



Brigham and Women's Hospital
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Update in MASLD

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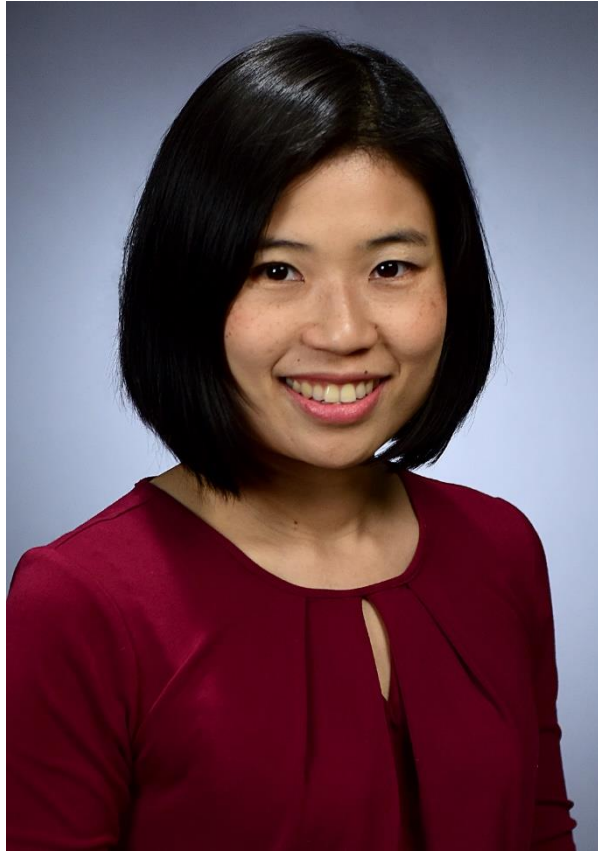


CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE



HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

M. Valerie Lin, MD



- Medicine Residency @ Pennsylvania Hospital, Penn Medicine
- Gastroenterology Fellowship @ Univ of Cincinnati Medical Center
- Advanced/Transplant Hepatology Fellowship @ MGH
- Assistant Professor of Medicine @ UMass School of Medicine
- Adjunct Assistant Professor of Medicine @ Tufts Univ
- Gastroenterologist/Hepatologist @ Lahey Hospital & Medical Center
- Director, Liver Tumor Program @ Lahey Hospital & Medical Center
- Associate Program Director of Internal Medicine Residency @ Lahey Hospital & Medical Center
- Associate Program Director of Advanced Hepatology Fellowship @ Lahey Hospital & Medical Center
- Clinical focus: Transplant oncology; metabolic steatohepatitis; chronic liver disease and cirrhosis
- Research focus: Transplant oncology & liver tumors; frailty and prehab in cirrhosis; acute on chronic liver failure; QI in MASLD



Disclosures

- I have no relevant financial relationships with ineligible companies.

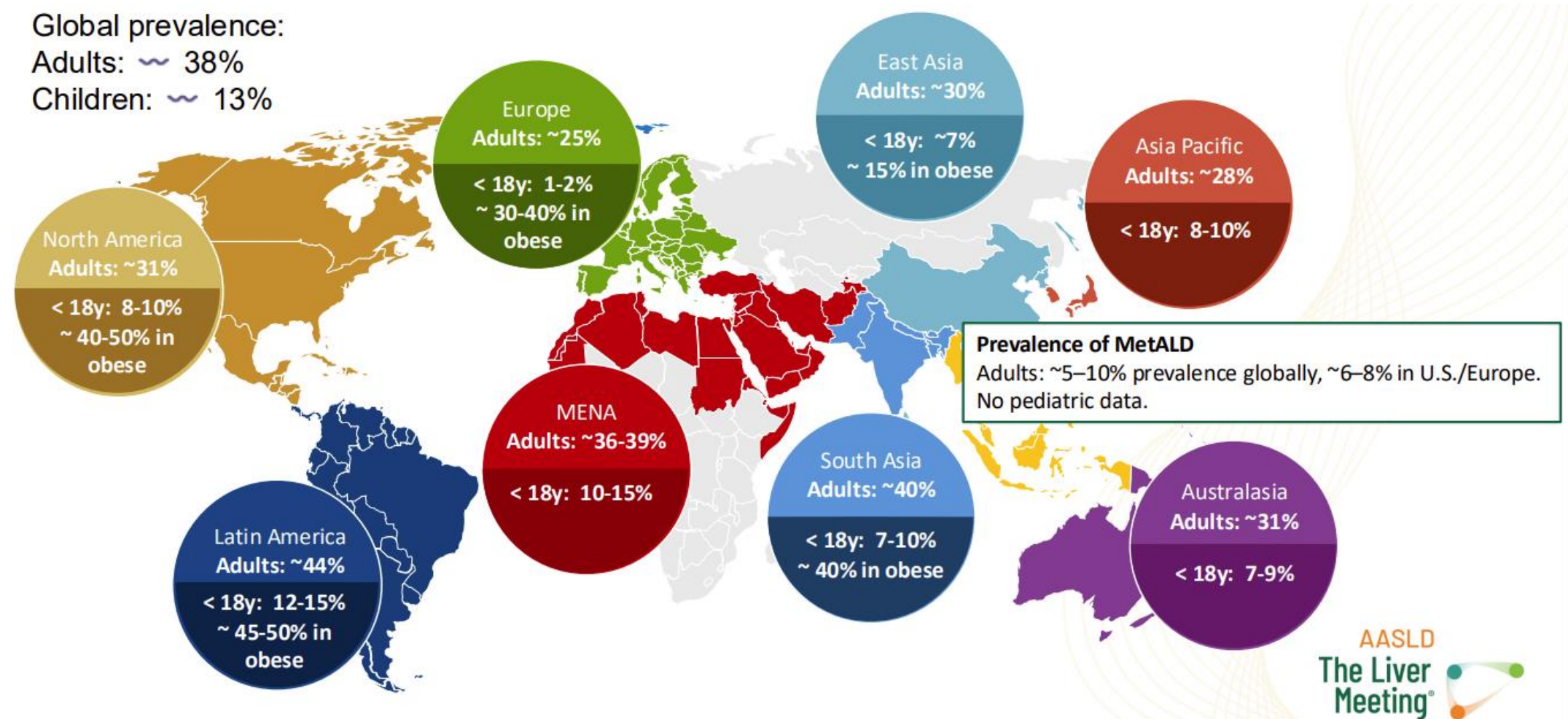


Objectives

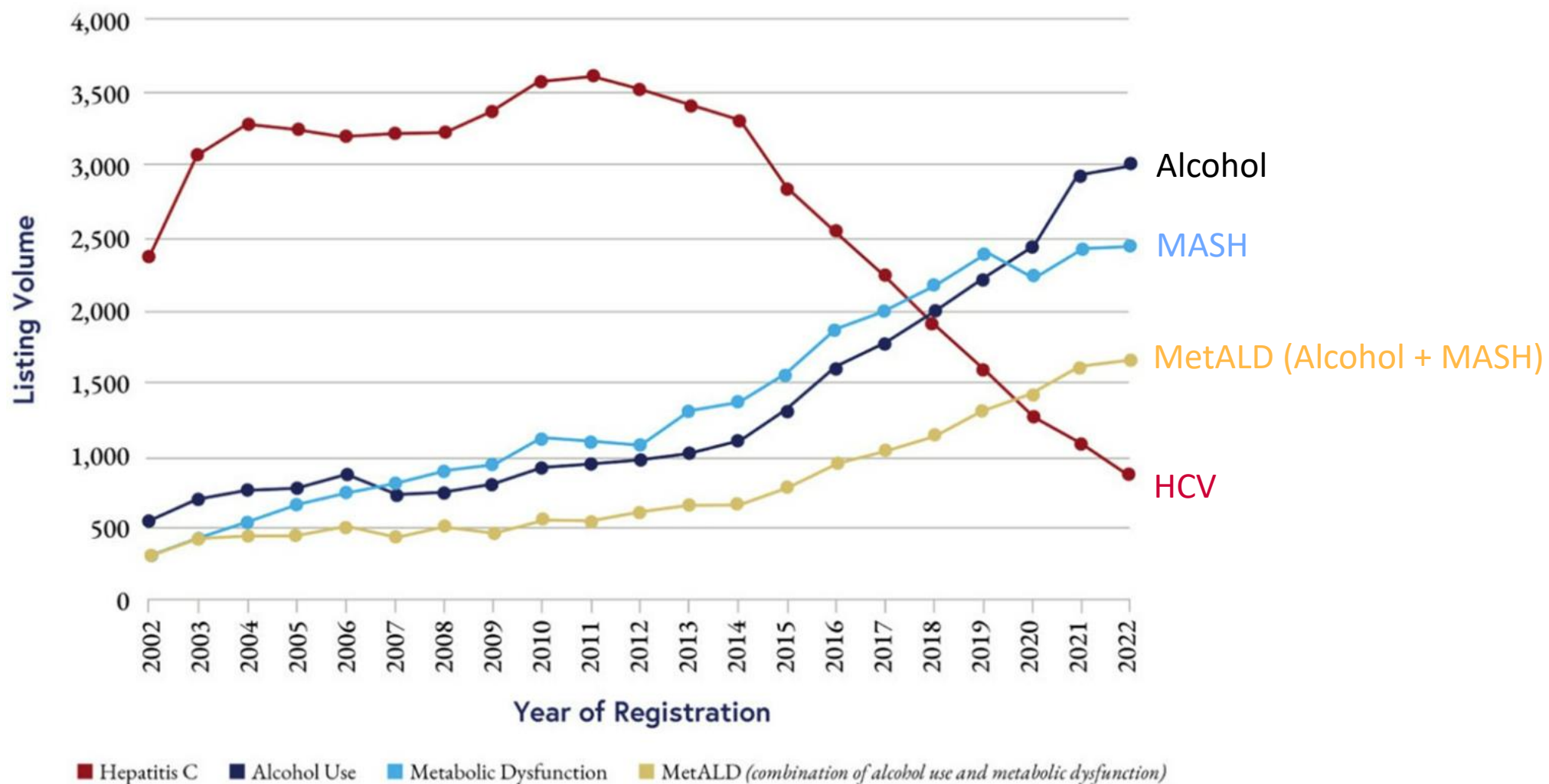
- Understand the new MASLD nomenclature and disease spectrum
- Identify who should be screened for MASLD
- Outline the stepwise risk stratification algorithm for MASLD
- Discuss evidence-based MASLD treatment options
- Review MASH therapeutic agents in the late-phase clinical trial



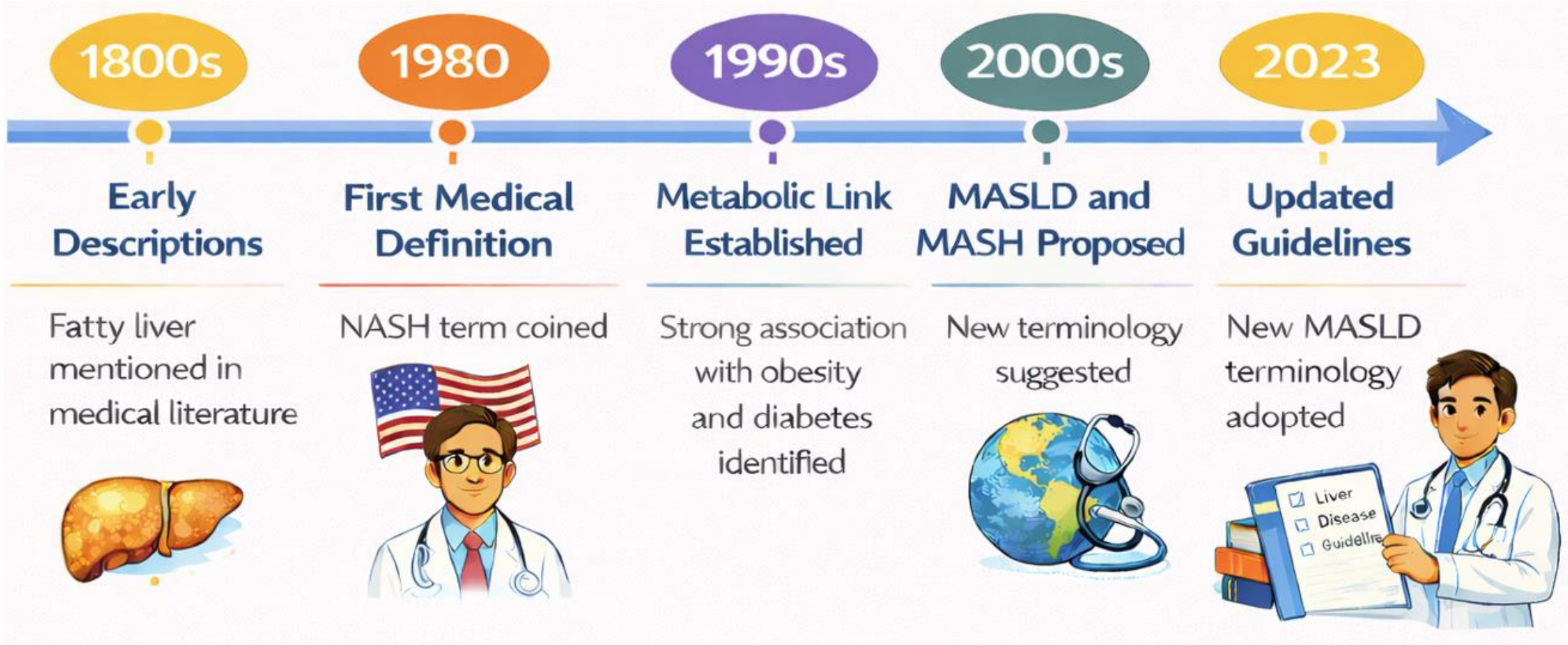
Prevalence of MASLD Worldwide in Adults & Children



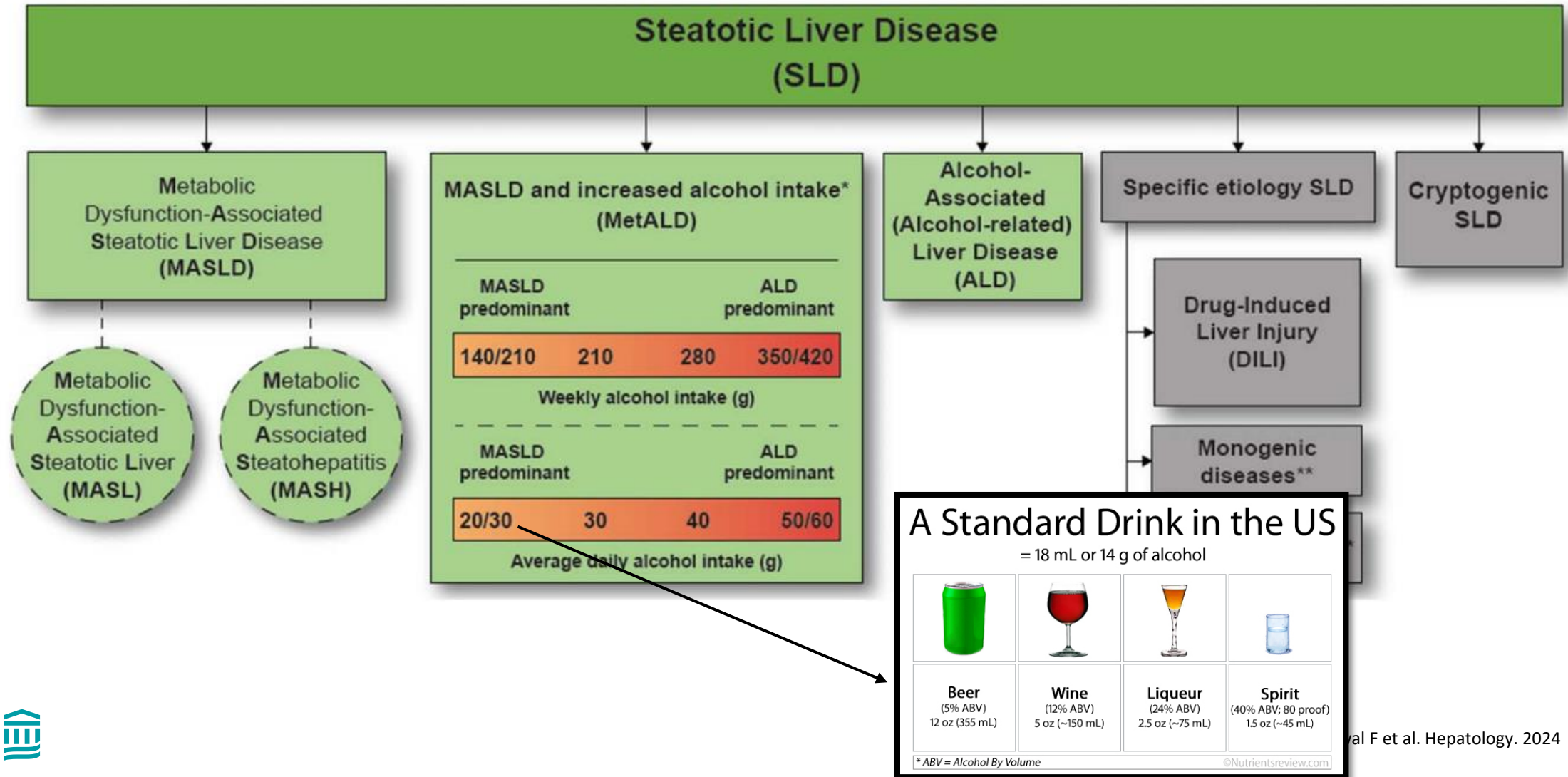
Trends in the Liver Transplant Waitlist by Etiology



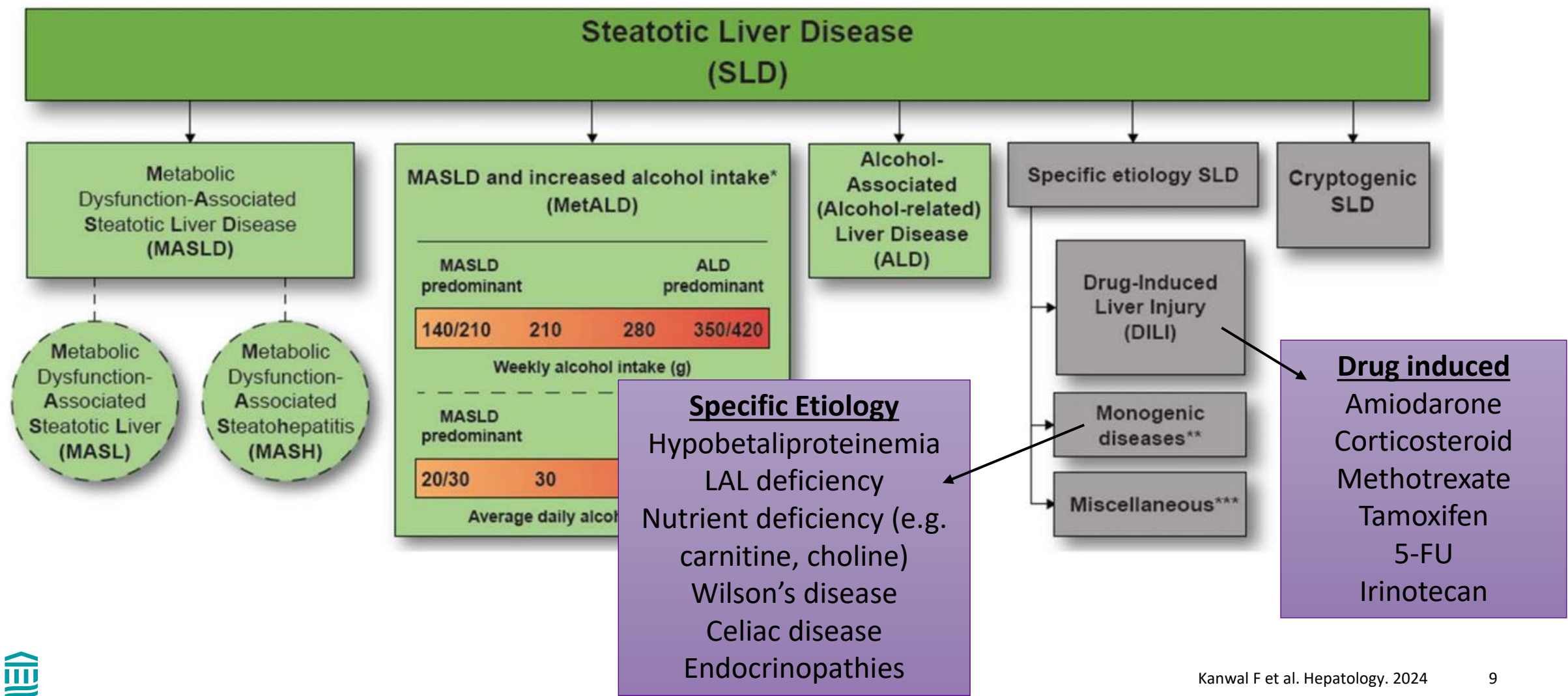
Historical Timeline of Fatty Liver Disease



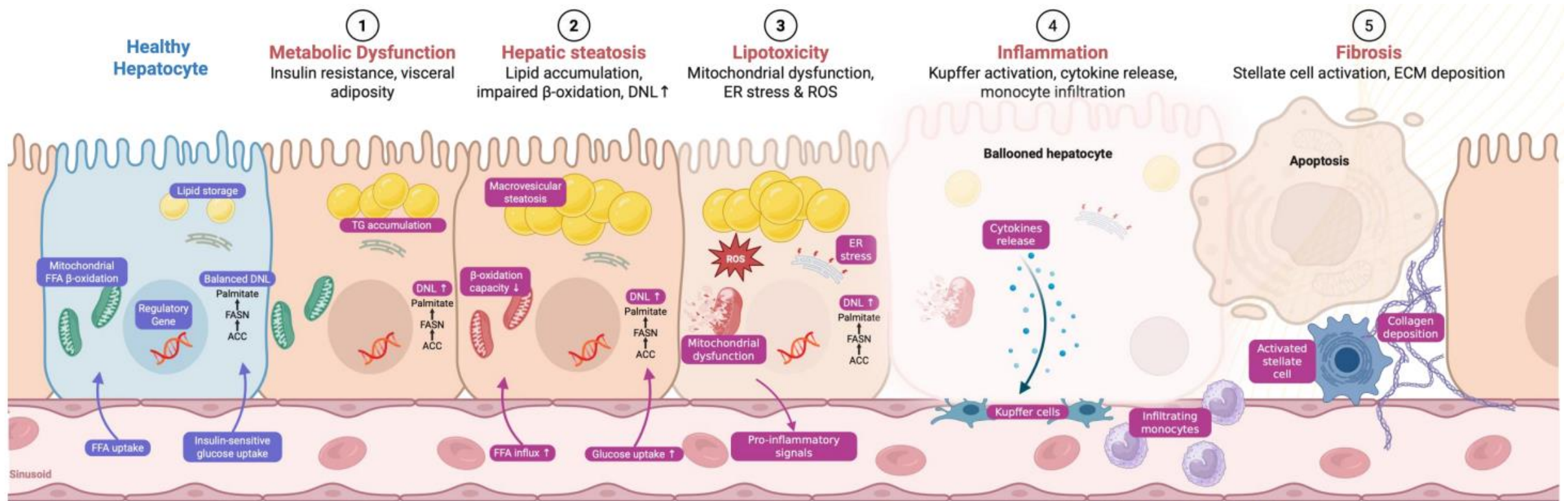
Steatotic Liver Disease Nomenclature



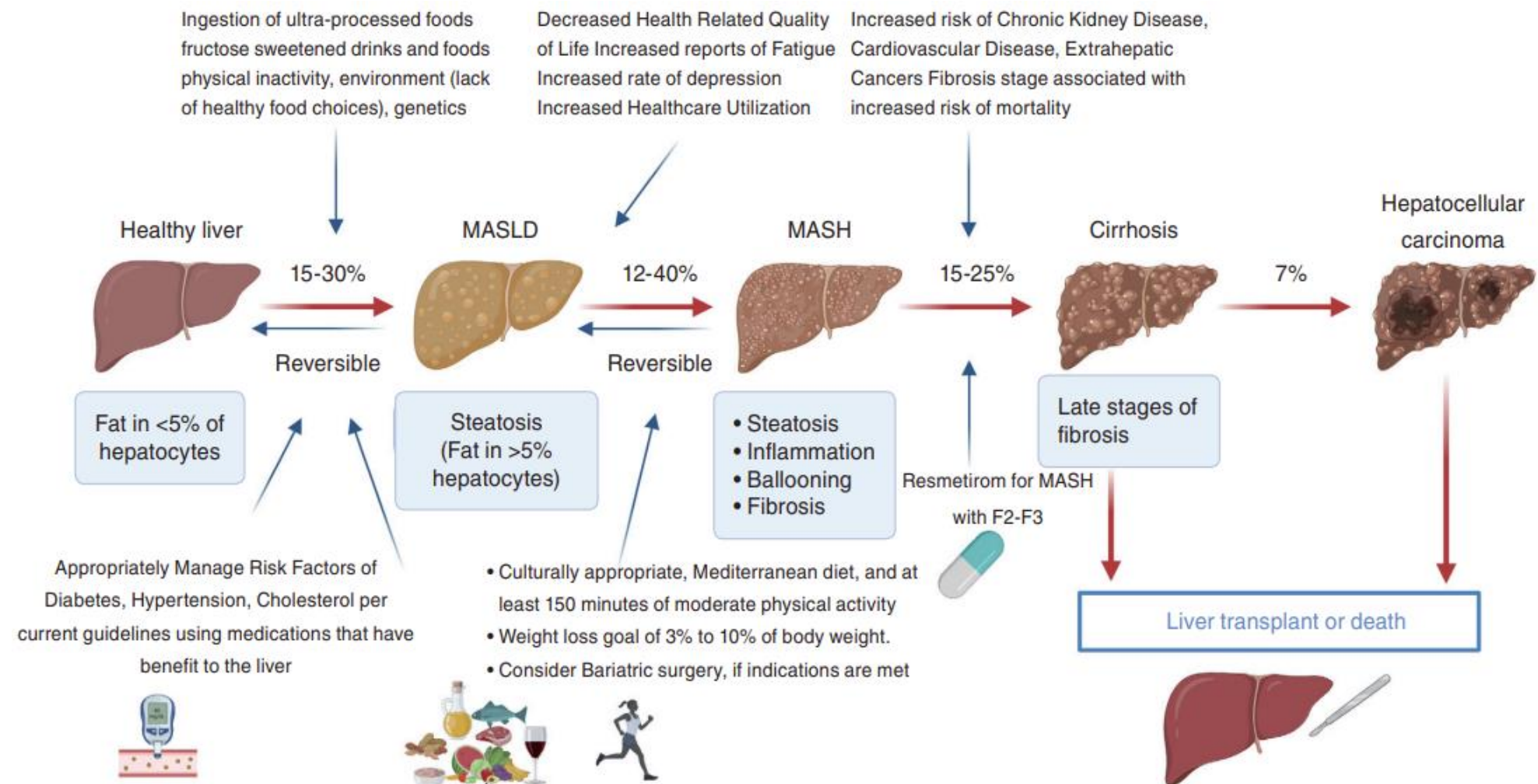
Steatotic Liver Disease Nomenclature



MASH Pathophysiology



MASLD Disease Spectrum



Case Study

- 45 yo **Hispanic** male
- PMHx: **T2D, hypertension and obesity (BMI 43)**
- FHx: **Mother is “overweight and has fatty liver”**
- **Social alcohol use**, ave 3-5 drinks/week
- Routine blood work:
 - LFT: **AST 55, ALT 60, ALP 175** and TB 0.8
 - Hgb 15g/dL, MCV 96, platelet **210k**
 - **Ferritin 400ng/dL**; iron saturation 25%
 - Negative viral and autoimmune serologies
- Ultrasound showed **hepatic steatosis**



Targeted MASLD Screening

- Universal screening is NOT recommended
- At-risk populations for MASLD:
 - Type 2 diabetes -> strongest predictor of advanced fibrosis
 - Elevated ALT/AST
 - Obesity (BMI > 30) or waist circumference > 102cm/88cm
 - Hypertension ($\geq 130/85$ mmHg)
 - Hyperlipidemia (TG ≥ 150 mg/dL)

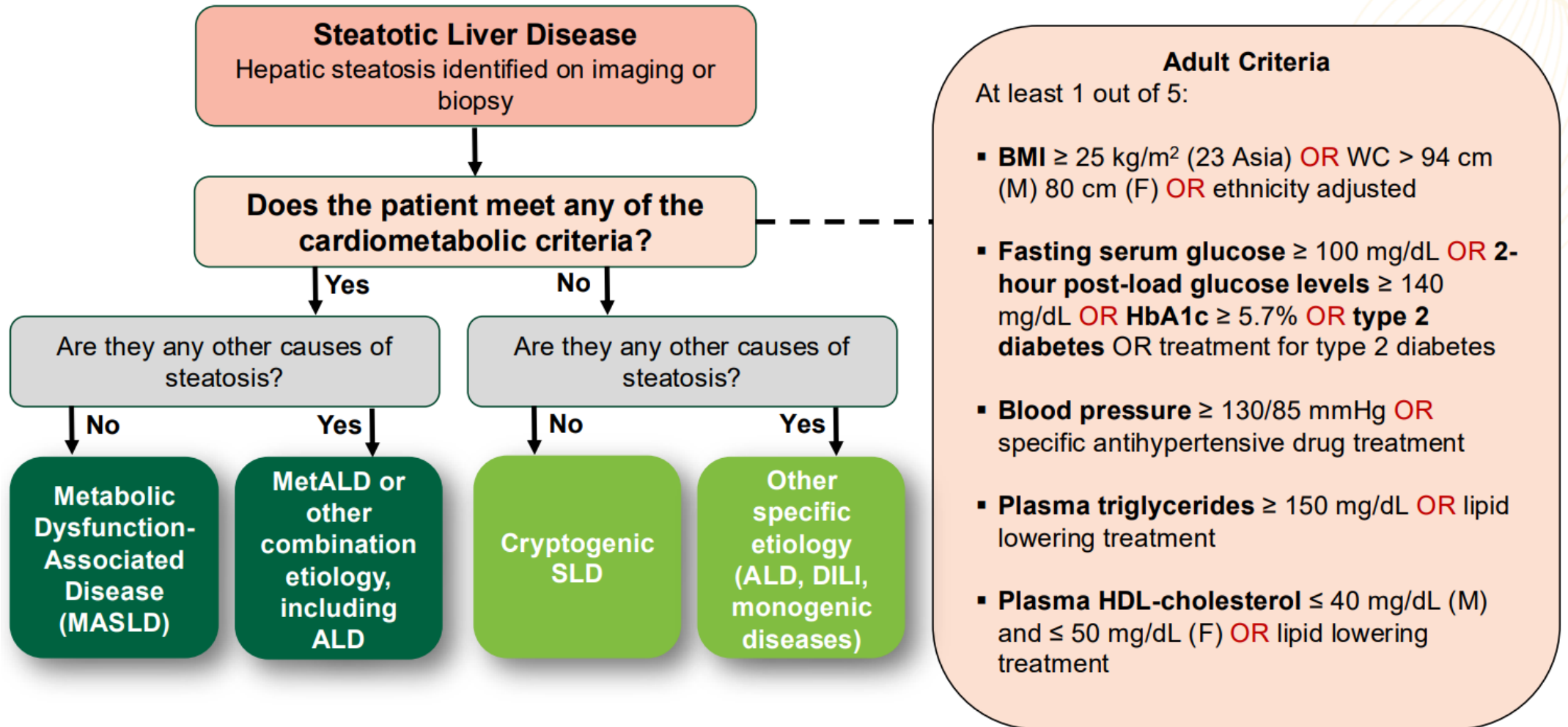


Additional MASLD Risk Factors to Consider

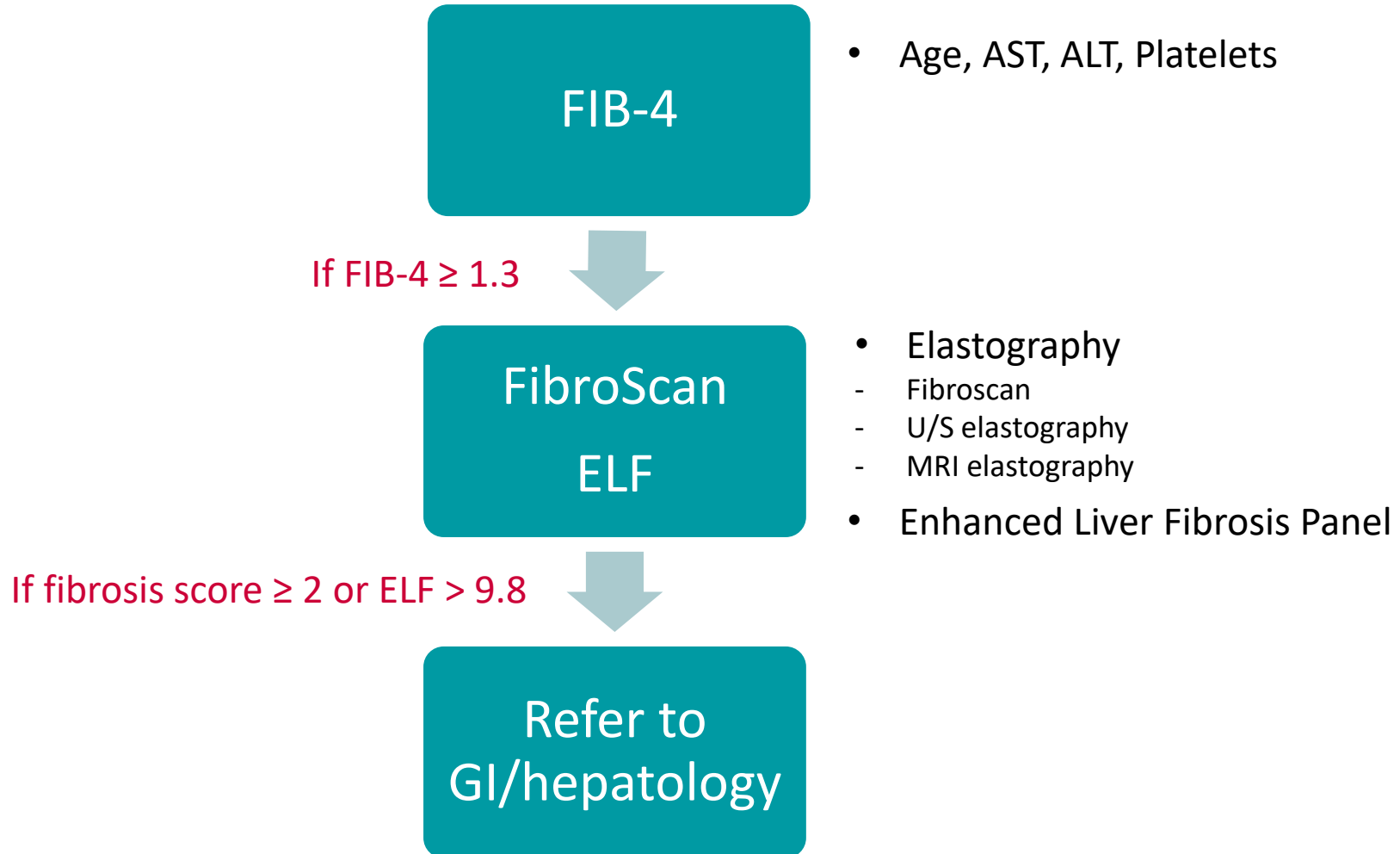
- Male has 2x prevalence than female
- Hispanic > White > African American
- Medical comorbidities – PCOS, CVD, OSA, insulin resistance
- Genetic polymorphisms associated with increase risk of MASH
 - PNPLA3/148M
 - TM6SF2
 - MBOAT7



Diagnosis of MASLD

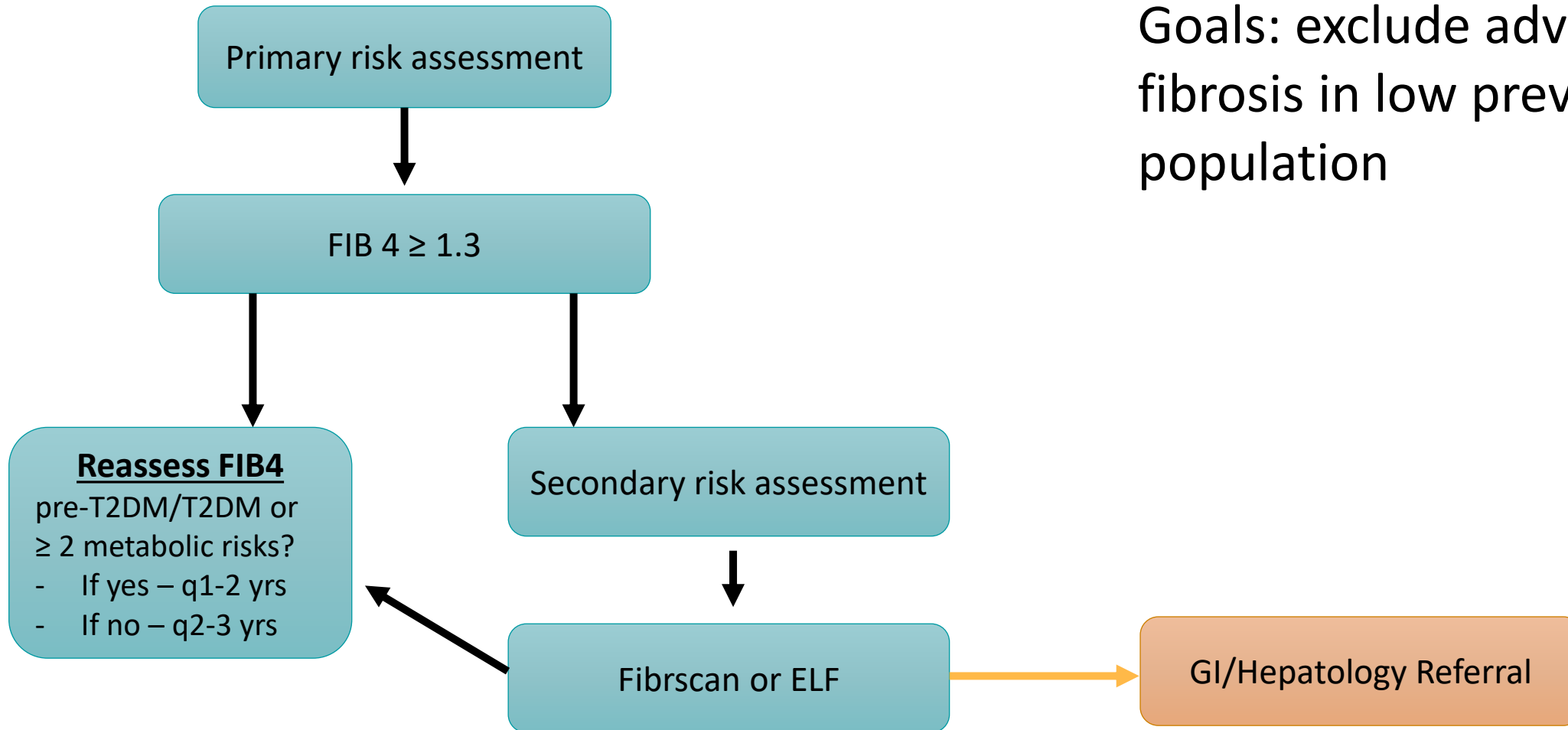


MASLD Stepwise Risk Stratification



MASLD Management Algorithm– Primary Care Setting

Goals: exclude advanced fibrosis in low prevalence population



Case Study

- 45 yo Hispanic male with:
 - $\geq 2x$ cardiometabolic risk factors
 - family history of fatty liver disease
 - Insignificant alcohol use
 - Mild transaminitis
 - U/S abdomen hepatic steatosis
- FIB-4 = 1.8
- Fibroscan (VCTE) = 10kPa



GI/Hepatology Referral

MASLD Management Algorithm– GI/Hepatology Setting

- Review/perform 1st or 2nd risk assessment
- Consider additional stratification

Intermediate or high risk

Consider liver biopsy

- indeterminate NITs
- diagnostic uncertainty
- persistently ↑LFTs

Suspect cirrhosis

(clinical, imaging, or ELF >11.3)

F0-1

F2-3

F3-4

Reassess in 2-3 years

- Reassess annually
- Pharmacotherapy

Cirrhosis management

Goals: identify and manage patients with “at risk” MASH or cirrhosis



Case Study

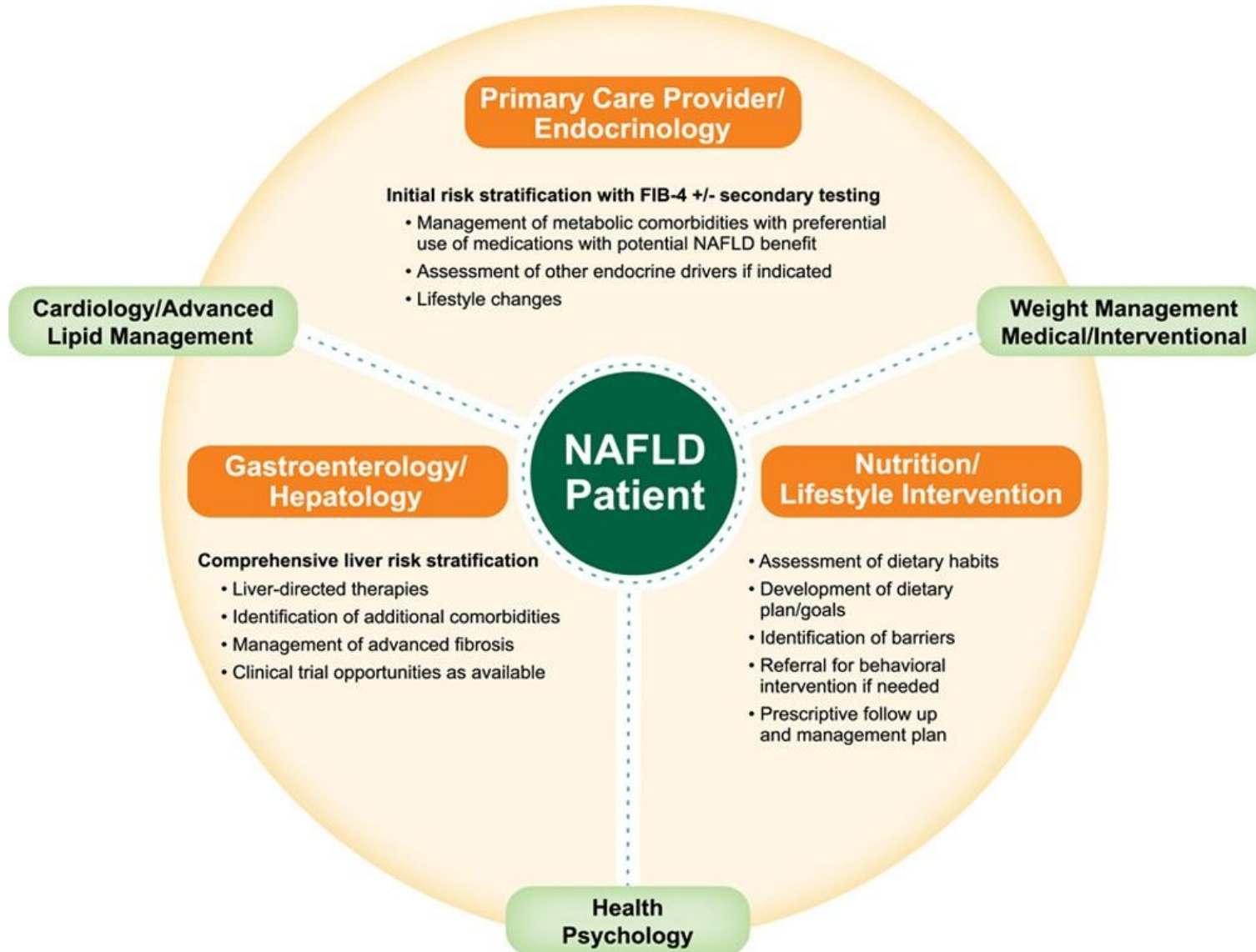
- 45 yo Hispanic male with:
 - ≥ 2 x cardiometabolic risk factors
 - family history of fatty liver disease
 - Insignificant alcohol use
 - Mild transaminitis
 - U/S abdomen hepatic steatosis
- Diet and lifestyle modification x 6 months
- Minimal weight loss
- Assessed at GI/Hepatology clinic
 - Repeat VCTE = 8kPa
 - ALT down to 50



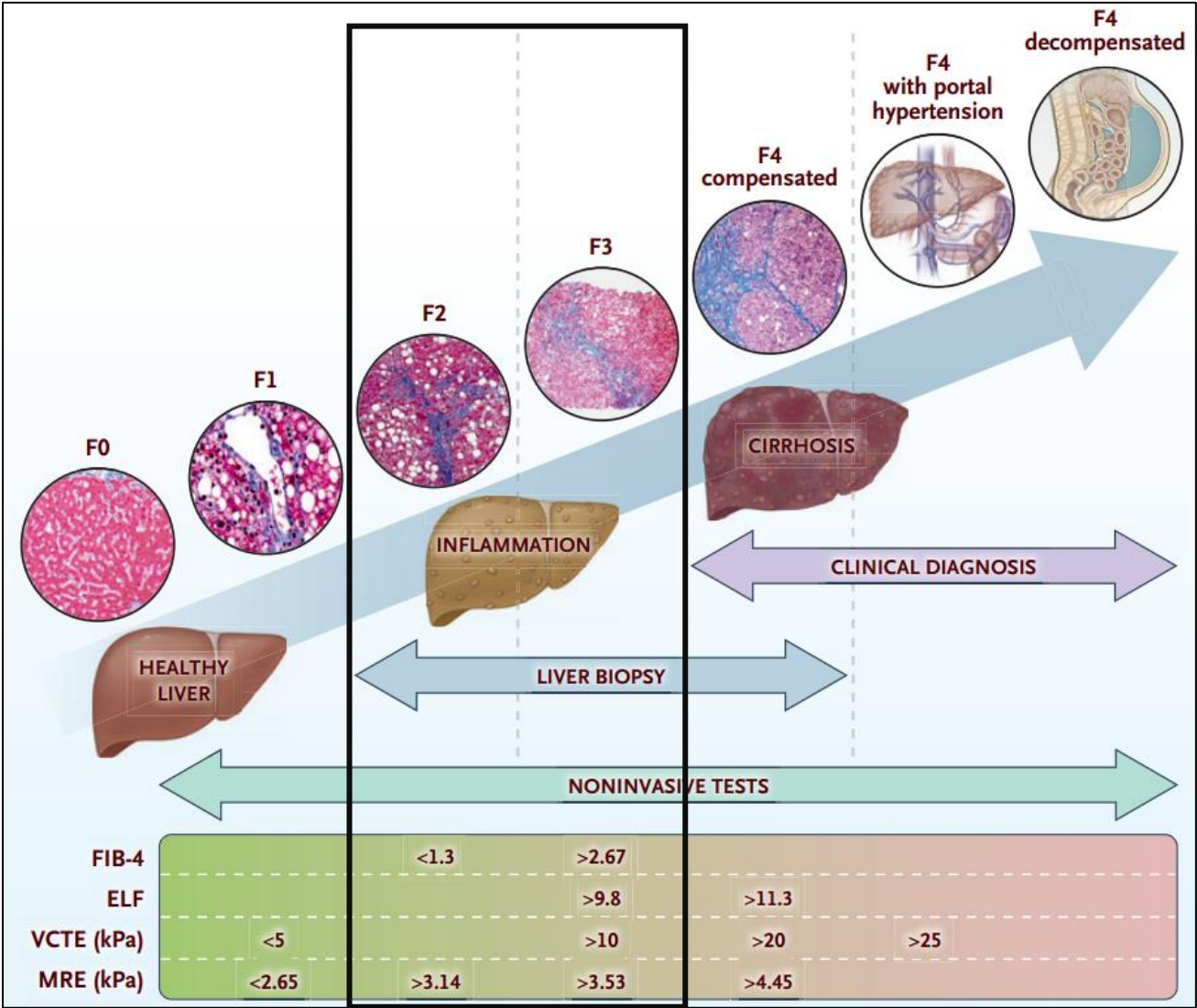
Treatment options?



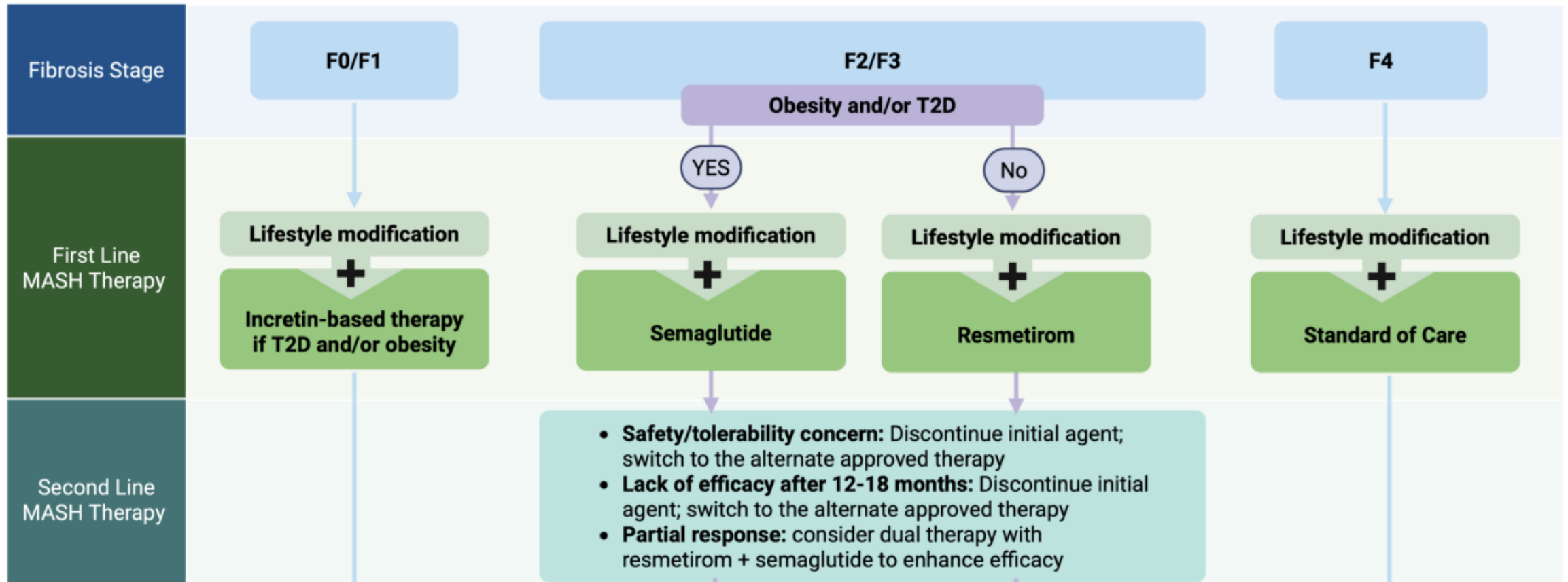
Multidisciplinary Approach to MASLD Treatment



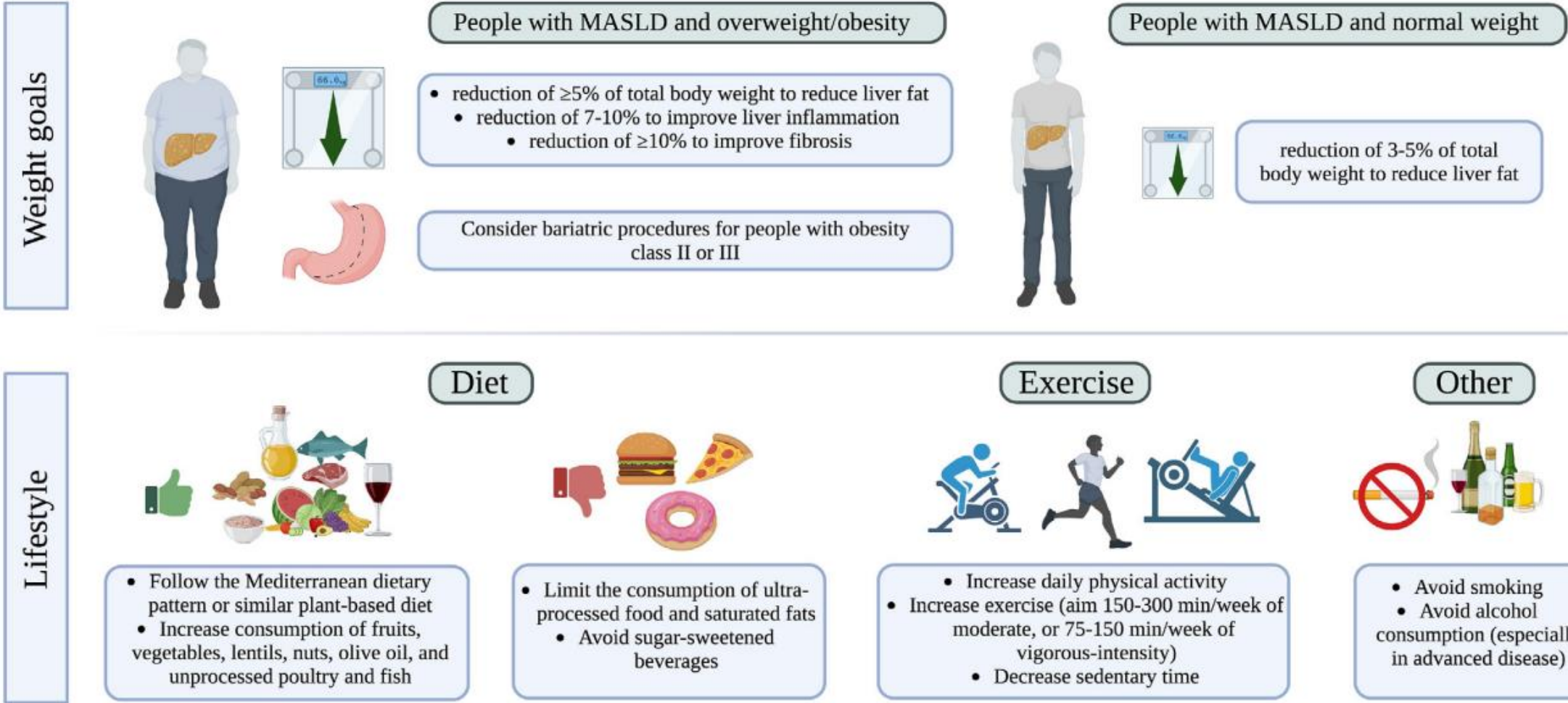
Stages of Liver Fibrosis



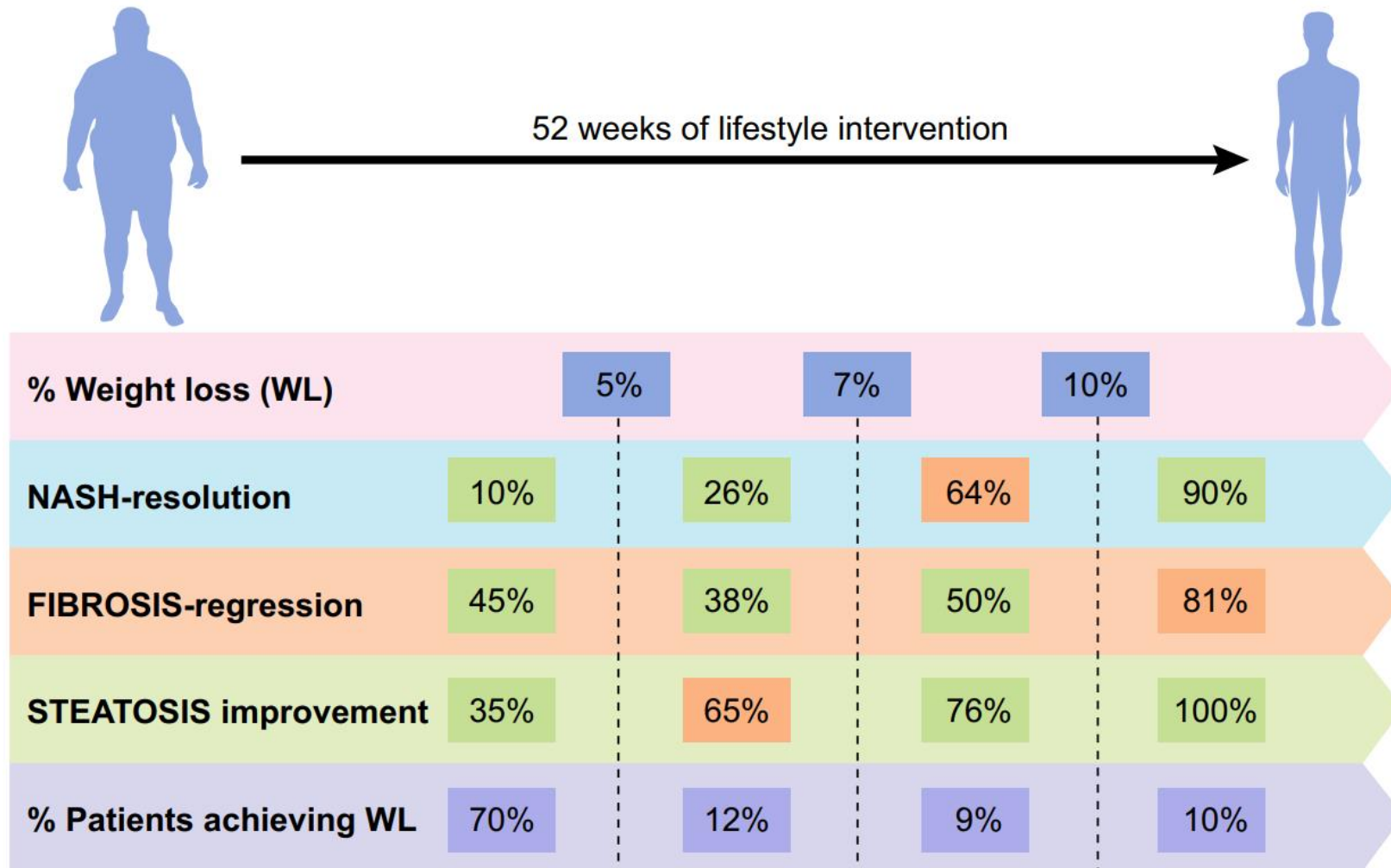
MASLD Treatment Algorithm by Fibrosis Stage



Lifestyle Recommendation for Patients with MASLD



Weight loss Remains the Key Treatment for MASLD

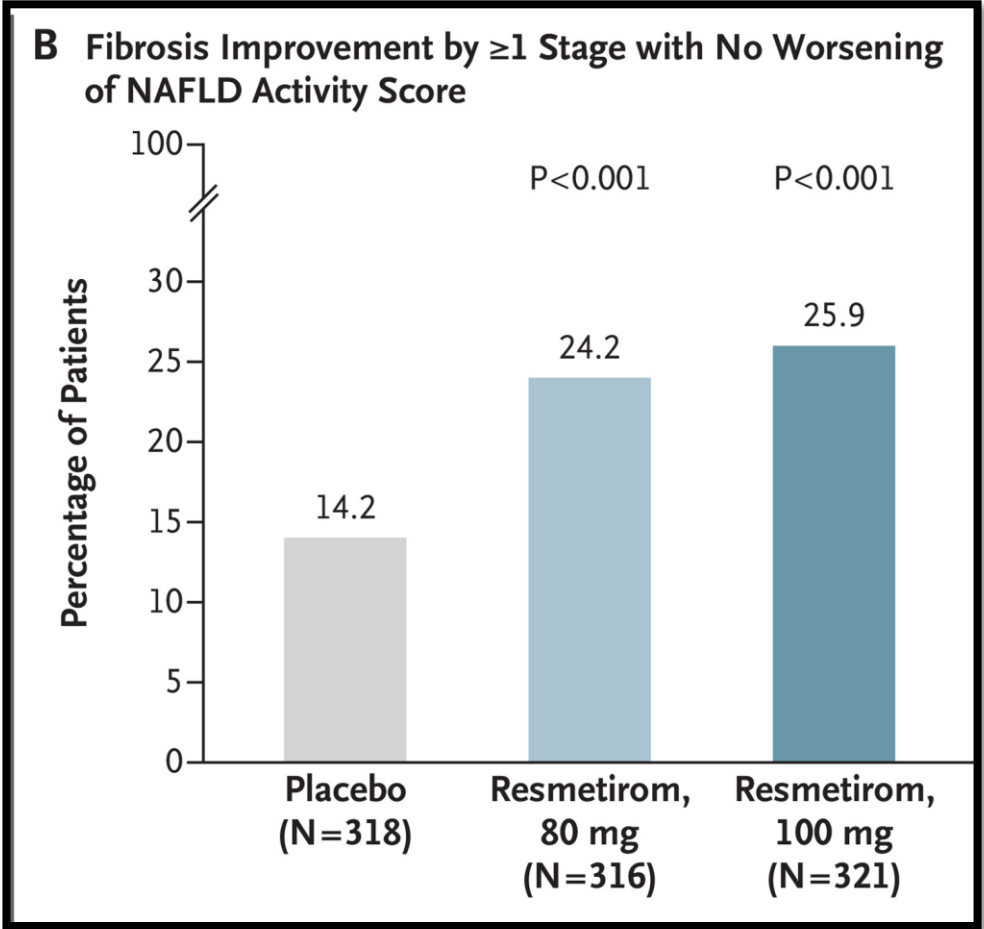
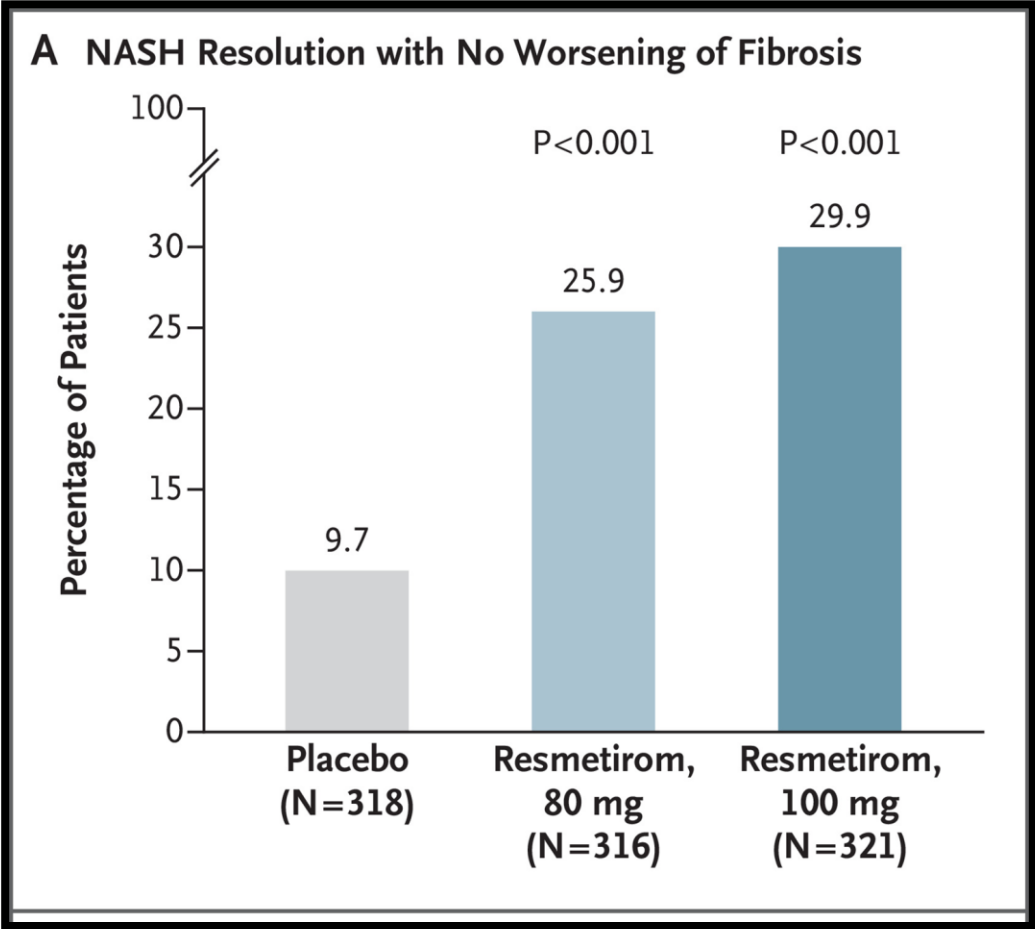


Resmetirom (Rezdiffra™) – FDA Approved in 2024

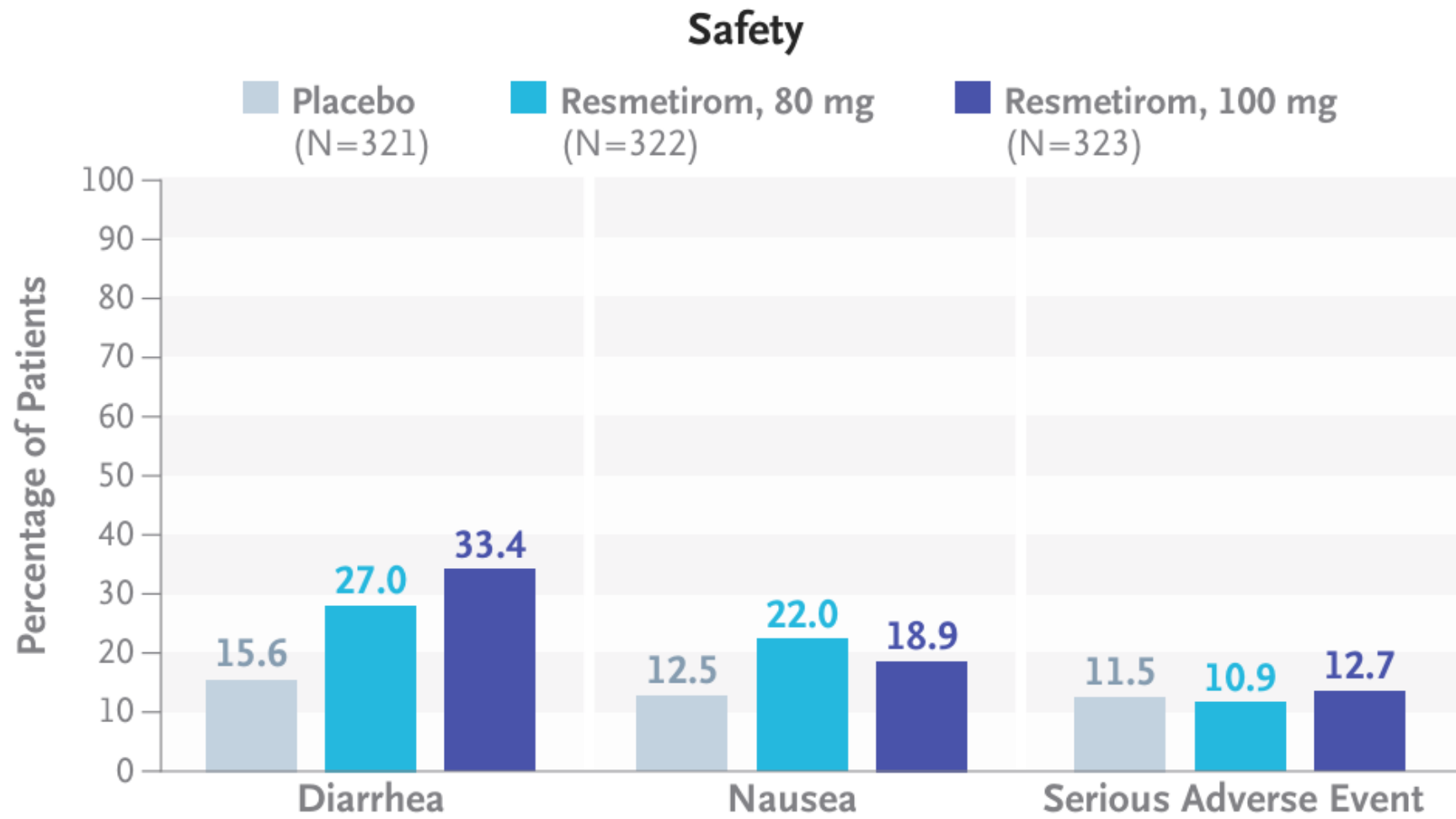
- First FDA-approved therapy for MASH
- Thyroid hormone receptor- β agonist - ↓hepatic fat & lipotoxicity
- Indicated in adult with non-cirrhotic MASH + F2-F3 fibrosis
- Administered orally, 80mg or 100mg daily
 - dose reduction if on cytochrome p450 inhibitors (e.g. clopidogrel)
- Not recommended in:
 - cirrhosis, uncontrolled active liver diseases or ongoing alcohol use
 - patients with symptomatic gallstone-related disorders
- Thyroid function assessment prior to treatment initiation



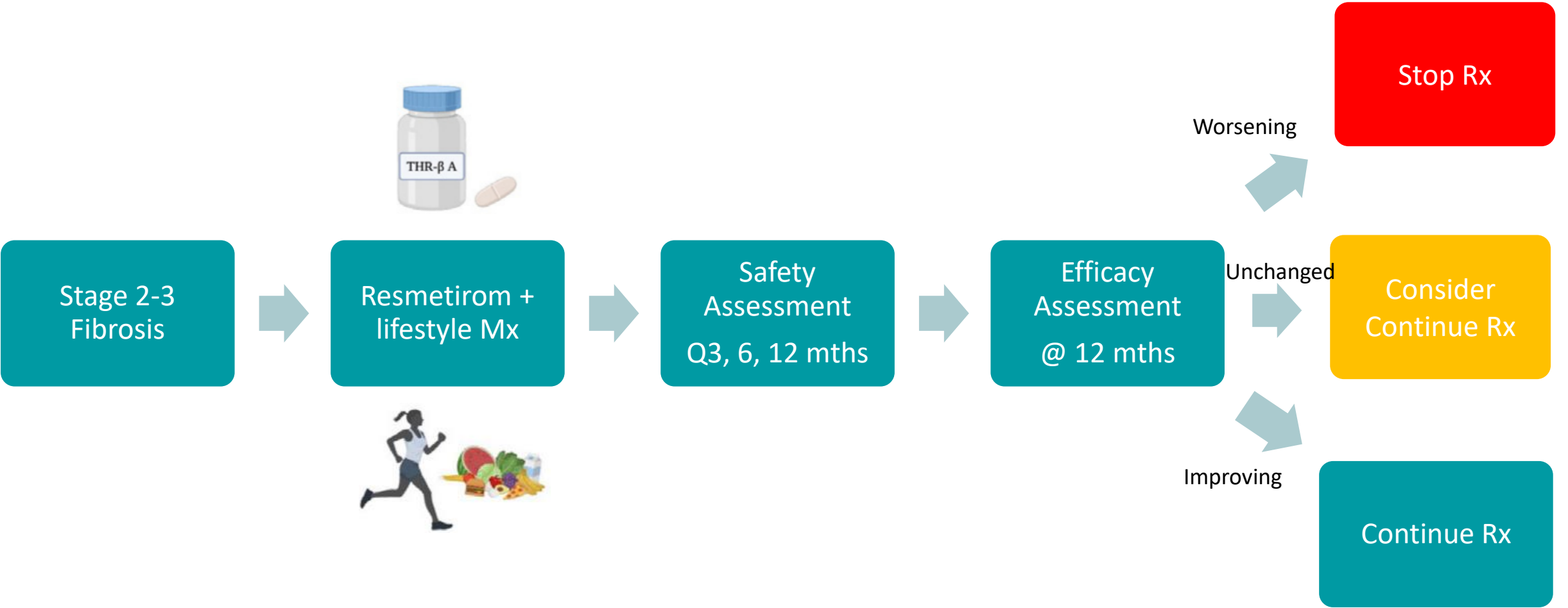
Resmetirom Study End Points (Masetro Trial)



Resmetirom Study Reported Side Effects (Masetro Trial)



Resmetirom Treatment Algorithm

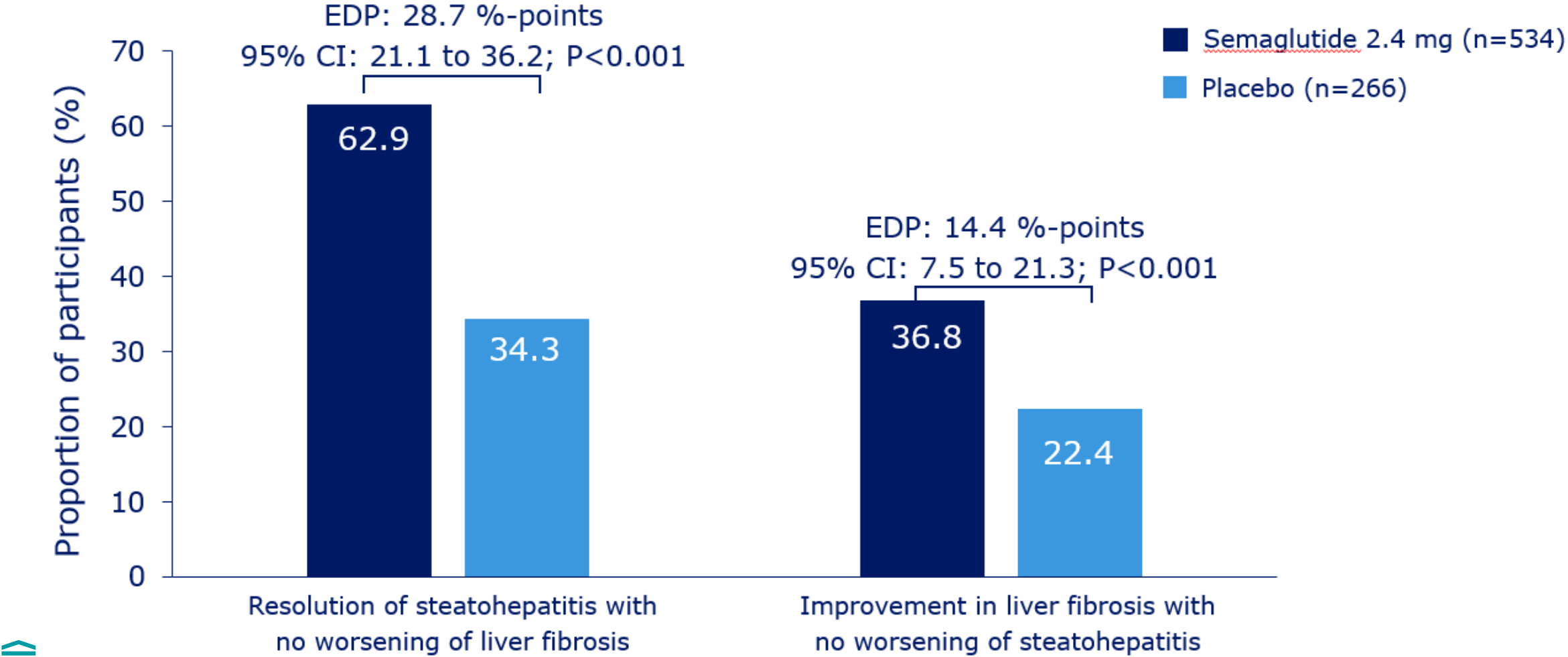


Semaglutide (Wegovy®) – FDA Approved in 08/2025

- Second FDA-approved therapy
- GLP-1 receptor agonist – weight loss, metabolic improvement and anti-inflammatory effects
- Indicated in adults with MASH + F2-F3 fibrosis
- Administered as weekly injection, 2.4mg
- Monitor for acute pancreatitis and acute gallbladder disease

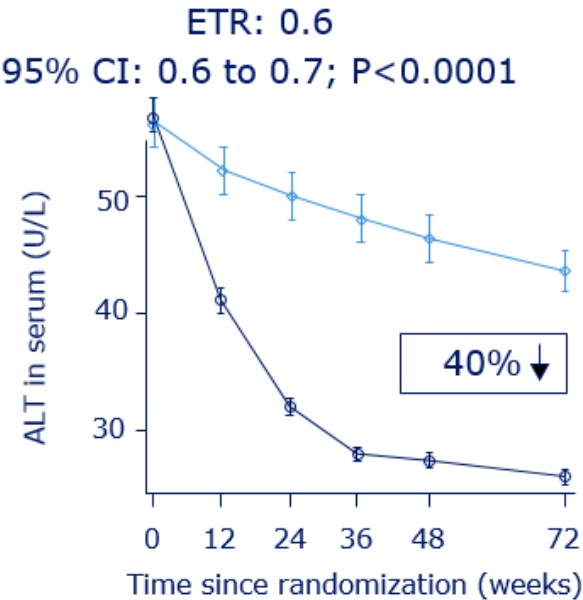


Semaglutide Study End Points (ESSENCE Trial)



Semaglutide Improves Liver Enzymes

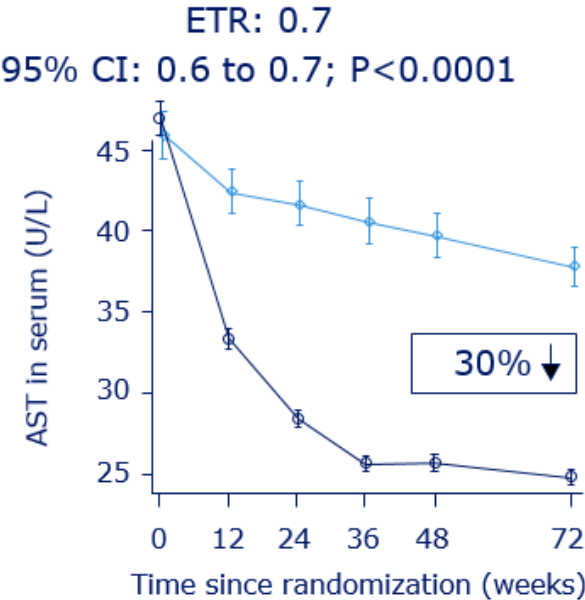
ALT



Number of participants

| | | | | | | |
|--------------------|-----|-----|-----|-----|-----|-----|
| Semaglutide 2.4 mg | 534 | 518 | 511 | 509 | 502 | 493 |
| Placebo | 266 | 258 | 255 | 252 | 246 | 236 |

AST

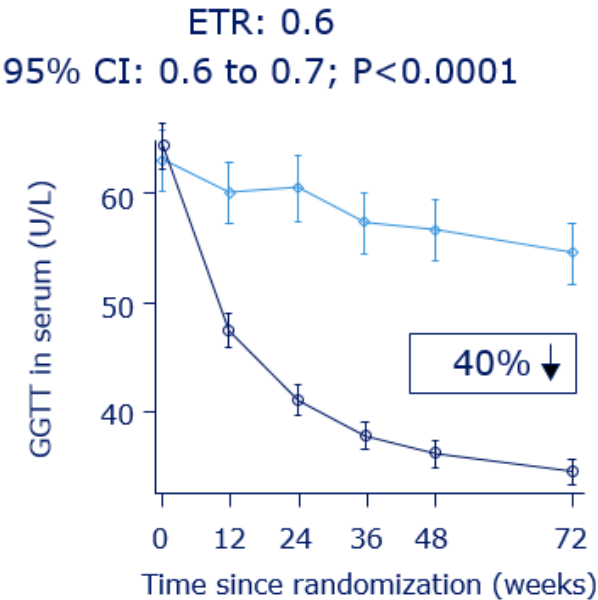


Number of participants

| | | | | | | |
|--------------------|-----|-----|-----|-----|-----|-----|
| Semaglutide 2.4 mg | 534 | 516 | 508 | 504 | 500 | 490 |
| Placebo | 266 | 257 | 257 | 251 | 246 | 236 |

○ Semaglutide 2.4 mg ◇ Placebo

GGT



Number of participants

| | | | | | | |
|--------------------|-----|-----|-----|-----|-----|-----|
| Semaglutide 2.4 mg | 534 | 520 | 512 | 510 | 503 | 494 |
| Placebo | 266 | 258 | 257 | 252 | 245 | 237 |

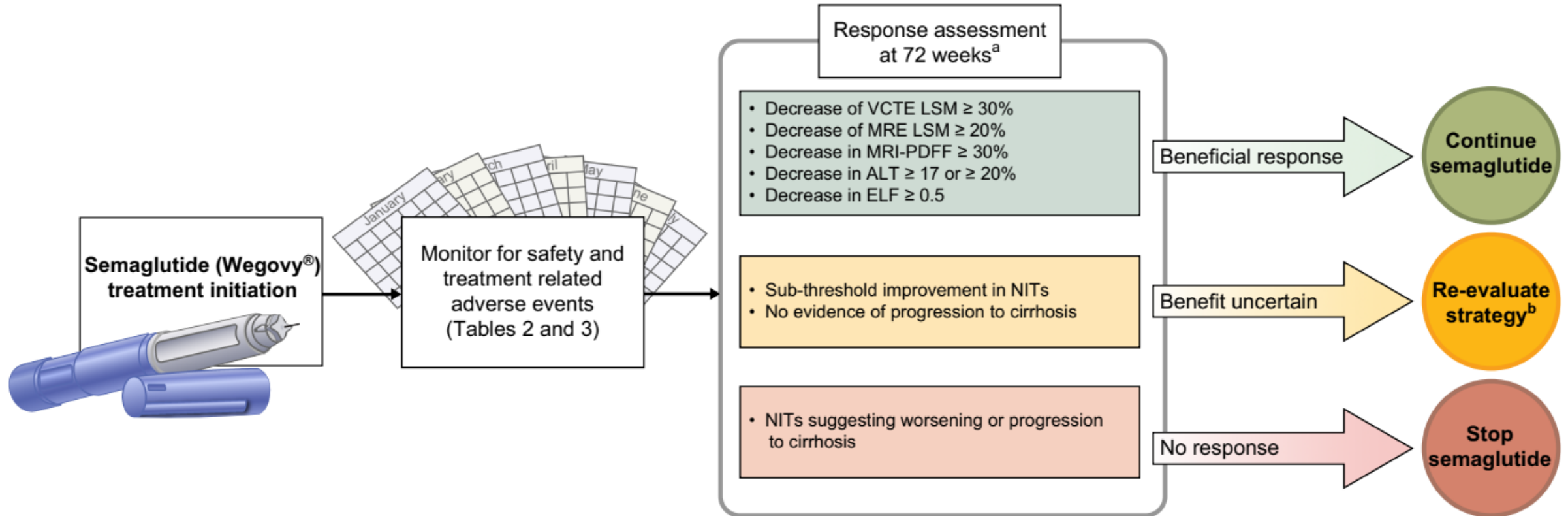


Semaglutide Safety Profile

| | Semaglutide 2.4 mg (N=800) | Placebo (N=395) |
|---|-------------------------------|--------------------|
| | n (%) | n (%) |
| All AEs | 690 (86.3) | 315 (79.7) |
| Fatal AEs | 3 (0.4) | 6 (1.5) |
| Serious AEs | 107 (13.4) | 53 (13.4) |
| AEs leading to trial discontinuation | 21 (2.6) | 13 (3.3) |
| AEs affecting ≥10% of participants | | |
| Nausea | 290 (36.3) | 52 (13.2) |
| Diarrhea | 215 (26.9) | 48 (12.2) |
| Constipation | 178 (22.3) | 33 (8.4) |
| Vomiting | 149 (18.6) | 22 (5.6) |
| COVID-19 | 134 (16.8) | 74 (18.7) |
| Decreased appetite | 112 (14.0) | 11 (2.8) |



Safety & Treatment Response Assessment for 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.

Case Study - Conclusion

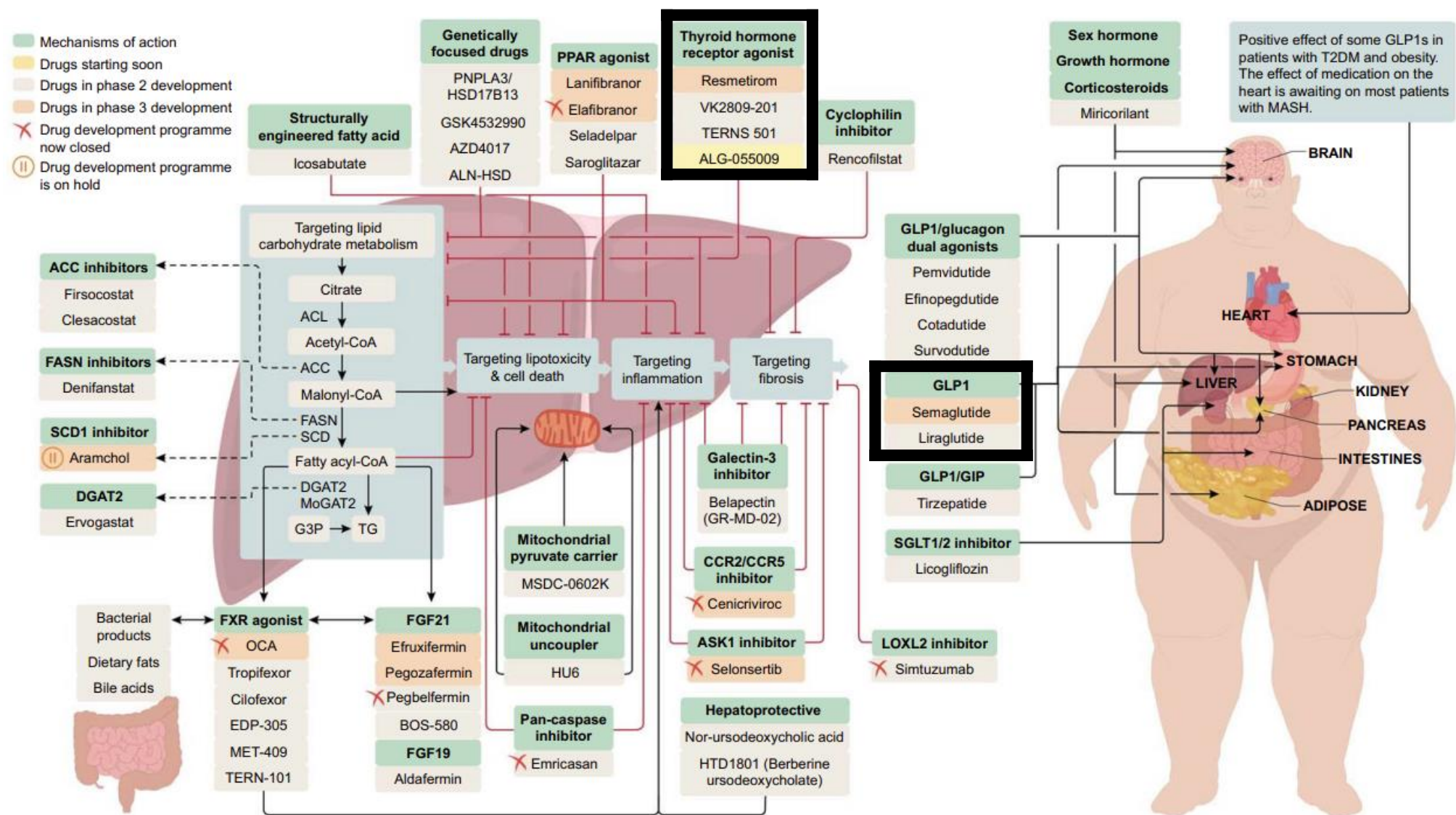
- 45 yo Hispanic male with:
 - $\geq 2x$ cardiometabolic risk factors
 - family history of fatty liver disease
 - Insignificant alcohol use
 - Mild transaminitis
 - U/S abdomen hepatic steatosis
- Ongoing lifestyle modifications
- Initiation of MASH specific treatment
- Monitor MASH treatment response
- Optimize Rx of cardiometabolic comorbidities



Semaglutide and/or
resmetirom



Current Pipeline of MASH Drugs



Promising MASH Therapeutic Agents in Late-Phase Clinical Trials and Their Targets

| Target/Class | Agent | Route | Primary Endpoint | Fibrosis Stage |
|---|--------------|-------|---|----------------|
| Thyroid hormone receptor β (THR- β) agonist | Resmetirom | PO | <ul style="list-style-type: none"> Fibrosis improvement & no worsening of MASH | F4 |
| | VK2809 | PO | <ul style="list-style-type: none"> Change in liver fat content MASH resolution without worsening of fibrosis | F1-3 |
| Peroxisome proliferator activated receptor (PPAR) agonist | Lanifibranor | PO | <ul style="list-style-type: none"> MASH improvement or resolution Fibrosis improvement | F1-F3 |
| | Saroglitazar | PO | <ul style="list-style-type: none"> MASH improvement or resolution without worsening of fibrosis Change in ALT | F2-F3 |
| | Pioglitazone | PO | <ul style="list-style-type: none"> MASH improvement | F1-F3 |



Promising MASH Therapeutic Agents in Late-Phase Clinical Trials and Their Targets

| Target/Class | Agent | Route | Primary Endpoint | Fibrosis Stage |
|--|--------------|--------|---|----------------|
| Glucagon-like peptide 1 (GLP1) receptor agonist | Survodutide | SC inj | <ul style="list-style-type: none"> MASH improvement without worsening of fibrosis | F2-F3 |
| Glucose-dependent insulintrophic polypeptide (GIP) + GLP1-RA | Tirzepatide | SC inj | <ul style="list-style-type: none"> MASH resolution without worsening of fibrosis Fibrosis improvement & no worsening of MASH | F2-F3 |
| Fibroblast growth factor 21 (FGF21) agonist | Efruxifermin | SC inj | <ul style="list-style-type: none"> Fibrosis improvement MASH resolution & improvement of fibrosis Fibrosis Improvement | F2-F3 F4 |
| | Pegozafermin | SC inj | <ul style="list-style-type: none"> Fibrosis improvement MASH resolution Time for 1st disease progression | F2-3 F4 |
| Fatty acid synthase (FASN) inhibitor | Denifanstat | Oral | <ul style="list-style-type: none"> Fibrosis improvement MASH resolution | F2-F3 |

Key Take Home Messages

- MASLD is the hepatic manifestation of metabolic syndrome
- Don't rely on liver enzymes alone
- Fibrosis is the key risk factor for liver-related outcome in MASLD
- FIB-4 is the best first step in assessing hepatic fibrosis
- Most patients can be managed in primary care & refer when there is increased fibrosis
- Lifestyle modification remains a critical player in the treatment paradigm
- Resmetirom and semaglutide are FDA approved MASH specific drugs
- Multiple MASH therapeutic agents are in the pipeline



Questions?

- Contact email: valerie.lin@lahey.org

