MASLD/MASH Management

Hepatology Perspective

May 8, 2026

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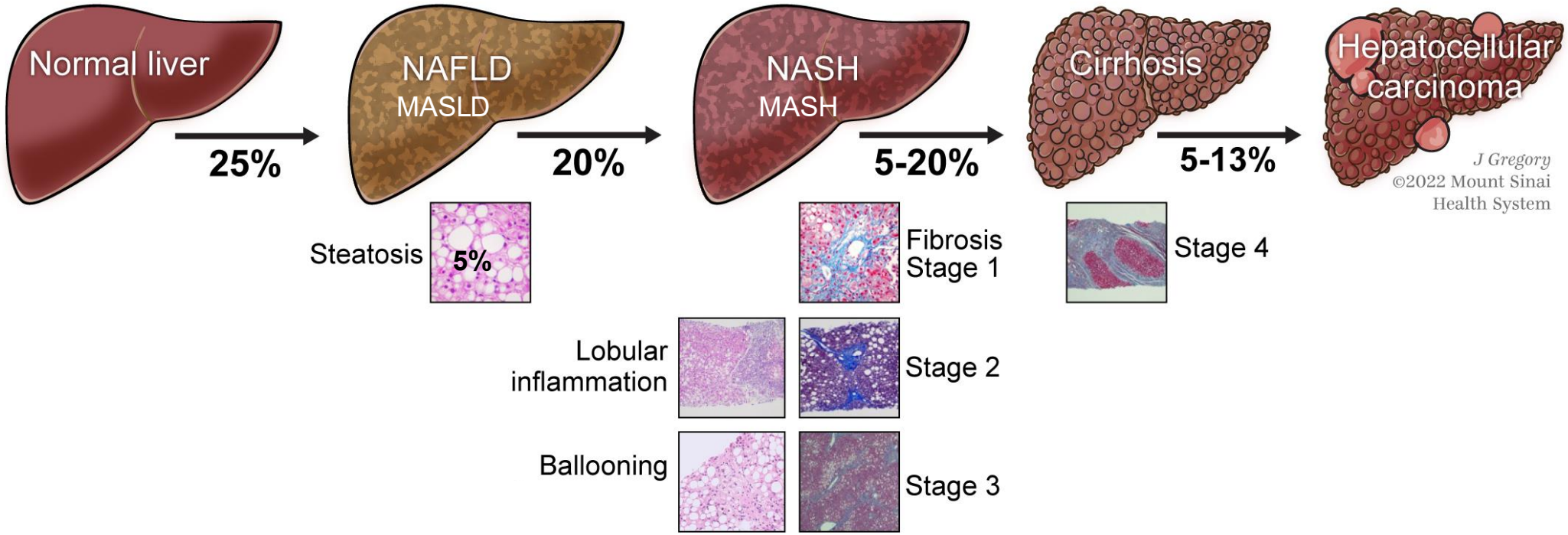
Director, MASLD/MASH Center of Excellence
Icahn School of Medicine at Mount Sinai

Outline

- Fibrosis Matters!!
- Risk Stratification for Significant Fibrosis: Role of NITs
  - When to refer to Hepatology
- FDA approved therapies for non-cirrhotic MASH
  - Indication to start
  - Monitoring Response to Treatment
- Emerging Therapies

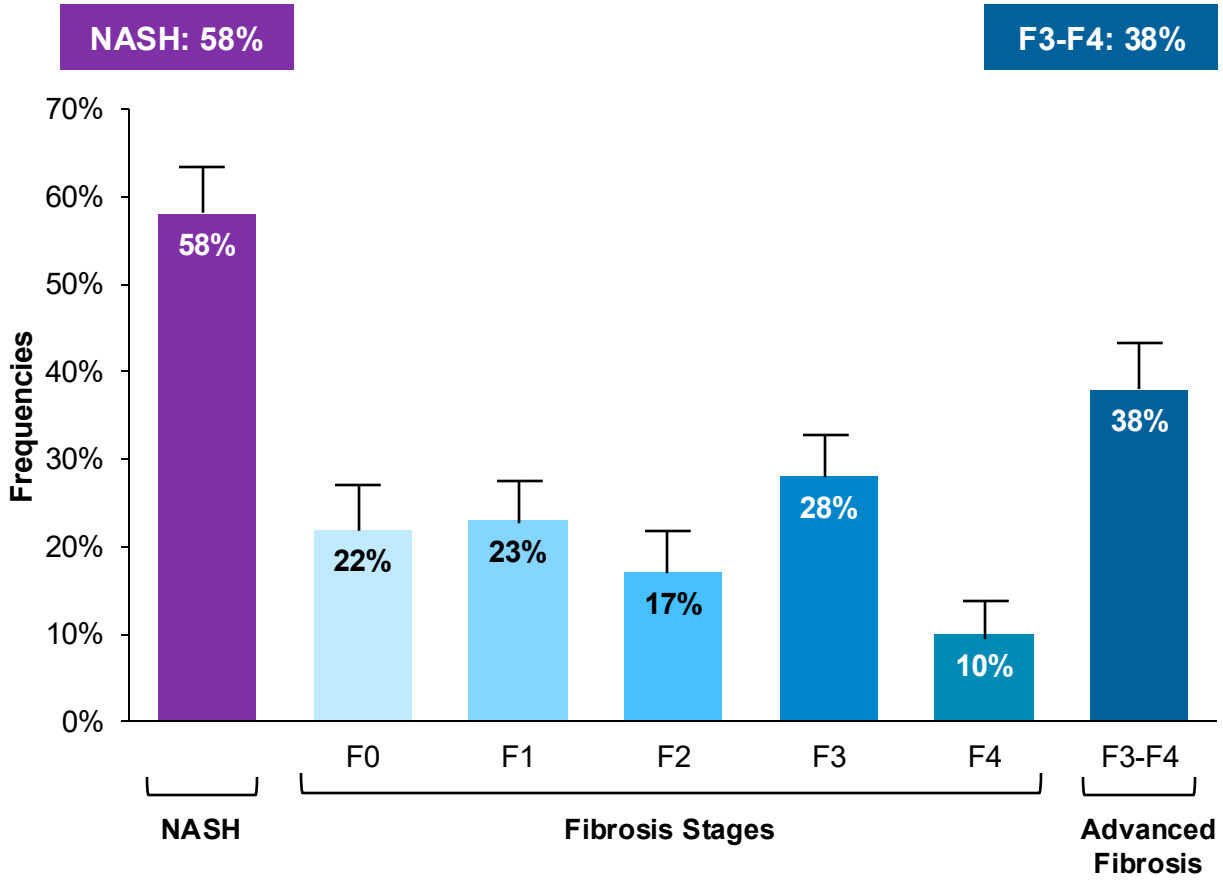
MASLD ranges from Simple Steatosis to Cirrhosis



Karim and Bansal, TOUCHReviews Endocrinology, 2023

High Prevalence of Advanced Fibrosis in T2D

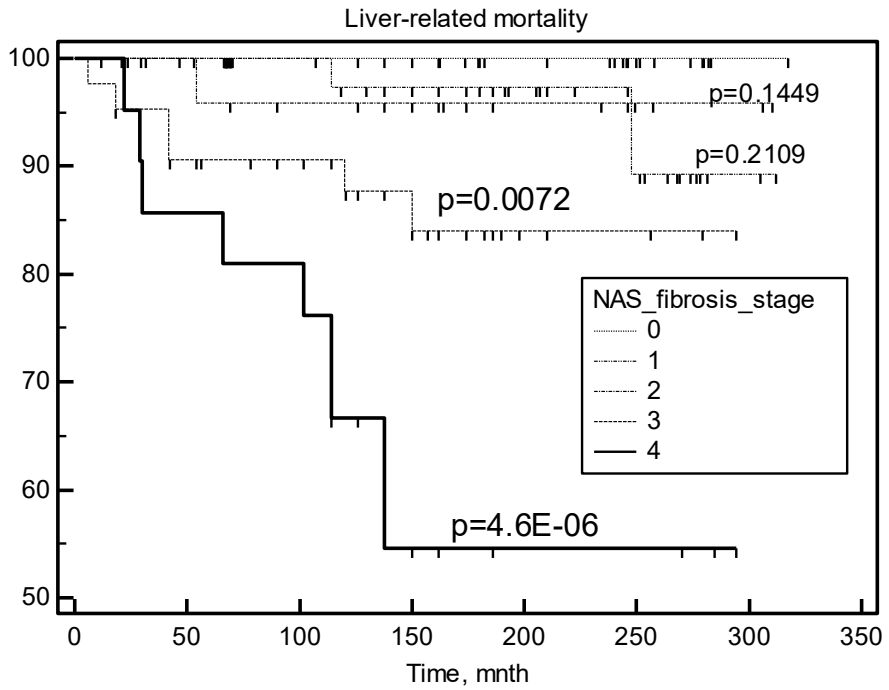
Prospective Prevalence Study of MASH and Advanced Fibrosis in T2D

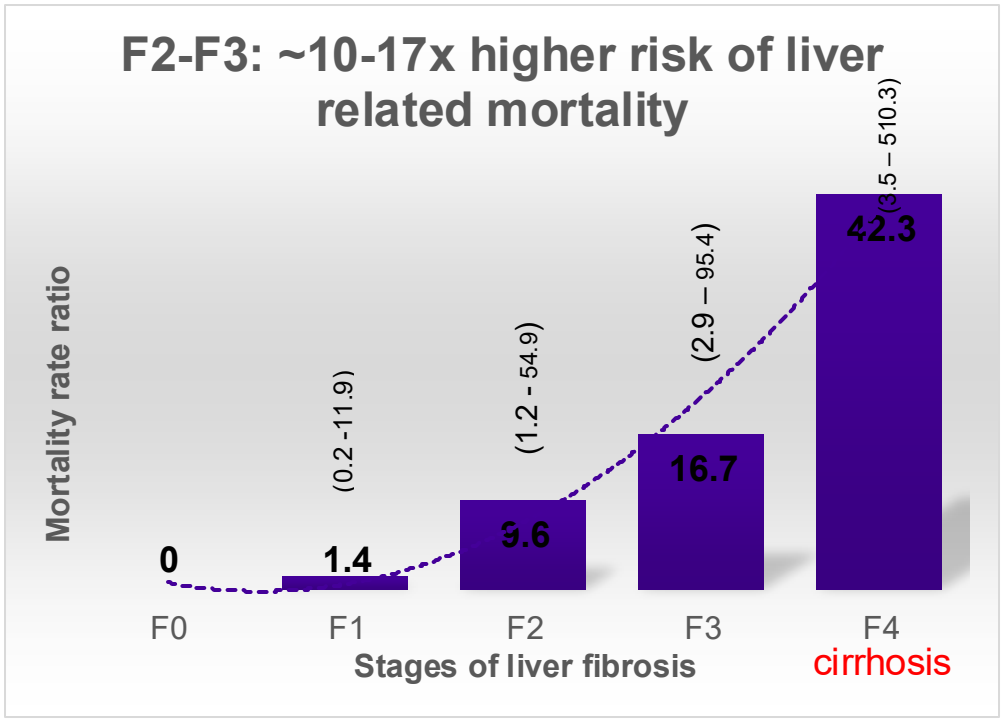


- 713 patients screened and referred to Hepatology
- 330 underwent liver biopsy if ALT persistently >20 IU/L in women and >30 IU/L in men
- 45% eligible for therapy for non-cirrhotic MASH (F2-F3)

Castera L et al, Diabetes Care, 2023

Fibrosis Drives Outcomes in MASLD



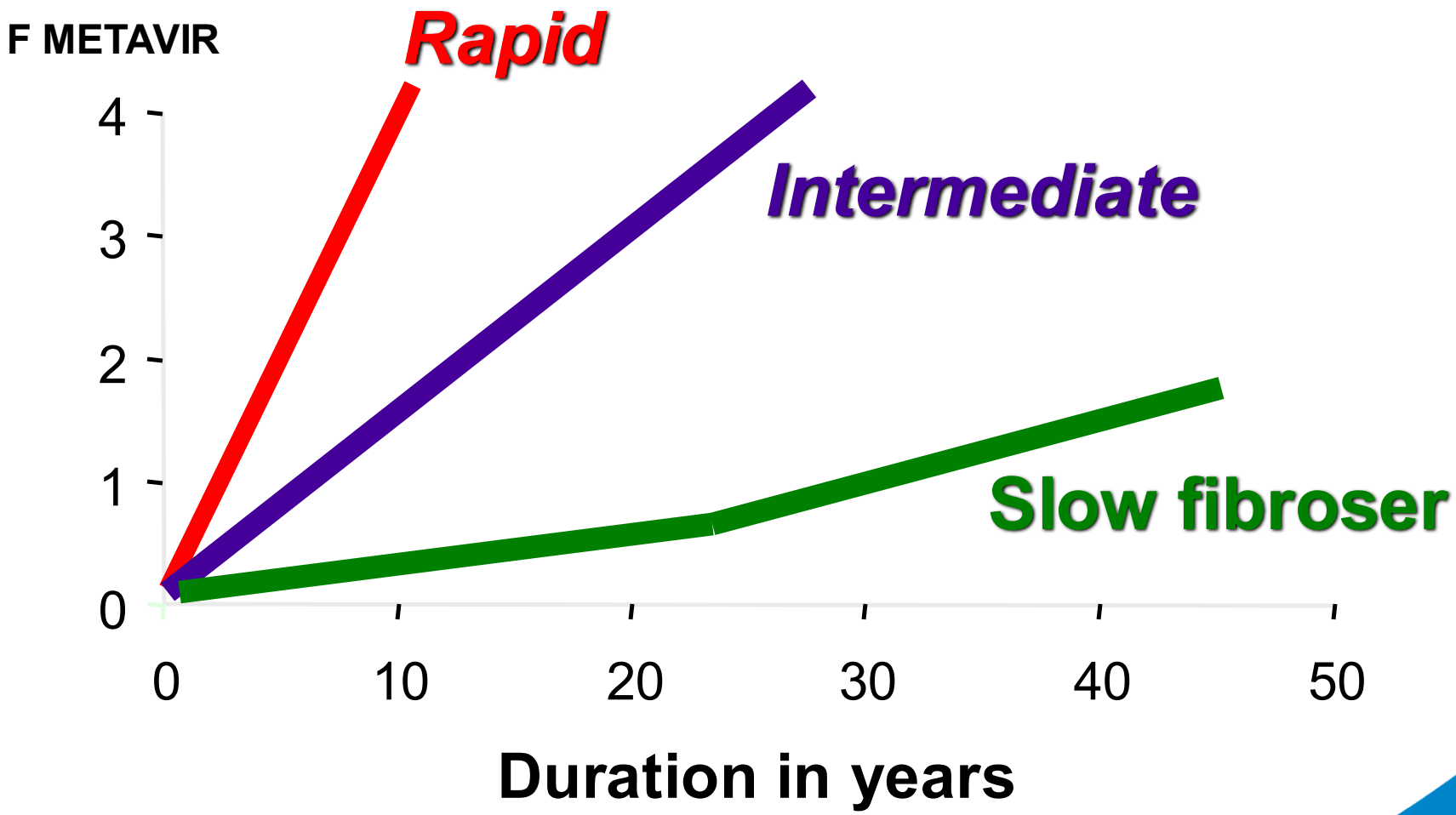


Younossi Z, et al., Hepatology, 2011

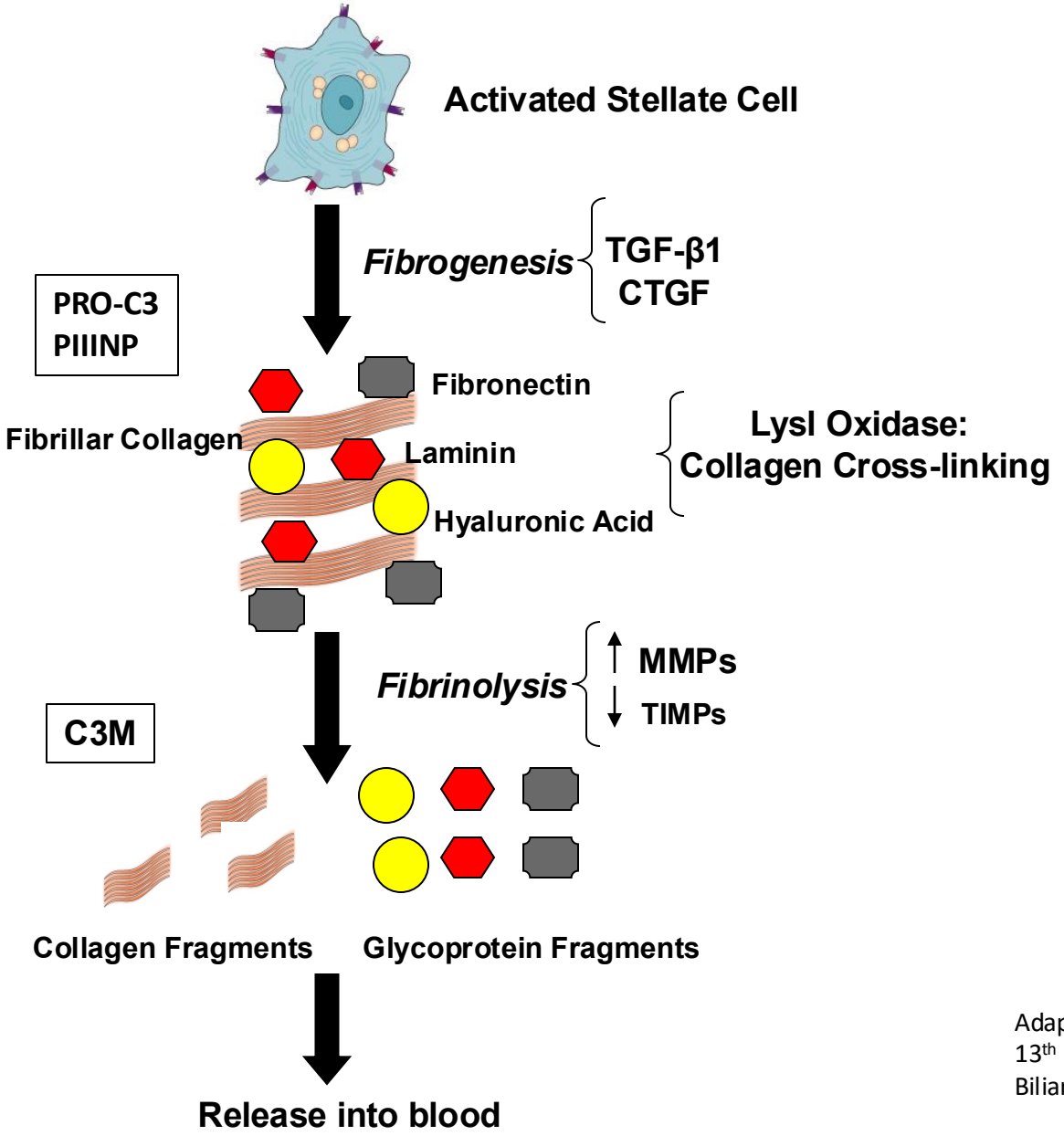
Younossi Z, et al., Hepatology, 2011

Dulai et al., Hepatology, 2017

Patients have Variable Fibrosis Progression



Fibrogenesis and Fibrinolysis: A Dynamic Process



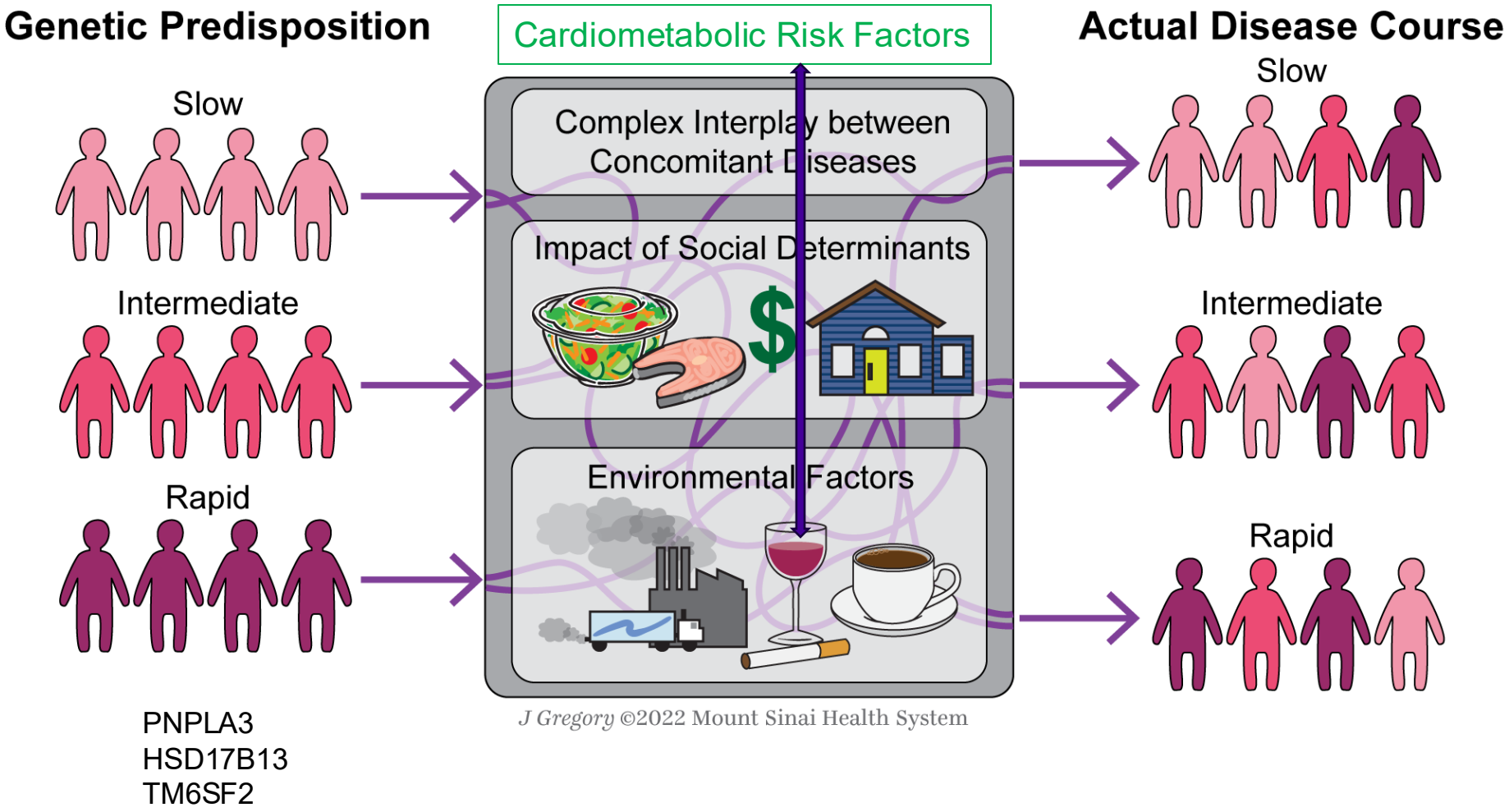
ELF=PIIINP, HA, TIMP1

ADAPT=Pro-C3, platelets, BMI, T2D,Age

Adapted from Bansal, *Hepatic Fibrogenesis*, 13th ed of Sherlock's Disease of the Liver and Biliary System, 2018

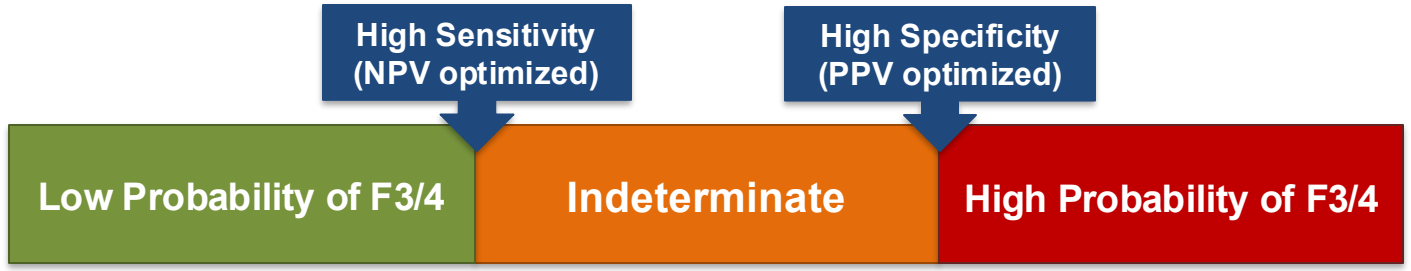
Determinants of Fibrosis Progression

Genes and the Environment

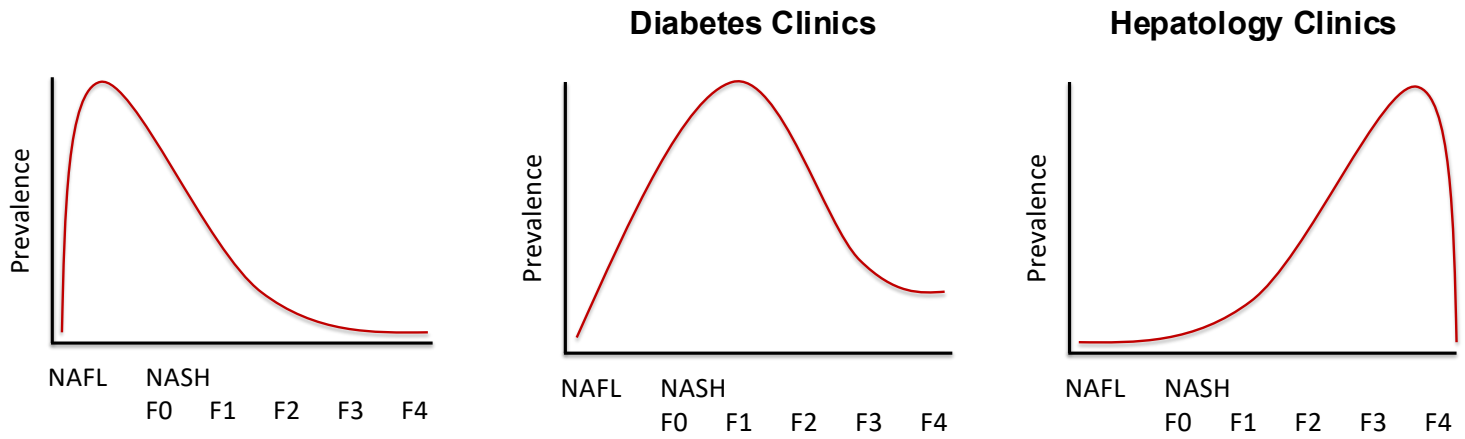


Bansal SK and Bansal MB, Aliment Pharmacol Ther. 2024;59(Suppl. 1):S10–S22

Non-Invasive Tests (NITs) for Liver Fibrosis: Context of Use Critical



Primary Care | **Secondary/Tertiary Care**

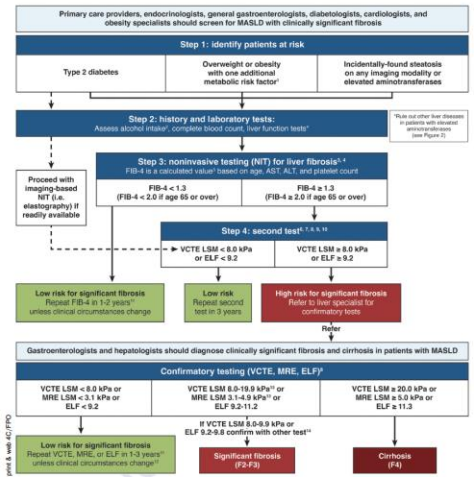


Population	Low prevalence of advanced (F3-4) disease	Increasing prevalence of advanced disease	High prevalence of advanced (F3-4) disease
Goal	Exclude severe disease	Identify patients with ≥F2 for referral and therapy	Identify patients with F(3-4) for intensive therapy/surveillance
Desirable Performance	**Higher NPV**		**Higher PPV**

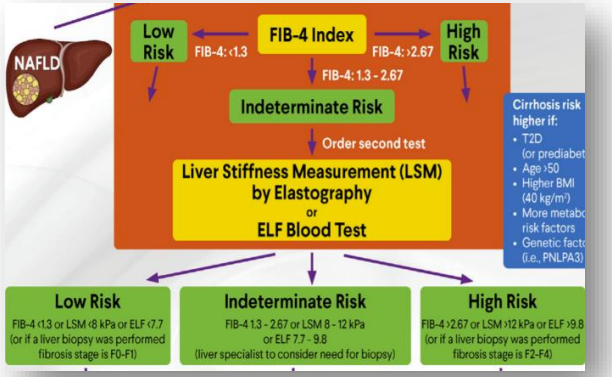
Screening for MASLD in Primary Care: The Stars Have Aligned

The Rule-Out Approach

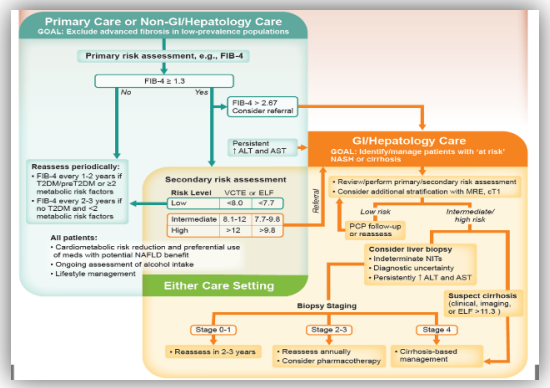
AGA



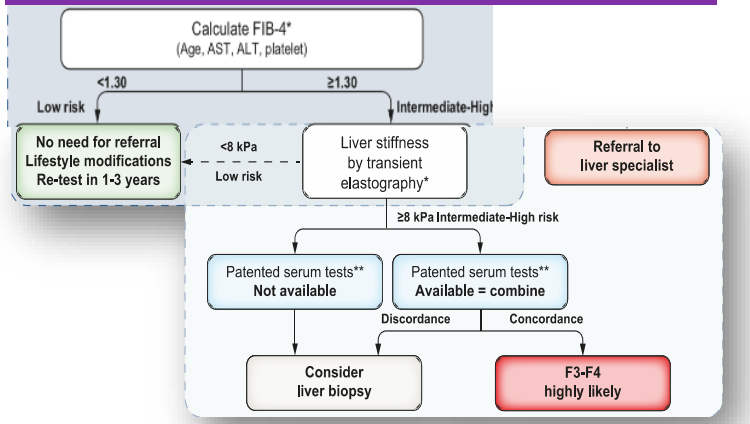
AACE/AASLD



AASLD



EASL



If age > 65
- Can use FIB-4>2.0 as cut off

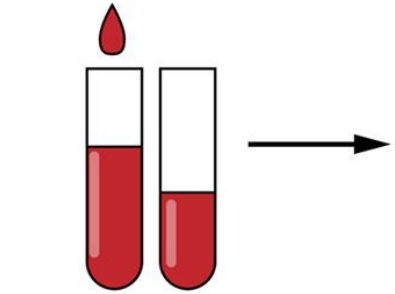
If age <35
- Can use FIB-4 >1.0 as cut off

Metabolic Risk Factors
- Central Obesity
- High Triglycerides
- Low HDL
- Hypertension
- Pre-Diabetes/Insulin Resistance

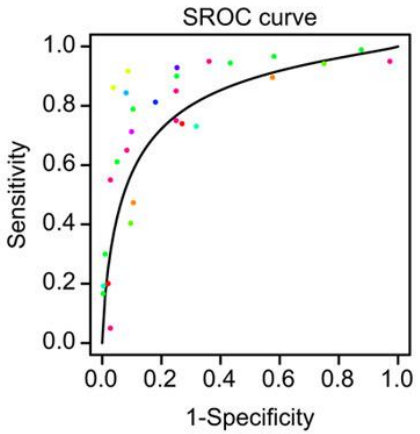
Steatosis on Imaging

Cusi K, et al. Endocr Pract. 2022
European Association for the Study of the Liver (EASL). J Hepatol. 2021
Kanwal F, et al. Gastroenterology. 2026
Rinella ME, et al. Hepatology. 2023

Serum Tests: ELF



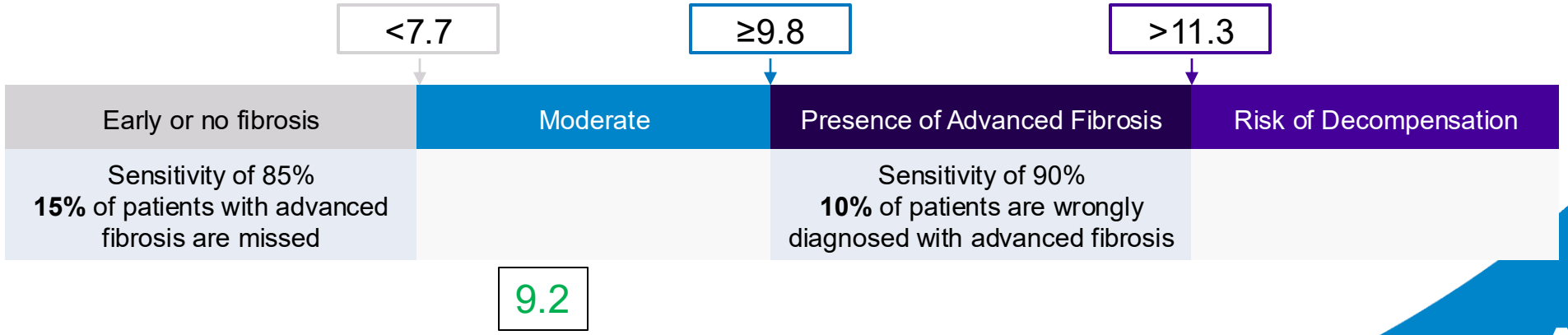
Enhanced Liver Fibrosis test;
A blood based biomarker for
diagnosis advanced fibrosis



Summary ROC Curve based on the multiple thresholds model using homogenized thresholds. Circles present information on sensitivity and specificity and each color corresponds to one study.

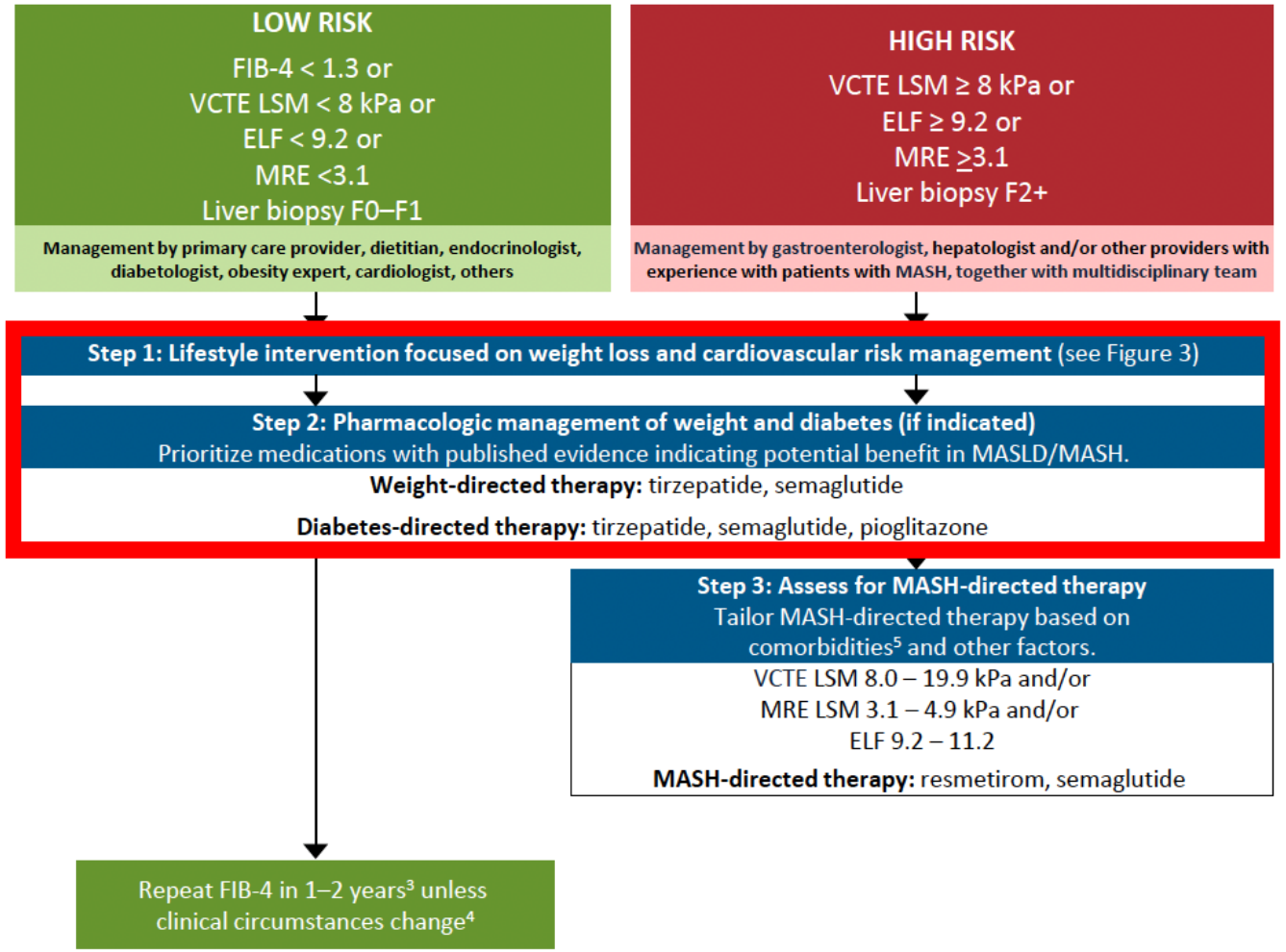
11 studies were included in the meta-analysis of advanced fibrosis
AUC: 0.83 (0.71, 0.90)
Sensitivity: 0.73 (0.60, 0.83)
Specificity: 0.80 (0.68, 0.88)

ELF Cut-off Scores and Accuracy for Measurement of Advanced Fibrosis



Vali Y, et al. J Hepatol. 2020
Day J, et al. J Appl Lab Med. 2019

Updated AGA Clinical Care Pathway



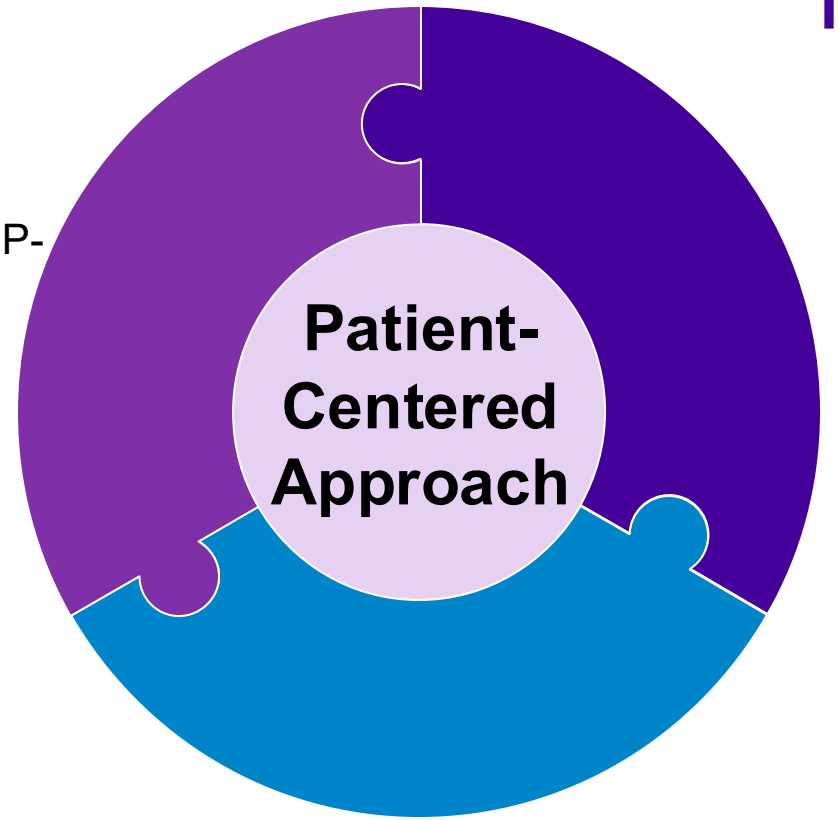
Kanwal F et al, Gastroenterology. 2026

Management
FDA-Approved Treatments

Lifestyle Recommendations for Treating MASH

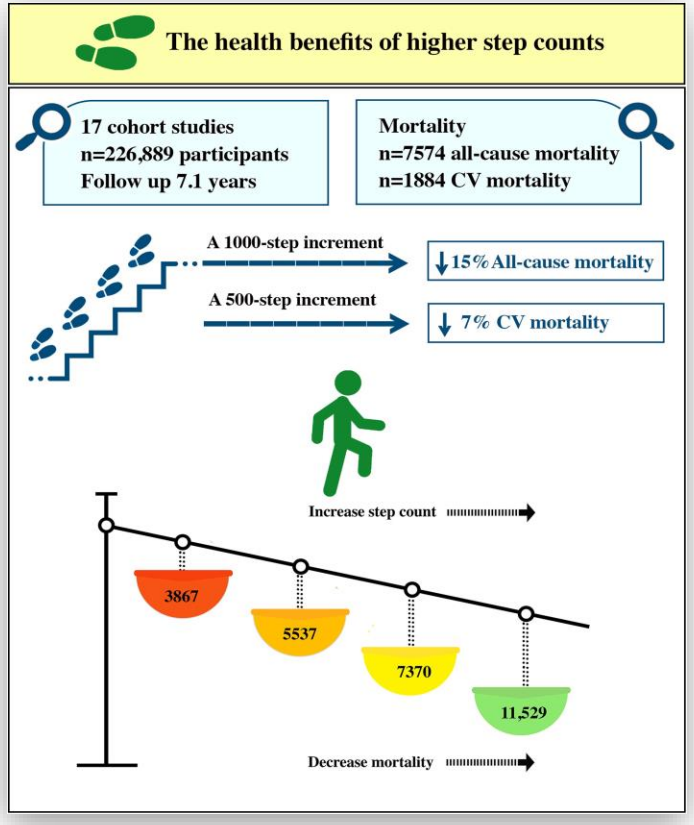
Treat Each Comorbidity

- Obesity: GLP1-RA or GLP-1RA/GIP
- Diabetes: Pioglitazone and/or GLP1-RA
- Dyslipidemia-Statin
- Hypertension
- Sleep apnea



Tackle Overweight/Obese Status

- Weight loss
- Exercise
- Diet

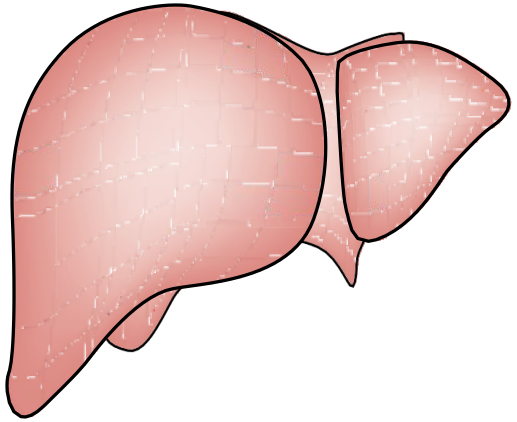


Cofactors: Dietary Modifiers

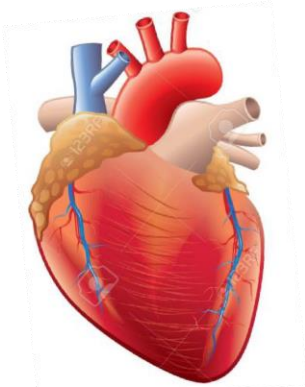
Alcohol, smoking, fructose, coffee, Mediterranean Diet

Cusi K, et al. Endocr Pract. 2022;28:528-562.
Banach M, et al. Eur J Prev Cardiol. 2023;30:1975-1985.

Differential Expression of THR α and β receptors



THR-β >> THR-α

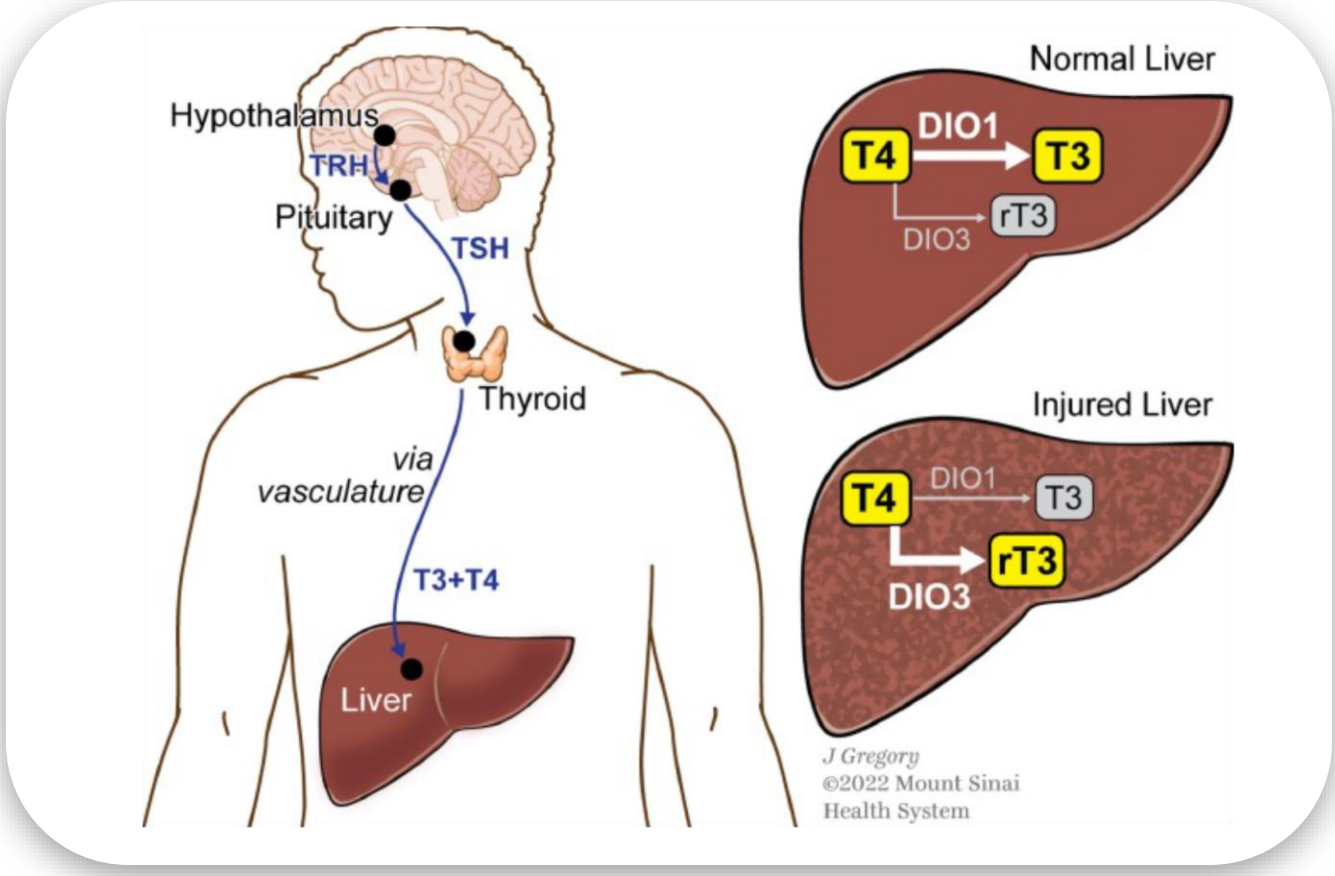


THR-α organs:

- **Bone (osteoporosis)**
- **Heart (rate and rhythm)**

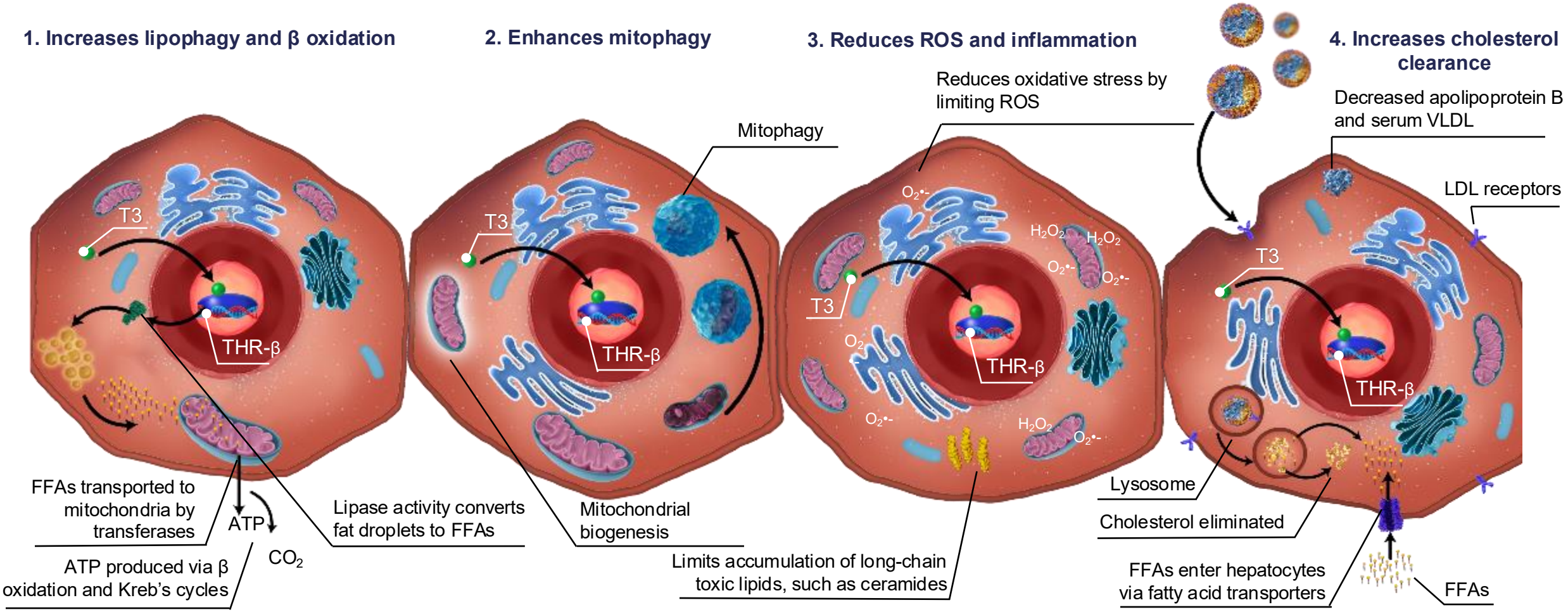
Low Serum Thyroid Hormone Levels Are Associated With MASLD

- Population studies have shown associations between MASLD and overt hypothyroidism, subclinical hypothyroidism and low thyroid hormone in the normal range[1-6]
- Top-ranked gene set downregulated in human fatty liver are T3-regulated genes
- Acute and chronic inflammation are associated with low intrahepatic thyroid hormone levels[8]
  - During MASH progression, reduction of DIO1 and increase of DIO3



1. Liangpunsakul S and Chalasani N, *J Clin Gastroenterol.* 2003;37(4):340-343; 2. Xu C, et al. *Clin Endocrinol (Oxf).* 2011;75(2):240-246; 3. Pagadala MR, et al. *Dig Dis Sci.* 2012;57(2):528-534; 4. Chung GE, et al. *J Hepatol.* 2012;57(1):150-156; 5. Ludwig U, et al. *BMC Endocr Disord.* 2015;15;15:41; 6. Bano A, et al. *J Clin Endocrinol Metab.* 2016;101(8):3204-3211; 7. Xu L, et al. *J Hepatol.* 2012;57(5):1153-1154; 8. Boelen A, et al. *J Endocrinol.* 2017 Apr;233(1):25-36

Role of THR-β in Hepatic Lipid Metabolism



ATP: adenosine triphosphate; CO_2: carbon dioxide; FFA: free fatty acid; H_2O_2: hydrogen peroxide; LDL: low-density lipoprotein; O_2•: oxygen radical; ROS: reactive oxygen species; T3: triiodothyronine; VLDL: very-low-density lipoprotein.

Ritter MJ, et al. *Hepatology*. 2020;72:742-752. Saponaro F, et al. *Front Med (Lausanne)*. 2020;7:331. Sinha RA, et al. *Nat Rev Endocrinol*. 2018;14:259-269. Taub R, et al. *Atherosclerosis*. 2013;230:373-380. Taub R, et al. NASH-TAG 2018. Presentation. Harrison SA, et al. *Lancet*. 2019;394:2012-2024.

Regulatory Framework for Drug Approval for MASH

Full Approval

Based on major adverse liver outcomes

Conditional Approval

Based on surrogate endpoint reasonably likely to predict clinical benefits

MASH resolution with no worsening of fibrosis
OR/AND
≥1 stage fibrosis improvement with no worsening of MASH

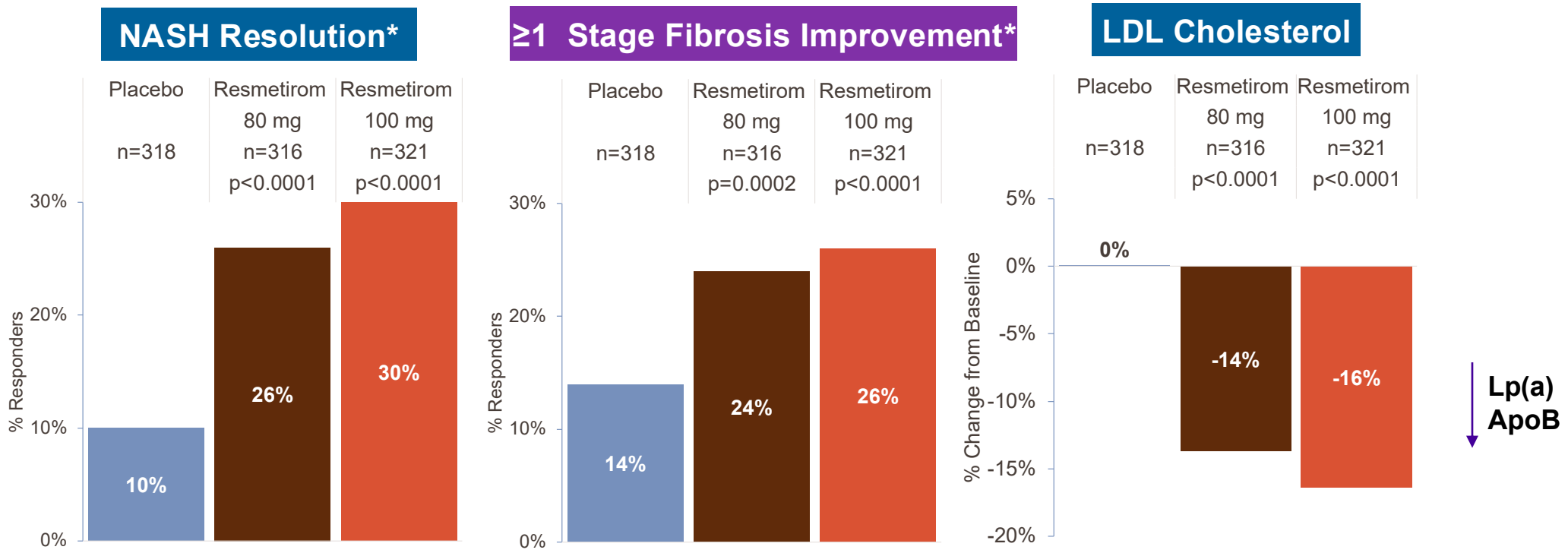
VERSUS

MASH resolution with no worsening of fibrosis
AND
≥1 stage fibrosis improvement with no worsening of MASH

Safety, Safety, Safety !!!

US Food and Drug Administration (FDA). NASH draft guidance. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/noncirrhotic-nonalcoholic-steatohepatitis-liver-fibrosis-developing-drugs-treatment. European Medicines Agency. Reflection paper. https://www.ema.europa.eu/en/reflection-papers-regulatory-requirements-development-medicinal-products-chronic-non-infectious-liver-diseases-pbc-psc-nash-scientific-guideline.

Phase 3 Trial: Dual Primary Endpoints (Week 52): Primary Analysis



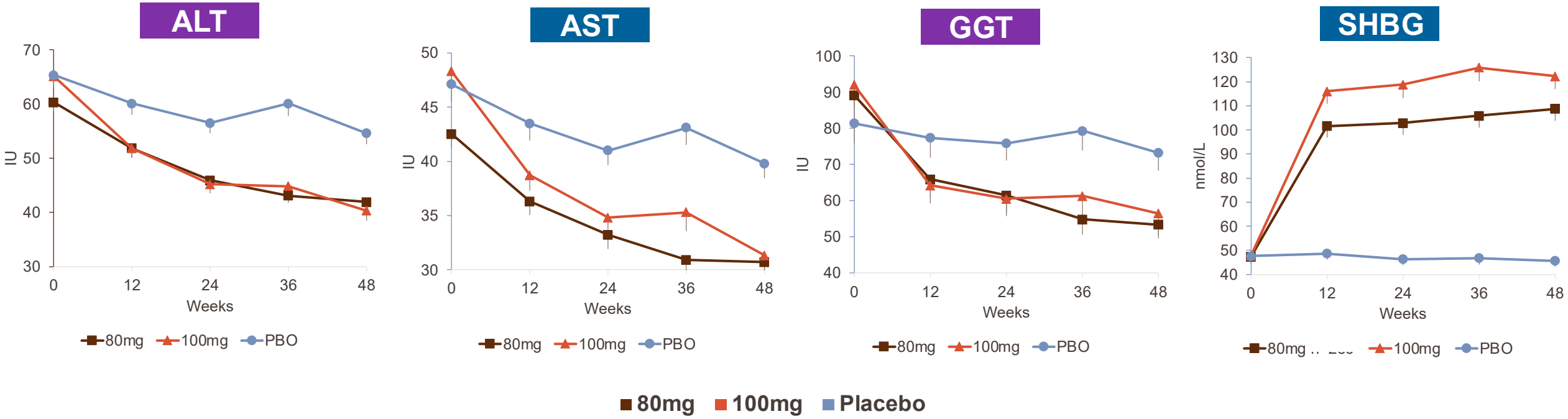
Both primary liver biopsy endpoints and the key secondary endpoint of LDL cholesterol lowering were met

Patients will continue to be followed for at least 5 years for clinical outcomes
FDA provided accelerated approval March 14, 2024

Harrison, NEJM, 2024

Change from Baseline in Liver Enzymes* & SHBG

- Significant reduction of liver enzymes relative to placebo, both percentage change and absolute reduction
- Associated with the biomarker SHBG that increases in proportion to Resmetirom reflecting target engagement (exposure)



- *Evaluated in patients with baseline ALT ≥30 IU.

Harrison, NEJM, 2024

Resmetirom is an oral, once-daily tablet that can be taken with or without food

Recommended dosage and administration

	80 mg	100 mg
Dosage	**One tablet QD**	**One tablet QD**
Weight	<100 kg (220 lbs)	≥100 kg (220 lbs)

Drug Interactions

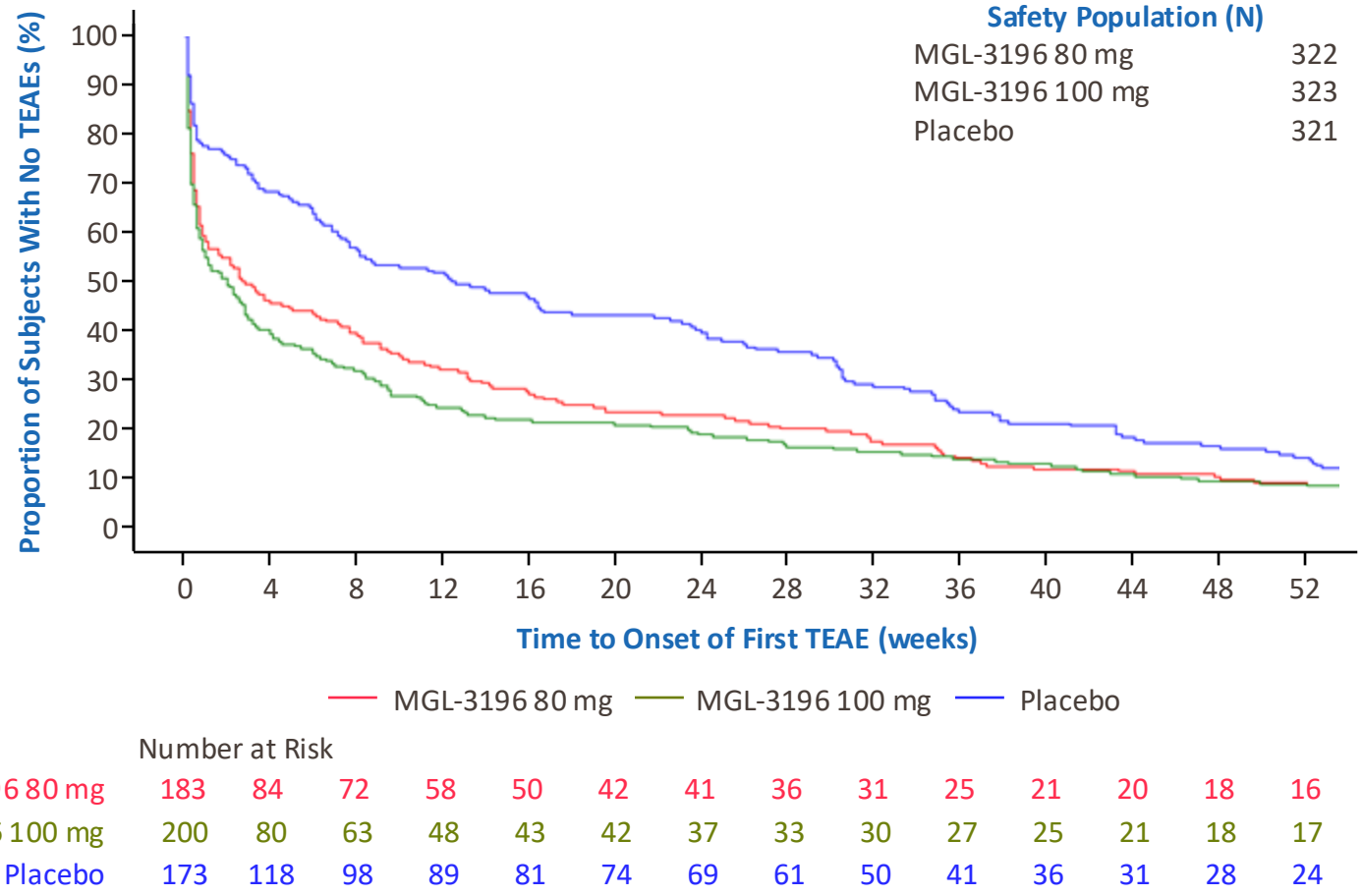
- Concomitant use of Resmetirom with strong CYP2C8 inhibitors (eg, gemfibrozil) or with OATP1B1 or OATP1B3 inhibitors (eg, cyclosporine) is not recommended
- For concomitant use of Resmetirom with moderate CYP2C8 inhibitors (eg, clopidogrel), reduce the dose of Resmetirom:
  – 60 mg if <100 kg (220 lbs) and 80 mg if ≥100 kg (220 lbs)
- Resmetirom increased plasma concentration of some statins.
  - Limit the daily dosage of rosuvastatin and simvastatin to 20 mg; pravastatin and atorvastatin to 40 mg

Onset of First GI-Related Event

- Diarrhea and nausea occurred more frequently in the resmetirom group than in the placebo group
- Generally stabilized by Week 12

Figure S13. Time to Onset of First Gastrointestinal Adverse Event

MGL-3196, resmetirom



Number at Risk

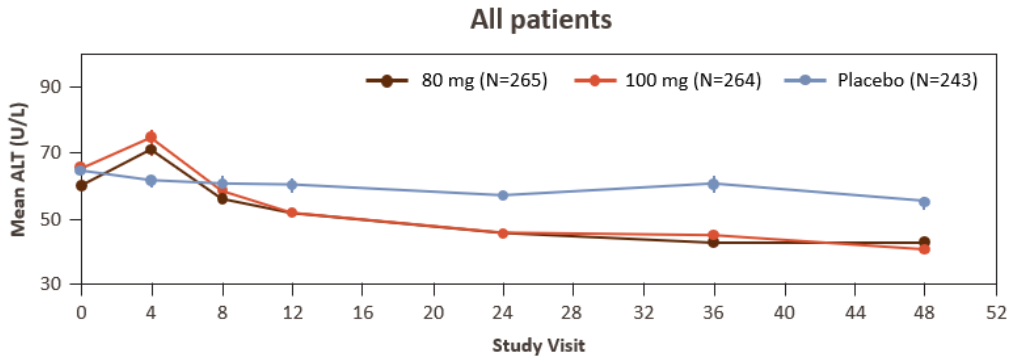
MGL-3196 80 mg	183	84	72	58	50	42	41	36	31	25	21	20	18	16
MGL-3196 100 mg	200	80	63	48	43	42	37	33	30	27	25	21	18	17
Placebo	173	118	98	89	81	74	69	61	50	41	36	31	28	24

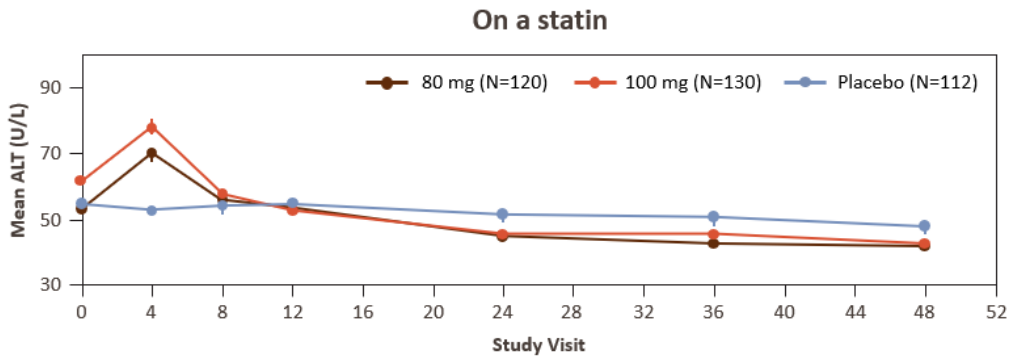
Harrison SA, et al. *N Engl J Med.* 2024;390(6):497-509.

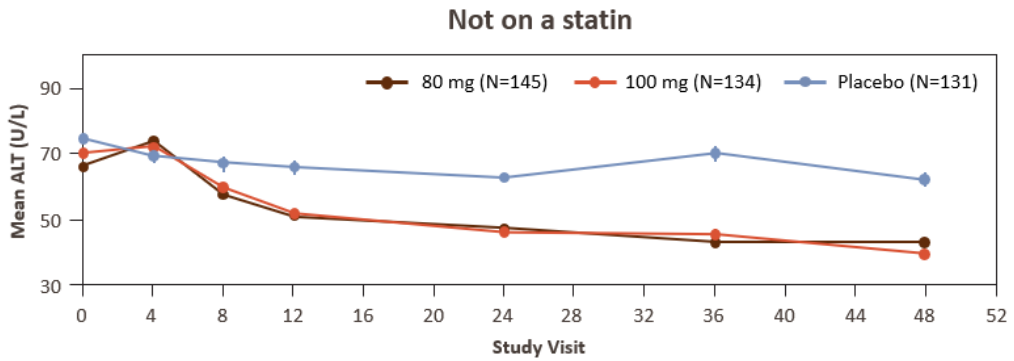
Initial Transient Increases in ALT Associated with Statin Use

- 49% Statin Use
- 98% in Current Recommended Dose
  - Rosuvastatin 20mg
  - Atorvastatin 40mg

- Patients taking a statin had lower baseline ALT levels than patients not taking a statin
  - Transient increases at Week 4 were observed in patients taking resmetirom and a statin
  - No significant elevations were observed in patients taking resmetirom but no statin
  - ALT levels improved relative to baseline over time in patients on resmetirom versus PBO, independent of statin use

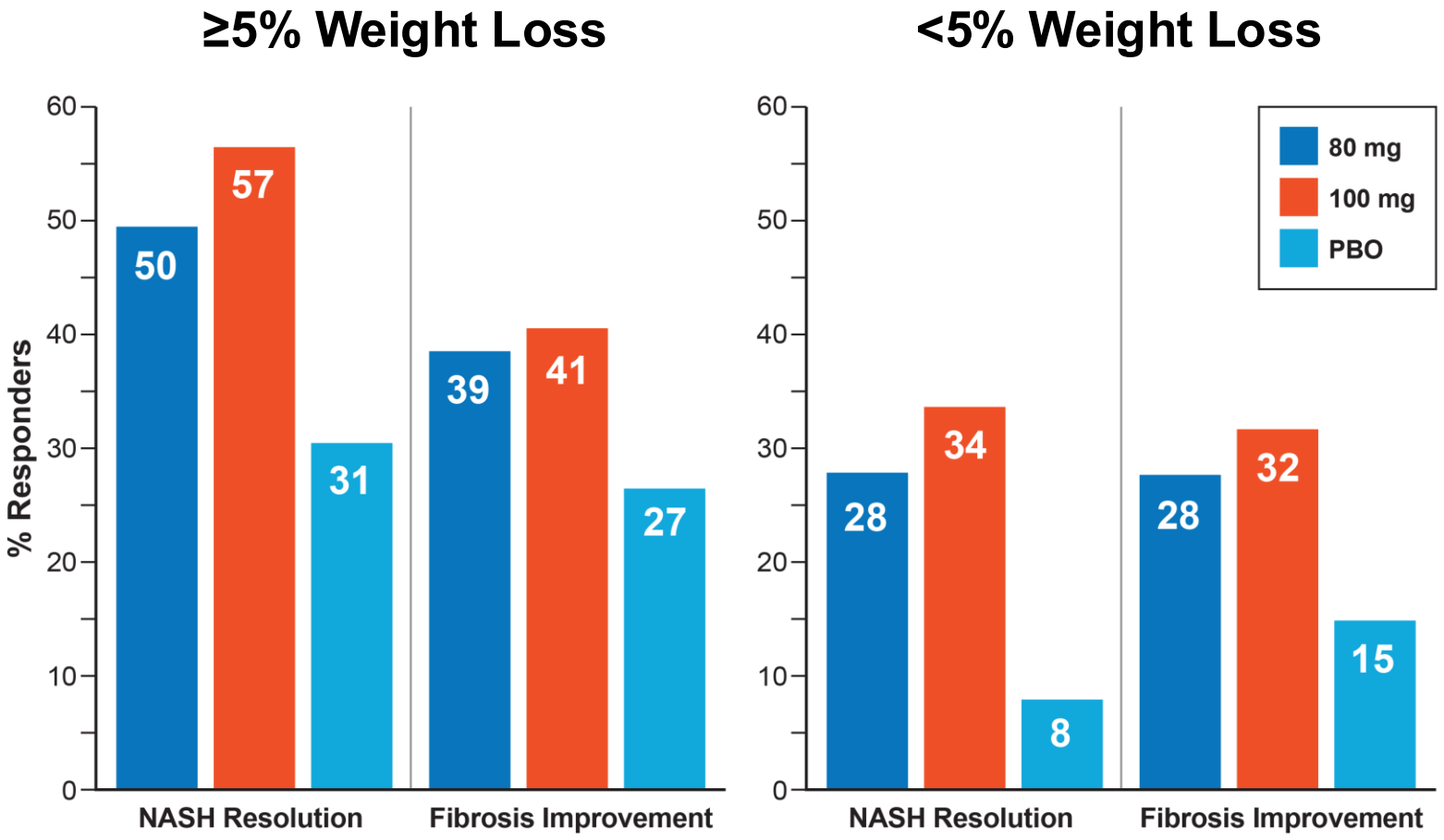






Bansal MB et al., Submitted
Baum S et al. The Liver Meeting. San Diego, CA; November 15-19, 2024. Abstract 3213

Weight Loss Enhances Resmetirom's Therapeutic Benefit in MASH



- Weight loss ≥5%
  - 22% of patients on resmetirom
  - 12% on placebo
  - Increased the percentage of patients with
    - Fibrosis improvement (41% vs 32%)
    - MASH resolution (57% vs 34%)
    - MRI PDFF reduction -69% vs -46%
    - LSM reduction (-4.6kPa vs 2.3kPa)

Implication for Oral Combo

Pair with an Oral GLP-1RA
Different Mechanism of Action
Addressing Comorbidities

Noureddin M et al. APT. 2025

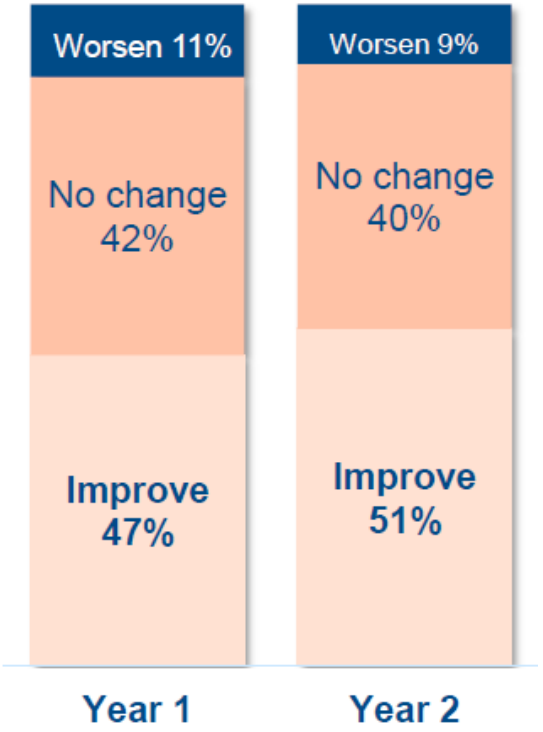
Resmetirom: MAESTRO-NASH Compensated Cirrhosis 2-Year Results

Reduction in Liver Stiffness

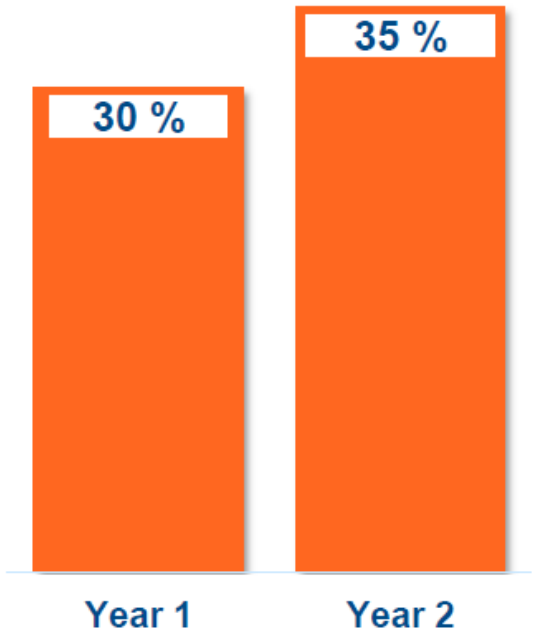
Open-label 80-mg resmetirom in cirrhosis: N=180 compensated MASH-cirrhosis (n=122 at year 2)
~62 years, BMI ~34 kg/m^2, platelets ~125 x 10^9/L

Mean Change From Baseline in VCTE

% With 25% Change From Baseline in VCTE



% With Conversion From F4 to Consistent With F3[a]



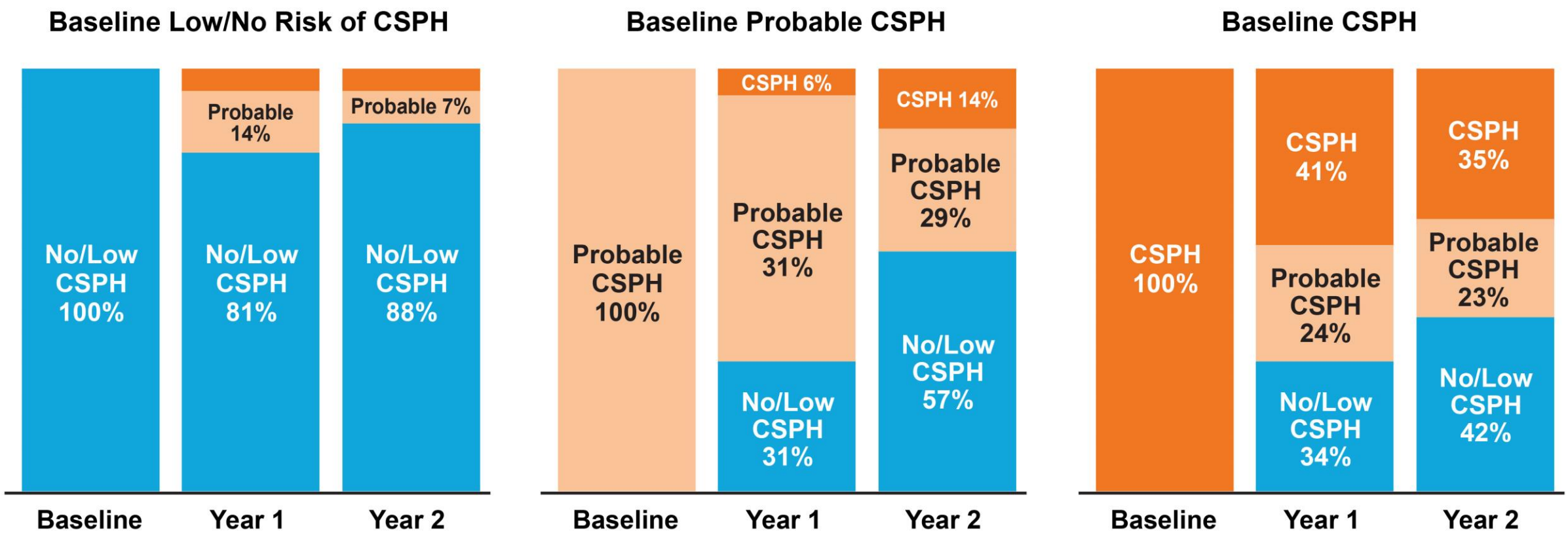
[a]Statistically significant compared with baseline.

Alkhouri N, et al. EASL Congress 2025. Abstract LBO-002.

Resmetirom: MAESTRO-NASH Compensated Cirrhosis 2-Year Results

Reduction in CSPF

Open-label 80-mg resmetirom in cirrhosis: N=180 compensated MASH-cirrhosis (n=122 at year 2)
~62 years, BMI ~34 kg/m^2, platelets ~125 x 10^9/L



CSPH: clinically significant portal hypertension.

Alkhouri N, et al. EASL Congress 2025. Abstract LBO-002.

Semaglutide
Adding To Existing FDA approvals

- Semaglutide (Wegovy®) was initially approved in 2021 for **chronic weight management** in adults with obesity or overweight accompanied by at least one weight-related comorbidity
  - This indication was extended in December 2022 to include pediatric patients aged 12 years and older.

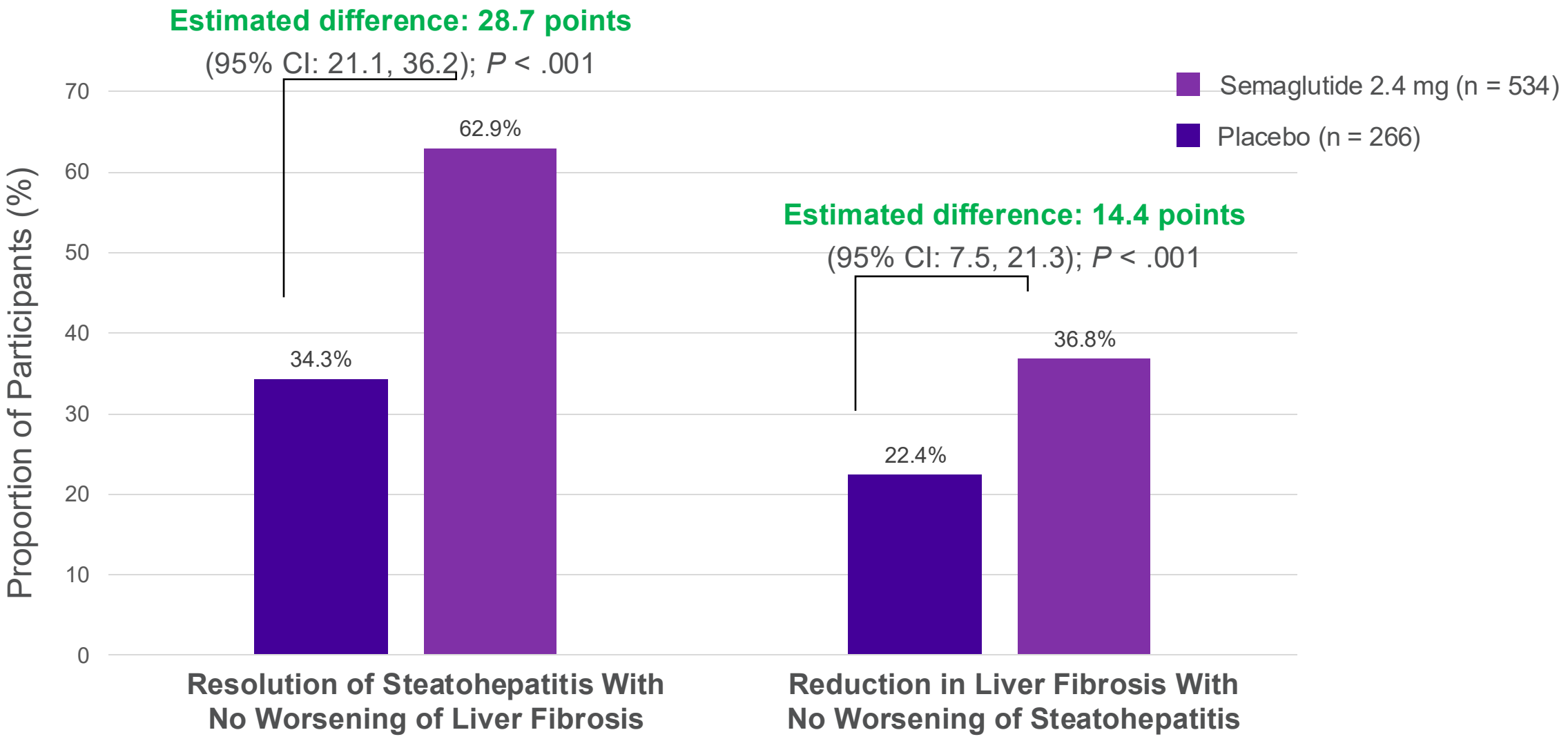
- In March 2024, semaglutide (Wegovy®) was approved to **reduce the risk of major adverse cardiovascular (CV) events** (CV death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established CV disease and either obesity or overweight.

- Semaglutide (Wegovy®) received accelerated approval from the US FDA on August 15, 2025 to treat **MASH with moderate-to-advanced fibrosis (consistent with F2-F3)**

AASLD The Liver Meeting®

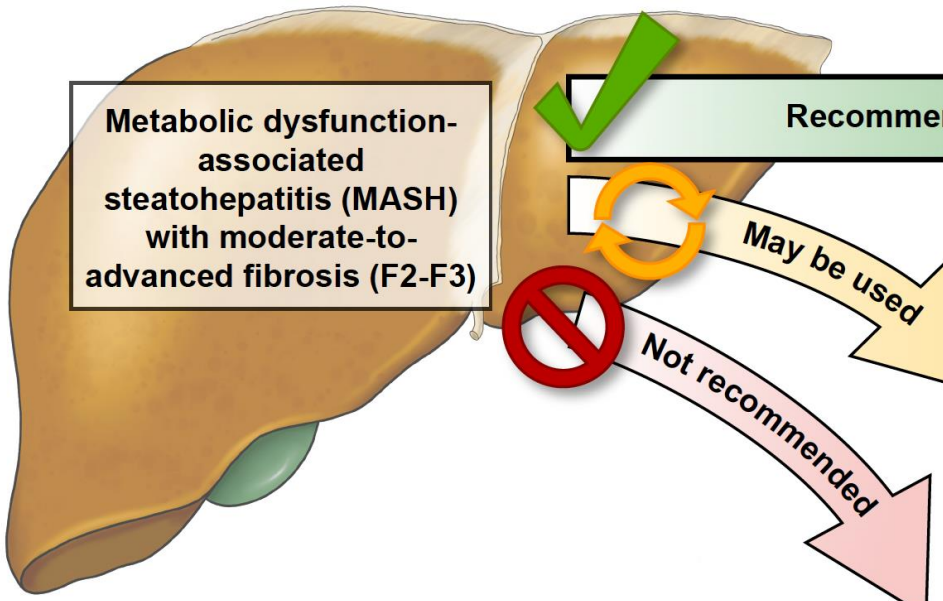
Semaglutide in MASH—Phase 3 ESSENCE Trial

Primary Endpoints



Sanyal AJ, et al. N Engl J Med. 2025

Patient Selection for either Resmetirom or Semaglutide



Metabolic dysfunction-associated steatohepatitis (MASH) with moderate-to-advanced fibrosis (F2-F3)

Recommended

Imaging-based NIT	VCTE: LSM 8 - 15 kPa[a] MRE: LSM 3.1 - 4.4 kPa[a]
Blood-based NIT	ELF 9.2 - 10.5
Liver histology	MASH with F2-F3[b]

May be used

- LSM values outside the recommended ranges[c]
  - VCTE: LSM 15-20 kPa
  - MRE: LSM 4.4-5 kPa
  - ELF: 10.5-11.3
- Other NIT data consistent with F2-F3

Not recommended

- Cirrhosis, including LSM via VCTE >20 kPa, MRE >5 kPa, or ELF score >11.3
- Concomitant active liver disease
- Pregnancy, personal or family history of medullary thyroid carcinoma (MTC), or patients with multiple endocrine neoplasia syndrome type 2 (MEN2)

- Cirrhosis, including LSM via VCTE >20 kPa or MRE >5 kPa
- Concomitant active liver disease
- Excess alcohol use (>20/30 g/d in women/men)
- Active thyroid disease

[a] Modified from the AASLD NILDA guidelines.[5]
[b] Liver biopsy is not routinely recommended for the diagnosis and staging of MASH with F2-3
[c] Refer to "Whom to treat" for details
VCTE – Vibration-controlled transient elastography; MRE – Magnetic resonance elastography; ELF – Enhanced liver fibrosis; LSM – Liver stiffness measurement; NIT – Non-invasive test.

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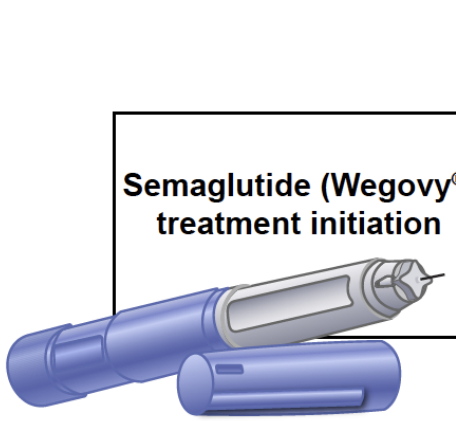
Assessment of Treatment Response to Semaglutide or Wegovy



Semaglutide (Wegovy®) treatment initiation

Monitor for safety and treatment related adverse events (Table 2)

Resmetirom (Assess response at 52 weeks)

Response assessment at 72 weeks[a]

- Decrease of VCTE LSM ≥ 30%
- Decrease of MRE LSM ≥ 20%
- Decrease in MRI-PDFF > 30%
- Decrease in ALT ≥ 17 or ≥ 20%
- Decrease in ELF ≥ 0.5

Beneficial response → **Continue semaglutide**

- Sub-threshold improvement in NITs
- No evidence of progression to cirrhosis

Benefit uncertain → **Re-evaluate strategy[b]**

- NITs suggesting worsening or progression to cirrhosis

No response → **Stop semaglutide**

[a] Assess based on the same imaging-based or blood-based markers used to determine treatment eligibility.

[b] Options may include re-optimizing lifestyle interventions and considering other therapy, with or without stopping semaglutide.

VCTE – Vibration-controlled transient elastography; MRE – Magnetic resonance elastography; ELF – Enhanced liver fibrosis; LSM – Liver stiffness measurement; NIT – Non-invasive test.

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Emerging Therapies

Rich Pipeline of Emerging Therapies

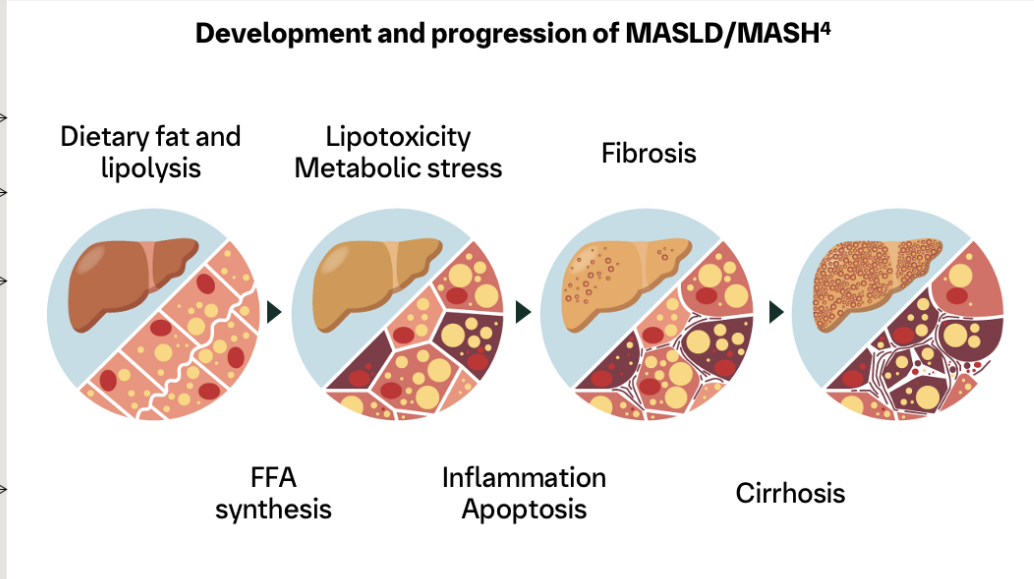
Agents in advanced development across the spectrum of MASLD/MASH:

Incretin and GCGR agonists

- **Survodutide** (GCGR/GLP-1R)[1]
- **Pemvidutide** (GCGR/GLP-1R)[2]
- **Retatrutide** (GCGR/GIPR/GLP-1R)[3]

Incretin agonist

- **Tirzepatide** (GLP-1R/GIPR)[5]



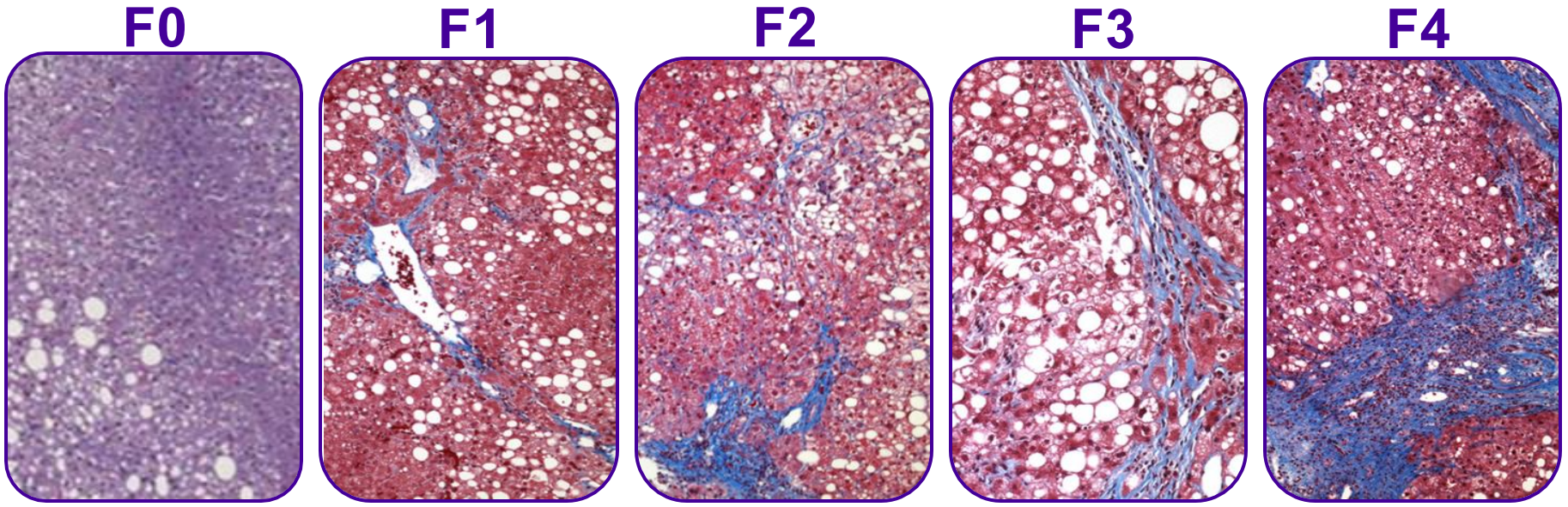
FGF21 agonists

- **Efruxifermin**[6]
- **Pegozafermin**[6]
- **Efimosfermin alfa**[7]

PPAR agonist

- **Lanifibranor**[8]

Summary: The Relay Race



MASH Cirrhosis
-No current FDA treatments
-Enroll in trials
-Carvedilol
-Statins
-HCC screening
- AFP and US q 6 months

NITs are good enough!!

GLP1-RA/Weight Loss Strategies/Aggressive Comorbidity Management

Liver-Directed Therapy

Thank you!

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