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CME OUTFITTERS



DIGGING DEEPER *into* ABNORMAL LIVER TEST RESULTS



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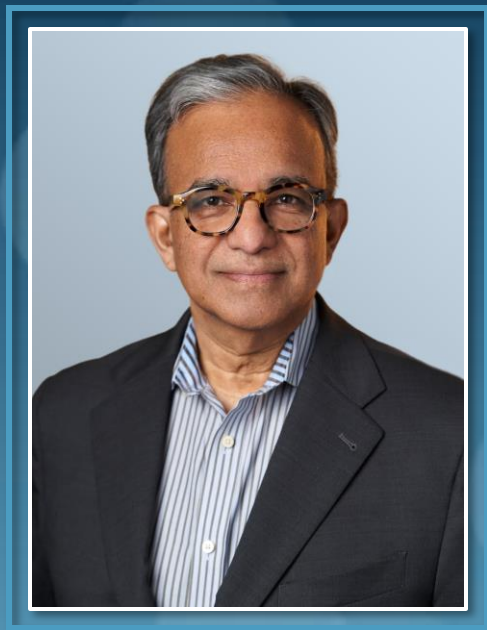
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The following individuals have no financial relationships to disclose:

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- ▶ Amanda K. Smith, PA-C (peer reviewer)
- ▶ Maria Morais, RN (patient planner)
- ▶ Keshia Pitt, PhD (planning committee)
- ▶ Warren Beckman (planning committee)
- ▶ Scott J. Hershman, MD, FACEHP, CHCP (planning committee)
- ▶ Sandra Caballero, PharmD (planning committee)
- ▶ Sharon Tordoff (planning committee)

**LEARNING
OBJECTIVE**

1

Identify signs and symptoms of PBC, MASLD, and MASH.

**LEARNING
OBJECTIVE**

2

Implement team-based strategies for early and accurate diagnosis of PBC, MASLD, and MASH.

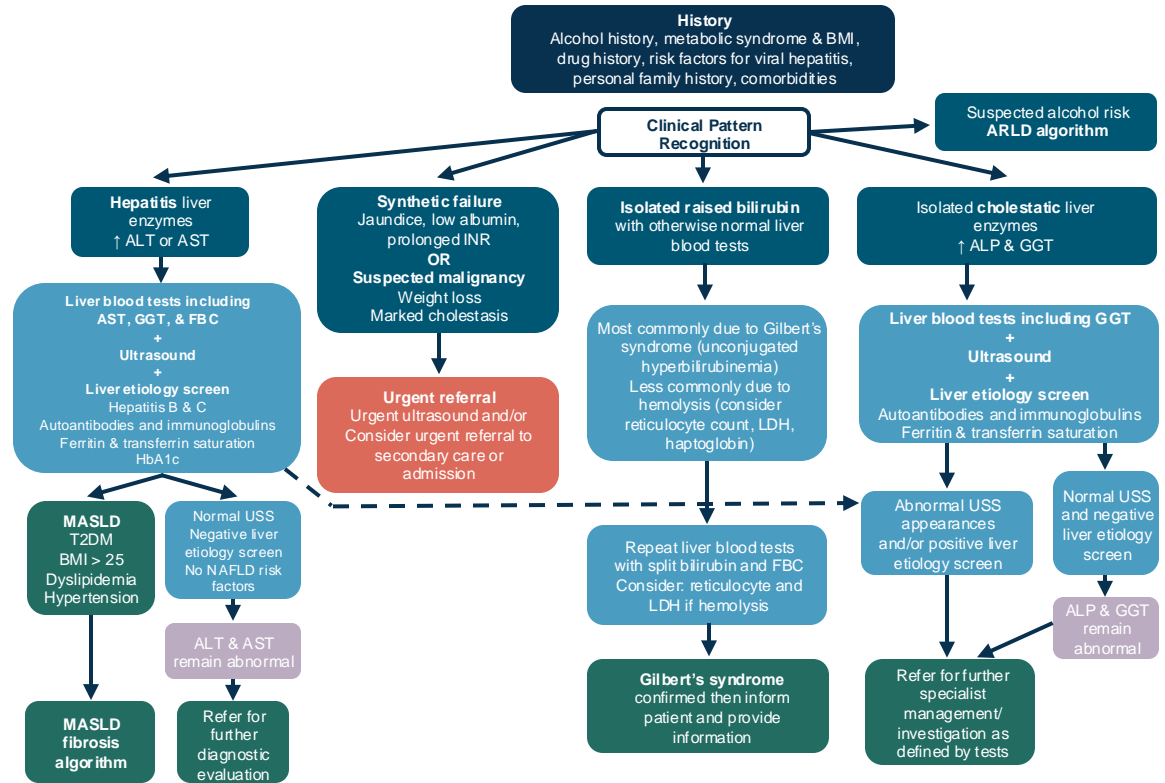
**LEARNING
OBJECTIVE**

3

Assess new and emerging therapeutic pathways for PBC, MASLD, and MASH which impact treatment decision-making.

LFTs: A Clinical Call to Action

- ▶ LFTs are invaluable tools in medicine
- ▶ Predictive value for many conditions
- ▶ Today, we will focus on PBC and MASLD/MASH



ALP = alkaline phosphatase; ALT = alanine aminotransferase; ARLD = alcohol-related liver disease; AST = aspartate transaminase; BMI = body mass index; FBC = full blood count; GGT = gamma-glutamyl transferase; INR = international normalized ratio; LDH = lactate dehydrogenase; LFT = liver function test; MASH = metabolic dysfunction-associated steatohepatitis; MASLD = metabolic dysfunction-associated steatotic liver disease; NAFLD = non-alcoholic fatty liver disease; T2DM = type 2 diabetes mellitus; USS = ultrasound scan.

Newsome P, et al. *Gut*. 2018;67(1):6-19.

Part 1

Primary Biliary Cholangitis (PBC)

Patient Case: Maggie



- ▶ 50-year-old advertising account executive



- ▶ 2021: visited primary care practitioner (PCP) for persistent fatigue and complaints of mild itching, mostly at night



- ▶ ALP was 380 U/L (normal range: < 120 U/L)
- ▶ Maggie's PCP attributed symptoms and elevated ALP to nonspecific causes (aging, stress)
 - ▶ Did not pursue further diagnostic tests or recommend hepatology referral

Patient Case: Maggie



- ▶ Over next 2 years, symptoms worsened



- ▶ 2025: severe fatigue and pruritus
- ▶ Maggie sought care from a specialist and was diagnosed with PBC with advanced fibrosis



- ▶ She now faces the challenge of managing liver disease and potential complications

Audience Response

Based on this case presentation, which of the following tests would have been a guideline-recommended first step toward an earlier diagnosis?

- A. Anti-nuclear antibody (ANA)
- B. Anti-mitochondrial antibody (AMA)
- C. Anti-glycoprotein 210 (gp210) or anti-speckled protein 100 (sp100)
- D. Liver biopsy
- E. I don't know

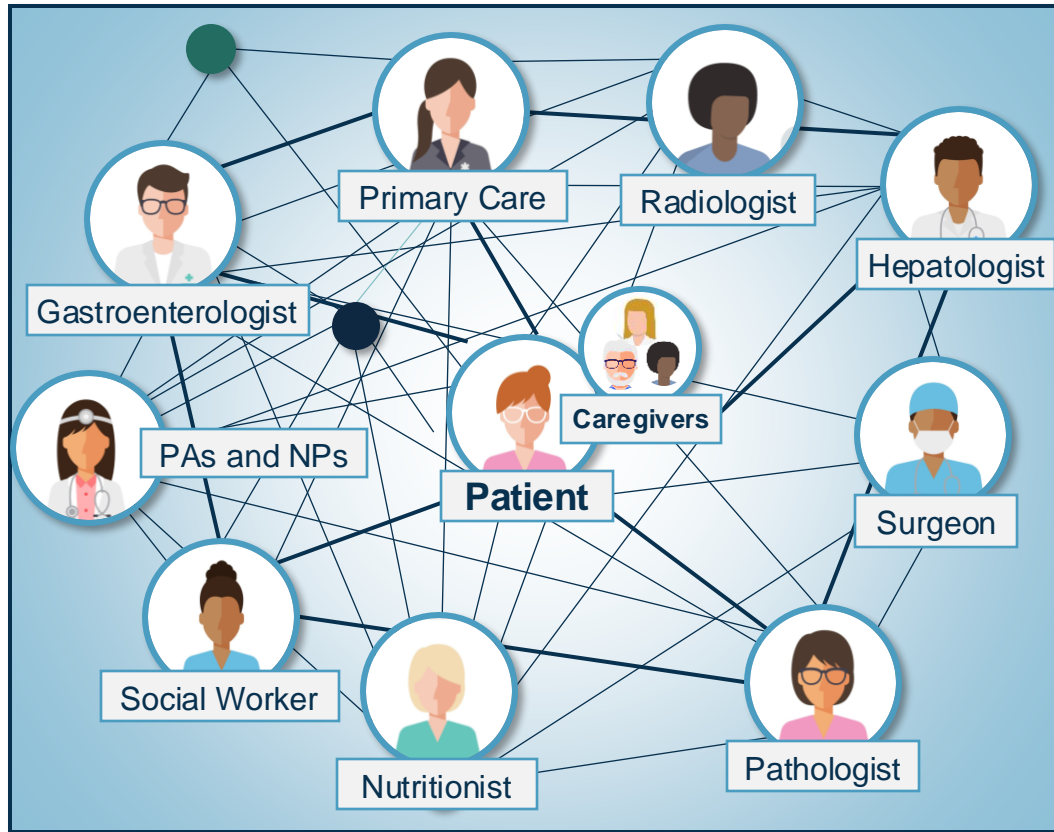
What is PBC?

- ▶ **Chronic, cholestatic, autoimmune disease** with a variable progressive course; may extend over decades
- ▶ Thought to be caused by a combination of **genetic** predisposition and **environmental** triggers
- ▶ “Common rare” disease: **most clinicians** will encounter PBC in practice
- ▶ Mostly seen in **women** in their **fifth or sixth decade** of life
- ▶ **~10% of cases occur in men**, often with advanced disease & worse prognosis
- ▶ Recent investigation shows increased global prevalence

How PBC Presents in the Clinic

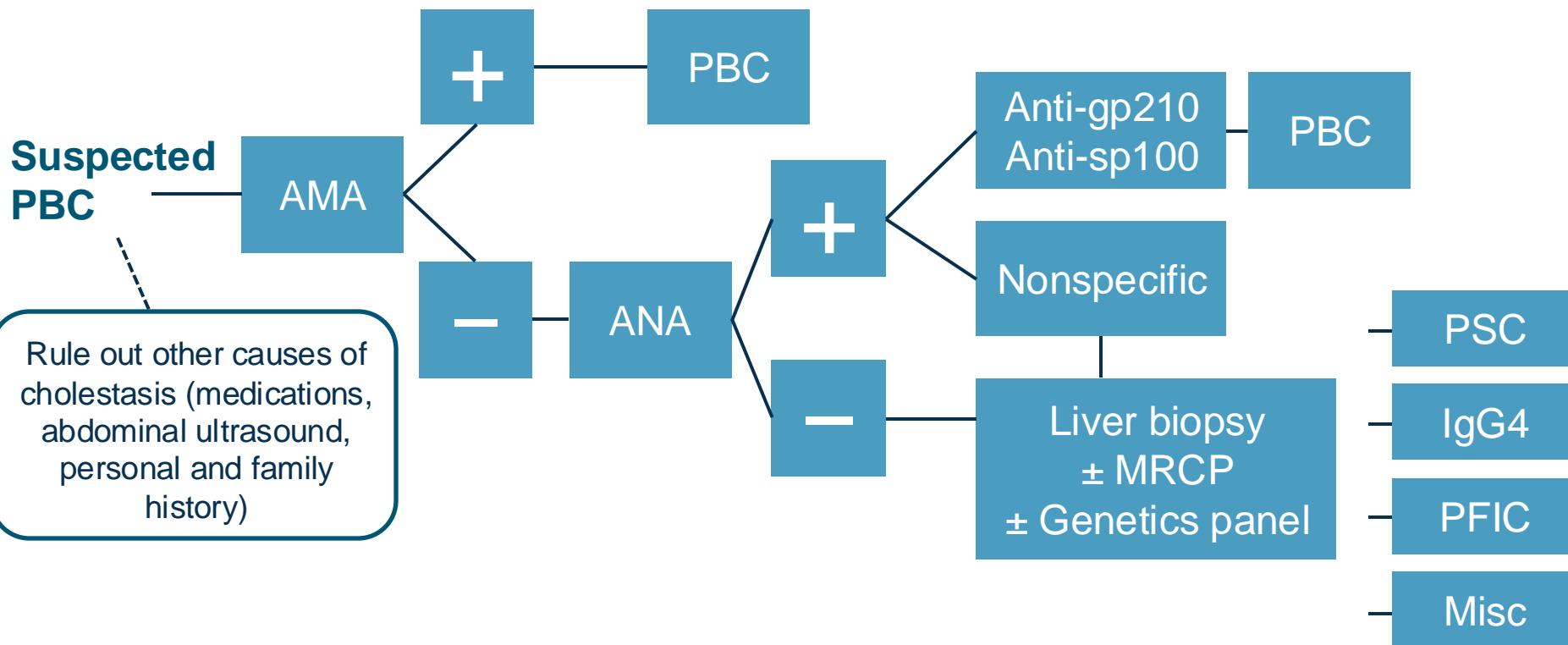
- ▶ **Fatigue** is reported in up to 80% of patients
- ▶ **Pruritus** has been reported to affect 20%-70% of patients
- ▶ Advanced cases may include ascites, esophageal varices, hepatic encephalopathy, and autoimmune disorders
- ▶ Can be asymptomatic, but **abnormal liver tests** should raise suspicion
- ▶ Prompt diagnosis (and subsequent treatment) is **critical** to prevent liver-related sequelae (e.g., cirrhosis, liver failure, need for transplantation, death)
- ▶ It can take **years** before a patient receives a diagnosis

Team-Based Approach for Managing PBC



A comprehensive team approach ensures all aspects of PBC management are addressed – from diagnosis and treatment to supportive care and long-term follow-up.

Diagnostic Pathways: PBC



Diagnosing PBC: AASLD Guidelines

PBC Diagnostic Criteria (2 of 3 must be met)

1. Biochemical evidence of cholestasis based on ALP elevation
2. Presence of AMAs or other PBC-specific autoantibodies, including sp100 or gp210, if AMA is negative
3. Histopathologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts (if biopsy is performed)

Audience Response

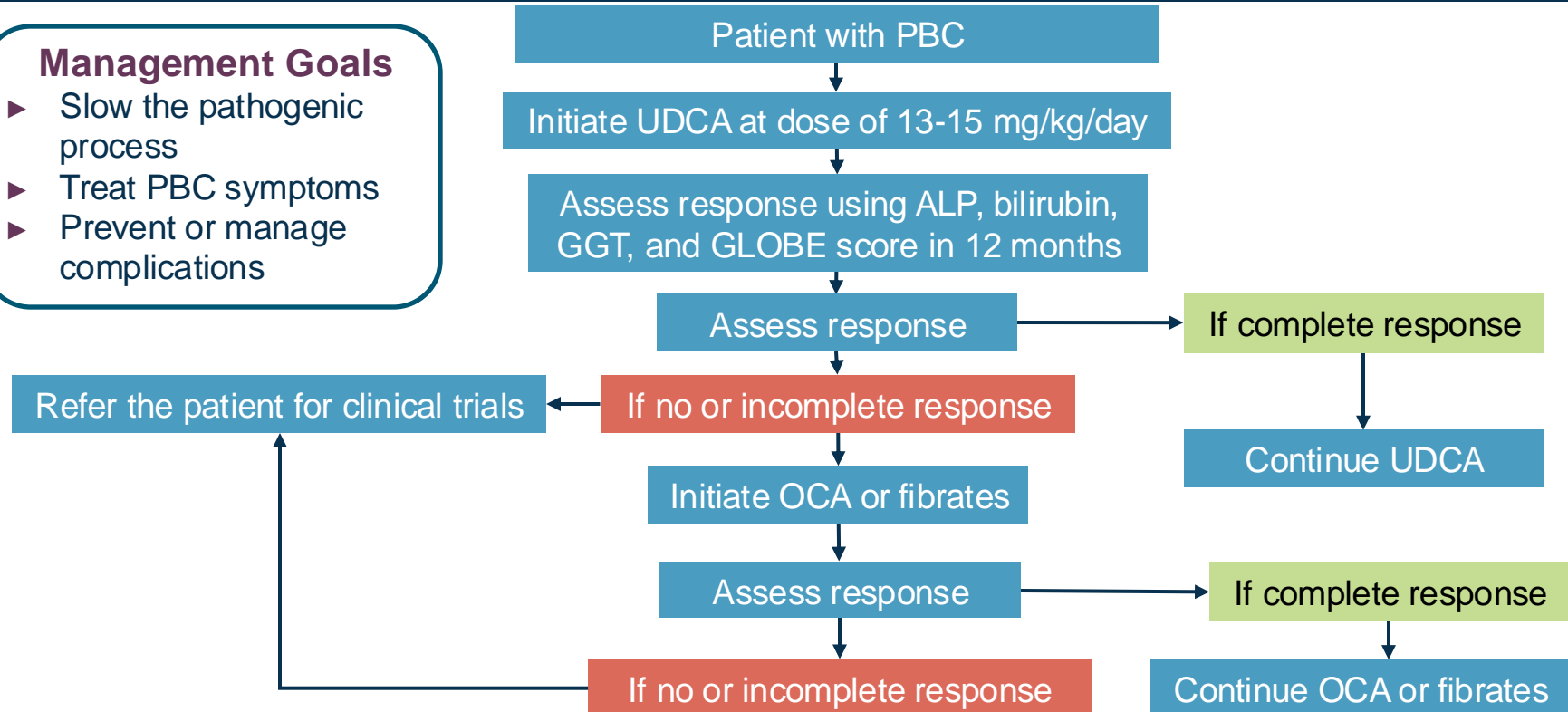
Which of the following treatments for PBC has shown significant biochemical response as well as improvement in pruritus?

- A. Elafibranor
- B. Obeticholic acid (OCA)
- C. Seladelpar
- D. A and C
- E. I don't know

Treatment Pathways: Conventional Therapies

Management Goals

- ▶ Slow the pathogenic process
- ▶ Treat PBC symptoms
- ▶ Prevent or manage complications



Why New Treatments Are Needed

▶ UDCA (first-line therapy)

- ▶ 25%-50% of patients do not have a biochemical response
- ▶ Non-responders have a fivefold risk of progression to cirrhosis and a threefold increase in age-adjusted mortality
- ▶ AEs can negatively impact patient QoL

▶ OCA (second-line therapy)

- ▶ Warning added for hepatic decompensation and failure in PBC with cirrhosis → AASLD revised guidance on OCA (2021)
- ▶ FDA panel voted 13 to 1 that confirmatory trials did not verify clinical benefits of OCA in PBC; pointed to harm vs benefit (2024)
- ▶ AEs (pruritus) led to significant discontinuation

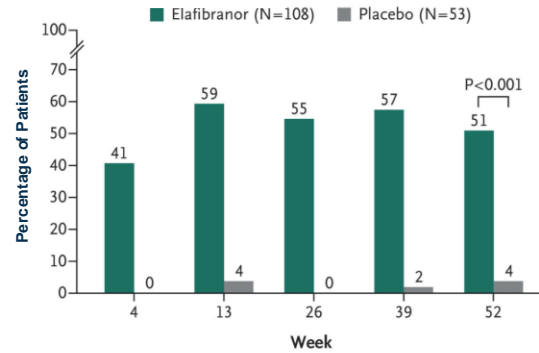
FDA-Approved Treatments for PBC

- ▶ **Elafibranor** – a dual peroxisome proliferator-activated receptor (PPAR) α and δ agonist
 - ▶ Approved by the FDA for PBC in June 2024
- ▶ **Seladelpar** – a selective peroxisome proliferator-activated receptor- δ (PPAR) agonist
 - ▶ Approved by the FDA for PBC in August 2024

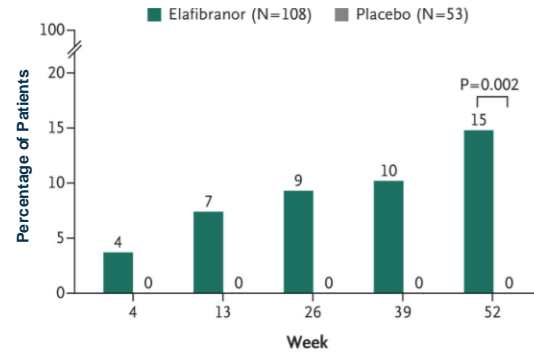
Elafibranor

ELATIVE: Phase III Results

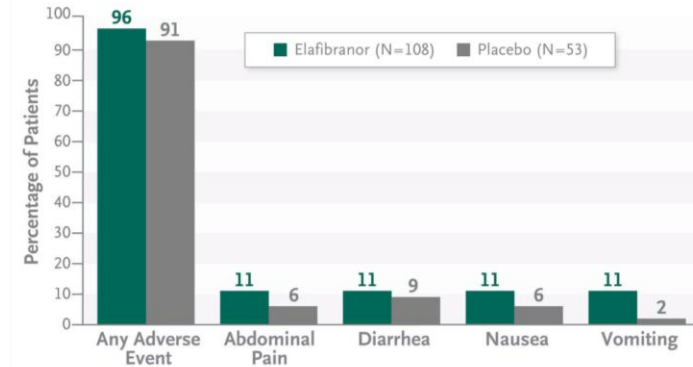
Biochemical Response



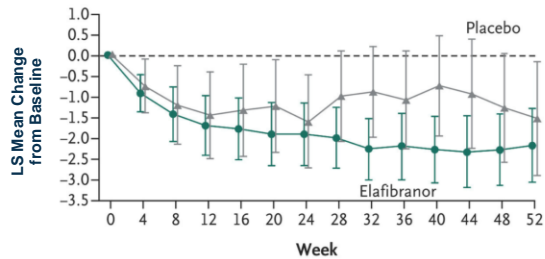
Normalization of Alkaline Phosphatase



Adverse Events



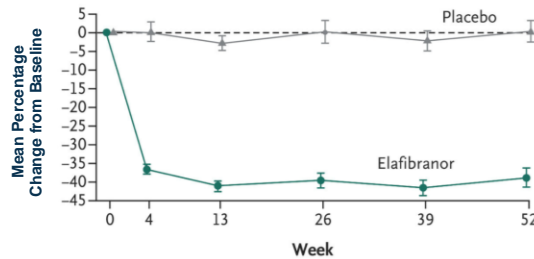
Change in Score on the Worst Itch Numeric Rating Scale (WI-NRS)



No. at Risk

Week	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Placebo	22	21	19	18	18	17	16	15	15	16	15	14	13	12
Elafibranor	44	41	40	39	40	38	37	34	35	34	32	34	35	32

Percentage Change in Alkaline Phosphatase Levels



No. at Risk

Week	0	4	13	26	39	52
Placebo	53	48	49	49	49	49
Elafibranor	108	104	107	104	102	94

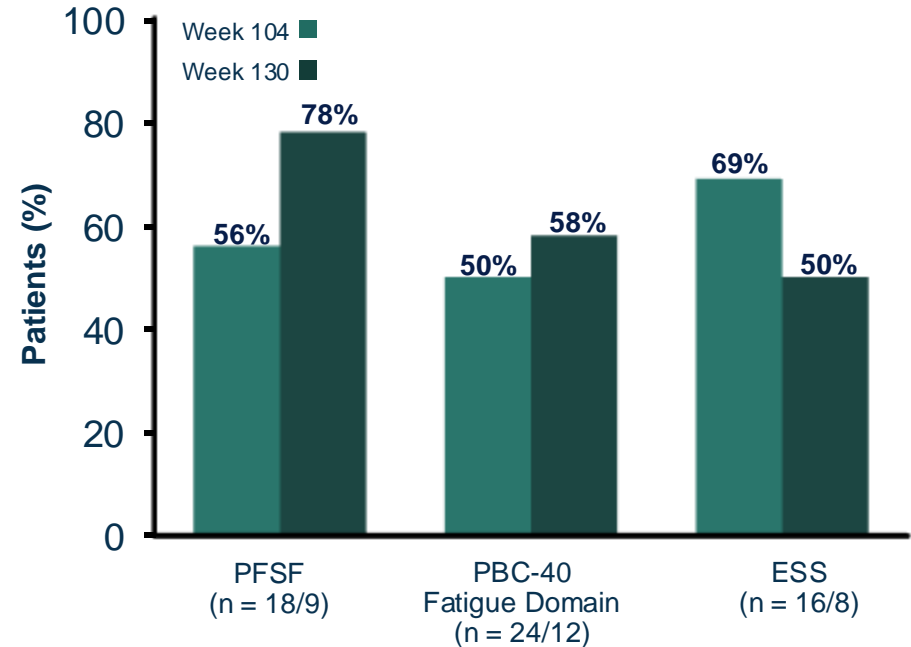
Conclusions:

In patients with PBC in whom UDCA was associated with inadequate response or unacceptable side effects, treatment with elafibranor led to greater improvements in relevant biochemical indicators of cholestasis than placebo.

ELATIVE: Impact of Elafibranor on Fatigue During the Open-Label Extension

- ▶ Patients randomized to elafibranor during double-blind phase included in open-label extension analysis measured fatigue and sleep domains*
- ▶ Clinically meaningful improvements shown with elafibranor treatment in patients with moderate-to-severe fatigue or excessive sleepiness at baseline

Improvement From Baseline With Elafibranor During Open-Label Extension

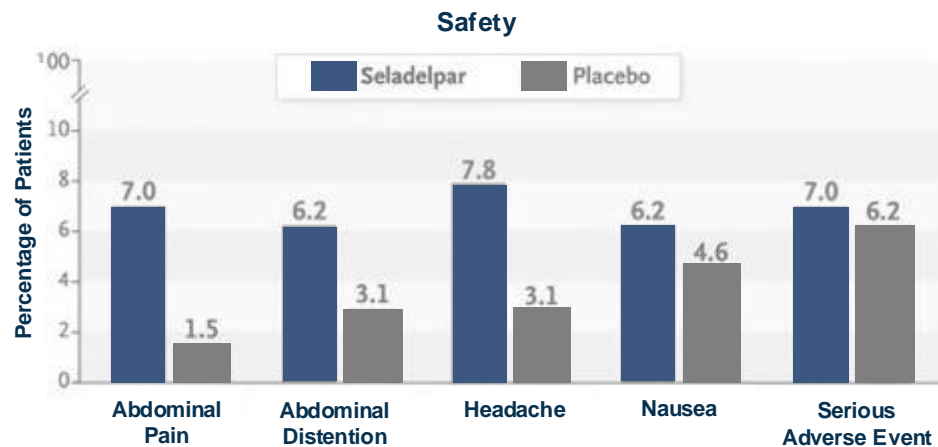
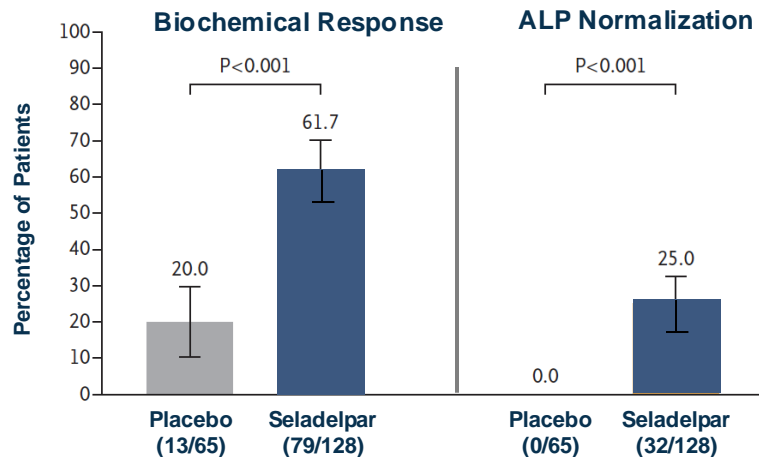


*PFSF 7a = Fatigue Short Form 7a.

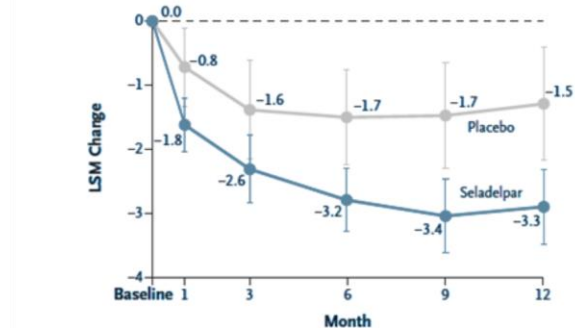
ESS = Epworth Sleepiness Scale.

Swain MG, et al. AASLD: The Liver Meeting; 2024. Abstract No. 5042. https://www.aasld.org/sites/default/files/2024-11/TLM2024LBA_20241115A.pdf.

Seladelpar – RESPONSE: Phase III Results

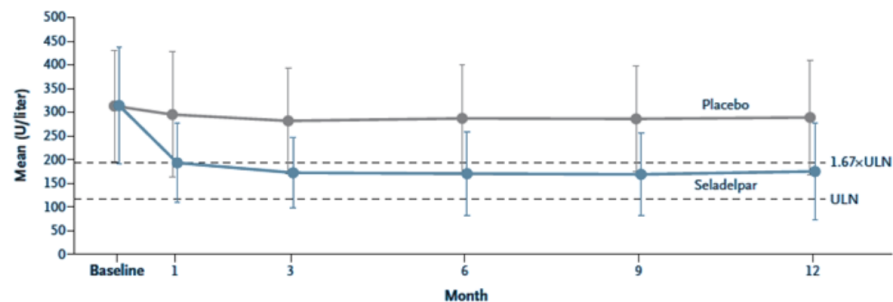


Patients with a Baseline Pruritus NRS Score ≥ 4



No. at Risk	Baseline	1	3	6	9	12
Placebo	23	22	22	20	20	16
Seladelpar	49	48	46	45	36	39

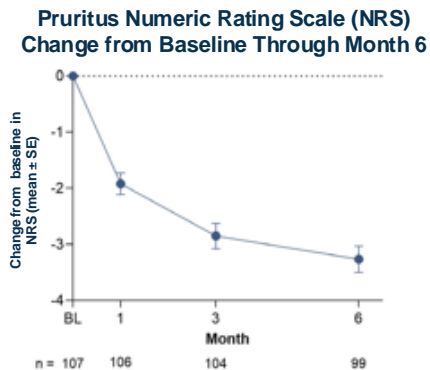
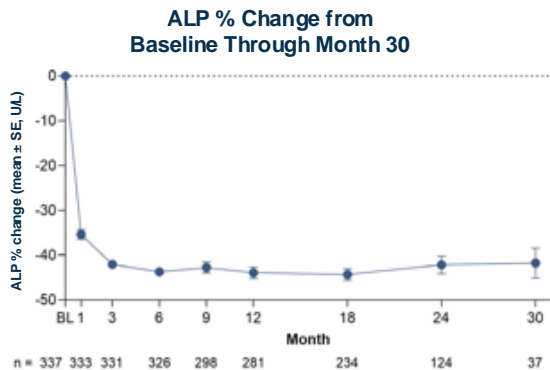
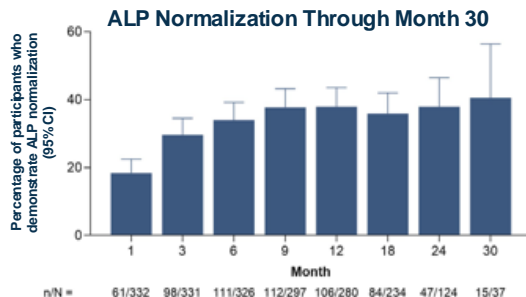
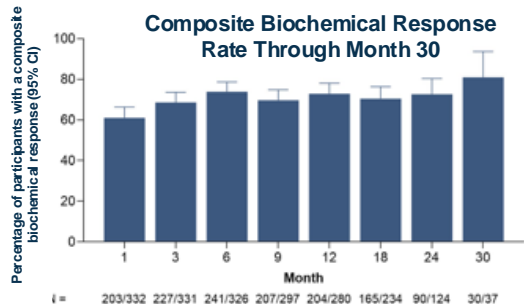
ALP Serum Level



No. at Risk	Baseline	1	3	6	9	12
Placebo	65	62	62	61	58	57
Seladelpar	128	125	125	122	117	114

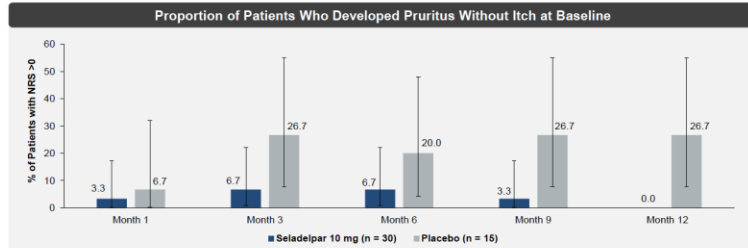
Seladelpar: AASLD 2024

ASSURE Study: 3-Year Study Outcomes



A Secondary Analysis of Patterns of Pruritus Change in RESPONSE

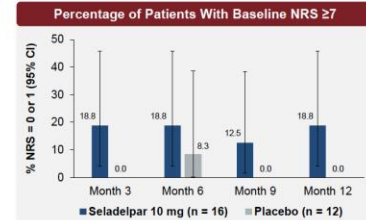
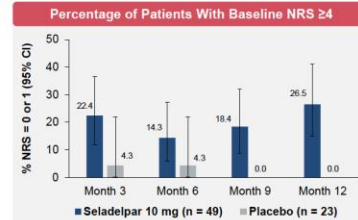
Development of Itch in Patients With NRS = 0 at Baseline



Among patients without itch at baseline, no patient receiving seladelpar developed itch at month 12

Near Pruritus Resolution (NRS 0 or 1) in Patients With Moderate to Severe and Severe Pruritus at Baseline

NRS ≥4 or ≥7 at Baseline



Over a quarter of patients with moderate to severe pruritus and nearly 20% of patients with severe pruritus at baseline experienced near resolution of itch at month 12 vs 0% of patients on placebo

Part 2
MASLD/MASH

Patient Case: Walter



- ▶ 61-year-old auto service supervisor



- ▶ T2D, dyslipidemia, hypertension
- ▶ Central adiposity (BMI = 32.7 kg/m²)
- ▶ High carb diet: 5-7 alcoholic drinks per week
- ▶ Complains of abdominal discomfort (right upper quadrant)
- ▶ Current meds: metformin, valsartan, hydrochlorothiazide

Patient Case: Walter



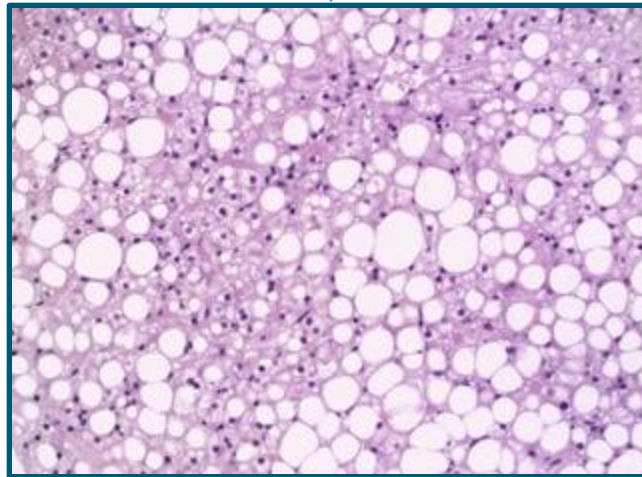
- ▶ ALT: 60 U/L
- ▶ AST: 65 U/L
- ▶ ALP: 110 U/L
- ▶ Total bilirubin: 1.4 mg/dL
- ▶ Albumin: 4.0 g/dL
- ▶ Platelets: 180,000/ μ L
- ▶ LDL: 130 mg/dL
- ▶ HDL: 36 mg/dL
- ▶ TG: 235 mg/dL
- ▶ A1C: 7.1%

Defining MASLD and MASH

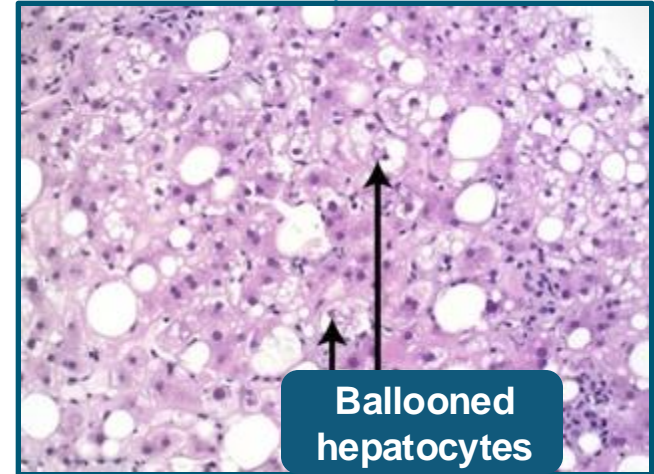
Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

Presence of steatosis in $\geq 5\%$ hepatocytes; minimal alcohol use
No other etiology for liver disease; no secondary causes of MASLD (e.g., meds, HIV, lipodystrophy)

- ▶ Global prevalence of MASLD is $\sim 30\%$ among adults
- ▶ Projected to rise with \uparrow rates of obesity, T2D, and metabolic syndrome



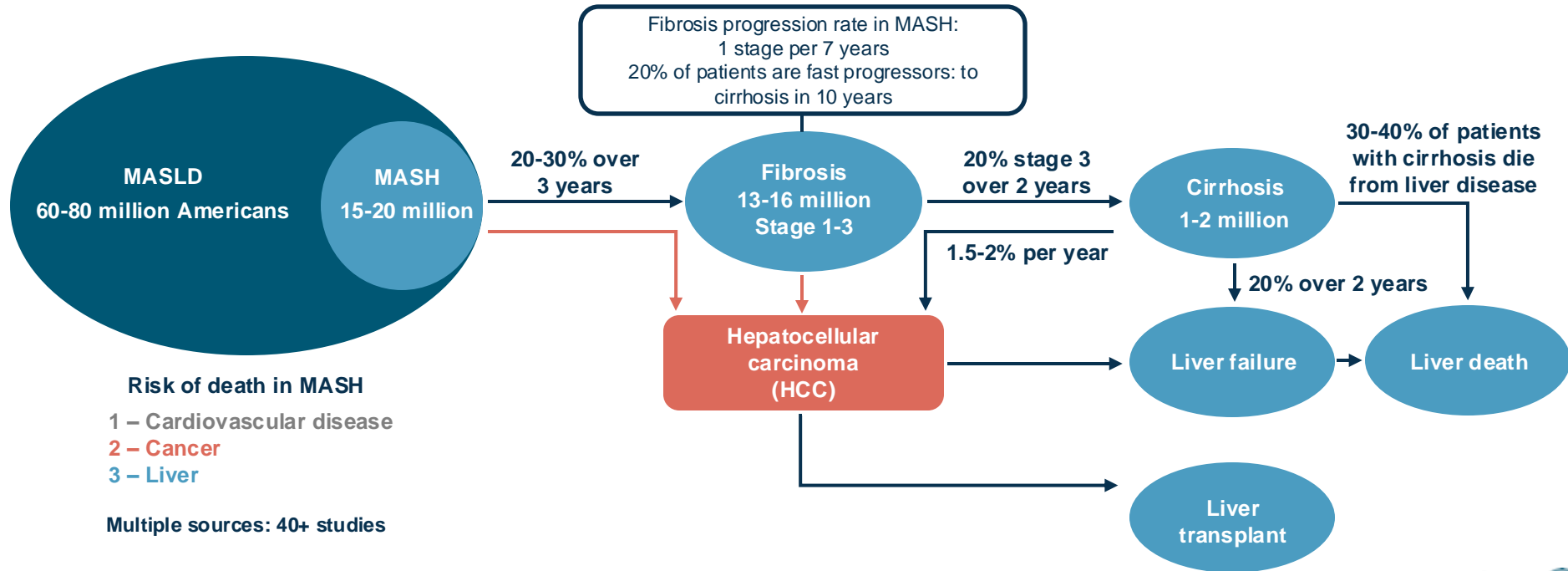
MASLD [Non-progressive]



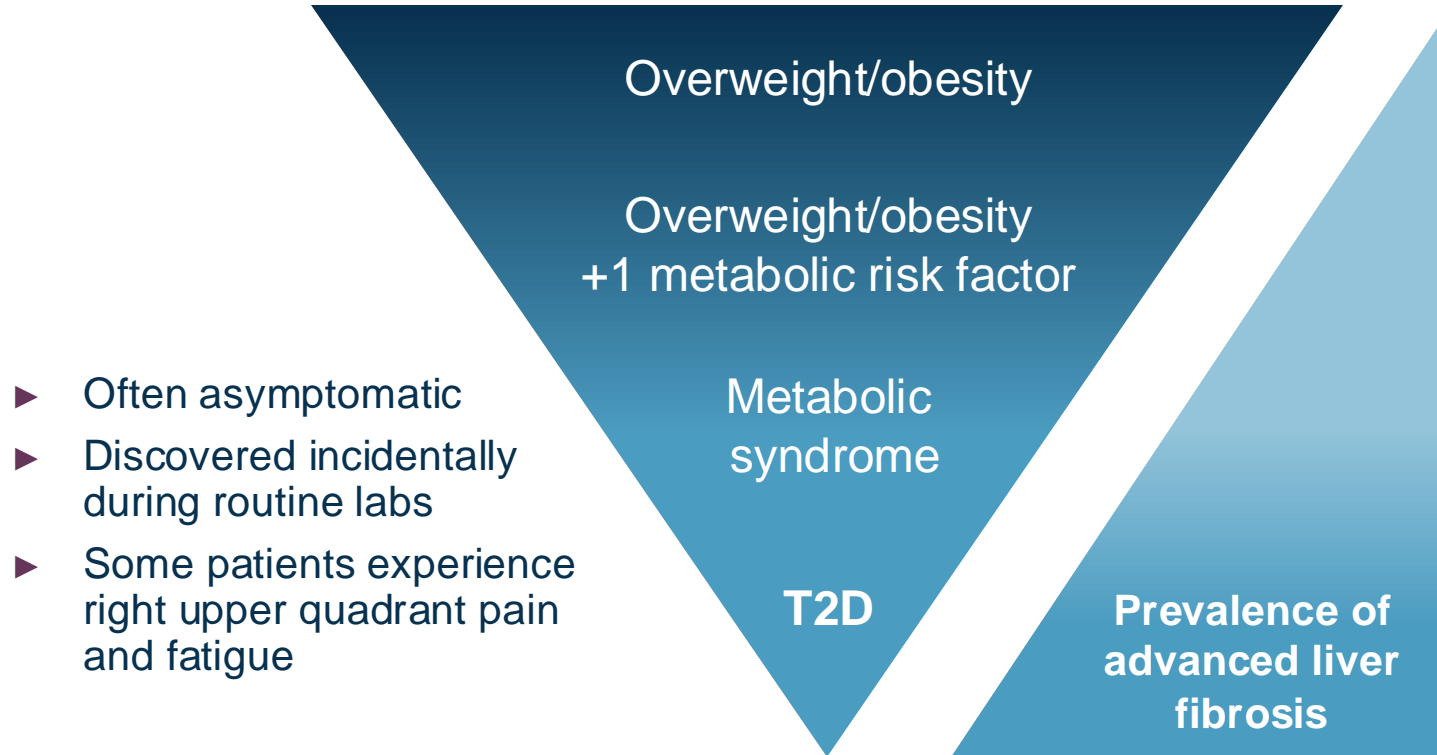
MASH (Metabolic Dysfunction-Associated Steatohepatitis) [Progressive]

MASLD/MASH: Prevalence and Natural History

- ▶ Global prevalence of MASLD is ~30%; among people with T2D: ~56%
- ▶ Global prevalence of MASH is between 1.5% and 6.5%; among people with T2D: ~37%



Populations at Risk for MASLD-Related Liver Outcomes



Noninvasive Testing for MASLD/MASH

Audience Response

You and Walter agree to screen for MASLD. Which of the following is the next step for risk stratification?

- A. Fibrosis-4 (FIB-4)
- B. Liver biopsy
- C. Magnetic resonance elastography (MRE)
- D. Transient elastography (e.g., FibroScan)
- E. I don't know

Exploring Noninvasive Tests: Fibrosis-4 (FIB-4) Index and NAFLD Fibrosis Score (NFS)

FIB-4

- ▶ Predicts advanced fibrosis in the liver
 - ▶ Age (years)
 - ▶ ALT (U/L)
 - ▶ AST (U/L)
 - ▶ Platelet count ($\times 10^9/L$)

Understanding the FIB-4 Score

Score < 1.3

Rules out advanced fibrosis
Sn: 74%; Sp: 71%

Indeterminate

Score > 2.67

Predicts advanced fibrosis
Sn: 33%; Sp: 98%

NFS

- ▶ Predicts liver fibrosis in patients with NAFLD
 - ▶ Age (years)
 - ▶ ALT (U/L)
 - ▶ AST (U/L)
 - ▶ BMI (kg/m^2)
 - ▶ Hyperglycemia
 - ▶ Platelet count ($\times 10^9/L$)

Understanding the NFS Score

Score < -1.455

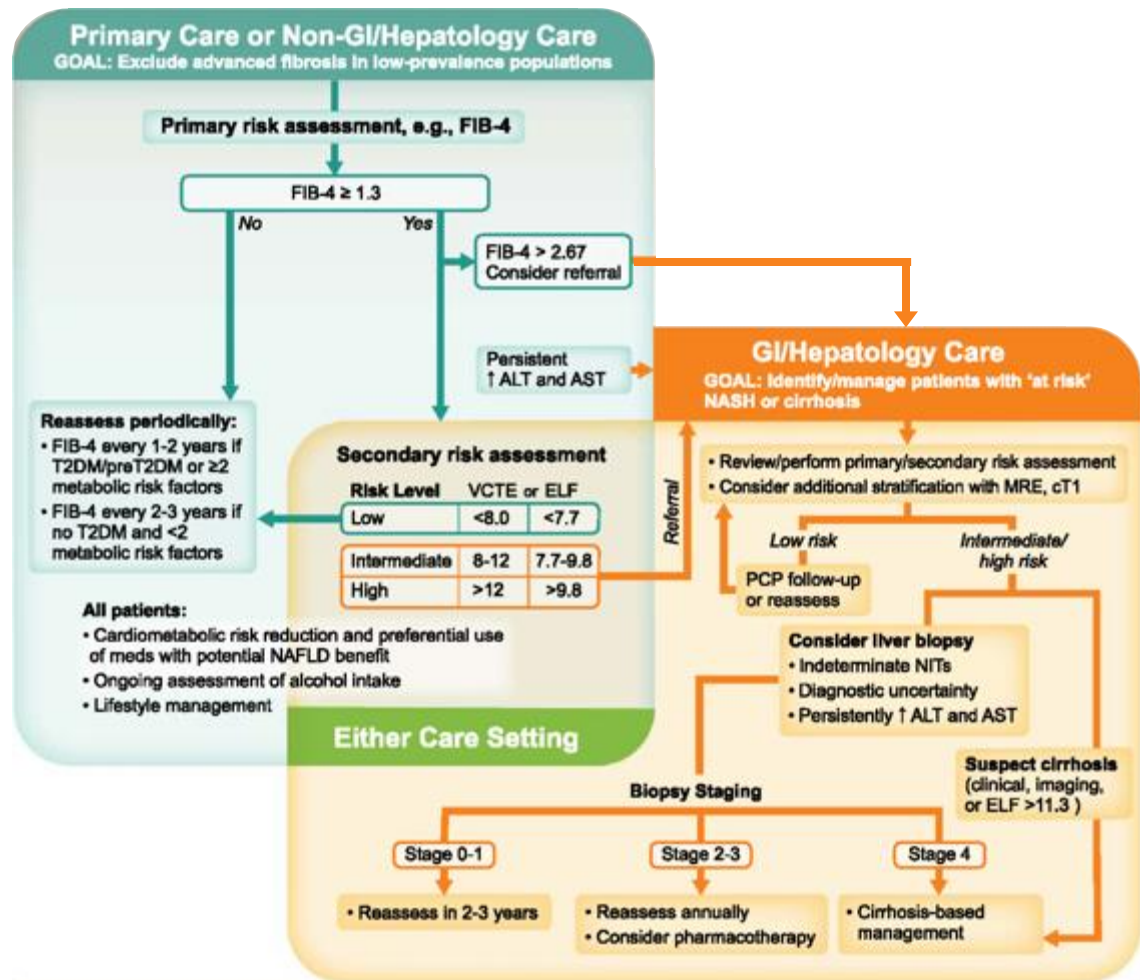
Rules out fibrosis
Sn: 82%; Sp: 77%

Indeterminate

Score > 0.66

Predicts fibrosis
Sn: 51%; Sp: 98%

MASLD: Algorithm for Evaluation of Patients at Risk Across Practice Settings



Exploring Noninvasive Tests: Enhanced Liver Fibrosis (ELF) Score

Proprietary blood test delivers information on liver fibrosis severity

Algorithm incorporates 3 common serum biomarkers:

- ▶ HA (hyaluronic acid)
- ▶ PIIINP (amino-terminal propeptide of type III procollagen)
- ▶ TIMP-1 (tissue inhibitor of metalloproteinase-1)

Understanding the ELF Score

Score 7.7

Rules out
fibrosis

Sn: 97%

Sp: 33%

Score 9.8

Predicts
fibrosis

Sn: 69%

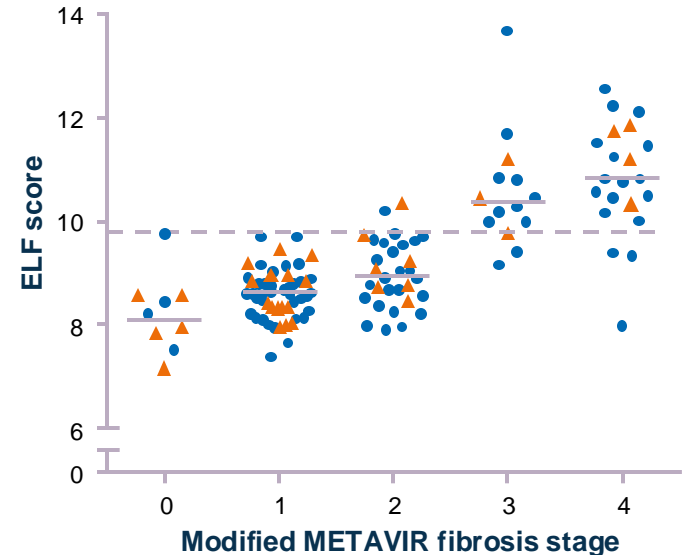
Sp: 98%

Score 11.3

Predicts
cirrhosis

Sn: 83%

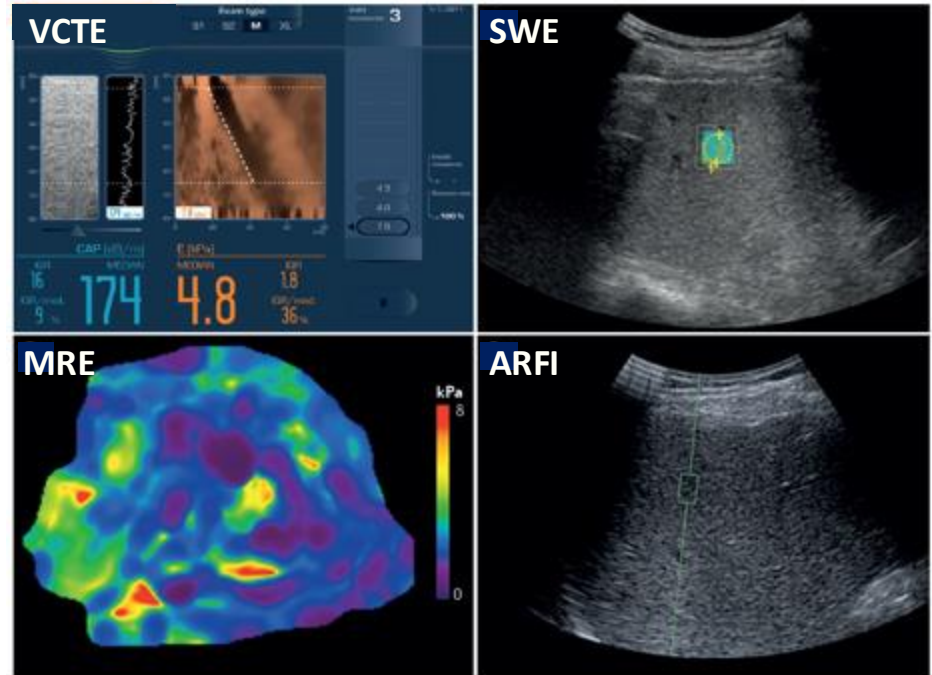
Sp: 97%



**ELF ≥ 9.8 is associated with
advanced fibrosis**

Elastography-Based Methods to Estimate Liver Stiffness

- ▶ VCTE (FibroScan) most widely used
 - ▶ ≥ 10 images are required
 - ▶ Accurate for stages F3-F4
 - ▶ Can estimate steatosis when used with CAP
- ▶ SWE/ARFI can be used to measure stiffness in a single region of interest
- ▶ MRE measures stiffness across multiple regions of interest



VCTE = vibration-controlled transient elastography; CAP = controlled attenuation parameter; SWE = shear wave elastography; ARFI = acoustic radiation force impulse imaging.

Tapper EB, et al. *Nat Rev Gastroenterol Hepatol.* 2018;15(5):274-282.

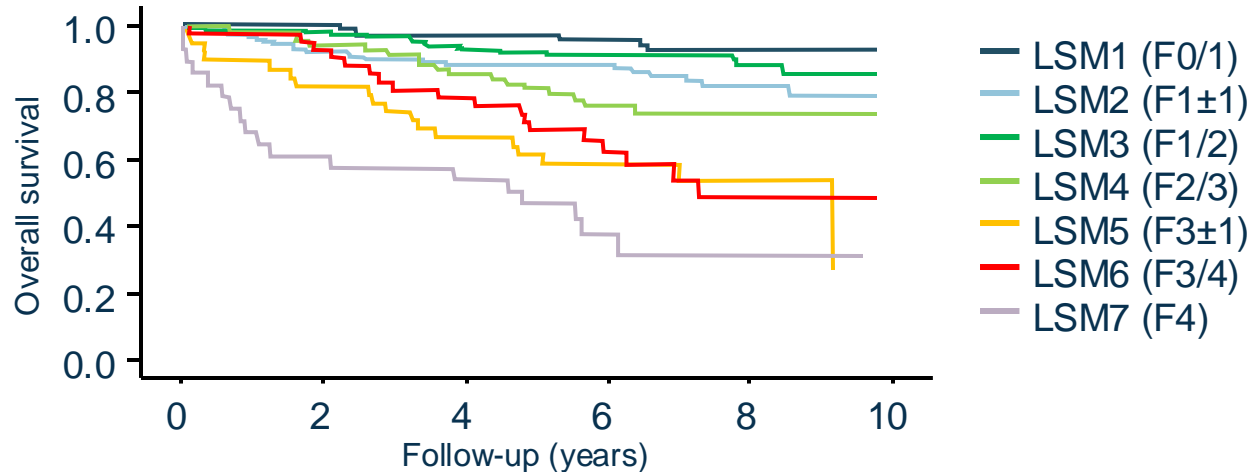
Liver Stiffness Measurement by FibroScan as a Noninvasive Biomarker of Fibrosis

A cross-sectional study of 452 patients with liver biopsy

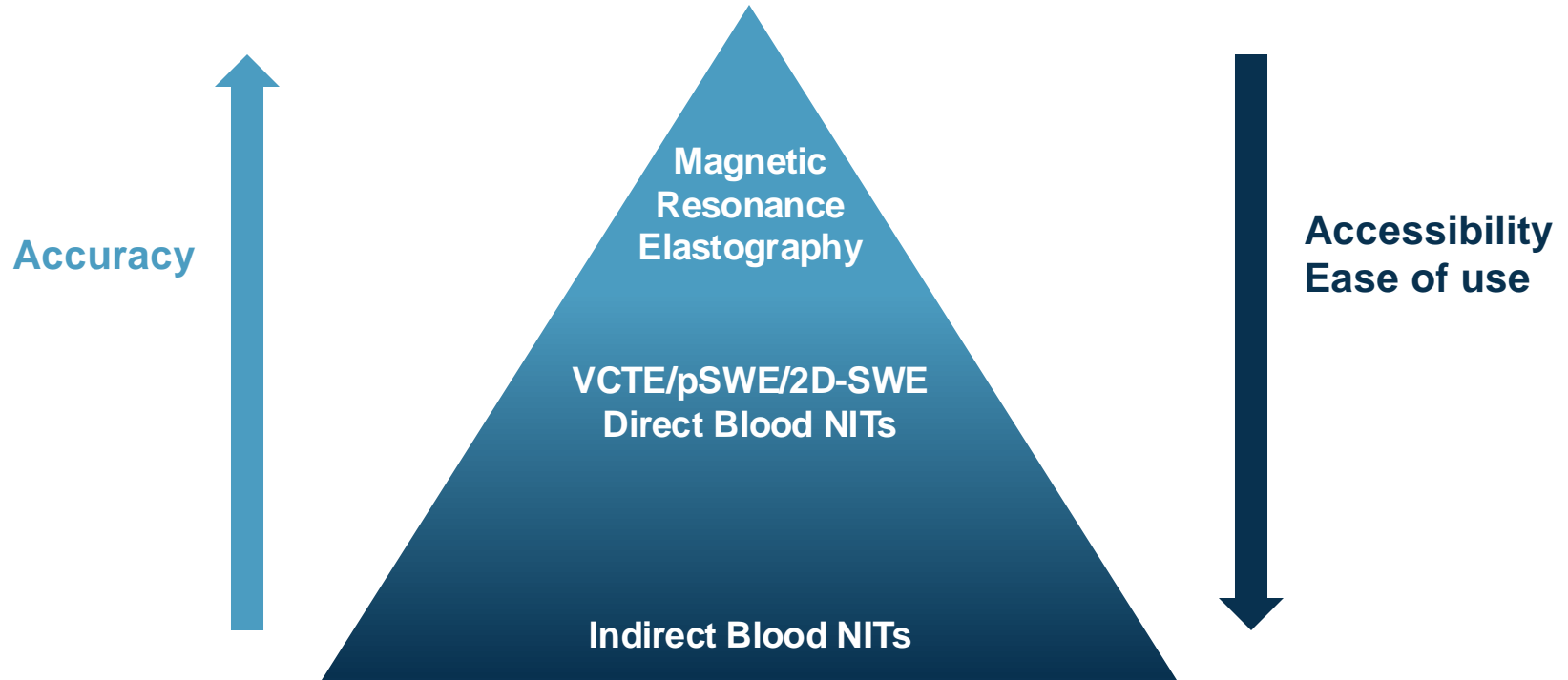
Fibrosis classification:
(equivalence in fibrosis stage)



Liver Stiffness Measure (LSM): 2.0 4.6 6.1 8.8 12.0 18.0 38.6 75.0 kPa



Comparative Accuracy and Accessibility of NITs

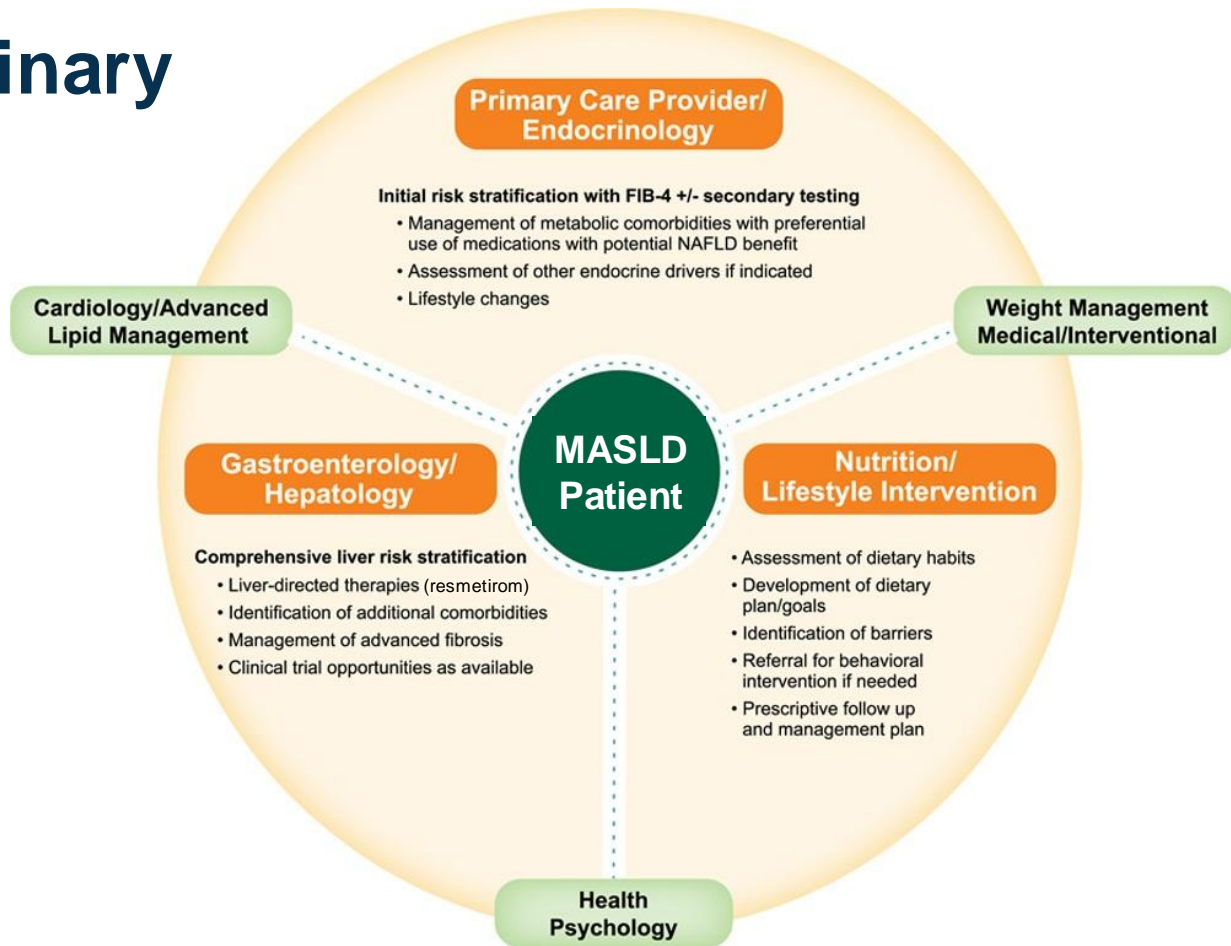


Treatment Summary for MASLD/MASH

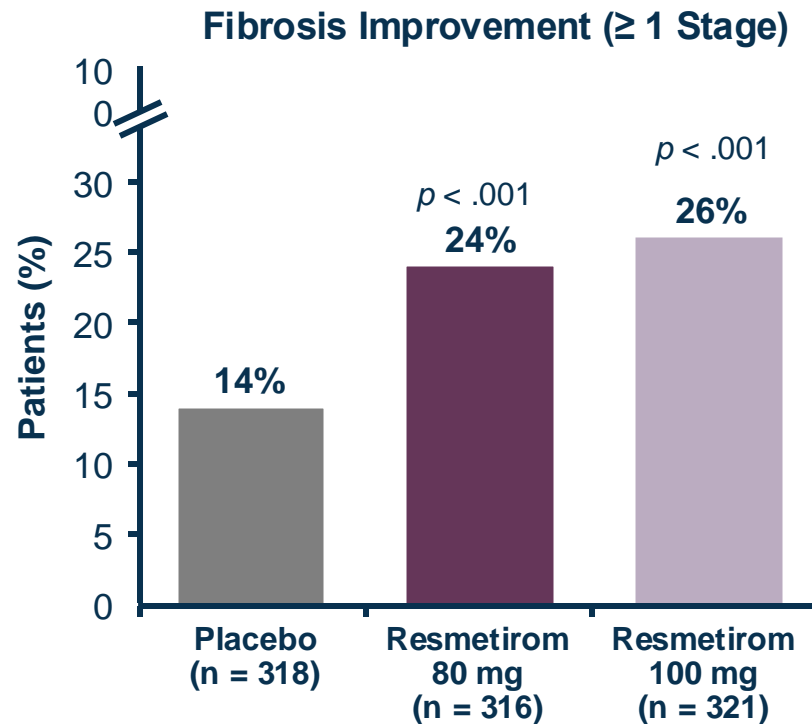
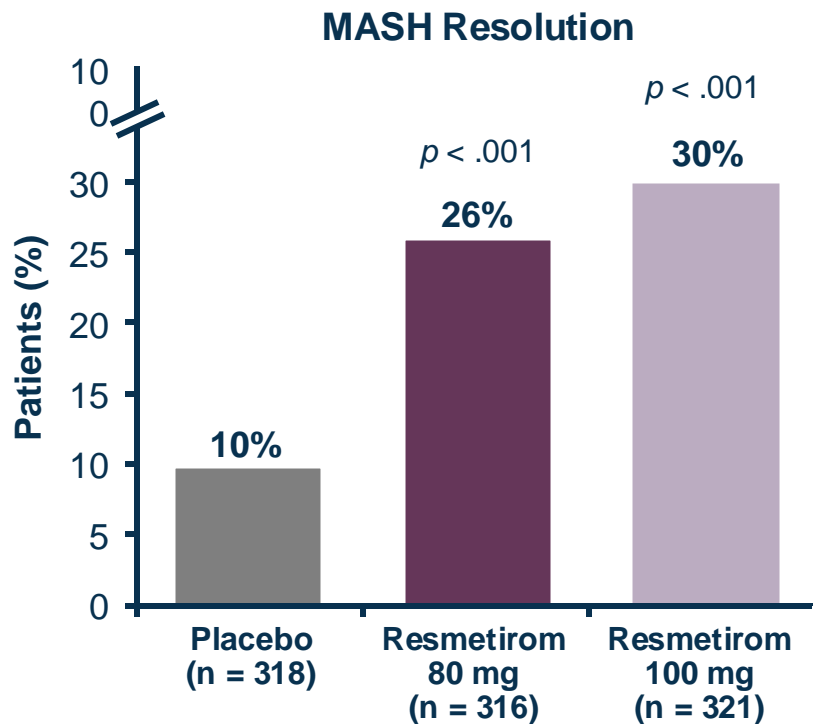
Treatment to Improve Patient Outcomes

- ▶ Treatment to optimize metabolic risk factors: weight loss is important
 - ▶ Treatment goal: 7%-10% weight loss
 - ▶ Weight loss of 3%-5% improves steatosis, but 7%-10% weight loss is needed to improve most histologic features of MASH, including fibrosis
 - ▶ Combination of Mediterranean diet and moderate exercise has improved visceral fat as well as hepatic fat
- ▶ Resmetirom was recently FDA approved as MASH-specific therapy
 - ▶ Approved March 2024 for noncirrhotic MASH with moderate to advanced liver fibrosis (stages F2 to F3) in conjunction with diet/exercise
- ▶ Promising data with GLP-1/GIP/Glucagon RA emerging
 - ▶ Semaglutide, tirzepatide, survodutide

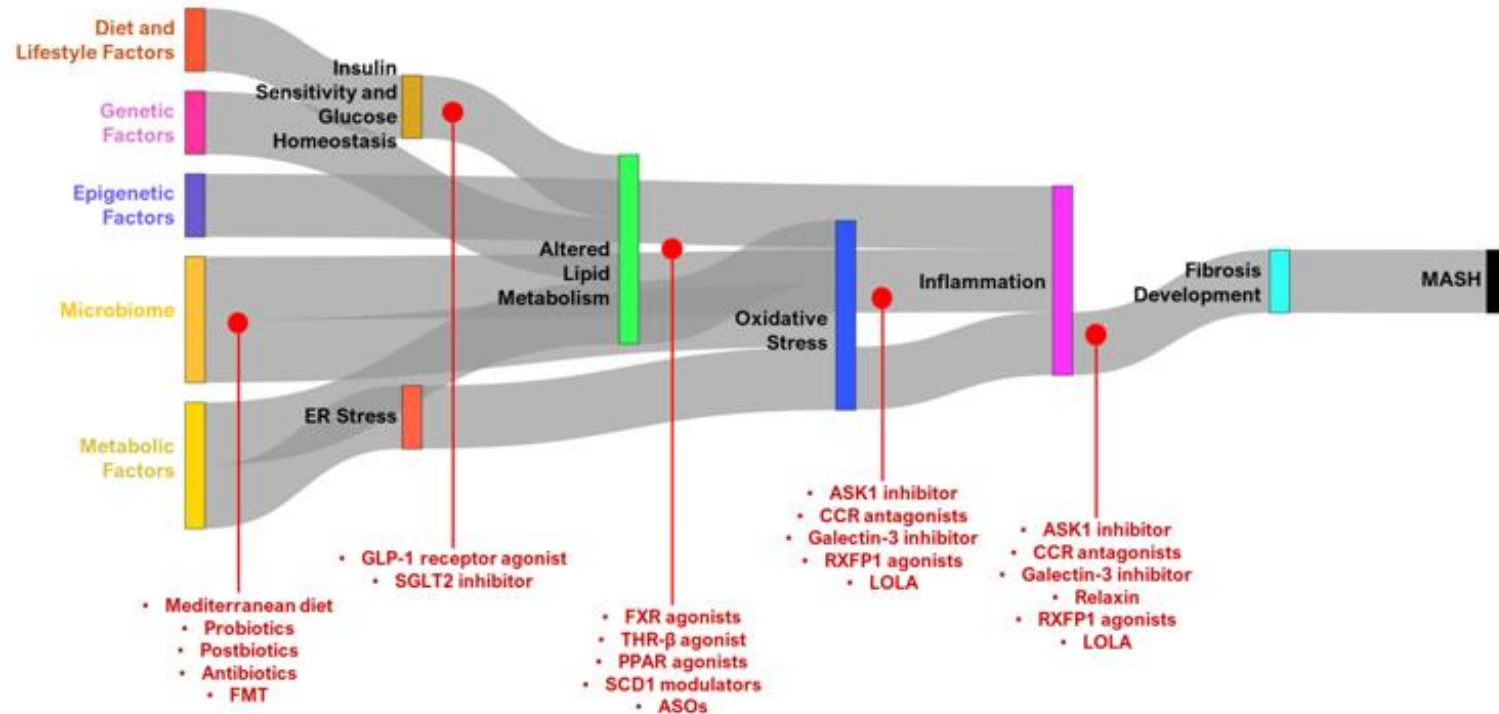
A Multidisciplinary Approach to MASLD



Resmetirom: Phase III Trial Results



Overview of Therapeutic Landscape: 2025



ASK1 = apoptosis signal-regulating kinase 1; ASOs = antisense oligonucleotides; CCR = C-C chemokine receptor; FMT = fecal microbiota transplantation; LOLA = L-ornithine L-aspartate; RXFP1 = relaxin/insulin-like family peptide receptor 1; SCD1 = stearyl-CoA desaturase 1; THR- β = thyroid hormone receptor beta.
 Devasia AG, et al. *Int J Mol Sci.* 2025;26(4):1778.

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

Put information into action! Consider the following goals, then *set a time frame* that fits with your work environment and *a reasonable improvement target* that aligns with your patient population.

- **Increase** the percentage of *patients screened for PBC* who present with elevated LFTs or symptoms (e.g., fatigue, pruritus, abdominal discomfort)
- **Increase** the percentage of *patients* with abnormal liver function tests *who receive proactive follow-up, including referrals*, for PBC or MASLD/MASH
- **Increase** the percentage of patients who are *treated* for PBC or MASLD/MASH *using appropriate contemporary clinical pathways* that include new options, when appropriate

QUESTIONS & ANSWERS

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