y
- < 1.3 -- if T2D and or 1 metabolic risks screen q3y
- ≥ 1.3 and ≤ 2.67 -- need assessment with USBTE refer if necessary
- > 2.67 -- high risk need referral

Scans for SLD

Diagnosing Steatosis

Traditional Ultrasound

- Not sensitive enough for steatosis (operator / body habitus)

Controlled Attenuation Parameter (CAP)

- **Point of Care** steatosis assessment (> 280)
- Not accurate in distinguishing quantity / grades

Low US Attenuation Rate

High US Attenuation Rate

MRI Proton Density Fat Fraction (PDFF)

- More accurate percentage of steatosis

Petta et al. *Hepatology*. 2017.

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USBTE

Transient Elastography

Measures low frequency elastic shear wave velocity through the liver

< 8 kPa **Rules out advanced fibrosis / cirrhosis**

> 12 kPa **Increased risk advanced fibrosis**

≥ 20 kPa **Can Rule-in cirrhosis**

Do Not Use … can be falsely elevated in
Heart failure, iron overload, hepatitis, ascites, non-fasting

ulio N and Trillaud H. *Diagnostic and Interventional Imaging*. 2013.

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Start with Lifestyle

Energy restriction
- ≥ 30% reduction
- Calorie restriction (750–1,000/day)
- 7–10% weight loss target
- Long-term maintenance approach

Fructose intake
- Avoid fructose-containing food and drink

Coffee consumption
- No liver-related limitations

Comprehensive lifestyle approach

Daily alcohol intake
- Strictly below 30 g men and 20g women

Macronutrient composition
- Low-to-moderate fat
- Moderate-to-high carbohydrate
- Low-carbohydrate ketogenic diets or high protein

Physical activity
- 150–200 min/week moderate intensity in 3–5 sessions
- Resistance training to promote musculoskeletal fitness and improve metabolic factors
- Exercise alone will not help significantl

SO CPG NAFLD. J Hepatol 2016;64:1388–402 modified

Mediterranean Diet & Olive Oil

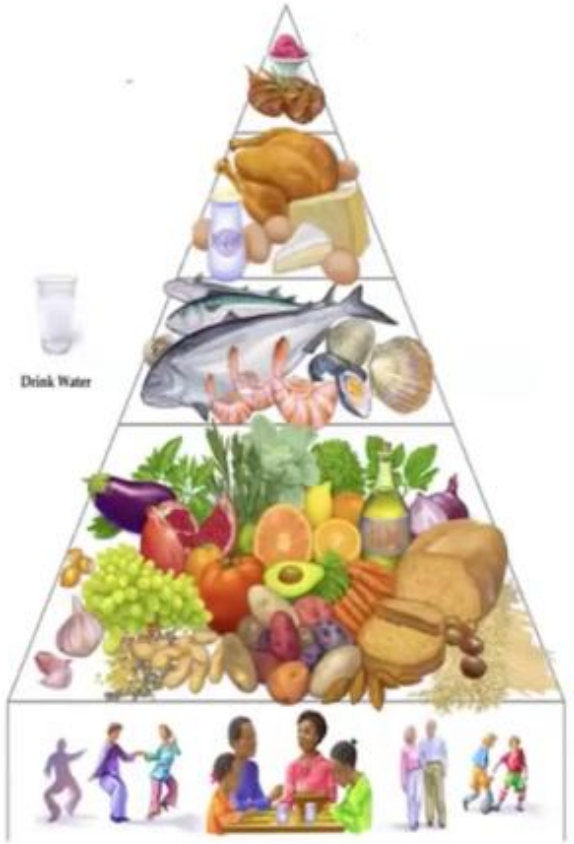
↑ **monounsaturated fatty acids**

↓steatosis on MRI compared to high fat / low carbohydrate

↓all-cause mortality, CV disease, cancer, obesity, diabetes

Modified Mediterranean Diet:
Carbohydrates to 30gm per meal / day

Tailor to culture / personal preferences



Haufe et al. Hepatology. 2011.

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ETOH

Alcohol: How Much Is Too Much?

12 ounces
5% ABV beer

8 ounces
7% ABV malt liquor

5 ounces
12% ABV wine

1.5 ounces
40% (80 proof)
ABV distilled spirits
(gin, rum, vodka,
whiskey, etc.)

https://www.cdc.gov/ncbddd/fasd/faqs.html

1 drink = ~14g ETOH

Daily Consumption (grams)	Women	Men
Mild	20	30
Moderate	21-39	31-59
Heavy	≥ 40	≥ 60

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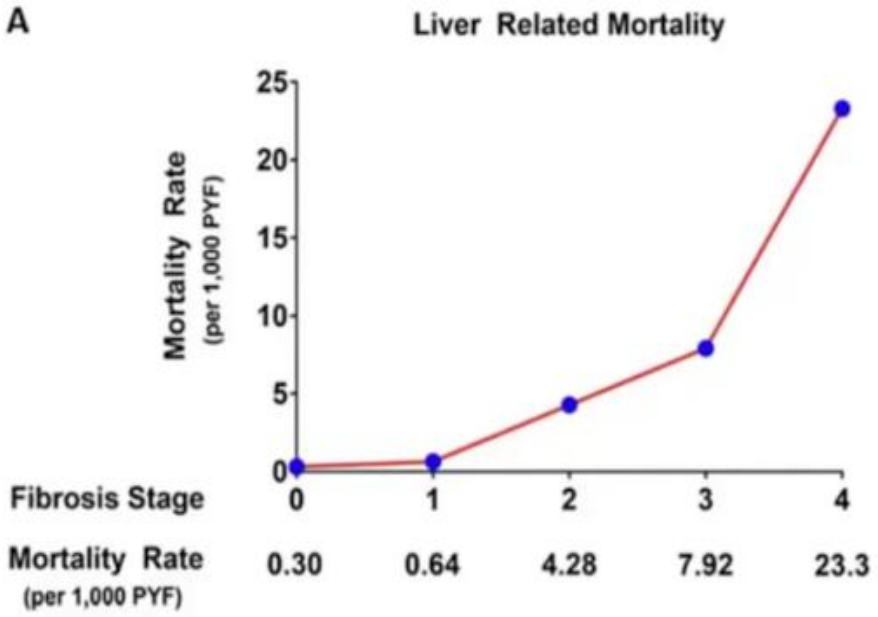
Mortality in MASLD

Liver Related Mortality Dependent on Fibrosis Stage



MASLD without Cirrhosis

Main Causes of Death:

- **Cardiovascular disease** (statins are ok!)
- **Malignancy**

Dulai et al. *Hepatology. 2017.*

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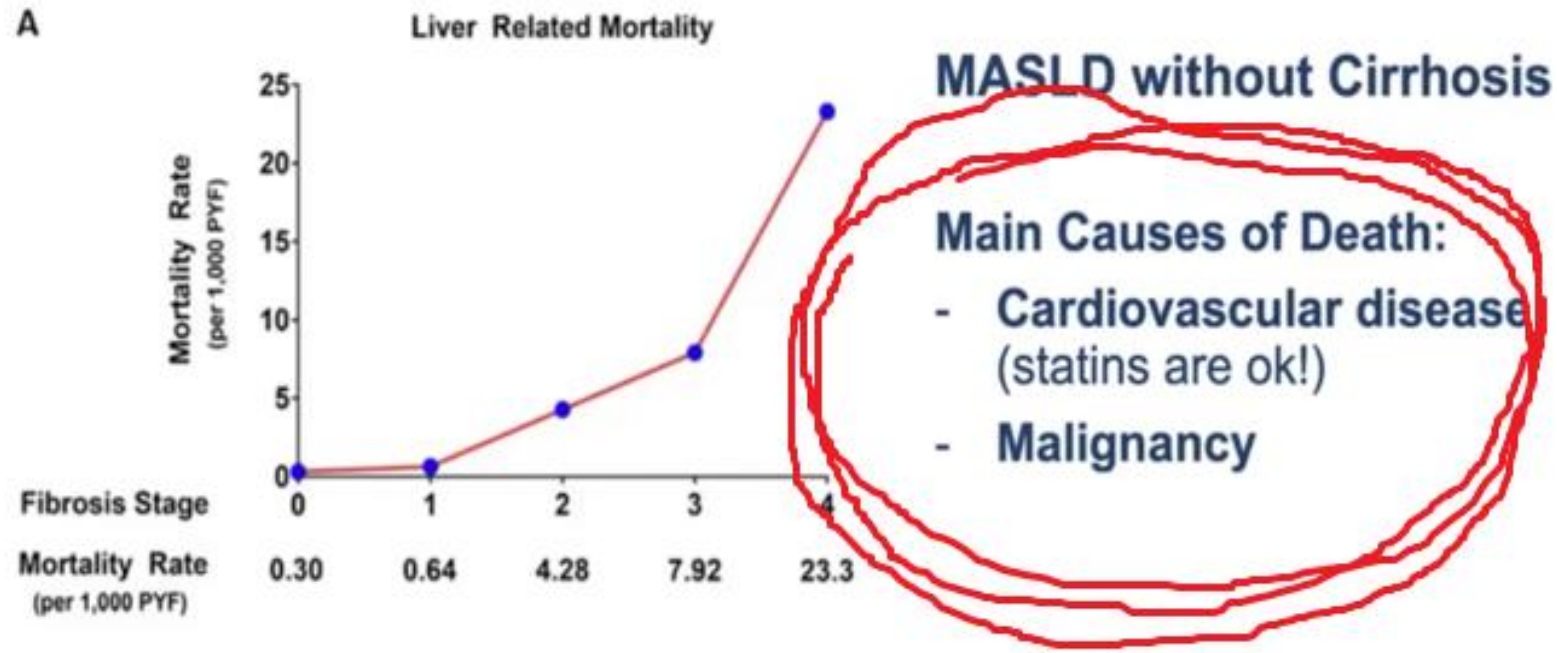
Mortality in MASLD

Liver Related Mortality Dependent on Fibrosis Stage



Dulai et al. *Hepatology*. 2017.

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Mortality in MASLD

...but death in MASLD is primarily *not* liver-related

Cause of death, N.	Population comparators	Nafld* All NAFLD
Cancer‡	3776	1343
Incidence rate§, per 1000 PY (95% CI)	4.8 (4.6 to 5.0)	9.3 (8.8 to 9.8)
Cardiovascular disease	5439	1199
Incidence rate§, per 1000 PY (95% CI)	6.9 (6.7 to 7.1)	8.3 (7.8 to 8.7)
Cirrhosis‡	121	413
Incidence rate§, per 1000 PY (95% CI)	0.2 (0.1 to 0.2)	2.8 (2.6 to 3.1)
Hepatocellular carcinoma‡	96	186
Incidence rate§, per 1000 PY (95% CI)	0.1 (0.1 to 0.2)	1.3 (1.1 to 1.5)
Other causes	3685	1008
Incidence rate§, per 1000 PY (95% CI)	4.7 (4.5 to 4.8)	6.9 (6.5 to 7.4)

1.7% liver 14.4% liver

- 10,568 patients with biopsy-confirmed NAFLD in Sweden
- Matched to population controls by age, sex, year, and county
- Evaluated causes of death

Even in a highly-selected population, the vast majority of patients with NAFLD do not die of liver disease

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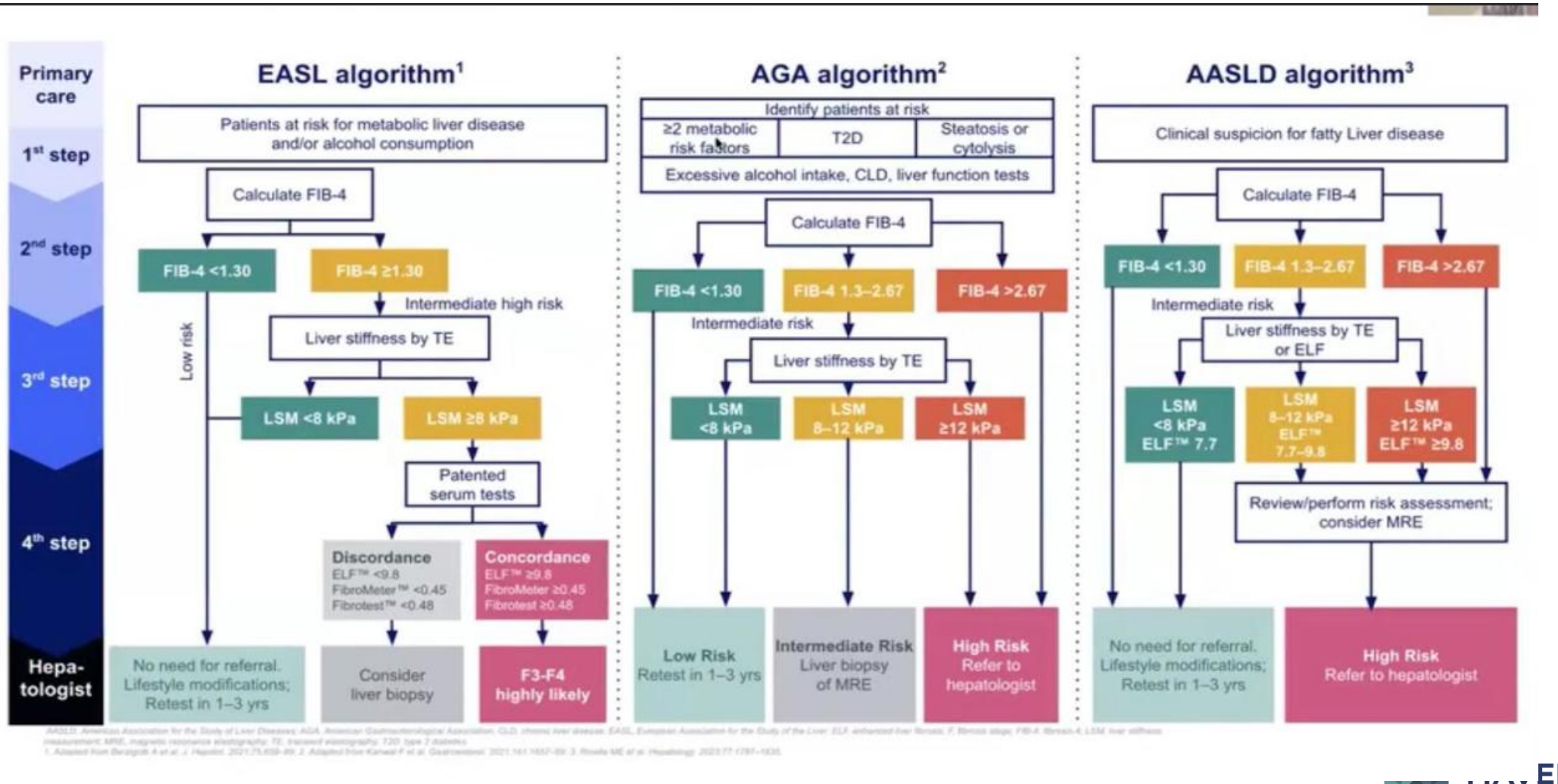


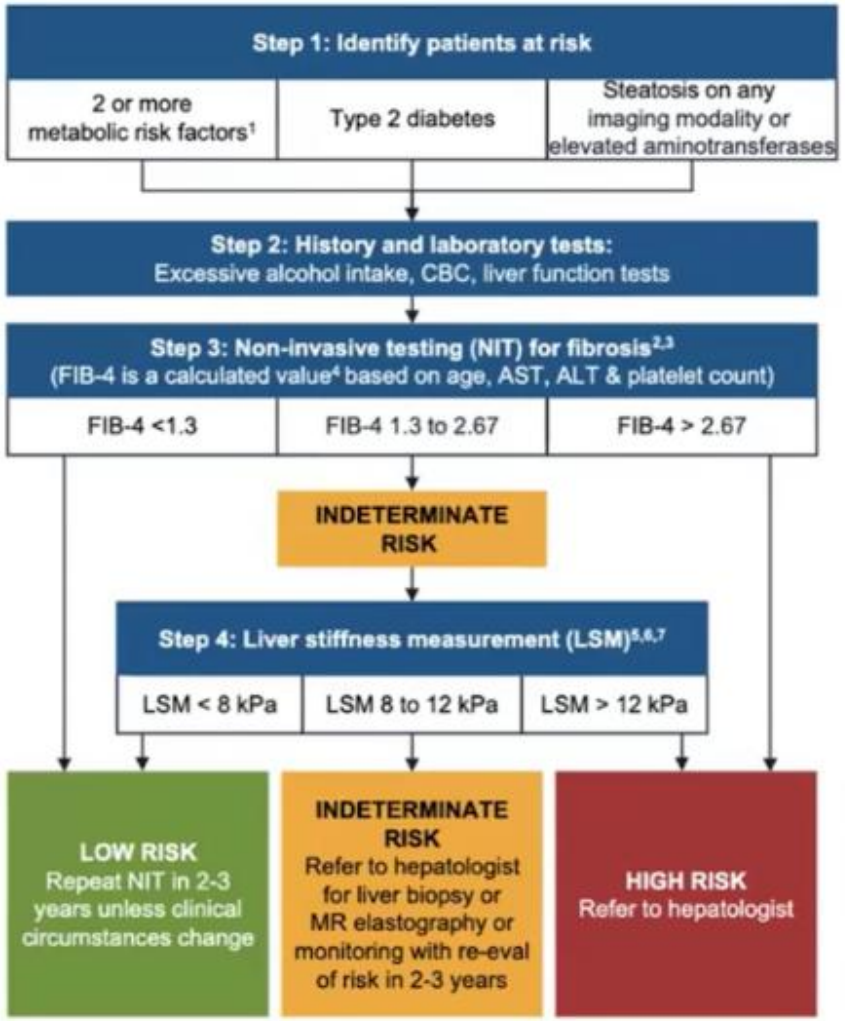
AASLD, American Association for the Study of Liver Diseases; AGA, American Gastroenterological Association; CLD, chronic liver disease; EASL, European Association for the Study of the Liver; ELF, enhanced liver fibrosis; F, fibrosis stage; FIB-4, fibrosis-4; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; TE, transient elastography; T2D, type 2 diabetes.

1. Adapted from Boursier A et al. J Hepatol. 2021;75:659–89. 2. Adapted from Kanwal F et al. Gastroenterol. 2021;161:1657–69. 3. Rinella ME et al. Hepatology. 2023;77:1797–1835.

Risk Factors

FIB-4

Liver Stiffness Measurement
(i.e. transient elastography, VCTE)



Kanwal et al. *Gastroenterology*. 2021.

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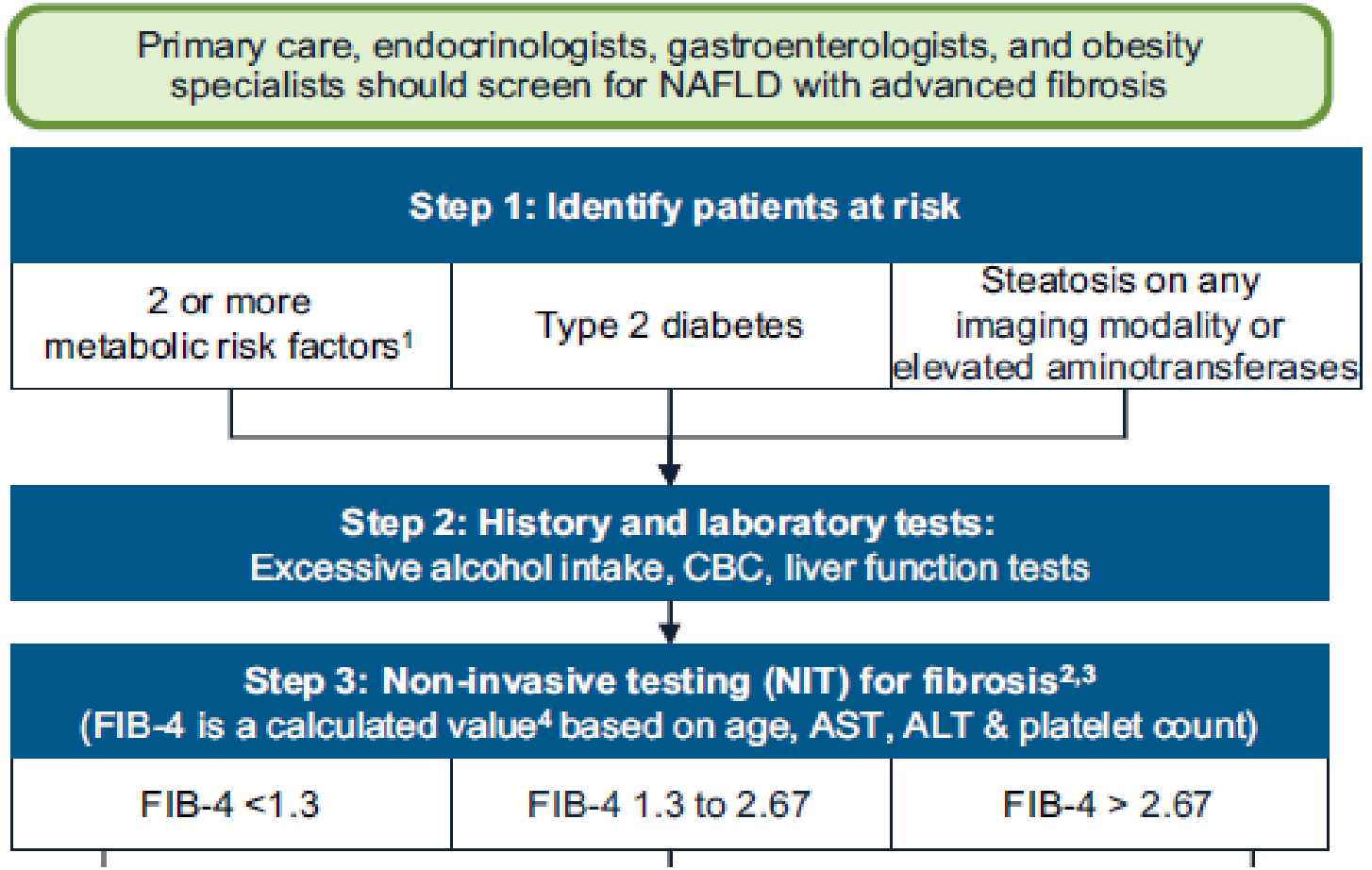

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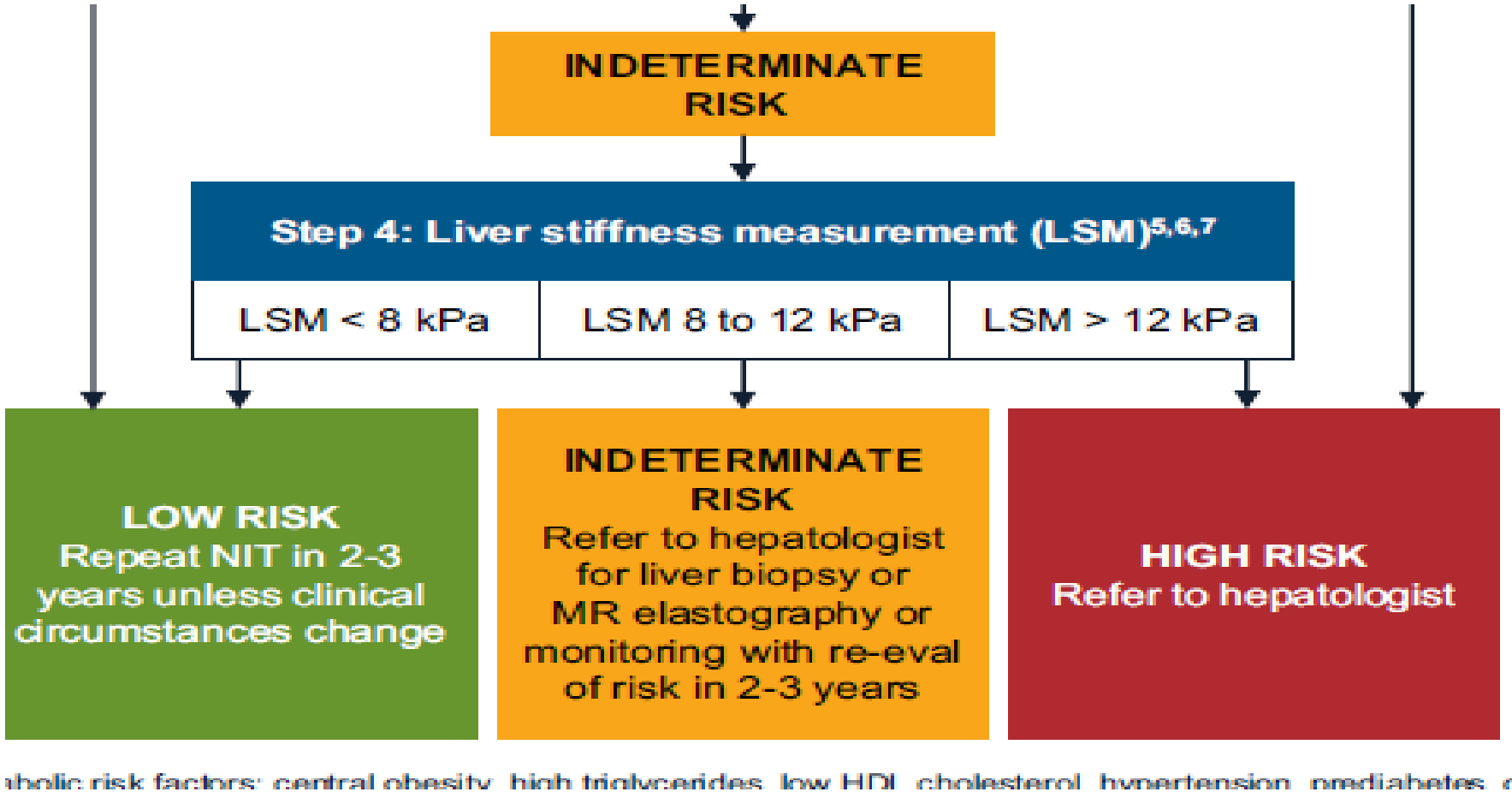

aholic risk factors: central obesity, high triglycerides, low HDL cholesterol, hypertension, prediabetes, or in

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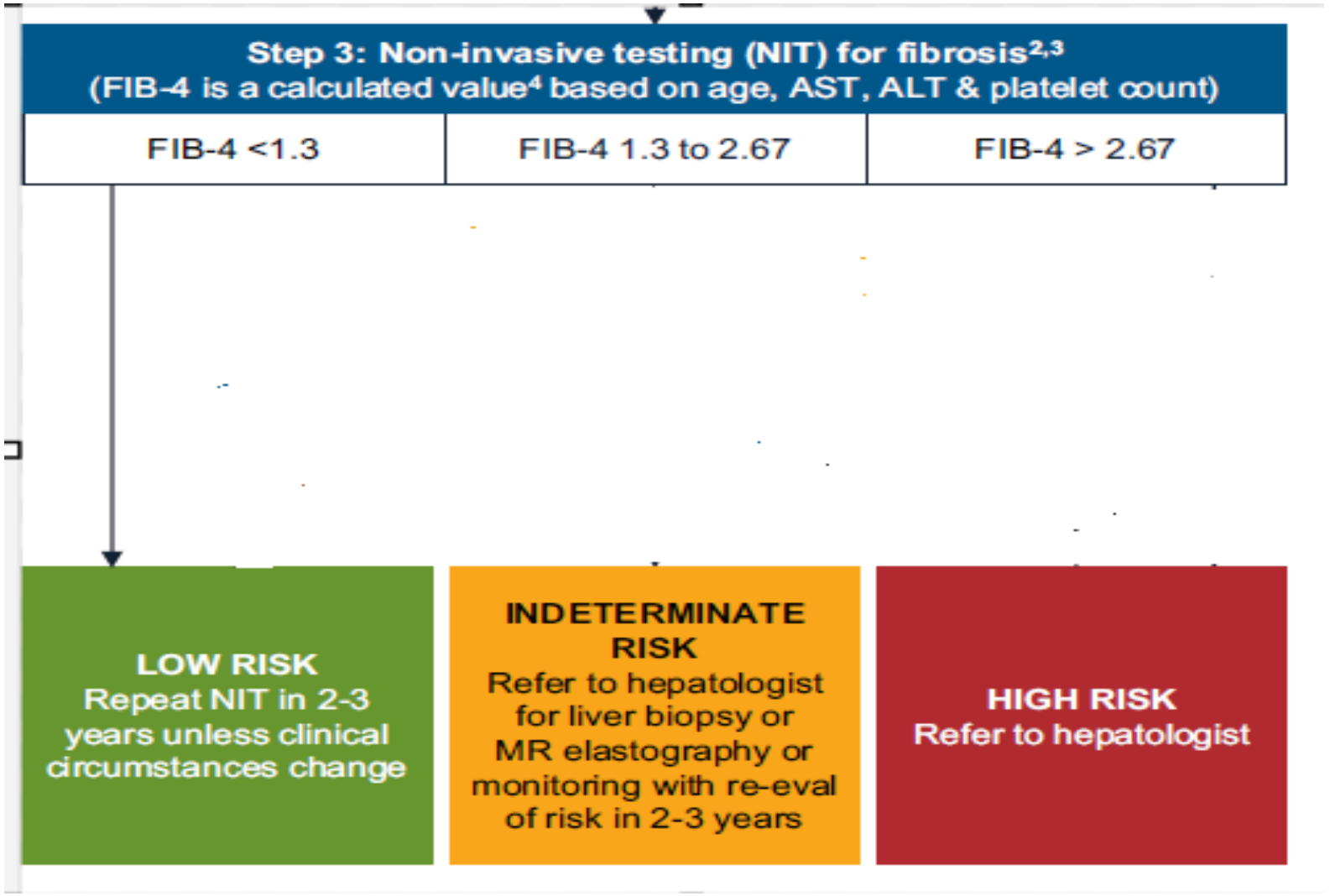

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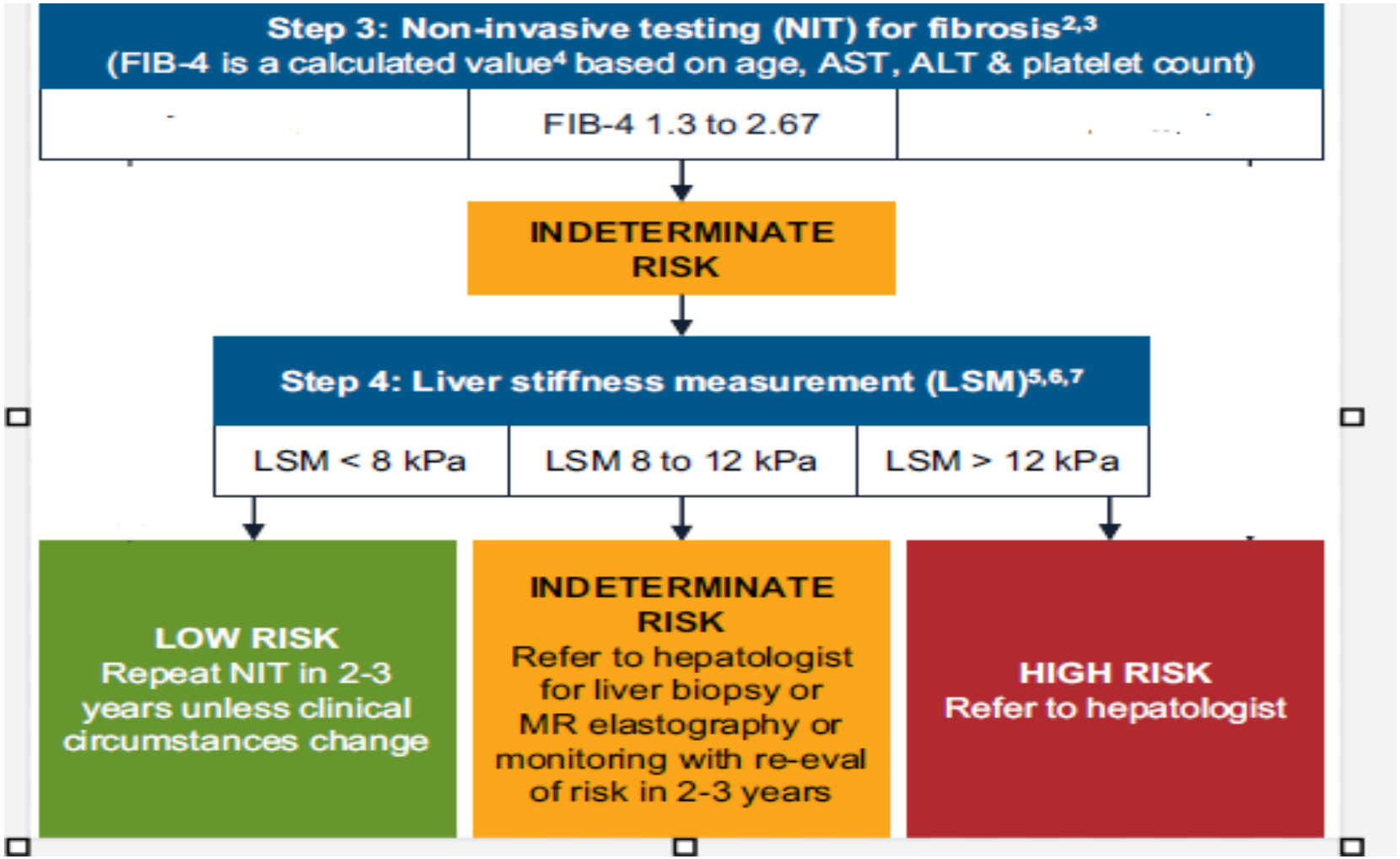
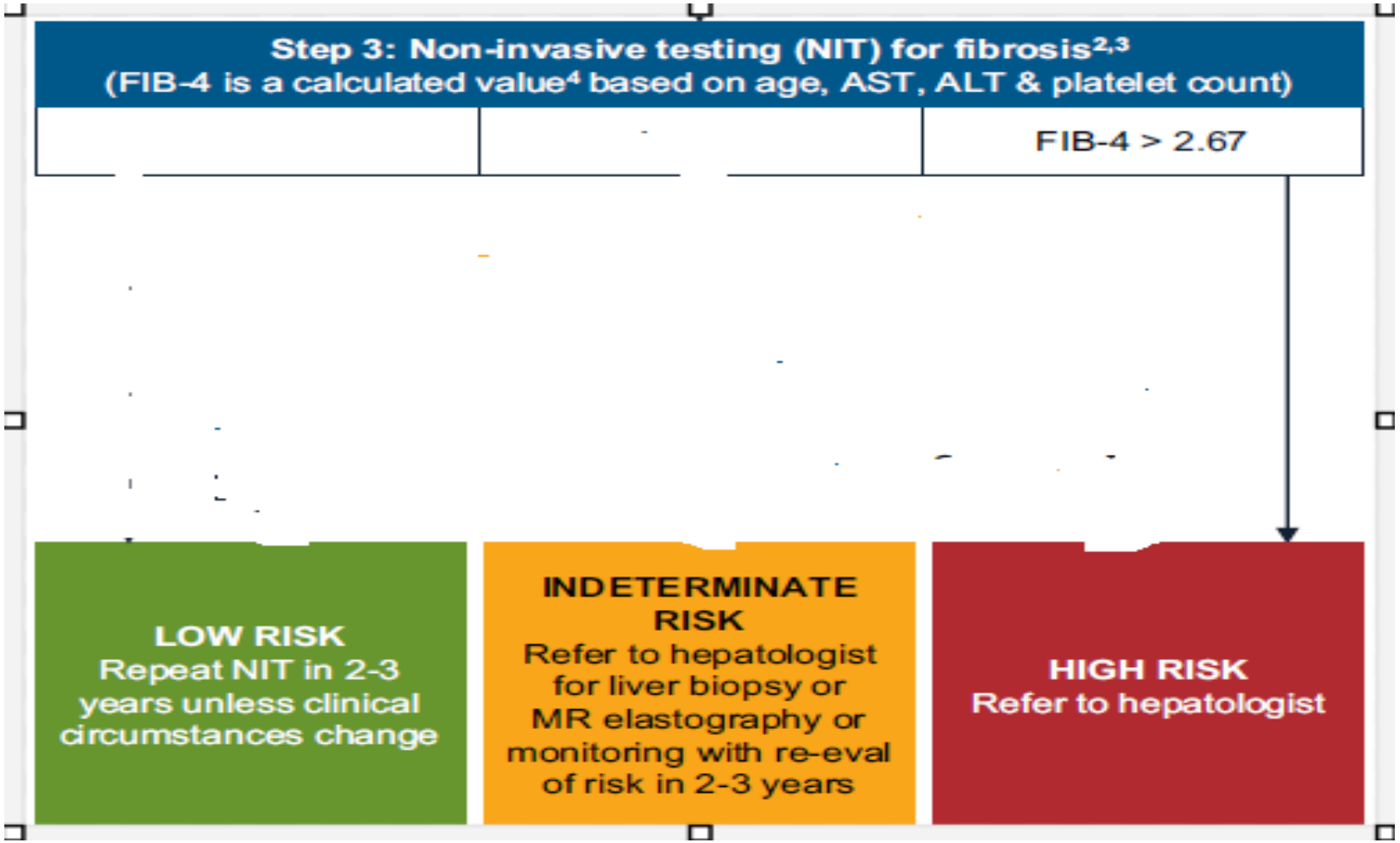

Step 3: Non-invasive testing (NIT) for fibrosis[2,3]
(FIB-4 is a calculated value[4] based on age, AST, ALT & platelet count)
FIB-4 1.3 to 2.67
INDETERMINATE RISK
Step 4: Liver stiffness measurement (LSM)[5,6,7]
LSM < 8 kPa
LSM 8 to 12 kPa
LSM > 12 kPa
LOW RISK
Repeat NIT in 2-3 years unless clinical circumstances change
INDETERMINATE RISK
Refer to hepatologist for liver biopsy or MR elastography or monitoring with re-eval of risk in 2-3 years
HIGH RISK
Refer to hepatologist


Step 3: Non-invasive testing (NIT) for fibrosis[2,3]
(FIB-4 is a calculated value[4] based on age, AST, ALT & platelet count)
FIB-4 > 2.67
LOW RISK
Repeat NIT in 2-3 years unless clinical circumstances change
INDETERMINATE RISK
Refer to hepatologist for liver biopsy or MR elastography or monitoring with re-eval of risk in 2-3 years
HIGH RISK
Refer to hepatologist

	LOW RISK FIB-4 < 1.3 or LSM < 8 kPa or liver biopsy F0-F1	INDETERMINATE RISK FIB-4 1.3 - 2.67 and/or LSM 8 - 12 kPa and liver biopsy not available	HIGH RISK[1] FIB-4 > 2.67 or LSM > 12 kPa or liver biopsy F2-F4
	Management by PCP, dietician, endocrinologist, cardiologist, others	Management by hepatologist with multidisciplinary team (PCP, dietician, endocrinologist, cardiologist, others)	
Lifestyle intervention[2]	Yes	Yes	Yes
Weight loss recommended if overweight or obese[3]	Yes May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Greater need for structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Strong need for structured weight loss programs, anti-obesity medications, bariatric surgery
Pharmacotherapy for NASH	Not recommended	Yes[4, 5, 6]	Yes[4, 5, 6, 7]
CVD risk reduction[8]	Yes	Yes	Yes
Diabetes care	Standard of care	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)

Kanwal et al Gastro 2021

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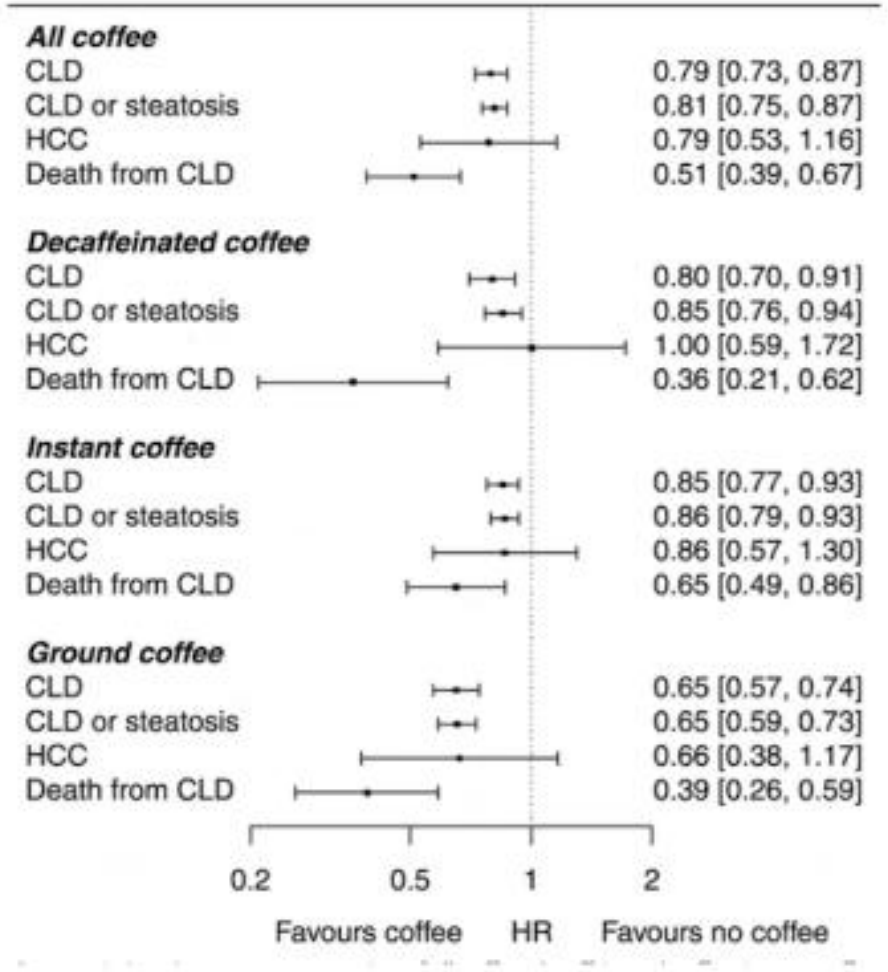
Coffee is Excellent!



Kennedy OJ et al. BMC Public Health. 2021.

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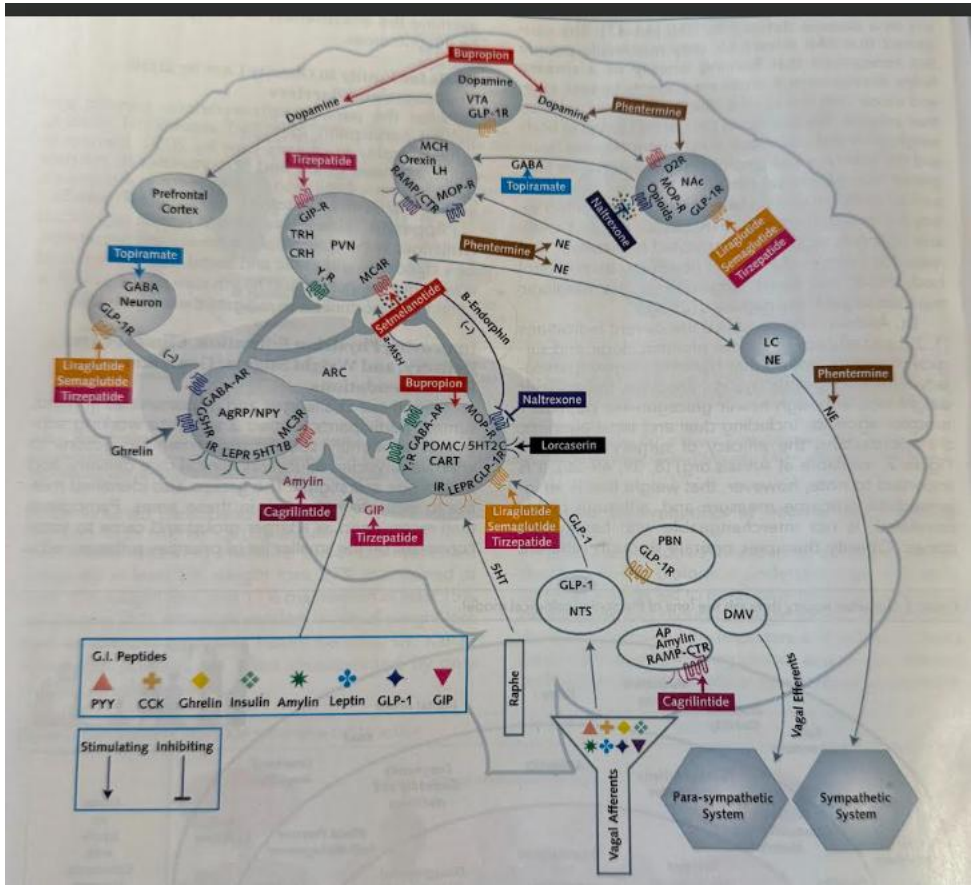
Obesity Neuroreceptors



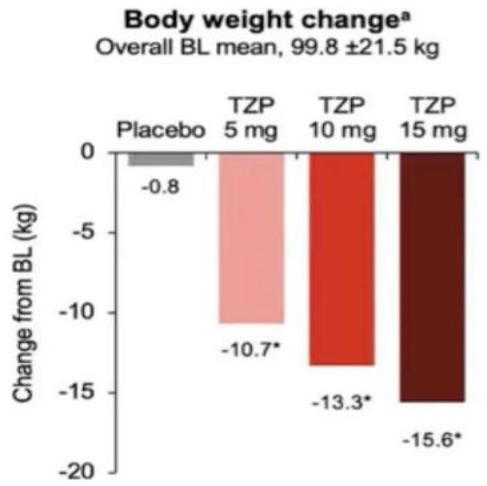
Medication for weight loss

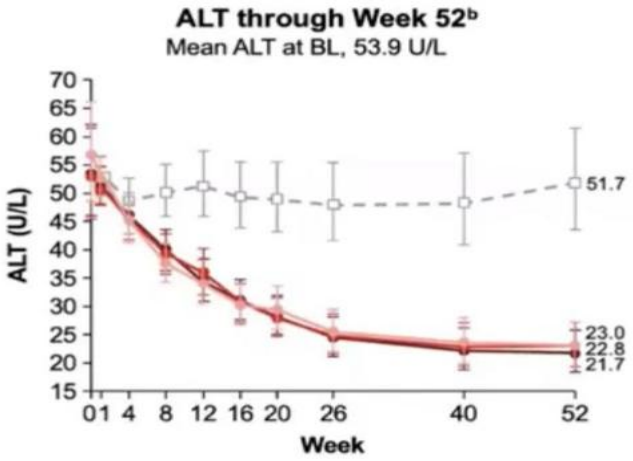
- Semaglutide GLP-1
- Tirzepatide GLP-1 and GIP

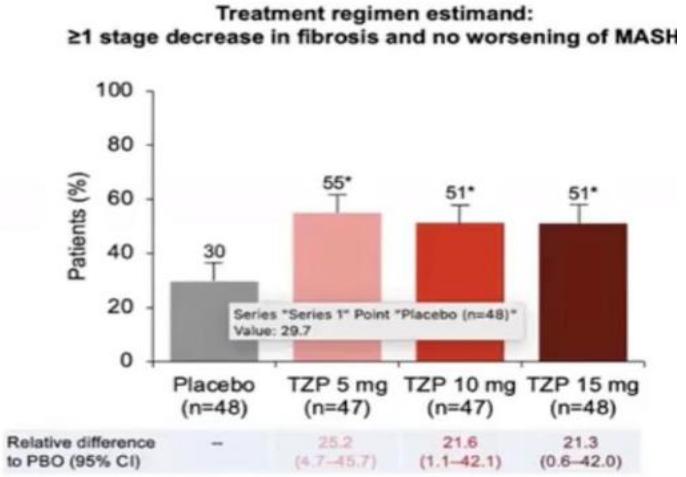
Both SC qwk meds
Both effect gastric emptying
Both have potential for pancreatic and biliary tract complications
Both may have positive cardiovascular effects

Medication for weight loss

Authors: Rohit Loomba, M.D., Mark L. Hartman, M.D., Eric J. Lawitz, M.D., Raj Vuppalanchi, M.D., Jérôme Boursier,







N Engl J Med. 2024; 391(4):299-310. DOI: 10.1056/NEJMoa2401943.

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First Specific Medication

Resmetirom (MAESETRO-NASH)

Liver-directed, thyroid hormone receptor beta (THR-β)–selective agonist

First FDA Approved Drug for MASH

Randomized, Double-Blind, Placebo Controlled Trial (52 weeks)

Inclusion Criteria

- Metabolic risk factors
- Fibroscan kPa consistent with F2-3
- Fibroscan CAP > 280
- > 8% liver fat on MRI-PDFF

Placebo (N=321)	Resmetirom 80 mg (N=322)	Resmetirom 100 mg (N=323)

Harrison et al. N Engl J Med. 2024.

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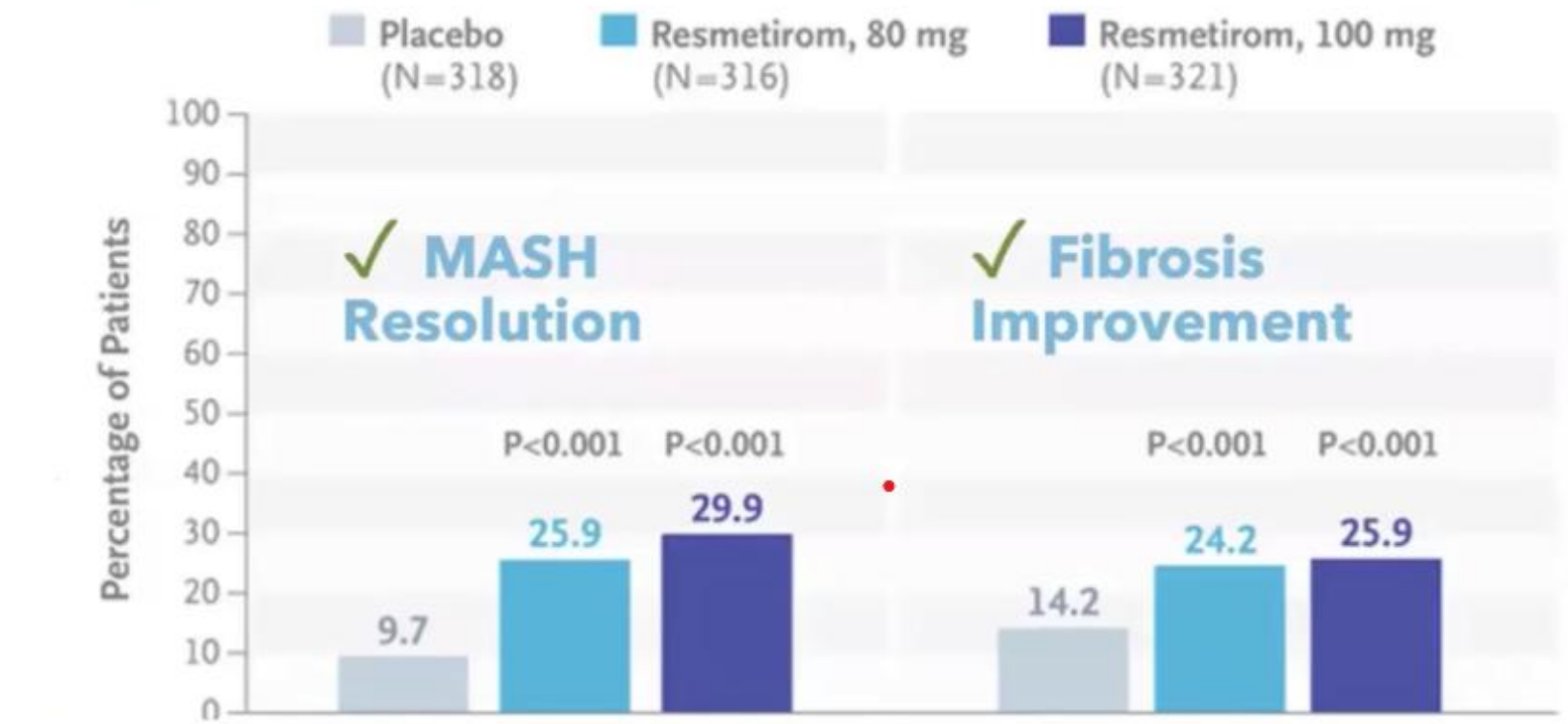
Resmetirom (MAESETRO-NASH)



Harrison et al. N Engl J Med. 2024.

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Take Home

- NAFLD is now MASLD
- NASH is now MASH
- ETOH plus SLD is MetALD
- Insulin resistance is a major factor
- Morbidity and mortality in pts with SLD is Cardiovascular and Cancer before decompensated cirrhosis
- Cirrhosis from SLD has all the potential complication of cirrhosis of other causes including HCC
- Identify advanced fibrosis F2 and above
- Resmetirom and semaglutide/tirzepatide are now approved

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Take Home

- Tirzepatide has the best weight loss in head to head with semaglutide
- Semaglutide may have more CV protection
- Both have some improvement in liver disease, both active inflammation and fibrosis
- Resmetirom is probably best as a second line drug
- What I tell you today especially about meds will be obsolete in 6 months

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Take Home

1. MASLD is a metabolic disease
2. Most patients with MASLD die of non-liver related events
3. GLP1 reduces non-liver related events
4. GLP1 reduces liver related events
5. A second agent can be added if there is still risk after optimizing the GLP1

Resources

- Liver Tox www.ncbi.nlm.nih.gov
- Medcalculators.Stanford.edu MELD
- MDCalc FIB-4
- Mayo for post-op mortality risk in cirrhosis
- VOCAL-Penn post-op mortality in cirrhosis

Resources

For our MAVEN Project clinic partners, we encourage you to submit any liver cases to the Maven hepatology group for consultation. Log into the MAVEN Community Portal at www.mavenproject.org.

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Contact

Philip Styne MD AGAF FACP
Philip.styne.md@gmail.com
407 617 9206

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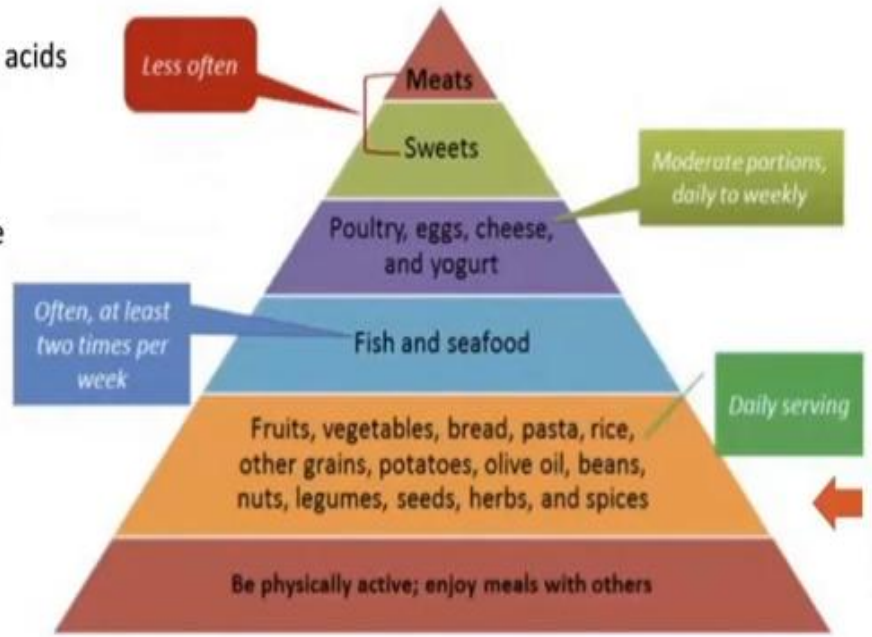
Recommended Diet : The Mediterranean Diet

High in:

- Monounsaturated, omega-3/omega-6 fatty acids
- Polyphenols
- Dietary fiber, prebiotics
- Plant proteins
- Water as drink of choice

Low in:

- Saturated and trans fat
- Animal protein
- Simple sugars



Could be adapted to different cultures but **extra virgin olive oil**

Grav. Nutritional Recommendations for Individuals with Diabetes. 2019. endotext.org.

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